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Internet-based cognitive behavioral therapy for prevention of depression during pregnancy and in the postpartum (iPDP): a protocol for a large scale randomized controlled trial

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Complete List of Authors:	Nishi, Daisuke; The University of Tokyo, Imamura, Kotaro Watanabe, Kazuhiro; The University of Tokyo, Department of Mental Health, Graduate School of Medicine Obikane, Erika Sasaki, Natsu Yasuma, Naonori; The University of Tokyo, ; Sekiya, Yuki Matsuyama, Yutaka; Univ Tokyo Kawakami, Norito; The University of Tokyo, Department of Mental Health
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6 in the postpartum (iPDP): a protocol for a large scale randomized controlled trial
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12 Authors: Daisuke Nishi, MD, PhD¹, Kotaro Imamura, PhD¹, Kazuhiro Watanabe, PhD¹, Erika
13
14 Obikane, MD¹, Natsu Sasaki, MD¹, Naonori Yasuma, MD¹, Yuki Sekiya, PhD¹, Yutaka
15
16 Matsuyama², PhD, Norito Kawakami, MD, PhD¹
17
18
19

20 ¹Department of Mental Health, Graduate School of Medicine, The University of Tokyo, 7-3-1
21
22 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
23

24 ²Department of Biostatistics, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo,
25
26 Bunkyo-ku, Tokyo 113-0033, Japan
27
28
29
30
31

32 Corresponding author: Daisuke Nishi
33

34 Department of Mental Health, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo,
35
36 Bunkyo-ku, Tokyo 113-0033, Japan
37

38 E-mail: d-nishi@m.u-tokyo.ac.jp
39
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Abstract

Introduction: The objective of this randomized controlled trial (RCT) is to examine the effects of smartphone-based cognitive behavioral therapy (CBT) in preventing the onset of major depressive episodes (MDE) among pregnant women.

Methods and analysis: The target study population will be pregnant women of 16 to 20 weeks gestation who are currently users of “Luna Luna Baby”, the most widely used app for pregnant women in Japan. Those who meet the eligibility criteria will be randomly allocated to the 6-module internet cognitive behavioral therapy (iCBT) program that was newly developed for pregnant women (n=2500), or to a treatment-as-usual control group (n=2500). Participants in the intervention groups will be required to complete the program by 32 weeks gestation. The primary outcomes are the number of new onsets of MDE, measured by using the World Health Organization Composite International Diagnostic Interview 3.0 (WHO-CIDI 3.0) at 32 weeks gestation and 3 months postpartum.

Ethics and dissemination: The study plan has been approved by the Research Ethics Review Board of the Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (2019150NI). If the intervention programs are found to produce a significant positive effect in this RCT, these programs can be made available for all users of the app in the future.

Key words: smartphone-based cognitive behavioral therapy, antenatal depression, postpartum depression, prevention

Trial registration number: UMIN000038190; Pre-results.

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Article Summary

Strengths and limitations of this study

- The large sample size of this RCT can lead to a definitive result of the effectiveness of the fully automated smartphone-based CBT program in preventing both antenatal and postpartum depression.
- The newly developed program designed to handle concerns extracted from pregnant women would be practical and expect low dropout.
- This study will also evaluate the implementation outcomes of the program, which will contribute to the dissemination and implementation of iCBT.
- This RCT will also clarify whether iCBT during pregnancy can prevent maternity blues.
- A limitation of this study is that all of the outcomes will be measured by self-report.

Introduction

Prevention of perinatal depression is a critical public health issue.[1] The prevalence of antenatal depression was reported to be 7.4% in the first trimester, 12.8% in the second trimester, and 12.0% in the third trimester;[2] and the prevalence of postpartum depression was estimated to be 17.7%, though there is significant heterogeneity across nations.[3] Antenatal depression is associated with failing to seek prenatal care, an inadequate diet and/or use of tobacco, alcohol, or other harmful substances, self-harm or attempted suicide, and postpartum depression; while postpartum depression is associated with negative outcomes such as physical and psychological abuse to their children, and infanticide.[4] Furthermore, perinatal depression can also affect development from fetus to adolescent and paternal depression.[5-10] Therefore, preventing perinatal depression in the antenatal period is crucially important.

Given the large number of pregnant women who have risk factors such as maternal anxiety, life stress, lack of social support, unintended pregnancy, domestic violence, lower income and education, and poor relationships, making it difficult to identify and screen all high-risk pregnant women,[11] universal prevention should be more valued. According to a systematic review and meta-analysis, psychological interventions have been recommended as the most effective approach to prevent antenatal and postpartum depression.[12] Cognitive behavioral therapy (CBT) has been broadly researched and reported to be highly effective among psychological interventions.[13,14] Previous meta-analyses showed that the effect size of psychological intervention as universal prevention for postpartum depression was reported to be 0.19[15] and 0.37.[13] The timing of interventions of RCTs included in these meta-analyses were both during pregnancy and postpartum.

With respect to universal prevention, fully automated internet-based CBT (iCBT) is desirable to face-to-face or guided iCBT in terms of accessibility, anonymity, and cost-effectiveness.[16] Although a systematic review showed a positive effect of iCBT for the improvement of perinatal depressive symptoms,[17] to our knowledge, there have been only two randomized controlled trials (RCTs) for universal prevention using automated iCBT during pregnancy.[18,19] These two studies

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2
3
4 did not assess the major depressive episode (MDE); instead, they used depressive symptoms as
5
6 outcomes. In addition, dropout from iCBT in these studies was relatively high (66% and 44%,
7
8 respectively). A large number of sessions and/or the length per session may be impractical for a
9
10 substantial number of pregnant women to complete, which may cause a high dropout rate. Thus, it
11
12 would be necessary to develop a program that is more acceptable and feasible for pregnant women.
13
14

15 The objective of this randomized controlled trial (RCT) is to examine the effectiveness of the
16
17 newly developed 6-sessions of 5 to 10-minutes, smartphone-based, automated iCBT programs in
18
19 preventing the onset of MDE at the third trimester and 3-months postpartum among pregnant women
20
21 currently in the second trimester. The program would be practical and could be utilized by many
22
23 pregnant women. In addition, intervention during early pregnancy will enable the prevention of not
24
25 only postpartum depression but also antenatal depression.
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29
30

31 **Methods and Analysis**

32 **Trial design**

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34
35 The study will be a two-arm, parallel-group, treatment-as-usual (TAU) controlled,
36
37 randomized trial. The allocation ratio of the intervention groups to the control group is 1:1. Random
38
39 assignments are stratified by K6 scores (groups of 4 points or less and groups of 5 points or more) in
40
41 the baseline survey. End-users of an app (“Luna Luna Baby” run by MTI Ltd.) that provides useful
42
43 information for pregnant women will be recruited. Follow-up assessments will be conducted at 32
44
45 weeks gestation and 3-months postpartum. This protocol is written in accordance with the Standard
46
47 Protocol Items: Recommendations for Interventional Trials guideline checklist.[20] Trial start date
48
49 was the 27th of November, 2019 and the last follow-up date will be the 31st of March, 2021.
50
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Participants

Pregnant women who have user IDs for the latest version of the app and meet the following criteria will be invited to participate in this RCT.

Eligibility criteria

1. Being over 20 years old
2. Being 16 to 20 weeks gestation
3. Not diagnosed with a major depressive episode in the past month by the web-based self-administered version of the WHO Composite International Diagnostic Interview 3.0 (WHO-CIDI 3.0)[21]
4. Not diagnosed with lifetime bipolar disorder (WHO-CIDI 3.0)
5. Ability to understand the research objectives and give consent

Pregnant women using the app register the date of the last menstruation and the expected date of childbirth in the app. Thus we can find out the number of weeks of pregnancy.

Recruitment

Figure 1 shows the study flow of this trial. MTI Ltd. sends an invitation message to potentially eligible pregnant women, which will include an explanation of the study and information on the eligibility criteria. After reading the explanation of the study, potential participants will be invited to give their consent on the app to participate in the study, and to complete and return the baseline survey.

1
2
3
4 MTI Ltd. will also send messages to study participants to join in follow-up assessments.
5
6

7 Five thousand pregnant women will be randomized to either the intervention group (n=2500),
8
9
10 or the control group (n=2500). Participants in the intervention groups will be required to complete the
11
12
13 intervention program within 12 weeks after the baseline survey.
14
15

16 Participants in the intervention groups will be required to complete the CBT program up to
17
18
19 32 weeks gestation. Participants will be asked not to share this information through any social network.
20
21
22 The participants will be reminded by a popup message to complete the program if they have not already
23
24
25 done so. Intervention programs will be closed at 32 weeks gestation.
26
27

28 Participants in the control group will not receive any intervention programs during the
29
30
31 intervention and follow-up period. General information about mental health during pregnancy will be
32
33
34 provided to participants in both the intervention group and the control group as a TAU.
35
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39

40 **Interventions**

41
42

43 A smartphone-based six-module CBT program designed for pregnant women was newly
44
45
46 developed. This program will be provided via the Luna Luna Baby app, so users of the app don't have
47
48
49 to download another app. Some components of the modules were derived from a previous iCBT
50
51
52 program that successfully prevented the onset of MDE among office workers.[22] Other components
53
54
55 such as behavioral activation based on values, self-compassion and mindfulness have been
56
57
58 incorporated, which could be regarded as the third wave CBT. The six modules are presented in a fixed
59
60

1
2
3
4 order, with one module accessible per week, from module 1 to module 6. It will take about 5 min to
5
6
7 complete each module. The program includes psychoeducation (module 1), case formulation based on
8
9
10 a cognitive behavioral model (module 2), behavioral activation (module 3), self-compassion (module
11
12
13 4), mindfulness (module 5), and problem-solving (module 6). Details of each of the components are
14
15
16 as follows.

17 18 19 **Psychoeducation (module 1)**

20
21
22 In this module, participants learn about the roles of what are generally called “negative”
23
24
25 emotions such as anxiety, depressive mood and anger. Each emotion is necessary for us; for example,
26
27
28 anxiety is a sign that warns us of some risk in the future, and promotes us to prepare for the future.
29
30
31 This module was designed to help participants face and deal with their own emotions in subsequent
32
33
34 modules.

35 36 37 **Case formulation based on cognitive-behavioral model (module 2)**

38
39
40 In this module, participants learn about a cognitive-behavioral (CB) model, especially the
41
42
43 five-part model (situation, thoughts, emotions, behavior and physical sensations) and a case
44
45
46 formulation based on this model.[23] Case formulation is a method used to understand the problems
47
48
49 of patients or clients. Case formulation is helpful for participants to choose an appropriate approach to
50
51
52 change the vicious circles of these five areas.

53 54 55 **Behavioral activation (module 3)**

56
57
58 Behavioral activation is a process to increase pleasurable and rewarding activities using
59
60

1
2
3
4 behavioral strategies such as activity scheduling. This module provides a behavioral activation
5
6
7 technique for enhancing participants' liveliness. In this module, participants learn about the theory of
8
9
10 behavioral activation and how to plan an activity schedule to increase pleasant activities. Participants
11
12
13 are also encouraged to identify their values, based on brief behavioral activation therapy for depression
14
15
16 (BATD),[24] and acceptance and commitment therapy (ACT).[25]
17

18 19 **Self-compassion (module 4)**

20
21
22 Self-compassion indicates a positive and caring attitude of a person towards herself in the face
23
24
25 of stressful events.[26] As a result of this attitude, individuals who are highly self-compassionate are
26
27
28 expected to experience higher individual well-being.[27] Three interrelated determine the self-
29
30
31 compassionate reactions to negative events and experiences: self-kindness, sense of common humanity
32
33
34 and mindfulness. In this module, participants learn the concept of self-compassion and how to express
35
36
37 compassion towards themselves.
38
39

40 41 **Mindfulness (module 5)**

42
43 Mindfulness is defined as “paying attention in a particular way: on purpose, in the present
44
45
46 moment, and nonjudgmentally”.[28] Mindful persons are likely to be aware of the physical sensation,
47
48
49 thoughts, and emotions at that moment, which enables them to stop their usual reactions to a stressful
50
51
52 event so that symptoms and problematic behaviors are likely to disappear. In this module, participants
53
54
55 learn about the concept of mindfulness and how to practice it through listening to voice guidance.
56
57

58 59 **Problem-solving (module 6)**

1
2
3
4 Problem-solving technique is a CB intervention that focuses on training adaptive problem-
5
6
7 solving attitudes and skills.[29] A rational problem-solving style contains the systematic application
8
9
10 of four problem-solving skills: (1) problem definition and formulation, (2) generation of alternative
11
12
13 solutions, (3) decision making and (4) solution implementation and verification. In this module,
14
15
16 participants learn about problem-solving skills to sort out the problem and make a list of solutions, and
17
18
19 assertiveness to communicate with their partners confidently.
20
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25 **Outcomes**

26
27
28 **Table 2** shows an overview of the outcome measures. Those who have not responded by more
29
30
31 than a week after the online questionnaire is distributed will receive a popup message to complete each
32
33
34 assessment.
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36

37 **Primary outcome**

38
39
40 The primary outcome is the onset of MDE during the 32 weeks gestation and 3 months
41
42
43 postpartum. The onset of MDE during the follow-up will be assessed using the web-based self-
44
45
46 administered version of the Japanese WHO-CIDI 3.0 depression section, according to DSM-IV-TR
47
48
49 criteria. The web version has been shown to have a good concordance with the clinical diagnosis of
50
51
52 MDE and to be reliable in a 1-year test-retest survey. An incident case with MDE will be identified if
53
54
55 a respondent reports an episode of MDE at either 32 weeks gestation or 3 months postpartum. An onset
56
57
58 month for an episode of MDE also will be requested. In addition, two other definitions are applied to
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4 identify sub-threshold depressive episodes: one requires a shorter duration of symptoms (i.e. 7 days or
5
6
7 more, rather than 2 weeks or more); the other one requires having a fewer symptoms (i.e. having 3
8
9
10 symptoms or more, instead of 5 symptoms or more).
11

12 13 **Secondary outcomes**

14 15 16 **The Edinburgh Postnatal Depression Scale (EPDS)**

17
18
19 EPDS is used most often for screening perinatal depression because it focuses on cognitive
20
21
22 symptoms of depression and excludes somatic items that can generate false positives during
23
24
25 pregnancy and postpartum. It consists of 10 items, with 0-3 points scored per item for a potential
26
27
28 scale score of 0-30. The higher scores indicate more severe depressive symptoms. EPDS will be
29
30
31 conducted at baseline, 32 weeks gestation, 1 week postpartum and 3 months postpartum.
32

33 34 **Kessler's Psychological Distress Scale (K6)**

35
36
37 Psychological distress is measured by the Japanese version of K6.[30,31] K6 consists of six
38
39
40 items assessing the frequency with which respondents have experienced symptoms of psychological
41
42
43 distress during the past 30 days. The response options range from 0 (none of the time) to 4 (all of the
44
45
46 time), and the total score ranges from 0 to 24. The higher scores indicate more severe psychological
47
48
49 distress. K6 will be conducted at baseline, 32 weeks gestation, 1 week postpartum and 3 months
50
51
52 postpartum.
53

54 55 **EuroQol -5 dimension-5 level (EQ-5D-5L)**

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57
58 General health status will be measured by the EQ-5D-5L.[32-34] It is a 5-dimensional utility
59
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4 instrument consisting of domains about morbidity, self-care, usual activities, pain or discomfort, and
5
6
7 anxiety or depression. Each domain is divided into 5 levels of severity (none, slight, moderate,
8
9
10 severe, extreme problems, or unable to). All responses are converted into a single index score of
11
12
13 general health status. ED-5D-5L will be conducted at baseline, 32 weeks gestation and 3 months
14
15
16 postpartum.

17 18 19 **Somatic symptom Scale-8 (SSS-8)**

20
21
22 Somatic symptoms will be measured by Japanese version of SSS-8.[35,36] SSS-8 consists
23
24
25 of 8 items that assess the following symptoms: stomach or bowel problems; back pain; pain in the
26
27
28 arms, legs, or joints; headaches; chest pain or shortness of breath; dizziness; feeling tired or having
29
30
31 low energy; and trouble sleeping. These items comprise the four symptom domains of
32
33
34 gastrointestinal, pain, cardiopulmonary, and fatigue. Respondents rate how much each symptom has
35
36
37 bothered them during the previous 7 days and score each item from 0 to 4: not at all (0), a little bit
38
39
40 (1), somewhat (2), quite a bit (3), and very much (4). The total score ranges from 0 to 32. A higher
41
42
43 score reflects a more severe somatic symptom burden. SSS-8 will be conducted at baseline, 32 weeks
44
45
46 gestation and 3 months postpartum.

47 48 49 **Tachikawa Resilience Scale (TRS)**

50
51
52 Resilience will be measured by TRS.[37] TRS consists of 10 items. All items are scored on
53
54
55 a 7-point scale from 1 (strongly disagree) to 7 (strongly agree), with a total score ranging from 10 to
56
57
58 70. Higher scores reflect higher resilience. TRS will be conducted at baseline, 32 weeks gestation
59
60

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4 and 3 months postpartum.
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6

7 **The Insomnia Severity Index (ISI)** 8 9

10 Insomnia will be measured by the Japanese version of ISI.[38,39] ISI consists of 7 items
11
12 assessing the severity of sleep-onset and sleep maintenance difficulties (both nocturnal and early
13
14 morning awakenings), satisfaction with the current sleep pattern, interference with daily functioning,
15
16 awareness of impairment attributed to the sleep problem, and degree of distress or concern caused by
17
18 the sleep problem. Each item is rated on a 0 to 4 scale and the total score ranges from 0 to 28. A
19
20 higher score suggests more severe insomnia. ISI will be conducted at baseline, 32 weeks gestation
21
22 and 3 months postpartum.
23
24
25
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30 **Cambridge-Hopkins questionnaire short form (CH-RLSq13)** 31 32

33 Restless legs syndrome (RLS) will be measured by the Japanese version of CH-
34
35 RLSq13.[40,41] CH-RLSq13 consists of 13 items. Diagnosis of RLS is performed using 10 items
36
37 consisting of questions about discomfort and stiffness of the lower limbs. In addition, 2 items ask
38
39 about the degree of pain and the frequency of occurrence and 1 item asks about the age of onset
40
41 (relevant to pregnancy in women). CH-RLSq13 will be conducted at baseline, 32 weeks gestation
42
43 and 3 months postpartum.
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51 **Maternal Anxiety Scale for 4-5-month-old children** 52 53

54 Maternal anxiety will be measured by the Maternal Anxiety Scale for 4-5-month-old
55
56 children.[42] This scale consists of 34 items. Eleven items assess childcare anxiety, 6 items assess
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58
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4 husbands' or partners' support, 5 items assess childcare satisfaction, 4 items assess ease of raising
5
6
7 children, 5 items assess a lack of confidence, and 3 items assess presence or absence of advisors. All
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9
10 items are scored on a 4-point scale from 1 (strongly disagree) to 4 (strongly agree). A higher score of
11
12
13 each subscale reflects a higher presence of each factor. This scale will be conducted at 3 months
14
15
16 postpartum.

17 18 19 **Medical economic costs**

20
21
22 For cost-effectiveness analysis, the presence or absence, frequency and duration of medical
23
24
25 service use, and the use of drugs over the prior three months will be asked at 32 weeks gestation and
26
27
28 3 months postpartum.

29 30 31 **Process evaluation**

32 33 34 **Implementation outcomes**

35
36
37 Time spent logged in to each module will be measured. Also, we will evaluate implementation
38
39
40 outcomes by self-report. Proctor and colleagues suggested 8 conceptually distinct implementation
41
42
43 outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost,
44
45
46 penetration, and sustainability.[43] However, a systematic review examined implementation outcomes
47
48
49 for mental health and behavioral health using evidence-based rating criteria and concluded that the
50
51
52 majority of instrumental outcomes were underdeveloped.[44] Recently, Weiner et al. developed
53
54
55 measures of acceptability, appropriateness, and feasibility because their outcomes are often used as
56
57
58 leading indicators and are conceptually distinct.[45] Three of the authors (DN, EO, NS) reviewed the
59
60

1
2
3
4 previous literature and selected the possible outcomes for each dimension of acceptability,
5
6
7 appropriateness, and feasibility. These implementation outcomes and satisfaction with the intervention
8
9
10 program will be asked about at 34 weeks gestation.
11

12 13 **Adverse effects**

14
15
16 Three of the authors (DN, EO, NS) reviewed the previous literature based on a systematic
17
18
19 review, and selected the possible adverse effects of the program, such as physical symptoms (e.g., tired
20
21
22 eyes, stiff shoulders), mental symptom (e.g., insomnia), dangerous experiences (e.g., collide with
23
24
25 people while walking and looking at the smartphone), too much use of the smartphone, and excessive
26
27
28 pressure to learn this program regularly. These potential adverse effects will be asked about at 34
29
30
31 weeks gestation.
32

33 34 **Data collection**

35
36
37 All data will be collected by the internet. If the entered data is incomplete, participants will
38
39
40 not be able to proceed the assessment.
41
42
43
44
45

46 47 **Sample size calculation**

48
49 Required sample size was calculated for the primary outcome. New onset of MDE during the
50
51
52 observation period in Japan and the effect size in hazard ratio are estimated to be 5% and 0.65,[46]
53
54
55 based on previous studies. Thirty percent of participants are expected to drop out of the follow-up
56
57
58 assessment. Given an α level of 0.05 (two-tailed) and a β level of 0.20, power Cox was performed with
59
60

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4 STATA 14.0 and the appropriate sample size was calculated to be 4812. Since a large number of
5
6
7 participants using the app will be recruited on one day, it is considered difficult to stop recruiting
8
9
10 immediately when the sample size is reached. Thus, the sample size was set at 5,000.
11
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15

16 **Randomization**

17
18
19 Participants who meet the inclusion criteria will be randomly allocated to the intervention
20
21
22 group or control group. Participants will be stratified into two strata according to the score of K6 (4 or
23
24
25 less, or 5 or more) on the baseline survey. MTI Ltd. will send baseline data stored in the cloud to
26
27
28 researchers. In addition to the analysis of the whole sample (to examine the universal intervention
29
30
31 effect), we will also analyze data by prespecified subgroups (to examine the selective intervention
32
33
34 effect). Using a computer-generated random allocation sequence, an independent biostatistician
35
36
37 created a stratified permuted-block random table. The block size of this RCT will be fixed at 4. The
38
39
40 stratified permuted-block random table will be password protected and blinded to the researcher. Only
41
42
43 the research assistant will be able to access it during the work of random allocation. MTI Ltd. will
44
45
46 make the study participants allocated to the intervention group available to view the iCBT program on
47
48
49 the app, based on the allocation provided by the research assistant.
50
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55 **Statistical methods**

56 57 58 **Main analysis** 59 60

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3
4 A survival analysis will be conducted to test for the effectiveness of the intervention on the
5
6
7 time to the onset of MDE while controlling for censoring effects due to the differential length of
8
9
10 follow-up or the completion of follow-up without an onset of MDE. Length of follow-up for each
11
12
13 participant will be represented by either the number of months between the baseline and the onset of
14
15
16 MDE or the end of the follow-up period (3-month postpartum, or 32 weeks gestation if a participant
17
18
19 dropped out at the 3-month postpartum follow-up), whichever comes first. The cumulative incidence
20
21
22 of MDE at the 32 weeks gestation and 3-month postpartum follow-up, as well as event-free survivals
23
24
25 at every follow-up month, will be estimated using the Kaplan–Meier method; the statistical
26
27
28 significance will be tested of the difference between the cumulative proportions of having MDE at 32
29
30
31 weeks gestation and 3-month postpartum follow-ups in the intervention and control groups. A log-
32
33
34 rank test will be conducted to test the difference in survival probabilities between the intervention and
35
36
37 the control groups. A single covariate Cox discrete time hazard model will also be used to test the
38
39
40 difference and estimate the hazard ratio (HR), with 95% confidence intervals (CIs), for having MDE
41
42
43 in the intervention group compared to the control group. The intervention effect will also be estimated,
44
45
46 adjusting for dependent censoring and using the inverse probability of the censoring weighted (IPCW)
47
48
49 method for conducting a sensitivity analysis.[47] The number needed to treat (NNT) to achieve
50
51
52 prevention of one case of the onset of MDE will be calculated at 32 weeks gestation and 3-month
53
54
55 postpartum follow-ups. A similar Cox discrete time hazard model also will be conducted using the two
56
57
58 types of sub-threshold diagnoses of depressive episodes to investigate the effects of iCBT on
59
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2
3
4 preventing depressive episodes, including subclinical cases. An intention-to-treat (ITT) analysis will
5
6
7 be conducted.
8
9

10 **Secondary analyses**

11
12
13 For secondary outcomes (i.e. EPDS, K6, SSS-8, TRS), mixed models for repeated measures
14
15
16 analyses will be conducted using a group (intervention or control) × time (baseline, 32 weeks gestation,
17
18
19 1 week postpartum or 3-month postpartum follow-up) interaction as an indicator of the intervention
20
21
22 effect. The level of statistical significance for all analyses in this study will be set at 0.05 (two-tailed),
23
24
25 and 95% CIs will be calculated. The effect size will be estimated in two ways. First, we will estimate
26
27
28 a regression coefficient for a group (the intervention group vs. the control group) x time (baseline and
29
30
31 follow-ups) interaction using the MIXED procedure, which will be converted to an effect size by
32
33
34 dividing by a pooled SD at baseline and at follow-ups. Second, we will calculate Cohen's d among
35
36
37 completers at baseline for each follow-up. ITT will be conducted as well. All statistical analyses will
38
39
40 be conducted using SPSS Statistics 21.0 (IBM Corp., USA).
41
42

43 **Subgroup analysis**

44
45
46 The effectiveness of the programs may differ according to the initial severity of psychological
47
48
49 distress. Therefore, we will use the stratification factor (i.e., participants who scored 4 or less/5 or more
50
51
52 in K6 at the baseline survey) and analyze the results according to the prespecified subgroups.
53
54

55 **Cost-effectiveness analysis**

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57
58 Quality-adjusted life-years (QALYs) will be calculated as the effectiveness, using the EQ-
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4 5D-5L, as the area under the curve defined by the unitality values at baseline and follow-ups.[48] As
5
6
7 for the costs, the cost of medical service use will be calculated based on the Survey of Medical Care
8
9
10 Activities in Public Health Insurance,[49] which shows the treatment expenses covered by public
11
12
13 health insurance in each diagnostic category. No intervention costs such as salary for therapists will
14
15
16 be calculated because the program is fully-automated. Mean differences for the calculated
17
18
19 effectiveness and costs will be compared between the intervention and control group.
20
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25 **Data monitoring and auditing**

26
27
28 Because the iCBT program is not regarded as an invasive intervention, it is not necessary to
29
30
31 set up a data monitoring board or to complete auditing in this trial.
32
33

34 **Data availability**

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37 Deidentified individual participant data will be available upon reasonable request after
38
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40 publication of the main analysis paper. Contact information is the email address of the corresponding
41
42
43 author.
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49 **Patient and public involvement**

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51
52 We utilized the function of the app “Luna Luna Baby” that allows users (pregnant women)
53
54
55 to talk to each other about their problems. We extracted essential topics that pregnant women are
56
57
58 concerned about based on 6393 text data, and developed programs for those topics. The topics were
59
60

1
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3
4 extracted by using a machine learning approach, based on the Latent Dirichlet Allocation (LDA).[50]
5
6

7 In this approach, morphological analysis was conducted for the text data from the pregnant women,
8
9
10 and nouns and adjectives about what they suffer were collected. The LDA model was implemented
11
12
13 by Scikit-learn version 0.21.3 (1) in Python. As a result, five topics were extracted: relationship with
14
15
16 partners, concern about weight gain, concern about pregnancy checkup, physical symptoms such as
17
18
19 pain, and dysfunction due to morning sickness. Since pregnancy checkup is considered to be a matter
20
21
22 of obstetrics, each module of the iCBT program has been developed to deal with the remaining 4
23
24
25 topics, namely, module 1, 2 and 4 focus on dysfunction due to morning sickness, module 3 on
26
27
28 concern about weight gain, module 5 on physical symptoms, and module 6 on relationship with
29
30
31 partners. We will not access this chatroom during the RCT.
32
33

34 In addition, three women who had experiences of pregnancy and childbirth (two researchers
35
36
37 and an ordinary mother) were invited to make comments on the intervention programs based on their
38
39
40 experiences and preferences. Two researchers above (EO, NS) also were involved in designing this
41
42
43 protocol.
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48

49 **Ethics and dissemination**

51 52 **Ethical and safety considerations**

53
54
55 Informed consent for the app will be obtained from all participants included in this study
56
57
58 after full explanation of the study. Candidates will be informed that their participation is voluntary,
59
60

1
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3
4 and that even after voluntarily participating, they can withdraw from the study at any time and their
5
6
7 withdrawal will cause no disadvantage to them. We expect no adverse health effects from this
8
9
10 intervention, except possible deterioration in depressive symptoms. The principal investigators will
11
12
13 communicate important protocol modification with the institutional review board.
14
15

16 **Data confidentiality**

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18
19 The collected data will be stored as linkable anonymizing data. The principal investigator
20
21
22 will have access to the final dataset after the trial and take responsibility for the integrity of the data
23
24
25 and the accuracy of analysis.
26
27

28 **Dissemination of research findings**

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30
31 The findings of this study will be disseminated through publications in peer-reviewed
32
33
34 international journals. Presentations of the findings will also be offered at relevant research
35
36
37 conferences, and local academic symposia and seminars. The principal investigator will be listed as
38
39
40 corresponding authors, and the authorship eligibility will be conformed to the International
41
42
43 Committee of Medical Journal Editors. If the intervention programs are found to be significantly
44
45
46 positively effective, the programs can be made available for all users of the app in the future.
47
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49
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51 **Discussion**

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53
54 The greatest strength of this study is to prove the effectiveness of the fully automated
55
56
57 smartphone-based CBT program on preventing both antenatal and postpartum depression. The
58
59
60 relatively short, newly developed programs for pregnant women would be practical and low dropout

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4 is expected. Furthermore, this study will assess diagnosis of MDE using CIDI. Many previous studies
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6
7 using iCBT have suggested its preventive effect on depression; however, no previous studies assessed
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9
10 the diagnosis of perinatal depression using the structural interview. This RCT with large sample size
11
12
13 can lead to a definitive result.

14
15
16 This study also will evaluate implementation outcomes of the program. Previous studies using
17
18
19 iCBT have assessed the satisfaction with their program; however, few studies evaluated
20
21
22 implementation outcomes including acceptability, adoption, appropriateness, feasibility, fidelity,
23
24
25 implementation cost, penetration, and sustainability.[43] This study will contribute to the
26
27
28 dissemination and implementation of iCBT in the future.

29
30
31 Another strength of this study is to add evidence of maternity blues. Maternity blues is highly
32
33
34 prevalent, and it can present a range of symptoms such as intense short-lasting dysphoric mood,
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36
37 irritability, anxiety, sleep disturbance, and poor concentration within the first week following
38
39
40 childbirth.[52] Maternity blues could lead to postpartum depression,[53] but to our knowledge, no
41
42
43 previous studies have shown a preventive strategy to deal with maternity blues. This RCT will clarify
44
45
46 whether iCBT during pregnancy can prevent maternity blues.

47
48
49 This study has several limitations. First, all outcomes will be measured by self-report, which
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51
52 could be affected by the perceptions of the participants. Second, users of the app are not regarded as
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55 representative of all pregnant women, though approximately 1 in 4 pregnant women in Japan are
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57
58 thought to use the app. Therefore, the findings of this study can not necessarily be generalizable.

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4 **Author contributions** DN conceived and designed the study. DN, KI, EO, NS, and YS contributed
5
6 creating programs. KW calculated sample size and developed analysis plan. DN wrote the first draft
7
8 of the manuscript, and all other authors revised the manuscript critically. All authors approved the final
9
10 version of the manuscript.
11

12
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14
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16

17
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19
20 or preparation of the manuscript.
21

22
23 **Competing interests** MTI Ltd. has been involved in this study as mentioned in the manuscript. NK
24
25 reports grants from Infocom Corp, Fujitsu Ltd, Fujitsu Software Technologies and TAK Ltd; personal
26
27 fees from Occupational Health Foundation, Japan Dental Association, Sekisui Chemicals, Junpukai
28
29 Health Care Center, Osaka Chamber of Commerce and Industry, outside the submitted work.
30

31 **Patient consent for publication** Obtained.
32

33
34 **Ethics approval** The study plan was approved by the Research Ethics Review Board of Graduate
35
36 School of Medicine/Faculty of Medicine, the University of Tokyo (2019150NI).
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42 **Figure legend:**
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44 Figure 1 Flow diagram of study participants
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Table 1 Contents of internet cognitive behavioral therapy program

Module No	Techniques for stress management
Module 1	Psychoeducation
Module 2	Case formulation based on cognitive behavioral model
Module 3	Behavioral activation
Module 4	Self-compassion
Module 5	Mindfulness
Module 6	Problem solving

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Table 2 Overview of measurements

Measurement	Aim	Baseline (T1)	32 weeks gestation (T2)	34 weeks gestation (T3)	1 week postpartum (T4)	3 months postpartum (T5)
<i>Primary outcomes</i>						
CIDI	Diagnosis of Major Depressive Episode	✓	✓			✓
<i>Secondary outcomes</i>						
EPDS	Depressive symptoms	✓	✓		✓	✓
K6	Psychological distress	✓	✓		✓	✓
ED-5D-5L	Quality of life	✓	✓			✓
SSS-8	Somatic symptoms	✓	✓			✓
TRS	Resilience	✓	✓			✓
ISI	Insomnia	✓	✓			✓
CH-RLSq13	Restless legs syndrome	✓	✓			✓
Maternal Anxiety Scale for 4-5 months children	Maternal anxiety					✓
Medical costs	Medical service use	✓	✓			✓
Implementation and satisfaction	Implementation outcomes			✓		
Adverse effects	Physical and mental symptoms			✓		
<i>Baseline assessments</i>						
Demographics		✓				
VAWS		✓				

CIDI, World Health Organization Composite International Diagnostic Interview 3.0; EPDS, The Edinburgh Postnatal Depression Scale; K6, Kessler's Psychological Distress Scale; ED-5D-5L, EuroQol -5 dimension-5 level; SSS-8, Somatic symptom Scale-8; TRS, Tachikawa Resilience Scale; ISI, The Insomnia Severity Index; CH-RLSq13, Cambridge-Hopkins questionnaire short form; VAWS, Violence Against Women Screen

(Consent form in Japanese)

同 意 書

東京大学医学系研究科長・医学部長 殿

研究課題「全自動化インターネット認知行動療法による妊娠うつ病・産後うつ病の予防」
(審査番号****)

私は、上記研究への参加にあたり、下記の説明文書の記載事項について説明を受け、これを十分理解しましたので本研究の研究対象者となることに同意いたします。

- 1、この研究の概要
- 2、研究参加の任意性と撤回の自由
- 3、個人情報の保護
- 4、研究結果の公表・開示
- 5、研究対象者にもたらされる利益及び不利益
- 6、研究終了後の資料（試料）等の取扱方針
- 7、あなたの費用負担
- 8、研究から生じる知的財産権の帰属
- 9、その他

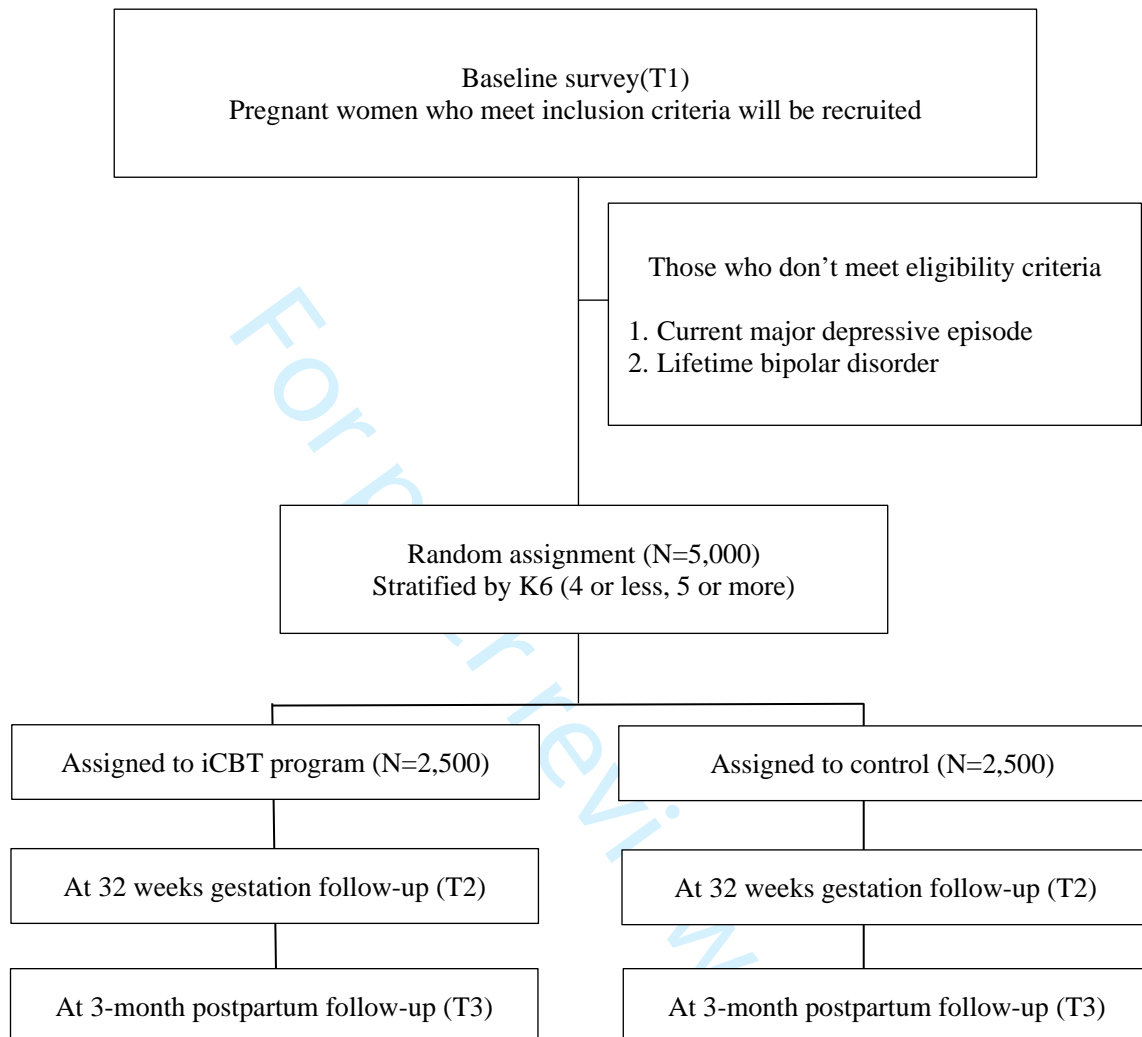
また、私に関わるデータは、将来、新たに計画・実施される研究のために、長期間の保存と研究への使用に同意いたします。

はい

いいえ

※同意の日付及び同意した人のIDはデータとして取得する。

Figure 1



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

			Page
	Reporting Item		Number
Administrative information			
Title	#1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym		1

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2
2			name of intended registry	
3				
4				
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	NA
7	data set		Registration Data Set	
8				
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10				
11	Protocol version	#3	Date and version identifier	2
12				
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	23
16			support	
17				
18				
19				
20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	23
21	responsibilities:			
22				
23	contributorship			
24				
25				
26				
27				
28	Roles and	#5b	Name and contact information for the trial sponsor	NA
29	responsibilities:			
30				
31	sponsor contact			
32				
33	information			
34				
35				
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38	Roles and	#5c	Role of study sponsor and funders, if any, in study	NA
39	responsibilities:		design; collection, management, analysis, and	
40			interpretation of data; writing of the report; and the	
41	sponsor and funder		decision to submit the report for publication, including	
42			whether they will have ultimate authority over any of	
43			these activities	
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52	Roles and	#5d	Composition, roles, and responsibilities of the	NA
53	responsibilities:		coordinating centre, steering committee, endpoint	
54			adjudication committee, data management team, and	
55	committees			
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other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods:			
Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

1 2 3 4 5 6 7 8 9 10	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
11 12 13 14 15 16 17 18	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-10
19 20 21 22 23 24 25 26 27	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
28 29 30 31 32 33 34 35	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
36 37 38 39 40	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-14

1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	6-7
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
5				
6				
7				
8				
9				
10				
11	Sample size	#14	Estimated number of participants needed to achieve	15
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any sample	
14			size calculations	
15				
16				
17				
18				
19				
20				
21	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6-7
22			reach target sample size	
23				
24				
25				
26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
31				
32				
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35				
36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	16
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
43				
44				
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52				
53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	16
54	concealment		central telephone; sequentially numbered, opaque,	
55				
56				
57				
58	mechanism			
59				
60				

sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#16c](#) Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions 16

Blinding (masking) [#17a](#) Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how 16

Blinding (masking): [#17b](#) If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial NA

Methods: Data collection, management, and analysis

Data collection plan [#18a](#) Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol 7

1	Data collection plan:	#18b	Plans to promote participant retention and complete	7
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
6				
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10				
11	Data management	#19	Plans for data entry, coding, security, and storage,	15
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
17				
18				
19				
20				
21				
22				
23	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	16-17
24			outcomes. Reference to where other details of the	
25			statistical analysis plan can be found, if not in the protocol	
26				
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31	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	17-18
32	analyses		adjusted analyses)	
33				
34				
35				
36	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	16-18
37	population and		adherence (eg, as randomised analysis), and any	
38	missing data		statistical methods to handle missing data (eg, multiple	
39			imputation)	
40				
41				
42				
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45				
46	Methods: Monitoring			
47				
48				
49	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	18-19
50	formal committee		summary of its role and reporting structure; statement of	
51			whether it is independent from the sponsor and	
52			competing interests; and reference to where further	
53				
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1 details about its charter can be found, if not in the
 2 protocol. Alternatively, an explanation of why a DMC is
 3 not needed
 4
 5
 6
 7

8	Data monitoring:	#21b	Description of any interim analyses and stopping	NA
9	interim analysis		guidelines, including who will have access to these	
10			interim results and make the final decision to terminate	
11			the trial	
12				
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17				
18	Harms	#22	Plans for collecting, assessing, reporting, and managing	15
19			solicited and spontaneously reported adverse events and	
20			other unintended effects of trial interventions or trial	
21			conduct	
22				
23				
24				
25				
26				
27				
28	Auditing	#23	Frequency and procedures for auditing trial conduct, if	19
29			any, and whether the process will be independent from	
30			investigators and the sponsor	
31				
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34				
35	Ethics and			
36	dissemination			
37				
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40				
41	Research ethics	#24	Plans for seeking research ethics committee / institutional	2
42	approval		review board (REC / IRB) approval	
43				
44				
45				
46	Protocol	#25	Plans for communicating important protocol modifications	20
47	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
48			relevant parties (eg, investigators, REC / IRBs, trial	
49			participants, trial registries, journals, regulators)	
50				
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6, 20
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
4				
5				
6				
7				
8				
9	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
13				
14				
15				
16	Confidentiality	#27	How personal information about potential and enrolled	20
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
20				
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26	Declaration of	#28	Financial and other competing interests for principal	23
27	interests		investigators for the overall trial and each study site	
28				
29				
30				
31				
32	Data access	#29	Statement of who will have access to the final trial	20
33			dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
35				
36				
37				
38				
39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
40	trial care		compensation to those who suffer harm from trial	
41			participation	
42				
43				
44				
45				
46				
47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	21
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
52				
53				
54				
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59				
60				

1 Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of 21
 2
 3 authorship professional writers
 4
 5

6 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full 19
 7
 8 reproducible protocol, participant-level dataset, and statistical code
 9
 10 research
 11
 12
 13

14 Appendices

15
 16
 17 Informed consent [#32](#) Model consent form and other related documentation NA
 18
 19 materials given to participants and authorised surrogates
 20
 21

22
 23 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of NA
 24
 25 biological specimens for genetic or molecular analysis in
 26
 27 the current trial and for future use in ancillary studies, if
 28
 29 applicable
 30
 31

32
 33 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
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BMJ Open

Internet-based cognitive behavioral therapy for prevention of depression during pregnancy and in the postpartum (iPDP): a protocol for a large scale randomized controlled trial

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4 Title: Internet-based cognitive behavioral therapy for prevention of depression during pregnancy and
5
6 in the postpartum (iPDP): a protocol for a large scale randomized controlled trial
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12 Authors: Daisuke Nishi, MD, PhD¹, Kotaro Imamura, PhD¹, Kazuhiro Watanabe, PhD¹, Erika
13
14 Obikane, MD¹, Natsu Sasaki, MD¹, Naonori Yasuma, MD¹, Yuki Sekiya, PhD¹, Yutaka
15
16 Matsuyama², PhD, Norito Kawakami, MD, PhD¹
17
18
19
20
21

22 ¹Department of Mental Health, Graduate School of Medicine, The University of Tokyo, 7-3-1
23
24 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
25

26 ²Department of Biostatistics, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo,
27
28 Bunkyo-ku, Tokyo 113-0033, Japan
29
30
31
32
33
34

35 Corresponding author: Daisuke Nishi
36

37 Department of Mental Health, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo,
38
39 Bunkyo-ku, Tokyo 113-0033, Japan
40
41

42 E-mail: d-nishi@m.u-tokyo.ac.jp
43
44
45
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Abstract

Introduction: The objective of this randomized controlled trial (RCT) is to examine the effects of smartphone-based cognitive behavioral therapy (CBT) in preventing the onset of major depressive episodes (MDE) among pregnant women.

Methods and analysis: The target study population will be pregnant women of 16 to 20 weeks gestation who are currently users of “Luna Luna Baby,” the most widely used app for pregnant women in Japan. Those who meet the eligibility criteria will be randomly allocated to the 6-module internet cognitive behavioral therapy (iCBT) program that was newly developed for pregnant women (n=2500), or to a treatment-as-usual control group (n=2500). Participants in the intervention groups will be required to complete the program by 32 weeks gestation. The primary outcomes are the number of new onsets of MDE, measured by using the World Health Organization Composite International Diagnostic Interview 3.0 (WHO-CIDI 3.0) at 32 weeks gestation and 3 months postpartum. Survival analysis will be conducted to test for the effectiveness of the intervention on the time to the onset of MDE.

Ethics and dissemination: The study plan has been approved by the Research Ethics Review Board of the Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (2019150NI). If the intervention programs are found to produce a significant positive effect in this RCT, these programs can be made available for all users of the app in the future.

Keywords: smartphone-based cognitive behavioral therapy, antenatal depression, postpartum depression, prevention

Trial registration number: UMIN000038190; Pre-results.

Issue date: 16th, Dec, 2019

Article Summary

Strengths and limitations of this study

- The large sample size of this RCT can lead to a definitive result of the effectiveness of the fully automated smartphone-based CBT program in preventing both antenatal and postpartum depression.
- The newly developed program was tailored for pregnant women by extracting essential topics for them based on data from consultations on pregnant women's concerns.
- This study will also evaluate the implementation outcomes of iCBT program, which will contribute to the dissemination and implementation of iCBT.
- This RCT will also clarify whether iCBT during pregnancy can prevent maternity blues.
- A limitation of this study is that all of the outcomes will be measured by self-report.

Introduction

Prevention of perinatal depression is a critical public health issue.[1] The prevalence of antenatal depression was reported to be 7.4% in the first trimester, 12.8% in the second trimester, and 12.0% in the third trimester;[2] and the prevalence of postpartum depression was estimated to be 17.7%, though there is significant heterogeneity across nations.[3] Antenatal depression is associated with failing to seek prenatal care, an inadequate diet and/or use of tobacco, alcohol, or other harmful substances, self-harm or attempted suicide, and postpartum depression; while postpartum depression is associated with negative outcomes such as physical and psychological abuse to their children, and infanticide.[4] Furthermore, perinatal depression can also affect development from fetus to adolescent and paternal depression.[5-10] Therefore, preventing perinatal depression in the antenatal period is crucially important.

Given the large number of pregnant women who have risk factors such as maternal anxiety, life stress, lack of social support, unintended pregnancy, domestic violence, lower income and education, and poor relationships, making it difficult to identify and screen all high-risk pregnant women,[11] universal prevention should be more valued. According to a systematic review and meta-analysis, psychological interventions have been recommended as the most effective approach to prevent antenatal and postpartum depression.[12] Cognitive behavioral therapy (CBT) has been broadly researched and reported to be highly effective among psychological interventions.[13,14] Previous meta-analyses showed that the effect size of psychological intervention as universal prevention, which refers to approaches designed for the whole population regardless of individual risk factors, for postpartum depression was reported to be 0.19[15] and 0.37.[13] The timing of interventions of RCTs included in these meta-analyses were both during pregnancy and postpartum.

With respect to universal prevention, fully automated internet-based CBT (iCBT) is preferable to face-to-face or guided iCBT in terms of accessibility, anonymity, and cost-effectiveness.[16] Although a systematic review showed a positive effect of iCBT for the improvement of perinatal

1
2
3
4 depressive symptoms,[17] to our knowledge, there have been only two randomized controlled trials
5
6 (RCTs) for universal prevention using automated iCBT during pregnancy.[18,19] These two studies
7
8 did not assess the major depressive episode (MDE); instead, they used depressive symptoms as
9
10 outcomes. In addition, a dropout from iCBT in these studies was relatively high (66% and 44%,
11
12 respectively). A large number of sessions and/or the length per session may be impractical for a
13
14 substantial number of pregnant women to complete, which may cause a high dropout rate. Thus, it
15
16 would be necessary to develop a program that is more acceptable and feasible for pregnant women.
17
18 In this regard, 6-sessions of 5 to 10-minutes iCBT programs were shown to be effective for
19
20 preventing depressive symptoms for workers.[20]
21
22

23
24 Moreover, to our knowledge, no previous randomized controlled trials (RCTs) have examined
25
26 the effect of iCBT on maternity blues. Maternity blues were characterized by psychological distress
27
28 with a peak at 3 to 5 days after childbirth, though diagnostic criteria have not been well established.
29
30 Maternity blues are highly prevalent and have been shown to be a risk factor for postpartum
31
32 depression [21]; thus, it will be relevant to develop the intervention to prevent not only perinatal
33
34 depression but also maternity blues.
35
36

37
38 The primary objective of this RCT is to examine the effectiveness of the newly developed 6-
39
40 sessions of 5 to 10-minutes, smartphone-based, automated iCBT programs in preventing the onset of
41
42 MDE at the third trimester and 3-months postpartum among pregnant women currently in the second
43
44 trimester. The secondary objectives are to examine the effectiveness of iCBT for preventing
45
46 maternity blues. The program would be practical and could be utilized by many pregnant women. In
47
48 addition, intervention during early pregnancy will enable the prevention of not only postpartum
49
50 depression but also antenatal depression.
51
52
53
54

55 **Methods and Analysis**

56 **Trial design**

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2
3
4 The study will be a two-arm, parallel-group, treatment-as-usual (TAU) controlled,
5
6 randomized trial. The allocation ratio of the intervention groups to the control group is 1:1. Random
7
8 assignments are stratified by Kessler's Psychological Distress Scale (K6) scores (groups of 4 points or
9
10 less and groups of 5 points or more) in the baseline survey. K6 is a self-report questionnaire, which
11
12 assesses psychological distress during the past 30 days. Users of the app ("Luna Luna Baby" run by
13
14 MTI Ltd.) will be recruited. The app provides the users for the growth of the fetus and the mental and
15
16 physical condition of the pregnant women according to the number of gestation weeks. Users register
17
18 the date of the last menstruation in the app; thus, we can find out the number of weeks of pregnancy.
19
20
21

22 Follow-up assessments will be conducted at 32 weeks gestation and 3-months postpartum.
23
24 This protocol is written in accordance with the Standard Protocol Items: Recommendations for
25
26 Interventional Trials guideline checklist.[22] The trial start date was the 27th of November, 2019, and
27
28 the last follow-up date will be the 31st of March, 2021.
29
30
31

32 33 **Participants**

34
35 Pregnant women who have user IDs for the latest version of the app and meet the following
36
37 criteria will be invited to participate in this RCT. Both primipara and multiparous women will be
38
39 included.
40
41

42 **Eligibility criteria**

- 43
44 1. Being over 20 years old
- 45
46 2. Being 16 to 20 weeks gestation
- 47
48 3. Not diagnosed with a MDE in the past month by the web-based self-administered version of the
49
50 WHO Composite International Diagnostic Interview 3.0 (WHO-CIDI 3.0)[23]
- 51
52 4. Not diagnosed with lifetime bipolar disorder (WHO-CIDI 3.0)
- 53
54
55
56
57

58 **Recruitment**

1
2
3
4 **Figure 1** shows the study flow of this trial. MTI Ltd. sends an invitation message to potentially
5
6 eligible pregnant women, which will include an explanation of the study and information on the
7
8 eligibility criteria. After reading the explanation of the study, potential participants will be invited to
9
10 give their consent on the app to participate in the study and to complete and return the baseline survey.
11
12 MTI Ltd. will also send messages to study participants to join in follow-up assessments.

13
14
15 Five thousand pregnant women will be randomized to either the intervention group (n=2500),
16
17 or the control group (n=2500). Participants in the intervention groups will be required to complete the
18
19 intervention program up to 32 weeks gestation. Participants will be asked not to share this information
20
21 through any social network. The participants will be reminded by a popup message to complete the
22
23 program if they have not already done so. Intervention programs will be closed at 32 weeks gestation.

24
25
26 Participants in the control group will not receive any intervention programs during the
27
28 intervention and follow-up period. General information about mental health during pregnancy will be
29
30 provided to participants in both the intervention group and the control group as a TAU.
31
32
33
34

35 **Interventions**

36
37 A smartphone-based six-module CBT program designed for pregnant women was newly
38
39 developed. Specifically, the first author (DN) developed the iCBT program with the collaboration of
40
41 co-authors (KI, EO, NS, and YS). The program was tailored for pregnant women by extracting
42
43 essential topics that pregnant women are concerned about. The details were shown in patient and public
44
45 involvement section. This program will be provided via the Luna Luna Baby app, so users of the app
46
47 don't have to download another app. Some components of the modules were derived from a previous
48
49 iCBT program that successfully prevented the onset of MDE among office workers.[20] Other
50
51 components such as behavioral activation based on values, self-compassion, and mindfulness have
52
53 been incorporated, which could be regarded as the third wave CBT. The six modules are presented in
54
55 a fixed order, with one module accessible per week, from module 1 to module 6 (Table 1). It will take
56
57
58
59
60

1
2
3
4 about 5 min to complete each module. The program includes psychoeducation (module 1), case
5
6 formulation based on a cognitive behavioral model (module 2), behavioral activation (module 3), self-
7
8 compassion (module 4), mindfulness (module 5), and problem-solving (module 6). Details of each of
9
10 the components are as follows.

11 12 **Psychoeducation (module 1)**

13
14
15 In this module, participants learn about the roles of what are generally called “negative”
16
17 emotions such as anxiety, depressive mood and anger. Each emotion is necessary for us; for example,
18
19 anxiety is a sign that warns us of some risk in the future and promotes us to prepare for the future. This
20
21 module was designed to help participants face and deal with their own emotions in subsequent modules.
22
23 As an example of anxious situations, a scene that a partner of a pregnant woman is busy working and
24
25 is not at home is used. As an example of sad situations, a scene when a pregnant woman suffers from
26
27 morning sickness but the boss does not understand is used.
28
29

30 31 **Case formulation based on cognitive-behavioral model (module 2)**

32
33 In this module, participants learn about a cognitive-behavioral (CB) model, especially the
34
35 five-part model (situation, thoughts, emotions, behavior, and physical sensations) and a case
36
37 formulation based on this model.[24] Case formulation is a method used to understand the problems
38
39 of patients or clients. Case formulation is helpful for participants to choose an appropriate approach to
40
41 change the vicious circles of these five areas. A scene when a pregnant woman suffers from morning
42
43 sickness but the boss does not understand is used as a case.
44
45

46 47 **Behavioral activation (module 3)**

48
49 Behavioral activation is a process to increase pleasurable and rewarding activities using
50
51 behavioral strategies such as activity scheduling. This module provides a behavioral activation
52
53 technique for enhancing participants’ liveliness. In this module, participants learn about the theory of
54
55 behavioral activation and how to plan an activity schedule to increase pleasant activities. Participants
56
57 are also encouraged to identify their values based on brief behavioral activation therapy for depression
58
59
60

1
2
3
4 (BATD),[25] and acceptance and commitment therapy (ACT).[26] A scene when a pregnant woman
5
6 would not like to go out because she has gained weight and is not motivated is used as a case.
7

8 **Self-compassion (module 4)**

9
10 Self-compassion indicates a positive and caring attitude of a person towards herself in the face
11
12 of stressful events.[27] As a result of this attitude, highly self-compassionate individuals are expected
13
14 to experience higher individual well-being.[28] Three interrelated determine the self-compassionate
15
16 reactions to negative events and experiences: self-kindness, sense of common humanity and
17
18 mindfulness. In this module, participants learn the concept of self-compassion and how to express
19
20 compassion towards themselves. A scene when a pregnant woman suffers from morning sickness and
21
22 is blaming herself for not being able to work as usual is used as a case.
23
24
25

26 **Mindfulness (module 5)**

27
28 Mindfulness is defined as “paying attention in a particular way: on purpose, in the present
29
30 moment, and nonjudgmentally”.[29] Mindful persons are likely to be aware of the physical sensation,
31
32 thoughts, and emotions at that moment, which enables them to stop their usual reactions to a stressful
33
34 event so that symptoms and problematic behaviors are likely to disappear. In this module, participants
35
36 learn about the concept of mindfulness and how to practice it through listening to voice guidance. A
37
38 scene when a pregnant woman feels anxiety due to tension and pain in the lower abdomen in spite of
39
40 obstetrically normal is used as a case.
41
42
43

44 **Problem-solving (module 6)**

45
46 Problem-solving technique is a CB intervention that focuses on training adaptive problem-
47
48 solving attitudes and skills.[30] A rational problem-solving style contains the systematic application
49
50 of four problem-solving skills: (1) problem definition and formulation, (2) generation of alternative
51
52 solutions, (3) decision making and (4) solution implementation and verification. In this module,
53
54 participants learn about problem-solving skills to sort out the problem and make a list of solutions, and
55
56 assertiveness to communicate with their partners confidently. A scene when a pregnant woman wants
57
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her partner to do more in housework and childcare is used as a case.

Outcomes

Table 2 shows an overview of the outcome measures. Those who have not responded by more than a week after the online questionnaire is distributed will receive a popup message to complete each assessment.

Primary outcome

The primary outcome is the onset of MDE during the 32 weeks gestation and 3 months postpartum. The onset of MDE during the follow-up will be assessed using the web-based self-administered version of the Japanese WHO-CIDI 3.0 depression section, according to DSM-IV-TR criteria. The web version has been shown to have a good concordance with the clinical diagnosis of MDE and to be reliable in a 1-year test-retest survey. An incident case with MDE will be identified if a respondent reports an episode of MDE at either 32 weeks gestation or 3 months postpartum. An onset month for an episode of MDE also will be requested. In addition, two other definitions are applied to identify sub-threshold depressive episodes: one requires a shorter duration of symptoms (i.e. 7 days or more, rather than 2 weeks or more); the other one requires having a fewer symptoms (i.e. having 3 symptoms or more, instead of 5 symptoms or more).

Secondary outcomes

The Edinburgh Postnatal Depression Scale (EPDS)

Depressive symptoms will be measured by the Japanese version of EPDS [31, 32]. EPDS is used most often for screening perinatal depression because it focuses on cognitive symptoms of depression and excludes somatic items that can generate false positives during pregnancy and postpartum. It consists of 10 items, with 0-3 points scored per item for a potential scale score of 0-30. The higher scores indicate more severe depressive symptoms. EPDS will be conducted at baseline, 32 weeks gestation, 1 week postpartum and 3 months postpartum.

Kessler's Psychological Distress Scale (K6)

Psychological distress is measured by the Japanese version of K6.[33,34] K6 consists of six items assessing the frequency with which respondents have experienced symptoms of psychological distress during the past 30 days. The response options range from 0 (none of the time) to 4 (all of the time), and the total score ranges from 0 to 24. The higher scores indicate more severe psychological distress. K6 will be conducted at baseline, 32 weeks gestation, 1 week postpartum and 3 months postpartum.

EuroQol -5 dimension-5 level (ED-5D-5L)

General health status will be measured by the Japanese version of EQ-5D-5L.[35-37] It is a 5-dimensional utility instrument consisting of domains about morbidity, self-care, usual activities, pain or discomfort, and anxiety or depression. Each domain is divided into 5 levels of severity (none, slight, moderate, severe, extreme problems, or unable to). All responses are converted into a single index score of general health status. ED-5D-5L will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Somatic symptom Scale-8 (SSS-8)

Somatic symptoms will be measured by Japanese version of SSS-8.[38,39] SSS-8 consists of 8 items that assess the following symptoms: stomach or bowel problems; back pain; pain in the arms, legs, or joints; headaches; chest pain or shortness of breath; dizziness; feeling tired or having low energy; and trouble sleeping. These items comprise the four symptom domains of gastrointestinal, pain, cardiopulmonary, and fatigue. Respondents rate how much each symptom has bothered them during the previous 7 days and score each item from 0 to 4: not at all (0), a little bit (1), somewhat (2), quite a bit (3), and very much (4). The total score ranges from 0 to 32. A higher score reflects a more severe somatic symptom burden. SSS-8 will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Tachikawa Resilience Scale (TRS)

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4 Resilience will be measured by TRS.[40] TRS consists of 10 items. All items are scored on
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6 a 7-point scale from 1 (strongly disagree) to 7 (strongly agree), with a total score ranging from 10 to
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8 70. Higher scores reflect higher resilience. TRS will be conducted at baseline, 32 weeks gestation
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10 and 3 months postpartum.

11 12 **The Insomnia Severity Index (ISI)**

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15 Insomnia will be measured by the Japanese version of ISI.[41,42] ISI consists of 7 items
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17 assessing the severity of sleep-onset and sleep maintenance difficulties (both nocturnal and early
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19 morning awakenings), satisfaction with the current sleep pattern, interference with daily functioning,
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21 awareness of impairment attributed to the sleep problem, and degree of distress or concern caused by
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23 the sleep problem. Each item is rated on a 0 to 4 scale and the total score ranges from 0 to 28. A
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25 higher score suggests more severe insomnia. ISI will be conducted at baseline, 32 weeks gestation
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27 and 3 months postpartum.

28 29 30 **Cambridge-Hopkins questionnaire short form (CH-RLSq13)**

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33 Restless legs syndrome (RLS) will be measured by the Japanese version of CH-
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35 RLSq13.[43,44] CH-RLSq13 consists of 13 items. Diagnosis of RLS is performed using 10 items
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37 consisting of questions about discomfort and stiffness of the lower limbs. In addition, 2 items ask
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39 about the degree of pain and the frequency of occurrence and 1 item asks about the age of onset
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41 (relevant to pregnancy in women). CH-RLSq13 will be conducted at baseline, 32 weeks gestation
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43 and 3 months postpartum.

44 45 46 **Maternal Anxiety Scale for 4-5-month-old children**

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49 Maternal anxiety will be measured by the Maternal Anxiety Scale for 4-5-month-old
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51 children.[45] This scale consists of 34 items. Eleven items assess childcare anxiety, 6 items assess
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53 husbands' or partners' support, 5 items assess childcare satisfaction, 4 items assess ease of raising
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55 children, 5 items assess a lack of confidence, and 3 items assess presence or absence of advisors. All
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57 items are scored on a 4-point scale from 1 (strongly disagree) to 4 (strongly agree). A higher score of
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4 each subscale reflects a higher presence of each factor. This scale will be conducted at 3 months
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6 postpartum.
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8 **Medical economic costs**

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10 For cost-effectiveness analysis, the presence or absence, frequency and duration of medical
11 service use, and the use of drugs over the prior three months will be asked at 32 weeks gestation and
12
13 3 months postpartum.
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17 **Process evaluation**

18 **Implementation outcomes**

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20 Time spent logged in to each module will be measured. Also, we will evaluate implementation
21 outcomes by self-report via survey. Proctor and colleagues suggested 8 conceptually distinct
22 implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity,
23 implementation cost, penetration, and sustainability.[46] However, a systematic review examined
24 implementation outcomes for mental health and behavioral health using evidence-based rating criteria
25 and concluded that the majority of instrumental outcomes were underdeveloped.[47] Recently, Weiner
26 et al. developed measures of acceptability, appropriateness, and feasibility because their outcomes are
27 often used as leading indicators and are conceptually distinct.[48] Three of the authors (DN, EO, NS)
28 reviewed the previous literature and selected the possible outcomes for each dimension of acceptability,
29 appropriateness, and feasibility. These implementation outcomes and satisfaction with the intervention
30 program will be asked about at 34 weeks gestation.
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46 **Adverse effects**

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48 Three of the authors (DN, EO, NS) reviewed the previous literature based on a systematic
49 review, and selected the possible adverse effects of the program, such as physical symptoms (e.g., tired
50 eyes, stiff shoulders), mental symptom (e.g., insomnia), dangerous experiences (e.g., collide with
51 people while walking and looking at the smartphone), too much use of the smartphone, and excessive
52 pressure to learn this program regularly. These potential adverse effects will be asked about at 34
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4 weeks gestation.

5 6 **Data collection**

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8 All data will be collected by the internet. If the entered data is incomplete, participants will
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10 not be able to proceed the assessment.
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13 14 15 **Sample size calculation**

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17 Required sample size was calculated for the primary outcome. New onset of MDE during the
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19 observation period in Japan and the effect size in hazard ratio are estimated to be 5% and 0.65,[49]
20
21 based on previous studies. Thirty percent of participants are expected to drop out of the follow-up
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23 assessment. Given an α level of 0.05 (two-tailed) and a β level of 0.20, power Cox was performed with
24
25 STATA 14.0 and the appropriate sample size was calculated to be 4812. Since a large number of
26
27 participants using the app will be recruited on one day, it is considered difficult to stop recruiting
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29 immediately when the sample size is reached. Thus, the sample size was set at 5,000.
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35 36 **Randomization**

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38 Participants who meet the inclusion criteria will be randomly allocated to the intervention
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40 group or control group. Participants will be stratified into two strata according to the score of K6 (4 or
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42 less, or 5 or more) on the baseline survey. MTI Ltd. will send baseline data to researchers. In addition
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44 to the analysis of the whole sample (to examine the universal intervention effect), we will also analyze
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46 data by prespecified subgroups (to examine the selective intervention effect). Using a computer-
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48 generated random allocation sequence, an independent biostatistician created a stratified permuted-
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50 block random table. The block size of this RCT will be fixed at 4. The stratified permuted-block
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52 random table will be password protected and blinded to the researcher. Only the research assistant will
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54 be able to access it during the work of random allocation. MTI Ltd. will make the study participants
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56 allocated to the intervention group available to view the iCBT program on the app, based on the
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4 allocation provided by the research assistant.
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8 **Statistical methods**

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10 **Main analysis**

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12 A survival analysis will be conducted to test for the effectiveness of the intervention on the
13 time to the onset of MDE while controlling for censoring effects due to the differential length of
14 follow-up or the completion of follow-up without an onset of MDE. Length of follow-up for each
15 participant will be represented by either the number of months between the baseline and the onset of
16 MDE or the end of the follow-up period (3-month postpartum, or 32 weeks gestation if a participant
17 dropped out at the 3-month postpartum follow-up), whichever comes first. The cumulative incidence
18 of MDE at the 32 weeks gestation and 3-month postpartum follow-up, as well as event-free survivals
19 at every follow-up month, will be estimated using the Kaplan–Meier method; the statistical
20 significance will be tested of the difference between the cumulative proportions of having MDE at 32
21 weeks gestation and 3-month postpartum follow-ups in the intervention and control groups. A log-
22 rank test will be conducted to test the difference in survival probabilities between the intervention and
23 the control groups. A single covariate Cox discrete time hazard model will also be used to test the
24 difference and estimate the hazard ratio (HR), with 95% confidence intervals (CIs), for having MDE
25 in the intervention group compared to the control group. The intervention effect will also be estimated,
26 adjusting for dependent censoring and using the inverse probability of the censoring weighted (IPCW)
27 method for conducting a sensitivity analysis.[50] The number needed to treat (NNT) to achieve
28 prevention of one case of the onset of MDE will be calculated at 32 weeks gestation and 3-month
29 postpartum follow-ups. A similar Cox discrete time hazard model also will be conducted using the two
30 types of sub-threshold diagnoses of depressive episodes to investigate the effects of iCBT on
31 preventing depressive episodes, including subclinical cases. An intention-to-treat (ITT) analysis will
32 be conducted. Multiple imputation will be performed.
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Secondary analyses

For secondary outcomes (i.e. EPDS, K6, SSS-8, TRS), mixed models for repeated measures analyses will be conducted using a group (intervention or control) \times time (baseline, 32 weeks gestation, 1 week postpartum or 3-month postpartum follow-up) interaction as an indicator of the intervention effect. This allow for missing data to be taken into account within the statistical model. The level of statistical significance for all analyses in this study will be set at 0.05 (two-tailed), and 95% CIs will be calculated. The effect size will be estimated in two ways. First, we will estimate a regression coefficient for a group (the intervention group vs. the control group) \times time (baseline and follow-ups) interaction using the MIXED procedure, which will be converted to an effect size by dividing by a pooled SD at baseline and at follow-ups. Second, we will calculate Cohen's d among completers at baseline for each follow-up. ITT will be conducted as well. All statistical analyses will be conducted using SPSS Statistics 21.0 (IBM Corp., USA).

Subgroup analysis

The effectiveness of the programs may differ according to the initial severity of psychological distress. Therefore, we will analyze the results according to the prespecified subgroups (i.e., participants who scored 4 or less/5 or more in K6 at the baseline survey).

Cost-effectiveness analysis

Quality-adjusted life-years (QALYs) will be calculated as the effectiveness, using the EQ-5D-5L, as the area under the curve defined by the unitality values at baseline and follow-ups.[51] As for the costs, the cost of medical service use will be calculated based on the Survey of Medical Care Activities in Public Health Insurance,[52] which shows the treatment expenses covered by public health insurance in each diagnostic category. No intervention costs such as salary for therapists will be calculated because the program is fully-automated. Mean differences for the calculated effectiveness and costs will be compared between the intervention and control group.

Data monitoring and auditing

Because the iCBT program is not regarded as an invasive intervention, it is not necessary to set up a data monitoring board or to complete auditing in this trial.

Data availability

Deidentified individual participant data will be available upon reasonable request after publication of the main analysis paper. Contact information is the email address of the corresponding author.

Patient and public involvement

We utilized the function of the app “Luna Luna Baby” that allows users (pregnant women) to talk to each other about their problems. We extracted essential topics that pregnant women are concerned about based on 6393 text data, and developed programs for those topics. Even MTI, Ltd. cannot identify the person who posted a text, thus the text data is anonymized data that cannot be linked. The procedure was approved by the ethic committee of the University of Tokyo. The topics were extracted by using a machine learning approach, based on the Latent Dirichlet Allocation (LDA).[53] In this approach, morphological analysis was conducted for the text data from the pregnant women, and nouns and adjectives about what they suffer were collected. The LDA model was implemented by Scikit-learn version 0.21.3 [54] in Python. As a result, five topics were extracted: relationship with partners, concern about weight gain, concern about pregnancy checkup, physical symptoms such as pain, and dysfunction due to morning sickness. Since pregnancy checkup is considered to be a matter of obstetrics, each module of the iCBT program has been developed to deal with the remaining 4 topics. We will not access this chatroom during the RCT.

In addition, three women who had experiences of pregnancy and childbirth (two researchers and a research partner with lived experience) were invited to make comments on the intervention programs based on their experiences and preferences. All of them experienced maternity blues or

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4 perinatal depression, though they did not visit psychiatrists. Two researchers above (EO, NS) also
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6 were involved in designing this protocol.
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10 **Ethics and dissemination**

11 **Ethical and safety considerations**

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15 Informed consent for the app will be obtained from all participants included in this study
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17 after full explanation of the study. Candidates will be informed that their participation is voluntary,
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19 and that even after voluntarily participating, they can withdraw from the study at any time and their
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21 withdrawal will cause no disadvantage to them. We expect no adverse health effects from this
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23 intervention, except possible deterioration in depressive symptoms. We will send messages to those
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25 who meet the criteria for MDE in the past month or for lifetime bipolar disorders at baseline to
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27 encourage them to see a psychiatrist. The principal investigators will communicate important
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29 protocol modification with the institutional review board.
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33 **Data confidentiality**

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35 The collected data will be stored as linkable anonymizing data. The principal investigator
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37 will have access to the final dataset after the trial and take responsibility for the integrity of the data
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39 and the accuracy of analysis.
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42 **Dissemination of research findings**

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44 The findings of this study will be disseminated through publications in peer-reviewed
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46 international journals. Presentations of the findings will also be offered at relevant research
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48 conferences, and local academic symposia and seminars. If important findings are obtained from this
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50 study, we will make a press release and provide a plain language summary for users of Luna Luna
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52 baby. The principal investigator will be listed as corresponding authors, and the authorship eligibility
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54 will be conformed to the International Committee of Medical Journal Editors. If the intervention
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56 programs are found to be significantly positively effective, the programs can be made available for
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4 all users of the app in the future.
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8 **Discussion** 9

10 The greatest strength of this study is to prove the effectiveness of the fully automated
11 smartphone-based CBT program on preventing both antenatal and postpartum depression. The
12 relatively short, newly developed programs for pregnant women would be practical and low dropout
13 is expected. Furthermore, this study will assess diagnosis of MDE using CIDI. Many previous studies
14 using iCBT have suggested its preventive effect on depression; however, no previous studies assessed
15 the diagnosis of perinatal depression using the structural interview. This RCT with large sample size
16 can lead to a definitive result.
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26 This study also will evaluate implementation outcomes of the program. Previous studies using
27 iCBT have assessed the satisfaction with their program; however, few studies evaluated
28 implementation outcomes including acceptability, adoption, appropriateness, feasibility, fidelity,
29 implementation cost, penetration, and sustainability.[46] This study will contribute to the
30 dissemination and implementation of iCBT in the future.
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37 Another strength of this study is to add evidence of maternity blues. Maternity blues is highly
38 prevalent, and it can present a range of symptoms such as intense short-lasting dysphoric mood,
39 irritability, anxiety, sleep disturbance, and poor concentration within the first week following
40 childbirth.[55] Maternity blues could lead to postpartum depression,[56] but to our knowledge, no
41 previous studies have shown a preventive strategy to deal with maternity blues. This RCT will clarify
42 whether iCBT during pregnancy can prevent maternity blues.
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51 This study has several limitations. First, all outcomes will be measured by self-report, which
52 could be affected by the perceptions of the participants. Second, users of the app are not regarded as
53 representative of all pregnant women, though approximately 1 in 4 pregnant women in Japan are
54 thought to use the app. Therefore, the findings of this study can not necessarily be generalizable. Third,
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follow-up period is not long enough, because a sizeable proportion of postpartum depression have onset after 3 months postpartum.

For peer review only

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4 **Author contributions** DN conceived and designed the study. DN, KI, EO, NS, and YS contributed
5
6 creating programs. NY and NK contributed to the development of study design. KW calculated sample
7
8 size. KW and YM developed analysis plan. DN wrote the first draft of the manuscript, and all other
9
10 authors revised the manuscript critically. All authors approved the final version of the manuscript.
11

12
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14
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16

17
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19
20 or preparation of the manuscript.
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23 **Competing interests** MTI Ltd. has been involved in this study as mentioned in the manuscript. NK
24
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26
27 fees from Occupational Health Foundation, Japan Dental Association, Sekisui Chemicals, Junpukai
28
29 Health Care Center, Osaka Chamber of Commerce and Industry, outside the submitted work.
30

31 **Patient consent for publication** Obtained.
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34 **Ethics approval** The study plan was approved by the Research Ethics Review Board of Graduate
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36 School of Medicine/Faculty of Medicine, the University of Tokyo (2019150NI).
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42 **Figure legend:**

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44 Figure 1 Flow diagram of study participants
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For peer review only

Table 1 Contents of internet cognitive behavioral therapy program

Module No	Techniques for stress management
Module 1	Psychoeducation
Module 2	Case formulation based on cognitive behavioral model
Module 3	Behavioral activation
Module 4	Self-compassion
Module 5	Mindfulness
Module 6	Problem solving

Table 2 Overview of measurements

		Baseline	32 weeks	34 weeks	1 week	3 months
		(T1)	gestation	gestation	postpartum	postpartum
Measurement	Aim	(T2)	(T3)	(T4)	(T5)	
<i>Primary outcomes</i>						
CIDI	Diagnosis of	✓	✓			✓
	Major Depressive					
	Episode					
<i>Secondary outcomes</i>						
EPDS	Depressive symptoms	✓	✓		✓	✓
K6	Psychological distress	✓	✓		✓	✓
ED-5D-5L	Quality of life	✓	✓			✓
SSS-8	Somatic symptoms	✓	✓			✓
TRS	Resilience	✓	✓			✓
ISI	Insomnia	✓	✓			✓
CH-RLSq13	Restless legs syndrome	✓	✓			✓
Maternal Anxiety						
Scale for 4-5 months children	Maternal anxiety					✓
Medical costs	Medical service	✓	✓			✓

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use

Implementation Implementation

✓

and satisfaction outcomes

Adverse effects Physical and

✓

mental symptoms

Baseline assessments

Demographics

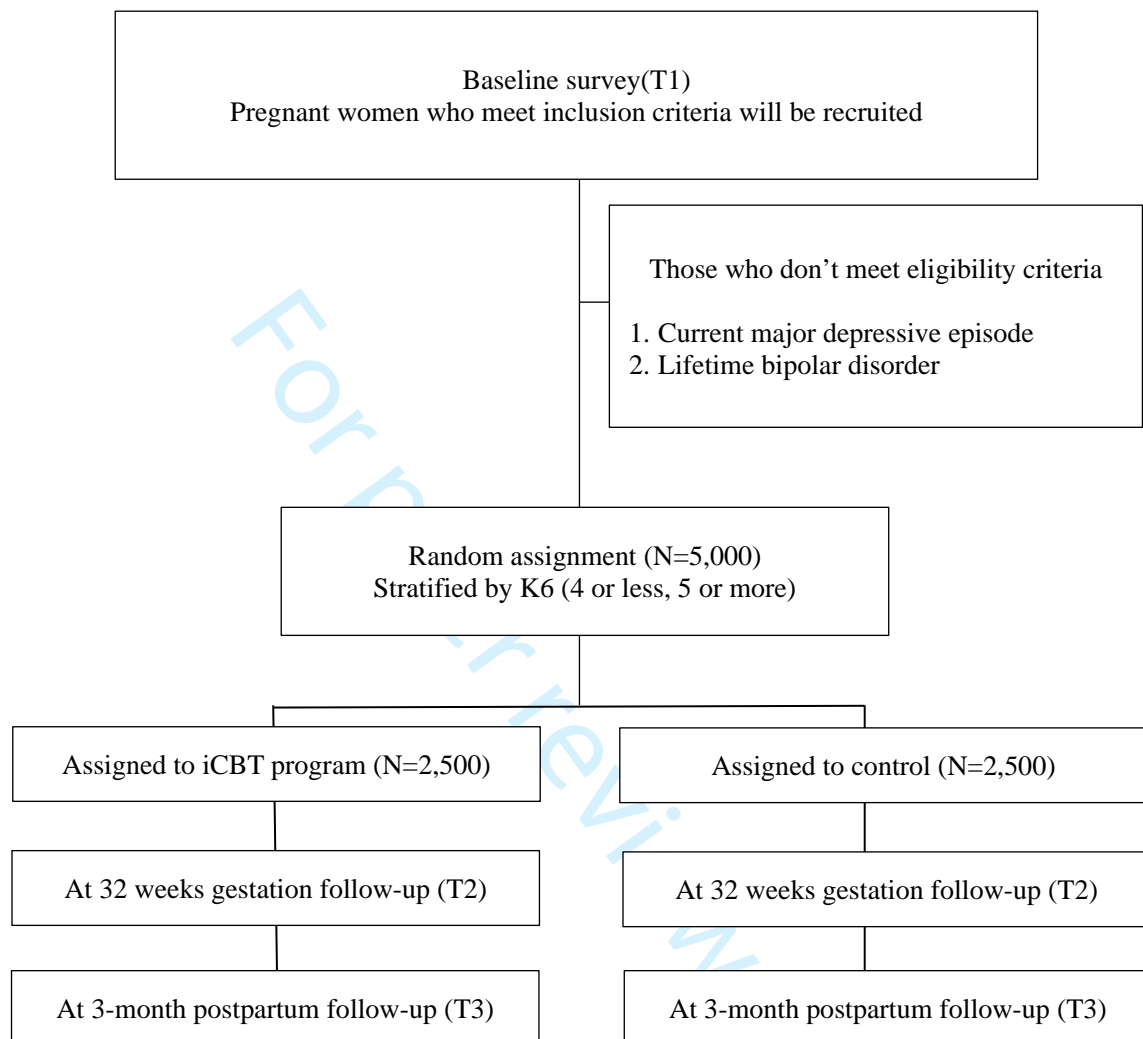
✓

VAWS

✓

CIDI, World Health Organization Composite International Diagnostic Interview 3.0; EPDS, The Edinburgh Postnatal Depression Scale; K6, Kessler's Psychological Distress Scale; ED-5D-5L, EuroQol -5 dimension-5 level; SSS-8, Somatic symptom Scale-8; TRS, Tachikawa Resilience Scale; ISI, The Insomnia Severity Index; CH-RLSq13, Cambridge-Hopkins questionnaire short form; VAWS, Violence Against Women Screen

Figure 1



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

			Page
	Reporting Item		Number
Administrative information			
Title	#1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym		1

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2
2			name of intended registry	
3				
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5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	NA
7	data set		Registration Data Set	
8				
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11	Protocol version	#3	Date and version identifier	2
12				
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15	Funding	#4	Sources and types of financial, material, and other	23
16			support	
17				
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19				
20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	23
21	responsibilities:			
22				
23	contributorship			
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28	Roles and	#5b	Name and contact information for the trial sponsor	NA
29	responsibilities:			
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31	sponsor contact			
32				
33	information			
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38	Roles and	#5c	Role of study sponsor and funders, if any, in study	NA
39	responsibilities:		design; collection, management, analysis, and	
40			interpretation of data; writing of the report; and the	
41	sponsor and funder		decision to submit the report for publication, including	
42			whether they will have ultimate authority over any of	
43			these activities	
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52	Roles and	#5d	Composition, roles, and responsibilities of the	NA
53	responsibilities:		coordinating centre, steering committee, endpoint	
54			adjudication committee, data management team, and	
55	committees			
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other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods:			
Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	6
2				
3			applicable, eligibility criteria for study centres and	
4			individuals who will perform the interventions (eg,	
5			surgeons, psychotherapists)	
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	7-10
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13	description		replication, including how and when they will be	
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15			administered	
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19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	NA
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21	modifications		interventions for a given trial participant (eg, drug dose	
22			change in response to harms, participant request, or	
23			improving / worsening disease)	
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29	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	14
30				
31	adherence		and any procedures for monitoring adherence (eg, drug	
32			tablet return; laboratory tests)	
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36	Interventions:	#11d	Relevant concomitant care and interventions that are	NA
37				
38	concomitant care		permitted or prohibited during the trial	
39				
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42	Outcomes	#12	Primary, secondary, and other outcomes, including the	10-14
43				
44			specific measurement variable (eg, systolic blood	
45			pressure), analysis metric (eg, change from baseline, final	
46			value, time to event), method of aggregation (eg, median,	
47			proportion), and time point for each outcome. Explanation	
48			of the clinical relevance of chosen efficacy and harm	
49			outcomes is strongly recommended	
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1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	6-7
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
5				
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11	Sample size	#14	Estimated number of participants needed to achieve	15
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any sample	
14			size calculations	
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21	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6-7
22			reach target sample size	
23				
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25				
26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
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36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	16
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
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53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	16
54	concealment		central telephone; sequentially numbered, opaque,	
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58	mechanism			
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sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#16c](#) Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions 16

Blinding (masking) [#17a](#) Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how 16

Blinding (masking): [#17b](#) If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial NA

Methods: Data collection, management, and analysis

Data collection plan [#18a](#) Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol 7

1	Data collection plan:	#18b	Plans to promote participant retention and complete	7
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
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11	Data management	#19	Plans for data entry, coding, security, and storage,	15
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
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23	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	16-17
24			outcomes. Reference to where other details of the	
25			statistical analysis plan can be found, if not in the protocol	
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31	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	17-18
32	analyses		adjusted analyses)	
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36	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	16-18
37	population and		adherence (eg, as randomised analysis), and any	
38	missing data		statistical methods to handle missing data (eg, multiple	
39			imputation)	
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46	Methods: Monitoring			
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48				
49	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	18-19
50	formal committee		summary of its role and reporting structure; statement of	
51			whether it is independent from the sponsor and	
52			competing interests; and reference to where further	
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1 details about its charter can be found, if not in the
 2 protocol. Alternatively, an explanation of why a DMC is
 3 not needed
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8	Data monitoring:	#21b	Description of any interim analyses and stopping	NA
9	interim analysis		guidelines, including who will have access to these	
10			interim results and make the final decision to terminate	
11			the trial	
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18	Harms	#22	Plans for collecting, assessing, reporting, and managing	15
19			solicited and spontaneously reported adverse events and	
20			other unintended effects of trial interventions or trial	
21			conduct	
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28	Auditing	#23	Frequency and procedures for auditing trial conduct, if	19
29			any, and whether the process will be independent from	
30			investigators and the sponsor	
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35	Ethics and			
36	dissemination			
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41	Research ethics	#24	Plans for seeking research ethics committee / institutional	2
42	approval		review board (REC / IRB) approval	
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46	Protocol	#25	Plans for communicating important protocol modifications	20
47	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
48			relevant parties (eg, investigators, REC / IRBs, trial	
49			participants, trial registries, journals, regulators)	
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6, 20
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
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8	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
9	ancillary studies		participant data and biological specimens in ancillary	
10			studies, if applicable	
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16	Confidentiality	#27	How personal information about potential and enrolled	20
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	23
27	interests		investigators for the overall trial and each study site	
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31	Data access	#29	Statement of who will have access to the final trial	20
32			dataset, and disclosure of contractual agreements that	
33			limit such access for investigators	
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39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
40	trial care		compensation to those who suffer harm from trial	
41			participation	
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47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	21
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
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1 Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of 21
 2
 3 authorship professional writers
 4
 5

6 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full 19
 7
 8 reproducible protocol, participant-level dataset, and statistical code
 9
 10 research
 11
 12

13 Appendices

14
 15
 16
 17 Informed consent [#32](#) Model consent form and other related documentation NA
 18
 19 materials given to participants and authorised surrogates
 20
 21

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 23 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of NA
 24
 25 biological specimens for genetic or molecular analysis in
 26
 27 the current trial and for future use in ancillary studies, if
 28
 29 applicable
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 33 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
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 35 License CC-BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a
 36
 37 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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