## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | 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 |
| **AUTHORS** | Nishi, Daisuke; Imamura, Kotaro; Watanabe, Kazuhiro; Obikane, Erika; Sasaki, Natsu; Yasuma, Naonori; Sekiya, Yuki; Matsuyama, Yutaka; Kawakami, Norito |

## VERSION 1 – REVIEW

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| **REVIEWER** | Danelle Pettman<br>Uppsala University, Sweden |
| **REVIEW RETURNED** | 08-Feb-2020 |

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| **GENERAL COMMENTS** | Summary<br>This was an interesting study with a nicely written and organised protocol. I particularly liked the idea that should the intervention prove successful the features would be made available to future users of the Luna Luna app. The below comments are to expand on certain points and improve clarity.<br><br>Abstract<br>1) A short summary of the planned method of analysis would be useful in the abstract.<br><br>Strengths and limitations<br>2) Second point – This could do with rewording for clarity, particularly the sentence; “handle concerns extracted from pregnant women”<br><br>3) Third point – please clarity what is meant by “the programme”<br>Introduction<br><br>4) Page 4 – line 45 - please define “universal prevention”<br><br>5) Page 4 – line 51- “is desirable to” may work better as “is preferable to”<br><br>6) In general, expanding the discussion of the evidence base for short session CBT both 5-10 minutes per module and over the course of 6 modules would enhance the introduction.<br><br>Methods and analysis<br>7) Page 5 – line 43 - As the K6 has not been mentioned in the protocol before this point it may be useful to explain that the K6 relates to psychological distress in this sentence. |

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| | 8) Page 5 – line 44 – The protocol could benefit from a fuller explanation of the Luna Luna app e.g, examples of the type of information provided to pregnant women.<br><br>9) Page 6 – line 19 – It may be useful to provide a rationale for the use of a 20 year cut-off as opposed to 18.<br><br>10) Page 6 - line 34 – Please outline how the ability to understand the research objectives is assessed?<br><br>11) Page 6 - line 37-40 -These sentences seem a little out of place. Perhaps it could be moved to the trail design section where you explain the Luna Luna app (see comment 8).<br><br>12) Page 7 - lines 10-19 - These sentences would benefit from being rewritten to flow better together.<br><br>13) Page 7 - lines 43-59 - The protocol would benefit from a more detailed description of the intervention development in this section. For example who developed the intervention and what tailoring of the intervention was made for a perinatal population. It may be useful to refer to the template for intervention description and replication (TIDieR) checklist and guide https://www.equator-network.org/reporting-guidelines/tidier/<br><br>14) Secondary outcome measures - mention that you are using a Japanese version of the EPDS and ED-5D-5L. The EPDS also needs a reference.<br><br>15) Page 16- line 25- Please explain “the cloud” very briefly.<br><br>16) Page 18 - line 37 - Please outline the method used for the ITT analysis.<br>Patient and public involvement<br><br>17) Page 19 – line 55- Please explain the consent procedures for this data extraction<br><br>18) Page 20 - lines 25-32- It is not clear how these topics are integrated into the modules. For example is module 1 a 5-10 minute module including both depression formulation and morning sickness? I think this information should be moved to the development of the intervention section suggested in comment 15.<br><br>19) Page 20 -line 37 - Consider changing title used for the mother assisting with the development the intervention e.g., research partner with lived experience or patient co-creator as opposed to “ordinary mother”. It might also be helpful to outline if developers of the intervention had experience of perinatal depression. It may also be useful to further explain the involvement e.g., where they invited to workshop or meeting/did they give feedback on intervention prototypes.<br><br>Ethics<br>20) The EPDS questionnaire asks the following question: “The thought of harming myself has occurred to me” are there procedures in place for high scoring mothers e.g., signposting to support services.<br><br>Dissemination of research findings |

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| | 21) Would it be possible to provide a plain language summary of the study for users of Luna Luna baby of the study results for those mothers who may be interested.<br><br>Discussion<br>22) Page 22 - line 31 – It would be beneficial to define “maternity blues”. Maternity blues is only referred to in the strength and weaknesses and discussion sections. It would enhance the protocol if the analysis of “maternity blues” was also discussed in the abstract/introduction /objectives.<br><br>23) Page 28 - I see table 1 but I do not see it referred to in the text |

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| **REVIEWER** | Bei Bei<br>Monash University, Australia |
| **REVIEW RETURNED** | 15-Feb-2020 |

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| **GENERAL COMMENTS** | This paper has all key components of a clinical trial protocol, and is clearly written and well presented. This trial is much needed in that it applies a universal prevention of postpartum depression with potentials to benefit a large population. I have only a few minor comments:<br>- The randomisation is stratified by K6 scores, could the authors please specify in analytic plans how stratifying variables will be incorporated in analyses?<br>- I have concerns that 3 months postpartum as the end point is too early, as a sizeable proportion of postpartum depression cases have onset that is after 3 months postpartum.<br>- Could the inclusion criteria specify whether both nulli- and multiparous women would be included?<br>- Health economic measures are discussed in the measures and analyses, but are not part of the aims. It may be helpful to add this as a secondary aim?<br>- “We will evaluate implementation outcomes by self-report”. Is this via survey or interviews? Who will complete these measures and how is this determined? If via interview, how many will be conducted and how will qualitative information be analysed?<br>- Please describe how missing data will be addressed in analyses. |

## VERSION 1 – AUTHOR RESPONSE

**Reviewer: 1**

Summary

This was an interesting study with a nicely written and organised protocol. I particularly liked the idea that should the intervention prove successful the features would be made available to future users of the Luna Luna app. The below comments are to expand on certain points and improve clarity.

**Response:** Thank you very much for reviewing our manuscript. We are pleased that the reviewer expressed positive feedback.

Abstract

1) A short summary of the planned method of analysis would be useful in the abstract.

**Response:** We briefly described a planned method of analysis in the abstract, as below.

“Survival analysis will be conducted to test for the effectiveness of the intervention on time to the onset of MDE.” (p2, line13-14)

Strengths and limitations

2) Second point – This could do with rewording for clarity, particularly the sentence; “handle concerns extracted from pregnant women”

**Response:** In accordance with the reviewer’s comment, we rewrote the second bullet as below.

“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.” (p3, line6-7)

3) Third point – please clarity what is meant by “the programme”

**Response:** In accordance with the reviewer’s comment, we corrected “the program” as “iCBT program”. (p3, line8)

Introduction

4) Page 4 – line 45 - please define “universal prevention”

**Response:** In accordance with the reviewer’s comment, we defined universal prevention as below.

“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]” (p4, line19-20)

5) Page 4 – line 51- “is desirable to” may work better as “is preferable to”

**Response:** In accordance with the reviewer’s comment, we corrected “is desirable to” as “is preferable to”. (p4, line23)

6) In general, expanding the discussion of the evidence base for short session CBT both 5-10 minutes per module and over the course of 6 modules would enhance the introduction.

**Response:** In accordance with the reviewer’s comment, we added the following sentence in the introduction.

“In this regard, 6-sessions of 5 to 10-minutes iCBT programs was shown to be effective for preventing depressive symptoms for workers [20].” (p5, line8-9)

Methods and analysis

7) Page 5 – line 43 - As the K6 has not been mentioned in the protocol before this point it may be useful to explain that the K6 relates to psychological distress in this sentence.

**Response:** In accordance with the reviewer’s comment, we explained K6 as below.

“Random assignments are stratified by Kessler’s Psychological Distress Scale (K6) scores (groups of 4 points or less and groups of 5 points or more) in the baseline survey. K6 is a self-report questionnaire, which assesses psychological distress during the past 30 days.” (p6, line3-5)

8) Page 5 – line 44 – The protocol could benefit from a fuller explanation of the Luna Luna app e.g, examples of the type of information provided to pregnant women.

**Response:** In accordance with the reviewer’s comment, we explained the app as below.

“The app provides the users for the growth of the fetus and the mental and physical condition of the pregnant women according to the number of gestation weeks.” (p6, line6-7)

9) Page 6 – line 19 – It may be useful to provide a rationale for the use of a 20 year cut-off as opposed to 18.

**Response:** According to “Ethical Guidelines for Medical and Health Research Involving Human Subjects” in Japan, the proxy (a person judged capable of representing the intents and best interests of the research subject, usually parents) is required to give the consent when we include people under the age of 20, thus we will recruit people being over 20 years old in this study.

10) Page 6 - line 34 – Please outline how the ability to understand the research objectives is assessed?

**Response:** We remove “Ability to understand the research objectives and give consent” from eligibility criteria, because those who become a user of this app are considered to be able to understand the purpose of this study.

11) Page 6 - line 37-40 -These sentences seem a little out of place. Perhaps it could be moved to the trail design section where you explain the Luna Luna app (see comment 8).

**Response:** In accordance with the reviewer’s comment, we moved the sentence to the trial section where we explain the app.

12) Page 7 - lines 10-19 - These sentences would benefit from being rewritten to flow better together.

**Response:** Thank you for your comment. We rewrote the sentences as below.

“Participants in the intervention groups will be required to complete the intervention program up to 32 weeks gestation.” (p7, line7-8)

13) Page 7 - lines 43-59 - The protocol would benefit from a more detailed description of the intervention development in this section. For example who developed the intervention and what tailoring of the intervention was made for a perinatal population. It may be useful to refer to the

template for intervention description and replication (TIDieR) checklist and guide https://www.equator-network.org/reporting-guidelines/tidier/

**Response:** In accordance with the reviewer’s comment, we added a more detailed description of the intervention development as below.

“Specifically, the first author (DN) developed the iCBT program with the collaboration of co-authors (KI, EO, NS and YS). The program was tailored for pregnant women by extracting essential topics that pregnant women are concerned about. The details were shown in patient and public involvement section.” (p7, line17-20)

14) Secondary outcome measures - mention that you are using a Japanese version of the EPDS and ED-5D-5L. The EPDS also needs a reference.

**Response:** In accordance with the reviewer’s comment, we mentioned that we will use a Japanese version of the EPDS and ED-5D-5L, and added references on EPDS, as below.

“Depressive symptoms will be measured by the Japanese version of EPDS [31, 32].” (p10, line32)

“General health status will be measured by the Japanese version of EQ-5D-5L.” (p11, line9)

15) Page 16- line 25- Please explain “the cloud” very briefly.

**Response:** We don’t think the description “stored in the cloud” is necessary, so we deleted it and simply noted as below.

“MTI Ltd. will send baseline data to researchers.” (p14, line18)

16) Page 18 - line 37 - Please outline the method used for the ITT analysis.

**Response:** For main analysis, we will perform multiple imputation. For secondary analyses, mixed models for repeated measures analyses allow for missing data to be taken into account within the statistical model. We described these as below.

“Multiple imputation will be performed.” (p15, line25)

“This allow for missing data to be taken into account within the statistical model.” (p16, line5)

Patient and public involvement

17) Page 19 – line 55- Please explain the consent procedures for this data extraction

**Response:** We explained procedures as below.

“Even MTI, Inc. 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.” (p17, line12-14)

18) Page 20 - lines 25-32- It is not clear how these topics are integrated into the modules. For example is module 1 a 5-10 minute module including both depression formulation and morning sickness? I think this information should be moved to the development of the intervention section suggested in comment 15.

**Response:** In accordance with the reviewer’s comment, we incorporated how these topics are integrated into the modules, as below.

(module 1)

“As an example of anxious situations, a scene that a partner of pregnant woman is busy working and is not at home is used. As an example of sad situations, a scene when a pregnant woman suffers from morning sickness but the boss does not understand is used.” (p8, line10-12)

(module 2)

“A scene when a pregnant woman suffers from morning sickness but the boss does not understand is used as a case.” (p8, line18-19)

(module 3)

“A scene when a pregnant woman would not like to go out because she has gained weight and is not motivated is used as a case.” (p9, line1-2)

(module 4)

“A scene when a pregnant woman suffers from morning sickness and is blaming herself for not being able to work as usual is used as a case.” (p9, line9-10)

(module 5)

“A scene when a pregnant woman feels anxiety due to tension and pain in the lower abdomen in spite of obstetrically normal is used as a case.” (p9, line16-18)

(module 6)

“A scene when a pregnant woman wants her partner to do more in housework and childcare is used as a case.” (p9, line25-p10, line1)

19) Page 20 -line 37 - Consider changing title used for the mother assisting with the development the intervention e.g., research partner with lived experience or patient co-creator as opposed to “ordinary mother”. It might also be helpful to outline if developers of the intervention had experience of perinatal depression. It may also be useful to further explain the involvement e.g., where they invited to workshop or meeting/did they give feedback on intervention prototypes.

**Response:** In accordance with the reviewer’s comment, we corrected “ordinary mother” as “research partner with lived experience”. All of them experienced maternity blues or perinatal depression, though she did not visit psychiatrists. We described as below.

“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 perinatal depression, though they did not visit psychiatrists.” (p17, line24-p18, line1)

Ethics

20) The EPDS questionnaire asks the following question: “The thought of harming myself has occurred to me” are there procedures in place for high scoring mothers e.g., signposting to support services.

**Response:** There are no procedures for those who scored on the item 10 of EPDS. However, we will send messages to those who meet the criteria for MDE in the past month or for lifetime bipolar disorders at baseline to encourage them to see a psychiatrist. We described as below.

“We will send messages to those who meet the criteria for MDE in the past month or for lifetime bipolar disorders at baseline to encourage them to see a psychiatrist.” (p18, line1012)

Dissemination of research findings

21) Would it be possible to provide a plain language summary of the study for users of Luna Luna baby of the study results for those mothers who may be interested.

**Response:** In accordance with the reviewer’s comment, we added the following sentence.

“If important findings are obtained from this study, we will make a press release and provide a plain language summary for users of Luna Luna baby.” (p18, line21-23)

Discussion

22) Page 22 - line 31 – It would be beneficial to define “maternity blues”. Maternity blues is only referred to in the strength and weaknesses and discussion sections. It would enhance the protocol if the analysis of “maternity blues” was also discussed in the abstract/introduction /objectives.

**Response:** In accordance with the reviewer’s comment, we added the following sentences in the introduction/objectives.

“Moreover, to our knowledge, no previous randomized controlled trials (RCTs) have examined the effect of iCBT on maternity blues. Maternity blues were characterized by psychological distress with a peak at 3 to 5 days after childbirth, though diagnostic criteria have not been well established. Maternity blues are highly prevalent and have been shown to be a risk factor for postpartum depression {Henshaw, 2004}, thus it will be relevant to develop the intervention to prevent not only perinatal depression but also maternity blues.” (p5, line10-15)

“The secondary objectives of this RCT are to examine the effectiveness of iCBT for preventing maternity blues.” (p5, line19-20)

23) Page 28 - I see table 1 but I do not see it referred to in the text

**Response:** We added “table 1” in the intervention section, as below.

“The six modules are presented in a fixed order, with one module accessible per week, from module 1 to module 6 (Table 1).” (p7, line15)

**Reviewer: 2**

This paper has all key components of a clinical trial protocol, and is clearly written and well presented. This trial is much needed in that it applies a universal prevention of postpartum depression with potentials to benefit a large population.

**Response:** Thank you very much for reviewing our manuscript. We are pleased that the reviewer expressed positive feedback.

- The randomisation is stratified by K6 scores, could the authors please specify in analytic plans how stratifying variables will be incorporated in analyses?

**Response:** We will analyze each subgroup, and will not incorporate a stratifying variable in the model. We rewrote this point as below.

"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)." (p16, line15-16)

- I have concerns that 3 months postpartum as the end point is too early, as a sizeable proportion of postpartum depression cases have onset that is after 3 months postpartum.

**Response:** We agree with the reviewer. The first reason why we set 3 months postpartum as the end point is that a systematic review (Gavin, 2005) showed point prevalence of major and minor postpartum depression was highest in the 3 months postpartum.

The second reason is feasibility. Many users of this app will stop using the app over time after childbirth, so it is very likely that dropout rates will increase over time.

We added this as one of the limitations of this study in discussion section, as below.

"Third, follow-up period is not long enough, because a sizeable proportion of postpartum depression have onset after 3 months postpartum." (p19, line25-p20, line2)

- Could the inclusion criteria specify whether both nulli- and multiparous women would be included?

**Response:** In accordance with the reviewer's comment, we added the following sentence in the participant section.

"Both primipara and multiparous women will be included." (p6, line16-17)

- Health economic measures are discussed in the measures and analyses, but are not part of the aims. It may be helpful to add this as a secondary aim?

**Response:** We recognize limitations in performing cost effectiveness analysis, such as the inability to examine the contents of medication, thus we decide that we don't mention it as a secondary objective of this RCT.

- "We will evaluate implementation outcomes by self-report". Is this via survey or interviews? Who will complete these measures and how is this determined? If via interview, how many will be conducted and how will qualitative information be analysed?

**Response:** This is via survey, and participants will complete these measures, as we noted "These implementation outcomes and satisfaction with the intervention program will be asked about at 34 weeks gestation" at the end of the implementation outcome section.

We added "via survey" in the first sentence of this section, as below.

"Also, we will evaluate implementation outcomes by self-report via survey." (p13, line10)

- Please describe how missing data will be addressed in analyses.

**Response:** For main analysis, we will perform multiple imputation. For secondary analyses, mixed models for repeated measures analyses allow for missing data to be taken into account within the statistical model. We described these as below.

"Multiple imputation will be performed." (p15, line25)

"This allow for missing data to be taken into account within the statistical model." (p16, line5)

**VERSION 2 – REVIEW**

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| **REVIEWER** | Danelle Pettman<br>Uppsala University, Sweden |
| **REVIEW RETURNED** | 02-Apr-2020 |

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| **GENERAL COMMENTS** | The authors have sufficiently answered the points I raised in my previous review - I have no amendments to add |

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| **REVIEWER** | Bei Bei<br>Monash University, Australia |
| **REVIEW RETURNED** | 21-Mar-2020 |

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| **GENERAL COMMENTS** | Thank you for addressing all my comments. This is a highly promising study, and I wish the authors all the best with data collection, and look forward to seeing the results! |