## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Protocol for the Healing After Loss (HeAL) Study: A randomized controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss |
| **AUTHORS** | Johnson, Jennifer; Price, Ann B.; Sikorskii, Alla; Key, Kent; Taylor, Brandon; Lamphere, Susan; Huff, Christine; Cinader, Morgan; Zlotnick, Caron |

## VERSION 1 – REVIEW

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| **REVIEWER** | Dadi, A.F.<br>Menzies School of Health Research, Centre for Child Development and Education |
| **REVIEW RETURNED** | 05-Nov-2021 |

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| **GENERAL COMMENTS** | This is a study protocol intended to investigate the effectiveness of IPT to treat major depressive disorder, depressive symptoms, PTSD symptoms. The authors are also intended to estimate the time that the women are treated from these disorders. The study is important as IPT and other such psychosocial interventions are the most recommended one in order to prevent the side effects associated with chemotherapies. Saying this, I have the following concerns that the authors should bear in mind while conducting this study.<br>1. The authors are intended to estimate the time to recovery from the disorders but I<br>strongly argue that this is not possible as the exact time will not be known but could be approximated in weeks or depends based on the time of assessment follow up.<br>2. Treatment definition needs further description- the 1290-minutes group?<br>3. "We found that entering new women into the groups every four weeks allows remaining women to see their own progress and encourages new women through example and peer counseling. This thing is not clear for me, are they new trainers or new women to be treated? If they are new women to be treated how the variation in difference time handled or why it is required?<br>4. It seems like you have revised the routine depression treatment CWD manual for this study, how this going to be a standard treatment you are comparing with? It is going to be that you are testing two new psychotherapies.<br>5. It is biological that a women can not conceive after age 45 years, is there any indication for this?<br>6. The first exclusion criteria is not clear for me, why we exclude them needs to be justified. |

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| | 7. Women in stable concurrent psychotherapy who are included are asked to suspend this treatment during the active study treatment phase, how you are dealing with washout period if they already started treatment?<br>8. I would recommend excluding PTSD patients or patients with concurrent symptoms and only focus on major depressive disorder for specificity of the study. Or conducting two separate trial group.<br>9. Randomization: Is it to mean you are going to much study participants from the two groups.<br>10. You are planned to measure severity, not sure why if you are not accounting in randomization or you are using to adjust for?<br>11. I can see how much your questionnaire is bulky that pose a significant burden on the women and affect the quality of their response? Think of the tradeoff between the overall quality of the study or other issues? I would strongly recommend reducing your secondary outcomes and just focus on your primary to minimize a burden on the women and ethical issue and quality.<br>12. You are using survival analysis and your time to recovery should be based on weeks of assessment.<br>13. Your outcome is a scale not a distinct outcome, how you use survival analysis? How it is valid to categorize the scale?<br>14. How you account for a variation between psychotherapists? |

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| **REVIEWER** | Jidong, Dung<br>Nottingham Trent University |
| **REVIEW RETURNED** | 10-Nov-2021 |

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| **GENERAL COMMENTS** | This protocol for RCT is timely with the potential to address a significant health concern of the under-researched population.<br><br> It would be beneficial to strengthen the rationale for the choice of the designated population/African Americans (e.g., beyond the understudied population). E.g., their features especially the perinatal issues compared to the other/BAME population? (cultural/family structure/socio-economic status/age/etc.)<br><br> Could more details be added on activities to be covered in each of the 12 sessions of both IPT and CWD? How long is each session? Is there going to be any difference in the time span for the online and future in person sessions?<br><br> Following on from the planned transition from online (due to Covid-19 pandemic) intervention to face-to-face sessions in the future, can anticipated challenges be highlighted and how they would be mitigated, and perhaps, what could be its potential impact on the overall research process and final findings?<br><br>Overall, this study seems to be well-designed and showed originality, rigour, and significance. |

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| **REVIEWER** | Kroll-Desrosiers, Aimee<br>Department of Veterans Affairs, Research |
| **REVIEW RETURNED** | 15-Nov-2021 |

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| **GENERAL COMMENTS** | Minor comments: |

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| | bmjopen-2021-057747: Study Protocol: Randomized controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss<br><br>This study protocol details a trial to examine the difference between IPT for perinatal loss compared to CWD. Perinatal loss is an understudied and important topic. This is a well-written protocol; I have only minor comments to be addressed.<br>Minor Comments:<br>- Lines 43-45 on page 9 in the CWD methods paragraph, 'that' should be 'than': "To ensure that the CWD intervention was distinct from IPT, we excluded the 2 sessions on social skills and emphasized pleasant activities that were individual rather that social."<br>- Note that in the "Exclusion criteria" list of the "Participants" paragraph in the methods, the sentence is missing a number (2).<br>- In the Recruitment paragraph, please be consistent with the use of either commas or semi-colons between items: "Recruitment also includes flyers and referrals from: (1) local birthing centers, emergency departments, OBGYN offices, and federally qualified health centers; (2) hotlines, support groups, family nurse partnerships; (3) funeral homes, (4) churches, daycare centers, other places where women and mothers congregate (WIC offices, Medicaid offices, etc.), (5) bus ads, and (6) online venues."<br>- In the Assessments paragraph, I am not quite sure what this sentence means and may need to be clarified: "RAs are certified interviewer-rated instruments prior to beginning interviews" |

## VERSION 1 – AUTHOR RESPONSE

### Reviewer 3

This study protocol details a trial to examine the difference between IPT for perinatal loss compared to CWD. Perinatal loss is an understudied and important topic. This is a well-written protocol; I have only minor comments to be addressed.

*Thank you!*

Lines 43-45 on page 9 in the CWD methods paragraph, 'that' should be 'than': "To ensure that the CWD intervention was distinct from IPT, we excluded the 2 sessions on social skills and emphasized pleasant activities that were individual rather that social."

*This correction has been made.*

Note that in the “Exclusion criteria” list of the “Participants” paragraph in the methods, the sentence is missing a number (2).

*This correction has been made.*

In the Recruitment paragraph, please be consistent with the use of either commas or semi-colons between items: “Recruitment also includes flyers and referrals from: (1) local birthing centers, emergency departments, OBGYN offices, and federally qualified health centers; (2) hotlines, support groups, family nurse partnerships; (3) funeral homes, (4) churches, daycare centers, other places where women and mothers congregate (WIC offices, Medicaid offices, etc.), (5) bus ads, and (6) online venues.”

*This correction has been made.*

In the Assessments paragraph, I am not quite sure what this sentence means and may need to be clarified: “RAs are certified interviewer-rated instruments prior to beginning interviews.” *Given word limitations, we deleted the sentence.*

**Reviewer 2**

Overall, this study seems to be well-designed and showed originality, rigour, and significance. *Thank you!*

It would be beneficial to strengthen the rationale for the choice of the designated population/African Americans (e.g., beyond the understudied population). E.g., their features especially the perinatal issues compared to the other/BAME population? (cultural/family structure/socio-economic status/age/etc.)

*We were confused by this question because the study participation is not limited by race or ethnicity and does not target any race or ethnicity specifically. The study does recruit from racially/ethnically diverse geographical areas, which is a strength in terms of increasing the diversity of the study sample. We have tried to clarify.*

Could more details be added on activities to be covered in each of the 12 sessions of both IPT and CWD?

*We struggled with how to provide this additional detail within the journal's word limit. Table 1 has detail on the IPT intervention. We also added references to pilot study paper and published manuals which describe the interventions in much greater detail.*

How long is each session?

*All group sessions are 90 minutes long (see first sentence of the second paragraph of the Methods section).*

Is there going to be any difference in the time span for the online and future in person sessions? *No.*

Following on from the planned transition from online (due to Covid-19 pandemic) intervention to face-to-face sessions in the future, can anticipated challenges be highlighted and how they would be mitigated, and perhaps, what could be its potential impact on the overall research process and final findings?

*We don't anticipate difficulties or impact on research process from switching to in person sessions once it is safe, because the pilot trial used in person sessions. We have clarified in the "research sites" section. We considered adding additional detail about procedures for online sessions, but the manuscript was already at the journal's word limit when we submitted it and other suggested edits (such as adding the "patient and public involvement" section and clarifying the LIFE measure) added additional words.*

**Reviewer 1**

This is a study protocol intended to investigate the effectiveness of IPT to treat major depressive disorder, depressive symptoms, PTSD symptoms. The authors are also intended to estimate the time that the women are treated from these disorders. The study is important as IPT and other such psychosocial interventions are the most recommended one in order to prevent the side effects associated with chemotherapies.

*Thank you. Please note that we have organized responses to reviewer comments below by topic.*

1. The authors are intended to estimate the time to recovery from the disorders but I strongly argue that this is not possible as the exact time will not be known but could be approximated in weeks or depends based on the time of assessment follow up. 13. Your outcome is a scale not a distinct outcome, how you use survival analysis? How it is valid to categorize the scale?

*We have added additional information on the Longitudinal Interview Follow-up Examination (LIFE). It was developed to be used as we propose to use it, and has been used to determine onset and offset of psychiatric disorder in more than 100 studies to date.*

*During follow-up, the Longitudinal Interval Follow-up Examination (LIFE), a standardized retrospective calendar-based interview, will be used to assess MDD and PTSD recovery. Unlike the SCID, which provides only a cross-sectional measure, the LIFE provides a structured way to track the severity and course of disorders over time. Interviewers anchor participants in the symptoms they were experiencing at the last assessment and then asking about any changes that*

*occurred week to week, using significant events as anchors. The LIFE uses Psychiatric Status Ratings (PSRs) to measure severity of DSM-5 symptoms on a scale of 1 (asymptomatic) to 6 (incapacitated) for each week. A PSR of 5 or 6 indicates the participant meets full diagnostic criteria for disorder. A PSR of 3 or 4 indicates subthreshold disorder. A PSR of 1 or 2 indicates the participant is not in episode. Interrater reliability and long-term test-retest reliability for the LIFE weekly diagnostic ratings is good to excellent for retrospective recall periods up to 12 months. The LIFE has been used in more than 100 studies to date. It is the gold-standard way of determining onset and offset of psychiatric disorder. Dr. Johnson has used this measure with good interrater reliability in many of her previous studies (e.g., U01 MH106660; R01 MH095230; R34 MH086682). At baseline, the LIFE will be used to determine the length of the current depressive and PTSD episodes. We will also use the LIFE to track participation in psychotherapeutic and psychopharmacologic treatment at baseline and follow-up.*

12. You are using survival analysis and your time to recovery should be based on weeks of assessment.

*We agree. Each participant will have approximately 28 weeks of assessment. Participants who reach the final assessment and have not yet recovered will be treated as censored. Because this is a standard approach to survival analysis and because of the word limit, we did not spell it out explicitly in the manuscript.*

2. Treatment definition needs further description- the 1290-minutes group?

*We have edited "12 90 minute groups" to "12 groups of 90 minutes each" for clarity.*

3. "We found that entering new women into the groups every four weeks allows remaining women to see their own progress and encourages new women through example and peer counseling. This thing is not clear for me, are they new trainers or new women to be treated? If they are new women to be treated how the variation in difference time handled or why it is required?

*They are new women to be treated. Every woman receives 12 group sessions. The groups are rolling, allowing new women to enter and previous group members to leave every 4 sessions, as their 12 sessions are completed. We have tried to clarify.*

4. It seems like you have revised the routine depression treatment CWD manual for this study, how this going to be a standard treatment you are comparing with? It is going to be that you are testing two new psychotherapies.

*This is partially true. In the trial, we excluded the CWD components that overlap with IPT (e.g. improving social support, communication) about 15% of CWD. So it is a modified version of CWD as opposed to an adapted version of CWD as the case with IPT. Both treatments were tested in the previous pilot trial (see Johnson et al, 2016). For clarity, we changed the language we used to no longer refer to CWD as a "standard" depression treatment.*

5. It is biological that a women cannot conceive after age 45 years, is there any indication for this? *This is not 100% true in the US. Regardless, we set the age range high (18-50) because we did not want adult women to be excluded due to age. With the age range we identified, essentially any adult women who experiences a perinatal loss will be included.*

6. The first exclusion criteria is not clear for me, why we exclude them needs to be justified.

*We include women who have experienced previous major depressive episodes. However, since the current trial evaluates treatments for depression following perinatal loss, we require that the current major depressive episode begin during or after the loss or news of problems with the pregnancy.*

7. Women in stable concurrent psychotherapy who are included are asked to suspend this treatment during the active study treatment phase, how you are dealing with washout period if they already started treatment?

*Unlike medication, there is no standard washout period for psychotherapy.*

8. I would recommend excluding PTSD patients or patients with concurrent symptoms and only focus on major depressive disorder for specificity of the study. Or conducting two separate trial group.

*Thank you for this suggestion. We focused on women with major depression after perinatal loss in the pilot trial, and found that more than half had concurrent PTSD. Therefore, we feature concurrent PTSD more prominently in this trial. It would limit generalizability to exclude women with concurrent PTSD. In addition, because we have already received money from the National Institutes of Health to conduct the study as we proposed it, we are not able to change major aspects of the design at this point. However, we added a sentence to the introduction about finding high concurrent rates of PTSD in the pilot trial.*

9. Randomization: Is it to mean you are going to much study participants from the two groups. *We are not using matching of study participants in this trial.*

10. You are planned to measure severity, not sure why if you are not accounting in randomization or you are using to adjust for?

*Depressive symptoms and PTSD symptoms are outcomes of the trial. We deleted the word*

*"severity" from the phrase "depressive symptom severity" to reduce confusion.*

11. I can see how much your questionnaire is bulky that pose a significant burden on the women and affect the quality of their response? Think of the tradeoff between the overall quality of the study or other issues. I would strongly recommend reducing your secondary outcomes and just focus on your primary to minimize a burden on the women and ethical issue and quality.

*We piloted the assessment battery in the previous (pilot) trial, and the participants found it acceptable. Furthermore, several of the measures (such as fear of subsequent pregnancies and loss beliefs) were added at the request of the community representatives we consulted. Nevertheless, participant burden is an important issue. Unfortunately, because we have already received money from the National Institutes of Health to conduct the study as we proposed it, we are not able to change major aspects of the design at this point.*

14. How will you account for a variation between psychotherapists?

*Testing therapist effects is not a planned part of the analysis. However, it is a good idea and we can add this as an exploratory analysis at the end of the trial.*

## VERSION 2 – REVIEW

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| **REVIEWER** | Dadi, A.F.<br>Menzies School of Health Research, Centre for Child Development and Education |
| **REVIEW RETURNED** | 18-Jan-2022 |

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| **GENERAL COMMENTS** | Thank you authors for addressing my concern. One thing that I still not convinced is on plan of analysis. The outcome is scale and if the authors want to categorize it will have three categories as stated, "A PSR of 5 or 6 indicates the participant meets full diagnostic criteria for disorder. A PSR of 3 or 4 indicates subthreshold disorder. A PSR of 1 or 2 indicates the participant is not in episode.". I can see the first group will be event, the third group will be censured, where will be the third category located? |

## VERSION 2 – AUTHOR RESPONSE

### Reviewer 1

One thing that I still not convinced is on plan of analysis. The outcome is scale and if the authors want to categorize it will have three categories as stated, "A PSR of 5 or 6 indicates the participant meets full diagnostic criteria for disorder. A PSR of 3 or 4 indicates subthreshold disorder. A PSR of 1 or 2 indicates the participant is not in episode." I can see the first group will be event, the third group will be censured, where will be the third category located?

*Page 11 of the manuscript explains that recovery is defined as 8 consecutive weeks of a PSR of 1-2. Individuals who have 8 consecutive weeks of PSR 1-2 will be considered to have experienced recovery from their major depressive episode. Those who do not will not be considered to have experienced recovery from their major depressive episode. This defines a discrete event for the survival analysis and is the standard approach for this measure. See Keller, M. B. (2003). Past, present, and future directions for defining optimal treatment outcome in depression: Remission and beyond. JAMA, 289(23), 3152-3160.*