

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for the Northern Babies longitudinal study: Predicting postpartum depression and improving parent-infant interaction with The Newborn Behavioral Observation
AUTHORS	Hoifodt, Ragnhild Sorensen; Nordahl, Dag; Pfuhl, Gerit; Landsem, Inger; Thimm, Jens; Ilstad, Linn Kathrin; Wang, Catharina

VERSION 1 - REVIEW

REVIEWER	Karen Hazell Raine The University of Sydney, Australia
REVIEW RETURNED	26-Feb-2017

GENERAL COMMENTS	<p>The protocol abstract outlines that the study will aim to i) explore protective and risk factors for postpartum depression (PPD) and ii) evaluate the effectiveness of the Newborn Behavioural Observation (NBO) delivered as a universal preventive intervention. Recruitment and power calculation should include the anticipated birth rate in the region.</p> <p>The procedure could be better defined through refining study protocol and assessments at different time points during the study (currently "Figure 1") into a table outlining the measures collected in terms of chronology and participants, that is, women/mothers, fathers/partners, parent/s-infants. Crucial measures/timepoints to further define and justify are:</p> <ul style="list-style-type: none"> • The Edinburgh Postnatal Depression Scale (EPDS) and Beck Depression Inventory (BDI) are currently shown to be administered at Time 1, 16 – 22 weeks gestation. The EPDS is shown to be administered at subsequent timepoints (2, 4,5,and6). The EPDS is a screening tool which does not identify cases of depressive illness in mothers or fathers; therefore how will cases of depression be defined/identified each group across time? • Participation in the parent-infant interaction observation measure (Emotional Availability Scale); will it be mothers and/or fathers participating in the observation? <p>The abstract claims that parents/families will be recruited during pregnancy and prevalence of PPD for men is cited in strengths/limitations section, however the study design and procedure does not specify how fathers/partners will be included. The reference (24) provided at line 16, page 4, is used to explain that mothers with symptoms of PPD are less adept to appropriately judge the emotional expression of infant faces, however the finding in the study referred to highlight that judgement of infant faces in the context of maternal mood disturbance is largely dependent on maternal anxiety symptoms.</p> <p>The reference (69) provided at line 29, page 6, is used to suggest that using the Newborn Behavioural Observation (NBO) as a universal intervention prevents maternal depressive symptoms;</p>
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	<p>however the pilot study numbers are not adequate to justify findings of significance. Depressive symptoms are transient across the perinatal period¹. The rationale for selecting the NBO over other potential mother-infant relationship focused interventions to prevent maternal depressive symptoms should be specifically justified. Overall, justification of the study design and methods should further consider justification of the current focus and measures used in terms of the following points:</p> <ul style="list-style-type: none"> • A range of mental health problems are prevalent and prone to recurrence or relapse across pregnancy and the postnatal (perinatal) period; symptoms of depression measured in the perinatal period may be a marker of other mental health problems^{2,3}. • There are a range of parental mental health problems that impact on parent-infant interaction; indeed mental health problems experienced by both mothers and fathers during the antenatal period impact on subsequent parent-infant interaction⁴. • Symptoms of depression measured in early pregnancy are more predictive of subsequent mother-infant interaction than a more proximal measure of depressive symptoms⁵. • The quality of parent-infant interaction, typically referred to as maternal (or primary caregiver) sensitivity is highly predictive of social, educational and relational outcomes for the child through to young adulthood⁶. I encourage the authors to consider the intricate complexity of concepts such as insecure (or disorganised) attachment, reflective function, mentalising and parental sensitivity in the context of emergent research in the field^{7,8,9}. • Parental 'ability to cope' may include consideration of personality characteristics^{10,11}. • Impact of negative self-schemas on the onset of maternal depression¹². <p>1. Matthey S, Ross-Hamid C. Repeat testing on the Edinburgh Depression Scale and the HADS-A in pregnancy: Differentiating between transient and enduring distress. <i>Journal of affective disorders</i> 2012;141(2-3):213-21. doi: 10.1016/j.jad.2012.02.037</p> <p>2. Bauer A, Parsonage M, Knapp M, et al. The costs of perinatal mental health problems. United Kingdom: Centre for Mental Health and London School of Economics, 2014.</p> <p>3. Patton GC, Romaniuk H, Spry E, et al. Prediction of perinatal depression from adolescence and before conception (VIHCS): 20-year prospective cohort study. <i>The Lancet</i> 2015;386(9996):875-83. doi: http://dx.doi.org/10.1016/S0140-6736(14)62248-0</p> <p>4. Parfitt Y, Pike A, Ayers S. The impact of parents' mental health on parent-baby interaction: a prospective study. <i>Infant behavior & development</i> 2013;36(4):599-608. doi: 10.1016/j.infbeh.2013.06.003</p> <p>5. Pearson RM, Melotti R, Heron J, et al. Disruption to the development of maternal responsiveness? The impact of prenatal depression on mother-infant interactions. <i>Infant behavior & development</i> 2012;35(4):613-26. doi: 10.1016/j.infbeh.2012.07.020</p> <p>6. Raby KL, Roisman GI, Fraley RC, et al. The Enduring Predictive Significance of Early Maternal Sensitivity: Social and Academic Competence Through Age 32 Years. <i>Child Development</i> 2015;86(3):695-708. doi: 10.1111/cdev.12325</p> <p>7. Kim P, Strathearn L, Swain JE. The maternal brain and its plasticity in humans. <i>Hormones and behavior</i> 2016;77:113-23. doi: 10.1016/j.yhbeh.2015.08.001</p> <p>8. Swain JE, Lorberbaum JP, Kose S, et al. Brain basis of early parent-infant interactions: psychology, physiology, and in vivo functional neuroimaging studies. <i>Journal of Child Psychology and Psychiatry</i> 2007;48(3-4):262-87. doi: 10.1111/j.1469-</p>
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	<p>7610.2007.01731.x</p> <p>9. Shah PE, Fonagy P, Strathearn L. Is attachment transmitted across generations? The plot thickens. <i>Clinical child psychology and psychiatry</i> 2010;15(3):329-45. doi: 10.1177/1359104510365449</p> <p>10. Belsky J, Crnic K, Woodworth S. Personality and Parenting - Exploring the mediating role of transient mood and daily hassles. <i>Journal of Personality</i> 1995;63(4):905-29. doi: 10.1111/j.1467-6494.1995.tb00320.x</p> <p>11. Prinzie P, Stams GJJM, Dekovic M, et al. The Relations Between Parents' Big Five Personality Factors and Parenting: A Meta-Analytic Review. <i>Journal of Personality and Social Psychology</i> 2009;97(2):351-62. doi: 10.1037/a0015823</p> <p>12. Evans J, Heron J, Lewis G, et al. Negative self-schemas and the onset of depression in women: longitudinal study. <i>British Journal of Psychiatry</i> 2005;186:302-07. doi: 10.1192/bjp.186.4.302</p>
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REVIEWER	<p>j. Kevin Nugent USA Firs tAuthor of the NBO</p>
REVIEW RETURNED	27-Feb-2017

GENERAL COMMENTS	<p>In sum, an excellent study design! The number of NBO interventions (three) and the built-in focus on quality of the relationship between clinician and family is a strong feature of the study design. The inclusion of fathers as a target group is also noteworthy. The Fidelity measure is particularly innovative as it is clearly designed to capture the individualized relationship-based nature of the NBO intervention and goes way beyond a simple dichotomous intervention v. control group comparison. Finally the range of outcomes is comprehensive.</p> <p>I would like to offer two references that could be added. The first has maternal sensitivity as the outcome, although a limitation is that it was measured by self-report and focus was on at-risk infants. The second study does look at the relationship between the NBO and PPD. While it did yield some promising results, the longitudinal study described in this proposal is well designed to shed light on many of the unanswered questions posed by that study.</p> <p>McManus, B., Nugent, J. K. (2012). A Neurobehavioral Intervention Incorporated into a State Early Intervention Program is Associated with Higher Perceived Quality of Care Among Parents of High-Risk Newborns. <i>Journal of Behavioral Health Services & Research</i>, 41, 3, 381-389.</p> <p>Nugent, J.K., Bartlett, J.D., & Valim, C. (2014). The effects of an infant-focused family-centered hospital and home visiting intervention on reducing symptoms of postpartum maternal depression: A pilot study. <i>Infants & Young Children</i>, 27(4), 292-304.</p> <p>The study rationale and the study design are both excellent. The aims are clearly described and the design is appropriate for meeting these aims. The treatment of the relevant depression literature (including the cognitive and transgenerational elements thereof) and its effects on the child and on the parent-child relationship is thorough, up-to-date and carefully reviewed. In terms of the design, even through it is not a randomized controlled trial, the longitudinal prospective nature of the design is well suited to the intervention</p>
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	<p>questions posed and to the “living” clinical context in which the study is being conducted. The power calculations are also excellent and the selected range of outcomes is comprehensive and the measures are well chosen to answer the research questions.</p> <p>There are many noteworthy features to this study. This is the first study to examine the effects of the NBO using a longitudinal design. The serial nature of the NBO intervention treatments (three sessions with the parents) is well positioned to test out the effects of this relationship-based approach. The Fidelity Measure is especially innovative as it is designed to include ratings of parental engagement and as such can capture the individualized nature of the NBO sessions in a way that goes beyond a simple standard intervention v. no intervention design. The rationale for the inclusion of fathers as a target group is also excellent. Finally, the wide range of innovative outcomes is especially impressive – which includes a wide range of outcomes</p>
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REVIEWER	Akanksha Jain St George's University Hospital London United Kingdom
REVIEW RETURNED	15-Apr-2017

GENERAL COMMENTS	<p>I feel the following Limitations. Please clarify:</p> <ol style="list-style-type: none"> 1. Is non-randomized cluster controlled design appropriate for this study? 2. Is it known that early diagnosis of PPD can in turn improve the developmental trajectory for children? 3. What is basis for assuming that NBO may reduce depressive symptomatology in mothers?
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Karen Hazell Raine

Response :Thank you so much for reviewing our paper and providing such useful comments. Thank you also very much for the provided references, we read them with great interest and have incorporated several of them in the manuscript.

- The protocol abstract outlines that the study will aim to i) explore protective and risk factors for postpartum depression (PPD) and ii) evaluate the effectiveness of the Newborn Behavioural Observation (NBO) delivered as a universal preventive intervention.
- Recruitment and power calculation should include the anticipated birth rate in the region

Response: This is included in the text on p. 9.

- The procedure could be better defined through refining study protocol and assessments at different

time points during the study (currently “Figure 1”) into a table outlining the measures collected in terms of chronology and participants, that is, women/mothers, fathers/partners, parent/s-infants.

Response: The figure is changed into a table, see p. 10 – 11.

- Crucial measures/timepoints to further define and justify are: The Edinburgh Postnatal Depression Scale (EPDS) and Beck Depression Inventory (BDI) are currently shown to be administered at Time 1, 16 – 22 weeks gestation. The EPDS is shown to be administered at subsequent timepoints (2, 4,5,and6). - The EPDS is a screening tool which does not identify cases of depressive illness in mothers or fathers; therefore how will cases of depression be defined/identified each group across time?

Response: We would like to thank the reviewer for pointing this out. It is a limitation of the study that we are measuring depressive symptoms and defining depressive cases based on self-report questionnaires and not by diagnosing depression properly with a diagnostic interview. To highlight this in the manuscript a comment is added to the strenght and limitation section on p. 3. In addition, we have included in the manuscript information about cut offs on the EPDS and information about how we will interpret depression severity by using the BDI-II. See p. 14 for both changes.

- Participation in the parent-infant interaction observation measure (Emotional Availability Scale); will it be mothers and/or fathers participating in the observation?

Response: Mothers will be participating in the observation. Changes are made in the text, p. 10 and p. 14.

- The abstract claims that parents/families will be recruited during pregnancy and prevalence of PPD for men is cited in strengths/limitations section, however the study design and procedure does not specify how fathers/partners will be included.

Response: Changes are made in the text on p. 9 to make this clearer.

- The reference (24) provided at line 16, page 4, is used to explain that mothers with symptoms of PPD are less adept to appropriately judge the emotional expression of infant faces, however the finding in the study referred to highlight that judgement of infant faces in the context of maternal mood disturbance is largely dependent on maternal anxiety symptoms.

Response: Changes are made to incorporate anxiety in describing the findings from the study. See p. 4

- The reference (69) provided at line 29, page 6, is used to suggest that using the Newborn Behavioural Observation (NBO) as a universal intervention prevents maternal depressive symptoms; however the pilot study numbers are not adequate to justify findings of significance.

Response: We agree that the results from the pilot study must be seen as preliminary and that the sample size is too small to draw any firm conclusions. Therefore, reporting of the study results is rephrased on p. 7. However, we do find it appropriate to cite this study’s preliminary positive results as part of the basis for choosing to investigate the effect of the NBO on depression in a larger study.

- Depressive symptoms are transient across the perinatal period¹. The rationale for selecting the NBO over other potential mother-infant relationship focused interventions to prevent maternal depressive symptoms should be specifically justified.

Response: The rationale for selecting NBO is that the intervention is brief, low-cost and can easily be integrated into routine postnatal care. In addition, due to its brief structure, the intervention should be feasible for families in the newborn period and can be delivered already around the time of birth. Modifications are made in the text, p. 7.

- Overall, justification of the study design and methods should further consider justification of the current focus and measures used in terms of the following points:

Response: We would like to thank the reviewer for raising these important points. In addition, we would like to thank for interesting references. We agree that these are all important factors. Unfortunately, in order to keep the study feasible, we have had to leave out measures of a variety of factors that may be of importance. This is commented on in the strength and limitation section on p.3. We see that the introduction may benefit from including some more breadth, and therefore, we have incorporated some of the points in the text and believe that this enhances the manuscript. However, at the risk of losing focus from the scope of the present study we cannot include all of these points in the manuscript.

- A range of mental health problems are prevalent and prone to recurrence or relapse across pregnancy and the postnatal (perinatal) period; symptoms of depression measured in the perinatal period may be a marker of other mental health problems^{2,3}.

Response: This is included in a comment in the strength and limitation section on p.3.

- There are a range of parental mental health problems that impact on parent-infant interaction; indeed mental health problems experienced by both mothers and fathers during the antenatal period impact on subsequent parent-infant interaction⁴.

Response: Changes made in text, p. 5. We have also made it clearer in the description of the aims that the focus is on pre- and postnatal predictors for a range of outcomes, see p. 7.

- Symptoms of depression measured in early pregnancy are more predictive of subsequent mother-infant interaction than a more proximal measure of depressive symptoms⁵.

Response: See above.

-The quality of parent-infant interaction, typically referred to as maternal (or primary caregiver) sensitivity is highly predictive of social, educational and relational outcomes for the child through to young adulthood⁶. I encourage the authors to consider the intricate complexity of concepts such as insecure (or disorganised) attachment, reflective function, mentalising and parental sensitivity in the context of emergent research in the field^{7,8,9}.

Response: We agree that the field is complex. However, describing this complexity in great detail is not possible within the scope of the present protocol. Still, we agree that it is important to highlight the complexity of these concepts. Therefore, changes have been made to the text on p. 5 and 6.

- Parental 'ability to cope' may include consideration of personality characteristics^{10,11}.

Response: We agree that personality characteristics may be an important factor in this field. That we do not specifically examine personality characteristics is incorporated as a limitation on p.3. However, we argue that the Young Schema Questionnaire (YSQ) inventory that is included in the study does tap into personality. In fact, the YSQ has shown substantial overlap with the Temperament and

Character Inventory (TCI) measure of personality (Halvorsen, M., Wang, C.E., Richter, J., Myrland, I., Pedersen, S.K., Eisemann, M., & Waterloo, K. (2009). Early maladaptive schemas, temperament and character traits in clinically depressed and previously depressed subjects. *Clinical Psychology and Psychotherapy*, 16, 394 – 407, doi: 10.1002/cpp.618.)

- Impact of negative self-schemas on the onset of maternal depression¹².

Response: Negative self-schemas is included in the introduction as a relevant predictor of maternal depression. There are different measures of negative self-schema. We argue that the current project covers this concept comprehensively by including the YSQ.

Reviewer: 2

J. Kevin Nugent

- In sum, an excellent study design! The number of NBO interventions (three) and the built-in focus on quality of the relationship between clinician and family is a strong feature of the study design. The inclusion of fathers as a target group is also noteworthy. The Fidelity measure is particularly innovative as it is clearly designed to capture the individualized relationship-based nature of the NBO intervention and goes way beyond a simple dichotomous intervention vs. control group comparison. Finally, the range of outcomes is comprehensive.

I would like to offer two references that could be added. The first has maternal sensitivity as the outcome, although a limitation is that it was measured by self-report and focus was on at-risk infants. The second study does look at the relationship between the NBO and PPD. While it did yield some promising results, the longitudinal study described in this proposal is well designed to shed light on many of the unanswered questions posed by that study.

Response: Thank you for the feedback and for suggesting these papers to us! We have read them with great interest and included the references in the manuscript.

Reviewer: 3

Akanksha, Jain

Response: Thank you very much for pointing out these limitations. Find our responses below.

- I feel the following Limitations. Please clarify:

1. Is non-randomized cluster controlled design appropriate for this study?

Response: We agree with the reviewer that the non-randomized design is a limitation of the study, as emphasized in the strengths and limitations section, p. 3. However, we do find that the non-randomized cluster controlled design is appropriate. Conducting studies of interventions delivered in regular practice poses many challenges to methodological rigor. We believe that a cluster-randomized design would have been preferable. However, in the present practice setting randomization of well-baby clinics (or individual clinicians) was not possible, due to administrative issues. Thus, for pragmatic reasons, a non-randomized design was chosen.

- 2. Is it known that early diagnosis if PPD can in turn improve the developmental trajectory for children?

Response: We do not diagnose depression in this study, but try to prevent and reduce depressive symptoms. The importance of reducing depression in the postpartum period is described thoroughly

in the introduction.
 This study should thus shed light on answering this question.

- 3. What is basis for assuming that NBO may reduce depressive symptomatology in mothers?

Response: The basis for assuming that NBO may reduce depressive symptoms, lies in the assumption that PPT can be conceptualized as a mother-infant relationship disorder. Thus, interventions improving parent-infant interactions can potentially improve and prevent maternal PPD.

VERSION 2 – REVIEW

REVIEWER	Karen Hazell Raine The University of Sydney, Australia
REVIEW RETURNED	09-Jun-2017

GENERAL COMMENTS	<p>Thank you for considering previous comments and addressing most matters noted. Minor editing will provide a more professional publication such as correctly noting PTSD (page 3) as Post Traumatic Stress Disorder (PTSD).</p> <p>The new table (pages 10 - 11) depicts time-points for measures, however the text refers to 'steps' To assist the reader please refer to time-points (T) in both the body of text and table.</p> <p>Response is provided to note that the text (p. 10 and p.14) has been updated to show that mothers will participate in the parent-infant observation measure (EAS); and also that father participation is more clearly described in the text on p.9; however it is not clear that fathers will participate in anything other than potentially being available for information and consent process. Furthermore, Table 1. (p. 10 - 11) notes that data collection for women/mothers and men/fathers is the same across all time-points including EAS. Please ensure accurate description of which data/measures are collected for women/mothers and/or men/fathers and align this with time-points in the table, power calculation and proposed statistical analyses.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
 Karen Hazell Raine
 The University of Sydney, Australia
 Please state any competing interests or state 'None declared': None to declare

Please leave your comments for the authors below
 Once again, thank you for reviewing our paper and providing such useful comments.
 Thank you for considering previous comments and addressing most matters noted. Minor editing will provide a more professional publication such as correctly noting PTSD (page 3) as Post Traumatic Stress Disorder (PTSD).

Answer: Changes are made in the text on p. 3.

The new table (pages 10 - 11) depicts time-points for measures, however the text refers to 'steps' To assist the reader please refer to time-points (T) in both the body of text and table.

Answer: Changes are made in the text on p. 9 – 10.

Response is provided to note that the text (p. 10 and p.14) has been updated to show that mothers will participate in the parent-infant observation measure (EAS); and also that father participation is more clearly described in the text on p.9; however it is not clear that fathers will participate in anything other than potentially being available for information and consent process. Furthermore, Table 1. (p. 10 - 11) notes that data collection for women/mothers and men/fathers is the same across all time-points including EAS. Please ensure accurate description of which data/measures are collected for women/mothers and/or men/fathers and align this with time-points in the table, power calculation and proposed statistical analyses.

Answer: Which data/measures that will be collected from both mothers and fathers and only mothers are now clearly shown in Table 1. Changes are also made in the text on p. 7-8 and on p. 15. Sample size is not based on the number of men recruited, as their allocation to the two groups is less predictable than for mothers. To make this clearer changes are made in the text on p. 9.