Author’s response to reviews

Title: Effectiveness of skin-to-skin contact versus care-as-usual in mothers and their full-term infants: Study protocol for a parallel-group randomized controlled trial

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Dr. Nawsheen Boodhun, Executive Editor
BMC Pediatrics
Floor 6, 236 Gray's Inn Road
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United Kingdom
Nijmegen, 19 May 2017

Dear Dr. Boodhun,

We would like to thank for your consideration of our manuscript entitled “Effectiveness of skin-to-skin contact versus care-as-usual in mothers and their full-term infants: Study protocol for a parallel-group randomized controlled trial” (BPED-D-16-00331).

We addressed the editorial feedback and we formatted the manuscript to adhere to the journal guidelines. Also, we carefully considered and addressed the comments of the reviewers. The modifications in the revised manuscript are marked in yellow. On the next pages, we offer detailed responses to the requests and comments.

We are confident that our responses adequately meet the expectations.

Most sincerely,

Kelly Cooijmans, MSc.

(also on behalf of the co-authors)

Comments: Jennifer Doering (Reviewer 1)

Comment 1. In several places, the words 'fullterms' and 'preterms' are used. It is recommended that adding the word 'infant' or 'neonate' to read 'fullterm infant' or 'preterm neonate' would portray a more humanizing view of the infant study participants.

Response 1: We now consequently use “full-term infants” and “preterm infants” throughout the manuscript instead of “fullterms” and “preterms” (see page 2-7).

Comment 2. In a couple of places, the word 'depression' is used when the paper should read 'depressive symptoms' or 'depression symptoms' as is done in other parts of the paper. I would expect the authors are aware that clinical depression requires a diagnostic interview, which is
frequently lacking in research studies. Where screening tools assess depressive symptoms, researchers should refrain from using the term 'depression' to depict a level of symptoms above the screening tool threshold unless there is an accompanying diagnostic interview that validates the presence of a diagnosis. For example, please see page 6, line 2 in addition to other places in the paper. Even researchers themselves have erroneously portrayed their measurement of depression symptoms as 'depression' implying clinical depression (For example, citation 12 does this).

Response 2: The reviewer is right. We now consequently include “depressive symptoms” instead of “depression” in the manuscript when the word “depression” was erroneously used (see page 3, 5, 6, 9, 10, 38, 40).

Comment 3. P6, line 8: Cites study #15 showing lower postpartum depression symptoms - Could the degree to which symptoms were lower be indicated? Was the decrease clinically significant or statistically significant? Including the sample size of this study would also be helpful.

Response 3: The study of Bigelow, Power, Maclellan-Peters, Alex and McDonald (2012) showed that mothers in the skin-to-skin contact (SSC) intervention group (n=30), compared to mothers in the control group (n=60), showed statistically significant lower levels of postpartum depressive symptoms at one week and one month after birth. We now included this information in the manuscript (see page 6, line 6-8).

Comment 4.1 I have a few questions about the research design that are not clear. If space allows and the authors could include the following information, it would strengthen the paper, but if this is not possible, it is information, then, that could be included in the paper publishing the data. Must SSC be done with the mother or could any caregiver provide the 1 hour/day of SSC?

Response 4.1: Mothers will be explicitly asked to provide their infants with at least one continuous and uninterrupted hour of maternal SSC, on a daily basis and for five weeks, starting immediately after birth. Other caregivers are allowed to provide supplementary hours of SSC to the infant which can be registered in the daily physical contact logbook (mother versus other caregivers). We now included this information in the manuscript (see page 16, line 18-21 & page 17, line 14-18).

Comment 4.2 Will the researchers assess whether other family members like fathers, grandparents, etc., be assisting the mother to carry out the study protocol? In other words, how
will you know it's only the mother who is engaging in the SSC, or is this an assumption of the study? This could be important feasibility data.

Response 4.2: See Response 4.1.

Comment 5. How will the study differentiate between SSC and breastfeeding contact? The protocol indicates that SSC is the placement of the infant prone between the breasts, but what is the chance that some women will count time breastfeeding during a SSC episode as SSC contact?

Response 5: We will provide all mothers in the intervention group with detailed written and oral instructions on SSC. Mothers in the SSC intervention group, will explicitly be asked to feed their child before SSC. However, we will not discourage breastfeeding during SSC. It is therefore possible that some infants will receive (some) breastfeeding during a SSC episode, but very unlikely that regular breastfeeding will be used by the mothers as a replacement of the required SSC hour as this would not be adherent with our written and oral instructions. We now added this information in the manuscript (see page 17, line 7-8).

Comment 6. Will the researchers directly ask about any safety events related to spending an hour in SSC? In other words, will the researchers directly ask about whether the mothers fall asleep with the infant prone will delivering SSC? This is a time when infants could be injured if they fall off due to the parent falling asleep. The authors indicate they'll assess for problems with the study protocol, but I would encourage specific questions about any "near-misses" or times when the mother fell asleep unexpectedly. Postpartum fatigue and sleepiness are high in this population of women.

Response 6: During the oral and written instructions, we will explain safety precautions during SSC. We will emphasize the importance of being awake and alert during SSC, and of avoiding drinking hot beverages during SSC to protect the infant. We thank the reviewer for the suggestion of including specific questions about maternal behavior during SSC. We will now personally ask the mother about problems in safety precautions during the second home visit on week five after birth. We added this information in the manuscript (page 17, line 8-12).

Comment 7.1. Does the 1 hour of SSC have to be uninterrupted? Can it be cumulative throughout a 24 hour period to count for the day (30" x 2, 15" x 4)?

Response 7.1: All mothers in the SSC condition will be requested and encouraged to provide their infants with at least one uninterrupted hour of maternal SSC, on a daily basis and for five
weeks, starting immediately after birth. We chose to ask for an uninterrupted, instead of cumulative, hour of SSC, for two reasons:

1) The average duration of the sleep cycle. For healthy full-term infants, the average duration of the sleep cycle is around 47 minutes (Stern, Marmelee, Akiyama, Schultz, & Wenner, 1969). The requested uninterrupted hour decreases the chance that infants need to be disturbed in the middle of a sleep cycle.

2) Shorter SSC episodes potentially decreases the effectiveness of SSC since undressing/dressing can be defined as a mild physical stressor for infants (Jansen, Beijers, Riksen-Walraven, & de Weerth, 2010). Asking mothers for uninterrupted hours of SSC requires to undress and dress their infant only once, instead of multiple times.

This information is now included in the manuscript (page 16, line 21-25 & page 17, line 1-2).

Comment 7.2. Also, the authors suggest that the lengthy SSC protocol that wasn't feasible in the cited study gave the current study rationale for decreasing to 1 hour/day and extending the time period to 5 weeks. Do the authors have any actual feasibility data from women who they discussed 1 hour/day x5 week? I have questions about the feasibility of even this amount of SSC, but perhaps the Netherlands parenting context (e.g., paid leave etc.) makes this amount of SSC over time more feasible.

Response 7.2: We do not have actual feasibility data. In the Netherlands, mothers are entitled to sixteen weeks paid maternity leave. The maternity leave typically starts between four and six weeks before the due date and ten weeks of the leave must be taken after the birth. We are confident that the paid leave makes the amount of SSC over time feasible for most mothers. We now added a statement that includes this information in the manuscript (page 16, line 15-16).

Comment 7.3. I wondered how the authors would handle the analysis if, say, the sample only adheres to the protocol, say, 60% of the time.

Response 7.3: As is stated on page 21, line 20-23, we will conduct intention-to-treat analyses, in which participants are compared according to the group they were randomly assigned to regardless of participants’ compliance or withdrawal from the study. We now explicitly included “SSC protocol adherence” in the manuscript on page 21, line 22, to better clarify the intention-to-treat analyses.

Comment 8.1. How will the authors measure and control for SSC done by mothers in the usual care group? SSC has been increasing in popularity both in hospitals at the time of birth and in
parenting guidelines and articles online and through social media. I didn't see the authors mention that the use of SSC will be assessed in the usual care group, but that could be a confounding variable.

Response 8.1: Mothers in both groups (so in the SSC intervention group as well as in the control group), will fill out the same daily contact logbook. In the daily logbook, all mothers will be asked to register 1) holding, 2) SSC or 3) no contact, for every 15 minutes with the use of simple lines. In the logbook, mothers are able to discriminate between holding and SSC by the mother or other caregivers, for example the father or grandparents. We rewrote the corresponding section to make it more clear that all mothers will register the same information (page 17, line 14-18, & Table 3).

Comment 8.2. Will the authors ensure that both study groups are equal on key variables like baseline depression and anxiety symptoms? As well as breastfeeding vs. bottlefeeding?

Response 8.2: We will use a stratified random block randomization method to ensure a balance between the SSC and the control condition for the primiparae versus multiparae mothers (see also page 15, line 18-20). Randomization assures that each participant has an equal chance of being allocated to both conditions. Besides the allocation, this randomization method also ensures comparable groups by avoiding confounding from known and unknown factors (Suresh, 2011). In sum, using this randomization method ensures that the groups will be comparable on key variables. We now explicitly included this information in the manuscript on page 15, line 20-21, to better clarify the randomization method. Before proceeding with analysing the data, we will check the two groups’ scores on key variables including depression and anxiety symptoms.

Comment 9. Will the authors collect data on sleep location? I ask, because bed-sharing could inadvertently introduce increased doses of skin contact above and beyond the 1 hour/day, which also could influence results.

Response 9: We agree with the reviewer, and we indeed collect data on sleep location. For the first twelve weeks, mothers will register the primary nightly sleep location of the infant for the previous week. We now added this information to Table 3.

Comment 10. P. 9 line 4: Instead of saying "through different pathways", I suggest further specificity by saying "through direct and indirect pathways".

Response 10: We now better specify the pathways in the manuscript (page 9, line 4) according to the reviewer’s suggestion.
Comment 11. P. 9 provides 3 hypotheses for how SSC may affect health outcomes. As I read, I wondered about one pathway and I share it here for the authors to consider. What about SSC having the effect of increasing breastfeeding (there's good evidence SSC increases breastfeeding initiation, exclusivity, and duration - and I hope all these variables are being collected in the study), and that breastfeeding provides both optimal nutrition to the infant, but also the transfer of bacteria from the infant's oral contact with the breast and hand contact with the breast during breastfeeding, with the infant subsequently sucking on the hand that had extended contact with the mother's skin during breastfeeding. I would think even culturing infant's hands for their bacterial flora would be worth pursuing.

Response 11: This is an interesting idea of a potential pathway and overlaps with our first suggested pathway (i.e. direct pathway that SSC could provide extra opportunities to exchange bacteria from the mother’s skin to the infant, see page 9, line 4-8). For a next study, it would indeed be interesting to investigate culturing infant’s hands for their bacterial flora and we thank the reviewer for this suggestion.

Comments: Ann E. Bigelow (Reviewer 2)

Comment 1. The demographics do not include maternal age or education. Both of these maternal variables have been shown to be correlates with maternal depression in previous studies, so they ideally should be added to the demographics collected. As the study has just started and enrolled mothers have not yet completed the protocol, these demographics could easily be added.

Response 1: We will collect the maternal age and maternal educational level, and have now included these variables in the manuscript (Table 3).

Comment 2. On Page 4, the authors imply that SSC and Kangaroo Mother Care (KMC) are the same, but they are not. SSC is a component of KMC, which also includes breastfeeding. The researchers plan to measure breastfeeding frequency and duration but it does not appear that breastfeeding is a necessary choice for inclusion in the study. If breastfeeding is a condition for inclusion, this should be made clear.

Response 2: The reviewer is right: KMC indeed includes SSC and breastfeeding, as well as maternal support. We are not planning to use breastfeeding and maternal support as inclusion criteria. We deleted the implication that SSC and KMC are the same in the manuscript (page 4, line 5).
Comment 3. Is the Experiences in Close Relationships (ECR) questionnaire assessing the mother's attachment to her partner, her own parents, or someone else?

Response 3: The Experience in Close Relationships (ECR) questionnaire examines the mother’s attachment to her current and previous partners. We now explicitly added this information in the manuscript (Table 3).

Comment 4. How will the cultural conceptions of parenting be used in the data analyses?

Response 4: The cultural conception of parenting will be used to examine and understand why participants are (not) able to adhere to the SSC protocol. We adapted the lay-out of Table 3 to better clarify the difference between eligibility criteria, demographics, physical contact information and variables that will be collected to gain insight into our SSC protocol feasibility and protocol adherence.

Comment 5. What will constitute cortisol synchrony between mother and infant during the infant bathing in week 5?

Response 5: Cortisol synchrony between mother and the infant during the bathing session in week 5 consists of the within mother-infant dyad cortisol associations (i.e. mother cortisol predicting infant cortisol, infant cortisol predicting mother cortisol).

With the use of multilevel models we will be able to examine cortisol synchrony between the mother and her infant. Cortisol synchrony will be examined for every saliva sample (pre-stress, peak-stress, recovery), for total stress cortisol concentrations (Area Under the Curve (AUC), and cortisol recovery (Recovery – Pre-stress). We have now clarified this in the manuscript (Table 1).

Comment 6. Is synchrony the only cortisol outcome assessed?

Response 6: Cortisol synchrony is the only salivary cortisol outcome for the mother. Physiological stress for the mother will be measured with hair cortisol samples. This information is included in Table 1. For the infant, physiological stress (cortisol reactivity and recovery) will be measured with the saliva samples of the infant during the bathing session. This information is included in Table 2.
Comment 7. The SSC log asks the mothers to log SSC or holding the infant. These are not the same; holding the infant may or may not be in SSC. Will the log of SSC be separate from the log of simply holding the infant? This would be important if the research is to track the effects of SSC per se.

Response 7: In the daily physical contact logbook, all mothers will be asked to register 1) holding, 2) SSC or 3) no contact, for every 15 minutes with the use of simple lines. In the logbook, mothers are able to discriminate between holding and SSC by the mother or other caregivers, for example the father or grandparents. We rewrote the corresponding section to make it more clear that all mothers will register the same information (page 17, line 14-18, & Table 3).

Comment 8. With the exception of a measure of maternal sensitivity during infant bathing in week 5, all of the data collected will be through questionnaires, logbooks, or physiological assessments. Although it may be too late to add more measures, it would be beneficial to have more behavioral assessments, e.g., attachment security at one year via the Strange Situation.

Response 8: We agree that more behavioral assessments would be beneficial for the study. Unfortunately, due to time and financial constraints we are unable to include additional behavioral assessments. For new follow-up assessments at older ages we will look for funding opportunities to include more behavioral measures.

Two Cautions:

1. The maternal oxytocin measure is from saliva. Although some reputable researchers have used measures of oxytocin from saliva, the measure has been criticized as unreliable (e.g., see Horvat-Gordon et al., 2005, Physiology & Behavior 84, 445-448; McCullough et al., 2013, Neuroscience and Biobehavioral Reviews, 37, 1485-1492). Salimetrics, a noted lab that supports salivary research studies in North America, does not currently have a reliable detection method for oxytocin in saliva.

Response 1.: We are aware that oxytocin measurements from saliva are not reliable (yet). During the designing phase of the study we read the literature, talked to our own lab, and also contacted Salimetrics about this problem. They are currently developing an assay that should make it possible to do oxytocin measures in saliva in the near future. While we wait for reliable analyses to be developed, we will keep the samples at -20 C.
2. If SSC is shown to reduce maternal depression in this low-risk sample, the researchers note that developing a program to use SSC as a preventative measure with high-risk mothers may be considered. Caution should be used here, as some mothers with histories of sexual abuse may find SSC with their infants to be a trigger. SSC may be of benefit to many high-risk mothers but they should be screened and monitored so that the intervention does not make their condition worse.

Response 2.: We are aware that caution should be used for using SSC in high-risk samples. We modified this statement in the manuscript (page 23, line 11-13).