Author’s response to reviews

Title: Effectiveness of Interventions during NICU Hospitalization on the Neurodevelopment of Preterm Infants: A Systematic Review Protocol

Authors:

Marilyn Aita (marilyn.aita@umontreal.ca)

Robyn Stremler (robyn.stremler@utoronto.ca)

Nancy Feeley (nancy.feeley@mcgill.ca)

Andréane Lavallée (andreane.lavallee@umontreal.ca)

Gwenaëlle De Clifford-Faugère (gwenaelle.de.clifford@umontreal.ca)

Version: 1 Date: 25 Aug 2017

Author’s response to reviews:

Please note that a file with answers to comments of reviewers was attached as a file.

Reviewer reports:

We would like to thank the reviewers for their time to review our manuscript and for their judicious comments.

Reviewer #1: Overall, this is a well written protocol and I enjoyed reading the manuscript.

However, I some concerns that I think the authors need to address in order to progress the protocol to publication:

1. Background: Could the authors reflect specifically on how they know that there are no existing or ongoing reviews in this topic area - have they performed scoping searches?

Scoping searches were performed through 3 main databases where systematic reviews are generally published: the Prospero database (publishing protocols), the Cochrane Neonatal Database as well as the NICE Evidence search. As highlighted in the manuscript in the background section, some systematic reviews were found in these databases where preterm infants’ neurodevelopment was measured but only after infants’ discharge from the NICU. Those systematic reviews are cited end referenced in the background section (see lines 21-24, 28).
2. Methods: Whilst I agree with inclusion/exclusion decisions, it would be helpful if the authors could include their rationale for these decisions, for example:

* Exclusion of certain study designs, such as case control and quasi-experimental with no randomisation procedure.

Only RCT are intended to be considered in this systematic review as this research design is the most suited one to properly answer the research question of this systematic review. Moreover, we decided to only include RCTs as this type of research design provides the highest evidence. Accordingly, strongest inferences can be concluded from systematic reviews which include RCTs with reliable findings (Charrois, 2015). The latest precision was added in the manuscript in the section of study designs (see lines 60-62).

* Only including studies 2001-2016

Neonatal care is evolving rapidly where the recent trend is that NICU are moving from open ward to single room or rooms of pods of 3 or 6. Accordingly, parents are more involved in care. Therefore, a limit of the 15 past years was applied in our review so that interventions retrieved would be appropriate for current NICUs. Although, we have changed our search from 2002 to 2017 to include studies with interventions published this year (see line 64).

* Exclusion of infants with major brain abnormalities

These infants are excluded from the review as their neurodevelopment might be influenced by their major brain abnormality. Also, interventions with these infants might have different components considering their healthcare situation and these interventions may not be generalizable to other preterm infants. For these reasons, infants with brain abnormalities were excluded as participants. Although, infants with brain abnormalities could serve as a specific population in another systematic review aiming at identifying interventions promoting neurodevelopment of these infants.

3. 3. Methods: Could the authors provide some firm examples of outcomes of interest that they’d expect to see? Are there any secondary outcomes of interest?

See answer to comment #6.
4. Methods: Will MESH/thesaurus terms be used as well as key words?

MESH/thesaurus terms which will be used for the search strategies of the different databases are shown in the search strategy for MEDLINE now included as an additional file (see answer to comment #5). In the manuscript it was stated that the search strategy was done with MESH/Thesaurus terms (line 101) and that an additional file is showing an example of the search strategy in MEDLINE (lines 103-104).

5. Methods: Could the authors include a provisional search strategy for one database, such as MEDLINE? This would be helpful to see.

An example of the search strategy for MEDLINE is now included in the manuscript as an additional file.

6. Outcomes: there is repetition relating to this hence my question about whether there are any secondary outcomes. I see later in the paper that these are outlined. Could the authors consider outlining outcomes (primary then secondary) only once? As per my earlier query, it would be good to see concrete examples of expected variables.

Primary outcome is now only outlined under the section of the inclusion and exclusion criteria of studies. Examples of this outcome are given in terms of potential standardized instruments, scales or tests which could have been used to assess neurodevelopment NICU during hospitalization: Assessment of Preterm Infants Behaviors (Als et al., 1995), NICU Network Neurobehavioral Scale (Lester & Tronick, 2004), General Assessment Movement (GMA) (Einspieler & Prechtl, 2005) and electroencephalography (EEG) (lines 94-97).

For secondary outcomes – see answers to comments about Primary outcome and Outcomes of reviewer 2.

We also have considered adding in the extraction data form the definition of neurodevelopment provided in the studies as well as the instruments, scales or tests use to measure this variable (lines 137-138).

7. Discussion: can the authors reflect on wider use of findings of this review? Reflecting that they will be published in a scientific journal to add to body of knowledge does not seem substantial enough. In terms of policy and practice (and implementation of interventions in NICU), what does the review provide?
Discussion was revised with wider considerations about how the findings of this systematic review may guide the clinical practice as well as research (lines 175-180).

Reviewer #2: Background: The background is comprehensive and clearly explains why the review is being undertaken.

Thank you.

Methods - PRISMA checklist:

#5c of the PRISMA checklist - you have 'reported roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol'. This information is provided under declarations. Please add in the appropriate page numbers. The appropriate pages numbers were included in the prima checklist.

The line numbers related to the funding were added in the Prisma checklist (lines p. 198-199). Please note that since the initial submission of this protocol to BMC Systematic Review, funding was obtained from the Quebec Network on Nursing Intervention Research (RRISIQ) and is now stated as the funder for this systematic review (rather than the starting research funds of MA at the Research center of the CHU Sainte-Justine).

#10 - Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated - It is standard for systematic reviews to have this. Can you please add a draft search strategy?

A search strategy for MEDLINE is now included as an additional file in the manuscript.

Study design: Can you please clarify whether the cluster trials need to be randomised, I assuming it should be cluster RCTs. Also how will you be including cross-over trials? What is a sufficient wash-out period for these types of trials to be acceptable? It is unusual to include this type of trial in a SR.

In the study design section, cluster trials were changed to cluster RCTs and cross-over trials will not be considered in this review (see lines 50-51).
Also what are you considering to be a quasi-RCT - please provide what you won't be accepting for example will you be accepting allocation by alternative births? This is a randomisation process just not a 'true' one.

Examples of the randomization process which will not be accepted was provided in the research designs: assigning alternatively participants, first half of participants to one group or first NICU receiving the intervention compared to a second one not receiving the intervention or assignment of participants by characteristic such as date of birth (see lines 56-58). Those will not be considered as they are not random assignment or reliably random. Therefore, RCTs using this type of randomization process may be attributed a high or unclear risk of bias for sequence generation on the Cochrane risk of bias assessment tool.

Why are you taking studies in the last 15 years? Also why won't studies to the most current date be accepted e.g. 2001-2017? Please justify this choice of dates and time frames.

See answer to the comment #2 (2nd asterisk) of reviewer #1.

Participants: You mention parents as participants and including data on them in the review, however, there is no mention of parent outcomes in the outcomes section. Please clarify or add relevant outcomes to the appropriate section.

The main objective of this systematic review is to evaluate the efficacy of interventions for promoting infants’ neurodevelopment. Thus, to improve clarity, the sentence about including studies reporting findings for both infants and parents was removed from the manuscript and infants are now only described in the participants section (lines 65-68).

Interventions - Will you be including multi-faceted interventions? I.e. more than just one aspect such as sensory stimulation. If so how will these be dealt with in the meta-analysis?

We added a sentence in the interventions section (lines 72-75) that multi-faceted interventions will be excluded from this review as it will be hard to estimate which component was more efficacious in promoting infants’ neurodevelopment and will preclude meta-analysis if applicable.

Primary outcomes: I'm not sure what you mean by this sentence (below Line 100-102): Studies where infants' neurodevelopment was evaluated following discharge and before 24 months of corrected age will be considered only if this outcome was also measured during hospitalization.
If the outcome needs to be during the hospitalisation then why the clarification of after discharge? If you don't include all studies for that intervention that have neurodevelopment assessment after discharge you can't do any statistical analysis with them as the outcome is biased by not including all relevant studies within the literature. This same comment is relevant for secondary outcomes. If you only include those studies that have had neurodevelopment assessed then it will be biased for physiological stability and sleep because you have missed out on other studies that have done this. How will you deal with this?

Good point. The specification about including studies which will have measured neurodevelopment after discharge was deleted in the manuscript as we are interested only in those which have assessed this outcome during preterm infants NICU hospitalization. For the same reason, physiological stability and sleep were deleted as secondary outcomes to focus only on neurodevelopment.

Outcomes: Can you please provide some standardised test examples for all of the outcomes. This will help to clarify neurodevelopment.

See answer to comment #6 of reviewer 1.

It is not clear what 'short-term' actually is. If an infant is born at 24 weeks, has an intervention and is assessed at 36 weeks compared to an infant born at 30 weeks and assessed at 36 weeks is this still short-term? Even though there is double the amount of time. In addition how will you take into account these time differences in your meta-analysis, particularly as preterm infants can have quite long hospital stays. Some clarification about 'short-term' and groupings for time points of assessment would be helpful.

Short-term was related to during NICU hospitalization, so as it is stated in the objective that our systematic review concentrates on neurodevelopment during NICU hospitalization, the term short-term was removed to avoid confusion.

The comment about the time differences in hospitalization is an important one – to deal with this issue, we have included the length of hospitalization in the NICU as a subgroup analysis if meta-analysis is possible (see line 160).

Data synthesis: Line 129 'too significant' please clarify what is this is?
The data synthesis was rephrased in the manuscript (lines 161-165). It is now indicated that if the studies’ heterogeneity is considerable, i.e. Chi2, p >0.1 and I2 ≥ 50%, the data synthesis will only be narrative. So, “too significant” was replaced by considerable which is now related to statistical significance.

Search Strategy: Is there a reason you are searching both MEDLINE and Pubmed? One or the other is normally sufficient. Cochrane tends to go with MEDLINE using the OVID platform.

Librarians have recommended to include both PubMed as well as Medline databases to be searched in our systematic review to have a more complete search of studies. PubMed includes MEDLINE but there are also non-MEDLINE citations from journals selectively indexed in this database. However, searches in MEDLINE can be more specific than PubMed as it uses the NLM controlled vocabulary, Medical Subject Headings (MeSH) to index citations – and is an added value to the Pubmed (see: https://www.nlm.nih.gov/pubs/factsheets/dif_med_pub.html). Thus, including both these databases in the systematic review will ensure an optimal search of studies.

Minor comments:

Line 47: which are described according to the study design (including publication language and year) - Please add a comma between publication and language.

A comma was added between publication and language (line 48 of the revised manuscript).

Line 76: Endnote is spelt incorrectly

EndNote is now spell appropriately.

Please reference the Egger test and the Mantel-Haenszel method.

The original references of the Egger test and the Mantel-Haenszel were added in the manuscript, see references 24 and 25.