PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Delivery Room Interventions to Prevent Bronchopulmonary Dysplasia in Preterm Infants: A Protocol for a Systematic Review and Network Meta-Analysis
AUTHORS	Mitra, Souvik; Disher, Timothy; Pichler, Gerhard; D'Souza, Brandon; Mccord, Helen; Chayapathi, Varsha; Jones, Karlee; Schm&#65533;lzer, Georg

VERSION 1 - REVIEW

REVIEWER	Elizabeth Foglia Children's Hospital of Philadelphia, USA
REVIEW RETURNED	16-Dec-2018

GENERAL COMMENTS	This is a detailed protocol for a network meta-analysis of delivery room interventions to prevent BPD among preterm infants <33 weeks gestation. The protocol provides the necessary details for the proposed methodology. While I appreciate the decision to dissociate "delivery room" interventions from the physical location of the delivery room, I suggest the authors clarify what is meant by interventions that are carried out during "the initial stabilization period." In the PROSPERO registry, the authors specify that infants must be randomized to (but not necessarily receive?) the intervention within the first hour after birth More clarity around eligibility criteria for the timing of the interventions themselves would be helpful.

REVIEWER	Chrstian Poets Tübingen University Hospital
REVIEW RETURNED	18-Dec-2018

GENERAL COMMENTS	The authors report their protocol for a Systematic Review and Network Meta-Analysis that should help clinicians to decide in which sequence they should employ various interventions to protect an infant’s lung. This is a rather elaborate and high-quality proposal. However, while I am not an expert in study methodology, a few clinical issues come to my mind which need addressing:

	- Why do they choose rather broad entry criteria regarding gestational age? In my view, including only infants <28 wk seems more appropriate. - What about interventions not mentioned in their manuscript, e.g. mode of ventilation (volume- vs. pressure-controlled), early clarithromycin/azithromycin for ureaplasma eradication or early breast milk/early bonding for BPD prevention? - The issue about other interventions may be explained by defining a more limited time span for these interventions (e.g., 1st postnatal hour), but as currently presented, the authors wish to include “the golden hours after birth“, which is ill-defined and may include several hours

REVIEWER	haolun shi University of Hong Kong
REVIEW RETURNED	23-Feb-2019

GENERAL COMMENTS	Report on “Delivery Room Interventions to Prevent Bronchopulmonary Dysplasia in Preterm Infants: A Protocol for a Systematic Review and Network Meta-Analysis ” The paper is a study protocol on a network meta-analysis to compare multiple delivery room interventions for prevention of BPD. Overall, I found the paper well-written and clear-motivated, with every aspects described comprehensively. I found no issues in the statistical methodology. Some points of minor revisions are recommended as follows. The authors may consider improving the paper with respect to the following aspects. 1. The protocol use component models as described by Welton et al., whichassume that “interventions across domains of the stabilization pathway are additive on the linear predictor scale (e.g. additive on logit scale for dichotomous outcomes)”. I found the “linear predictor scale” very confusing, and it would be better to simply write “additive on logit scale for dichotomous outcomes” while indicating briefly what the dichotomous outcome is. 2. It would be better if the author can discuss in more details the prior usedfor the Bayesian random effect model in treatment comparison. 3. Page 16, line 17. Please indicate the reference for Dias et al. 4. I am interested to see how the author conduct the sensitivity analysisusing the empirically estimated informative prior distribution described by Turner et al. It would be better if the author can supply more details.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a detailed protocol for a network meta-analysis of delivery room interventions to prevent BPD among preterm infants <33 weeks’ gestation. The protocol provides the necessary details for the proposed methodology.

Response: Thank you

While I appreciate the decision to dissociate "delivery room" interventions from the physical location of the delivery room, I suggest the authors clarify what is meant by interventions that are carried out during "the initial stabilization period."

Response: This has been clarified

In the PROSPERO registry, the authors specify that infants must be randomized to (but not necessarily receive?) the intervention within the first hour after birth

Response: This is correct, our intention is to include only studies were infants are randomized within the 1st hour after birth. However, we wanted to be sure we do not miss any study and therefore we use the first 4 hours windows for study inclusion. However, the final study selection will be limited to the first hour.

More clarity around eligibility criteria for the timing of the interventions themselves would be helpful.

Response: Thank you, we hoped that we clarified this.

Reviewer: 2

The authors report their protocol for a Systematic Review and Network Meta-Analysis that should help clinicians to decide in which sequence they should employ various interventions to protect an infant's lung. This is a rather elaborate and high-quality proposal. However, while I am not an expert in study methodology, a few clinical issues come to my mind which need addressing:

- Why do they choose rather broad entry criteria regarding gestational age? In my view, including only infants <28 weeks seems more appropriate.

Response: Thank you, we have chosen <33 weeks as many studies might not have limited their gestational age to <28 weeks' gestation. We hope to perform subgroup analysis of <28 weeks versus 29-32 weeks to address this issue.

- What about interventions not mentioned in their manuscript, e.g. mode of ventilation (volume- vs. pressure-controlled), early clarithromycin/azithromycin for ureaplasma eradication or early breast milk/early bonding for BPD prevention?

Response: We agree with the reviewer, that all the above interventions are very important and have a potential influence on BPD. We will include volume- vs. pressure-controlled by including studies with respiratory function monitoring in the delivery room. As we aim to include only studies within the first hour after birth, and therefore believe that early clarithromycin/azithromycin for ureaplasma eradication or early breast milk might not be an option for this review.

- The issue about other interventions may be explained by defining a more limited time span for these interventions (e.g., 1st postnatal hour), but as currently presented, the authors wish to include "the golden hours after birth", which is ill-defined and may include several hours

Response: Thank you, we have clarified this in the method section. It now states “within the 1st golden hours after birth”.

Reviewer: 3

Report on “Delivery Room Interventions to Prevent Bronchopulmonary Dysplasia in Preterm Infants: A Protocol for a Systematic Review and Network Meta-Analysis”

The paper is a study protocol on a network meta-analysis to compare multiple delivery room interventions for prevention of BPD. Overall, I found the paper well-written and clear-motivated, with every aspect described comprehensively. I found no issues in the statistical methodology.

Response: Thank you

Some points of minor revisions are recommended as follows.

The authors may consider improving the paper with respect to the following aspects.

1. The protocol use component models as described by Welton et al., which assume that “interventions across domains of the stabilization pathway are additive on the linear predictor scale (e.g. additive on logit scale for dichotomous outcomes)”. I found the “linear predictor scale” very confusing, and it would be better to simply write “additive on logit scale for dichotomous outcomes” while indicating briefly what the dichotomous outcome is.

Response: This section has now been modified to read:

“These models assume that interventions across domains of the stabilization pathway are additive on additive on logit scale for dichotomous outcomes (e.g. mortality).”

2. It would be better if the author can discuss in more details the prior used for the Bayesian random effect model in treatment comparison.

Response: The discussion of priors has been modified to read:

“We will fit a Bayesian hierarchical model with weakly informative priors (i.e. normal with mean zero and standard deviation 5 for outcomes on the logit scale) adjusting for correlation of multi-arm trials, and assuming a common-within network heterogeneity variance (uniform on 0-2). “

3. Page 16, line 17. Please indicate the reference for Dias et al.

Response: This has now been inserted - Dias, S., Sutton, A. J., Welton, N. J., & Ades, A. E. (2012). NICE technical support document 3: Heterogeneity: Subgroups, meta-regression, bias, and bias-adjustment. Retrieved from http://www.nicedsu.org.uk

4. I am interested to see how the author conduct the sensitivity analysis using the empirically estimated informative prior distribution described by Turner et al. It would be better if the author can supply more details.

Response: The informative priors estimated by Turnet et al are primarily of use when estimates of between trial heterogeneity are dominated by the usual vague prior. This results in unfeasible credible intervals for odds ratios (e.g. approaching infinity). We have clarified their use as follows:

If the posterior estimate of between-study variance shows signs of prior dominance (e.g. extreme values and long tails, odds ratios approaching infinity), we will assess whether using the empirically estimated informative prior distribution described by Turner et al(43) provides more sensible estimates. If the network structure is such that estimates of credible intervals are sufficiently different from original trial estimates and lack clinical validity, we will also present results from a fixed effect model. In this case, we will caution against overinterpretation of credible intervals.

VERSION 2 – REVIEW

REVIEWER	haolun shi University of Hong Kong
REVIEW RETURNED	25-Mar-2019

GENERAL COMMENTS	I recommend acceptance.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Reviewer Name: haolun shi

Institution and Country: University of Hong Kong

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

I recommend acceptance.

Response: Thank you