BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028066
Article Type:	Protocol
Date Submitted by the Author:	21-Nov-2018
Complete List of Authors:	Mitra, Souvik; Dalhousie University, IWK Health Center, Department of Pediatrics Disher, Timothy; School of Nursing, Dalhousie University Pichler, Gerhard; Medical University of Graz, Research Unit for Neonatal Micro- and Macrocirculation, Department of Pediatrics D'Souza, Brandon; IWK Health Centre, Department of Respiratory Therapy Mccord, Helen; Dalhousie University, IWK Health Center, Department of Pediatrics Chayapathi, Varsha; Dalhousie University, IWK Health Center, Department of Pediatrics Jones, Karlee; Dalhousie University, IWK Health Center, Department of Pediatrics Schm&#65533;lzer, Georg; Royal Alexandra Hospital, Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, ; University of Alberta, Department of Pediatrics
Keywords:	Infants, Bronchopulmonary dysplasia, Delivery Room, Newborn

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

Souvik Mitra MD MSc[1], Tim Disher PhD(c), RN[2], Gerhard Pichler MD[3], Brandon D'Souza BHSc, RRT[6], Helen Mccord MN[1], Varsha Chayapathi MBBS, DNB[1], Karlee Jones BScPharm, ACPR[1], Georg M. Schmölzer MD, PhD[4,5]

[1]Department of Pediatrics, Dalhousie University, IWK Health Center, Halifax, Canada

[2]School of Nursing, Dalhousie University, Halifax Nova Scotia, Canada

[3]Research Unit for Neonatal Micro- and Macrocirculation, Department of Pediatrics, Medical University of Graz, Austria

[4]Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, Royal Alexandra Hospital, Edmonton, Alberta, Canada

[5]Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

[6]Department of Respiratory Therapy, IWK Health Centre, Halifax, Nova Scotia, Canada

Corresponding author:

Georg M. Schmölzer, MD, PhD

Centre for the Studies of Asphyxia and Resuscitation,

Neonatal Research Unit, Royal Alexandra Hospital,

10240 Kingsway Avenue NW,

T5H 3V9, Edmonton, Alberta, Canada

Telephone +1 780 735 4660

Fax: +1 780 735 4072

Email: georg.schmoelzer@me.com

Conflict of Interest:

SM, GP, VC, have declared no conflict of interest. TD provides methodological advice for Cornerstone Research Group Inc. Cornerstone Research Group Inc. consults for various pharmaceutical and medical device companies. BD has provided device training and educational presentations to clinicians on behalf of Mallinckrodt Pharmaceuticals. GMS has registered the RETAIN neonatal resuscitation board (Tech ID 2017083) and RETAIN neonatal resuscitation video game (Tech ID 2017086) under Canadian copyright, and GMS is the owner of RETAIN Labs Inc. (https://www.playretain.com), which is distributing these games.

Keywords: INFANTS, NEWBORN, DELIVERY ROOM, BRONCHOPULMONARY DYSPLASIA

Funding sources

We would like to thank the public for donating money to our funding agencies: GMS is a recipient of the Heart and Stroke Foundation/University of Alberta Professorship of Neonatal Resuscitation, a National New Investigator of the Heart and Stroke Foundation Canada and an Alberta New Investigator of the Heart and Stroke Foundation Alberta. This research has been facilitated by the Women and Children's Health Research Institute through the generous support of the Stollery Children's Hospital Foundation.

Abstract: 250 words

Manuscript: 3,963 words

Tables: 1

Figures: 1

Author's contribution:

Conception and design: GMS, SM

Data analysis plan: GMS, SM, GP, TD, BDS, HM, VC, KJ

Drafting of the article: GMS, SM, GP, TD, BDS, HM, VC, KJ

Critical revision of the article for important intellectual content: GMS, SM, GP, TD, BDS, HM, VC, KJ

Final approval of the article: GMS, SM, GP, TD, BDS, HM, VC, KJ

Abbreviations:

BPD	- Bronchopulmonary dysplasia
ELGAN	- Extremely low gestational age newborns
IQ	- Intelligence quotient
CPAP	- Continuous positive airway pressure
NMA	- Network meta-analysis
RE	- Random-effects model
RCT	- Randomized controlled trials
INSURE	- Intubate-Surfactant-Extubate technique
LISA/MIST	- Less-invasive surfactant administration/minimally invasive surfactant therapy
ROB	- Risk of bias
CrIs	- Credible intervals
RR	- Risk ratio
SUCRA	- Surface Under the Cumulative Ranking curve
FE	- Fixed-effect model
FOL	- First-order loops
SMAA	- Stochastic multicriteria acceptability analysis

Abstract

Introduction

As gestational age decreases, incidence of bronchopulmonary dysplasia (BPD) and chronic lung disease increases. There are many interventions used in the delivery room to prevent acute lung injury and consequently BPD in these patients. The availability of different treatment options often poses a practical challenge to the practicing neonatologist when it comes to making an evidence based choice as the multitude of pairwise systematic reviews including Cochrane reviews that are currently available only provide a narrow perspective through head-to-head comparisons.

Methods and Analysis

To overcome this challenge, this review will use Bayesian network meta-analysis approach which allows the comparison of the multiple delivery room interventions for prevention of BPD. This systematic review will summarize the available evidence from randomized clinical trials using a Bayesian network meta-analysis to determine the effectiveness and safety of delivery room interventions for prevention of BPD.

Ethics and Dissemination

The proposed protocol is a network meta-analysis, which has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). We hope that this review will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants.

Strengths and limitations of this study

Strengths:

- Comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work
- Use the novel method for rating the confidence in the estimates recommended by the GRADE working group
- We will employ a novel Stochastic multicriteria acceptability analysis model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes

Limitations:

- We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions
- Potential to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results

Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory morbidity associated with premature birth. BPD is defined as either need of supplemental oxygen at i) 28 days postnatal age(1), or ii) 36 weeks' postmenstrual age with or without compatible clinical and radiographic findings(2). BPD affects 30-60% of prematurely born infants with the incidence being inversely proportional to gestational age(3). With increased survival of extremely low gestational age newborns (ELGAN), the incidence of BPD continues to increase despite improvement in neonatal care practices over the last two decades(3). BPD is known to be associated with long-term respiratory morbidity that persists into adolescence and adulthood(4,5). There is also increasing evidence that BPD and duration on supplemental oxygen have long-term adverse effects on cognitive and academic achievement with each percent increase in BPD rate being associated with a 0.01 standard deviation decrease in intelligence quotient (IQ) (0.15 IQ points) ($p<0.001$)(6,7).

Several antenatal, perinatal, and postnatal factors contribute to the development of BPD. It is postulated that early lung injury and inflammation play an important role in the pathogenesis of BPD (8,9). In the fetus, the gas exchange organ is the placenta and the function of gas exchange is transferred from the placenta to the lungs immediately after birth. Therefore, the newborn infant's lungs must open and be aerated to allow the transition from fetal to postnatal circulation and physiology. However, in ELGANs, several physiological factors prevent this transition. These include lack of surfactant leading to increased alveolar surface tension, non-compliant chest wall, and weak respiratory muscles(10-12). Therefore, most ELGANs require assisted ventilation and/or supplemental oxygen after birth to ensure optimal gas exchange. However, both therapies may also induce lung inflammation due to barotrauma and/or volutrauma and oxygen-free radical generation thereby initiating the pathogenesis of BPD. Therefore, any interventions targeted at limiting lung injury and oxidative stress during resuscitation in the delivery room immediately after the birth may help to prevent the development of BPD or reduce its severity.

A number of clinical trials have been conducted on a variety of delivery room interventions, including i) interventions prior to initiating breathing support (i.e., clamping vs. milking the umbilical cord); ii) interventions around initial breathing support (i.e., continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation, sustained lung inflation or endotracheal intubation); iii) interventions related to improving lung compliance (i.e., prophylactic

surfactant therapy including the different variations in its administration modalities); iv) interventions related to minimizing oxidative stress (i.e., higher vs. lower oxygen saturation targets), v) use of cerebral oximetry, and vi) other potentially beneficial therapies such as caffeine administration (Figure 1)(13,14).

The availability of multiple potential interventions in a resuscitation scenario often poses a practical challenge to health care professionals as to which sequence of interventions would provide the greatest likelihood of minimizing BPD and which interventions are unnecessary and unlikely to be of any benefit(13). There have been previous systematic reviews and pairwise meta-analyses on the different competing interventions such as initial breathing support and oxygen saturation targets(15-17). However, these meta-analyses, though well conducted, provide a narrow perspective to the situation where a sequence of non-competing interventions occur within a short time-frame whereas each intervention has potentially competing variations. Use of a network meta-analysis (NMA) framework may help to provide a more feasible, comprehensive and evidence-based solution to the dilemma that health care professionals face during resuscitation of ELGANs with regards to multiple competing interventions aimed at mitigating lung injury. The Cochrane handbook considers NMA as a highly valuable tool to evaluate and rank treatment options according to their safety and effectiveness(18). Bayesian NMA have been proposed as an effective method for evaluating the effectiveness of multiple competing interventions(18-20). Delivery room interventions consist of a sequence of non-competing category of interventions and within each category there are several potentially competing interventions (Figure 1). Given that many of these competing delivery room interventions have not been compared in head-to-head studies, we expect that some of the possible comparisons between the interventions will not have direct evidence. Hence, we will perform a random effects network meta-analysis (NMA). Delivery room interventions will be defined as all potential interventions in the immediate postnatal period(21-23).

OBJECTIVES

To determine the relative effectiveness of commonly practiced delivery room interventions for preterm infants born <33 weeks of gestation in preventing BPD using a Bayesian network meta-analysis.

METHODS & DESIGN

This systematic review and NMA protocol has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). This protocol was developed following the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance(24). The final report will comply with the recommendations of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions(25).

Search Strategy

We will search from their inception to August 2018, the following databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). We will use combination of controlled terms (Medical Subject Heading, MeSH, and Emtree), and free-text terms with various synonyms for the different possible delivery room interventions and BPD. Search alerts will be set up for monthly notification and the search will be repeated before the final manuscript submission to identify any new relevant trials. Search strategies have been developed with liaison with an experienced librarian. No language, publication status or date limit will be used. The search strategies have been detailed in appendix A.

We will seek registered details of selected trials in the U.S. National Institutes of Health resource (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform Search Portal. We intend to obtain additional grey literature from personal communication from experts in the field, reviewing the reference lists of relevant articles, abstracts and conference proceedings (Society for Pediatric Research, European Society for Pediatric Research) and seeking results of unpublished trials. We intend to contact authors of unpublished work and authors of published trials in order to clarify information that is not clear in the articles.

Eligibility Criteria

We will include randomized controlled trials (RCTs) that evaluate the effectiveness of commonly practiced delivery room interventions. Studies will have to have the following characteristics regarding participants, intervention, control and type of study.

a) Participants: Preterm infants (<33 weeks) requiring intervention(s) during neonatal transition within the golden hours after birth

b) Interventions include the following: i) cord management (including immediate cord clamping, delayed cord clamping, cord milking, and/or resuscitation attached to the cord); ii) respiratory support (including positive pressure ventilation, CPAP, sustained lung inflation, and/or intubation, and mechanical ventilation); iii) surfactant delivery (type of surfactant delivered via endotracheal tube or laryngeal mask, INSURE (Intubate-Surfactant-Extubate) technique, LISA/MIST (less-invasive surfactant administration/minimally invasive surfactant therapy), and/or nebulized surfactant administration; iv) initial fractional concentration of inspired oxygen (FiO_2) (≤ 0.3 or ≥ 0.6); v) monitoring during resuscitation (respiratory function monitor, near-infrared spectroscopy); vi) medication (e.g., caffeine citrate, or diuretics); vii) use of heated, humidified gas

c) Comparator: One or more of the above interventions compared to each other or no treatment.

Since interventions possible in a delivery room are largely related to delivery room resources, we have *a priori* decided to only include interventions that the infants were subjected to in the immediate postnatal period irrespective of whether these interventions were physically carried out in the room where the infant was born. Studies that examined interventions that were carried out after the initial stabilization period will be excluded from the review.

Outcomes

Our primary outcome is bronchopulmonary dysplasia (defined as oxygen requirement at 36 weeks'postmenstrual age). Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria)(26); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. All the outcomes, its definitions and measures are detailed in the table 1.

Patient and Public Involvement

Neither patients nor public were involved in the development of the research question or design of this study. This network meta-analysis does not recruit any patients. The study will be published and presented at conferences to healthcare professionals.

Study selection

The titles and abstracts retrieved will be screened by two independent reviewers in duplicate to assess its eligibility using the Covidence platform (27). As a second step, the full text articles of the potentially eligible studies will be screened to assess their eligibility. We will include the full text of all studies for which both reviewers agree about their inclusion. For both steps, any disagreements between the reviewers will be resolved by discussion and if no agreement can be reached, a third member of the team will decide whether the study shall be included or not. We will refer to inclusion and exclusion criteria during the screening process. Records of ineligible full text articles along with the reason for ineligibility will be saved for future reference. Eligible articles citations will be uploaded to Covidence. We will present the PRISMA flow diagram(28) demonstrating the search and screening process.

Data Abstraction

A pre-specified standardized data extraction form in a Microsoft Excel sheet will be used to extract the data from the eligible studies. The data extraction form will be pilot tested independently by all reviewers before its use, to standardize the process. Eight reviewers will carry out the extraction, working independently in pairs and in duplicate. In case of disagreement in assessing the methodological quality of the study we will try to resolve it by consensus. If consensus cannot be reached a third designated reviewer will be involved. We will contact authors of primary studies, during data extraction, to provide any missing information.

Node Formation

Within each component of the stabilization pathway, we anticipate the identification numerous similar non-competing interventions (e.g. multiple synthetic and natural surfactants). In an iterative process, clinical experts (GS, SM, GP) blinded to the implications for effect estimates, will come to consensus on definitions of nodes and be presented with the implications of those decisions via network diagrams (e.g. lumping causing the loss of trials comparing lumped interventions, splitting causing disconnected networks). Experts will then be asked to identify whether groups of treatments should be defined as classes (e.g. natural vs synthetic surfactant) or lumped together. Class-based models have the advantage of offering an estimate of class effect as well as shrunken effects of individual treatments, while lumping can allow for more robust estimation of between-trial variability, and can reduce the probability of chance violations of NMA

assumptions. This process will be repeated until a consensus decision is reached on the node making algorithm that meets the criteria of satisfying clinical demands, preserving the assumption that interventions within nodes are sufficiently similar, and presenting data in the least aggregated form possible(29).

Assessment of Risk of Bias

The risk of bias (ROB) of eligible studies will be assessed according to a modified version of the Cochrane Collaboration's ROB tool(18). The six criteria to be assessed are sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain will be assigned a score 'definitely low risk', or 'definitely high risk' or 'unclear risk'. Two independent reviewers will assess the ROB. We will try to reach consensus when disagreements between two reviewers when assessing the methodological quality of the studies. Nevertheless, if consensus cannot be reached, a third reviewer will resolve it.

Measures of Treatment Effect

Effect estimates along with 95% credible intervals (CrIs) will be estimated using risk ratios (RR) calculated using methods described by Dias, using the baseline risk parameter to convert odds ratios to risk ratios(29). When random effect models are used estimates will also be accompanied by their 95% predictive interval representing the interval within which we would expect the treatment effect of a future study to lie(30,31). Relative treatment rankings will be summarized using mean ranks with their 95% credible intervals and the Surface Under the Cumulative Ranking curve (SUCRA) values and cumulative probability rankograms(32). SUCRAs range from 0% to 100% with values of 100% representing a hypothetical treatment that is always best without uncertainty.

Assessment of reporting bias

We will construct a comparison adjusted funnel plot for the network to assess the potential publication bias and small-study effects(33), if we retrieve at least 10 studies. We will inspect plots visually for evidence of asymmetry and if publication bias is suspected we will conduct a sensitivity analysis using models described by Mavridis, Welton and Salanti(34).

Assessment of Transitivity Assumption

Clinical experts (GS, GP, SM) will assess trial characteristics using tables and visualizations to assess whether the transitivity assumption is likely to hold. The characteristics to be evaluated are those that are expected to be effect modifiers and will include gestational age, birth weight, baseline event risk, and ROB. These assessments will be made prior to any meta-analysis to limit to influence of presence or absence of statistical heterogeneity on the assessment of the transitivity assumption. The decision to pool data will be based on consensus. If it is determined that quantitative synthesis is inappropriate, we will summarize our findings narratively.

Direct treatment comparisons

Given that we expect clinical and methodological heterogeneity among the studies (see below in Rating the Confidence in Estimates section), which in turn will create statistical heterogeneity, we will pool evidence for each treatment comparison using a Bayesian random-effects (RE) model(35). In comparison to the fixed-effect model (FE), the RE model is conservative in the sense that it accounts for both within- and between-study variability. The RE model assumes that the observed treatment effect for a study is a combination of a treatment effect common to all studies plus a component specific to that study alone(36,37). Models will be based on standard code modified to include minimally informative priors on baselines, treatment effects, and between trial heterogeneity (38). These priors generally provide more stable estimates, particularly in cases where data are sparse, will be developed using the approach described by Gabry *et al* (39,40).

The Network Meta-Analysis

For each outcome, we will present the network diagram and a forest plot compared against the common comparator with the network estimates as well as league tables showing all pairwise comparisons. To capture the non-competing nature of interventions along the stabilization pathway and to directly fulfill the research objectives we will use component models as described by Welton *et al*(41). These models 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). In

the absence of direct evidence for a given comparison an indirect comparison will provide an estimate of the treatment effect. In the presence of direct evidence, the NMA will provide a combined estimate (i.e., direct and indirect evidence)(32). For instance, in a triangular network ABC composed by studies that directly compare A vs. B and A vs. C treatments, we can indirectly estimate the effect of B vs. C treatments. In case direct evidence of B vs. C treatment comparison is also available, then a combined estimate of direct and indirect evidence of B vs. C can be calculated using a NMA.

We will fit a Bayesian hierarchical model with weakly informative priors adjusting for correlation of multi-arm trials, and assuming a common-within network heterogeneity variance. We will assess heterogeneity by estimating the magnitude of the between-study variance (42). If the posterior estimate of between-study variance shows signs of prior dominance (e.g. extreme values and long tails), we will conduct sensitivity analysis using the empirically estimated informative prior distribution described by Turner *et al*(43). Markov chains will be run for a sufficient number of iterations to reach convergence, which we will assess on the basis of the Brooks-Gelman-Rubin diagnostic, with values less than 1.05 considered acceptable if consistent with visual inspection of convergence and time series plots(44). All analyses will be performed in JAGS or similar software via the statistical program R(45,46).

Assessment of Inconsistency

Inconsistency is the statistical manifestation of the violation of the transitivity assumption, which presents as a disagreement between direct and indirect estimates (loop inconsistency), and/or inconsistency between studies that inform the same treatment comparison, but include a different number of treatment arms (design inconsistency). To evaluate both design and loop inconsistency, we will apply the design-by-treatment interaction model with random inconsistency effects (47,48). These findings will be interpreted within the context of the estimate of between-trial variance as these concepts are closely related and difficult to separate. For example, large estimates of between-trial variance are indicative of heterogeneity within direct comparisons but may also be the result of inconsistency between direct and indirect evidence.

Exploration of heterogeneity and inconsistency

We will perform a network meta-regression using of potential effect modifiers to explore important heterogeneity and/or inconsistency. We propose, the following potential sources of heterogeneity, which could be possible effect modifiers: gestational age, birth weight and ROB. We hypothesize that lower gestational age, and low ROB will be related to less effectiveness of interventions. Overall risk of bias will be determined by taking the average of the three most important risk of bias items identified by expert consensus (sequence generation, allocation concealment, and blinding). Meta-regression models will assume a single shared coefficient for all non-baseline treatments(42). Interpretation of meta-regression models will be in keeping with suggestions from Dias et al., namely: (1) Inclusion of the coefficient leads to a decrease in the estimate of between-study variance; and (2) The 95% credible intervals of the estimated coefficient exclude the null (42).

Sensitivity Analyses

We plan to perform sensitivity analyses of different heterogeneity priors to assess the robustness of results(35,43,49). Further, findings from component models will be compared against a model without this assumption. In both cases, we will compare model fit using both absolute (residual deviance) and relative (DIC) measures as well as a qualitative assessment of whether the analysis leads to an important change in effect estimates.

Rating the confidence in estimates of the effect

We will assess the confidence in the estimates for each outcome using the GRADE approach (50). For this purpose, two authors will independently do the assessment. The confidence in the estimates will be based on four levels: high, moderate, low and very low. For the direct comparisons we will assess and rate each outcome based on the categories: ROB imprecision, inconsistency and publication bias(51-55). To assist with assessment of each domain, we will use threshold plots, which show the smallest change in study/contrast level estimates required to change the conclusions of the analysis.

We will assess and rate the confidence in all the indirect comparisons –if available- obtained from first order loops following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. Transitivity, also called similarity(56), is the assumption that an indirect comparison is a valid method to compare two treatments that have

not been compared in a head-to-head trial, because the studies are sufficiently similar in important clinical and methodological characteristics, or in other words, that they are similar in their distributions of effect modifiers(57,58). Then, we will rate the confidence in each NMA effect estimate using the higher rating when both direct and indirect evidence are present.

We will assess and rate the confidence in estimates of effect from the direct comparisons in our pairwise meta-analyses described previously. To rate the confidence in the indirect comparisons, we will focus our assessments on first-order loops (FOLs), i.e., loops connected to the interventions of interest through only one other intervention. For instance, if for A, B and C interventions, there are direct comparisons of A vs. B (AB) and B vs. C (BC), we will be able to indirectly estimate the effects of A vs. C (AC). The AC indirect estimation will be a FOL. We will choose the FOLs with the lowest variances for rating the confidence as they contribute the most to the estimates of effect.

Within FOLs, the indirect comparison confidence will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For example, if we find that AB has moderate confidence and BC has high confidence, we will judge the associated indirect comparison, AC, as moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption has been violated.

Our overall judgment of confidence in the NMA estimate for any pairwise comparison will be the higher of the confidence rating amongst the contributing direct and indirect comparisons. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates have inconsistency. For this purpose, the GRADE approach recommends to assess the incoherence (or inconsistency as described in the 'The Network Meta-Analysis' section) criteria, which is defined as the differences between direct and indirect estimates of effect(59).

Multi-criteria Acceptability Analysis

Network meta-analyses provide an estimate of effect estimates of competing interventions, but this alone is not sufficient to aid decision making. We will aim to supplement this review with a stochastic multi-criteria acceptability analysis using methods defined by Tervonen, and Van Valkenhoef(60). These methods use a partial value function to allow for a quantitative risk-benefit analysis across multiple outcomes, given an ordinal ranking of importance for decision making

(e.g. Mortality > BPD). Based on the best fitting NMA model, we will conduct stochastic multicriteria acceptability analyses (SMAA): One without preference criteria, and a second with preference criteria determined by expert consensus. Since SMAA is based on estimates constrained to the interval [0,1] we will calculate absolute risk of outcomes based on either a suitably designed observational trial or, if unavailable, a pooled control arm risk of included studies in the reference treatment(61). If treatments require the tradeoff of common (e.g. BPD) and very rare (e.g. mortality) events, we will use the 95% credible interval hull approach(62). The outputs of the SMAA will be a rankogram outlining the probability that a treatment is best, second best, etc., a vector of central weights, a confidence factor for the preference free model; and the rankogram for the ordered model. The vector of central weights provides a summary of the implied preferences required to hold an *a priori* preference for one treatment or another (i.e. the outcome preference implied by a clinician's current practice). The confidence factor is the probability that a treatment is best given these preferences, and is used as a measure of uncertainty.

Discussion

Interventions in the immediate postnatal period may have long-term clinical implications. This NMA will provide the relative effectiveness of commonly practiced delivery room interventions for preterm infants born <33 weeks of gestation in preventing BPD. To the best of our knowledge this will be the first review that will examine the relative effectiveness of each delivery room intervention individually and in combination with respect to important clinical outcomes using novel statistical techniques. Its results will be of interest for a broad range of audience: practice guideline developers, pediatricians, neonatologists, policy makers and researchers, as it could be used to provide clinical recommendations for the choice of sequence of delivery room interventions.

Our review will have several methodological strengths. First, we will implement a wide comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work. Second, we will use the novel method for rating the confidence in the estimates recommended by the GRADE working group. Third, we will employ a novel SMAA model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes(60). On the other hand, we anticipate some methodological challenges while undertaking such a review. We anticipate some degree of clinical

heterogeneity while considering such a large number of competing and non-competing delivery room interventions. Based on the number of interventions identified following the systematic review, we may have to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results.

We hope that this review will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants.

Figure legend:

Figure 1: Physiological sequence of potential delivery room interventions

Table 1. A priori defined outcome measures

Outcome Measure	Definition
Bronchopulmonary dysplasia	No. of neonates who require oxygen at 36 weeks' postmenstrual age (PMA)
Mortality	Death before discharge
Severe intraventricular hemorrhage	No. of neonates with grades 3-4 based on the Papile criteria
Air leak syndromes	No. of neonates with pneumothorax or pulmonary interstitial emphysema confirmed by chest X ray
Retinopathy of prematurity (any stage)	No. of neonates with any stage of Retinopathy of prematurity as per the international classification of Retinopathy of prematurity
Neurodevelopmental impairment	No. of infants with any degree of neurodevelopmental impairment as assessed by a standardized and validated assessment tool, a child developmental specialist or both, at any age reported (outcome data grouped at 12, 18 and 24 months if available)

References

1. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. Journal of Pediatrics 1979;95(5 Pt 2):819-23.
2. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82(4):527-32.
3. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sánchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotten CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015;314(10):1039-51.
4. Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics 2006; 118: 108–113.
5. Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the Epicure study. Am J Respir Crit Care Med 2010; 182: 237–245.
6. Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, Baley J, Singer LT. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics. 2003;112(5):e359
7. Twilhaar ES, Wade RM, de Kieviet JF, van Goudoever JB, van Elburg RM, Oosterlaan J. Cognitive Outcomes of Children Born Extremely or Very Preterm since the 1990s and

Associated Risk Factors: A Meta-analysis and Meta-regression. JAMA Pediatr. 2018;172(4):361-367

8. Hillman NH, Moss TJM, Kallapur SG, Bachurski C, Pillow JJ, Polglase GR et al. Brief, large tidal volume ventilation initiates lung injury and a systemic response in fetal sheep. Am J Respir Crit Care Med 2007; 176: 575–581.
9. Wallace MJ, Probyn ME, Zahra VA, Crossley K, Cole TJ, Davis PG et al. Early biomarkers and potential mediators of ventilation-induced lung injury in very preterm lambs. Respir Res 2009; 10: 19.
10. Obladen M. Factors influencing surfactant composition in the newborn infant. Eur J Pediatr 1978; 128: 129–143.
11. Heldt GP, McIlroy MB. Distortion of chest wall and work of diaphragm in preterm infants. J Appl Physiol (1985) 1987; 62: 164–169.
12. Heldt GP, McIlroy MB. Dynamics of chest wall in preterm infants. J Appl Physiol (1985) 1987; 62: 170–174.
13. Foglia EE, Jensen EA, Kirpalani H. State of the Art Review: Delivery room interventions to prevent bronchopulmonary dysplasia in extremely preterm infants. Journal of perinatology : official journal of the California Perinatal Association. 2017;37(11):1171-1179.
14. Rich WD, Leone T, Finer NN. Delivery room intervention: improving the outcome. Clin Perinatol. 2010;37(1):189-202
15. Fogarty M, Osborn DA, Askie LM, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. The American Journal of Obstetrics & Gynecology 2018;218:1–18.

16. Schmölzer GM, Kumar M, Pichler G, et al. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ 2013;347:f5980
17. Pichler G, Urlesberger B, Schwaberger B, et al. Cerebral Oxygen Saturation to Guide Oxygen Delivery in Preterm Neonates for the Immediate Transition after Birth: A 2-Center Randomized Controlled Pilot Feasibility Trial. J Pediatr 2016;170:73–4.
18. Collaboration TC. The Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Higgins JPT, and Green, S., editor2011.
19. Jansen JP, Crawford B, Bergman G, Stam W. Bayesian Meta-Analysis of Multiple Treatment Comparisons: An Introduction to Mixed Treatment Comparisons. Value in Health. 2008;11(5):956-64.
20. Jonas DE, Wilkins TM, Bangdiwala S, Bann CM, Morgan LC, Thaler KJ, Amick HR, Gartlehner G. Findings of Bayesian Mixed Treatment Comparison Meta-Analyses: Comparison and Exploration Using Real-World Trial Data and Simulation [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Feb. Available from http://www.ncbi.nlm.nih.gov/books/NBK126109/ Accessed November 10, 2018.
21. Vento M, Cheung P-Y, Aguar M, et al. The first golden minutes of the extremely-low-gestational-age neonate: a gentle approach. Neonatology 2009;95:286–98.
22. Peleg B, Globus O, Granot M, et al. “Golden Hour” quality improvement intervention and short-term outcome among preterm infants. J Perinatol 2018;31:289.
23. Shah V, Hodgson K, Seshia M, et al. Golden hour management practices for infants <32 weeks gestational age in Canada. Paediatr Child Health 2018;23:70–6.

24. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

25. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777-84.

26. Papile L-A, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529–34

27. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org

28. PRISMA. Preferred Reporting Items for Systematic Reviews and Meta-Analyses [online]. [cited 2018 Accessed April 20]. Available from: http://www.prisma-statement.org/statement.htm

29. Introduction to Evidence Synthesis. In: Network Meta-Analysis for Decision Making [Internet]. John Wiley & Sons, Ltd; 2018. p. 1–17. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118951651.ch1

30. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011;342.

31. Higgins J, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2009;172(1):137-59.

32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71.

33. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical Tools for Network Meta-Analysis in STATA. PLoS One. 2013;8(10).

34. Mavridis D, Welton NJ, Salanti G. A selection model for accounting for publication bias in a full network meta-analysis. Stat Med. 2014;33:5399–412.

35. Lambert PC, Sutton AJ, Burton PR, Abrams KR, Jones DR. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. Statistics in medicine. 2005;24(15):2401.

36. Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. Annals of Internal Medicine. 2014;160(4):267-70.

37. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.

38. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials. Med Decis Mak. 2013;33:607.

39. Gelman A, Carlin J, Stern H, Dunson D, Vehtari A, Rubin D. Chapter 2: Single Parameter models. In: Bayesian data analysis. Third Edit. New York: CRC Press; 2015.

40. Gabry J, Simpson D, Vehtari A, Betancourt M, Gelman A. Visualization in Bayesian workflow. 2017;2. http://arxiv.org/abs/1709.01449.

41. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: Psychological interventions in coronary heart disease. Am J Epidemiol. 2009;169:1158–65.

42. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence Synthesis for Decision Making 3: Subgroups, Meta-Regression, Bias, and Bias-Adjustment. Med Decis Mak [Internet]. 2013;33(5):597–606. Available from: http://mdm.sagepub.com/content/33/5/597.full.pdf+html Accessed November 10, 2018

43. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. International journal of epidemiology. 2012;41(3):818-27.

44. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. Statistical science. 1992:457-72.

45. Plummer, M., 2016. JAGS: Just another Gibbs sampler. Available at http://mcmc-jags.sourceforge.net/. Accessed March, 14, 2017.

46. R Core Team. R: A language and environment for statistical computing. 2018. https://cran.r-project.org/.

47. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades a E. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making [Internet]. 2013;33(5):641–56.

48. Jackson D, Barrett JK, Rice S, White IR, Higgins JPT. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. Stat Med. 2014;33:3639–54.

49. Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. J Clin Epidemiol. 2015;68(1):52-60.

50. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

51. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology. 2011;64(4):401-6.

52. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). Journal of clinical epidemiology. 2011;64(4):407-15.

53. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. Journal of clinical epidemiology. 2011;64(12):1283-93.

54. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. Journal of clinical epidemiology. 2011;64(12):1294-302.

55. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. Journal of clinical epidemiology. 2011;64(12):1277-82.

56. Donegan S, Williamson P, Gamble C, Tudur-Smith C. Indirect comparisons: a review of reporting and methodological quality. PLoS One. 2010;5(11):e11054.

57. Baker SG, Kramer BS. The transitive fallacy for randomized trials: if A bests B and B bests C in separate trials, is A better than C? BMC Med Res Methodol. 2002;2:13.

58. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Annals of internal medicine. 2013;159(2):130-7.

59. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630.

60. Van Valkenhoef G, Tervonen T, Zhao J, De Brock B, Hillege HL, Postmus D. Multicriteria benefit-risk assessment using network meta-analysis. J Clin Epidemiol. 2012;65:394–403.

61. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 5: The baseline natural history model. Med Decis Mak. 2013;33(5):657–70.

62. Tervonen T. New directions in Stochastic Multicriteria Acceptability Analysis. 2007 Dec 1 [cited 2018 Nov 11]; Available from: http://www.utupub.fi/handle/10024/28151

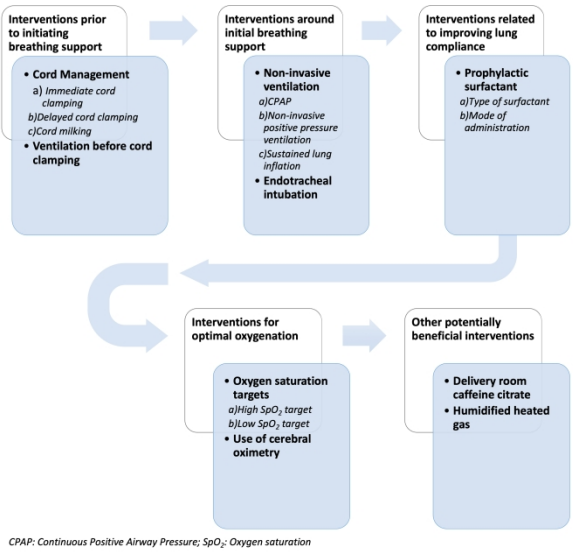

Figure 1: Physiological sequence of potential delivery room interventions

903x508mm (144 x 144 DPI)

Appendix 1: Search strategy for EMBASE, Medline, and PubMed

EMBASE

(newborn OR infant OR neonate OR preterm OR premature) AND [randomized controlled trial]/lim

AND

(continuous AND positive AND airway AND pressure OR cpap OR (nasal AND continuous AND positive AND airway AND pressure) OR ncpap OR (positive AND pressure AND ventilation) OR (intermittent AND positive AND pressure AND ventilation) OR (sustained AND lung AND inflation) OR (sustained AND inflation) OR si) AND [randomized controlled trial]/lim

OR

(supplemental AND oxygen OR (supplemental AND oxygen AND during AND resuscitation) OR oxygen OR surfactant OR (surfactant AND administration) OR (surfactant AND administration, AND early) OR (surfactant AND administration, AND late) OR (minimally AND invasive AND surfactant AND therapy) OR ('less invasive' AND surfactant AND administration)) AND [randomized controlled trial]/lim

OR

(lisa OR intubation OR (endotracheal AND intubation) OR (mechanical AND ventilation) OR caffeine OR (caffeine AND citrate) OR (respiratory AND function AND monitor) OR (delayed AND cord AND clamping) OR (cord AND milking)) AND [randomized controlled trial]/lim

AND

(randomized AND controlled AND trial OR 'randomized controlled trial':it OR (clinical AND trial)) AND [randomized controlled trial]/lim

AND

[randomized controlled trial]/lim AND [embase]/lim AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim)

Limited to embryo from Age Groupsfetus from Age Groupsnewborn from Age Groupsinfant from Age Groups

Medline

Set	Run Search **MEDLINE** **Search History - " BPD"**
#5	#3 AND #2 AND #1 Refined by: **PUBLICATION TYPES:** (RANDOMIZED CONTROLLED TRIAL) *DocType=All document types; Language=All languages;*
#4	#3 AND #2 AND #1 *DocType=All document types; Language=All languages;*
#3	(MH=randomized controlled trial OR TS=randomized controlled trial OR TS=clinical trial) *AND* **DOCUMENT TYPES:** (Randomized Controlled Trial) *DocType=All document types; Language=All languages;*
#2	TS=continuous positive airway pressure OR TS=CPAP OR TS=nasal continuous positive airway pressure OR TS=nCPAP OR TS=positive pressure ventilation OR TS=intermittent positive pressure ventilation OR TS=sustained lung inflation OR TS=sustained inflation OR TS=SI OR TS=supplemental oxygen OR TS=supplemental oxygen during resuscitation OR TS=oxygen OR TS=surfactant OR TS=surfactant administration OR TS=surfactant administration, early OR TS=surfactant administration, late OR TS=minimally invasive surfactant therapy OR TS=less-invasive surfactant administration OR TS=LISA OR TS=intubation OR TS=endotracheal intubation OR TS=mechanical ventilation OR TS=caffeine OR TS=caffeine citrate OR TS=respiratory function monitor OR TS=delayed cord clamping OR TS=cord milking *DocType=All document types; Language=All languages;*
#1	TS=newborn OR TS=premature OR TS=infant OR TS=neonate OR TS=preterm *DocType=All document types; Language=All languages;*

PubMed

#1 MeSH descriptor: [Infant] explode all trees

#2 infant*:ti,ab

#3 neonat*:ti,ab

#4 newborn*:ti,ab

#5 preterm:ti,ab

#6 premature:ti,ab

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 "continuous positive airway pressure":ti,ab

#9 "positive pressure ventilation":ti,ab

#10 (sustained near/2 inflation):ti,ab

#11 (supplemental near/2 oxygen):ti,ab

#12 oxygen:ti,ab

#13 surfactant:ti,ab

#14 intubation:ti,ab

#15 (mechanical* near/1 ventilat*):ti,ab

#16 caffeine:ti,ab

#17 "respiratory function monitor":ti,ab

#18 (cord near/2 ((clamping and delayed) or milking)):ti,ab

#19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18

#20	#7 and #19

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028066.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Mar-2019
Complete List of Authors:	Mitra, Souvik; Dalhousie University, IWK Health Center, Department of Pediatrics Disher, Timothy; School of Nursing, Dalhousie University Pichler, Gerhard; Medical University of Graz, Research Unit for Neonatal Micro- and Macrocirculation, Department of Pediatrics D'Souza, Brandon; IWK Health Centre, Department of Respiratory Therapy Mccord, Helen; Dalhousie University, IWK Health Center, Department of Pediatrics Chayapathi, Varsha; Dalhousie University, IWK Health Center, Department of Pediatrics Jones, Karlee; Dalhousie University, IWK Health Center, Department of Pediatrics Schm&#65533;lzer, Georg; Royal Alexandra Hospital, Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, ; University of Alberta, Department of Pediatrics
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Research methods
Keywords:	Infants, Bronchopulmonary dysplasia, Delivery Room, Newborn

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

Souvik Mitra MD MSc[1], Timothy Disher PhD(c), RN[2], Gerhard Pichler MD[3], Brandon D'Souza BHSc, RRT[6], Helen Mccord MN[1], Varsha Chayapathi MBBS, DNB[1], Karlee Jones BScPharm, ACPR[1], Georg M. Schmölzer MD, PhD[4,5]

[1]Department of Pediatrics, Dalhousie University, IWK Health Center, Halifax, Canada

[2]School of Nursing, Dalhousie University, Halifax Nova Scotia, Canada

[3]Research Unit for Neonatal Micro- and Macrocirculation, Department of Pediatrics, Medical University of Graz, Austria

[4]Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, Royal Alexandra Hospital, Edmonton, Alberta, Canada

[5]Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

[6]Department of Respiratory Therapy, IWK Health Centre, Halifax, Nova Scotia, Canada

Corresponding author:

Georg M. Schmölzer, MD, PhD

Centre for the Studies of Asphyxia and Resuscitation,

Neonatal Research Unit, Royal Alexandra Hospital,

10240 Kingsway Avenue NW,

T5H 3V9, Edmonton, Alberta, Canada

Telephone +1 780 735 4660

Fax: +1 780 735 4072

Email: georg.schmoelzer@me.com

Conflict of Interest:

SM, GP, VC, have declared no conflict of interest. TD provides methodological advice for Cornerstone Research Group Inc. Cornerstone Research Group Inc. consults for various pharmaceutical and medical device companies. BD has provided device training and educational presentations to clinicians on behalf of Mallinckrodt Pharmaceuticals. GMS has registered the RETAIN neonatal resuscitation board (Tech ID 2017083) and RETAIN neonatal resuscitation video game (Tech ID 2017086) under Canadian copyright, and GMS is the owner of RETAIN Labs Inc. (https://www.playretain.com), which is distributing these games.

Keywords: INFANTS, NEWBORN, DELIVERY ROOM, BRONCHOPULMONARY DYSPLASIA

Funding sources

We would like to thank the public for donating money to our funding agencies: GMS is a recipient of the Heart and Stroke Foundation/University of Alberta Professorship of Neonatal Resuscitation, a National New Investigator of the Heart and Stroke Foundation Canada and an Alberta New Investigator of the Heart and Stroke Foundation Alberta. This research has been facilitated by the Women and Children's Health Research Institute through the generous support of the Stollery Children's Hospital Foundation.

Abstract: 250 words

Manuscript: 3,963 words

Tables: 1

Figures: 1

Author's contribution:

Conception and design: GMS, SM

Data analysis plan: GMS, SM, GP, TD, BDS, HM, VC, KJ

Drafting of the article: GMS, SM, GP, TD, BDS, HM, VC, KJ

Critical revision of the article for important intellectual content: GMS, SM, GP, TD, BDS, HM, VC, KJ

Final approval of the article: GMS, SM, GP, TD, BDS, HM, VC, KJ

Abbreviations:

BPD	- Bronchopulmonary dysplasia
ELGAN	- Extremely low gestational age newborns
IQ	- Intelligence quotient
CPAP	- Continuous positive airway pressure
NMA	- Network meta-analysis
RE	- Random-effects model
RCT	- Randomized controlled trials
INSURE	- Intubate-Surfactant-Extubate technique
LISA/MIST	- Less-invasive surfactant administration/minimally invasive surfactant therapy
ROB	- Risk of bias
CrIs	- Credible intervals
RR	- Risk ratio
SUCRA	- Surface Under the Cumulative Ranking curve
FE	- Fixed-effect model
FOL	- First-order loops
SMAA	- Stochastic multicriteria acceptability analysis

Abstract

Introduction

As gestational age decreases, incidence of bronchopulmonary dysplasia (BPD) and chronic lung disease increases. There are many interventions used in the delivery room to prevent acute lung injury and consequently BPD in these patients. The availability of different treatment options often poses a practical challenge to the practicing neonatologist when it comes to making an evidence based choice as the multitude of pairwise systematic reviews including Cochrane reviews that are currently available only provide a narrow perspective through head-to-head comparisons.

Methods and Analysis

We will conduct a systematic review of all randomized controlled trials evaluating delivery room interventions within the 1st golden hour after birth for prevention of BPD. The primary outcome BPD. Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. We will search Medline, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) as well as grey literature resources. Two reviewers will independently screen titles and abstracts, review full texts, extract information, and assess the risk of bias (ROB) and the confidence in the estimate (with Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach). This review will use Bayesian network meta-analysis approach which allows the comparison of the multiple delivery room interventions for prevention of BPD. We will perform a Bayesian network meta-analysis to combine the pooled direct and indirect treatment effect estimates for each outcome, effectiveness, and safety of delivery room interventions for prevention of BPD.

Ethics and Dissemination

The proposed protocol is a network meta-analysis, which has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). The results will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants. Furthermore, we will identify knowledge gaps and will encourage further research for other

therapeutic options. Therefore, its results will be disseminated through peer-reviewed publications and conference presentations. Due to the nature of the design, no ethics approval is necessary.

Strengths and limitations of this study

Strengths:

- Comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work
- Use the novel method for rating the confidence in the estimates recommended by the GRADE working group
- We will employ a novel Stochastic multicriteria acceptability analysis model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes

Limitations:

- We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions
- Potential to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results

Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory morbidity associated with premature birth. BPD is defined as either need of supplemental oxygen at i) 28 days postnatal age(1), or ii) 36 weeks' postmenstrual age with or without compatible clinical and radiographic findings(2). BPD affects 30-60% of prematurely born infants with the incidence being inversely proportional to gestational age(3). With increased survival of extremely low gestational age newborns (ELGAN), the incidence of BPD continues to increase despite improvement in neonatal care practices over the last two decades(3). BPD is known to be associated with long-term respiratory morbidity that persists into adolescence and adulthood(4,5). There is also increasing evidence that BPD and duration on supplemental oxygen have long-term adverse effects on cognitive and academic achievement with each percent increase in BPD rate being associated with a 0.01 standard deviation decrease in intelligence quotient (IQ) (0.15 IQ points) ($p<0.001$)(6,7).

Several antenatal, perinatal, and postnatal factors contribute to the development of BPD. It is postulated that early lung injury and inflammation play an important role in the pathogenesis of BPD (8,9). In the fetus, the gas exchange organ is the placenta and the function of gas exchange is transferred from the placenta to the lungs immediately after birth. Therefore, the newborn infant's lungs must open and be aerated to allow the transition from fetal to postnatal circulation and physiology. However, in ELGANs, several physiological factors prevent this transition. These include lack of surfactant leading to increased alveolar surface tension, non-compliant chest wall, and weak respiratory muscles(10-12). Therefore, most ELGANs require assisted ventilation and/or supplemental oxygen after birth to ensure optimal gas exchange. However, both therapies may also induce lung inflammation due to barotrauma and/or volutrauma and oxygen-free radical generation thereby initiating the pathogenesis of BPD. Therefore, any interventions targeted at limiting lung injury and oxidative stress during resuscitation in the delivery room immediately after the birth may help to prevent the development of BPD or reduce its severity.

A number of clinical trials have been conducted on a variety of delivery room interventions, including i) interventions prior to initiating breathing support (i.e., clamping vs. milking the umbilical cord); ii) interventions around initial breathing support (i.e., continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation, sustained lung inflation or endotracheal intubation); iii) interventions related to improving lung compliance (i.e., prophylactic

surfactant therapy including the different variations in its administration modalities); iv) interventions related to minimizing oxidative stress (i.e., higher vs. lower oxygen saturation targets), v) use of cerebral oximetry, and vi) other potentially beneficial therapies such as caffeine administration (Figure 1)(13,14).

The availability of multiple potential interventions in a resuscitation scenario often poses a practical challenge to health care professionals as to which sequence of interventions would provide the greatest likelihood of minimizing BPD and which interventions are unnecessary and unlikely to be of any benefit(13). There have been previous systematic reviews and pairwise meta-analyses on the different competing interventions such as initial breathing support and oxygen saturation targets(15-17). However, these meta-analyses, though well conducted, provide a narrow perspective to the situation where a sequence of non-competing interventions occur within a short time-frame whereas each intervention has potentially competing variations. Use of a network meta-analysis (NMA) framework may help to provide a more feasible, comprehensive and evidence-based solution to the dilemma that health care professionals face during resuscitation of ELGANs with regards to multiple competing interventions aimed at mitigating lung injury. The Cochrane handbook considers NMA as a highly valuable tool to evaluate and rank treatment options according to their safety and effectiveness(18). Bayesian NMA have been proposed as an effective method for evaluating the effectiveness of multiple competing interventions(18-20). Delivery room interventions consist of a sequence of non-competing category of interventions and within each category there are several potentially competing interventions (Figure 1). Given that many of these competing delivery room interventions have not been compared in head-to-head studies, we expect that some of the possible comparisons between the interventions will not have direct evidence. Hence, we will perform a random effects network meta-analysis (NMA). Delivery room interventions will be defined as all potential interventions in the immediate postnatal period(21-23).

OBJECTIVES

To determine the relative effectiveness of commonly practiced delivery room interventions for preterm infants born <33 weeks of gestation in preventing BPD using a Bayesian network meta-analysis.

METHODS & DESIGN

This systematic review and NMA protocol has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). This protocol was developed following the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance(24). The final report will comply with the recommendations of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions(25).

Search Strategy

We will search from their inception to August 2018, the following databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). We will use combination of controlled terms (Medical Subject Heading, MeSH, and Emtree), and free-text terms with various synonyms for the different possible delivery room interventions and BPD. Search alerts will be set up for monthly notification and the search will be repeated before the final manuscript submission to identify any new relevant trials. Search strategies have been developed with liaison with an experienced librarian. No language, publication status or date limit will be used. The search strategies have been detailed in appendix A.

We will seek registered details of selected trials in the U.S. National Institutes of Health resource (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform Search Portal. We intend to obtain additional grey literature from personal communication from experts in the field, reviewing the reference lists of relevant articles, abstracts and conference proceedings (Society for Pediatric Research, European Society for Pediatric Research) and seeking results of unpublished trials. We intend to contact authors of unpublished work and authors of published trials in order to clarify information that is not clear in the articles.

Eligibility Criteria

We will include randomized controlled trials (RCTs) that evaluate the effectiveness of commonly practiced delivery room interventions. Studies will have to have the following characteristics regarding participants, intervention, control and type of study.

a) Participants: Preterm infants (<33 weeks) requiring intervention(s) during neonatal transition within the 1st golden hour after birth

b) Interventions include the following: i) cord management (including immediate cord clamping, delayed cord clamping, cord milking, and/or resuscitation attached to the cord); ii) respiratory support (including positive pressure ventilation, CPAP, sustained lung inflation, and/or intubation, and mechanical ventilation); iii) surfactant delivery (type of surfactant delivered via endotracheal tube or laryngeal mask, INSURE (Intubate-Surfactant-Extubate) technique, LISA/MIST (less-invasive surfactant administration/minimally invasive surfactant therapy), and/or nebulized surfactant administration; iv) initial fractional concentration of inspired oxygen (FiO_2) (≤ 0.3 or ≥ 0.6); v) monitoring during resuscitation (respiratory function monitor, near-infrared spectroscopy); vi) medication (e.g., caffeine citrate, or diuretics); vii) use of heated, humidified gas

c) Comparator: One or more of the above interventions compared to each other or no treatment.

Since interventions possible in a delivery room are largely related to delivery room resources, we have *a priori* decided to only include interventions that the infants were subjected to in the immediate postnatal period irrespective of whether these interventions were physically carried out in the room where the infant was born. Studies that examined interventions that were carried out after the initial stabilization period will be excluded from the review.

Outcomes

Our primary outcome is bronchopulmonary dysplasia (defined as oxygen requirement at 36 weeks'postmenstrual age). Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria)(26); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. All the outcomes, its definitions and measures are detailed in the table 1. We aim to perform one subgroup analysis comparing infants <28 weeks versus 29-32 weeks.

Patient and Public Involvement

Neither patients nor public were involved in the development of the research question or design of this study. This network meta-analysis does not recruit any patients. The study will be published and presented at conferences to healthcare professionals.

Study selection

The titles and abstracts retrieved will be screened by two independent reviewers in duplicate to assess its eligibility using the Covidence platform (27). As a second step, the full text articles of the potentially eligible studies will be screened to assess their eligibility. We will include the full text of all studies for which both reviewers agree about their inclusion. For both steps, any disagreements between the reviewers will be resolved by discussion and if no agreement can be reached, a third member of the team will decide whether the study shall be included or not. We will refer to inclusion and exclusion criteria during the screening process. Records of ineligible full text articles along with the reason for ineligibility will be saved for future reference. Eligible articles citations will be uploaded to Covidence. We will present the PRISMA flow diagram(28) demonstrating the search and screening process.

Data Abstraction

A pre-specified standardized data extraction form in a Microsoft Excel sheet will be used to extract the data from the eligible studies. The data extraction form will be pilot tested independently by all reviewers before its use, to standardize the process. Eight reviewers will carry out the extraction, working independently in pairs and in duplicate. In case of disagreement in assessing the methodological quality of the study we will try to resolve it by consensus. If consensus cannot be reached a third designated reviewer will be involved. We will contact authors of primary studies, during data extraction, to provide any missing information.

Node Formation

Within each component of the stabilization pathway, we anticipate the identification numerous similar non-competing interventions (e.g. multiple synthetic and natural surfactants). In an iterative process, clinical experts (GS, SM, GP) blinded to the implications for effect estimates, will come to consensus on definitions of nodes and be presented with the implications of those decisions via network diagrams (e.g. lumping causing the loss of trials comparing lumped interventions, splitting causing disconnected networks). Experts will then be asked to identify whether groups of treatments should be defined as classes (e.g. natural vs synthetic surfactant) or lumped together. Class-based models have the advantage of offering an estimate of class effect as well as shrunken effects of individual treatments, while lumping can allow for more robust

estimation of between-trial variability, and can reduce the probability of chance violations of NMA assumptions. This process will be repeated until a consensus decision is reached on the node making algorithm that meets the criteria of satisfying clinical demands, preserving the assumption that interventions within nodes are sufficiently similar, and presenting data in the least aggregated form possible(29).

Assessment of Risk of Bias

The risk of bias (ROB) of eligible studies will be assessed according to a modified version of the Cochrane Collaboration's ROB tool(18). The six criteria to be assessed are sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain will be assigned a score 'definitely low risk', or 'definitely high risk' or 'unclear risk'. Two independent reviewers will assess the ROB. We will try to reach consensus when disagreements between two reviewers when assessing the methodological quality of the studies. Nevertheless, if consensus cannot be reached, a third reviewer will resolve it.

Measures of Treatment Effect

Effect estimates along with 95% credible intervals (CrIs) will be estimated using risk ratios (RR) calculated using methods described by Dias, using the baseline risk parameter to convert odds ratios to risk ratios(29). When random effect models are used estimates will also be accompanied by their 95% predictive interval representing the interval within which we would expect the treatment effect of a future study to lie(30,31). Relative treatment rankings will be summarized using mean ranks with their 95% credible intervals and the Surface Under the Cumulative Ranking curve (SUCRA) values and cumulative probability rankograms(32). SUCRAs range from 0% to 100% with values of 100% representing a hypothetical treatment that is always best without uncertainty.

Assessment of reporting bias

We will construct a comparison adjusted funnel plot for the network to assess the potential publication bias and small-study effects(33), if we retrieve at least 10 studies. We will

inspect plots visually for evidence of asymmetry and if publication bias is suspected we will conduct a sensitivity analysis using models described by Mavridis, Welton and Salanti(34).

Assessment of Transitivity Assumption

Clinical experts (GS, GP, SM) will assess trial characteristics using tables and visualizations to assess whether the transitivity assumption is likely to hold. The characteristics to be evaluated are those that are expected to be effect modifiers and will include gestational age, birth weight, baseline event risk, and ROB. These assessments will be made prior to any meta-analysis to limit to influence of presence or absence of statistical heterogeneity on the assessment of the transitivity assumption. The decision to pool data will be based on consensus. If it is determined that quantitative synthesis is inappropriate, we will summarize our findings narratively.

Direct treatment comparisons

Given that we expect clinical and methodological heterogeneity among the studies (see below in Rating the Confidence in Estimates section), which in turn will create statistical heterogeneity, we will pool evidence for each treatment comparison using a Bayesian random-effects (RE) model(35). In comparison to the fixed-effect model (FE), the RE model is conservative in the sense that it accounts for both within- and between-study variability. The RE model assumes that the observed treatment effect for a study is a combination of a treatment effect common to all studies plus a component specific to that study alone(36,37). Models will be based on standard code modified to include minimally informative priors on baselines, treatment effects, and between trial heterogeneity (38). These priors generally provide more stable estimates, particularly in cases where data are sparse, will be developed using the approach described by Gabry *et al* (39,40).

The Network Meta-Analysis

For each outcome, we will present the network diagram and a forest plot compared against the common comparator with the network estimates as well as league tables showing all pairwise comparisons. To capture the non-competing nature of interventions along the stabilization pathway and to directly fulfill the research objectives we will use component models as described by Welton

et al(41). These models assume that interventions across domains of the stabilization pathway are additive on additive on logit scale for dichotomous outcomes (e.g. mortality). In the absence of direct evidence for a given comparison an indirect comparison will provide an estimate of the treatment effect. In the presence of direct evidence, the NMA will provide a combined estimate (i.e., direct and indirect evidence)(32). For instance, in a triangular network ABC composed by studies that directly compare A vs. B and A vs. C treatments, we can indirectly estimate the effect of B vs. C treatments. In case direct evidence of B vs. C treatment comparison is also available, then a combined estimate of direct and indirect evidence of B vs. C can be calculated using a NMA.

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). We will assess heterogeneity by estimating the magnitude of the between-study variance (42). 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. Markov chains will be run for a sufficient number of iterations to reach convergence, which we will assess on the basis of the Brooks-Gelman-Rubin diagnostic, with values less than 1.05 considered acceptable if consistent with visual inspection of convergence and time series plots(44). All analyses will be performed in JAGS or similar software via the statistical program R(45,46).

Assessment of Inconsistency

Inconsistency is the statistical manifestation of the violation of the transitivity assumption, which presents as a disagreement between direct and indirect estimates (loop inconsistency), and/or inconsistency between studies that inform the same treatment comparison, but include a different number of treatment arms (design inconsistency). To evaluate both design and loop inconsistency, we will apply the design-by-treatment interaction model with random inconsistency

effects (47,48). These findings will be interpreted within the context of the estimate of between-trial variance as these concepts are closely related and difficult to separate. For example, large estimates of between-trial variance are indicative of heterogeneity within direct comparisons but may also be the result of inconsistency between direct and indirect evidence.

Exploration of heterogeneity and inconsistency

We will perform a network meta-regression using of potential effect modifiers to explore important heterogeneity and/or inconsistency. We propose, the following potential sources of heterogeneity, which could be possible effect modifiers: gestational age, birth weight and ROB. We hypothesize that lower gestational age, and low ROB will be related to less effectiveness of interventions. Overall risk of bias will be determined by taking the average of the three most important risk of bias items identified by expert consensus (sequence generation, allocation concealment, and blinding). Meta-regression models will assume a single shared coefficient for all non-baseline treatments(42). Interpretation of meta-regression models will be in keeping with suggestions from Dias et al., namely: (1) Inclusion of the coefficient leads to a decrease in the estimate of between-study variance; and (2) The 95% credible intervals of the estimated coefficient exclude the null (42).

Sensitivity Analyses

We plan to perform sensitivity analyses of different heterogeneity priors to assess the robustness of results(35,43,49). Further, findings from component models will be compared against a model without this assumption. In both cases, we will compare model fit using both absolute (residual deviance) and relative (DIC) measures as well as a qualitative assessment of whether the analysis leads to an important change in effect estimates.

Rating the confidence in estimates of the effect

We will assess the confidence in the estimates for each outcome using the GRADE approach (50). For this purpose, two authors will independently do the assessment. The confidence in the estimates will be based on four levels: high, moderate, low and very low. For the direct comparisons we will assess and rate each outcome based on the categories: ROB imprecision, inconsistency and publication bias(51-55). To assist with assessment of each

domain, we will use threshold plots, which show the smallest change in study/contrast level estimates required to change the conclusions of the analysis.

We will assess and rate the confidence in all the indirect comparisons –if available- obtained from first order loops following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. Transitivity, also called similarity(56), is the assumption that an indirect comparison is a valid method to compare two treatments that have not been compared in a head-to-head trial, because the studies are sufficiently similar in important clinical and methodological characteristics, or in other words, that they are similar in their distributions of effect modifiers(57,58). Then, we will rate the confidence in each NMA effect estimate using the higher rating when both direct and indirect evidence are present.

We will assess and rate the confidence in estimates of effect from the direct comparisons in our pairwise meta-analyses described previously. To rate the confidence in the indirect comparisons, we will focus our assessments on first-order loops (FOLs), i.e., loops connected to the interventions of interest through only one other intervention. For instance, if for A, B and C interventions, there are direct comparisons of A vs. B (AB) and B vs. C (BC), we will be able to indirectly estimate the effects of A vs. C (AC). The AC indirect estimation will be a FOL. We will choose the FOLs with the lowest variances for rating the confidence as they contribute the most to the estimates of effect.

Within FOLs, the indirect comparison confidence will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For example, if we find that AB has moderate confidence and BC has high confidence, we will judge the associated indirect comparison, AC, as moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption has been violated.

Our overall judgment of confidence in the NMA estimate for any pairwise comparison will be the higher of the confidence rating amongst the contributing direct and indirect comparisons. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates have inconsistency. For this purpose, the GRADE approach recommends to assess the incoherence (or inconsistency as described in the 'The Network Meta-Analysis' section) criteria, which is defined as the differences between direct and indirect estimates of effect(59).

Multi-criteria Acceptability Analysis

Network meta-analyses provide an estimate of effect estimates of competing interventions, but this alone is not sufficient to aid decision making. We will aim to supplement this review with a stochastic multi-criteria acceptability analysis using methods defined by Tervonen, and Van Valkenhoef(60). These methods use a partial value function to allow for a quantitative risk-benefit analysis across multiple outcomes, given an ordinal ranking of importance for decision making (e.g. Mortality > BPD). Based on the best fitting NMA model, we will conduct stochastic multicriteria acceptability analyses (SMAA): One without preference criteria, and a second with preference criteria determined by expert consensus. Since SMAA is based on estimates constrained to the interval [0,1] we will calculate absolute risk of outcomes based on either a suitably designed observational trial or, if unavailable, a pooled control arm risk of included studies in the reference treatment(61). If treatments require the tradeoff of common (e.g. BPD) and very rare (e.g. mortality) events, we will use the 95% credible interval hull approach(62). The outputs of the SMAA will be a rankogram outlining the probability that a treatment is best, second best, etc., a vector of central weights, a confidence factor for the preference free model; and the rankogram for the ordered model. The vector of central weights provides a summary of the implied preferences required to hold an *a priori* preference for one treatment or another (i.e. the outcome preference implied by a clinician's current practice). The confidence factor is the probability that a treatment is best given these preferences, and is used as a measure of uncertainty.

Discussion

Interventions in the immediate postnatal period may have long-term clinical implications. This NMA will provide the relative effectiveness of commonly practiced delivery room interventions for preterm infants born <33 weeks of gestation in preventing BPD. To the best of our knowledge this will be the first review that will examine the relative effectiveness of each delivery room intervention individually and in combination with respect to important clinical outcomes using novel statistical techniques. Its results will be of interest for a broad range of audience: practice guideline developers, pediatricians, neonatologists, policy makers and researchers, as it could be used to provide clinical recommendations for the choice of sequence of delivery room interventions.

Our review will have several methodological strengths. First, we will implement a wide comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work. Second, we will use the novel method for rating the confidence in the estimates recommended by the GRADE working group. Third, we will employ a novel SMAA model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes(60). On the other hand, we anticipate some methodological challenges while undertaking such a review. We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions. Based on the number of interventions identified following the systematic review, we may have to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results.

We hope that this review will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants.

Figure legend:

Figure 1: Physiological sequence of potential delivery room interventions

Table 1. A priori defined outcome measures

Outcome Measure	Definition
Bronchopulmonary dysplasia	No. of neonates who require oxygen at 36 weeks' postmenstrual age (PMA)
Mortality	Death before discharge
Severe intraventricular hemorrhage	No. of neonates with grades 3-4 based on the Papile criteria
Air leak syndromes	No. of neonates with pneumothorax or pulmonary interstitial emphysema confirmed by chest X ray
Retinopathy of prematurity (any stage)	No. of neonates with any stage of Retinopathy of prematurity as per the international classification of Retinopathy of prematurity
Neurodevelopmental impairment	No. of infants with any degree of neurodevelopmental impairment as assessed by a standardized and validated assessment tool, a child developmental specialist or both, at any age reported (outcome data grouped at 12, 18 and 24 months if available)

References

1. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. Journal of Pediatrics 1979;95(5 Pt 2):819-23.
2. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82(4):527-32.
3. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sánchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotten CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015;314(10):1039-51.
4. Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics 2006; 118: 108–113.
5. Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the Epicure study. Am J Respir Crit Care Med 2010; 182: 237–245.
6. Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, Baley J, Singer LT. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics. 2003;112(5):e359
7. Twilhaar ES, Wade RM, de Kieviet JF, van Goudoever JB, van Elburg RM, Oosterlaan J. Cognitive Outcomes of Children Born Extremely or Very Preterm since the 1990s and

Associated Risk Factors: A Meta-analysis and Meta-regression. JAMA Pediatr. 2018;172(4):361-367

8. Hillman NH, Moss TJM, Kallapur SG, Bachurski C, Pillow JJ, Polglase GR et al. Brief, large tidal volume ventilation initiates lung injury and a systemic response in fetal sheep. Am J Respir Crit Care Med 2007; 176: 575–581.
9. Wallace MJ, Probyn ME, Zahra VA, Crossley K, Cole TJ, Davis PG et al. Early biomarkers and potential mediators of ventilation-induced lung injury in very preterm lambs. Respir Res 2009; 10: 19.
10. Obladen M. Factors influencing surfactant composition in the newborn infant. Eur J Pediatr 1978; 128: 129–143.
11. Heldt GP, McIlroy MB. Distortion of chest wall and work of diaphragm in preterm infants. J Appl Physiol (1985) 1987; 62: 164–169.
12. Heldt GP, McIlroy MB. Dynamics of chest wall in preterm infants. J Appl Physiol (1985) 1987; 62: 170–174.
13. Foglia EE, Jensen EA, Kirpalani H. State of the Art Review: Delivery room interventions to prevent bronchopulmonary dysplasia in extremely preterm infants. Journal of perinatology : official journal of the California Perinatal Association. 2017;37(11):1171-1179.
14. Rich WD, Leone T, Finer NN. Delivery room intervention: improving the outcome. Clin Perinatol. 2010;37(1):189-202
15. Fogarty M, Osborn DA, Askie LM, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. The American Journal of Obstetrics & Gynecology 2018;218:1–18.

16. Schmölzer GM, Kumar M, Pichler G, et al. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ 2013;347:f5980
17. Pichler G, Urlesberger B, Schwaberger B, et al. Cerebral Oxygen Saturation to Guide Oxygen Delivery in Preterm Neonates for the Immediate Transition after Birth: A 2-Center Randomized Controlled Pilot Feasibility Trial. J Pediatr 2016;170:73–4.
18. Collaboration TC. The Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Higgins JPT, and Green, S., editor2011.
19. Jansen JP, Crawford B, Bergman G, Stam W. Bayesian Meta-Analysis of Multiple Treatment Comparisons: An Introduction to Mixed Treatment Comparisons. Value in Health. 2008;11(5):956-64.
20. Jonas DE, Wilkins TM, Bangdiwala S, Bann CM, Morgan LC, Thaler KJ, Amick HR, Gartlehner G. Findings of Bayesian Mixed Treatment Comparison Meta-Analyses: Comparison and Exploration Using Real-World Trial Data and Simulation [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Feb. Available from http://www.ncbi.nlm.nih.gov/books/NBK126109/ Accessed November 10, 2018.
21. Vento M, Cheung P-Y, Aguar M, et al. The first golden minutes of the extremely-low-gestational-age neonate: a gentle approach. Neonatology 2009;95:286–98.
22. Peleg B, Globus O, Granot M, et al. “Golden Hour” quality improvement intervention and short-term outcome among preterm infants. J Perinatol 2018;31:289.
23. Shah V, Hodgson K, Seshia M, et al. Golden hour management practices for infants <32 weeks gestational age in Canada. Paediatr Child Health 2018;23:70–6.

24. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

25. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777-84.

26. Papile L-A, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529–34

27. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org

28. PRISMA. Preferred Reporting Items for Systematic Reviews and Meta-Analyses [online]. [cited 2018 Accessed April 20]. Available from: http://www.prisma-statement.org/statement.htm

29. Introduction to Evidence Synthesis. In: Network Meta-Analysis for Decision Making [Internet]. John Wiley & Sons, Ltd; 2018. p. 1–17. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118951651.ch1

30. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011;342.

31. Higgins J, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2009;172(1):137-59.

32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71.

33. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical Tools for Network Meta-Analysis in STATA. PLoS One. 2013;8(10).

34. Mavridis D, Welton NJ, Salanti G. A selection model for accounting for publication bias in a full network meta-analysis. Stat Med. 2014;33:5399–412.

35. Lambert PC, Sutton AJ, Burton PR, Abrams KR, Jones DR. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. Statistics in medicine. 2005;24(15):2401.

36. Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. Annals of Internal Medicine. 2014;160(4):267-70.

37. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.

38. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials. Med Decis Mak. 2013;33:607.

39. Gelman A, Carlin J, Stern H, Dunson D, Vehtari A, Rubin D. Chapter 2: Single Parameter models. In: Bayesian data analysis. Third Edit. New York: CRC Press; 2015.

40. Gabry J, Simpson D, Vehtari A, Betancourt M, Gelman A. Visualization in Bayesian workflow. 2017;2. http://arxiv.org/abs/1709.01449.

41. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: Psychological interventions in coronary heart disease. Am J Epidemiol. 2009;169:1158–65.

42. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence Synthesis for Decision Making 3: Subgroups, Meta-Regression, Bias, and Bias-Adjustment. Med Decis Mak [Internet]. 2013;33(5):597–606. Available from: http://mdm.sagepub.com/content/33/5/597.full.pdf+html Accessed November 10, 2018

43. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. International journal of epidemiology. 2012;41(3):818-27.

44. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. Statistical science. 1992:457-72.

45. Plummer, M., 2016. JAGS: Just another Gibbs sampler. Available at http://mcmc-jags.sourceforge.net/. Accessed March, 14, 2017.

46. R Core Team. R: A language and environment for statistical computing. 2018. https://cran.r-project.org/.

47. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades a E. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making [Internet]. 2013;33(5):641–56.

48. Jackson D, Barrett JK, Rice S, White IR, Higgins JPT. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. Stat Med. 2014;33:3639–54.

49. Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. J Clin Epidemiol. 2015;68(1):52-60.

50. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

51. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology. 2011;64(4):401-6.

52. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). Journal of clinical epidemiology. 2011;64(4):407-15.

53. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. Journal of clinical epidemiology. 2011;64(12):1283-93.

54. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. Journal of clinical epidemiology. 2011;64(12):1294-302.

55. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. Journal of clinical epidemiology. 2011;64(12):1277-82.

56. Donegan S, Williamson P, Gamble C, Tudur-Smith C. Indirect comparisons: a review of reporting and methodological quality. PLoS One. 2010;5(11):e11054.

57. Baker SG, Kramer BS. The transitive fallacy for randomized trials: if A bests B and B bests C in separate trials, is A better than C? BMC Med Res Methodol. 2002;2:13.

58. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Annals of internal medicine. 2013;159(2):130-7.

59. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630.

60. Van Valkenhoef G, Tervonen T, Zhao J, De Brock B, Hillege HL, Postmus D. Multicriteria benefit-risk assessment using network meta-analysis. J Clin Epidemiol. 2012;65:394–403.

61. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 5: The baseline natural history model. Med Decis Mak. 2013;33(5):657–70.

62. Tervonen T. New directions in Stochastic Multicriteria Acceptability Analysis. 2007 Dec 1 [cited 2018 Nov 11]; Available from: http://www.utupub.fi/handle/10024/28151

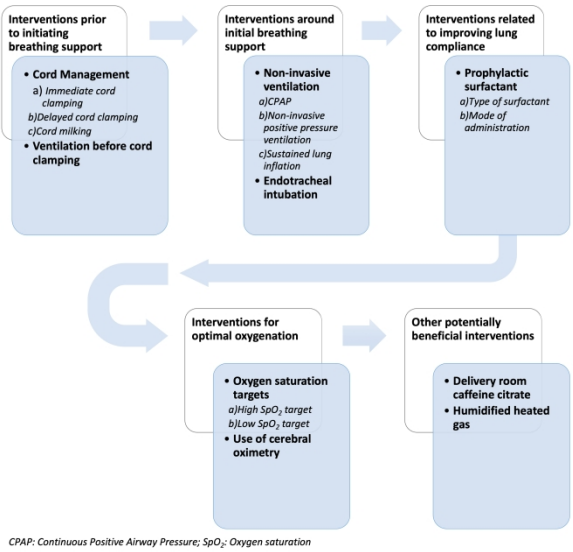

Figure 1: Physiological sequence of potential delivery room interventions

903x508mm (144 x 144 DPI)

Appendix 1: Search strategy for EMBASE, Medline, and PubMed

EMBASE

(newborn OR infant OR neonate OR preterm OR premature) AND [randomized controlled trial]/lim

AND

(continuous AND positive AND airway AND pressure OR cpap OR (nasal AND continuous AND positive AND airway AND pressure) OR ncpap OR (positive AND pressure AND ventilation) OR (intermittent AND positive AND pressure AND ventilation) OR (sustained AND lung AND inflation) OR (sustained AND inflation) OR si) AND [randomized controlled trial]/lim

OR

(supplemental AND oxygen OR (supplemental AND oxygen AND during AND resuscitation) OR oxygen OR surfactant OR (surfactant AND administration) OR (surfactant AND administration, AND early) OR (surfactant AND administration, AND late) OR (minimally AND invasive AND surfactant AND therapy) OR ('less invasive' AND surfactant AND administration)) AND [randomized controlled trial]/lim

OR

(lisa OR intubation OR (endotracheal AND intubation) OR (mechanical AND ventilation) OR caffeine OR (caffeine AND citrate) OR (respiratory AND function AND monitor) OR (delayed AND cord AND clamping) OR (cord AND milking)) AND [randomized controlled trial]/lim

AND

(randomized AND controlled AND trial OR 'randomized controlled trial':it OR (clinical AND trial)) AND [randomized controlled trial]/lim

AND

[randomized controlled trial]/lim AND [embase]/lim AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim)

Limited to embryo from Age Groupsfetus from Age Groupsnewborn from Age Groupsinfant from Age Groups

Medline

Set	Run Search **MEDLINE** **Search History - " BPD"**
#5	#3 AND #2 AND #1 Refined by: **PUBLICATION TYPES:** (RANDOMIZED CONTROLLED TRIAL) *DocType=All document types; Language=All languages;*
#4	#3 AND #2 AND #1 *DocType=All document types; Language=All languages;*
#3	(MH=randomized controlled trial OR TS=randomized controlled trial OR TS=clinical trial) *AND* **DOCUMENT TYPES:** (Randomized Controlled Trial) *DocType=All document types; Language=All languages;*
#2	TS=continuous positive airway pressure OR TS=CPAP OR TS=nasal continuous positive airway pressure OR TS=nCPAP OR TS=positive pressure ventilation OR TS=intermittent positive pressure ventilation OR TS=sustained lung inflation OR TS=sustained inflation OR TS=SI OR TS=supplemental oxygen OR TS=supplemental oxygen during resuscitation OR TS=oxygen OR TS=surfactant OR TS=surfactant administration OR TS=surfactant administration, early OR TS=surfactant administration, late OR TS=minimally invasive surfactant therapy OR TS=less-invasive surfactant administration OR TS=LISA OR TS=intubation OR TS=endotracheal intubation OR TS=mechanical ventilation OR TS=caffeine OR TS=caffeine citrate OR TS=respiratory function monitor OR TS=delayed cord clamping OR TS=cord milking *DocType=All document types; Language=All languages;*
#1	TS=newborn OR TS=premature OR TS=infant OR TS=neonate OR TS=preterm *DocType=All document types; Language=All languages;*

PubMed

#1 MeSH descriptor: [Infant] explode all trees

#2 infant*:ti,ab

#3 neonat*:ti,ab

#4 newborn*:ti,ab

#5 preterm:ti,ab

#6 premature:ti,ab

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 "continuous positive airway pressure":ti,ab

#9 "positive pressure ventilation":ti,ab

#10 (sustained near/2 inflation):ti,ab

#11 (supplemental near/2 oxygen):ti,ab

#12 oxygen:ti,ab

#13 surfactant:ti,ab

#14 intubation:ti,ab

#15 (mechanical* near/1 ventilat*):ti,ab

#16 caffeine:ti,ab

#17 "respiratory function monitor":ti,ab

#18 (cord near/2 ((clamping and delayed) or milking)):ti,ab

#19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18

#20	#7 and #19

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028066.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Jun-2019
Complete List of Authors:	Mitra, Souvik; Dalhousie University, IWK Health Center, Department of Pediatrics Disher, Timothy; School of Nursing, Dalhousie University Pichler, Gerhard; Medical University of Graz, Research Unit for Neonatal Micro- and Macrocirculation, Department of Pediatrics D'Souza, Brandon; IWK Health Centre, Department of Respiratory Therapy Mccord, Helen; Dalhousie University, IWK Health Center, Department of Pediatrics Chayapathi, Varsha; Dalhousie University, IWK Health Center, Department of Pediatrics Jones, Karlee; Dalhousie University, IWK Health Center, Department of Pediatrics Schm&#65533;lzer, Georg; Royal Alexandra Hospital, Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, ; University of Alberta, Department of Pediatrics
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Research methods
Keywords:	Infants, Bronchopulmonary dysplasia, Delivery Room, Newborn

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

Souvik Mitra MD MSc[1], Timothy Disher PhD(c), RN[2], Gerhard Pichler MD[3], Brandon D'Souza BHSc, RRT[6], Helen Mccord MN[1], Varsha Chayapathi MBBS, DNB[1], Karlee Jones BScPharm, ACPR[1], Georg M. Schmölzer MD, PhD[4,5]

[1]Department of Pediatrics, Dalhousie University, IWK Health Center, Halifax, Canada

[2]School of Nursing, Dalhousie University, Halifax Nova Scotia, Canada

[3]Research Unit for Neonatal Micro- and Macrocirculation, Department of Pediatrics, Medical University of Graz, Austria

[4]Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, Royal Alexandra Hospital, Edmonton, Alberta, Canada

[5]Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

[6]Department of Respiratory Therapy, IWK Health Centre, Halifax, Nova Scotia, Canada

Corresponding author:

Georg M. Schmölzer, MD, PhD

Centre for the Studies of Asphyxia and Resuscitation,

Neonatal Research Unit, Royal Alexandra Hospital,

10240 Kingsway Avenue NW,

T5H 3V9, Edmonton, Alberta, Canada

Telephone +1 780 735 4660

Fax: +1 780 735 4072

Email: georg.schmoelzer@me.com

Conflict of Interest:

SM, GP, VC, have declared no conflict of interest. TD provides methodological advice for Cornerstone Research Group Inc. Cornerstone Research Group Inc. consults for various pharmaceutical and medical device companies. BD has provided device training and educational presentations to clinicians on behalf of Mallinckrodt Pharmaceuticals. GMS has registered the RETAIN neonatal resuscitation board (Tech ID 2017083) and RETAIN neonatal resuscitation video game (Tech ID 2017086) under Canadian copyright, and GMS is the owner of RETAIN Labs Inc. (https://www.playretain.com), which is distributing these games.

Keywords: INFANTS, NEWBORN, DELIVERY ROOM, BRONCHOPULMONARY DYSPLASIA

Funding sources

We would like to thank the public for donating money to our funding agencies: GMS is a recipient of the Heart and Stroke Foundation/University of Alberta Professorship of Neonatal Resuscitation, a National New Investigator of the Heart and Stroke Foundation Canada and an Alberta New Investigator of the Heart and Stroke Foundation Alberta. This research has been facilitated by the Women and Children's Health Research Institute through the generous support of the Stollery Children's Hospital Foundation.

Abstract: 250 words

Manuscript: 3,963 words

Tables: 1

Figures: 1

Author's contribution:

Conception and design: GMS, SM

Data analysis plan: GMS, SM, GP, TD, BDS, HM, VC, KJ

Drafting of the article: GMS, SM, GP, TD, BDS, HM, VC, KJ

Critical revision of the article for important intellectual content: GMS, SM, GP, TD, BDS, HM, VC, KJ

Final approval of the article: GMS, SM, GP, TD, BDS, HM, VC, KJ

Abbreviations:

BPD	- Bronchopulmonary dysplasia
ELGAN	- Extremely low gestational age newborns
IQ	- Intelligence quotient
CPAP	- Continuous positive airway pressure
NMA	- Network meta-analysis
RE	- Random-effects model
RCT	- Randomized controlled trials
INSURE	- Intubate-Surfactant-Extubate technique
LISA/MIST	- Less-invasive surfactant administration/minimally invasive surfactant therapy
ROB	- Risk of bias
CrIs	- Credible intervals
RR	- Risk ratio
SUCRA	- Surface Under the Cumulative Ranking curve
FE	- Fixed-effect model
FOL	- First-order loops
SMAA	- Stochastic multicriteria acceptability analysis

Abstract

Introduction

As gestational age decreases, incidence of bronchopulmonary dysplasia (BPD) and chronic lung disease increases. There are many interventions used in the delivery room to prevent acute lung injury and consequently BPD in these patients. The availability of different treatment options often poses a practical challenge to the practicing neonatologist when it comes to making an evidence based choice as the multitude of pairwise systematic reviews including Cochrane reviews that are currently available only provide a narrow perspective through head-to-head comparisons.

Methods and Analysis

We will conduct a systematic review of all randomized controlled trials evaluating delivery room interventions within the 1st golden hour after birth for prevention of BPD. The primary outcome BPD. Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. We will search from their inception to August 2018, the following databases: Medline, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) as well as grey literature resources. Two reviewers will independently screen titles and abstracts, review full texts, extract information, and assess the risk of bias (ROB) and the confidence in the estimate (with Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach). This review will use Bayesian network meta-analysis approach which allows the comparison of the multiple delivery room interventions for prevention of BPD. We will perform a Bayesian network meta-analysis to combine the pooled direct and indirect treatment effect estimates for each outcome, effectiveness, and safety of delivery room interventions for prevention of BPD.

Ethics and Dissemination

The proposed protocol is a network meta-analysis, which has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). The results will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants. Furthermore, we will identify knowledge gaps and will encourage further research for other

therapeutic options. Therefore, its results will be disseminated through peer-reviewed publications and conference presentations. Due to the nature of the design, no ethics approval is necessary.

Strengths and limitations of this study

Strengths:

- Comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work
- Use the novel method for rating the confidence in the estimates recommended by the GRADE working group
- We will employ a novel Stochastic multicriteria acceptability analysis model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes

Limitations:

- We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions
- Potential to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results

Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory morbidity associated with premature birth. BPD is defined as either need of supplemental oxygen at i) 28 days postnatal age(1), or ii) 36 weeks' postmenstrual age with or without compatible clinical and radiographic findings(2). BPD affects 30-60% of prematurely born infants with the incidence being inversely proportional to gestational age(3). With increased survival of extremely low gestational age newborns (ELGAN), the incidence of BPD continues to increase despite improvement in neonatal care practices over the last two decades(3). BPD is known to be associated with long-term respiratory morbidity that persists into adolescence and adulthood(4,5). There is also increasing evidence that BPD and duration on supplemental oxygen have long-term adverse effects on cognitive and academic achievement with each percent increase in BPD rate being associated with a 0.01 standard deviation decrease in intelligence quotient (IQ) (0.15 IQ points) ($p<0.001$)(6,7).

Several antenatal, perinatal, and postnatal factors contribute to the development of BPD. It is postulated that early lung injury and inflammation play an important role in the pathogenesis of BPD (8,9). In the fetus, the gas exchange organ is the placenta and the function of gas exchange is transferred from the placenta to the lungs immediately after birth. Therefore, the newborn infant's lungs must open and be aerated to allow the transition from fetal to postnatal circulation and physiology. However, in ELGANs, several physiological factors prevent this transition. These include lack of surfactant leading to increased alveolar surface tension, non-compliant chest wall, and weak respiratory muscles(10-12). Therefore, most ELGANs require assisted ventilation and/or supplemental oxygen after birth to ensure optimal gas exchange. However, both therapies may also induce lung inflammation due to barotrauma and/or volutrauma and oxygen-free radical generation thereby initiating the pathogenesis of BPD. Therefore, any interventions targeted at limiting lung injury and oxidative stress during resuscitation in the delivery room immediately after the birth may help to prevent the development of BPD or reduce its severity.

A number of clinical trials have been conducted on a variety of delivery room interventions, including i) interventions prior to initiating breathing support (i.e., clamping vs. milking the umbilical cord); ii) interventions around initial breathing support (i.e., continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation, sustained lung inflation or endotracheal intubation); iii) interventions related to improving lung compliance (i.e., prophylactic

surfactant therapy including the different variations in its administration modalities); iv) interventions related to minimizing oxidative stress (i.e., higher vs. lower oxygen saturation targets), v) use of cerebral oximetry, and vi) other potentially beneficial therapies such as caffeine administration (Figure 1)(13,14).

The availability of multiple potential interventions in a resuscitation scenario often poses a practical challenge to health care professionals as to which sequence of interventions would provide the greatest likelihood of minimizing BPD and which interventions are unnecessary and unlikely to be of any benefit(13). There have been previous systematic reviews and pairwise meta-analyses on the different competing interventions such as initial breathing support and oxygen saturation targets(15-17). However, these meta-analyses, though well conducted, provide a narrow perspective to the situation where a sequence of non-competing interventions occur within a short time-frame whereas each intervention has potentially competing variations. Use of a network meta-analysis (NMA) framework may help to provide a more feasible, comprehensive and evidence-based solution to the dilemma that health care professionals face during resuscitation of ELGANs with regards to multiple competing interventions aimed at mitigating lung injury. The Cochrane handbook considers NMA as a highly valuable tool to evaluate and rank treatment options according to their safety and effectiveness(18). Bayesian NMA have been proposed as an effective method for evaluating the effectiveness of multiple competing interventions(18-20). Delivery room interventions consist of a sequence of non-competing category of interventions and within each category there are several potentially competing interventions (Figure 1). Given that many of these competing delivery room interventions have not been compared in head-to-head studies, we expect that some of the possible comparisons between the interventions will not have direct evidence. Hence, we will perform a random effects network meta-analysis (NMA). Delivery room interventions will be defined as all potential interventions in the immediate postnatal period(21-23).

OBJECTIVES

To determine the relative effectiveness of commonly practiced delivery room interventions for preterm infants born <33 weeks of gestation in preventing BPD using a Bayesian network meta-analysis.

METHODS & DESIGN

This systematic review and NMA protocol has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). This protocol was developed following the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance(24). The final report will comply with the recommendations of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions(25).

Search Strategy

We will search from their inception to August 2018, the following databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). We will use combination of controlled terms (Medical Subject Heading, MeSH, and Emtree), and free-text terms with various synonyms for the different possible delivery room interventions and BPD. Search alerts will be set up for monthly notification and the search will be repeated before the final manuscript submission to identify any new relevant trials. Search strategies have been developed with liaison with an experienced librarian. No language, publication status or date limit will be used. The search strategies have been detailed in appendix A.

We will seek registered details of selected trials in the U.S. National Institutes of Health resource (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform Search Portal. We intend to obtain additional grey literature from personal communication from experts in the field, reviewing the reference lists of relevant articles, abstracts and conference proceedings (Society for Pediatric Research, European Society for Pediatric Research) and seeking results of unpublished trials. We intend to contact authors of unpublished work and authors of published trials in order to clarify information that is not clear in the articles.

Eligibility Criteria

We will include randomized controlled trials (RCTs) that evaluate the effectiveness of commonly practiced delivery room interventions. Studies will have to have the following characteristics regarding participants, intervention, control and type of study.

a) Participants: Preterm infants (<33 weeks) requiring intervention(s) during neonatal transition within the 1st golden hour after birth

b) Interventions include the following: i) cord management (including immediate cord clamping, delayed cord clamping, cord milking, and/or resuscitation attached to the cord); ii) respiratory support (including positive pressure ventilation, CPAP, sustained lung inflation, and/or intubation, and mechanical ventilation); iii) surfactant delivery (type of surfactant delivered via endotracheal tube or laryngeal mask, INSURE (Intubate-Surfactant-Extubate) technique, LISA/MIST (less-invasive surfactant administration/minimally invasive surfactant therapy), and/or nebulized surfactant administration; iv) initial fractional concentration of inspired oxygen (FiO_2) ($\leq$0.3 or $\geq$0.6); v) monitoring during resuscitation (respiratory function monitor, near-infrared spectroscopy); vi) medication (e.g., caffeine citrate, or diuretics); vii) use of heated, humidified gas

c) Comparator: One or more of the above interventions compared to each other or no treatment.

Since interventions possible in a delivery room are largely related to delivery room resources, we have *a priori* decided to only include interventions that the infants were subjected to in the immediate postnatal period irrespective of whether these interventions were physically carried out in the room where the infant was born. Studies that examined interventions that were carried out after the initial stabilization period (no randomization within the first hour after birth e.g., feeding, indomethacin, antibiotics) will be excluded from the review. Furthermore, studies must have randomized within the first hour after birth to be eligible. This approach potentially will include studies with randomization within the first hour after birth but study intervention administration within the first two hours after birth (e.g. surfactant or caffeine administration).

Outcomes

Our primary outcome is bronchopulmonary dysplasia (defined as oxygen requirement at 36 weeks'postmenstrual age). Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria)(26); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. All the outcomes, its definitions and measures are detailed in the table 1. We aim to perform one subgroup analysis comparing infants <28 weeks versus 29-32 weeks.

Patient and Public Involvement

Neither patients nor public were involved in the development of the research question or design of this study. This network meta-analysis does not recruit any patients. The study will be published and presented at conferences to healthcare professionals.

Study selection

The titles and abstracts retrieved will be screened by two independent reviewers in duplicate to assess its eligibility using the Covidence platform (27). As a second step, the full text articles of the potentially eligible studies will be screened to assess their eligibility. We will include the full text of all studies for which both reviewers agree about their inclusion. For both steps, any disagreements between the reviewers will be resolved by discussion and if no agreement can be reached, a third member of the team will decide whether the study shall be included or not. We will refer to inclusion and exclusion criteria during the screening process. Records of ineligible full text articles along with the reason for ineligibility will be saved for future reference. Eligible articles citations will be uploaded to Covidence. We will present the PRISMA flow diagram(28) demonstrating the search and screening process.

Data Abstraction

A pre-specified standardized data extraction form in a Microsoft Excel sheet will be used to extract the data from the eligible studies. The data extraction form will be pilot tested independently by all reviewers before its use, to standardize the process. Eight reviewers will carry out the extraction, working independently in pairs and in duplicate. In case of disagreement in assessing the methodological quality of the study we will try to resolve it by consensus. If consensus cannot be reached a third designated reviewer will be involved. We will contact authors of primary studies, during data extraction, to provide any missing information.

Node Formation

Within each component of the stabilization pathway, we anticipate the identification numerous similar non-competing interventions (e.g. multiple synthetic and natural surfactants). In an iterative process, clinical experts (GS, SM, GP) blinded to the implications for effect estimates, will come to consensus on definitions of nodes and be presented with the implications of those decisions via network diagrams (e.g. lumping causing the loss of trials comparing lumped

interventions, splitting causing disconnected networks). Experts will then be asked to identify whether groups of treatments should be defined as classes (e.g. natural vs synthetic surfactant) or lumped together. Class-based models have the advantage of offering an estimate of class effect as well as shrunken effects of individual treatments, while lumping can allow for more robust estimation of between-trial variability, and can reduce the probability of chance violations of NMA assumptions. This process will be repeated until a consensus decision is reached on the node making algorithm that meets the criteria of satisfying clinical demands, preserving the assumption that interventions within nodes are sufficiently similar, and presenting data in the least aggregated form possible(29).

Assessment of Risk of Bias

The risk of bias (ROB) of eligible studies will be assessed according to a modified version of the Cochrane Collaboration's ROB tool(18). The six criteria to be assessed are sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain will be assigned a score 'definitely low risk', or 'definitely high risk' or 'unclear risk'. Two independent reviewers will assess the ROB. We will try to reach consensus when disagreements between two reviewers when assessing the methodological quality of the studies. Nevertheless, if consensus cannot be reached, a third reviewer will resolve it.

Measures of Treatment Effect

Effect estimates along with 95% credible intervals (CrIs) will be estimated using risk ratios (RR) calculated using methods described by Dias, using the baseline risk parameter to convert odds ratios to risk ratios(29). When random effect models are used estimates will also be accompanied by their 95% predictive interval representing the interval within which we would expect the treatment effect of a future study to lie(30,31). Relative treatment rankings will be summarized using mean ranks with their 95% credible intervals and the Surface Under the Cumulative Ranking curve (SUCRA) values and cumulative probability rankograms(32). SUCRAs range from 0% to 100% with values of 100% representing a hypothetical treatment that is always best without uncertainty.

Assessment of reporting bias

We will construct a comparison adjusted funnel plot for the network to assess the potential publication bias and small-study effects(33), if we retrieve at least 10 studies. We will inspect plots visually for evidence of asymmetry and if publication bias is suspected we will conduct a sensitivity analysis using models described by Mavridis, Welton and Salanti(34).

Assessment of Transitivity Assumption

Clinical experts (GS, GP, SM) will assess trial characteristics using tables and visualizations to assess whether the transitivity assumption is likely to hold. The characteristics to be evaluated are those that are expected to be effect modifiers and will include gestational age, birth weight, baseline event risk, and ROB. These assessments will be made prior to any meta-analysis to limit to influence of presence or absence of statistical heterogeneity on the assessment of the transitivity assumption. The decision to pool data will be based on consensus. If it is determined that quantitative synthesis is inappropriate, we will summarize our findings narratively.

Direct treatment comparisons

Given that we expect clinical and methodological heterogeneity among the studies (see below in Rating the Confidence in Estimates section), which in turn will create statistical heterogeneity, we will pool evidence for each treatment comparison using a Bayesian random-effects (RE) model(35). In comparison to the fixed-effect model (FE), the RE model is conservative in the sense that it accounts for both within- and between-study variability. The RE model assumes that the observed treatment effect for a study is a combination of a treatment effect common to all studies plus a component specific to that study alone(36,37). Models will be based on standard code modified to include minimally informative priors on baselines, treatment effects, and between trial heterogeneity (38). These priors generally provide more stable estimates, particularly in cases where data are sparse, will be developed using the approach described by Gabry *et al* (39,40).

The Network Meta-Analysis

For each outcome, we will present the network diagram and a forest plot compared against the common comparator with the network estimates as well as league tables showing all pairwise comparisons. To capture the non-competing nature of interventions along the stabilization pathway and to directly fulfill the research objectives we will use component models as described by Welton *et al*(41). These models assume that interventions across domains of the stabilization pathway are additive on additive on logit scale for dichotomous outcomes (e.g. mortality). In the absence of direct evidence for a given comparison an indirect comparison will provide an estimate of the treatment effect. In the presence of direct evidence, the NMA will provide a combined estimate (i.e., direct and indirect evidence)(32). For instance, in a triangular network ABC composed by studies that directly compare A vs. B and A vs. C treatments, we can indirectly estimate the effect of B vs. C treatments. In case direct evidence of B vs. C treatment comparison is also available, then a combined estimate of direct and indirect evidence of B vs. C can be calculated using a NMA.

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). We will assess heterogeneity by estimating the magnitude of the between-study variance (42). 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. Markov chains will be run for a sufficient number of iterations to reach convergence, which we will assess on the basis of the Brooks-Gelman-Rubin diagnostic, with values less than 1.05 considered acceptable if consistent with visual inspection of convergence and time series plots(44). All analyses will be performed in JAGS or similar software via the statistical program R(45,46).

Assessment of Inconsistency

Inconsistency is the statistical manifestation of the violation of the transitivity assumption, which presents as a disagreement between direct and indirect estimates (loop inconsistency), and/or inconsistency between studies that inform the same treatment comparison, but include a different number of treatment arms (design inconsistency). To evaluate both design and loop inconsistency, we will apply the design-by-treatment interaction model with random inconsistency effects (47,48). These findings will be interpreted within the context of the estimate of between-trial variance as these concepts are closely related and difficult to separate. For example, large estimates of between-trial variance are indicative of heterogeneity within direct comparisons but may also be the result of inconsistency between direct and indirect evidence.

Exploration of heterogeneity and inconsistency

We will perform a network meta-regression using of potential effect modifiers to explore important heterogeneity and/or inconsistency. We propose, the following potential sources of heterogeneity, which could be possible effect modifiers: gestational age, birth weight and ROB. We hypothesize that lower gestational age, and low ROB will be related to less effectiveness of interventions. Overall risk of bias will be determined by taking the average of the three most important risk of bias items identified by expert consensus (sequence generation, allocation concealment, and blinding). Meta-regression models will assume a single shared coefficient for all non-baseline treatments(42). Interpretation of meta-regression models will be in keeping with suggestions from Dias et al., namely: (1) Inclusion of the coefficient leads to a decrease in the estimate of between-study variance; and (2) The 95% credible intervals of the estimated coefficient exclude the null (42).

Sensitivity Analyses

We plan to perform sensitivity analyses of different heterogeneity priors to assess the robustness of results(35,43,49). Further, findings from component models will be compared against a model without this assumption. In both cases, we will compare model fit using both absolute (residual deviance) and relative (DIC) measures as well as a qualitative assessment of whether the analysis leads to an important change in effect estimates.

Rating the confidence in estimates of the effect

We will assess the confidence in the estimates for each outcome using the GRADE approach (50). For this purpose, two authors will independently do the assessment. The confidence in the estimates will be based on four levels: high, moderate, low and very low. For the direct comparisons we will assess and rate each outcome based on the categories: ROB imprecision, inconsistency and publication bias(51-55). To assist with assessment of each domain, we will use threshold plots, which show the smallest change in study/contrast level estimates required to change the conclusions of the analysis.

We will assess and rate the confidence in all the indirect comparisons –if available- obtained from first order loops following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. Transitivity, also called similarity(56), is the assumption that an indirect comparison is a valid method to compare two treatments that have not been compared in a head-to-head trial, because the studies are sufficiently similar in important clinical and methodological characteristics, or in other words, that they are similar in their distributions of effect modifiers(57,58). Then, we will rate the confidence in each NMA effect estimate using the higher rating when both direct and indirect evidence are present.

We will assess and rate the confidence in estimates of effect from the direct comparisons in our pairwise meta-analyses described previously. To rate the confidence in the indirect comparisons, we will focus our assessments on first-order loops (FOLs), i.e., loops connected to the interventions of interest through only one other intervention. For instance, if for A, B and C interventions, there are direct comparisons of A vs. B (AB) and B vs. C (BC), we will be able to indirectly estimate the effects of A vs. C (AC). The AC indirect estimation will be a FOL. We will choose the FOLs with the lowest variances for rating the confidence as they contribute the most to the estimates of effect.

Within FOLs, the indirect comparison confidence will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For example, if we find that AB has moderate confidence and BC has high confidence, we will judge the associated indirect comparison, AC, as moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption has been violated.

Our overall judgment of confidence in the NMA estimate for any pairwise comparison will be the higher of the confidence rating amongst the contributing direct and indirect comparisons.

However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates have inconsistency. For this purpose, the GRADE approach recommends to assess the incoherence (or inconsistency as described in the 'The Network Meta-Analysis' section) criteria, which is defined as the differences between direct and indirect estimates of effect(59).

Multi-criteria Acceptability Analysis

Network meta-analyses provide an estimate of effect estimates of competing interventions, but this alone is not sufficient to aid decision making. We will aim to supplement this review with a stochastic multi-criteria acceptability analysis using methods defined by Tervonen, and Van Valkenhoef(60). These methods use a partial value function to allow for a quantitative risk-benefit analysis across multiple outcomes, given an ordinal ranking of importance for decision making (e.g. Mortality > BPD). Based on the best fitting NMA model, we will conduct stochastic multicriteria acceptability analyses (SMAA): One without preference criteria, and a second with preference criteria determined by expert consensus. Since SMAA is based on estimates constrained to the interval [0,1] we will calculate absolute risk of outcomes based on either a suitably designed observational trial or, if unavailable, a pooled control arm risk of included studies in the reference treatment(61). If treatments require the tradeoff of common (e.g. BPD) and very rare (e.g. mortality) events, we will use the 95% credible interval hull approach(62). The outputs of the SMAA will be a rankogram outlining the probability that a treatment is best, second best, etc., a vector of central weights, a confidence factor for the preference free model; and the rankogram for the ordered model. The vector of central weights provides a summary of the implied preferences required to hold an *a priori* preference for one treatment or another (i.e. the outcome preference implied by a clinician's current practice). The confidence factor is the probability that a treatment is best given these preferences, and is used as a measure of uncertainty.

Discussion

Interventions in the immediate postnatal period may have long-term clinical implications. This NMA will provide the relative effectiveness of commonly practiced delivery room interventions for preterm infants born <33 weeks of gestation in preventing BPD. To the best of our knowledge this will be the first review that will examine the relative effectiveness of each delivery room intervention individually and in combination with respect to important clinical

outcomes using novel statistical techniques. Its results will be of interest for a broad range of audience: practice guideline developers, pediatricians, neonatologists, policy makers and researchers, as it could be used to provide clinical recommendations for the choice of sequence of delivery room interventions.

Our review will have several methodological strengths. First, we will implement a wide comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work. Second, we will use the novel method for rating the confidence in the estimates recommended by the GRADE working group. Third, we will employ a novel SMAA model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes(60). On the other hand, we anticipate some methodological challenges while undertaking such a review. We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions. Based on the number of interventions identified following the systematic review, we may have to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results.

We hope that this review will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants.

Figure legend:

Figure 1: Physiological sequence of potential delivery room interventions

Table 1. A priori defined outcome measures

Outcome Measure	Definition
Bronchopulmonary dysplasia	No. of neonates who require oxygen at 36 weeks' postmenstrual age (PMA)
Mortality	Death before discharge
Severe intraventricular hemorrhage	No. of neonates with grades 3-4 based on the Papile criteria
Air leak syndromes	No. of neonates with pneumothorax or pulmonary interstitial emphysema confirmed by chest X ray
Retinopathy of prematurity (any stage)	No. of neonates with any stage of Retinopathy of prematurity as per the international classification of Retinopathy of prematurity
Neurodevelopmental impairment	No. of infants with any degree of neurodevelopmental impairment as assessed by a standardized and validated assessment tool, a child developmental specialist or both, at any age reported (outcome data grouped at 12, 18 and 24 months if available)

References

1. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. Journal of Pediatrics 1979;95(5 Pt 2):819-23.
2. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82(4):527-32.
3. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sánchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotten CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015;314(10):1039-51.
4. Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics 2006; 118: 108–113.
5. Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the Epicure study. Am J Respir Crit Care Med 2010; 182: 237–245.
6. Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, Baley J, Singer LT. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics. 2003;112(5):e359
7. Twilhaar ES, Wade RM, de Kieviet JF, van Goudoever JB, van Elburg RM, Oosterlaan J. Cognitive Outcomes of Children Born Extremely or Very Preterm since the 1990s and

Associated Risk Factors: A Meta-analysis and Meta-regression. JAMA Pediatr. 2018;172(4):361-367

8. Hillman NH, Moss TJM, Kallapur SG, Bachurski C, Pillow JJ, Polglase GR et al. Brief, large tidal volume ventilation initiates lung injury and a systemic response in fetal sheep. Am J Respir Crit Care Med 2007; 176: 575–581.
9. Wallace MJ, Probyn ME, Zahra VA, Crossley K, Cole TJ, Davis PG et al. Early biomarkers and potential mediators of ventilation-induced lung injury in very preterm lambs. Respir Res 2009; 10: 19.
10. Obladen M. Factors influencing surfactant composition in the newborn infant. Eur J Pediatr 1978; 128: 129–143.
11. Heldt GP, McIlroy MB. Distortion of chest wall and work of diaphragm in preterm infants. J Appl Physiol (1985) 1987; 62: 164–169.
12. Heldt GP, McIlroy MB. Dynamics of chest wall in preterm infants. J Appl Physiol (1985) 1987; 62: 170–174.
13. Foglia EE, Jensen EA, Kirpalani H. State of the Art Review: Delivery room interventions to prevent bronchopulmonary dysplasia in extremely preterm infants. Journal of perinatology : official journal of the California Perinatal Association. 2017;37(11):1171-1179.
14. Rich WD, Leone T, Finer NN. Delivery room intervention: improving the outcome. Clin Perinatol. 2010;37(1):189-202
15. Fogarty M, Osborn DA, Askie LM, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. The American Journal of Obstetrics & Gynecology 2018;218:1–18.

16. Schmölzer GM, Kumar M, Pichler G, et al. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ 2013;347:f5980
17. Pichler G, Urlesberger B, Schwaberger B, et al. Cerebral Oxygen Saturation to Guide Oxygen Delivery in Preterm Neonates for the Immediate Transition after Birth: A 2-Center Randomized Controlled Pilot Feasibility Trial. J Pediatr 2016;170:73–4.
18. Collaboration TC. The Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Higgins JPT, and Green, S., editor2011.
19. Jansen JP, Crawford B, Bergman G, Stam W. Bayesian Meta-Analysis of Multiple Treatment Comparisons: An Introduction to Mixed Treatment Comparisons. Value in Health. 2008;11(5):956-64.
20. Jonas DE, Wilkins TM, Bangdiwala S, Bann CM, Morgan LC, Thaler KJ, Amick HR, Gartlehner G. Findings of Bayesian Mixed Treatment Comparison Meta-Analyses: Comparison and Exploration Using Real-World Trial Data and Simulation [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Feb. Available from http://www.ncbi.nlm.nih.gov/books/NBK126109/ Accessed November 10, 2018.
21. Vento M, Cheung P-Y, Aguar M, et al. The first golden minutes of the extremely-low-gestational-age neonate: a gentle approach. Neonatology 2009;95:286–98.
22. Peleg B, Globus O, Granot M, et al. “Golden Hour” quality improvement intervention and short-term outcome among preterm infants. J Perinatol 2018;31:289.
23. Shah V, Hodgson K, Seshia M, et al. Golden hour management practices for infants <32 weeks gestational age in Canada. Paediatr Child Health 2018;23:70–6.

24. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

25. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777-84.

26. Papile L-A, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529–34

27. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org

28. PRISMA. Preferred Reporting Items for Systematic Reviews and Meta-Analyses [online]. [cited 2018 Accessed April 20]. Available from: http://www.prisma-statement.org/statement.htm

29. Introduction to Evidence Synthesis. In: Network Meta-Analysis for Decision Making [Internet]. John Wiley & Sons, Ltd; 2018. p. 1–17. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118951651.ch1

30. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011;342.

31. Higgins J, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2009;172(1):137-59.

32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71.

33. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical Tools for Network Meta-Analysis in STATA. PLoS One. 2013;8(10).

34. Mavridis D, Welton NJ, Salanti G. A selection model for accounting for publication bias in a full network meta-analysis. Stat Med. 2014;33:5399–412.

35. Lambert PC, Sutton AJ, Burton PR, Abrams KR, Jones DR. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. Statistics in medicine. 2005;24(15):2401.

36. Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. Annals of Internal Medicine. 2014;160(4):267-70.

37. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.

38. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials. Med Decis Mak. 2013;33:607.

39. Gelman A, Carlin J, Stern H, Dunson D, Vehtari A, Rubin D. Chapter 2: Single Parameter models. In: Bayesian data analysis. Third Edit. New York: CRC Press; 2015.

40. Gabry J, Simpson D, Vehtari A, Betancourt M, Gelman A. Visualization in Bayesian workflow. 2017;2. http://arxiv.org/abs/1709.01449.

41. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: Psychological interventions in coronary heart disease. Am J Epidemiol. 2009;169:1158–65.

42. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence Synthesis for Decision Making 3: Subgroups, Meta-Regression, Bias, and Bias-Adjustment. Med Decis Mak [Internet]. 2013;33(5):597–606. Available from: http://mdm.sagepub.com/content/33/5/597.full.pdf+html Accessed November 10, 2018

43. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. International journal of epidemiology. 2012;41(3):818-27.

44. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. Statistical science. 1992:457-72.

45. Plummer, M., 2016. JAGS: Just another Gibbs sampler. Available at http://mcmc-jags.sourceforge.net/. Accessed March, 14, 2017.

46. R Core Team. R: A language and environment for statistical computing. 2018. https://cran.r-project.org/.

47. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades a E. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making [Internet]. 2013;33(5):641–56.

48. Jackson D, Barrett JK, Rice S, White IR, Higgins JPT. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. Stat Med. 2014;33:3639–54.

49. Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. J Clin Epidemiol. 2015;68(1):52-60.

50. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

51. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology. 2011;64(4):401-6.

52. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). Journal of clinical epidemiology. 2011;64(4):407-15.

53. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. Journal of clinical epidemiology. 2011;64(12):1283-93.

54. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. Journal of clinical epidemiology. 2011;64(12):1294-302.

55. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. Journal of clinical epidemiology. 2011;64(12):1277-82.

56. Donegan S, Williamson P, Gamble C, Tudur-Smith C. Indirect comparisons: a review of reporting and methodological quality. PLoS One. 2010;5(11):e11054.

57. Baker SG, Kramer BS. The transitive fallacy for randomized trials: if A bests B and B bests C in separate trials, is A better than C? BMC Med Res Methodol. 2002;2:13.

58. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Annals of internal medicine. 2013;159(2):130-7.

59. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630.

60. Van Valkenhoef G, Tervonen T, Zhao J, De Brock B, Hillege HL, Postmus D. Multicriteria benefit-risk assessment using network meta-analysis. J Clin Epidemiol. 2012;65:394–403.

61. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 5: The baseline natural history model. Med Decis Mak. 2013;33(5):657–70.

62. Tervonen T. New directions in Stochastic Multicriteria Acceptability Analysis. 2007 Dec 1 [cited 2018 Nov 11]; Available from: http://www.utupub.fi/handle/10024/28151

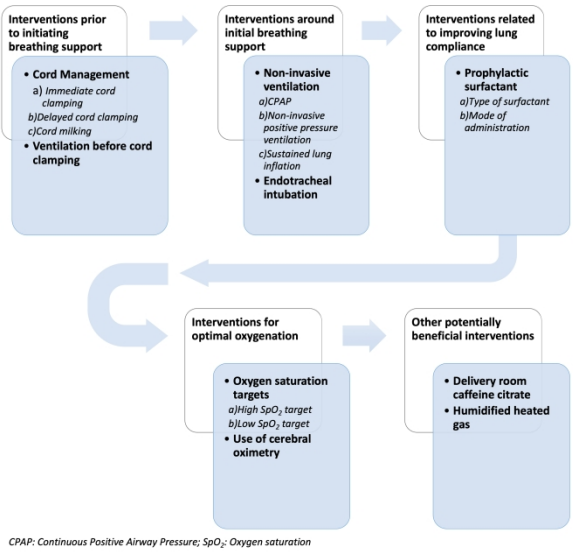

Figure 1: Physiological sequence of potential delivery room interventions

903x508mm (144 x 144 DPI)

Appendix 1: Search strategy for EMBASE, Medline, and PubMed

EMBASE

(newborn OR infant OR neonate OR preterm OR premature) AND [randomized controlled trial]/lim

AND

(continuous AND positive AND airway AND pressure OR cpap OR (nasal AND continuous AND positive AND airway AND pressure) OR ncpap OR (positive AND pressure AND ventilation) OR (intermittent AND positive AND pressure AND ventilation) OR (sustained AND lung AND inflation) OR (sustained AND inflation) OR si) AND [randomized controlled trial]/lim

OR

(supplemental AND oxygen OR (supplemental AND oxygen AND during AND resuscitation) OR oxygen OR surfactant OR (surfactant AND administration) OR (surfactant AND administration, AND early) OR (surfactant AND administration, AND late) OR (minimally AND invasive AND surfactant AND therapy) OR ('less invasive' AND surfactant AND administration)) AND [randomized controlled trial]/lim

OR

(lisa OR intubation OR (endotracheal AND intubation) OR (mechanical AND ventilation) OR caffeine OR (caffeine AND citrate) OR (respiratory AND function AND monitor) OR (delayed AND cord AND clamping) OR (cord AND milking)) AND [randomized controlled trial]/lim

AND

(randomized AND controlled AND trial OR 'randomized controlled trial':it OR (clinical AND trial)) AND [randomized controlled trial]/lim

AND

[randomized controlled trial]/lim AND [embase]/lim AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim)

Limited to embryo from Age Groupsfetus from Age Groupsnewborn from Age Groupsinfant from Age Groups

Medline

Set	Run Search **MEDLINE** **Search History - " BPD"**
#5	#3 AND #2 AND #1 Refined by: **PUBLICATION TYPES:** (RANDOMIZED CONTROLLED TRIAL) *DocType=All document types; Language=All languages;*
#4	#3 AND #2 AND #1 *DocType=All document types; Language=All languages;*
#3	(MH=randomized controlled trial OR TS=randomized controlled trial OR TS=clinical trial) *AND* **DOCUMENT TYPES:** (Randomized Controlled Trial) *DocType=All document types; Language=All languages;*
#2	TS=continuous positive airway pressure OR TS=CPAP OR TS=nasal continuous positive airway pressure OR TS=nCPAP OR TS=positive pressure ventilation OR TS=intermittent positive pressure ventilation OR TS=sustained lung inflation OR TS=sustained inflation OR TS=SI OR TS=supplemental oxygen OR TS=supplemental oxygen during resuscitation OR TS=oxygen OR TS=surfactant OR TS=surfactant administration OR TS=surfactant administration, early OR TS=surfactant administration, late OR TS=minimally invasive surfactant therapy OR TS=less-invasive surfactant administration OR TS=LISA OR TS=intubation OR TS=endotracheal intubation OR TS=mechanical ventilation OR TS=caffeine OR TS=caffeine citrate OR TS=respiratory function monitor OR TS=delayed cord clamping OR TS=cord milking *DocType=All document types; Language=All languages;*
#1	TS=newborn OR TS=premature OR TS=infant OR TS=neonate OR TS=preterm *DocType=All document types; Language=All languages;*

PubMed

#1 MeSH descriptor: [Infant] explode all trees

#2 infant*:ti,ab

#3 neonat*:ti,ab

#4 newborn*:ti,ab

#5 preterm:ti,ab

#6 premature:ti,ab

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 "continuous positive airway pressure":ti,ab

#9 "positive pressure ventilation":ti,ab

#10 (sustained near/2 inflation):ti,ab

#11 (supplemental near/2 oxygen):ti,ab

#12 oxygen:ti,ab

#13 surfactant:ti,ab

#14 intubation:ti,ab

#15 (mechanical* near/1 ventilat*):ti,ab

#16 caffeine:ti,ab

#17 "respiratory function monitor":ti,ab

#18 (cord near/2 ((clamping and delayed) or milking)):ti,ab

#19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18

#20	#7 and #19

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	113-114
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	15
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	3
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	36-42
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	36-42
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	36-42
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	135-190
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	192-195
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	222-247
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	205-220
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	205-220
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	275-282
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	263-273
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	275-282
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	249-256
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	249-256
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	300-308
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	310-446
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	310-446
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	310-446
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	310-446
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	448-466
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	411-446