

# Steroid Use for Established Bronchopulmonary Dysplasia: Study Protocol for a Systematic Review and Meta-analysis.

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## Protocol

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# Abstract

## Background

Bronchopulmonary dysplasia (BPD) is a serious chronic respiratory condition that affects approximately 60% of preterm infants born before 27 weeks' gestation, and leads to both, short and long-term pulmonary and non-pulmonary complications. Infants suffering from BPD are difficult to wean off of respiratory support, delaying feeding advancement and hospital discharge. Postnatal steroids during the first three weeks of life have been demonstrated to be effective in decreasing the incidence of BPD, however concerns in relation to neurodevelopmental outcomes are reported as well. On the contrary, data regarding the use of late postnatal steroids, once BPD is established are sparse and inconsistent. Here, we report a protocol for a systematic review, which aims to determine the efficacy and long-term safety of post-natal steroids for the treatment of established BPD in preterm infants.

## Methods

MEDLINE, Embase, Cochrane databases and sources of grey literature will be searched with no time or language restriction for studies that evaluated the use of postnatal steroids for preterm infants with established BPD. Odds ratios and 95% confidence intervals will be determined and pooled using a random effects model. For the studies that cannot be combined in the meta-analysis, a narrative synthesis of the results will be provided.

## Discussion

The use of steroids as a therapeutic option for established BPD, after reaching the critical phase of the disease, is limited by the concern of possible neurological side effects that were documented for the preventive use of this medication. However, steroid treatment for established BPD may be administered in an attempt to reduce length of stay and home oxygen therapy, which are both associated with high levels of parental stress and healthcare costs. Moreover, a late timing for steroid treatment may show a more favourable safety profile in terms of neurodevelopment outcomes, considering the added postnatal brain maturation of these infants. As BPD is one of the neonatal complications that lack an effective course-modifying treatment approach to-date, the proposed systematic review offers considerable clinical relevance.

## Systematic review registration

The protocol is registered in the PROSPERO register (registration number CRD42021218881).

## Background

Bronchopulmonary dysplasia (BPD) is a serious chronic respiratory condition that affects many preterm infants (1–4). Despite improvements in neonatal care, the rates of BPD have not decreased over the last few decades (1). Approximately 60% of infants born at less than 27 weeks' gestation are diagnosed with

BPD (2,3,5). BPD definition has changed over the years. The current definition of BPD is based on the need of supplemental oxygen and/or respiratory support at 36 weeks post menstrual age (PMA) (6). BPD is classified into 3 grades of severity depending on the amount of oxygen and the type of respiratory support needed (6). BPD is also often non-specifically referred to as chronic lung disease (CLD) of prematurity.

The pathogenesis of BPD is considered multifactorial. Prematurity itself and the subsequent arrest of lung maturation at the early stages of lung development is the major determinant of the disease. In addition, prenatal events, including placental dysfunction, pre-eclampsia, intrauterine growth restriction (IUGR), chorioamnionitis, maternal smoking, and postnatal iatrogenic insults, such as nutritional deficiencies, direct injury from mechanical ventilation and oxygen toxicity, further worsen the picture, all playing a role in the resulting pulmonary inflammation (2,7). Infants suffering from severe BPD are difficult to wean from respiratory support, they often experience feeding intolerance and intermittent hypoxic episodes (8), requiring prolonged hospital stay and often needing discharge on home on oxygen (6). BPD is also burdened by long-term consequences, which include impaired lung function and architecture, recurrent respiratory infections, and poor neurodevelopmental outcomes. Respiratory difficulties may continue well into adolescence and adulthood (9–12).

Currently, BPD lacks a safe and effective treatment. The use of postnatal steroids within the first 3 weeks of life has been proven to be effective in reducing the incidence of BPD. However, their use is limited due to the possible long-term neurodevelopmental consequences (13). Steroid treatment for established BPD could be tried in an attempt of reducing length of stay (LOS) and home oxygen therapy, which are both associated with a high level of parental stress and health economic burden. Although the concern about the risk of neurodevelopmental impairment remains, a late timing for steroid treatment may show a more favourable safety profile in terms of neurodevelopment outcomes, considering the added postnatal brain maturation of these infants. However, data on the use of steroids in preterm infants suffering from established BPD and the inability to wean off oxygen/ventilation is sparse and inconsistent. A systematic approach to the evidence synthesis towards this potential treatment approach could be beneficial. Here, we report a protocol for a systematic review, which has a two-fold aim: (i) to determine if the late treatment with post-natal steroids in preterm infants suffering from established BPD affects LOS, duration of oxygen dependency and survival, compared to those receiving no treatment; (ii) to identify if preterm infants treated with late rescue steroid treatment for established BPD are at an increased risk for long-term neurodevelopmental delay when compared to those who did not receive late steroids.

## Methods And Analysis

### Protocol and Registration

We followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols 2015 (PRISMA-P) (14). The completed PRISMA-P checklist is provided in an online supplementary file. The protocol is registered with the PROSPERO international prospective register of

systematic reviews (registration number CRD42021218881). The final review will be reported following the updated PRISMA statement (15). Important amendments to this protocol will be reported and published with the results of the review.

## **PICO (Population Intervention Comparator Outcome) Questions**

This study aims to answer to two PICO questions:

- 1) In preterm infants suffering from established BPD, does rescue treatment with postnatal steroids versus no treatment affect LOS, duration of oxygen dependency and survival before discharge from the neonatal intensive care unit (NICU)? (Efficacy evaluation)
- 2) Are preterm infants treated with late rescue steroids for established BPD at increased risk for long-term neurodevelopment delay up to 2 and 6 years of age as compared to the infants that did not receive late steroids? (Safety evaluation)

## **Study Selection Criteria**

Studies will be included or excluded if they meet our inclusion or exclusion criteria, respectively, as outlined below.

### *Types of Participants*

Inclusion criteria:

- 1) Preterm babies born < 32 weeks gestational age (GA)
- 2) Infants diagnosed with established BPD at 36 weeks PMA
- 3) Infants still receiving respiratory support in the form of invasive ventilation, non-invasive ventilation, and/or supplemental oxygen at 36 weeks PMA

Exclusion criteria:

- 1) Infants with lung malformations, lung hemorrhage or non-prematurity related lung disease

Where relevant, studies of mixed sample (e.g. steroid treatment for evolving and established BPD) are identified, the study authors will be contacted to provide data on all the patients treated starting from 36 weeks PMA. If the authors are unwilling or unable to provide this information, the study will not be included.

### *Types of Studies*

Inclusion criteria:

This systematic review will include case series, case control studies, cohort studies, non-randomized or randomized trials that evaluate postnatal steroids for preterm infants with established BPD. Both, prospective and retrospective studies will be included.

Exclusion criteria:

Studies will not be included in this systematic review if they are qualitative thematic analysis, narrative reviews, editorials, systematic reviews, or expert opinions.

### *Type of Intervention*

Inclusion criteria:

The type of intervention measured in this systematic review is the late use of steroids in the treatment of established BPD in preterm infants in the NICU from 36 weeks PMA to discharge. Steroid treatments include, but are not limited to betamethasone, hydrocortisone, dexamethasone, methylprednisolone, and prednisolone. Interventions are eligible regardless of the dose, route of administration (for example, orally, parenterally, or via nebulizer), duration, and intensity.

Exclusion criteria:

Studies focusing on steroid administration before 36 weeks PMA or on other intervention for established BPD.

### *Type of comparator*

We will include studies that have control groups with placebo, other drugs or no drug administration. In case the comparator is another drug, comparators are eligible regardless of the dose, route of administration (for example, orally, parenterally, or via nebulizer), duration, and intensity. Case series will be included for narrative analysis only.

### *Time Frame*

The timeframe for outcome evaluation will differ depending on the outcomes.

All the short term efficacy outcomes, but mortality, will be considered from birth to discharge from the NICU. Mortality will be considered starting from 36 weeks PMA.

The short-term safety outcomes will be considered starting from 36 weeks PMA, to make sure they reflect the effect of the steroid treatment and not the pre-existing conditions. In case the timeframe of the listed complications is not specified or unclear, the study authors will be contacted to provide the specific data. If the authors are unwilling or unable to provide this information, the additional outcomes will not be included in the analysis for that study.

The long term efficacy and safety outcomes will be considered from 18 months up to 6 year of age.

## *Setting*

Study setting will be NICU stay and post-discharge follow-up clinics

## *Language and publication time*

No time or language restriction will be applied.

## **Outcome Measurement**

### *Primary outcomes:*

The two primary outcomes of interest of this systematic review are efficacy and safety of postnatal steroids use for preterm infants with established BPD according to the 2 PICO questions. Primary outcomes will be assessed as follows:

1) Efficacy will be assessed as:

- i) total duration of oxygen dependency (total days during NICU stay), meaning duration of invasive and/or non-invasive ventilation and/or low flow supplemental oxygen
- ii) length of stay in days and PMA at discharge (days from birth to discharge home). In case studies include transferred infants from other hospitals, the total duration of NICU stay (in the original and the referral hospitals) must be available in the article. In cases when the total duration of NICU stay for transferred infants is not specified or unclear, the study authors will be contacted to provide data on the total LOS in NICU. If the authors are unwilling or unable to provide this information, the LOS outcome will not be included for the analysis for that study
- iii) discharge with home oxygen or home ventilation through tracheostomy (yes/no)
- iv) mortality during NICU stay (death for any cause, death for respiratory causes if available after 36 weeks PMA to discharge from the NICU).

2) Safety will be assessed as neurodevelopmental delay, reported as incidence of cerebral palsy, deafness, blindness and cognitive delay defined by Bayley-III scale, autism spectrum disorder (ASD) and emotional behavioural abnormalities such as attention deficit hyperactivity disorder (ADHD), as defined by DSM-5 (16).

### *Secondary short-term efficacy outcomes during NICU stay:*

1) Duration of invasive ventilation as total days during NICU stay, in case administered up to 36 weeks PMA. Invasive ventilation modes include conventional ventilation, high frequency oscillatory ventilation (HFOV), high frequency jet ventilation (HFJV), neurally adjusted ventilator assist (NAVA). Invasive ventilation can be administered either via endotracheal tube or tracheostomy.

- 2) Duration of non-invasive respiratory support as total days during NICU stay. Non-invasive respiratory support modes include: continuous positive airway pressure (CPAP), biphasic positive airway pressure (BiPAP), synchronized and non-synchronized non-invasive ventilation (NIV), high flow nasal cannula (HFNC) (>2 l/min), administered with any facial interface deemed appropriate by the researchers.
- 3) Total duration of ventilator dependency (total days during NICU stay): duration of invasive and/or non-invasive ventilation
- 4) Duration of low flow oxygen dependency as total days during NICU stay: duration of days spent on low flow supplemental oxygen ( $\leq 2$  l/min), which can be administered through nasal cannula or hood.
- 5) Incidence, duration and severity of bradycardia (drop in heart rate of  $< 80$  bpm), desaturations (drop in oxygen saturation  $< 85\%$ ), and apnea of prematurity (stopping of breathing for more than 15 seconds); and time spent outside the saturation ranges (minutes per day).
- 6) Incidence of spontaneous resolution, need for stimulation and/or mask ventilation of apneic spells.
- 7) Feeding difficulties (incidence and duration of significant gastric residuals, gastroesophageal reflux, abdominal distention, vomiting)
- 8) Time to reach full enteral feeds (days of life and PMA)

*Secondary long-term efficacy outcomes after NICU discharge*

- 1) Duration of home oxygen use (total days after NICU stay, whenever applicable)
- 2) Number and severity of respiratory symptoms (symptoms of asthma, need for asthma medications (relievers and/or preventers), incidence and severity of respiratory tract infections)
- 3) Physical exercise capacity as cardiopulmonary exercise (CPET) tests (16)
- 4) Lung function tests (defined by spirometry testing)
- 5) Hospital re-admissions for any cause and for respiratory causes
- 6) Feeding difficulties (incidence and duration of significant gastroesophageal reflux, vomiting)
- 7) Mortality after NICU discharge (death from any cause, death from respiratory causes if available after discharge from the NICU)

*Secondary short-term safety outcomes during NICU stay:*

- 1) Lower respiratory tract infections (including pneumonia, lung abscesses)
- 2) Late-onset sepsis proven by invasive cultures, including but not limited to blood stream infections, septic shock, meningitis

- 3) Local fungal (including but not limited to mucocutaneous or cutaneous candidiasis)
- 4) Local bacterial infections (including but not limited to cellulitis, erysipelas, impetigo, folliculitis)
- 5) Systemic bacterial infections proven by invasive cultures (including but not limited to pneumonia, sinusitis, thrombophlebitis, peritonitis, bacteremia, endophthalmitis, septic arthritis, and osteomyelitis.)
- 6) Systemic fungal infections proven by invasive cultures (including but not limited to pneumonia, sinusitis, thrombophlebitis, peritonitis, fungemia, endophthalmitis, septic arthritis, and osteomyelitis.)
- 7) Viral infections (including but not limited to bronchiolitis, sepsis like syndrome, encephalitis.)
- 8) Weight gain or weight loss trends during or after steroid treatment (up to discharge) in terms of dropping or gaining percentile lines or change weight z-scores by two or more standard deviations
- 9) Poor growth in terms of weight, head circumference and length (defined by appropriate percentile charts). Poor growth can be defined as growth below 10th percentile, growth below 3rd percentile, dropping percentile lines or weight z-scores below minus two or minus three standard deviations
- 10) Development of systemic hypertension, defined as persistent systolic and/or diastolic blood pressure that exceeds the 95th percentile for postmenstrual age values
- 11) Blood sugar imbalance, either incidence and severity of hypoglycemia (defined as blood sugar below 45 mg/dl) or hyperglycemia (defined as blood sugar above 250 mg/dl and/or requiring need for insulin therapy)
- 12) Incidence and severity of electrolyte disturbances, such as hyponatremia (defined as plasmatic sodium below 135 mmol/l) or hyperkalemia (defined as ionized calcium below 4 mg/dl or total calcium below 8)
- 13) Incidence of secondary adrenal insufficiency, defined as decreased levels of cortisol and/or adrenocorticotrophic hormone (ACTH), at rest or after the ACTH stimulation test
- 14) Incidence and severity of osteopenia of prematurity, defined as elevated alkaline phosphatase and/or decreased phosphate and/or radiographic changes
- 15) Gastrointestinal bleeding (hematemesis and/or melena) and/or gastrointestinal perforation (defined by clinical deterioration and radiographic findings).

*Secondary long-term safety outcomes after discharge up to school age (6 years):*

- 1) Failure to thrive, defined as growth below 10th percentile, growth below 3rd percentile, dropping percentile lines or weight z-scores below minus two or minus three standard deviations

2) Development of systemic hypertension, defined as defined as persistent systolic and/or diastolic blood pressure that exceeds the 95th percentile for postmenstrual age values

3) Incidence of secondary adrenal insufficiency, defined as decreased levels of cortisol and/or ACTH, at rest or after the ACTH stimulation test

## Search Strategy

The databases MEDLINE, Embase will be searched for this systematic review. In consultation with a research librarian (KW), a standardized search strategy will be employed using a standardized set of keywords and operators. No other filtering or restrictions will be applied to the search strategy. Additional strategies to identify studies included manual reviews of reference lists from key articles that fulfilled our eligibility criteria and use of "related articles" feature in PubMed. Studies included in relevant systematic reviews searched in MEDLINE, Embase and Cochrane database will be used as well if they fulfill our eligibility criteria.

The electronic database search will be supplemented by searching for grey literature: trial protocols through clinical registers (ISRCTN registry and ClinicalTrials), thesis dissertation (sourced through NDLT and EthOS), conference proceedings (searched by web of science and Embase) and other grey literature databases (OpenGrey and Trip database)

Search query for MEDLINE is as follows:

(steroid[tiab] OR steroids[tiab] OR betamethasone[tiab] OR dexamethasone[tiab] OR hydrocortisone[tiab] OR prednisolone[tiab] OR glucocorticoids[tiab] OR budesonide[tiab] OR methylprednisolone[tiab] OR "Steroids"[Mesh:NoExp] OR "Betamethasone"[Mesh] OR "Dexamethasone"[Mesh] OR "Hydrocortisone"[Mesh] OR "Prednisolone"[Mesh] OR "Glucocorticoids"[Mesh] OR "Budesonide"[Mesh:NoExp] OR "Methylprednisolone"[Mesh]) AND (infant[tiab] OR infants[tiab] OR newborn[tiab] OR newborns[tiab] OR neonate[tiab] OR neonates[tiab] OR neonatal[tiab] OR postnatal[tiab] OR "Infant"[Mesh] OR "Intensive Care Units, Neonatal"[Mesh]) AND ("bronchopulmonary dysplasia"[tiab] OR BDP[tiab] OR "respiratory distress syndrome"[tiab] OR "ventilator-induced lung injury"[tiab] OR "ventilator-induced lung injuries"[tiab] OR "chronic lung disease"[tiab] OR "chronic lung diseases"[tiab] OR CLD[tiab] OR "chronic lung injury"[tiab] OR "chronic lung injuries"[tiab] OR "artificial respiration"[tiab] OR "artificial respirations"[tiab] OR "mechanical respiratory support"[tiab] OR "mechanical ventilation"[tiab] OR "mechanical ventilations"[tiab] OR "non-invasive ventilation"[tiab] OR "non-invasive ventilations"[tiab] OR "noninvasive ventilation"[tiab] OR "noninvasive ventilations"[tiab] OR "nasal intermittent ventilation"[tiab] OR NIV[tiab] OR "nasal intermittent positive pressure ventilation"[tiab] OR NIPPV[tiab] OR "continuous positive airway pressure"[tiab] OR CPAP[tiab] OR "high flow nasal cannula"[tiab] OR "oxygen inhalation therapy"[tiab] OR "oxygen inhalation therapies"[tiab] OR "Infant, Premature, Diseases"[Mesh:NoExp] OR "Bronchopulmonary Dysplasia"[Mesh] OR "Respiratory Distress Syndrome, Newborn"[Mesh] OR "Neonatal Respiratory Distress Syndrome"[Mesh] OR "Ventilator-Induced Lung Injury"[Mesh:NoExp] OR "Respiration, Artificial"[Mesh:NoExp] OR "Noninvasive Ventilation"[Mesh] OR "Continuous Positive Airway Pressure"

[Mesh] OR "Oxygen Inhalation Therapy"[Mesh:NoExp]) NOT (review[pt] OR "systematic review"[pt] OR "preclinical study"[ti]) NOT ("animals"[mesh] NOT "humans"[mesh])

## **Data management**

Literature search results will be uploaded to the Distiller Systematic Review (DistillerSR®) software (Ottawa, Canada), an Internet based software program that facilitates the study selection process. Screening questions and forms for level 1 (title and abstract screening) and 2 (full text screening), based on the inclusion and exclusion criteria, will be developed and tested. For level 2 screening, full text articles will be uploaded with screening questions to DistillerSR. Before each screening step, a calibration exercise will be performed to pilot and refine the screening questions.

## **Study Selection Process**

The articles will be split into two sequential groups for feasibility reasons. Each group will be assessed for titles and abstracts independently by two authors, for a total of four authors (SS, RC, AR, KZ). First, the two independent reviewers will screen article titles and abstracts in duplicate using an initial screening questionnaire. Subsequently full-text screening for all the articles retained will be conducted against our eligibility criteria. For each screening step (title and abstract and full text), calibration exercises will be performed on 10 random articles to ensure adequate inter-reviewer correlation. A match between authors will need to be reached before an article enters full-text review. Any disagreement will be settled by consensus and when not possible a third author will be contacted for resolution (MP). We will seek additional information from study authors where necessary to resolve questions about eligibility. For level 2, we will record the reasons for excluding trials. The review authors will not be blinded to the journal titles or to the study authors or institutions

## **Data Extraction**

Data-extraction forms will be developed a priori and pilot-tested by our team using a standardized extraction form on DistillerSR®. Two independent reviewers will perform the data extraction using a single charting and audit approach using the quality control function in DistillerSR®. The extraction forms will be piloted on five random studies to ensure the approach to data charting will be consistent and in line with the research question and purpose. Each reviewer will chart half of the articles and audit the other half. In case of disagreement between the reviewers, a third independent reviewer will be consulted. The team will discuss results, and the data charting form will be continuously updated in an iterative process in order to be inclusive of other aspects of the treatment that may not be listed a priori in the first place,

The following information will be extracted to become Table #1:

- 1) Lead author, year of publication and country of origin
- 2) Sample size (total and per group)

- 3) Study design
- 4) Inclusion and exclusion criteria
- 5) Setting
- 6) Definition of BPD

The following information will be extracted to populate Tables #2 (observational studies), #3 (interventional, non-randomized studies), #4 (interventional, randomized studies):

- 1) Purpose of study/study objectives
- 2) Patient characteristics (including type of respiratory support required)
- 3) Details of steroid intervention implemented (including the type, duration and frequency of treatment)
- 4) Results reported (including raw numbers, summary statistics, and adjusted analysis on BPD where available).

For articles in which data cannot be extracted, the corresponding author of the manuscript will be contacted a total of three times.

### **Risk of Bias Assessment**

Methodological quality will be assessed by two authors independently using the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) Scale for cohort or case-control studies. In the ROBINS-I tool assesses risk of bias in six different domains (bias due to confounding, bias in selection of participants, bias in classification of intervention, bias due to intervention deviations, bias due to missing data, bias in outcome measurement, bias in result reporting). Studies are classified as low, moderate, serious, critical, unknown risk of bias (17). If consensus scoring on individual and total scores of the ROBINS-I Scale is not reached by the two authors, a third author will be contacted for resolution.

The Cochrane risk-of-bias tool will be used to assess the risk of bias of randomized trials. For each domain (allocation sequence, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias) the risk of bias will be assessed as low, high, or unclear. Potential discrepancies during the data extraction process and assessment of risk of bias will be resolved by discussion and consensus among all reviewers

### **Data analysis**

Summary data for each article will be presented as means and standard deviations, or frequency and percentages, as appropriate. For dichotomous outcomes, the odds ratio (OR) with 95% confidence interval (CI) will be calculated from the data provided in the studies. ORs adjusted for potential confounders will be extracted from the studies reporting these data. For continuous outcomes, the mean difference (95%

CI) or standardized mean differences (95% CI), if different measurement scales are used, will be calculated. When studies report continuous variables as median and range or interquartile range, we will estimate the mean and standard deviation using the method of Wan et al (18).

Meta-analysis and meta-regressions will be performed with comprehensive meta-analysis software (Biostat, Inc., Englewood, USA). We will perform meta-analysis assuming that we will find at least two studies suitable for inclusion. When a meta-analysis is not possible, due to an insufficient number of studies, we will provide a narrative description of the study results. We will pool data from studies that are sufficiently similar to make this appropriate.

We will account for the expected heterogeneity, by using a random-effects model. This model accounts for variability between studies as well as within studies. Statistical heterogeneity will be assessed by Cochran's Q statistic and by the  $I^2$  statistic, which is derived from Q and describes the proportion of total variation that is due to heterogeneity beyond chance.

To explore differences between studies that might be expected to influence the effect size, we will perform univariate random-effects meta-regression (method of moments), in case at least 10 studies are available. A probability value of less than 0.05 (0.10 for heterogeneity) will be considered statistically significant. The potential sources of variability defined a priori to analyze with subgroup analyses and/or meta-regression for short and long term efficacy outcomes will be: type of respiratory support (mechanical ventilation, NIV, BiPAP, CPAP, nasal cannula/low-flow oxygen), gestational age, birth weight, sex, steroid treatment course (type of steroid used, duration and frequency of treatment), other ongoing treatments (ie, diuretics, bronchodilators, pulmonary vasodilators, or vitamin A), previous treatment with steroids before 36 PMA (type of steroid used, age at treatment), neonatal morbidity (complication of prematurity, respiratory infections, late onset sepsis, pulmonary hypertension, poor growth, difficulty feeding, developmental delay), the oxygen saturation target defined as low target (85–89%) or high target (91–95%), definition of established BPD and severity of BPD (moderate versus severe forms). For long-term neurodevelopment outcomes, socio-economical status, time of evaluation, country of birth will be considered as well.

Subgroup analyses will be conducted according to the mixed-effect model. In this model, a random-effect model is used to combine studies within each subgroup, and a fixed-effect model is used to combine subgroups and yield the overall effect. The study-to-study variance is not assumed to be the same for all subgroups. This value is computed within subgroups and not pooled across subgroups.

We will use the Egger's regression test and funnel plots to assess publication bias

## **Data synthesis**

A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and findings of the included studies. For the studies that cannot be combined in the meta-analysis, a narrative synthesis of the results will be provided.

The quality of evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology. The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Additional domains may be considered where appropriate. Quality will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of effect)

## Discussion

This systematic review will be performed to identify the efficacy outcomes of late steroid use in preterm infants diagnosed with BPD. We will also assess risk of long-term neurodevelopment complications in relation to late steroid use in preterm infants. BPD remains a very serious condition that affects a large percentage of preterm infants, often leading to long-term complications. There is currently no safe or effective treatment for BPD. In this context a systematic review could offer an evidence-base to individualize and streamline management strategies potentially alleviating the negative sequelae for these preterm infants. Postnatal steroids during the first three weeks of life have been demonstrated to be effective in decreasing the incidence of BPD, however concerns in relation to neurodevelopment outcomes are reported as well (12). Various local and national guidelines suggest that dexamethasone can be used for infants with a very high risk of BPD (20–22). Although no RCTs have been conducted to confirm this approach, the results from different meta-analysis suggest that for infants at high risk for BPD (> 65% risk), steroids are not only safe but may actually improve long-term neurodevelopment outcomes, by reducing the neurological complications related to severe BPD, while steroids administered to infants at low risk (< 35% risk) for BPD seem associated to a worse neurodevelopment (23, 24). Steroids are also recommended for weaning infants from invasive ventilation after the first 2–3 weeks of life (20). Several types and regimens of postnatal steroids have been tried for prevention purposes. Although level of quality is low, a moderately early-initiated (8–14 days of life), medium cumulative dose (2–4 mg/kg) of systemic dexamethasone may be the most appropriate corticosteroid regimen for preventing BPD or mortality at 36 weeks PMA (25). Regardless of the strategy used to prevent BPD, after the acute phase of lung disease, prolonged non-invasive ventilation is often required for preterm infants suffering from BPD. These infants often suffer from intermittent hypoxic episodes, that increase the risk of long term disabilities, especially if protracted after 36 weeks PMA (26). Moreover feeding autonomy is usually reached later when non-invasive ventilation is required for extended periods of time (27, 28). As a consequence, these infants require prolonged admissions and may require home oxygen therapy. Both, extended hospital stay and home oxygen, are associated with high parental stress that may be evident until 2 years after discharge and high health care costs (29, 30). Often the need for non-invasive ventilation or low-flow oxygen after 36 weeks PMA poses a therapeutic dilemma to the neonatologist. Steroid treatment may be able to reduce LOS and home oxygen therapy. However, given the reported long-

term complications of early steroids, physicians are often reluctant to propose a rescue treatment with steroids, when the infant is not critically ill. As a consequence data on treatment of established BPD with steroids are sparse and inconsistent. Although late steroid treatment after 50 days of life is known to be less effective in reducing the incidence of BPD (4), there is a significant gap in research regarding the use of steroids to wean off respiratory support or oxygen therapy in established BPD. Therefore, this systematic review and meta-analysis focus to ascertain the validity of such an intervention. Review findings will be presented at the international neonatal meetings for early dissemination of observations and feedback. The results will also be submitted for publication in peer reviewed journals, thus assisting neonatal professionals and parents with informed decision making regarding the efficacy and safety of late steroid treatment in the NICU for established BPD.

## List Of Abbreviations

BPD Bronchopulmonary dysplasia

PMA Post-menstrual age

NICU Neonatal Intensive Care Unit

BW Birth weight

GA Gestational age

OR Odds ratio

CI Confidence interval

MD Mean difference

## Declarations

### Ethics Approval and Consent to Participate

Not applicable.

### Consent for Publication

Not applicable.

### Availability of Data and Materials

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

### Competing Interests

The authors declare they have no competing interests.

## Funding

Systematic review process will receive funding from the Medical University of Warsaw, departmental funding. The sponsor did not take part in the study design and realization. This funding will support the data collection, data management, analyses and publication fees. The funder will not be involved in any other aspect of the project, such as the design of the project's protocol and analysis plan, the collection and analyses. The funder will have no input on the interpretation or publication of the study results.

## Authors' Contributions

SS drafted the review protocol, AR, RC and KZ reviewed the manuscript. WK has developed the search strategy. MP has led the protocol design and editing. NA developed the project idea. JS obtained the funds and is the corresponding author for the review. NA, JS, RP and EV have contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. EV provided statistical and systematic review expertise. All authors contributed intellectual content, provided feedbacks, edited and approved the final manuscript

## Acknowledgements

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