Cochrane Library

Cochrane Database of Systematic Reviews

Vestibular stimulation for promoting development and preventing morbidity in preterm infants (Protocol)

Prescott MG, Wróblewska-Seniuk K, Lenells M, Fiander M, Soll R, Bruschettini M

Prescott MGlenton, Wróblewska-Seniuk K, Lenells M, Fiander M, Soll R, Bruschettini M.
Vestibular stimulation for promoting development and preventing morbidity in preterm infants (Protocol).
Cochrane Database of Systematic Reviews 2024, Issue 9. Art. No.: CD016072.
DOI: 10.1002/14651858.CD016072.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Vestibular stimulation for promoting development and preventing morbidity in preterm infants

Marcus Glenton Prescott[1], Katarzyna Wróblewska-Seniuk[2], Mikaela Lenells[3,4], Michelle Fiander[5], Roger Soll[6], Matteo Bruschettini[7]

[1]St. Olavs Hospital, Trondheim, Norway. [2]II Department of Neonatology, Poznan University of Medical Sciences, Poznan, Poland. [3]Women and Children's Health, Karolinska Institute, Stockholm, Sweden. [4]FoUU, Karolinska University Hospital, Stockholm, Sweden. [5]Cochrane Neonatal Group, Halifax, Canada. [6]Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA. [7]Cochrane Sweden, Department of Research and Education, Lund University, Skåne University Hospital, Lund, Sweden

Contact: Matteo Bruschettini, matteo.bruschettini@med.lu.se.

Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 9, 2024.

Citation: Prescott MGlenton, Wróblewska-Seniuk K, Lenells M, Fiander M, Soll R, Bruschettini M. Vestibular stimulation for promoting development and preventing morbidity in preterm infants (Protocol). *Cochrane Database of Systematic Reviews* 2024, Issue 9. Art. No.: CD016072. DOI: 10.1002/14651858.CD016072.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of vestibular stimulation compared to standard care or non-vestibular stimulation for physical and neurological development in preterm infants.

To assess whether the effects of vestibular stimulation differ according to gestational age at birth; the type, frequency, and duration of the intervention; and settings, such as the country where the study is conducted.

BACKGROUND

At birth, newborns experience a large and rapid change in their environment, from the intrauterine to the extrauterine, which requires them to adapt to survive and avoid injury and illness quickly.

The uterus is an environment that is fluid-filled, temperature controlled, well-cushioned from external trauma, dark [1, 2], and with a low sound level [3, 4], overall reducing external stimuli and restricting the range of movement [5]. Furthermore, the fetus is surrounded by external rhythmic stimuli, such as the mother's heartbeat and breathing, walking, speech, and music [6], and vestibular stimuli from the mother's movement.

In contrast, the world of the neonate is suddenly dry, cold (or at least not temperature-controlled), bright, and noisy, where every bump is felt keenly by the infant. The infant is no longer exposed to the same external rhythmic or vestibular stimuli [5].

Description of the condition

A regular, term pregnancy lasts 37 to 42 weeks, where the last weeks are spent preparing for extrauterine life. Preterm labor and premature birth are anything less than 37 completed weeks of pregnancy, and are further divided into moderate to late (32 to 37 weeks), very preterm (28 to 31 weeks), and extremely preterm (< 28 weeks) [7, 8]. Of all live births, 11.1% are considered premature, with a wide range from 5% in some European countries to 18% in some African countries [9].

The premature infant may lack, in part or in whole, some of the adaptive features for extrauterine life that develop toward the end of gestation. Because of that, the degree of prematurity influences the risk of certain complications and their severity, such as breathing difficulties from immature lungs, surfactant deficiency, difficulties regulating body temperature from less body fat, reduced ability to regulate blood sugar and excrete bilirubin, cardiovascular complications, fluid loss, and a reduced ability to ensure sufficient nutrition [8, 10].

The premature infant therefore has an increased risk of poor outcomes, in part from the same etiology as the preterm birth (such as maternal illness, placental insufficiency, etc.), and in part because of being less developed and thus less adapted to the extrauterine environment than term children. Increasing degree of prematurity may increase the risk of death, low birthweight, lung problems, infection, poor feeding, cognitive dysfunctions, sensory deficits, etc. Indeed, of 5.3 million deaths in children under five years of age in 2019, 17.7% were due to preterm birth complications, making prematurity the leading cause of death in children in that age group, ahead of lower respiratory infections (11.6%) and diarrhea (9.1%) [11].

Furthermore, there is a concern that the stay and treatment in a neonatal intensive care unit (NICU), although necessary, may have deleterious effects on the neonate. The already at-risk infant may be exposed to the environmental changes mentioned above, but also to painful procedures, frequent examinations, diaper changes, and care from many different people. This may cause the infant additional stress and increase the risk of adverse events, as well as affect the infant's early attachment to their parents [12, 13,14, 15, 16, 17].

One aspect of the environmental changes a neonate experiences is the need to relate to the world around it via its vestibular system. This system gives the sense of balance and body position relative to external forces like gravity and acceleration/deceleration. It consists of a peripheral portion, including the inner ear, and a central portion, including the brainstem and cerebellum [12, 13]. The vestibular system starts developing early, with the beginnings of vestibular organs around 7 weeks of gestation, and continues throughout the pregnancy, with a fully developed Moro-reflex around 32 weeks of gestation, and vestibular pathways reaching maturity around 39 weeks [14]. However, the vestibular system is likely mature enough, with connections between the peripheral and central parts, to respond to vestibular stimuli already at 25 weeks gestational age [18]. In the intrauterine environment, the fetus will receive rhythmic stimulation from the maternal heartbeat and movements while breathing, walking, etc., in addition to near-constant vestibular stimulation from the buoyancy of the amniotic fluid [19]. In a healthy, term infant, this system will be stimulated by changing body positions and movement when lifted, carried, nursed, changed, etc. However, for the premature neonate, this stimulation may be lacking to a greater or lesser degree.

Description of the intervention and how it might work

The vestibular system begins to develop during pregnancy as one of the first sensory systems. Human vestibular system morphogenesis is finished by the 49th day of pregnancy, and during the 8th and 9th months of intrauterine life, the vestibular nerve is myelinated and starts functioning [18]. Responses to vestibular stimulation have been documented as early as 25 weeks of gestational age [18]. After birth, the vestibular system is stimulated and strengthened by any movement that causes a newborn to change position or to gently rock, roll, bounce, swing, or spin. Stimulation of the vestibular system is crucial for muscle tone development.

Compared to fetuses of the same gestational age, who receive vestibular stimulation from an average of 5000 maternal steps per day, preterm babies experience very little vestibular rhythmic stimulation, as they spend most of the time in the incubator in a horizontal position [20, 6].

It has been suggested that targeted vestibular stimulation in the premature infant may improve neurodevelopmental outcomes (motor function, balance, sensory processing, learning) [19, 6], sleep patterns [21, 20], pain response, heart rate, respiration, apnea [22, 23], and sucking behaviors and feeding skills [24]. It can also increase such neuromotor functions as passive muscle tone, active motility, posture, oral motor function, and neuromuscular maturity [25, 24].

Multiple modalities for giving vestibular stimulation have been proposed and attempted, including the following.

- Rocking performed by caregivers carrying the infant or by placing the infant in a rocking bed or hammock. This may mimic the movement and rhythm the fetus experiences in utero from maternal walking and infant in utero movement [25, 26, 23, 24].
- Swinging the baby around performed by caregivers.
- Placing the infant on waterbeds or air mattresses giving vestibular-proprioceptive stimulation, either oscillating head-to-foot or side-to-side (usually 8 to 16 pulses per minute, at regular or irregular intervals) or non-oscillating, for giving vestibulo-proprioceptive stimulation similar to that experienced

by the fetus. This may be continuous or periodic of variable duration [27, 22, 19, 28].

- A caregiver holding the infant sits in a mechanical vestibular system, a chair placed on a gliding system, allowing for smooth horizontal linear motion at variable frequencies [24].

Comparisons have included holding and pacifier use [24], non-oscillating beds, different frequencies and regularity [19], non-rocking beds [23], nesting in prone [25] or lateral position [26], or some kind of regular incubator mattress [20].

It has been shown that rocking helps develop some sensory modalities, such as visual and auditory [22, 19, 24]. Apneic episodes occur less frequently when rocking stimulation is used, and it lowers the necessity of respiratory treatment [22, 23, 24]. These results demonstrate the powerful impact vestibular stimulation can have on a variety of physiological processes, including breathing. The infant's attention can then be directed toward external events, like reacting to their surroundings, as the increased neural stability and discharge synchrony among vestibular afferents provided by rocking decreases the intensity of the infant's internal needs, such as crying and/or disorganized states [29].

Preterm newborns' respiratory rhythms have also been effectively trained by the use of rhythmic vestibular stimulation, which may have significant and immediate effects on their health [30]. The authors found that 42 to 50 cycles per minute is the ideal rocking rate for synchronization with the respiratory rhythm. Tuck and colleagues built a rocking bed that induces a consistent cephalocaudal rocking motion [23]. The amount of apnea in preterm newborns was lower in rocking beds than in motionless ones [23]. In their research [31], Barlow and colleagues provided preterm babies with seven separate rocking stimulations (linear horizontal motion stimuli) with varying rates, demonstrating that preterm babies respond to a particular stimulation by increasing their respiratory rates while keeping a steady pulse [24].

Since vestibular system development depends on the gestational age, it seems that the benefits of vestibular stimulation might depend on the preterm newborns' maturity. The results might also differ depending on the type of intervention, how frequently it is provided, the length of each session, and how long it is administered.

Why it is important to do this review

Multiple modalities for vestibular stimulation of infants have been proposed and attempted, with many variations of type, duration, frequencies, directionality, etc., comparisons, and outcomes. Studies have shown differences in efficacy for seemingly similar interventions, sometimes directly opposite of each other.

A 2006 Cochrane review on developmental care for promoting development and preventing morbidity in preterm infants found numerous studies examining multiple interventions, including modification of external stimuli, for different outcomes. While showing an overall benefit, the effects of various interventions could often not be teased apart, and many outcomes did not demonstrate a consistent effect [32], or were found to have overall poor-quality evidence for neurodevelopmental interventions in preterm infants [33]. This review covered various interventions initiated during NICU hospitalization without focusing on vestibular stimulation.

An updated, rigorous review of different modalities of vestibular stimulation and their variations on diverse outcome measures is therefore needed to assess their efficacy. This review may help guide further research and clinical practice. Moreover, it is also important to evaluate which equipment may be necessary to comfort neonates in the future NICU environment and for the market of equipment developed intended to comfort neonates (e.g. hammocks or chairs with rocking, etc.).

OBJECTIVES

To assess the benefits and harms of vestibular stimulation compared to standard care or non-vestibular stimulation for physical and neurological development in preterm infants.

To assess whether the effects of vestibular stimulation differ according to gestational age at birth; the type, frequency, and duration of the intervention; and settings, such as the country where the study is conducted.

METHODS

For this protocol, we have followed methodological guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* and reporting guidance per PRISMA-P [34, 35, 36]. For the review, we will follow methodological guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* [34] and MECIR (Methodological Expectations for Cochrane Intervention Reviews) [37], and report the review following PRISMA [34, 38, 39].

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) or quasi-RCTs (i.e. allocation is decided by an approximation of randomization, e.g. allocation by patient ID number). We will include cluster-randomized trials and exclude cross-over trials because they will not be able to report on neurodevelopmental outcomes, which develop over time. We will exclude non-randomized cohort studies because they are prone to bias due to confounding by indication or by residual confounding, both of which may influence results [40] [41].

Types of participants

We will include newborn infants that are preterm (born at less than 37 weeks' completed gestation) that have been admitted to the NICU.

Where the population of a study only partially overlaps with our intended population, we will attempt to acquire patient-level data. Where this is not possible, we will include the study if a majority of participants meet our inclusion criteria. Specific decisions will be assessed ad hoc case-by-case and clearly documented in the review. We will conduct sensitivity analyses to assess the impact of such decisions [34].

Types of interventions

We will include the following two comparisons.

- Any vestibular stimulation versus no intervention. We will combine different types of vestibular stimulations in the same analysis, including:

- bundle of vestibular stimulation (e.g. rocking and waterbed stimulation);
- rocking;
- swinging;
- hammock;
- waterbed stimulation;
- air mattress;
- other types of vestibular stimulation.

- Vestibular stimulation type A (e.g. single intervention such as rocking or bundled interventions) versus type B (e.g. single intervention such as waterbed stimulation or other bundled interventions)

The intervention may be continuous (i.e. administered without interruption for at least 24 hours) or intermittent (i.e. administered at intervals with pauses in-between for at least 24 hours). We will exclude studies where the intervention is administered for less than 24 hours, considering that interventions need time to be effective, but also that short interventions could potentially have a positive or negative effect.

The intervention may be delivered by a health professional or primary caregiver, or a combination of both. Interventions may also be delivered by technology (i.e. technical equipment that delivers vestibular stimulation). If we identify trials where multiple interventions or co-interventions have been administered, we will group these based on the 'main' intervention component.

Outcome measures

Critical outcomes

- Major neurodevelopmental disability:
  - cerebral palsy;
  - developmental delay (Bayley Mental Developmental Index [42, 43]; or Griffiths Mental Development Scale assessment [44] > 2 standard deviations [SDs] below the mean);
  - intellectual impairment (intelligent quotient [IQ] > 2 SDs below the mean);
  - blindness (vision < 6/60 in both eyes);
  - sensorineural deafness requiring amplification [45].

We plan to evaluate each of these components as a separate outcome and extract data on each long-term outcome from studies that evaluated children after 18 months' chronological age. We plan to separately assess data on children 18 to 24 months of age and on those 3 to 5 years of age. We will also report each component of this composite outcome (major neurodevelopmental disability).

- Neonatal death (first 28 days) or during initial hospitalization (assessed at discharge)

The number of cases of major neurodevelopmental disability (as defined above) and neonatal death will be assessed as potential adverse events/harms of the intervention itself.

We will not exclude studies based on outcome measures, though we will analyze only relevant reported outcomes. We will contact study authors for further information as necessary, including where there is uncertainty if all measured outcomes have been reported.

Important outcomes

- Intraventricular hemorrhage: grades 1 to 4 (according to Papile classification [46]); severe intraventricular hemorrhage: ultrasound diagnosis grades 3 and 4 (assessed at discharge)
- Duration of hospital stay in days (assessed at discharge)
- Weight gain in grams (assessed at discharge)
- Number of days till full oral feeding (assessed at discharge)
- Apnea: number of episodes (defined as interruption of breathing for more than 20 seconds) during exposure to the intervention (assessed at discharge)

Search methods for identification of studies

Electronic searches

A draft search strategy was written by an Information Specialist (MF) (Supplementary material 1). We will conduct searches without language limits. We will conduct searches for trials without date limits; we will limit searches for systematic reviews to the most recent two years. Searches will be peer-reviewed based on Peer Review of Electronic Search Strategies criteria [47, 48]. We will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies (CRS);
- Ovid MEDLINE(R) All, 1946 forward;
- Ovid Embase, 1974 forward;
- CINAHL (Cumulative Index to Nursing and Allied Health Literature), EBSCOhost, 1982 forward
- Epistemonikos (www.epistemonikos.org/en/).

Searching other resources

We will search the following trial registries:

- National Library of Medicine trial registry (clinicaltrials.gov/);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int/Default.aspx);
- ISRCTN registry (www.isrctn.com/).

We will search for conference abstracts, published during the past five years, as available, for:

- Perinatal Society of Australia and New Zealand (PSANZ);
- Pediatric Academic Societies (PAS);
- European Academy of Paediatric Societies (EAPS).

We will search for errata or retractions for studies selected for inclusion via PubMed and Retraction Watch. We will check the reference lists of systematic reviews on vestibular stimulation or related subjects.

Data collection and analysis

We will use the standard methods of Cochrane Neonatal Group.

Selection of studies

Search results will be managed in EndNote and Covidence [49]; duplicates will be removed using both software packages. We will use Cochrane's Screen4Me to reduce screening activities by the authors [50, 51, 52, 53]. Screen4Me comprises three components:

- Known Assessments (a service that matches records in the search results to records that have been screened by Cochrane Crowd and labeled as 'RCT' or 'not an RCT');
- The RCT classifier (a machine-learning model that distinguishes RCTs from non-RCTs);
- Cochrane Crowd (Cochrane's crowdsourcing platform, through which contributors from around the world help to identify randomized trials and other types of healthcare-related research).

We will use, at minimum, the first two components of Screen4Me; the decision to use Cochrane Crowd will be based on the the number of results remaining following classification using Known Assessments and RCT Classifier. References categorized as non-RCTs through the Known Assessments and the RCT Classifier will be added to the irrelevant segment of Covidence [49]. This approach means that references will be available for the purposes of de-duplication when the review is updated, and for verification purposes should questions arise about the accuracy of Screen4Me categorization. We will present the results of Screen4Me in a figure in the full review.

Two review authors (KWS, ML) will independently screen all remaining titles and abstracts and exclude those that do not meet inclusion criteria. Two review authors will then independently assess all full-text articles for eligibility. Any disagreements arising during the screening process will be resolved by discussion. We will document the reasons for excluding studies at the full-text stage in a 'Characteristics of excluded studies' table. We will collate multiple reports of the same study so that each study, rather than each report or reference, is the unit of interest in the review; we will group related reports under a single study ID. We will also provide any information obtained about ongoing studies. We will present the results of our study selection in a PRISMA flow diagram [54, 55].

Data extraction and management

Full-text articles will be screened in Covidence [49], and data will be extracted using a modified version of the data extraction form from the Cochrane Effective Practice and Organization of Care Group data collection checklist [56]. We will pilot the form within the review team using a sample of included studies. Two review authors (MB, ML) will independently extract data for included studies.

We will extract the following characteristics for each included study:

- administrative details: study author(s), published or unpublished, year of publication, year in which study was conducted, presence of vested interest, details of other relevant papers cited;
- study characteristics: study registration, study design type, study setting, number of study centers and location, informed consent, ethics approval, completeness of follow-up (e.g. greater than 80%);
- participants: number randomized, number lost to follow-up/ withdrawn, number analyzed, mean gestational age, gestational age range, mean corrected age or corrected age range, inclusion criteria, place of residence, race/ethnicity/culture/language, occupation, sex, religion, education, socio-economic status, social capital, age, sexual orientation, and disability and exclusion criteria;
- interventions: initiation, type, frequency and duration of intervention, including tempo of rhythmic stimulation;
- outcomes: outlined above in Outcome measures.

We will resolve any disagreements by discussion.

We will describe ongoing studies identified by our search and document available information such as the primary author, research question(s), methods, and outcome measures, together with the anticipated reporting date in a 'Characteristics of ongoing studies' table.

If there are any missing data or uncertainties regarding trial methods, we will contact the trial authors/investigators for clarification. Two review authors (ML, MGP) will enter data into Cochrane's RevMan software [57]. We will replace any standard error of the mean (SEM) by the corresponding standard error (SE).

Risk of bias assessment in included studies

We will use Cochrane's RoB 2 tool to assess risk of bias in randomized trials included in the review [58, 59]. We will use a RoB 2 Excel tool to implement RoB 2 (www.riskofbias.info/welcome/rob-2-0-tool). The outcomes to be assessed for each study are described in Certainty of the evidence assessment.

Two review authors (ML, MGP, or KWS) will independently assess the risk of bias (low risk of bias, some concerns, high risk of bias) for each outcome. Any discrepancies in judgments will be resolved through discussion or by consultation with a third review author (RS or MB). We will assess the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [58].

- Bias arising from the randomization process
- Bias due to deviations from intended interventions (we will assess assignment to the interventions at baseline, i.e. the 'intention-to-treat' effect)
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To address these types of bias, we will use the signaling questions recommended in RoB 2 and make a judgment based on the following options.

- 'Yes': if there is firm evidence that the question was fulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'Probably yes': a judgment was made that the question was fulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'No': if there was firm evidence that the question was unfulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'Probably no': a judgment was made that the question was unfulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'No information': if the study report provided insufficient information to permit a judgment.

We will then use the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias:

- low risk of bias;
- some concerns;
- high risk of bias.

This approach will allow the review authors to derive an overall risk of bias rating for each outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judged the trial at low risk of bias for all domains for the result.
- 'Some concerns': we judged the trial to raise some concerns in at least one domain for the result, but not at high risk of bias for any domain.
- 'High risk of bias': we judged the trial at high risk of bias in at least one domain for the result, or we judged the trial to have some concerns for multiple domains such that our confidence in the result is substantially lowered.

If we include cluster-randomized trials, we will use RoB 2 for cluster-randomized trials and follow the guidance in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [60].

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results using risk ratios (RR) and risk differences (RD) with 95% confidence intervals (CIs). We will calculate the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) with 95% CIs if there is a statistically significant reduction (or increase) in RD.

Continuous data

For continuous data, we will use the mean difference (MD) when outcomes were measured in the same way between trials. We will use the standardized mean difference (SMD) to combine data from trials that used different methods to measure the same outcome. Where trials report continuous data as median and interquartile range (IQR), and data pass the test of skewness, we will convert median to mean, and estimate the SD as IQR/1.35 [34].

Unit of analysis issues

The unit of analysis in RCTs will be the individual neonate. An infant will only be considered once for analysis in RCTs. The unit of analysis in cluster-randomized trials will be the participating neonatal unit or section of a neonatal unit or hospital. For cluster-randomized trials, we will abstract information on the study design and unit of analysis for each study, indicating whether clustering of observations is present due to allocation to the intervention at the group level, or clustering of individually randomized observations (e.g. infants within clinics). We will abstract available statistical information needed to account for the implications of clustering on the estimation of outcome variances, such as design effects or intracluster correlations (ICCs), and whether the study adjusted results for the correlations in the data. In cases where studies do not account for clustering, we will ensure that appropriate adjustments are made to the effective sample size following Cochrane guidance [34]. Where possible, we will derive the ICC for these adjustments from the trial itself, or from a similar trial. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering, by imputing a range of values of ICC.

We will not include cross-over trials, as they do not allow the use of outcomes that require time to develop/discover.

If a trial has multiple arms (i.e. several different vestibular stimulations) compared to the same control condition, we will either combine groups to create a single pair-wise comparison, or select the pair of interventions that most closely matches the definitions given in Types of interventions and exclude the others. We will include the arm where different vestibular stimulations are used compared to the control group where no specific intervention was introduced. If there are several arms with various vestibular stimulations, we will combine them into one group. We will acknowledge this potential selective bias of data used for analysis in the Discussion section of the review.

Dealing with missing data

We intend to carry out analysis on an intention-to-treat basis for all included outcomes. Whenever possible, we will analyze all participants in the treatment group to which they were randomized, regardless of the actual treatment received. If we identify important missing data (in the outcomes) or require clarification, we will contact the original investigators for the additional information. We will make explicit the assumptions of any methods used to deal with missing data.

For missing dichotomous outcomes, we will include participants with incomplete or missing data in the sensitivity analyses by imputing them according to the following scenarios.

- Extreme-case analysis favoring the experimental intervention (best-worst-case scenario): none of the dropouts/participants lost from the experimental arm but all the dropouts/participants lost from the control arm experienced the outcome, including all randomized participants in the denominator.
- Extreme-case analysis favoring the control (worst-best-case scenario): all dropouts/participants lost from the experimental arm but none from the control arm experienced the outcome, including all randomized participants in the denominator.

Where the outcome is a negative, such as mortality, a lower number will support the intervention over the control; where the outcome is a positive, a lower number would favor the control.

For continuous outcomes, we will calculate missing SDs using reported P values or CIs [34]. If calculation is not possible, we will impute an SD as the highest SD reported in the other trials for the corresponding treatment group and outcome.

We will address the potential impact of missing data on the findings of the review in the Discussion section.

Reporting bias assessment

We will assess reporting bias by comparing the stated primary outcomes and secondary outcomes and reported outcomes. Where study protocols are available, we will compare these to the full publications to determine the likelihood of reporting bias. We will document studies that evaluate the interventions in a potentially eligible infant population but do not report on any of our critical

and important outcomes in the 'Characteristics of included studies' tables.

We will use funnel plots to screen for publication bias when there is a sufficient number of studies (> 10) reporting a given outcome. If publication bias is suggested by a significant asymmetry of the funnel plot on visual assessment, we will incorporate this in our assessment of the certainty of evidence [61]. If fewer than 10 studies are eligible for meta-analysis, the ability to detect publication bias will be largely diminished, in which case we will simply note our inability to rule out possible publication bias or small-study effects.

Synthesis methods

We plan analysis for the previously specified outcomes for the following comparisons: any vestibular stimulation versus no intervention; vestibular stimulation type A (e.g. single intervention such as rocking or bundled interventions) versus type B (e.g. single intervention such as waterbed stimulation or other bundled interventions).

If we identify several studies that are considered sufficiently similar, we will conduct meta-analysis using RevMan software [57]. For categorical outcomes, we will calculate the typical estimates of RR and RD, each with its 95% CI; for continuous outcomes, we will calculate the MD or the SMD, each with its 95% CI. We will use a fixed-effect model to combine data where it is reasonable to assume that studies were estimating the same underlying treatment effect [62, 63]. Cochrane neonatal reviews have typically used a fixed-effect model, as: 1) preterm neonates are relatively similar in terms of their general condition as they are less likely to be influenced by confounding factors that take time to develop; and 2) the inclusion criteria reflect narrow research questions. Interventions administered to neonates are also considered relatively easily standardized due to a controlled environment in the NICU and standard basic care protocol. Taking this into consideration, a fixed effect model is more sensitive in detecting small effect sizes. If there is evidence of clinical heterogeneity, we will try to explain it based on the different study characteristics and subgroup analyses. We will use forest plots to graphically represent the study data.

If we judge meta-analysis to be inappropriate, we will analyze and interpret individual trials separately and generate an outcome table with effect estimates for studies at low risk of bias. We will follow methodological guidance from Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* and Synthesis Without Meta-analysis (SWiM) reporting guidance [64, 65].

Investigation of heterogeneity and subgroup analysis

We will interpret any test results for subgroup differences with caution, considering the potential for confounding with other study characteristics and the observational nature of comparisons, as described in Section 10.11.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* [34]. We will consider any subgroup analyses with fewer than five studies per category as not producing meaningful results and will therefore not present these. If and when subgroup analyses are possible, we will perform meta-analysis and a formal statistical test for interaction to examine subgroup differences (e.g. Cochran's Q test, meta-regression [66, 62]).

Given the potential of intervention effectiveness to be related to gestational age, we plan to conduct subgroup analyses to see whether the intervention is more effective.

We plan to carry out the following subgroup analyses that may contribute to heterogeneity in the effects of the intervention.

- Gestational age: extremely preterm (less than 28 weeks of gestation); very preterm (less than 32 weeks of gestation); moderate to late preterm (32 weeks of gestation or more)
- Sex, dichotomized to male and female
- Type of intervention (rocking or swinging by a caretaker, waterbeds, air mattresses, mechanical vestibular systems, other vestibular interventions)
- Frequency of intervention (# per day)
- Duration of intervention sessions (minutes, hours)
- Duration of intervention period (days, weeks)

We will use the main outcomes (those specified for the summary of findings table) in subgroup analyses if there are enough studies reporting the outcomes to support valid subgroup comparisons (at least five studies per subgroup).

Equity-related assessment

We will report any relevant characteristics that are included in the acronym PROGRESS-Plus (place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socio-economic status, social capital, age, sexual orientation, and disability), and whether our neonatal population would be subject to any health inequity in terms of the interventions that we will assess. We anticipate very small differences in terms of financing between high-, middle-, or low-income country settings and populations in terms of the interventions included in our review. However, what might differ between high-, middle-, or low-income countries is the person delivering the intervention, which could deem some populations at a disadvantage, for instance if the intervention is delivered by a health professional rather than the primary caregivers. This is due to evidence suggesting that infants may distinguish whether their primary caregiver changes diapers or feeds them, and that this may positively influence their development by reducing stress [67]. We will descriptively assess this in our review. In our summary of findings table, we will highlight and present any differences in baseline risks in our neonatal population that might cause disadvantages.

Sensitivity analysis

We will conduct sensitivity analyses to explore the effect of the methodological quality of studies, and check to ascertain whether studies with a high risk of bias (in at least two domains) overestimate the effect of treatment.

Differences in the design of included studies might also affect the results of the systematic review. We will perform a sensitivity analysis to compare the effects of vestibular stimulation in truly randomized trials as opposed to quasi-randomized trials.

We will conduct sensitivity analyses for decisions regarding inclusion of studies with a subset of eligible participants.

Certainty of the evidence assessment

We will use the GRADE approach, as outlined in the *GRADE Handbook,* to assess the certainty of evidence for the following clinically relevant outcomes [68].

- Major neurodevelopmental disability at 18 to 24 months corrected age:
  - cerebral palsy;
  - developmental delay (Bayley Mental Developmental Index [42, 43]; or Griffiths Mental Development Scale assessment [44] > 2 SDs below the mean);
  - intellectual impairment (IQ > 2 SDs below the mean);
  - blindness (vision < 6/60 in both eyes);
  - sensorineural deafness requiring amplification [45].
- Death during initial hospitalization
- Weight gain in grams (assessed at discharge)

Major neurodevelopmental disability and neonatal death as critical outcomes will be assessed as potential adverse effects/harms of the intervention itself.

We will create two summary of findings tables:

- any vestibular stimulation versus no intervention;
- vestibular stimulation type A (e.g. single intervention such as rocking or bundled interventions) versus type B (e.g. single intervention such as waterbed stimulation or other bundled interventions).

Two review authors (ML, MB) will independently assess the evidence for each of the outcomes listed above. Any disagreements will be resolved by discussion or by consulting a third review author (MGP or KWS). The overall RoB 2 judgments for each outcome will inform the GRADE assessments. We will consider evidence from RCTs as high certainty, downgrading one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use GRADEpro GDT software [69] to create the summary of findings table to report the certainty of evidence.

The GRADE approach results in an assessment of the certainty of a body of evidence as one of the following four grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Consumer involvement

This review protocol has been developed with the involvement of consumers, with assistance from the parents of premature children who have required NICU care, and as one review author (ML) is a parent to an extremely preterm child. We expect that this will have made an important contribution to the research question and design and will be of further importance when interpreting data and in the dissemination and translation of findings.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016072.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

Acknowledgements

The Methods section of this protocol is based on a standard template used by Cochrane Neonatal.

We would like to thank Cochrane Neonatal: Jane Cracknell, Managing Editor; and Bill McGuire, Co-coordinating Editor, who provided editorial and administrative support. We would particularly like to thank Jane Cracknell for providing editorial guidance to authors and editing support.

Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Nai Ming Lai, School of Medicine, Faculty of Health and Medical Sciences, Taylor's University, Malaysia;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Ben Ridley, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Jacob Hester, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Lisa Winer, Cochrane Central Production Service;
- Peer reviewers (provided comments and recommended an editorial decision): Domen Vozel, MD, PhD, otorhinolaryngology, head and neck surgery specialist. Department of Otorhinolaryngology and Cervicofacial Surgery, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Slovenia (clinical/content review); J Provasi, CHArt, EPHE-PSL (clinical/content review); Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review); Yuan Chi, Beijing Yealth Technology Co Ltd, McMaster University (search review).

We especially want to thank Guro Grongstad Børsting for providing consumer input in the design of our protocol.

Contributions of authors

MGP reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

KWS reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

ML reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

MF reviewed the literature to inform the protocol, contributed to writing the draft, and reviewed and approved the final version of the protocol.

RS identified the topic of the review, reviewed the literature to inform the protocol, and reviewed and approved the final version of the protocol.

MB reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

Declarations of interest

MGP has no interests to declare.

KWS has no interests to declare.

ML has no interests to declare.

MF is the Managing Editor and Information Specialist of Cochrane Neonatal; she did not participate in the editorial acceptance of this review.

RS is the Coordinating Editor of Cochrane Neonatal, Vice President and Director of Clinical Trials of the Vermont Oxford Network, and Professor at the Larner College of Medicine, University of Vermont. He did not participate in the editorial processes for this review. He has a grant from Gerber Foundation to update reviews on interventions for pain and discomfort.

MB is an Associate Editor for Cochrane Neonatal; he had no involvement in the editorial processing of this protocol.

Sources of support

Internal sources

- Institute for Clinical Sciences, Lund University, Lund, Sweden

  MB is employed by this organization

External sources

- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.
- Region Skåne and Skåne University Hospital, Lund University, Sweden

  Cochrane Sweden received support from Region Skåne and Skåne University Hospital Lund University

Registration and protocol

Cochrane approved the proposal of this review in August 2023.

Data, code and other materials

Data sharing not applicable to this article as it is a protocol, so no datasets were generated or analyzed.

As part of the published Cochrane review protocol, the following is made available for download for users of the Cochrane Library: search strategies.

As part of the published Cochrane review, the following will be made available for download for users of the Cochrane Library: full search strategies for each database; full citations of each unique report for all studies included, ongoing or awaiting classification, or excluded at full-text screening, in the final review; study data, including study information, study arms, and study results or test data; consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows. Appropriate permissions will be obtained for such use. Analyses and data management will be conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods. Template data extraction forms from (49, Excel) will be available from the authors on reasonable request.

REFERENCES

1. Hazelhoff EM, Dudink J, Meijer JH, Kervezee L. Beginning to see the light: lessons learned from the development of the circadian system for optimizing light conditions in the neonatal intensive care unit. *Frontiers in Neuroscience* 2021;**15**:634034. [DOI: 10.3389/fnins.2021.634034]

2. Ciarleglio CM, Axley JC, Strauss BR, Gamble KL, McMahon DG. Perinatal photoperiod imprints the circadian clock. *Nature Neuroscience* 2021;**14**(1):25–7. [DOI: 10.1038/nn.2699]

3. Morris BH, Philbin MK, Bose C. Physiological effects of sound on the newborn. *Journal of Perinatology* 2000;**20**(8 Pt 2):S55-60. [DOI: 10.1038/sj.jp.7200451]

4. Wachman EM, Lahav A. The effects of noise on preterm infants in the NICU. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2011;**96**(4):F305-9.

5. Morton S, Brodsky D. Fetal physiology and the transition to extrauterine life. *Clinics in Perinatology* 2017;**43**(3):395-407. [DOI: 10.1016/j.clp.2016.04.001]

6. Provasi J, Blanc L, Carchon I. The importance of rhythmic stimulation for preterm infants in the NICU. *Children (Basel)* 2021;**8**(8):660. [DOI: 10.3390/children8080660] [PMID: 34438551]

7. World Health Organization. Preterm birth. www.who.int/news-room/fact-sheets/detail/preterm-birth (accessed 30 September 2023).

8. World Health Organization. WHO recommendations for care of the preterm or low-birth-weight infant. Licence: CC BY-NC-SA 3.0 IGO edition. Geneva: World Health Organization, 2022. [ISBN: 978-92-4-005826-2] [URL: www.who.int/publications/i/item/9789240058262]

9. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012;**379**(9832):2162-72. [DOI: 10.1016/S0140-6736(12)60820-4]

10. Ramachandrappa A, Jain L. The late preterm infant. In: Martin RJ, Fanaroff AA, Walsh MC, editor(s). Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 10th edition. Amsterdam (NL): Elsevier, 2015:582-7. [ISBN: 978-1455756179]

11. Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the sustainable development goals. *Lancet Child and Adolescent Health* 2022;**6**(2):106-15. [DOI: 10.1016/S2352-4642(21)00311-4]

12. Dieterich M, Brandt T. The bilateral central vestibular system: its pathways, functions, and disorders. *Annals of the New York Academy of Sciences* 2015;**1343**(1):10-26. [DOI: 10.1111/nyas.12585]

13. Kingma H, Berg van der R. Anatomy, physiology, and physics of the peripheral vestibular system. *Handbook of Clinical Neurology* 2016;**137**:1-16. [DOI: 10.1016/B978-0-444-63437-5.00001-7]

14. O'Reilly R, Grindle C, Zwicky EF, Morlet T. Development of the vestibular system and balance function: differential diagnosis in the pediatric population. *Otolaryngologic Clinics of North America* 2011;**44**(2):251-71. [DOI: 10.1016/j.otc.2011.01.001]

15. Kleberg A, Westrup B. Family centered developmental supportive care according to NIDCAP [Familjecentrerad utvecklingsstödjande vård enligt NIDCAP]. In: Lagercrantz H, Hellström-Westas L, Norman M, editor(s). Neonatologi. 2nd edition. Lund (SE): Studentlitteratur AB, 2008. [ISBN: 978-91-44-04643-3]

16. Weber A, Harrison TM. Reducing toxic stress in the NICU to improve infant outcomes. *Nursing Outlook* 2020;**67**(2):169-89. [DOI: 10.1016/j.outlook.2018.11.002]

17. Ballard RA. Attachment challenges with premature or sick infants. In: Martin RJ, Fanaroff AA, Walsh MC, editor(s). Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 10th edition. Amsterdam (NL): Elsevier, 2015:636-8. [ISBN: 978-1455756179]

18. Nandi R, Luxon LM. Development and assessment of the vestibular system. *International Journal of Audiology* 2009;**47**(9):566-77. [DOI: 10.1080/14992020802324540]

19. Korner AF, Schneider P, Forrest T. Effects of vestibular-proprioceptive stimulation on the neurobehavioral development of preterm infants: a pilot study. *Neuropediatrics* 1983;**14**(3):170-5. [DOI: 10.1055/s-2008-1059573]

20. Korner AF, Lane NM, Berry KL, Rho JM, Brown BW. Sleep enhanced and irritability reduced in preterm infants: differential efficacy of three types of waterbeds. *Journal of Developmental & Behavioral Pediatrics* 1990;**11**(5):240-6. [PMID: 2258442]

21. Cordero L, Clark DL, Schott L. Effects of vestibular stimulation on sleep states in premature infants. *American Journal of Perinatology* 1986;**3**(4):319-24. [DOI: 10.1055/s-2007-999888]

22. Korner AF, Kraemer HC, Haffner ME, Cosper LM. Effects of waterbed flotation on premature infants: a pilot study. *Pediatrics* 1975;**56**(3):361-7. [PMID: 1080560]

23. Tuck SJ, Monin P, Duvivier C, May T, Vert P. Effect of a rocking bed on apnoea of prematurity. *Archives of Disease in Childhood* 1982;**57**(6):475-7. [DOI: 10.1136/adc.57.6.475] [PMID: 7092314]

24. Zimmerman E, Barlow SM. The effects of vestibular stimulation rate and magnitude of acceleration on central pattern generation for chest wall kinematics in preterm infants. *Journal of Perinatology* 2011;**32**:614-20. [DOI: 10.1038/jp.2011.177]

25. Keller A, Arbel N, Merlob P, Davidson S. Neurobehavioral and autonomic effects of hammock positioning in infants with very low birth weight. *Pediatric Physical Therapy* 2003;**15**(1):3-7. [DOI: 10.1097/01.PEP.0000049507.48347.26]

26. Ribas CG, Andreazza MG, Cabral Neves V, Valderramas S. Effectiveness of hammock positioning in reducing pain and improving sleep-wakefulness state in preterm infants. *Respiratory Care* 2019;**64**(4):384-9. [DOI: 10.4187/respcare.06265] [PMID: 30944226]

27. Jones RA. A controlled trial of a regularly cycled oscillating waterbed and a non-oscillating waterbed in the prevention of apnoea in the preterm infant. *Archives of Disease in Childhood* 1981;**56**(11):889-91. [PMID: 7030228]

28. Saigal S, Watts J, Campbell D. Randomized clinical trial of an oscillating air mattress in preterm infants: effect on apnea, growth, and development. *Journal of Pediatrics* 1986;**109**(5):857-64. [DOI: 10.1016/s0022-3476(86)80714-4] [PMID: 3534202]

29. Korner AF, Ruppel EM, Rho JM. Effects of water beds on the sleep and motility of theophylline treated preterm infants. *Pediatrics* 1982;**70**:864–69.

30. Sammon MP, Darnall RA. Entrainment of respiration to rocking in premature infants: coherence analysis. *Journal of Applied Physiology* 1994;**77**:1548–54. [DOI: 10.1152/jappl.1994.77.3.1548]

31. Barlow SM, Finan DS, Lee J, Chu S. Synthetic orocutaneous stimulation entrains preterm infants with feeding difficulties to suck. *Journal of Perinatology* 2008;**28**(8):541–8. [DOI: 10.1038/jp.2008.57]

32. Symington AJ, Pinelli J. Developmental care for promoting development and preventing morbidity in preterm infants. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No: CD001814. [DOI: 10.1002/14651858.CD001814.pub2]

33. Aita M, De Clifford Faugère G, Lavallée A, Feeley N, Stremler R, Rioux É, et al. Effectiveness of interventions on early neurodevelopment of preterm infants: a systematic review and meta-analysis. *BMC Pediatrics* 2021;**21**(1):210. [DOI: 10.1186/s12887-021-02559-6]

34. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

35. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015;**4**(1):1. [DOI: 10.1186/2046-4053-4-1] [PMID: 2555424]

36. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;**350**:g7647. [DOI: 10.1136/bmj.g7647] [PMID: 25555855]

37. Higgins JP, Lasserson T, Thomas J, Flemyng E, Churchill R. Methodological Expectations of Cochrane Intervention Reviews Version August 2023. Cochrane, 2023. Available from community.cochrane.org/mecir-manual.

38. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71. [DOI: 10.1136/bmj.n71] [PMID: 33782057]

39. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;**372**:n160. [DOI: 10.1136/bmj.n160] [PMID: 33781993]

40. Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *American Journal of Epidemiology* 2007;**166**(6):646-55. [DOI: 10.1093/aje/kwm165]

41. Kyriacou DN, Lewis RJ. Confounding by indication in clinical research. *JAMA* 2016;**316**(7):1818-9. [DOI: 10.1001/jama.2016.16435]

42. Bayley N. Bayley Scales of Infant Development–II. San Antonio, TX: Psychological Corporation, 1993.

43. Bayley N. Bayley Scales of Infant and Toddler Development. 3rd edition. San Antonio, TX: Harcourt Assessment, 2006.

44. Griffiths R. The Abilities of Babies: a Study of Mental Measurement. London (UK): University of London Press, 1954.

45. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database of Systematic Reviews* 2013, Issue 1. Art. No: CD003311. [DOI: 10.1002/14651858.CD003311.pub3]

46. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 g. *Journal of Pediatrics* 1978;**92**(4):529-34. [DOI: 10.1016/s0022-3476(78)80282-0]

47. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *Journal of Clinical Epidemiology* 2016;**75**:40-6. [DOI: 10.1016/j.jclinepi.2016.01.021. Epub 2016 Mar 19]

48. McGowan J, Sampson M, Salzwedel D, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Explanation and Elaboration (PRESS E&E). Ottawa: CADTH, 2016. [URL: www.cadth.ca/sites/default/files/pdf/CP0015_PRESS_Update_Report_2016.pdf]

49. Covidence. Version accessed 23 October 2023. Melbourne, Australia: Veritas Health Innovation, 2023. Available at covidence.org.

50. Marshall IJ, Noel-Storr AH, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying randomized controlled trials:

an evaluation and practitioner's guide. *Research Synthesis Methods* 2018;**9**(4):602-14. [DOI: 10.1002/jrsm.1287]

51. Noel-Storr AH, Dooley G, Wisniewski S, Glanville J, Thomas J, Cox S. Cochrane centralised search service showed high sensitivity identifying randomised controlled trials: a retrospective analysis. *Journal of Clinical Epidemiology* 2020;**127**:142-50. [DOI: 10.1016/j.jclinepi.2020.08.008]

52. Noel-Storr AH, Dooley G, Elliott J, Steele E, Shemilt I, Mavergames C. An evaluation of Cochrane crowd found that crowdsourcing produced accurate results in identifying randomised trials. *Journal of Clinical Epidemiology* 2021;**4356**(21):00008-1. [DOI: 10.1016/j.jclinepi.2021.01.006]

53. Thomas J, McDonald S, Noel-Storr AH, Shemilt I, Elliott J, Mavergames C. Machine learning reduces workload with minimal risk of missing studies: development and evaluation of an RCT classifier for Cochrane Reviews. *Journal of Clinical Epidemiology* 2021;**133**:140-51. [DOI: 10.1016/j.jclinepi.2020.11.003]

54. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLOS Medicine* 2009;**6**(7):e1000100. [DOI: 10.1136/bmj.b2700]

55. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006-12. [DOI: 10.1016/j.jclinepi.2009.06.005]

56. Cochrane Effective Practice and Organisation of Care Review Group. Data collection check list. Available at methods.cochrane.org/sites/methods.cochrane.org.bias/files/uploads/EPOC%20Data%20Collection%20Checklist.pdf (accessed 12 July 2023).

57. Review Manager (RevMan). Version 7.12.0. The Cochrane Collaboration, 2024. Available at https://revman.cochrane.org.

58. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

59. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. [DOI: 10.1136/bmj.l4898]

60. Higgins JP, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

61. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34. [DOI: 10.1136/bmj.315.7109.629] [PMID: 9492687]

62. Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook/archive/v6.3.

63. Dettori JR, Norvell DC, Chapman JR. Fixed-effect vs random-effects models for meta-analysis: 3 points to consider. *Global Spine Journal* 2022;**12**(7):1624-26. [DOI: 10.1177/21925682221110527] [PMID: 35723546]

64. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**368**:l6890. [DOI: 10.1136/bmj.l6890] [PMID: 31948937]

65. McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

66. Borenstein M, Higgins JP. Meta-analysis and subgroups [Meta-analysis and subgroups]. *Prevention Science* 2013;**14**(2):134-43. [DOI: 10.1007/s11121-013-0377-7]

67. Welch MG, Firestein MR, Austin J, Hane AA, Stark RI, Hofer MA, et al. Family nurture intervention in the neonatal intensive care unit improves social-relatedness, attention, and neurodevelopment of preterm infants at 18 months in a randomized controlled trial. *Journal of Child Psychology and Psychiatry* 2015;**56**:1202-11. [DOI: 10.1111/jcpp.12405]

68. Schünemann H, Brożek J, Guyatt G, Oxman A, editor. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

69. GRADEpro GDT. Version accessed 14 September 2023. Hamilton (ON): McMaster University (developed by Evidence Prime), 2023. Available at https://www.gradepro.org.