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Neurally adjusted ventilatory assist versus conventional mechanical ventilation for congenital diaphragmatic hernia in neonates (Protocol)

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[Intervention Protocol]

Neurally adjusted ventilatory assist versus conventional mechanical ventilation for congenital diaphragmatic hernia in neonates

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ABSTRACT

Objectives

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

To evaluate the benefits and harms of neurally adjusted ventilatory assist versus conventional mechanical ventilation for congenital diaphragmatic hernia in neonates.

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BACKGROUND

Description of the condition

Congenital diaphragmatic hernia (CDH) is a developmental anomaly arising from the failure of normal closure of the pleuroperitoneal folds between the 4th and 10th weeks of gestation. It is characterised by a defect in the diaphragm that allows herniation of abdominal organs into the thoracic cavity, and is most frequently detected during routine prenatal ultrasonography by the visualisation of this displacement. It interferes with normal lung development, resulting in intrauterine pulmonary hypoplasia and abnormal pulmonary vasculature [1]. As a consequence, affected neonates have vulnerable lungs and often require gentle ventilation strategies to minimise respiratory complications [2].

Description of the intervention and how it might work

Conventional invasive ventilation (CV) strategies, such as synchronised intermittent mandatory ventilation (SIMV), assist-control ventilation (AC), pressure support ventilation (PSV), and synchronised intermittent mandatory ventilation + pressure support ventilation (SIMV-PSV), are commonly used in neonates with CDH. Volume-targeted ventilation has been introduced as a lung-protective approach to provide gentle ventilation. In this mode, the ventilator delivers time-cycled breaths with a preset inspiratory pressure that is automatically adjusted to achieve a target tidal volume. Although breaths may be triggered by the infant's inspiratory effort via a flow sensor, fixed pressure and time-cycled settings can still lead to patient–ventilator asynchrony [3].

Neurally adjusted ventilatory assist (NAVA) is a newer respiratory modality in neonates compared to conventional ones. It uses the electrical activity of the diaphragm (Edi), measured via an orogastric catheter, to trigger, proportionally assist, and terminate each breath according to the infant's respiratory effort. By coupling ventilatory support directly to the infant's neural respiratory drive, NAVA provides a more physiological form of ventilation than conventional modes, which rely on preset pressures and time-cycled breaths. This strategy aims to improve patient–ventilator synchrony and potentially reduce ventilator-induced lung injury. NAVA may be particularly beneficial for neonates with vulnerable lungs, such as those with CDH [4].

Why it is important to do this review

Despite advances in neonatal ventilation, there is currently no consensus on the optimal invasive ventilation strategy for infants with CDH. NAVA is a relatively new modality compared with CV modes. While NAVA has been studied in neonates with CDH in recent clinical trials, evidence regarding its short-term respiratory effects remains limited [5, 6]. In order to maximise the evidence we gather for this review, we will include both randomised and non-randomised studies of interventions evaluating these effects. Although previous narrative reviews have summarised the available evidence regarding NAVA use, evidence comparing NAVA with conventional invasive ventilation modes remains limited in infants with CDH [7, 8]. The findings of this review may provide clinicians with additional evidence to guide the delivery of gentle and physiologically appropriate ventilation for this vulnerable population [9].

OBJECTIVES

To evaluate the benefits and harms of neurally adjusted ventilatory assist versus conventional mechanical ventilation for congenital diaphragmatic hernia in neonates.

METHODS

This protocol has followed guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* [10] and is reported following PRISMA-P [11]. We will conduct the review following methodological and reporting guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* [12]; guidance from the Cochrane Non-Randomised Studies of Interventions Methods Group [13, 14]; MECIR (Methodological Expectations for Cochrane Intervention Reviews) (15); and PRISMA [16, 17].

Criteria for considering studies for this review

Types of studies

We will include prospective randomised controlled trials (RCTs), cluster-RCTs, and non-randomised studies of interventions (NRSIs) (comparative cohort studies and case-control studies).

We will exclude quasi-randomised trials because of their susceptibility to bias. Although NRSIs are also susceptible to bias, the cohort and case-control designs included in this review allow for structured assessment and, where possible, statistical adjustment for confounding using the ROBINS-I v2 framework [18]; quasi-randomised trials, by contrast, involve allocation methods (e.g. alternation, date of birth) that introduce systematic bias in group assignment that cannot be adequately addressed through such adjustment.

Types of participants

We will include studies of neonates (infants' corrected age (CA) of less than one month (i.e. chronological age minus the number of weeks the infant was born before 40 weeks' gestation) born at ≥ 34 weeks of gestation who were diagnosed with CDH and invasively mechanically ventilated in the neonatal intensive care unit (NICU) after surgery. If a study includes a mixed population and does not report data separately for the eligible subgroup, we will contact the study authors to request subgroup-specific data. If data are not available, we will exclude the study from qualitative and quantitative synthesis for that outcome.

Types of interventions

We will include studies comparing NAVA versus CV strategies with or without volume targeting, specifically:

- NAVA versus synchronised intermittent mandatory ventilation (SIMV);
- NAVA versus assist-control ventilation (AC);
- NAVA versus pressure support ventilation (PSV); and
- NAVA versus synchronised intermittent mandatory ventilation + pressure support ventilation (SIMV-PSV).

Outcome measures

We will include studies that plan to measure our outcomes of interest, regardless of whether they report data for the particular outcome.

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Critical outcomes

Short term (within the first two weeks after surgery)

- Duration (days) between first invasive mechanical ventilation and first extubation attempt

Intermediate term (until hospital discharge after surgery)

- Duration (days) of invasive mechanical ventilation

Important outcomes

Short term (within the first two weeks after surgery)

- Maximum level of inspiratory pressure (PIP) used by the infant, measured on the ventilator, where higher values greater than 20 cm H_2O indicate increased ventilatory support requirements
- Maximum level of oxygenation index (OI), where values greater than 25 indicate increased ventilatory support requirements
- Re-intubation within 72 hours of extubation attempt

Intermediate term (until hospital discharge after surgery)

- Length of hospital stay (LOS)
- Number of infants diagnosed with bronchopulmonary dysplasia (BPD) (defined as infants who received oxygen for more than 28 days and required oxygen or pressure support)

Search methods for identification of studies

Electronic searches

A draft strategy, preceded by a search narrative [19], has been written by an Information Specialist (MF), and is provided in Supplementary material 1. The strategy omits methodological filters because retrieval is very low and the addition of three filters for randomised trials, non-randomised trials, and systematic reviews (the latter for reference checking) would make the strategies long and complicated for no good purpose. Searches will be run without date or language limits using the following sources.

- Ovid MEDLINE(R) All, 1946 to Daily Update
- Ovid Embase 1974-
- Ovid Emcare, 1995-
- Cochrane CENTRAL Register of Controlled Trials, via CRS
- Web of Science: Science, Emerging Sources, Conference Proceedings – Science, and SciELO Citation Indices; and the Korean Journal Database
- Scopus
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (https://clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (https://trialsearch.who.int/Default.aspx)

Searching other resources

We will conduct manual searches of the following conference proceedings for the past five years.

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

We will check the reference lists of studies eligible for inclusion and reviews related to ventilatory treatment of CDH. We will contact authors of eligible ongoing studies and experts in the field to enquire about studies our searches may not have identified.

We will conduct forward citation searching of studies identified for inclusion in this review using Citation Chaser or Web of Science.

We will search for retractions or errata related to included studies using Retraction Watch Database and PubMed.

Data collection and analysis

If we identify a study or studies conducted by the authors of this review, other review authors will independently undertake selection, data extraction, risk of bias, and GRADE assessment of the study or studies. In the event that multiple review authors are involved in an included study, we will recruit additional independent colleagues to undertake these tasks, with either an acknowledgement or authorship on the review, depending on their contribution.

Selection of studies

We will conduct screening using Covidence [20]. Two review authors (CA and ANE) will independently screen titles/abstracts, and the full-texts of references that we retain following title/abstract assessment. Our selection decisions will be based on our Criteria for considering studies for this review. We will resolve disagreements at any point in the screening process by discussion or by consulting a third review author (SW).

If abstracts or articles require translation into English to determine their eligibility, we will use a translation service such as DeepL or Google Translate. We will report any use of such software in the review. In cases where a document cannot be translated by software, we will seek a human translator.

We will collate multiple reports of the same study so that the study, not the reference, is the unit of interest in the review. We will document our reasons for excluding any studies during the full-text review.

We will describe the selection process narratively and in a PRISMA flow diagram [16, 17].

Data extraction and management

Two review authors (CA and ANE) will independently extract data using a data extraction form within Covidence [20]. We will pilot the form on a sample of two studies and refine it if necessary. We will resolve disagreements by discussion or in consultation with a third review author (SW). We will import the data into Review Manager (RevMan) [21].

We will extract the following characteristics from each included study.

- Identifying information: authors, year of publication, country, study design
- Participant details: inclusion/exclusion criteria, number enrolled and assessed, baseline characteristics provided in the studies (e.g. gestational age (GA), birthweight)
- Intervention and comparator descriptions
- Outcomes, as described in Outcome measures, and key results

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- Declarations of interest and funding sources

If we identify ongoing studies, we will provide as much information as we are able to obtain, including an expected completion date.

Where necessary, we will contact trial authors to clarify or obtain missing data.

Risk of bias assessment in included studies

Randomised controlled trials

For randomised controlled trials, two review authors (CA, ANE) will independently assess the risk of bias at the outcome level using the Cochrane RoB 2 Excel tool [22, 23]. We will use the RoB 2 extension for cluster-RCTs. We will resolve disagreements by discussion or by consulting a third review author (SW).

We will use the following five domains of bias, to assess risk of bias, for individually randomised trials.

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in the measurement of the outcome
- Bias in the selection of the reported result

To address these types of bias in RCTs, we will use the signalling 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 judgement 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 judgement 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 allow any judgement.

We will assess the risk of bias with respect to the intention-to-treat (ITT) effect, that is, the effect of assignment to the intervention at baseline, regardless of adherence to the assigned ventilation strategy. Our risk of bias assessments will inform our interpretation of the review's findings and sensitivity analyses.

Non-randomised studies of interventions

For non-randomised studies of interventions (NRSIs), two review authors (CA, ANE) will use the ROBINS-I v2 tool [18], conducting their assessment according to Chapter 25 of the *Cochrane Handbook for Systematic Reviews of Interventions* [14]. We will resolve disagreements by discussion or by consulting a third review author (SW).

A priori, we identified the following baseline confounders as particularly relevant to this review: gestational age, birthweight, timing of surgical repair, severity of pulmonary hypertension, size of the diaphragmatic defect, and use of sedative or neuromuscular blocking agents.

We will assess the risk of bias across the following ROBINS-I version 2 domains [18].

- Bias due to confounding
- Bias in classification of interventions
- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To address these types of bias in NRSIs, we will use the signalling questions for each domain following the ROBINS-I version 2 guidance and will assign an overall risk of bias judgement (low, moderate, serious, critical, or no information) based on the combined assessment across all domains [18].

Both RCTs and NRSIs

We will assess the risk of bias, at the outcome level, for both RCTs and NRSIs for the following outcomes.

- Duration of invasive mechanical ventilation, measured in days, assessed within the first two weeks after diaphragmatic surgery (short term)
- Duration of invasive mechanical ventilation, measured in days, assessed at hospital discharge after diaphragmatic surgery (intermediate term)
- Maximum level of inspiratory pressure (PIP) used by the infant, measured on the ventilator, in the short term
- Maximum level of oxygenation index (OI) in the short term
- Re-intubation within 72 hours following extubation attempt in the short term
- Duration of length of hospital stay (LOS) after surgery in the intermediate term
- Number of diagnoses of BPD, which is defined as infants who received oxygen for more than 28 days and required oxygen or pressure support in the intermediate term

We will present outcome-specific risk of bias judgements alongside forest plots, for both RCTs and NRSIs. We will generate traffic plots using an online Robvis visualisation tool (https://www.riskofbias.info/welcome/robvis-visualization-tool).

Where we need to clarify or confirm information relevant to risk of bias assessments, we will contact study authors by email. We will request additional details regarding study design, randomisation procedures, deviations from intended interventions, outcome definitions, and missing data. If we receive no response after two contact attempts over a four-week period, we will make risk of bias judgements based on the available information.

Measures of treatment effect

We will summarise continuous outcomes, including duration of invasive mechanical ventilation, ventilator pressures, oxygenation indices, and length of hospital stay, using mean differences (MDs) with 95% confidence intervals (CIs), as these outcomes will be measured using the same units across studies or should be easily converted to the same unit [24].

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We will summarise binary outcomes, including re-intubation within 72 hours following extubation and BPD, using risk ratios (RRs) with 95% CIs [24].

We will interpret the magnitude of the effect by considering its clinical relevance in neonates with congenital diaphragmatic hernia. Given the established association between prolonged mechanical ventilation (seven days or more) and increased BPD risk, we will interpret effect estimates with consideration of whether the intervention meaningfully reduces exposure to prolonged ventilation [25, 26, 27]. In addition, we will interpret ventilatory parameters in light of clinically relevant reference thresholds: OI < 25 and PIP < 25 cm H_2O as indicative of a more favourable respiratory profile [28, 29].

Unit of analysis issues

For multi-arm trials comparing more than one relevant intervention group with a single control group, we will avoid double-counting of participants by either combining relevant intervention groups into a single group or by splitting the shared control group evenly across comparisons, as appropriate. For cluster-randomised trials, we will adjust the effective sample size using the reported intracluster correlation coefficient, or an external ICC if analyses have not been appropriately adjusted for clustering [24, 30].

For studies reporting repeated outcome measurements at multiple time points, we will use data corresponding to the predefined time points of interest (short term: within the first two weeks after surgery; intermediate term: until hospital discharge after surgery). If multiple measurements are available within the same time window, we will select the most clinically relevant or highest reported value, as prespecified.

Dealing with missing data

When we identify apparently missing or unclear data at the study, outcome, or summary data level, we will contact study authors to request clarification or additional information. We will make up to two contact attempts over a two-week period. If data remain unavailable after four weeks, we will base our analyses on the available data. When summary statistics required for meta-analysis are not reported, we will derive or impute values where appropriate using methods recommended in the *Cochrane Handbook*, and we will clearly report any assumptions or calculations used. We will assess the potential impact of missing outcome data and imputed or converted summary statistics through our prespecified sensitivity analyses, where sufficient studies are available [12]. We will address the potential impact of missing data in the 'Discussion' section of the review.

Reporting bias assessment

If at least 10 studies are included in a meta-analysis, we will generate a funnel plot and examine it for asymmetry, considering Egger's regression test where appropriate [31]. If fewer than 10 studies are included in the review, we will assess reporting bias qualitatively, taking into account trial registry records, published protocols, and discrepancies between registered and reported outcomes. Two review authors (CA and ANE) will independently assess the risk of bias due to missing results in a synthesis. We will resolve disagreements through discussion or by consulting a third review author (SW).

Synthesis methods

Randomised controlled trials

Where at least two studies are sufficiently similar in terms of participants and interventions, and analyse the same outcome, we will perform meta-analysis in accordance with Chapters 10 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* [32, 33]. We will conduct multiple meta-analyses, examining each outcome separately.

We will summarise dichotomous outcomes (e.g. BPD, re-intubation within 72 hours following extubation) as RRs with 95% CIs [32]. We will summarise continuous outcomes (e.g. duration of invasive mechanical ventilation, PIP, OI) as MDs with 95% CIs. We will use standardised mean differences (SMDs) only when different scales are applied to measure the same outcome.

We will use the random-effects model because we anticipate clinical and methodological heterogeneity. Between-study variance (τ^2) will be estimated using the Restricted Maximum Likelihood (REML) estimator. We will use the Hartung-Knapp-Sidik-Jonkman method to calculate confidence intervals when at least three studies are included and the estimate of heterogeneity is greater than zero. In pooled analysis of two studies, or where the estimate of heterogeneity is zero, we will use the Wald-type confidence intervals. We will assess heterogeneity by visual inspection of forest plots, the I^2 statistic, and the between-study variance (τ^2). We will not base model selection solely on I^2 thresholds. Where substantial heterogeneity is identified, we will explore potential sources through prespecified subgroup and sensitivity analyses. If meta-analysis is not appropriate due to substantial heterogeneity or limited data, we will synthesise the results narratively following Synthesis Without Meta-analysis (SWiM) reporting guidance [34].

Non-randomised studies of interventions

Where at least two non-randomised studies are sufficiently similar in terms of participants and interventions, and analyse the same outcome, we will perform meta-analysis in accordance with Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* [35]. We will analyse NRSIs separately from RCTs and will not pool randomised and non-randomised evidence in the same meta-analysis due to differences in study design and susceptibility to confounding.

Given the range of non-randomised study designs that may be included (e.g. cohort studies with concurrent or historical controls, controlled before–after studies, and pre–post cohort studies), we will select the summary effect measure based on the design and data reported. Where studies include a comparator group, we will extract adjusted effect estimates where available (e.g. RRs, odds ratios, hazard ratios, or adjusted MDs) and preferentially use estimates that account for potential confounding. If multiple adjusted models are reported, we will extract the estimate from the model we judge to have the most appropriate adjustment for key confounders.

For studies reporting within-group changes over time (e.g. pre-post cohort studies without a comparator), we will summarise outcomes as change scores where available (mean change with standard deviation). Where change scores are not reported, we will use pre- and post-intervention values to estimate the effect, where

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appropriate. We will summarise continuous outcomes as MDs or SMDs with 95% CIs depending on whether outcomes are measured using the same or different scales.

Where studies with similar designs and outcome measures are available, we will pool results using the random-effects model with REML estimation to account for expected clinical and methodological heterogeneity. The Hartung-Knapp-Sidik-Jonkman method will be used to calculate confidence intervals when at least three studies are included and the estimate of between-study heterogeneity is greater than zero; otherwise, Wald-type confidence intervals will be used. We will not include studies judged to be at critical risk of bias using ROBINS-I v2 in quantitative synthesis, in accordance with the guidance in Chapter 24.6.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* [35], but we will describe them narratively where appropriate.

Where appropriate, we will conduct meta-analyses separately according to NRSI design (e.g. controlled observational studies versus uncontrolled pre–post studies). We will assess heterogeneity through visual inspection of forest plots, the I^2 statistic, and the between-study variance (τ^2).

If meta-analysis is not appropriate due to heterogeneity in study design, intervention characteristics, or outcome measurement, we will synthesise the findings narratively following Synthesis Without Meta-analysis (SWiM) reporting guidance [33, 34].

Investigation of heterogeneity and subgroup analysis

Heterogeneity

We will explore high statistical heterogeneity in the outcomes by visually inspecting the forest plots [12]. We will interpret the I^2 statistic according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions*, taking into account the magnitude and direction of effects, the strength of evidence for heterogeneity (e.g. the P value from the Chi^2 test), and the clinical and methodological diversity across studies [32]. As a rough guide: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity [32].

If we note statistical heterogeneity that may be important, we will explore the possible causes (e.g. differences in study quality, participants, intervention regimens, or outcome assessments).

Where statistical heterogeneity is significant, we will interpret the results of the meta-analyses accordingly; and we will downgrade the certainty of evidence in the summary of findings tables, according to the GRADE recommendations.

Subgroup analysis

We will consider subgroup analyses with fewer than 10 studies per category to be insufficient to reliably detect differences in effects, and any such findings will not be highlighted in the review's results.

We plan to conduct subgroup analysis based on gestational age.

- Preterm infants (< 37 weeks' gestation)
- Term infants (≥ 37 weeks' gestation)

As only infants born ≥ 34 weeks' gestation are eligible for inclusion, this subgroup analysis will compare late preterm infants (34+0 to 36+6 weeks' gestation) with term infants (≥ 37 weeks' gestation).

The degree of prematurity may modify the effect of ventilation strategies due to differences in lung maturity and susceptibility to ventilator-induced lung injury. We anticipate that preterm infants may demonstrate greater relative benefit from NAVA.

We will conduct subgroup analyses using study-level data. We will assess for differences between subgroups using the tests for interaction provided in RevMan [21].

Sensitivity analysis

In accordance with Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions*, we will perform sensitivity analyses to assess the robustness of the synthesised results where sufficient studies are available [32].

We plan to conduct the following sensitivity analyses.

- Excluding randomised controlled trials judged to be at overall high risk of bias (RoB 2)
- Excluding non-randomised studies judged to be at serious risk of bias (ROBINS-I v2)
- Excluding studies in which summary statistics were imputed or converted (e.g. estimated standard deviations or converted medians)
- Assessing the impact of missing outcome data where sufficient information is available

Given that there is no formal statistical test that can be used for sensitivity analysis, we will make informal comparisons between the different ways of estimating the effect under different assumptions. Changes in the P values should not be used to judge whether there is a difference between the main analysis and sensitivity analysis, since statistical significance may be lost with fewer studies included. We will report sensitivity analysis results in tables rather than forest plots.

Certainty of the evidence assessment

We will use the GRADE approach [36] and GRADEpro GDT software [37] to assess the certainty of evidence and create summary of findings tables. Two review authors (CA and ANE) will independently assess the certainty of the evidence for each of the clinically important comparisons and outcomes listed below. We will resolve disagreements by discussion or by consulting a third review author (SW).

Comparisons

- NAVA versus synchronised intermittent mandatory ventilation (SIMV)
- NAVA versus assist-control ventilation (AC)
- NAVA versus pressure support ventilation (PSV)
- NAVA versus synchronised intermittent mandatory ventilation + pressure support ventilation (SIMV-PSV)

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Outcomes

- Duration of invasive mechanical ventilation, measured in days, assessed in the short term (within the first two weeks after surgery)
- Duration of invasive mechanical ventilation, measured in days, assessed in the intermediate term (until hospital discharge after surgery)
- Maximum level of inspiratory pressure (PIP) used by the infant, measured on the ventilator, in the short term (within the first two weeks after surgery)
- Maximum level of oxygenation index (OI) in the short term (within the first two weeks after surgery)
- Re-intubation within 72 hours following extubation in the short term (within the first two weeks after surgery)
- Duration of length of hospital stay (LOS) after surgery in the intermediate term (until hospital discharge after surgery)
- Number of diagnoses of BPD, which is defined as infants who received oxygen for more than 28 days and required oxygen or pressure support in the intermediate term (until hospital discharge after surgery)

Randomised controlled trials

We will consider evidence from RCTs as high certainty, but we will downgrade the evidence by one level for serious (or two levels for very serious) limitations based upon the following factors: study design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias.

Non-randomised studies of interventions

We will consider evidence from NRSIs as starting at 'high certainty' as informed by ROBINS-I v2 guidance [18] and will downgrade the certainty level in the presence of serious concerns, based on five considerations: study limitations, inconsistency, imprecision, indirectness, and publication bias [38].

We will justify our decisions to downgrade the certainty of the evidence using explanatory footnotes.

Equity considerations

We will not investigate health inequities in this review. This review focuses on neonatal intensive care ventilation strategies for CDH, and we anticipate that the included studies will provide insufficient and inconsistent reporting of equity-related characteristics (e.g. socioeconomic status, ethnicity, place of residence) to support meaningful equity analyses.

Consumer involvement

We will not involve consumers or members of the public in the conduct of this review. This review addresses a technical question regarding invasive ventilation strategies in neonatal intensive care for congenital diaphragmatic hernia, and we do not anticipate that direct consumer involvement would influence methodological decisions. However, one of our outcomes, BPD, is included in COIN (Core Outcomes in Neonatology) [39], which was developed with input from patients.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016375.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

Acknowledgements

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The following people conducted the editorial process for this protocol.

- Sign-off Editor (final editorial decision): Rupa Sarkar, Editor in Chief, Cochrane
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sam Hinsley, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, selected peer reviewers, collated peer-reviewer comments, and supported editorial team): Cynthia Stafford, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Laura MacDonald, Cochrane Central Production Service
- Peer reviewers (provided comments and recommended an editorial decision): Tom Patterson, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review)

Contributions of authors

SS conceived the review question and provided overall clinical and scientific leadership for the protocol.

CA and SS designed and co-ordinated the protocol process.

SS and CA led the operational development of the manuscript and review workflow.

ANE advised on statistical analysis plans.

JC and MF provided editorial and information specialist support, including development of the search strategy.

SW provided independent methodological oversight.

All authors contributed to refinement of the protocol and approved the final manuscript.

Declarations of interest

CA has no commercial or non-commercial conflicts of interest relevant to this review.
ANE has no commercial or non-commercial conflicts of interest relevant to this review.
SW has no commercial or non-commercial conflicts of interest relevant to this review.

MF is a Managing Editor and Information Specialist with the Cochrane Neonatal Review Group; she took no part in the editorial

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assessment or acceptance of this protocol. She has no commercial or non-commercial conflicts of interest relevant to this review.

JC is a Managing Editor with the Cochrane Neonatal Review Group; she took no part in the editorial assessment or acceptance of this protocol. She has no commercial or non-commercial conflicts of interest relevant to this review.

SS participated in a one-off Medical Advisory Board meeting for Maquet Critical Care AB (Aktiebolag, the Swedish term for a limited/stock company) in 2024. He has received honoraria from Getinge for educational speaking engagements related to neonatal ventilation, including invited lectures, workshops, and conference presentations. SS is an author on the NAN-C study [5] that is eligible for inclusion in this review. He will not be involved in study selection decisions, data extraction, risk of bias assessment, or GRADE assessment for this study.

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Registration and protocol

Cochrane approved the proposal for this review in November 2025.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol. No datasets were generated or analysed.

Disclosure of artificial intelligence use

We used ChatGPT (OpenAI; GPT-5.5, accessed July 2026) and DeepL Translator (DeepL SE; Version 25.9.42781299, accessed July 2026) to assist with language editing and improving the clarity of the manuscript. All AI-assisted outputs were critically reviewed, edited, and verified by the review authors. The review authors retain full responsibility for the scientific content, interpretation, accuracy, and final wording of the manuscript.

When conducting the review, we will not use artificial intelligence tools for study selection, data extraction, risk of bias assessment, certainty of evidence assessment, statistical analyses, or decision-making about the conduct of the review.

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