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# Fluid restriction for treatment of symptomatic patent ductus arteriosus in preterm infants (Protocol)

MacLellan A, Cameron AJ, Cooper C, Mitra S

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[Intervention Protocol]

# Fluid restriction for treatment of symptomatic patent ductus arteriosus in preterm infants

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## ABSTRACT

### Objectives

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

To assess the effectiveness and safety of fluid restriction for symptomatic patent ductus arteriosus (PDA) in preterm infants.

To determine if fluid restriction (parenterally, enterally, or both) with or without diuretics reduces morbidity and mortality in preterm infants with a symptomatic PDA.


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# BACKGROUND

## Description of the condition

Ductus arteriosus is a blood vessel connecting the main pulmonary artery and proximal descending aorta. During fetal life, this vessel allows blood to travel between the pulmonary artery and the aorta, bypassing the lungs, with the direction of blood flow determined by the pressure gradient from the pulmonary vasculature (Philips 2022). In the fetus, as pulmonary vascular resistance is usually high, the ductus arteriosus will normally divert blood from the pulmonary artery to the aorta (right to left shunt). Post birth, when pulmonary vascular resistance normally lowers, the blood tends to travels from the aorta to the pulmonary artery (left to right shunt). After birth, the ductus arteriosus usually undergoes active constriction and eventual obliteration (Philips 2022). However, sometimes the ductus arteriosus remains patent in the neonate, which is called patent ductus arteriosus (PDA). If a PDA is clinically symptomatic, it can lead to pulmonary edema, and reduced cerebral, renal, and mesenteric perfusion from continued left to right blood shunting (Clyman 2012). There are various approaches to PDA treatment, but evidence is unclear as to which treatment, if any, most effectively reduces morbidity and mortality (Clyman 2012). This review will refer to PDA in premature infants that is hemodynamically significant (hs-PDA), based on either clinically determined criteria or from transthoracic echocardiogram.

## Description of the intervention

Optimizing fluid therapy is important for preterm infants who are too unwell to tolerate oral feeds, or who have yet to develop the ability to feed orally (Bell 2014). Fluids can be administered parenterally (crystalloid, colloid, blood products, medication, parenteral nutrition) or enterally (milk or formula, medication, trophic feeds [Abbas 2019]). Typically, in preterm infants, fluids are initiated at a volume of 60 mL/kg/day to 80 mL/kg/day, and increased by 10 mL/kg/day to 20 mL/kg/day, to a volume of about 150 mL/kg/day by five to seven days of age (Yu 2005). The volume of fluid administered, either parentally or enterally, is an important consideration in the management of PDA. A systematic review of randomized controlled trials (RCTs) found that restriction of fluid intake among preterms was associated with a decrease in the occurrence of a symptomatic PDA (Bell 2014). However, variability existed in how fluid restriction was defined in preterm infants. In the systematic review by Bell 2014, fluid intake timing and duration in the fluid restriction arm of the included studies ranged from fluid restriction from 24 hours of birth to 28 days of age, or fluid restriction up to the first five days of age. Variability also existed in how volume cut-off or range was specified in the definition of fluid restriction (Bell 2014).

In this protocol, we refrained from pre-specifying the volume and duration of fluid restriction, to capture all possible interventions that were instituted with the intention to provide less volume of fluid in the intervention group than in the control group. The review will provide an opportunity to describe the variability in the definition of fluid restriction for the management of a symptomatic PDA.

## How the intervention might work

Reduction of circulating fluid volume by restricting fluid intake enterally or parenterally has been shown to reduce the development of PDA and related morbidities, such as necrotizing enterocolitis (Bell 2014). It has also been suggested that fluid restriction improves left atrial overload associated with PDA shunting (Conrad 2019).

However, fluid restriction is not without its own risks, including the potential to jeopardize sufficient nutrition, or contribute to the compromise of systemic circulation. An observational study of very low birthweight infants with a hemodynamically significant PDA showed that energy and protein intake declined with fluid restriction, and could contribute to lower postnatal growth in the first 28 days of life (Hansson 2019). If fluid restriction results in deficiencies in nutrient intake, this can lead to malnutrition and growth inhibition (Hansson 2019). Another observational study for PDA treatment in preterm infants showed that fluid restriction resulted in reduced blood flow to the superior vena cava, an estimate of reduced systemic circulation (De Buyst 2012). There is also reduced postductal perfusion to the gut and kidneys in the presence of a symptomatic PDA (Wong 1990). Restriction of fluids may further worsen postductal perfusion, thereby contributing to end organ ischemia (Wong 1990).

Reduction of circulating fluid volume may also be achieved by using diuretics, such as furosemide (Thompson 2018). However, the use of diuretics, such as furosemide, can prolong the patency of a PDA, due to its pharmacological action to increase prostaglandin activity (Thompson 2018). Therefore, despite helping to reduce circulating fluid volume, the use of diuretics, in addition to restricted fluid intake, may or may not help in the treatment of a symptomatic PDA. A Cochrane Review on the use of furosemide in indomethacin-treated infants with PDA failed to demonstrate a reduction in failure of PDA closure with the use of furosemide (risk ratio [RR] 1.25; 95% confidence interval [CI] 0.62 to 2.52 [Brion 2001]).

## Why it is important to do this review

Bell 2014 demonstrated that fluid restriction reduced the incidence of symptomatic PDA. Clinicians may extrapolate this evidence to proactively restrict fluids for the treatment of a symptomatic PDA, as there is no Cochrane Review evaluating this specific intervention. A recent position statement from the Canadian Pediatric Society provides a weak recommendation in favor of fluid restriction for conservative PDA management, but highlights the dearth of high quality research in this area (Mitra 2022). This Cochrane Review will provide clinicians with a synthesis of existing evidence for the use of fluid restriction to treat symptomatic PDA in neonates.

# OBJECTIVES

To assess the effectiveness and safety of fluid restriction for symptomatic patent ductus arteriosus (PDA) in preterm infants.

To determine if fluid restriction (parenterally, enterally, or both) with or without diuretics reduces morbidity and mortality in preterm infants with a symptomatic PDA.

# METHODS

## Criteria for considering studies for this review

### Types of studies

We will include all published randomized controlled trials (RCTs), quasi-RCTs, cluster-RCTs, and cross-over RCTs, regardless of


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language or year of publication. We will only include unpublished RCTs if the study authors agree to provide details of the trial methodology, so that we can adequately ascertain the internal validity of the study.

### Types of participants

We will include neonates who were born preterm (< 37 weeks' gestational age), or low birth weight infants (less than 2500 g), with a hemodynamically significant patent ductus arteriosus (PDA), diagnosed either clinically or by echocardiographic criteria in the neonatal period (< 28 days). We will include studies that include this specific participant group as a subgroup.

A hemodynamically significant PDA will be defined by these echo criteria.

1. A moderate to large transductal diameter (PDA diameter greater than 1.5 mm with or without unrestrictive pulsatile flow, i.e. maximum systolic shunt velocity less than 2 m/second),
2. With or without evidence of pulmonary over-circulation (left atrium to aortic root ratio greater than 1.5, or isovolumetric relaxation time less than 55 m/seconds, or E:A ratio of 1.0 or greater, or left ventricular output greater than 300 mL/kg/minute, or diastolic disturbance in the main pulmonary artery),
3. With or without evidence of systemic hypoperfusion (absent/reversed diastolic flow in the postductal descending aorta or celiac trunk or middle cerebral artery [El-Khuffash 2013; Mitra 2020]).

A hemodynamically significant PDA will be defined clinically as a precordial murmur, with one or more of the following signs: tachycardia, hyperdynamic precordial impulse, widened pulse pressure, bounding pulses, worsening respiratory status, cardiac failure, or hypotension (El-Khuffash 2013; Mitra 2020).

### Types of interventions

We will include studies using therapeutic restriction of parenteral or enteral (or both) fluids, with or without diuretics. Control groups will receive standard fluid intake, defined as no parenteral or enteral restriction, with or without diuretic use. We will include the following comparisons.

Comparison 1: fluid restriction without diuretic use versus liberal fluid intake without diuretic use

Comparison 2: fluid restriction with diuretic use versus liberal fluid intake without diuretic use

Comparison 3: fluid restriction without diuretic use versus liberal fluid intake with diuretic use

Comparison 4: fluid restriction with diuretic use versus liberal fluid intake with diuretic use

### Types of outcome measures

#### *Primary outcomes*

1. Closure of PDA (determined via echocardiographic criteria)

#### *Secondary outcomes*

1. All-cause mortality at 36 weeks' postmenstrual age (PMA)
2. Need for interventional closure of the PDA
3. Need for treatment with a cyclooxygenase inhibitor
4. Chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD), defined as use of supplemental oxygen > 28 days of age in infants born after 32 weeks' gestation (NIH 1979), or use of supplemental oxygen at 36 weeks' postmenstrual age in infants born before 32 weeks' gestation (Jobe 2001)
5. Duration of ventilator support (days)
6. Duration of need for supplementary oxygen (days)
7. Pneumothorax
8. Pulmonary hemorrhage
9. Pulmonary hypertension, defined as hypoxemia refractory to oxygen therapy, or to lung recruitment strategies (partial pressure of oxygen in arterial blood [$PaO2_2$] less than 55 mmHg, despite fraction of inspired air [$FiO_2$] of 1.0) associated with a preductal to postductal oxygen gradient greater than 20 mmHg [Roberts 1997; Walsh-Sukys 2000])
10. Intraventricular hemorrhage (IVH; grades I to IV) on cranial ultrasound, as per Papile classification (Papile 1978)
11. Severe IVH (grades III and IV) on cranial ultrasound, as per Papile classification
12. Periventricular leukomalacia (PVL) any grade (grade 1 or greater), on the basis of ultrasound or magnetic resonance imaging (de Vries 1992)
13. Necrotising enterocolitis (NEC; any stage), defined as Bell's stage II or greater, or any grade requiring surgery (Bell 1978)
14. Spontaneous intestinal perforation
15. Time to regain birth weight (days)
16. Retinopathy of prematurity (ROP), according to the international classification of ROP (ICCROP 2005)
17. Definite sepsis, defined as clinical symptoms and signs of sepsis plus a positive bacterial culture in a specimen obtained from normally sterile fluids, or tissue obtained at postmortem
18. Oliguria, defined as less than 1 mL/kg/hour
19. Duration of hospitalization, defined as total length of hospitalization from birth to discharge home or mortality (days)
20. Electrolyte disturbance, defined as either hyponatremia, hypernatremia, hypokalemia, or hyperkalemia

## Search methods for identification of studies

The draft search strategy was developed by the Cochrane Neonatal Information Specialist (CC).

### Electronic searches

We will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (current issue);
- MEDLINE Ovid (MEDALL; 1946 to present);
- Embase Ovid (1980 to present).

The bibliographic search strategy is recorded in Appendix 1, and it ill take the following form: ((search terms for Neonates) AND (terms for fluid restriction) AND (terms for PDA) AND (filters for randomized studies OR systematic reviews)).

We will use the Cochrane Neonatal search terms to limit searches to the Neonatal population, and methodological filters to restrict


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retrieval to trials and systematic reviews. We will conduct searches without limit to language, publication year, or publication status.

### Searching other resources

We will undertake the following supplementary searches (Cooper 2017).

#### *Trials registry resources*

We will search:

- National Institute of Health Clinical Trials.gov (www.clinicaltrials.gov/);
- The World Health Organisations (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal);
- Australian New Zealand Clinical Trials Registry (ANZCTR; www.anzctr.org.au/).

#### *Searching for systematic reviews*

We will retain systematic reviews, which are identified during the search for studies, for reference checking. We will also search Epistemonikos (www.epistemonikos.org/).

#### *Searching conferences*

We will identify conference proceedings through our search of Embase. We will also handsearch abstract books, as they are available, for conferences, such as American Pediatric Society; Society of Pediatric Research; and European Society of Paediatric Research. We will report details of years accessed in our review.

#### *Checking references*

We will check the reference lists of included studies and the reference lists of related systematic reviews to identify studies not captured in the database searches.

#### *Contacting authors*

See Dealing with missing data.

## Data collection and analysis

For each included study, we will collect information about the method of randomization, blinding, intervention, stratification, and whether the trial was single- or multicenter. We will note information regarding trial participants, including birth weight, gestational age, number of participants, type of fluid restriction, route of administration, diuretic use. We will analyze the clinical outcomes noted in Types of outcome measures.

### Selection of studies

We will download all titles and abstracts retrieved by electronic and handsearching to Covidence, a reference management database, and remove duplicates. We (AM and AC) will individually screen the search results by title and abstract for studies that possibly meet the inclusion criteria. We will obtain the full text of each article that is potentially eligible, and AM and AC will independently assess the full-text reports. We will resolve any disagreements through discussion, and consensus with the third review author (SM). The unit of interest for the review is the study; we will group multiple reports and papers related to a single study under a single reference ID. We will record the article selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009), and characteristics of included and excluded studies tables (Moher 2009).

If the search yields more than 500 results, we will use the Cochrane's Screen4Me workflow for assessing search results. Screen4Me has three components:

1. Known assessments (a service that matches records in the search results to records that have already been screened in Cochrane Crowd and labeled as RCT or not an RCT);
2. The RCT classifier (machine-learning model that distinguishes RCTs from non-RCTs); and
3. Cochrane Crowd(Cochrane's citizen science platform to identify and describe health evidence), if needed.

### Data extraction and management

We (AM and AC) will independently extract, assess, and code all data for each study, using a standardized, piloted data extraction form, developed in Microsoft Excel, and modified from the Cochrane Effective Practice and Organization of Care Group data collection checklist (EPOC 2017). For each study, AM and AC will enter the extracted data into RevMan Web, and SM will check data entry (RevMan Web 2022).

We will collect the following information from each included study.

1. Administrative details: name of review author carrying out data extraction; study ID (and any other unique trial identifiers); name and contact address of first/corresponding author of included trial; year of publication; year in which study was conducted; presence of vested interest; citation of included trial; language of trial and details of any duplicate publications
2. Study characteristics: study registration; trial design (type of RCT); location of trial; setting; informed consent; ethics approval; sample size; study duration; treatment arms; method of randomization; length of follow-up; completeness of follow-up; trial registration data
3. Participants: sex; mean gestational age; birth weight; number of participants randomized; inclusion and exclusion criteria; number of participants lost to follow-up/withdrawn; number of participants analyzed
4. Characteristics of interventions: number of treatment arms; description of experimental and control arm(s); timing, dose, and route and duration of administration of intervention; concomitant medications; other differences between intervention arms
5. Outcomes: all relevant arm-level data on critical and secondary outcomes, outlined in Types of outcome measures. We will also collect data on stated outcome measures that have been defined in a manner different from our stated definitions

We will resolve any disagreements by discussion. We will describe ongoing studies identified by our search, detailing the primary author, research question(s), methods, and outcome measures, together with an estimate of the reporting date, and report them in the characteristics of ongoing studies table.

Should any queries arise, or for cases in which additional data are required, we will contact study investigators/authors for clarification. We will replace any standard error of the mean (SEM) by the corresponding standard deviation (SD).


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### Assessment of risk of bias in included studies

Using Cochrane's RoB 1, AM and AC will independently assess the risk of bias (low, high, or unclear) of all included trials, for the following domains (Higgins 2017).

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

We will resolve disagreements by consensus, or discussion with the third review author (SM). See Appendix 2 for more details regarding the risk of bias for each domain. We will assess overall risk of bias according to three categories:

1. Low risk of bias: we will classify the trial as low risk of bias overall, if we classified all domains at low risk of bias;
2. Unclear risk of bias: we will classify the trial as unclear risk of bias overall, if we classify one or more domains as unclear risk of bias, and no domain at high risk of bias;
3. High risk of bias: we will classify the trial as high risk of bias overall, if we classify at least one domain at high risk of bias.

### Measures of treatment effect

#### *Dichotomous data*

For dichotomous data, we will present results using risk ratios (RRs) and risk differences (RDs) 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 are measured in the same way between trials. We will use the standardized mean difference (SMD) to combine trials that measured the same outcome but used different methods. When trials report continuous data as median and interquartile range (IQR), and data pass the test of skewness, we will convert the mean to a median, and estimate the standard deviation as IQR/1.35.

If data are not reported in an RCT in a format that can be entered directly into a meta-analysis, we will convert them to the required format, using information in Chapter 6 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2022).

### Unit of analysis issues

We will undertake the primary analysis on individuals randomized. We will extract information on the study design and unit of analysis for each study. For cluster-RCTs (e.g. participants within clinics), we will indicate whether clustering of observations is present due to allocation to the intervention at the group level, or clustering of individually randomized observations. We will extract available statistical information needed to account for the implications of clustering on the estimation of outcome variances, such as design effects or intra-cluster correlations (ICC), and whether the study adjusted for the correlations in the data (Higgins 2022). If the study does not account for clustering, we will ensure that appropriate adjustments are made to the effective sample size, following Cochrane guidelines. When 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.

If trials have multiple arms that are compared against the same control condition, which will be included in the same meta-analysis, we will either combine groups to create a single pair-wise comparison, or select one pair of interventions and exclude the others.

In the meta-analysis and data synthesis, we will only include the first-phase data from cross-over trials.

### Dealing with missing data

When data are missing, and cannot be derived as described, we will approach the analysis as follows:

1. We will contact the original study investigator to request the missing data;
2. Where possible, we will impute missing SDs using the coefficient of variation (CV), or calculate them from other available statistics, including standard errors, confidence intervals, t values, and P values;
3. If we assume the data are missing at random, we will analyze the data without imputing any missing values;
4. If we cannot assume this, we will impute the missing outcomes with replacement values, assuming all had a poor outcome, and conduct sensitivity analyses to assess changes in the direction or magnitude of the effect resulting from data imputation.

When feasible, we will carry out analysis on an intention-to-treat basis for all outcomes. When possible, we will analyze all participants in the treatment group to which they were randomized, regardless of the actual treatment received. We will make explicit the assumptions of any methods we used to deal with missing data. We will perform sensitivity analyses for trials with versus without missing data, to assess how sensitive results are to reasonable changes in the underlying assumptions. We will address the potential impact of missing data on the findings of the review in the Discussion section.

### Assessment of heterogeneity

We will describe the clinical diversity and methodological variability of the studies in the review text and study tables, describing the study characteristics, including design features, population characteristics, and intervention details.

To assess statistical heterogeneity, we will visually inspect forest plots, and describe the direction and magnitude of the effects and the degree of overlap between confidence intervals. We will also consider the statistics generated in forest plots that measure statistical heterogeneity. We will use the $I^2$ statistic to quantify inconsistency among the trials in each analysis. We will also consider the P value from the $Chi^2$ test to assess if this heterogeneity is significant ($P < 0.1$). If we identify substantial heterogeneity, we will report the finding and explore possible explanatory factors, using prespecified subgroup analyses.


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We will use the following as a rough guideline to interpret the $I^2$ value, rather than a simple threshold. Our interpretation will take into account that measures of heterogeneity ($I^2$ and $Tau^2$) provide estimates with high uncertainty when the number of studies is small (Deeks 2022).

1. less than 40% might not represent important heterogeneity
2. 30% to 60% may represent moderate heterogeneity
3. 50% to 90% may represent substantial heterogeneity
4. more than 75% may represent considerable heterogeneity

**Assessment of reporting biases**

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

We will create funnel plots to screen for publication bias when more than 10 studies report on the same outcome. If publication bias is suggested by a significant asymmetry of the funnel plot on visual assessment, we will incorporate this into our assessment of certainty of evidence (Egger 1997).

To assess outcome reporting bias, we will also check trial protocols against published reports. For trials registered after 1 July 2005, we will screen the WHO International Clinical Trials Registry Platform for the a priori trial protocol, to evaluate if selective reporting of outcomes is present (De Angelis 2004).

**Data synthesis**

If we identify multiple studies that we consider to be sufficiently similar, we will undertake a meta-analysis using RevMan Web (RevMan Web 2022). 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 (Higgins 2022). For dichotomous outcomes, we will calculate RR and RD, each with its 95% CI; for continuous outcomes, we will calculate the MD or the SMD, each with its 95% CI. If we judge meta-analysis to be inappropriate, we will analyse and interpret individual trials separately. If we find evidence of clinical heterogeneity, we will try to explain this, based on the different study characteristics and subgroup analyses (Campbell 2019).

**Subgroup analysis and investigation of heterogeneity**

We will interpret tests for subgroup effect differences with caution, given the potential for confounding with other study characteristics, and the observational nature of the comparisons. Subgroup analyses with fewer than five studies per category are unlikely to be adequate to ascertain valid difference in effects, and we will not highlight them in our results. We will not undertake subgroup comparisons when there are fewer than ten studies available for meta-analysis. When subgroup comparisons are possible, we will undertake a stratified meta-analysis and a formal statistical test for interaction to examine subgroup differences that could account for effect heterogeneity (Higgins 2022).

Given the potential differences in the intervention effectiveness related to concomitant diuretic use and route of fluid intake, we will conduct subgroup comparisons to see if the intervention effectiveness varies with type of diuretic used, and route of fluid intake (i.e. parenteral or enteral).

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

Subgroup analysis will evaluate the effectiveness and safety of fluid restriction on ductal closure/ductal reduction, based on the following criteria.

1. Gestational age (less than 28 weeks, 28 weeks or more)
2. Birth weight (less than 1000 g, 1000 g or more)
3. Method used to diagnose a hemodynamically significant PDA (by echocardiographic, clinical criteria, or both)
4. Parenteral versus enteral fluid restriction
5. Use of loop diuretics
6. Use of thiazide diuretics
7. Use of potassium sparing diuretics
8. Use of aldosterone antagonist diuretics

**Sensitivity analysis**

We plan to conduct sensitivity analyses to determine whether the findings are affected by including only studies at low risk of bias.

If we note substantial variation in the definition of fluid restriction, with respect to the volume or duration of fluid restriction (or both), we plan to conduct sensitivity analyses to determine whether the findings were affected by severe fluid restriction (total fluid intake in the intervention group restricted to less than 75% of the total fluid intake in the control group), or prolonged duration of fluid restriction (duration of restriction more than 7 days), or both.

Based on available information, we plan to undertake sensitivity analyses for these outcomes.

1. Closure of PDA (determined via echocardiographic criteria)
2. All-cause mortality at 36 weeks' postmenstrual age
3. Need for interventional closure of PDA
4. Need for treatment with a cyclooxygenase inhibitor

Since there is no formal statistical test that can be used for sensitivity analysis, we will provide informal comparisons between the different ways of estimating the effect under different assumptions. We will not use changes in the P values to judge whether there is a difference between the main analysis and sensitivity analysis, since significance may be lost with fewer included studies.

We will report sensitivity analysis results in tables rather than forest plots.

**Summary of findings and assessment of the certainty of the evidence**

We will use the GRADE approach, as outlined in the *GRADE Handbook* to assess the certainty of evidence for the following clinically relevant outcomes (Schünemann 2013).

1. Closure of patent ductus arteriosus
2. All-cause mortality at 36 weeks' postmenstrual age
3. Need for interventional closure of the patent ductus arteriosus


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4. Need for treatment with a cyclooxygenase inhibitor
5. Bronchopulmonary dysplasia
6. Severe intraventricular hemorrhage
7. Duration of hospitalization

Two review authors (AM and AC) will independently assess the certainty of the evidence for each of the stated outcomes. We will consider evidence from randomised controlled trials as high certainty, downgrading the evidence one level for serious (or two levels for very serious) limitations based on 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 to create a summary of findings table and report the certainty of the evidence (Schünemann 2022).

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

1. High: we are very confident that the true effect lies close to that of the estimate of the effect
2. 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
3. Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
4. 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

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# APPENDICES

## Appendix 1. MEDLINE Ovid search strategy

**Search narrative** Cooper 2018**:** the aim of this search is to identify studies reporting randomised controlled trials, or systematic reviews, which address the following research objectives:

1. To assess the effectiveness and safety of fluid restriction for symptomatic patent ductus arteriosus in preterm infants; and
2. To determine if fluid restriction (parenterally and/or enterally) with or without diuretics reduces morbidity and mortality in preterm infants with a symptomatic PDA.

Database: MEDLINE (MEDALL)

Host: Ovid

Data parameters: 1946 to June 23, 2022

Date of search: 24 June 2022

| Search strategy | Search context |
|---|---|
| 1 exp infant, newborn/ or Intensive Care, Neonatal/ or Intensive Care Units, Neonatal/ or Gestational Age/ (705026)<br><br>2 (babe or babes or baby* or babies or gestational age? or infant? or infantile or infancy or low birth weight or<br><br>low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-matures<br><br>or prematures or prematurity or pre-maturity or preterm or preterms or pre term? or preemie or preemies or premies or<br><br>premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or<br><br>NICUs).ti,ab,kw,kf. (999398)<br><br>3 or/1-2 | Lines 1-2 represent the population search terms for this review, namely neonates. This is the search filter developed by the Cochrane Neonatal group May 2022 edition.<br><br>Line 1 searches on controlled indexing (in this case, MeSH – represented by /) and Line 2 searches using free-text. Free-text terms are searched in the following bibliographic fields:<br><br>• ti = title;<br>• ab = abstract;<br>• kw = author selected keyword; and<br>• kf = keyword headings selected by authors. |
| 4 exp Fluid Therapy/ (21667)<br><br>5 ((fluid* or breastmilk or formula or hydrat* or liquid* or milk or rehydrat* or water) adj4 (consum* or depriv* or<br><br>diuresis or diuretic or drink* or enteral* or feed* or intake or intravenous* or IV or manag* or oral* or parenteral* or<br><br>restrict* or supply or therap*)).ti,ab,kw,kf. (177804) | Lines 4-5 represent the intervention cluster for the review. Again, we harmonize controlled indexing (line 4, in this case indexing is 'exploded' (represented by exp) to capture fluid therapy or hypodermoclysis) and free-text search terms (line 5). The free-text terms were chosen by the review's clinical authors (AM, AC and SM) and scoped by CC. We use a proximity marker (adj4) which searches for the |


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*(Continued)*

| | |
|---|---|
| 6 4 or 5 (191185) | terms in the left cluster within three words of right cluster and in any order. For instance:<br><br>Fluid therapies<br><br>or<br><br>Therapies which include fluids |
| 7 exp Ductus Arteriosus, Patent/ (9545)<br><br>8 exp Ductus Arteriosus/ (3075)<br><br>9 (ductus or PDA).ti,ab,kw,kf. (27892)<br><br>10 7 or 8 or 9 (30611) | Lines 7-9 are the secondary population cluster of terms. According to the inclusion criteria of our review, an eligible study must be focused on a neonate with hemodynamically significant-PDA. |
| 11 randomized controlled trial.pt. (571453)<br><br>12 controlled clinical trial.pt. (94917)<br><br>13 randomized.ti,ab. (613852)<br><br>14 placebo.ti,ab. (235527)<br><br>15 drug therapy.fs. (2503919)<br><br>16 randomly.ti,ab. (386061)<br><br>17 trial.ti,ab. (703075)<br><br>18 groups.ti,ab. (2396357)<br><br>19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (5453320)<br><br>20 (quasirandom* or quasi-random* or randomi* or randomly).ti,ab,kw,kf. (1049450)<br><br>21 (control* adj2 (group? or random* or trial? or study)).ti,ab,kw,kf. (1044853)<br><br>22 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII" or ("Phase 2" or "phase2" or "phase II" or P2 or<br><br>"PII")).ti,ab,kw,kf. (178684)<br><br>23 20 or 21 or 22 (1758932)<br><br>24 19 or 23 (5807951) | Our review is limited to studies reporting randomized trials and systematic reviews.<br><br>We use the Cochrane HSSS SM (lines 11-18 (Lefebvre 2021)), with additional search terms for sensitivity for randomized studies (lines 20-21) and studies which report by trial phase but not randomization (lines 22-23, a filter by Cooper et al (Cooper 2019)) |
| 25 meta-analysis/ or "systematic review"/ or network meta-analysis/ [/ finds same as.pt. syntax] (277636)<br><br>26 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw. (273905)<br><br>27 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 | We used the CADTH filter to limit to systematic reviews (searchfilters.cadth.ca) |


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*(Continued)*

analy*)).ti,ab,kf,kw. (34841)

28 (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw. (35649)

29 (hand search* or handsearch*).ti,ab,kf,kw. (10524)

30 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw. (32350)

31 meta-analysis as topic/ or network meta-analysis/ (25184)

32 (meta analy* or metanaly* or meta regression* or metaregression*).ti,ab,kf,kw. (239771)

33 (medline or cochrane or pubmed or medlars or embase or cinahl).ab. (292818)

34 (cochrane or systematic review?).jw. (19295)

35 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (554971)

| | |
|---|---|
| 36 3 and 6 and 10 and 24 (105)<br><br>37 3 and 6 and 10 and 35 (23)<br><br>38 36 or 37 (109) | Line 36 combines: terms for neonates AND terms for fluid therapy AND terms for PDA AND terms for trials.<br><br>Line 37 combines: terms for neonates AND terms for fluid therapy AND terms for PDA AND terms for systematic reviews.<br><br>We combine both searches in Line 38 for de-duplication across the search. This completes the search in MEDLINE. |

## Appendix 2. RoB 1

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the risk of bias of the trials. For each trial, we will seek information regarding the method of randomization, blinding, and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at a low, high, or unclear risk of bias. Two review authors will separately assess each study. We will resolve any disagreements by discussion. We will add this information to the characteristics of included studies table. We will evaluate the following issues and enter the findings into the risk of bias table.

**Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?**

For each included study, we will categorize the method used to generate the allocation sequence as:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

**Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?**

For each included study, we will categorize the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomization; consecutively numbered, sealed, opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk


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**Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?**

For each included study, we will categorize the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or class of outcomes. We will categorize the methods as:

- low risk, high risk, or unclear risk for participants; and
- low risk, high risk, or unclear risk for personnel.

**Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?**

For each included study, we will categorize the methods used to blind outcome assessment. We will assess blinding separately for different outcomes or class of outcomes. We will categorize the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors

**Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?**

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorize the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

**Selective reporting bias. Are reports of the study free of the suggestion of selective outcome reporting?**

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely, and so cannot be used; the study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

**Other sources of bias. Was the study apparently free of other problems that could put it at high risk of bias?**

For each included study, we will describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk.

If needed, we plan to explore the impact of the level of bias by undertaking sensitivity analyses.

## CONTRIBUTIONS OF AUTHORS

AM drafted the protocol and approved the final version of the protocol.

AC reviewed all drafts and approved the final version of the protocol.


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SM conceived the project, reviewed all drafts, and approved the final version of the protocol.

CC wrote the draft search strategy and search methods.

## DECLARATIONS OF INTEREST

AM declares no conflict of interest.

AC declares no conflict of interest.

SM is the principal investigator of a Canadian Institutes of Health Research (CIHR)-funded prospective study on the relative effectiveness and safety of pharmacotherapeutic agents for treatment of patent ductus arteriosus (PDA) in preterm infants. SM reports working as a neonatologist at a tertiary care neonatal intensive care unit in IWK Health Center (Halifax, Nova Scotia, Canada), where they attend to preterm infants diagnosed with a PDA. SM is an Associate Editor for Cochrane Neonatal, but will take no part in the editorial processes for this protocol or subsequent review.

CC is an Information Specialist employed by Cochrane Neonatal, but will take no part in the peer review or editorial processes related to this protocol or subsequent review.

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  none

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