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## Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants (Review)

Romantsik O, Smit E, Odd DE, Bruschettini M

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[Intervention Review]

# Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants

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## ABSTRACT

### Background

Intraventricular haemorrhage (IVH) is a major complication of preterm birth. Large haemorrhages are associated with a high risk of disability and hydrocephalus. Instability of blood pressure and cerebral blood flow in the newborn are postulated as causative factors. Another mechanism may involve reperfusion damage from oxygen free radicals. It has been suggested that phenobarbital stabilises blood pressure and may protect against free radicals. This is an update of a review first published in 2001 and updated in 2007 and 2013.

### Objectives

To assess the benefits and harms of the postnatal administration of phenobarbital in preterm infants at risk of developing IVH compared to control (i.e. no intervention or placebo).

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, CINAHL and clinical trial registries in January 2022. A new, more sensitive search strategy was developed, and searches were conducted without date limits.

### Selection criteria

We included randomised controlled trials (RCTs) or quasi-RCTs in which phenobarbital was given within the first 24 hours of life to preterm infants identified as being at risk of IVH because of gestational age below 34 weeks, birth weight below 1500 g or respiratory failure. Phenobarbital was compared to no intervention or placebo. We excluded infants with serious congenital malformations.

### Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were all grades of IVH and severe IVH (i.e. grade III and IV); secondary outcomes were ventricular dilation or hydrocephalus, hypotension, pneumothorax, hypercapnia, acidosis, mechanical ventilation, neurodevelopmental impairment and death. We used GRADE to assess the certainty of the evidence for each outcome.

### Main results

We included 10 RCTs (792 infants).

The evidence suggests that phenobarbital results in little to no difference in the incidence of IVH of any grade compared with control (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.84 to 1.19; risk difference (RD) 0.00, 95% CI -0.06 to 0.07;  $I^2$  for RD = 65%; 10 RCTs, 792 participants; low certainty evidence) and in severe IVH (RR 0.88, 95% CI 0.64 to 1.21; 10 RCTs, 792 participants; low certainty evidence).

The evidence is very uncertain about the effect of phenobarbital on posthaemorrhagic ventricular dilation or hydrocephalus (RR 0.62, 95% CI 0.31 to 1.26; 4 RCTs, 271 participants; very low certainty evidence), mild neurodevelopmental impairment (RR 0.57, 95% CI 0.15 to 2.17; 1 RCT, 101 participants; very low certainty evidence), and severe neurodevelopmental impairment (RR 1.12, 95% CI 0.44 to 2.82; 2 RCTs, 153 participants; very low certainty evidence). Phenobarbital may result in little to no difference in death before discharge (RR 0.88, 95% CI 0.64 to 1.21; 9 RCTs, 740 participants; low certainty evidence) and mortality during study period (RR 0.98, 95% CI 0.72 to 1.33; 10 RCTs, 792 participants; low certainty evidence) compared with control.

We identified no ongoing trials.

### Authors' conclusions

The evidence suggests that phenobarbital results in little to no difference in the incidence of IVH (any grade or severe) compared with control (i.e. no intervention or placebo). The evidence is very uncertain about the effects of phenobarbital on ventricular dilation or hydrocephalus and on neurodevelopmental impairment. The evidence suggests that phenobarbital results in little to no difference in death before discharge and all deaths during the study period compared with control.

Since 1993, no randomised studies have been published on phenobarbital for the prevention of IVH in preterm infants, and no trials are ongoing. The effects of postnatal phenobarbital might be assessed in infants with both neonatal seizures and IVH, in both randomised and observational studies. The assessment of benefits and harms should include long-term outcomes.

## PLAIN LANGUAGE SUMMARY

### What are the benefits and risks of phenobarbital for preventing bleeding to the brain in babies born too early?

#### Key messages

- Giving phenobarbital (a medicine used to control seizures) to babies born too early may have little to no effect in preventing intraventricular haemorrhage (bleeding to the brain) and death.
- The evidence is very uncertain about the effect of phenobarbital on preventing ventricular dilation (enlarged spaces in the brain) and long-term brain development.

#### What is bleeding to the brain (intraventricular haemorrhage)?

Large bleeds in the centre of the brain can cause disability or death in babies born too early. Unstable blood pressure and blood flow to the brain are believed to cause bleeding into the fluid-filled cavities of the brain (ventricles).

#### What did we want to find out?

Phenobarbital is believed to stabilise blood pressure and therefore potentially help prevent bleeding to the brain. We wanted to find out whether phenobarbital was better than no medicine or a placebo (a 'dummy' treatment that does not contain any medicine but looks or tastes identical to the medicine being tested) to prevent bleeding to the brain.

#### What did we do?

We searched for studies that compared giving phenobarbital against no medicines. We compared and summarised the results of these studies and rated our confidence in the evidence, based on factors such as study methods and size.

#### What did we find?

We included 10 studies (792 babies).

The evidence suggests that phenobarbital has little to no effect in preventing bleeding to the brain. The evidence is very uncertain about the effect of phenobarbital on dilation of the ventricles in the brain and long-term development. The evidence suggests that phenobarbital has little to no effect in preventing deaths. We identified no ongoing trials.

#### What are the limitations of the evidence?

It is possible that people conducting the studies were aware of what treatment they were giving. Not all the studies provided data about everything that we were interested in. The studies were very small.

#### How up to date is this evidence?

This review updates our previous review. The evidence is up to date to January 2022.

## SUMMARY OF FINDINGS

### Summary of findings 1. Phenobarbital compared to control for the prevention of intraventricular haemorrhage in preterm infants

#### Phenobarbital compared to placebo or no intervention for the prevention of IVH in preterm infants

**Patient or population:** preterm infants with or at risk of IVH

**Setting:** neonatal intensive care units

**Intervention:** phenobarbital

**Comparison:** placebo or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	Risk with phenobarbital				
IVH any grade (Papile classification) during hospitalisation	Study population		RR 1.00 (0.84 to 1.19)  RD 0.00 (-0.06 to 0.07)	792 (10 RCTs)	⊕⊕⊕⊕ Low <sup>1 2</sup>	The evidence suggests that phenobarbital results in little to no difference in the incidence of IVH (any grade) compared with control
	388 per 1000	388 per 1000 (326 to 462)				
Severe IVH (Papile classification) during hospitalisation	Study population		RR 0.88 (0.64 to 1.21)  RD -0.02 (-0.07 to 0.03)	792 (10 RCTs)	⊕⊕⊕⊕ Low <sup>1 3</sup>	The evidence suggests that phenobarbital results in little to no difference in the incidence of severe IVH compared with control
	161 per 1000	142 per 1000 (103 to 195)				
Ventricular dilation or hydrocephalus during hospitalisation	Study population		RR 0.62 (0.31 to 1.26)  RD -0.05 (-0.12 to 0.02)	271 (4 RCTs)	⊕⊕⊕⊕ Very low <sup>1 4</sup>	The evidence is very uncertain about the effect of phenobarbital on ventricular dilation or hydrocephalus
	129 per 1000	80 per 1000 (40 to 163)				
Mild neurodevelopmental impairment at 27 months of age	Study population		RR 0.57 (0.15 to 2.17)	101 (1 RCT)	⊕⊕⊕⊕ Very low <sup>5 6</sup>	The evidence is very uncertain about the effect of phenobarbital on mild neurodevelopmental impairment
	111 per 1000	63 per 1000 (17 to 241)				

						RD -0.05 (-0.16 to 0.06)
Severe neurodevelopmental impairment at 9 to 27 months of age	Study population					RR 1.12 (0.44 to 2.82)
	99 per 1000	111 per 1000 (43 to 279)	153 (2 RCTs)	⊕⊕⊕⊕	Very low <sup>4 7</sup>	The evidence is very uncertain about the effect of phenobarbital on severe neurodevelopmental impairment
						RD 0.01 (-0.09 to 0.11)
Death before discharge	Study population					RR 0.88 (0.64 to 1.21)
	173 per 1000	152 per 1000 (111 to 209)	740 (9 RCTs)	⊕⊕⊕⊕	Low <sup>1 3</sup>	The evidence suggests that phenobarbital results in little to no difference in death before discharge compared with control
						RD -0.02 (-0.07 to 0.03)
All deaths during the study	Study population					RR 0.98 (0.72 to 1.33)
	166 per 1000	163 per 1000 (120 to 221)	792 (10 RCTs)	⊕⊕⊕⊕	Low <sup>1 3</sup>	The evidence suggests that phenobarbital results in little to no difference in all deaths during study compared with control
						RD 0.00 (0.05 to 0.05)

\***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  
CI: confidence interval

IVH: intraventricular haemorrhage

RD: risk difference

RR: risk ratio

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** 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 certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

1 Downgraded by one level for high or unclear risk of bias in all domains of the risk of bias tool.

2 Downgraded by one level for inconsistency ( $I^2 = 58\%$ ).

3 Downgraded by one level for imprecision of the estimates.

4 Downgraded by two levels for imprecision of the estimates, due to wide CIs and low sample size.

5 Downgraded by one level for high risk of performance bias and unclear risk for detection and reporting bias.

- 6 Downgraded by two levels for imprecision for wide CIs in one study with very low sample size and few events.  
7 Downgraded by one level for high or unclear risk of bias in most domains (all except attrition bias).

## BACKGROUND

### Description of the condition

Intraventricular haemorrhage (IVH) is a major complication of preterm birth, and severe haemorrhages (grade 3 or higher) or haemorrhages associated with parenchymal brain lesions (grade 4) have a high rate of disability (Cizmeci 2019; Shankaran 2020; Stoll 2015; Vohr 1989; Younge 2017). Massive IVH may result in death from hypovolaemia, and severe haemorrhages may result in hydrocephalus in infants who survive, causing neurodevelopmental impairment (Cizmeci 2019; Luyt 2020; Shankaran 2020; Stoll 2015; Volpe 1995; Whitelaw 2007). In preterm infants, IVH originates not from an artery, but rather from capillaries of the subependymal germinal matrix (Romantsik 2019). The particular vulnerability of premature infants is thought to result from a subependymal germinal matrix that is rich in immature vessels poorly supported by connective tissue (Ballabh 2014; Gould 1987; Hambleton 1976), marked fluctuations in cerebral blood flow (Mullaart 1994; Pasternak 1983; Perlman 1983) and severe respiratory problems that result in major swings in intrathoracic and venous pressure that are then transmitted to the fragile germinal matrix (Nakamura 1990; Volpe 2008). In addition, there is evidence that ischaemia followed by reperfusion plays a role in the pathogenesis of IVH and that cerebral ischaemia may result from IVH. This may take the form of periventricular haemorrhagic infarction (Volpe 1995; Volpe 2008). Periventricular haemorrhagic infarction lesions are typically unilateral and continuous with the margin of the lateral ventricle. The aetiology is thought to be changes in cerebrospinal fluid (CSF) homeostasis on the one hand due to obstruction of venous drainage by a blood clot and, on the other hand, hypersecretion of CSF through the activation of Toll-like receptor (TLR)-4 and the nuclear factor- $\kappa$ B inflammatory pathway (Aquilina 2012; Karimy 2017). Interventions aimed at the prevention of IVH or its consequences may be targeted at any one (or more) of the above mechanisms.

### Diagnosis of IVH by ultrasound

Initially, the diagnosis of IVH was made by cerebral computed tomography (CT). However, now, cranial ultrasound can be conducted cotside and does not expose the infant to any ionising radiation. This enables whole populations of infants to be safely and ethically examined. Indeed, Papile's classification of IVH was originally developed for CT (Papile 1978), but was quickly implemented by ultrasonographers:

- grade I haemorrhage is confined to the subependymal germinal matrix with no blood clot in the lumen;
- grade II haemorrhage is a small haemorrhage within the ventricular lumen without ventricular dilation;
- grade III haemorrhage is a large haemorrhage sufficient to expand the ventricle from the amount of blood
- grade IV haemorrhage is IVH plus parenchymal haemorrhagic venous infarction (Volpe 1995).

Although ultrasound diagnosis of low-grade IVH is not perfect, with a sensitivity of 61% and specificity varying between 80% and 100%, the diagnosis of severe IVH with ultrasound shows high sensitivity (90%) and specificity (100%) (Hope 1988; Parodi 2015).

### Timing of IVH

Approximately 80% of IVH occurs within 72 hours of birth, but, in a considerable proportion of cases, IVH is visible on the first scan within a few hours of birth (Levene 1982; Volpe 2008). This means that interventions to prevent IVH should ideally start before delivery and should be continued soon after birth.

### Description of the intervention

Phenobarbital is a barbiturate that acts on GABA<sub>A</sub> receptors in the central nervous system. Phenobarbital prolongs and potentiates the action of gamma aminobutyric acid (GABA) on GABA<sub>A</sub> receptors and may activate the receptors directly. Phenobarbital is frequently used in children as an anticonvulsant.

### How the intervention might work

#### Postnatal phenobarbital

The administration of postnatal phenobarbital for the prevention of IVH in low-birthweight infants was suggested in the 1980s based on the following data:

1. the observation that phenobarbital may dampen fluctuations in systemic blood pressure in premature infants (Wimberley 1982);
2. evidence that treatment with phenobarbital reduces the incidence of intracranial haemorrhage in newborn beagles made hypertensive with phenylephrine (Goddard 1987);
3. experimental evidence that barbiturates can partially protect the brain against hypoxic-ischaemic damage (Steen 1979);
4. the suggestion that the free radical-scavenging capacity of phenobarbital may protect the brain after hypoxia-ischaemia (Ment 1985).

However, very few studies on phenobarbital for the prevention of IVH have been published in the following decades.

#### Drug side effects

Phenobarbital and other barbiturates may cause respiratory depression, with consequent respiratory acidosis and the need for mechanical ventilation; cardiac depression; and hypotension (Kumar 2021; Maitre 2013; Sharpe 2020). Furthermore, concerns have been raised about the effects of chronic exposure to phenobarbital on long-term neurodevelopment (Kwan 2004). In addition, data from studies in rats report an increase in apoptosis (cell death) in the immature brain following postnatal administration (Bittigau 2002; Forcelli 2011; Forcelli 2012; Kaushal 2016).

#### Why it is important to do this review

One previous systematic review on this topic (Horbar 1992), including eight trials, concluded that postnatal phenobarbital did not reduce the frequency or severity of IVH in preterm infants. This Cochrane systematic review was first published in 2013 (Smit 2013) in order to include studies after 1988, as well as outcomes not included in the Horbar 1992 review. This 2023 review is an update of the Smit 2013 review, which was originally titled 'Postnatal phenobarbital for the prevention of intraventricular haemorrhage'.



## OBJECTIVES

To assess the benefits and harms of postnatal administration of phenobarbital in preterm infants at risk of developing IVH compared to control (i.e. no intervention or placebo).

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All controlled trials, whether randomised or quasi-randomised, in which postnatal phenobarbital was compared to control treatment of preterm infants at risk of IVH. We included cross-over trials and cluster-randomised trials.

#### Types of participants

We included:

- newborn infants (less than 24 hours old) with a gestational age of less than 34 weeks or a birthweight less than 1500 grams;
- preterm newborn infants with gestational ages of 33 to 36 weeks or birthweights up to 1750 grams if they were mechanically ventilated.

We also planned to include studies reporting on a subset of the aforementioned population, provided results were available for this subset alone.

We excluded infants with serious congenital malformations.

#### Types of interventions

Phenobarbitone (phenobarbital) by intravenous or intramuscular injection starting within 24 hours of birth, with or without maintenance therapy for up to seven days. The comparator was no intervention or placebo.

We planned to include studies where co-interventions were administered to both arms (e.g. phenobarbital plus heparin versus placebo plus heparin). We planned to exclude studies where co-interventions were administered to one arm only (e.g. phenobarbital plus heparin versus placebo without heparin; phenobarbital without heparin versus placebo plus heparin).

#### Types of outcome measures

The following outcome measures do not form part of the eligibility criteria.

#### Primary outcomes

- All grades of IVH (Papile 1978)
- Severe IVH (i.e. grade III and IV IVH)

#### Secondary outcomes

- Ventricular dilation or hydrocephalus
- Hypotension (mean arterial pressure < 30 mmHg) during the first week of life
- Pneumothorax or interstitial emphysema during the first week of life
- Hypercapnia (> 8 kPa or 60 mmHg) during the first week of life
- Acidosis (pH < 7.2) during the first week of life

- Mechanical ventilation (including infants who were ventilated at enrolment)
- Mild neurodevelopmental impairment (developmental quotient (DQ) < 80 or motor abnormality on examination)
- Severe neurodevelopmental impairment (clinical cerebral palsy or DQ below the range that can be measured)
- Death before discharge from hospital
- Death at any time during the study

### Search methods for identification of studies

A new, more-sensitive search strategy was developed for this update and searches were run without date, language or publication type limits. Strategies were written by Information Specialists at Cochrane Sweden and peer reviewed using the PRESS Checklist (McGowan 2016a; McGowan 2016b). A methodological filter was used to restrict retrieval to RCTs and quasi-randomised trials.

#### Electronic searches

The following databases were searched without language, publication year, publication type or publication status restrictions in January 2022.

- Cochrane Central Register of Controlled Trials (CENTRAL; 18 January 2022, Issue 1), via Wiley
- MEDLINE via EbscoHost (1966 to 18 January 2022)
- EMBASE via Elsevier (1966 to 18 January 2022)
- CINAHL Complete via EbscoHost (1966 to 18 January 2022)

#### Searching other resources

Trial registration records were identified using CENTRAL and by independent searches of the US National Library of Medicine ([clinicaltrials.gov](http://clinicaltrials.gov)), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; <https://www.who.int/clinical-trials-registry-platform/ictcp-search-portal>).

We identified conference abstracts using CENTRAL and Embase.

We screened the reference lists of related studies and systematic reviews not identified by the database searches.

We searched for errata or retractions for included studies published on PubMed ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)).

#### Data collection and analysis

For each study included, we collected information regarding the method of randomisation, blinding, intervention and stratification, as well as whether the trial was a single or multi-centre study. We noted information regarding trial participants, including gestational age and birthweight. We analysed the clinical outcomes listed in the [Types of outcome measures](#).

#### Selection of studies

We used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises the following three components:

1. known assessments (a service that matches records in the search results to records that have already been screened and labelled as 'RCT' or 'not an RCT' in Cochrane Crowd, Cochrane's

citizen science platform where the Crowd helps identify and describe health evidence);

2. the RCT classifier (a machine-learning model that distinguishes RCTs from non-RCTs);
3. Cochrane Crowd (<http://crowd.cochrane.org>).

For more information about Screen4Me and the evaluations that have been undertaken, please go to the Screen4Me web page on the Cochrane Information Specialist's portal ([https://community.cochrane.org/sites/default/files/uploads/Reporting\\_Guidance\\_Screen4Me\\_FINAL.pdf](https://community.cochrane.org/sites/default/files/uploads/Reporting_Guidance_Screen4Me_FINAL.pdf)).

Additional detailed information regarding evaluations of the Screen4Me components has been published elsewhere (Marshall 2018; Noel-Storr 2020; Noel-Storr 2021; Thomas 2020).

Two review authors (OR, MB) independently screened the titles and abstracts of references remaining after categorisation by Screen4Me. Two review authors independently screened the full text of references included based on title abstract (MB, OR). We resolved disagreements by discussion and, if necessary, by consultation with a third review author (ES). We excluded studies published only in abstract form unless the final results of the trial were reported and all necessary information could be ascertained from the abstract, authors or both. We reviewed studies for relevance by assessing study design, types of participants, interventions provided and outcome measures reported. We have provided details of the studies excluded in the [Characteristics of excluded studies](#) table, along with reasons for exclusion. We contacted trial authors if the details of a primary trial were unclear. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009) and 'Characteristics of included studies' table.

We used Covidence for screening (<https://www.covidence.org>).

### Data extraction and management

Two review authors (MB, OR) independently extracted data using a data extraction form integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group data collection checklist (Cochrane EPOC Group 2017). We piloted the form within the review team, using a sample of included studies. We extracted the following characteristics from each included study:

1. administrative details (i.e. study author(s); published or unpublished; year of publication; year in which the study was conducted; presence of vested interest; details of other relevant papers cited);
2. study (study design; type, duration and completeness of follow-up (e.g. greater than 80%); country and location of study; informed consent; ethics approval);
3. participants (sex; birthweight; gestational age; number of participants);
4. interventions (initiation, dose and duration of administration);
5. outcomes (as mentioned above under [Types of outcome measures](#)).

We resolved disagreements by discussion or consultation with a third review author (ES). We described ongoing studies identified by our search, when available, detailing the primary author, research question(s), methods and outcome measures, together

with an estimate of the reporting date. This information is reported in the Characteristics of ongoing studies table.

If any queries arose (e.g. discrepancies in the way outcomes were defined in the trials and the definitions in [Types of outcome measures](#)), or if additional data would have been required, we contacted the study investigators/authors for clarification. Two review authors (PB, CR) used Cochrane statistical software for data entry (Review Manager 2020). We replaced any standard error of the mean (SEM) with the corresponding standard deviation (SD).

### Assessment of risk of bias in included studies

Two review authors (MB, OR) used the Cochrane risk of bias tool to independently assess the risk of bias (low, high or unclear) for all included trials for the following domains (Higgins 2011):

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- any other bias.

Any disagreements were resolved by discussion or by a third assessor. For a more detailed description of the risk of bias for each domain, see [Appendix 1](#).

### Measures of treatment effect

#### Dichotomous data

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

#### Continuous data

For continuous data, we used the mean difference (MD) when outcomes were measured in the same way between trials. We used the standardised mean difference (SMD) to combine trials that measured the same outcome but used different methods. Where trials reported continuous data as the median and interquartile range (IQR) and data passed the test of skewness, we converted the median to mean and estimated the SD as IQR/1.35.

### Unit of analysis issues

We performed the primary analysis per individual randomised. We abstracted 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 randomised observations (e.g. patients within clinics). Available statistical information needed to account for the implications of clustering on the estimation of outcome variances were abstracted, such as design effects or intracluster correlations, and whether the study adjusted results for correlations in the data. In cases where the study did not account for clustering, we ensured that appropriate adjustments were made to the effective sample size following Cochrane guidance (Higgins

2020). Where possible, we derived the intracluster correlation (ICC) for these adjustments from the trial itself, or from a similar trial. If an appropriate ICC was unavailable, we conducted sensitivity analyses to investigate the potential effect of clustering by imputing a range of ICC values.

If any trials had multiple arms that were compared against the same control condition that was included in the same meta-analysis, we either combined groups to create a single pair-wise comparison or selected one pair of interventions and excluded the others.

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

### Dealing with missing data

We conducted analyses on an intention-to-treat basis for all included outcomes. Whenever possible, we analysed all participants in the treatment group to which they were randomised, regardless of the actual treatment received. If we identified important missing data (in the outcomes) or unclear data, we requested the missing data by contacting the original investigators. We made explicit the assumptions of any methods used to deal with missing data. We planned to perform sensitivity analyses to assess how sensitive the results are to reasonable changes in the assumptions made, but there were no missing data. We planned to address the potential impact of missing data on the findings of the review in the [Discussion](#) section.

### Assessment of heterogeneity

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

To assess statistical heterogeneity, we visually inspected forest plots and describe the direction and magnitude of effects, as well as the degree of overlap between CIs. We also considered the statistics generated in forest plots that measure statistical heterogeneity. We used the  $I^2$  statistic to quantify inconsistency among the trials in each analysis. We also considered the P value from the Chi<sup>2</sup> test to assess whether this heterogeneity is significant ( $P < 0.1$ ). If we identified substantial heterogeneity, we reported the finding and explored possible explanatory factors using prespecified subgroup analysis.

We graded the degree of heterogeneity as follows:

- 0% to 40% may not represent important heterogeneity;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- greater than 75% may represent considerable heterogeneity.

A rough guideline was used to interpret the  $I^2$  value rather than a simple threshold, and our interpretation took into account the understanding that measures of heterogeneity ( $I^2$  and Tau) are estimated with high uncertainty when the number of studies is small ([Deeks 2020](#)).

### Assessment of reporting biases

We assessed reporting bias by comparing the stated primary and secondary outcomes against reported outcomes. Where

study protocols were available, we compared these to the full publications to determine the likelihood of reporting bias. Studies using the interventions in a potentially eligible infant population but not reporting on any of the primary and secondary outcomes were documented in the '[Characteristics of included studies](#)' tables.

We used the funnel plots to screen for publication bias where there was a sufficient number of studies ( $> 10$ ) reporting the same outcome. If publication bias was suggested by a significant asymmetry of the funnel plot on visual assessment, we incorporated this in our assessment of certainty of evidence ([Egger 1997](#)). If our review includes few studies eligible for meta-analysis, the ability to detect publication bias will be largely diminished and we would simply note our inability to rule out possible publication bias or small study effects.

### Data synthesis

We performed a meta-analysis using Review Manager 5 ([Review Manager 2020](#)). For categorical outcomes, we calculated the typical estimates of RR and RD, each with its 95% CI; for continuous outcomes, we calculated the MD or SMD, each with its 95% CI. We used a fixed-effect model to combine data where it is reasonable to assume that studies were estimating the same underlying treatment effect. We analysed and interpreted individual trials separately when we judged meta-analysis to be inappropriate. In case of evidence of clinical heterogeneity, we planned to explain this based on the different study characteristics and subgroup analyses.

### Subgroup analysis and investigation of heterogeneity

Tests for subgroup differences in effects are to be interpreted with caution given the potential for confounding with other study characteristics and the observational nature of the comparisons (see [Section 10.11.2 Cochrane Handbook version 6](#)). In particular, subgroup analyses with fewer than five studies per category are unlikely to be adequate to ascertain valid differences in effects and, had we been able to conduct subgroup analyses, we would not have highlighted these in our results. If we had performed subgroup analyses, we had planned to conduct stratified meta-analysis and a formal statistical test for interaction to examine subgroup differences that could account for effect heterogeneity (e.g. Cochran's Q test, meta-regression) ([Borenstein 2013](#); [Higgins 2020](#)).

Given the potential differences in the intervention effectiveness related to gestational age (extremely preterm infants are more vulnerable) and the need for mechanical ventilation, we planned to conduct subgroup comparisons to see whether the intervention is more effective for certain groups where data were available. We considered the following groups for subgroup analysis, where data were available, and restricted these analyses to the main outcomes:

- gestational age less than 30 weeks;
- infants on mechanical ventilation.

These analyses were not conducted because gestational age overlapped across the included studies and all studies included infants on mechanical ventilation.

## Sensitivity analysis

We planned to conduct sensitivity analyses to explore the effects of the methodological quality of trials, checking to ascertain whether studies with a high risk of bias (in at least two domains) overestimated the effect of treatment, but this analysis was not conducted because only one of the included trials had an overall low risk of bias (Whitelaw 1983). Differences in study design of included trials may also affect the results of the systematic review. We planned to perform a sensitivity analysis to compare the effects of phenobarbital in truly randomised trials as opposed to quasi-randomised trials, but this was not done because only one of the included studies was a quasi-randomised trial (Morgan 1982).

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

The summary of findings tables (Summary of findings 1) address the effects of phenobarbital dosage in all enrolled infants. We used the GRADE approach to assess the certainty of evidence for the following (clinically relevant) outcomes (Schünemann 2013):

- all grades of IVH;
- severe IVH (i.e. grade III and IV IVH);
- ventricular dilation or hydrocephalus;
- mild neurodevelopmental impairment (DQ < 80 or motor abnormality on examination);
- severe neurodevelopmental impairment (clinical cerebral palsy or DQ below the range that can be measured);
- death before discharge from hospital;
- death at any time during the study.

Two review authors (OR, MB) independently assessed the certainty of the evidence for each of the seven outcomes

above. We considered evidence from RCTs as high-certainty, but downgraded the evidence by 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 the presence of publication bias. We used GRADEpro GDT to create a summary of findings table to report the certainty of the evidence. The GRADE approach resulted 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.

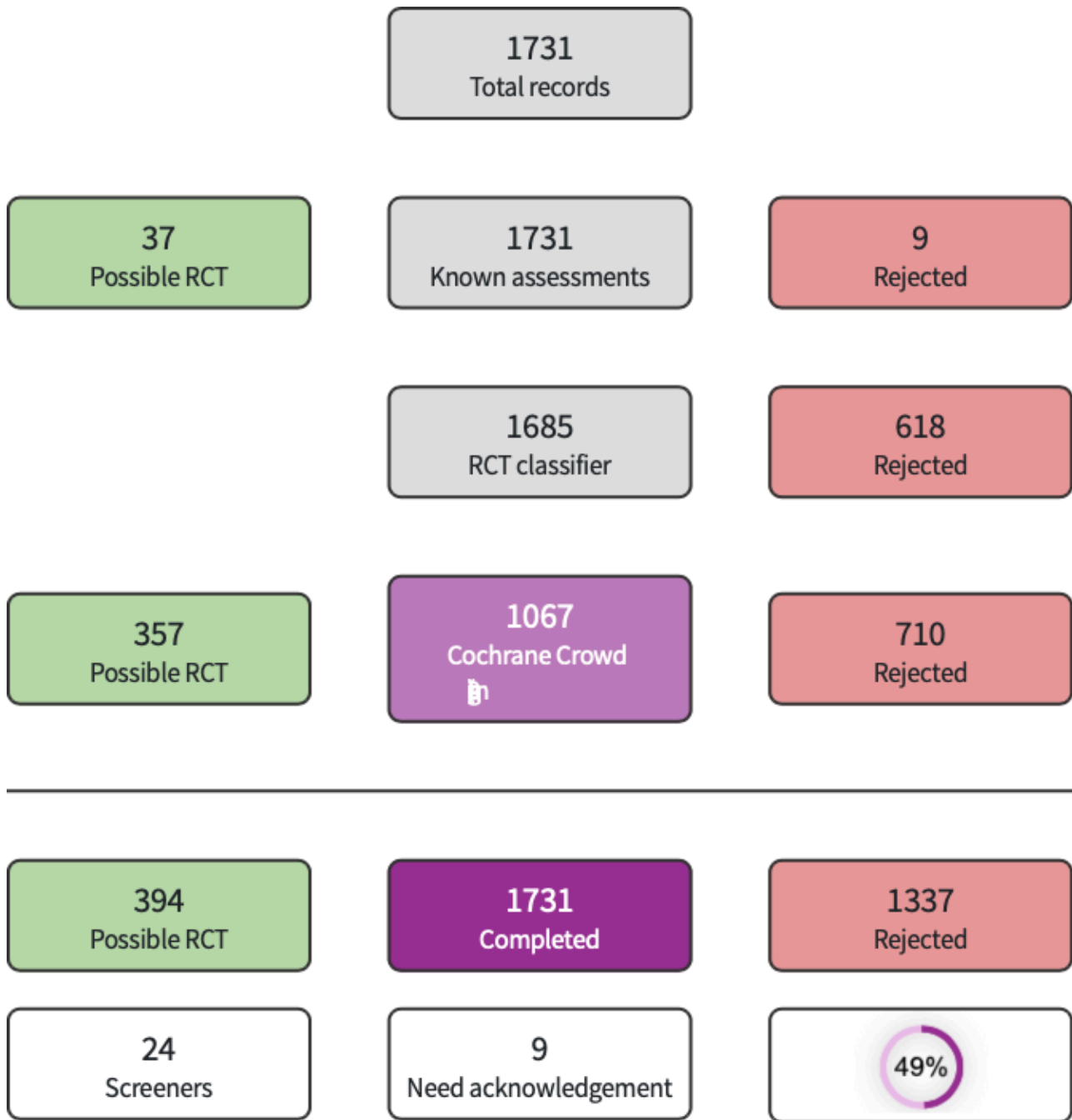
## RESULTS

### Description of studies

#### Results of the search

The search run in January 2022 identified 2060 search results (1731 after de-duplication). In assessing the studies, we used Cochrane's Screen4Me workflow to help identify potential reports of randomised trials. The results of the Screen4Me assessment process are shown in Figure 1.

**Figure 1. Screen4Me summary diagram.**



We then imported the remaining 394 studies left after the Screen4Me assessment to Covidence; 13 additional duplicates were removed by Covidence, leaving 381 studies for assessment. We excluded 369 studies after screening the title and abstract and

another two studies after full text screening, leaving 10 RCTs for inclusion in this analysis (Figure 2). We did not identify any ongoing studies.

**Figure 2. Prisma flow diagram.**

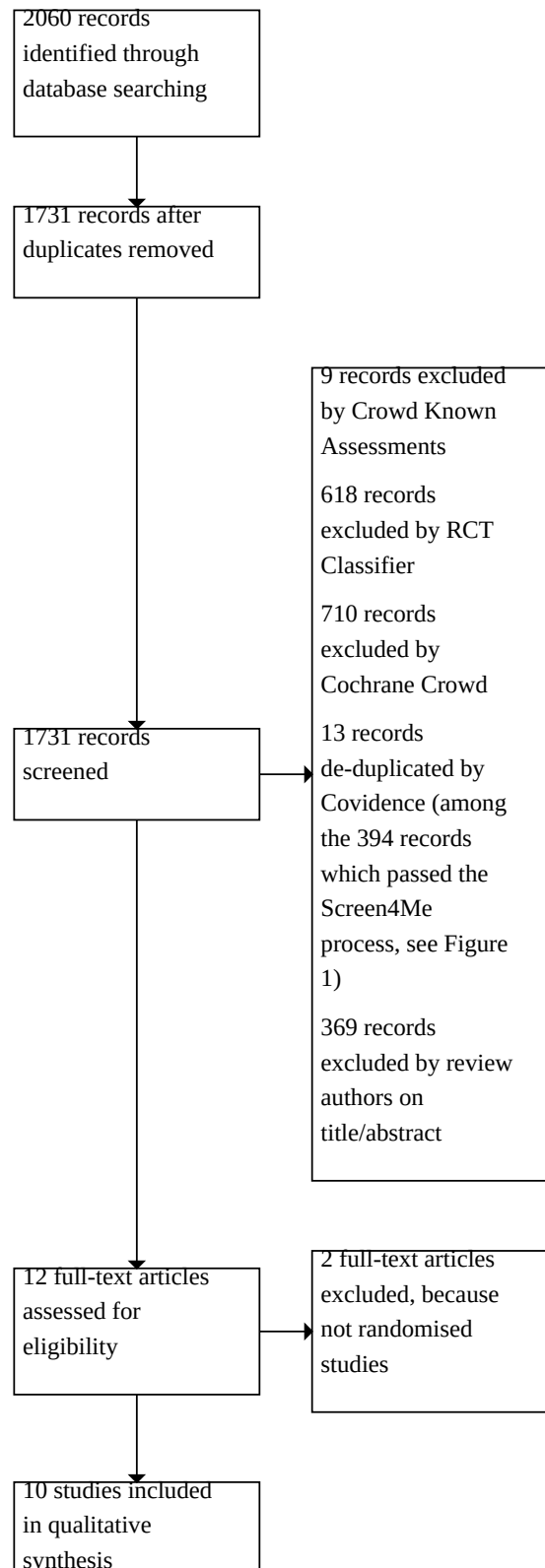
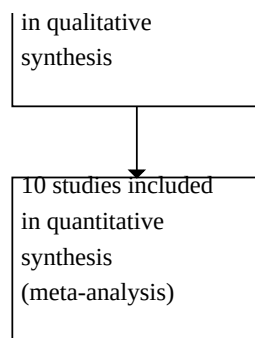


Figure 2. (Continued)



### Included studies

We included 10 studies enrolling 792 infants (Anwar 1986; Bedard 1984; Donn 1981; Kuban 1986; Mas-Munoz 1993; Morgan 1982; Porter 1985; Ruth 1985; Ruth 1988; Whitelaw 1983). One of the studies was funded by a private company (Mead Johnson) (Kuban 1986). Two studies declared funding sources from public institutions (Ruth 1988; Whitelaw 1983). Most studies did not declare whether funding was received.

### Participants

The infants in the studies were relatively similar, being preterm infants who were at risk of IVH either because of gestational age below 34 weeks, birthweight below 1500 g, respiratory distress syndrome requiring mechanical ventilation or a combination of these factors (Table 1). Cranial ultrasound was conducted before trial entry in only six trials and infants who already had IVH were thereby excluded. It is likely that some infants in the trials already had IVH before randomisation (Anwar 1986; Donn 1981; Ruth 1985; Ruth 1988). In two trials, infants in the treatment group were older than those in the control group (Bedard 1984; Morgan 1982). In another study, newborns in the phenobarbital group had lower gestational age and birthweight (Kuban 1986). In Porter's trial, newborns in the control group had lower Apgar scores at both 1 and 5 minutes than those in the treatment group (Porter 1985), whereas in Morgan's trial there were more outborn patients in the control group (Morgan 1982). Five studies were conducted in the USA (Anwar 1986; Bedard 1984; Donn 1981; Kuban 1986; Porter 1985), two were conducted in England (Morgan 1982; Whitelaw 1983), two were conducted in Finland (Ruth 1985; Ruth 1988), and one was conducted in Mexico (Mas-Munoz 1993).

### Variations in the intervention in included studies

The indication for phenobarbital administration was IVH prevention in all 10 studies. Three studies required respiratory support as an obligatory entry criterion (Kuban 1986; Mas-Munoz 1993; Morgan 1982).

In all trials, treatment started with the injection of a loading dose of phenobarbital, the dose varying between 20 mg/kg (seven trials) and 30 mg/kg (three trials; Table 1). Six of the trials divided the loading dose into two separate injections administered at 90-minute, four-hour or 12-hour intervals. The loading dose of phenobarbital was administered intravenously in eight studies. In one trial, both intravenous and intramuscular

routes of administration were used (Whitelaw 1983), whereas in another trial phenobarbital was administered intramuscularly (Morgan 1982). Except for the studies by Morgan 1982 and Whitelaw 1983, the trials used a maintenance dose of phenobarbital: either 2.5 mg/kg every 12 hours (Anwar 1986; Bedard 1984; Donn 1981; Kuban 1986; Mas-Munoz 1993); or 5 mg/kg every 24 hours (Porter 1985; Ruth 1985; Ruth 1988). In five trials, maintenance therapy with phenobarbital was given for three to seven days, whereas in four studies the duration of phenobarbital treatment was not clear (Anwar 1986; Kuban 1986; Mas-Munoz 1993; Morgan 1982). Blood concentrations of phenobarbital were measured in all trials except one (Ruth 1985). Placebo was used in three trials (Kuban 1986; Ruth 1988; Whitelaw 1983), but was not revealed to clinicians in the two double-blind trials (Kuban 1986; Whitelaw 1983).

### Outcomes in included studies

The main outcome, IVH, was ascertained by ultrasonography in all 10 trials. Eight studies used the classification of Papile 1978 to grade IVH, whereas the IVH definitions of Shankaran 1982 and Levene 1982 were used in Bedard 1984 and Whitelaw 1983, respectively.

All studies provided some data on mortality. Mortality data from Kuban 1986 were not given in the original publication, but were subsequently reported in the follow-up paper (Krishnamoorthy 1990). Data on the potential adverse effects of phenobarbital treatment were provided in some studies: hypotension in two (Donn 1981; Kuban 1986); hypercapnia in six (Anwar 1986; Bedard 1984; Donn 1981; Morgan 1982; Porter 1985; Whitelaw 1983); and acidosis in five (Bedard 1984; Kuban 1986; Morgan 1982; Porter 1985; Whitelaw 1983). The rate of mechanical ventilation was reported in all 10 studies, but the duration of mechanical ventilation was reported in only one (Mas-Munoz 1993). All 10 trials reported the rate of pneumothorax for both groups.

See [Characteristics of included studies](#) table.

### Excluded studies

Following full text screening, we excluded two studies (Cooke 1982; Saliba 1991). Cooke 1982 is a letter to the editor. Saliba 1991 is described as cross-over trial, but all infants first received placebo, then phenobarbital. That study reported no relevant effects of phenobarbital on cerebral blood flow velocity, heart rate, mean arterial blood pressure or blood gases (see [Characteristics of excluded studies](#)).

Three previously included studies have been moved to [Additional references](#) because they were not randomised, as was clear from the titles ([Liang 2009](#); [Zhang 2009](#)), or abstract ([Sluncheva 2006](#)). As per Cochrane methods, only RCTs and quasi-RCTs are included in Cochrane reviews, and the full text of these studies should not have been assessed.

Three previously excluded studies have been moved to [Additional references](#): two were not randomised or quasi-randomised studies, as was clear from the titles and abstracts ([Chen 2008](#); [Hope 1982](#)), and one did not meet the gestational age inclusion criteria, as was clear from the abstract ([Liu 2010](#)).

### **Risk of bias in included studies**

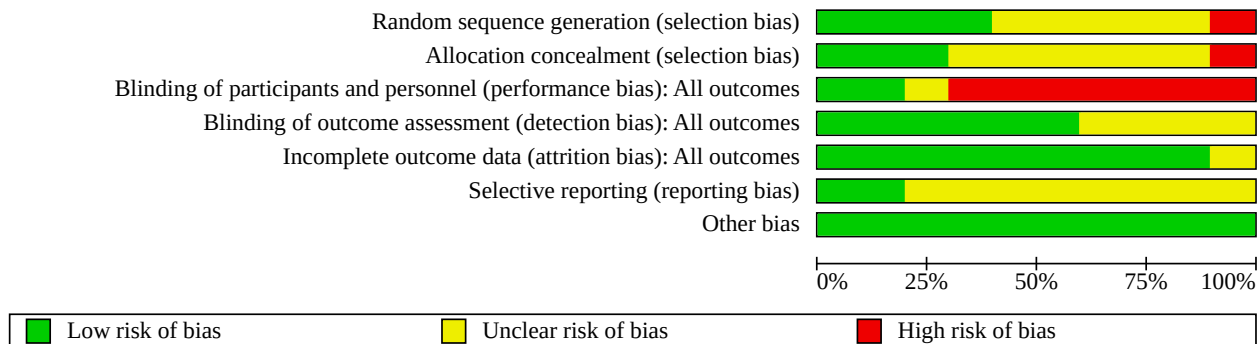
See [Figure 3](#); [Figure 4](#).



**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Anwar 1986	?	?	-	?	+	?	+
Bedard 1984	+	?	-	+	+	?	+
Donn 1981	+	+	-	+	+	?	+
Kuban 1986	?	?	+	+	+	+	+
Mas-Munoz 1993	?	?	-	?	?	?	+
Morgan 1982	-	-	-	+	+	?	+
Porter 1985	?	?	-	+	+	?	+
Ruth 1985	?	?	?	?	+	?	+
Ruth 1988	+	+	-	?	+	?	+
Whitelaw 1983	+	+	+	+	+	+	+

**Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**



**Allocation**

Of the nine trials stated to be randomised, the method of randomisation was described only by [Bedard 1984](#) (deck of cards), [Donn 1981](#) (lottery) and [Ruth 1988](#) (lottery). It was not clear how allocation concealment was achieved in any of these nine randomised trials. [Morgan 1982](#) used alternate rather than random allocation with no attempt at allocation concealment (high risk of bias). It was evident in only one of the trials that allocation concealment was achieved ([Whitelaw 1983](#)). Two trials used numbered identical vials and were double-blind ([Kuban 1986](#); [Whitelaw 1983](#)).

**Blinding**

In the open trials by [Donn 1981](#), [Morgan 1982](#), [Bedard 1984](#), [Porter 1985](#), [Anwar 1986](#), [Ruth 1988](#) and [Mas-Munoz 1993](#), it is likely that the medical and nursing staff knew the treatment allocation. Thus, there is the possibility that the clinical care given to the two groups could have been biased by the knowledge and beliefs of the clinical staff.

**Incomplete outcome data**

In [Kuban 1986](#), 11 of 291 (4%) infants enrolled were withdrawn after randomisation. In [Ruth 1988](#), 10 of 111 (9%) infants enrolled were excluded because of gestational age less than 25 weeks or congenital anomaly. In [Whitelaw 1983](#), two of 32 (6%) infants were excluded because of congenital anomalies and these two infants were replaced in the randomisation. None of the other trials reported the exclusion of any infants after enrolment. Only [Ruth 1988](#) reported long-term follow-up and achieved 100% ascertainment of survivors at 27 months of age.

**Selective reporting**

All the trials except those by [Anwar 1986](#) and [Mas-Munoz 1993](#) described the main endpoint, ultrasound or CT diagnosis of IVH, as being determined by ultrasonographers and radiologists who had no knowledge of treatment allocation. In [Ruth 1988](#), the neurologist and psychologist assessing neurodevelopment at 27 months were blinded to treatment allocation.

**Other potential sources of bias**

We did not identify any other potential sources of bias.

**Effects of interventions**

See: [Summary of findings 1 Phenobarbital compared to control for the prevention of intraventricular haemorrhage in preterm infants](#)

**Prophylactic administration of phenobarbital in preterm infants at risk of developing IVH**

**Primary outcomes**

**All grades of IVH**

Data were available from all 10 trials for this outcome. The evidence suggests that phenobarbital results in little to no difference in the incidence of IVH (any grade) compared with control (RR 1.00, 95% CI 0.84 to 1.19; I<sup>2</sup> for RR = 58%; RD 0.00, 95% CI -0.06 to 0.07; I<sup>2</sup> for RD = 65%; 10 studies, 792 participants; [Analysis 1.1](#)). The certainty of the evidence is low for limitations in study design (downgraded by one level) and inconsistency (downgraded by one level).

**Severe IVH**

Data were available from all 10 trials for this outcome. The evidence suggests that phenobarbital results in little to no difference in the incidence of severe IVH compared with control (RR 0.88, 95% CI 0.64 to 1.21; I<sup>2</sup> for RR = 37%; RD -0.02, 95% CI -0.07 to 0.03; I<sup>2</sup> for RD = 50%; 10 studies, 792 participants; [Analysis 1.2](#)). The certainty of the evidence is low for limitations in study design (downgraded by one level) and imprecision of the estimate (downgraded by one level).

**Secondary outcomes**

**Posthaemorrhagic ventricular dilation or hydrocephalus**

Four trials reported this outcome. The evidence is very uncertain about the effect of phenobarbital on ventricular dilation or hydrocephalus (RR 0.62, 95% CI 0.31 to 1.26; I<sup>2</sup> for RR = 21%; RD -0.05, 95% CI -0.12 to 0.02; I<sup>2</sup> for RD = 63%; 4 studies, 271 participants; [Analysis 1.3](#) ([Anwar 1986](#); [Donn 1981](#); [Ruth 1985](#); [Ruth 1988](#)). The certainty of the evidence is very low for limitations in study design (downgraded by one level) and imprecision of the estimate (downgraded by two levels).

**Hypotension**

Three trials reported this outcome. The evidence is very uncertain about the effect of phenobarbital on hypotension (RR 1.18, 95% CI 0.97 to 1.43; I<sup>2</sup> for RR = 0%; RD 0.09, 95% CI -0.01 to 0.19; I<sup>2</sup> for RD = 0%; 3 studies, 382 participants; [Analysis 1.4](#)) ([Donn 1981](#);

Bedard 1984; Kuban 1986). The certainty of the evidence is very low for limitations in study design (downgraded by one level), and imprecision of the estimate (downgraded by two levels).

#### Pneumothorax/interstitial emphysema

Eight trials reported this outcome. Phenobarbital may result in little to no difference in pneumothorax/interstitial emphysema (RR 1.28, 95% CI 0.92 to 1.77;  $I^2$  for RR = 33%; RD 0.04, 95% CI -0.01 to 0.10;  $I^2$  for RD = 49%; 8 studies, 682 participants; Analysis 1.5) (Bedard 1984; Donn 1981; Kuban 1986; Mas-Munoz 1993; Morgan 1982; Porter 1985; Ruth 1988; Whitelaw 1983). The certainty of the evidence is low for limitations in study design (downgraded by one level) and imprecision of the estimate (downgraded by one level).

#### Hypercapnia

Five trials reported this outcome. The evidence is very uncertain about the effect of phenobarbital on hypercapnia (RR 1.00, 95% CI 0.73 to 1.37;  $I^2$  for RR = 0%; RD 0.00, 95% CI -0.12 to 0.12;  $I^2$  for RD = 0%; 5 studies, 241 participants; Analysis 1.6) (Bedard 1984; Donn 1981; Morgan 1982; Porter 1985; Whitelaw 1983). The certainty of the evidence is very low for limitations in study design (downgraded by one level) and imprecision of the estimate (downgraded by two levels).

#### Acidosis

Six trials reported this outcome. The evidence is very uncertain about the effect of phenobarbital on acidosis (RR 1.16, 95% CI 0.90 to 1.51;  $I^2$  for RR = 19%; RD 0.04, 95% CI -0.03 to 0.12;  $I^2$  for RD = 0%; 6 studies, 521 participants; Analysis 1.7) (Bedard 1984; Donn 1981; Kuban 1986; Morgan 1982; Porter 1985; Whitelaw 1983). The certainty of the evidence is very low for limitations in study design (downgraded by one level), imprecision of the estimate (downgraded by one level) and inconsistency (downgraded by one level) for different definitions used for acidosis.

#### Mechanical ventilation

Six trials reported this outcome. Phenobarbital may increase need for mechanical ventilation (RR 1.16, 95% CI 1.04 to 1.28;  $I^2$  for RR = 7%; RD 0.11, 95% CI 0.04 to 0.19;  $I^2$  for RD = 0%; 6 studies, NNT = 9375 participants; Analysis 1.8) (Bedard 1984; Donn 1981; Morgan 1982; Ruth 1985; Ruth 1988; Whitelaw 1983). The certainty of the evidence is low for limitations in study design (downgraded by one level) and imprecision of the estimate (downgraded by one level).

#### Mild neurodevelopmental impairment

One trial reported this outcome. The evidence is very uncertain about the effect of phenobarbital on mild neurodevelopmental impairment (RR 0.57, 95% CI 0.15 to 2.17; RD -0.05, 95% CI -0.16 to 0.06;  $I^2$  not applicable; 1 study, 101 participants; Analysis 1.9) (Ruth 1988). The certainty of the evidence is very low for limitations in study design (downgraded by one level) and imprecision of the estimate (downgraded by two levels).

#### Severe neurodevelopmental impairment

Two trials reported this outcome. The evidence is very uncertain about the effect of phenobarbital on severe neurodevelopmental impairment (RR 1.12, 95% CI 0.44 to 2.82;  $I^2$  for RR = 0%; RD 0.01, 95% CI -0.09 to 0.11;  $I^2$  for RD = 0%; 2 studies, 153 participants; Analysis 1.10) (Ruth 1985; Ruth 1988). The certainty of the evidence is very low for limitations in study design (downgraded

by one level) and imprecision of the estimate (downgraded by two levels).

#### Mortality prior to hospital discharge

Nine trials reported this outcome. The evidence suggests that phenobarbital results in little to no difference in death before discharge compared with control (RR 0.88, 95% CI 0.64 to 1.21;  $I^2$  for RR = 6%; RD -0.02, 95% CI -0.07 to 0.03;  $I^2$  for RD = 20%; 9 studies, 740 participants; Analysis 1.11) (Anwar 1986; Bedard 1984; Donn 1981; Kuban 1986; Mas-Munoz 1993; Morgan 1982; Porter 1985; Ruth 1988; Whitelaw 1983). The certainty of the evidence is low for limitations in study design (downgraded by one level) and imprecision of the estimate (downgraded by one level).

#### Mortality during the study period

Data were available from all 10 trials for this outcome. The evidence suggests that phenobarbital results in little to no difference in all deaths compared with control (RR 0.98, 95% CI 0.72 to 1.33;  $I^2$  for RR = 23%; RD 0.00, 95% CI -0.05 to 0.05;  $I^2$  for RD = 34%; 10 studies, 792 participants; Analysis 1.12). The certainty of the evidence is low for limitations in study design (downgraded by one level) and imprecision of the estimate (downgraded by one level).

## DISCUSSION

### Summary of main results

We evaluated the benefits and harms of phenobarbital compared with control (i.e. no intervention or placebo) in preterm infants. Ten studies (corresponding to 792 infants) were included.

Overall, the evidence suggests that phenobarbital results in little to no difference in the incidence of IVH (any grade or severe) compared with control. Among the secondary outcomes of this review, the evidence is very uncertain about the effects of phenobarbital on ventricular dilation or hydrocephalus and on neurodevelopmental impairment. The evidence suggests that phenobarbital results in little to no difference in death before discharge compared with control.

We identified no ongoing trials.

### Overall completeness and applicability of evidence

The primary outcomes of this review (i.e. the incidence of IVH of any grade and severe IVH) were reported by all included studies. Eight studies found no difference in the incidence of this outcome between phenobarbital and control, but very few infants were enrolled in those studies; one study reported a reduction in IVH among infants receiving phenobarbital (Donn 1981), whereas another reported an increase in IVH, although in that trial the group receiving phenobarbital was significantly lighter and had a shorter gestation period (Kuban 1986). Because different definitions were used for acidosis, the meta-analysis for acidosis should be treated with caution. Similarly, prophylactic phenobarbital treatment would, on average, result in one extra infant receiving mechanical ventilation for every nine preterm infants treated, but the certainty of the evidence is low.

Although the dosages of phenobarbital varied, all studies gave plasma phenobarbital concentrations in the recommended anticonvulsant range for 72 hours, the period during which IVH usually occurs. A cause for concern was that four of the trials did

not have a normal cranial ultrasound scan as an entry criterion. The trial that found that postnatal phenobarbital reduced IVH was an open trial that lacked a prerandomisation cerebral ultrasound scan (Donn 1981). Some of the IVH reported could have arisen before the administration of phenobarbital. The double-blind Kuban 1986 trial was planned with adequate sample size; however, randomisation did not result in the two groups having similar risk factors for IVH because the group receiving phenobarbital had a significantly greater risk for IVH than the control group did at the time of randomisation. These factors in the trials of Donn 1981 and Kuban 1986 could contribute to the heterogeneity found for the outcome all grades of IVH.

We noted late timing (e.g. later than 6 hours in 2 studies) of the initial phenobarbital injection and the splitting of loading doses in six studies (Table 1). In these situations, it could have been more than 12 hours before anticonvulsant plasma concentrations of phenobarbital were achieved; and yet, many IVHs start by 12 hours of age. The difficulty in achieving therapeutic blood concentrations of phenobarbital before many IVHs have started was one reason for testing antenatal maternal administration of phenobarbital, which has been assessed in a separate Cochrane review (Crowther 2010).

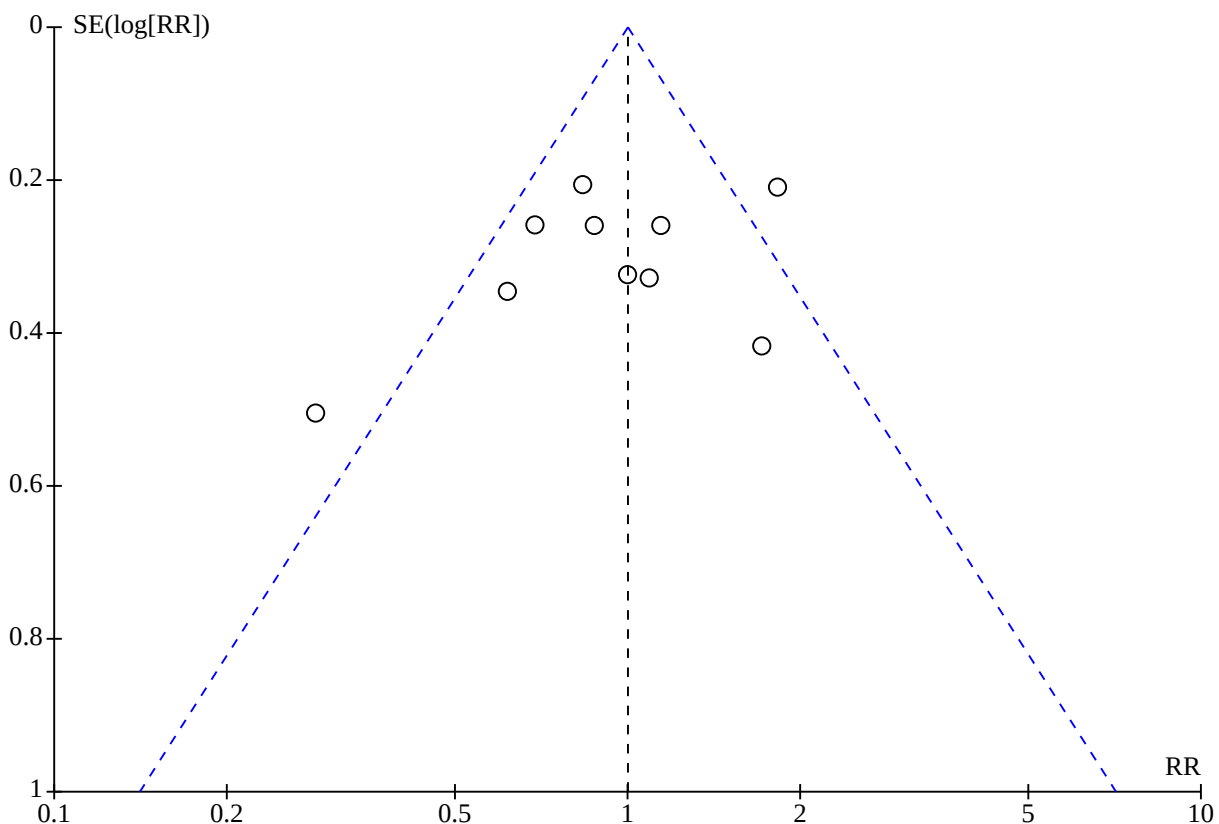
Since the original publication of this review, it has become apparent that administration of anti-epileptic drugs in the newborn period may have a harmful effect on the developing brain.

Phenobarbital has a proapoptotic effect in newborn rat brains (Bittigau 2002). More recently, it has been shown that neonatal rat exposure to a single dose of phenobarbital results in reduced synaptic connectivity in the striatum (Forcelli 2012). It would have been helpful if more of the included studies had monitored neurodevelopment.

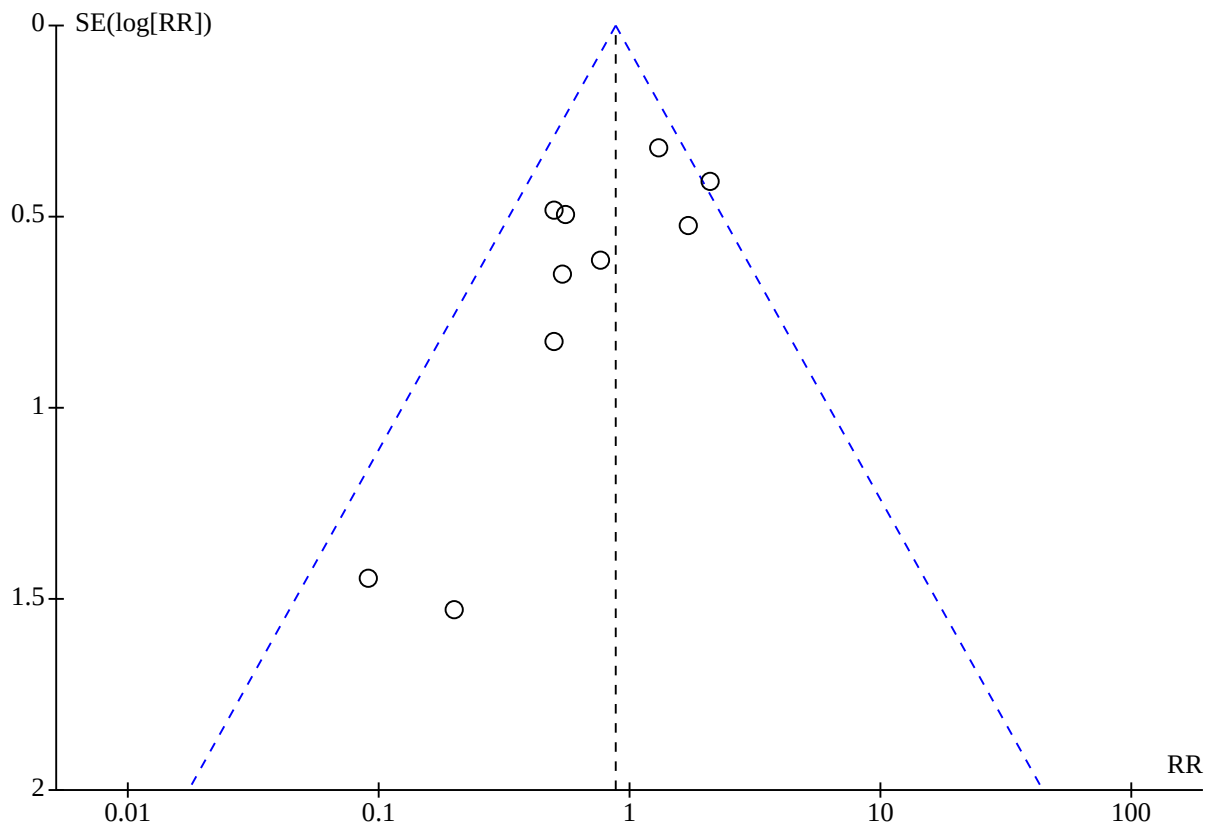
### Quality of the evidence

According to the GRADE approach, the overall certainty of evidence for critical outcomes for phenobarbital administration for any indication ranged from low to very low (see Summary of findings 1). All outcomes were downgraded (one level) because of limitations in study design (i.e. unclear high risk of bias in different domains, mainly selection bias, performance bias and reporting bias; Figure 4). Most outcomes were downgraded for imprecision, by either one or two levels, because of few events, low sample size and wide CIs. The outcome 'IVH any grade' was downgraded by one level because of inconsistency ( $I^2 = 58%$ ). Where the certainty of evidence was low included IVH (any grade or severe) and mortality (death before discharge; all deaths during the study period). The evidence for ventricular dilation or hydrocephalus and neurodevelopmental impairment (mild or severe) was rated as very low (i.e. it was downgraded due to limitations in study design (one level) and imprecision of the estimates (one level)). We detected no publication bias using funnel plots (Figure 5; Figure 6).

**Figure 5. Funnel plot of comparison: 1 Phenobarbital versus control, Outcome: 1.1 All intraventricular haemorrhage.**



**Figure 6. Funnel plot of comparison: 1 Phenobarbital versus control, Outcome: 1.2 Severe intraventricular haemorrhage.**



**Potential biases in the review process**

We kept the thresholds for gestational age as defined in [Types of participants](#), although IVH rarely occurs beyond a gestational age of 32 weeks. Two studies were excluded: one non-randomised trial ([Cooke 1982](#)); and one cross-over, non-randomised trial in which all infants first received placebo and then phenobarbital ([Saliba 1991](#)). Although the authors of this Cochrane Review were not involved in any of the included trials, some of us conducted primary studies (both clinical and preclinical) on IVH in preterm newborns: this may have created an intellectual bias in preparing this review.

**Agreements and disagreements with other studies or reviews**

A non-Cochrane review of postnatal phenobarbital for preterm infants included eight trials and noted the heterogeneity between trials concerning any IVH and severe IVH ([Horbar 1992](#)). The author of that review concluded that postnatal phenobarbital could not be recommended, but raised the question as to whether, in specific settings, phenobarbital may be beneficial. In addition, that review did not present data on ventricular dilation, neuromotor impairment, mechanical ventilation, hypotension, pneumothorax or acidosis ([Horbar 1992](#)).

The previous updates of this Cochrane Review by [Whitelaw 2007](#) and [Smit 2013](#) included one additional study each. In this 2022 update, one new study has been included ([Ruth 1985](#)); this is an older study, but it was identified because search strategies

were revised to increase sensitivity and the search was conducted without date limits. Three previously included studies have been excluded in this review because they were not randomised ([Liang 2009](#); [Sluncheva 2006](#); [Zhang 2009](#)).

This review supports the conclusion of [Horbar 1992](#) that phenobarbital does not reduce the frequency of IVH, severe IVH or death, and suggests that phenobarbital may increase the need for mechanical ventilation, but the certainty of the evidence is low. The data now available do not identify any specific setting in which prophylactic phenobarbital may reduce the risk of IVH.

Prophylactic antenatal phenobarbital is the subject of a separate Cochrane systematic review that concluded that the trials with most reliable methodology showed no evidence that the intervention was effective in reducing IVH ([Crowther 2010](#)).

**AUTHORS' CONCLUSIONS**

**Implications for practice**

The evidence suggests that phenobarbital results in little to no difference in the incidence of intraventricular haemorrhage (IVH; any grade or severe) compared with control (i.e. no intervention or placebo). The evidence is very uncertain about the effects of phenobarbital on ventricular dilation or hydrocephalus and on neurodevelopmental impairment. The evidence suggests that phenobarbital results in little to no difference in death before discharge compared with control.

## Implications for research

Since 1993, no randomised studies have been published on phenobarbital for the prevention of IVH in preterm infants, and there are no ongoing trials. The effects of postnatal phenobarbital might be assessed in infants with both neonatal seizures and IVH in both randomised and observational studies. The assessment of benefits and harms should include long-term outcomes, such as cognition, motor, visual and hearing function.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Anwar 1986

<b>Study characteristics</b>	
Methods	Open randomised controlled trial
Participants	Preterm infants with a birthweight < 1500 g and no congenital malformations, and no maternal phenobarbital administration (n = 58)
Interventions	Two loading doses of phenobarbital 10 mg/kg, intravenously, starting before 6 hours of age and the second loading dose 12 hours later, followed by a maintenance dose of 2.5 mg/kg every 12 hours for 7 days. Maintenance doses were adjusted to achieve trough phenobarbital concentrations of 20 mg/L to 30 mg/L
Outcomes	Papile grade of IVH by ultrasound on days 1, 3 and 7, posthaemorrhagic hydrocephalus, death  It is not clear that the ultrasonographers were blinded to treatment allocation
Notes	Country: USA  Cerebral ultrasound was not performed prior to trial entry, so it was not possible to exclude babies who already had IVH before the first dose of phenobarbital  Funding sources/declarations of interest were not stated
<b>Risk of bias</b>	
Bias	Authors' judgement    Support for judgement
Random sequence generation (selection bias)	Unclear risk    No information provided on how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk    No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk    Intervention was most likely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk    No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk    Complete follow-up of all participants
Selective reporting (reporting bias)	Unclear risk    Insufficient information to make a judgement because we have no access to a trial protocol
Other bias	Low risk    None

**Bedard 1984**
**Study characteristics**

Methods	Open RCT
Participants	Infants < 24 hours old with birthweights < 1500 g or gestation < 33 weeks were all eligible. Infants with gestational ages of 33 to 36 weeks or a birthweight > 1500 g were eligible if they required mechanical ventilation for respiratory distress syndrome. Another requirement was a cranial ultrasound scan showing no haemorrhage (n = 42)
Interventions	Two intravenous loading doses of phenobarbital 10 mg/kg 12 hours apart, followed by maintenance doses of 2.5 mg/kg, intravenously or orally, every 12 hours for 6 days
Outcomes	Ultrasound diagnosis of IVH grade as mild (grade I or II on the Papile scale) or medium/severe (grade III or IV on the Papile scale), death mechanical ventilation; pneumothorax, hypotension (< 2SD below mean), pH < 7.2, pCO <sub>2</sub> > 60 mmHg, pCO <sub>2</sub> < 25 mmHg, bicarbonate administration (for metabolic acidosis)
Notes	<p>Country: USA</p> <p>Of 95 potential trial participants, 42 were excluded because of IVH on the initial ultrasound scan. The control group were, on average, 1.1 weeks less mature and 220 g lighter than the phenobarbital group. No infants were excluded after enrolment</p> <p>Funding sources/declarations of interest were not stated</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by using a deck of cards
Allocation concealment (selection bias)	Unclear risk	It is not clear how blinding to treatment allocation was achieved
Blinding of participants and personnel (performance bias) All outcomes	High risk	Intervention was most likely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was done by a paediatric radiologist unaware of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was complete
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement because we have no access to a trial protocol
Other bias	Low risk	None

**Donn 1981**
**Study characteristics**

Methods	Open RCT
Participants	<p>Infants with birthweights &lt; 1500 g admitted to the neonatal intensive care unit within 6 hours and without congenital malformations, and where the mother had not received barbiturates during pregnancy (n = 60)</p> <p>No information on infants excluded or lost after enrolment</p>
Interventions	Two loading doses of 10 mg/kg phenobarbital each administered intravenously 12 hours apart. Maintenance doses of 2.5 mg/h every 12 hours were started 12 hours after the second loading dose. Doses were adjusted to maintain serum phenobarbital concentrations in the range 20 µg/mL to 30 µg/mL for 7 days
Outcomes	Papile grade of IVH on ultrasound, ventriculomegaly, mechanical ventilation, pneumothorax requiring drainage, hypercapnia (pCO <sub>2</sub> > 60 mm Hg), hypotension (systolic blood pressure 10 mmHg below the expected value or impaired perfusion), bicarbonate therapy, death
Notes	<p>Country: USA</p> <p>Cerebral ultrasound was not performed prior to trial entry, so it was not possible to exclude babies who already had IVH before the first dose of phenobarbital</p> <p>Funding sources/declarations of interest were not stated</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation is described as by lottery
Allocation concealment (selection bias)	Low risk	No information provided, but it is likely the next allocation was not known in advance because a lottery system was used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Most likely there was no blinding of intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was done by ultrasonographers and neuroradiologists unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants were followed-up. Infants who died underwent postmortem examination to ensure complete diagnosis of IVH
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement because we have no access to a trial protocol
Other bias	Low risk	None

**Kuban 1986**
**Study characteristics**

Methods	Randomised double-blind controlled trial
Participants	Inclusion criteria were birthweight < 1751 g; endotracheal intubation before 12 hours; the absence of congenital anomalies; no evidence of intracranial haemorrhage on ultrasound scan; and neonatal phenobarbital concentration < 5 µg/mL (n = 280). Of 291 infants enrolled, 11 had to be withdrawn and were excluded from analysis. Forty-eight infants were excluded from enrolment because IVH was already present
Interventions	Two loading doses of phenobarbital 10 mg/kg or placebo, intravenously, at a 30-minute interval. Twelve hours later, the baby received the first of nine maintenance doses of 2.5 mg/kg or placebo at 12-hour intervals
Outcomes	Papile grade of IVH on ultrasound scan (any haemorrhage or severe grade III or IV), haemorrhage, acidosis (pH < 7.2 on day 1), pneumothorax/pulmonary interstitial emphysema, hypotension (< 30 mmHg on day 1)  Mortality data were obtained through personal communication between Dr Kuban and Dr Horbar, although age at death was not clear
Notes	Country: USA  The randomisation did not give a similar gestational age in the two treatment groups. Thus, 52.4% of the phenobarbital group had a gestational age < 30 weeks, compared with 41.5% of the control group. The authors attempted to allow for this imbalance by analysis within weight groups  The study was funded by Mead Johnson; declarations of interest were not stated

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Table of random numbers used. The group receiving phenobarbital was significantly lighter and had a shorter gestation
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical numbered ampoules were prepared by the pharmacy; participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The ultrasonographers were not aware of treatment allocation when assessing the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants were followed up; infants who died underwent postmortem examination to assess for IVH  Eleven of 291 (3.8%) infants enrolled were withdrawn after randomisation
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it appears the published report included all reported outcomes, including those that were prespecified
Other bias	Low risk	None

**Mas-Munoz 1993**
**Study characteristics**

Methods	Open controlled trial
Participants	Newborn infants with gestational ages of 27 to 34 weeks and who were ventilator dependent (n = 60) No information on infants excluded or lost after enrolment
Interventions	Phenobarbital 20 mg/kg, intravenously, as a loading dose within 12 hours of birth, followed by phenobarbital 2.5 mg/kg every 12 hours for the next 5 days
Outcomes	Cerebral ultrasound every 48 hours for 14 days, IVH graded as I/II or III/IV on the Papile scale, death. It is not clear whether the ultrasonographers were blind to treatment allocation
Notes	Country: Mexico  Cerebral ultrasound was not performed prior to trial entry, so it was not possible to exclude babies who already had IVH before the first dose of phenobarbital  Funding sources/declarations of interest were not stated.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not described. Infants in the phenobarbital group were 5 days older and 150 g heavier than those in the placebo group
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were most likely not blinded for the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not clear whether the ultrasonographers were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on infants excluded or lost after enrolment
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement because we have no access to a trial protocol
Other bias	Low risk	None

**Morgan 1982**
**Study characteristics**

Methods	An open controlled trial using alternate allocation
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**Morgan 1982** (Continued)

Participants	<p>Infants with birthweights below 1250 g and infants with birthweights of 1250 g to 1500 g who required mechanical ventilation in the first 24 hours. An ultrasound scan showing the absence of IVH was also a requirement (n = 60)</p> <p>No information on infants excluded or lost after enrolment</p>
Interventions	A loading dose of 20 mg/kg phenobarbital, intramuscularly, at a median time of 2 hours after birth (range 1 to 22 hours)
Outcomes	Papile grade of IVH on ultrasound, death, pneumothorax, hypercapnia (pCO <sub>2</sub> > 8 kPa), acidosis (pH < 7.15). The age limit for death was not specified, but 'one cot death' occurred at home at 4 months
Notes	<p>Country: England</p> <p>Funding sources/declarations of interest were not stated</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternate allocation (quasi-random)
Allocation concealment (selection bias)	High risk	Next allocation always known because of alternate allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were most likely not blinded for intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An experienced observer unaware of treatment allocation assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All subjects were followed up, but no information was provided on post-mortem diagnoses in infants who died
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement because we had no access to a trial protocol
Other bias	Low risk	None

**Porter 1985**
**Study characteristics**

Methods	Open RCT
Participants	<p>Newborn infants with a birthweight &lt; 1500 g with a normal cerebral ultrasound scan before 6 hours of birth and receiving respiratory support (n = 19)</p> <p>No information on infants excluded after enrolment</p>



**Porter 1985** (Continued)

Interventions	A loading dose of phenobarbital 30 mg/kg, intravenously, within 6 hours of birth, followed by a maintenance dose of 5 mg/kg per day for 72 hours
Outcomes	Cerebral ultrasound scans were performed daily by sonographers who were blinded to the initial treatment allocation. Outcomes were IVH graded according to the Papile scale, mechanical ventilation, pneumothorax, hypercapnia (> 60 mmHg), acidosis (pH < 7.15) and death
Notes	Country: USA  Funding sources/declarations of interest were not stated

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote, 'Infants were randomly assigned by lottery to treatment or control groups'
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment allocation was most likely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cerebral ultrasound scans were performed daily by sonographers who were blinded to the initial treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement because we have no access to a trial protocol
Other bias	Low risk	None

**Ruth 1985**
**Study characteristics**

Methods	Open RCT
Participants	Preterm infants with birthweights below 1500 g with postnatal age less than 2 hours (n = 52)
Interventions	Phenobarbitone intravenously in two loading doses of 15 mg/kg, 4 hours apart, starting before the age of 2 hours. Daily maintenance dose of 5 mg/kg starting 24 hours after the first dose, for 5 days  No information on the control group
Outcomes	Incidence of IVH by grade, ventricular dilatation, hydrocephalus, need for mechanical ventilation, neurological assessment at the age of 9 months
Notes	Country: Finland

**Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants (Review)**

**Ruth 1985** (Continued)

Funding sources/declarations of interest were not stated

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatment allocation was most likely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All subjects were followed up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement because we have no access to a trial protocol
Other bias	Low risk	None

**Ruth 1988**

**Study characteristics**

Methods	Open RCT
Participants	<p>Infants with birthweights &lt; 1501 g and gestational age <math>\geq</math> 25 weeks, &lt; 4 hours old; infants with malformations or maternal barbiturate treatment were excluded (n = 101)</p> <p>Originally, 111 infants were enrolled, but 10 were excluded (seven in the phenobarbital group and three in the control group) either because the gestational age was &lt; 25 weeks or because of congenital anomaly</p>
Interventions	Two loading doses of phenobarbital 15 mg/kg, intravenously, given 4 hours apart. Maintenance treatment with phenobarbital 5 mg/kg per day was started 24 hours after the first dose and continued for 5 days
Outcomes	Cerebral ultrasound scans were performed on days 1, 3, 5 and 7 and then weekly. Outcomes were IVH graded according to the Papile scale, neurodevelopmental assessed at 27 months of age, neonatal death, postnatal death, mechanical ventilation (total and > 7 days) and pneumothorax
Notes	<p>Country: Finland</p> <p>Cerebral ultrasound was not performed prior to trial entry, so it was not possible to exclude babies who already had IVH before the first dose of phenobarbital</p>

**Ruth 1988** (Continued)

Funding sources from public institutions

<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Randomisation was done by lottery
Allocation concealment (selection bias)	Low risk	No information provided, but next allocation unlikely to have been known in advance because a lottery system was used for treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided, but participants and personnel were most likely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinded outcome assessment for both cranial ultrasound and neurodevelopmental outcome at 27 months
Incomplete outcome data (attrition bias) All outcomes	Low risk	Originally, 111 infants were enrolled, but 10 were excluded (seven in the phenobarbital group and three in the control group) either because the gestational age was < 25 weeks or because of congenital anomaly  Long-term (27 months) follow-up reported for all survivors
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement because we have no access to a trial protocol
Other bias	Low risk	None

**Whitelaw 1983**

<b>Study characteristics</b>	
Methods	Randomised double-blind controlled trial; the infants received numbered, identical ampoules for injection
Participants	Infants < 1500 g with a normal cerebral ultrasound scan in the first 4 hours (n = 60). Two infants were excluded after randomisation because of congenital malformations and were replaced
Interventions	Phenobarbital 20 mg/kg or isotonic saline given intravenously or intramuscularly within 4 hours of birth. No maintenance doses given
Outcomes	IVH on cerebral ultrasound scans performed daily for 2 weeks and then weekly. Grading 1, 2, 3 according to Levene initially; subsequently reclassified to be compatible with Papile grading. Mechanical ventilation after injection, pneumothorax, hypercapnia (pCO <sub>2</sub> > 8 kPa), acidosis (pH < 7.2), death before discharge from hospital
Notes	Country: England  Funding sources from public institutions
<b>Risk of bias</b>	

**Whitelaw 1983** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The method of randomisation was not described in the paper, but was clarified by personal communication with Professor Whitelaw as a table of random numbers.
Allocation concealment (selection bias)	Low risk	No risk of prior knowledge of next allocation because a random numbers table was used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The infants received numbered, identical ampoules for injection and participants and personnel were unaware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cranial ultrasound was performed and assessed by personnel unaware of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two infants were excluded after randomisation because of congenital malformations and were replaced
Selective reporting (reporting bias)	Low risk	The published report included all expected outcomes, including those pre-specified
Other bias	Low risk	None

IVH: intraventricular haemorrhage

 pCO<sub>2</sub>: partial pressure of carbon dioxide

SD: standard deviation

**Characteristics of excluded studies** [ordered by study ID]

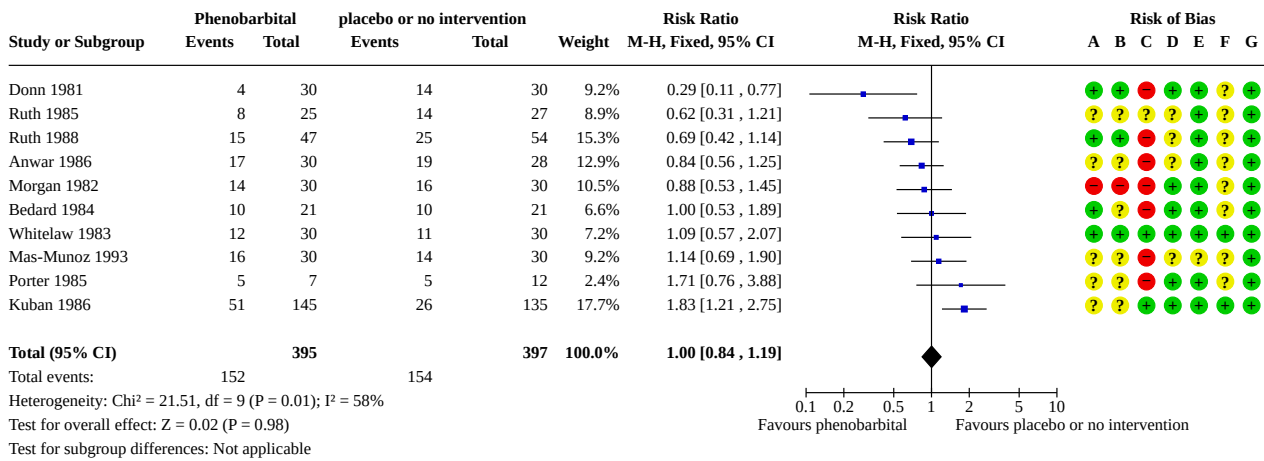
Study	Reason for exclusion
<a href="#">Cooke 1982</a>	Not a randomised trial
<a href="#">Saliba 1991</a>	Cross-over, not randomised trial

**DATA AND ANALYSES**
**Comparison 1. Phenobarbital versus control**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1.1 All intraventricular haemorrhage</a>	10	792	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.19]
<a href="#">1.2 Severe intraventricular haemorrhage</a>	10	792	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Ventricular dilation or hydrocephalus	4	271	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.31, 1.26]
1.4 Hypotension	3	382	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.97, 1.43]
1.5 Pneumothorax/interstitial emphysema	8	682	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.92, 1.77]
1.6 Hypercapnia	5	241	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.73, 1.37]
1.7 Acidosis	6	521	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.90, 1.51]
1.8 Use of mechanical ventilation	6	375	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.04, 1.28]
1.9 Mild neurodevelopmental impairment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.10 Severe neurodevelopmental impairment	2	153	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.44, 2.82]
1.11 Death before discharge	9	740	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.21]
1.12 All deaths during study	10	792	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.72, 1.33]

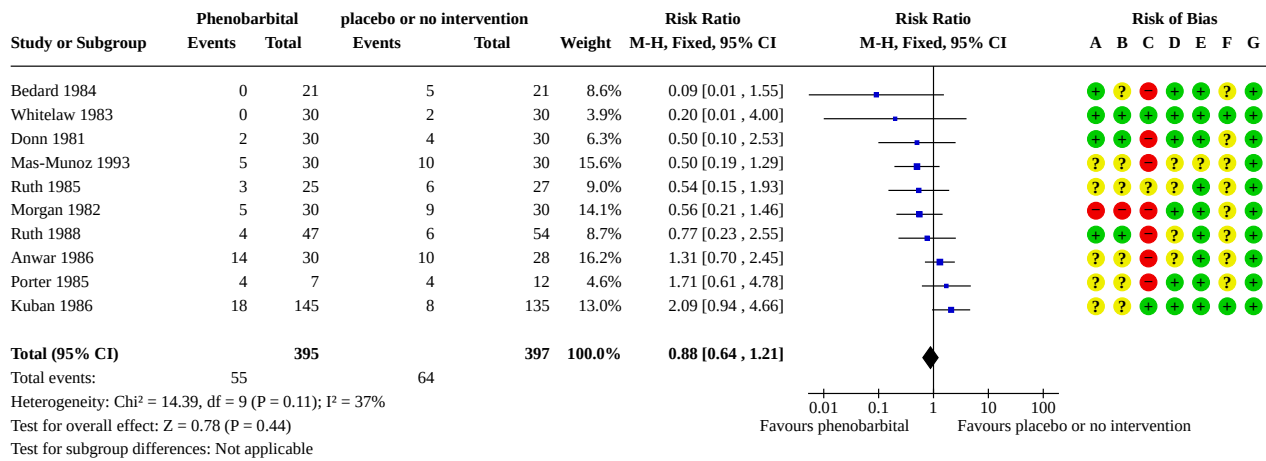
**Analysis 1.1. Comparison 1: Phenobarbital versus control, Outcome 1: All intraventricular haemorrhage**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

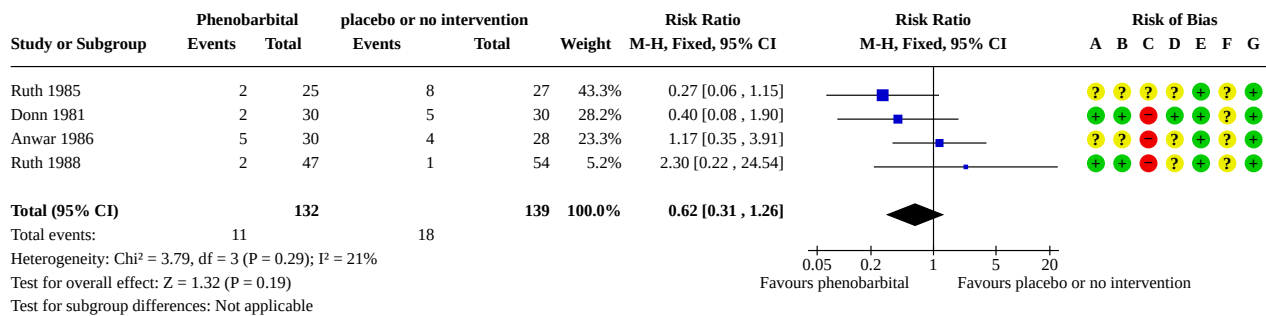
**Analysis 1.2. Comparison 1: Phenobarbital versus control, Outcome 2: Severe intraventricular haemorrhage**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

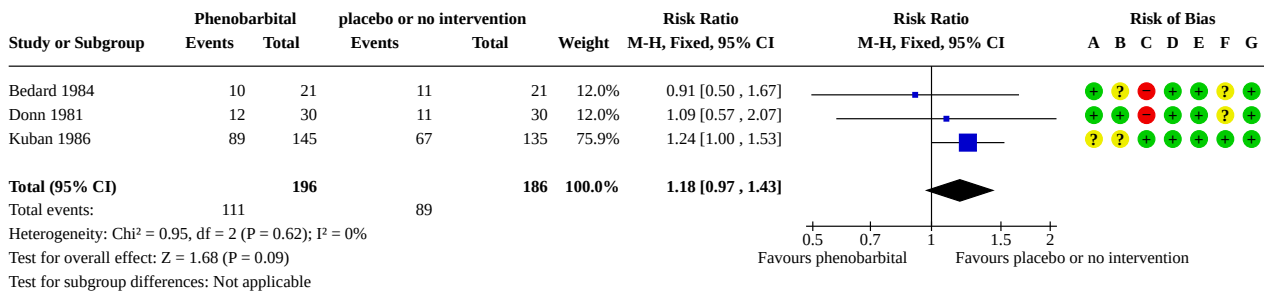
**Analysis 1.3. Comparison 1: Phenobarbital versus control, Outcome 3: Ventricular dilation or hydrocephalus**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

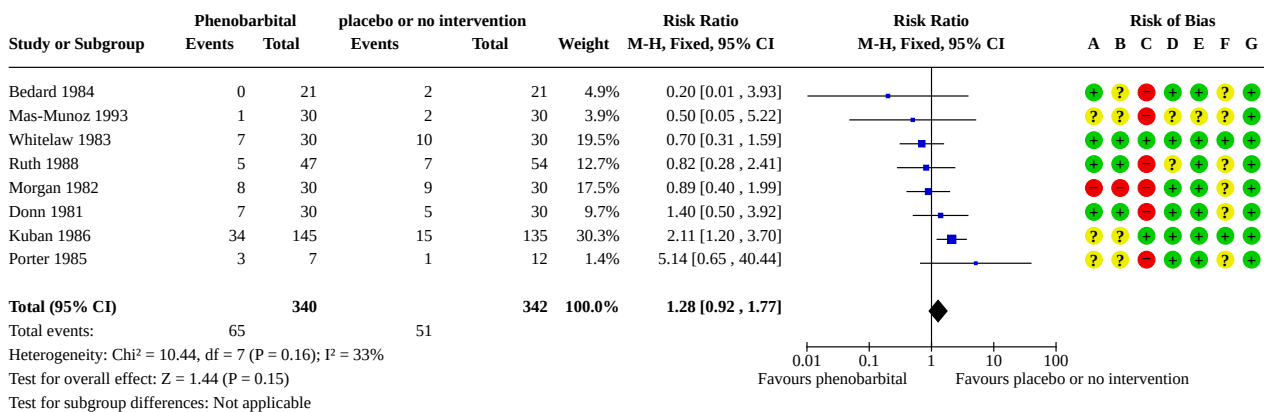
**Analysis 1.4. Comparison 1: Phenobarbital versus control, Outcome 4: Hypotension**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

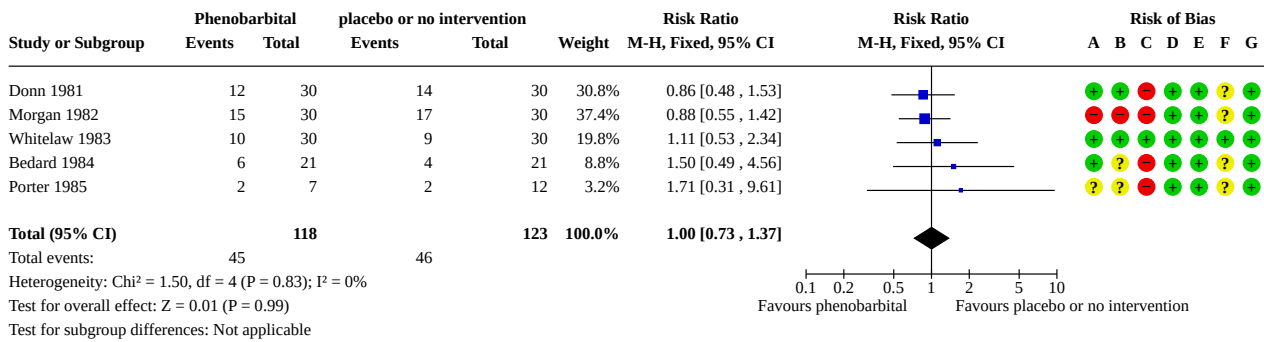
**Analysis 1.5. Comparison 1: Phenobarbital versus control, Outcome 5: Pneumothorax/interstitial emphysema**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

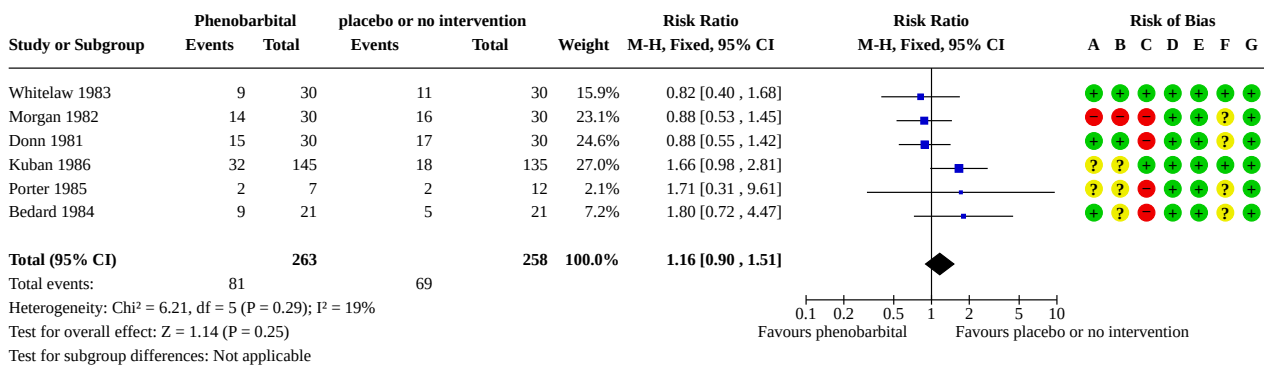
**Analysis 1.6. Comparison 1: Phenobarbital versus control, Outcome 6: Hypercapnia**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Analysis 1.7. Comparison 1: Phenobarbital versus control, Outcome 7: Acidosis**

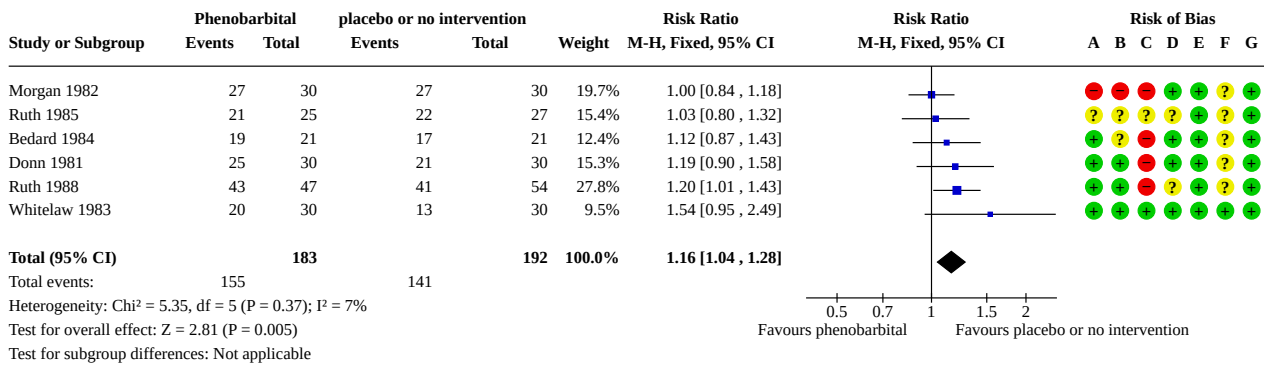


**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias



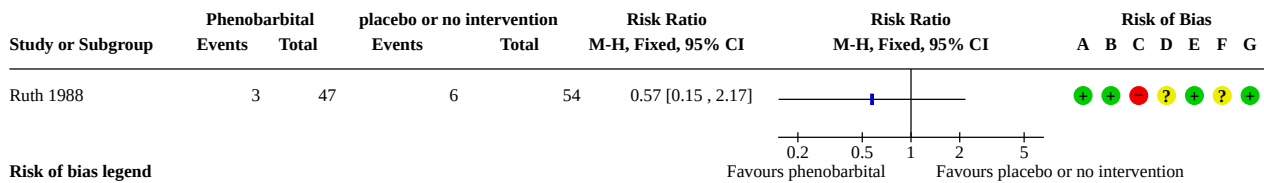
**Analysis 1.8. Comparison 1: Phenobarbital versus control, Outcome 8: Use of mechanical ventilation**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

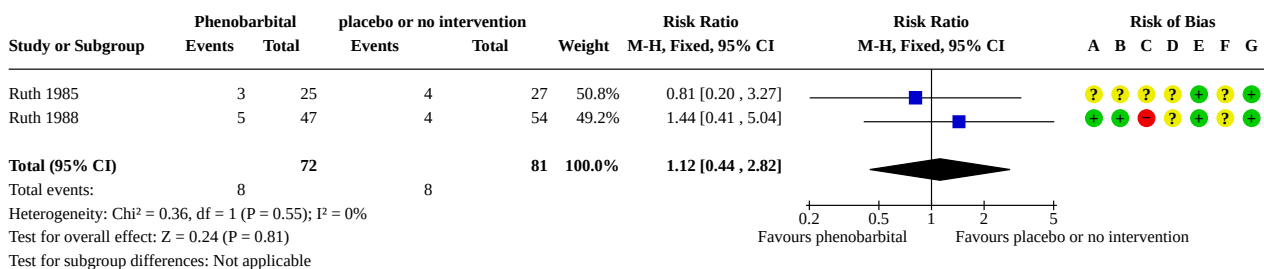
**Analysis 1.9. Comparison 1: Phenobarbital versus control, Outcome 9: Mild neurodevelopmental impairment**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

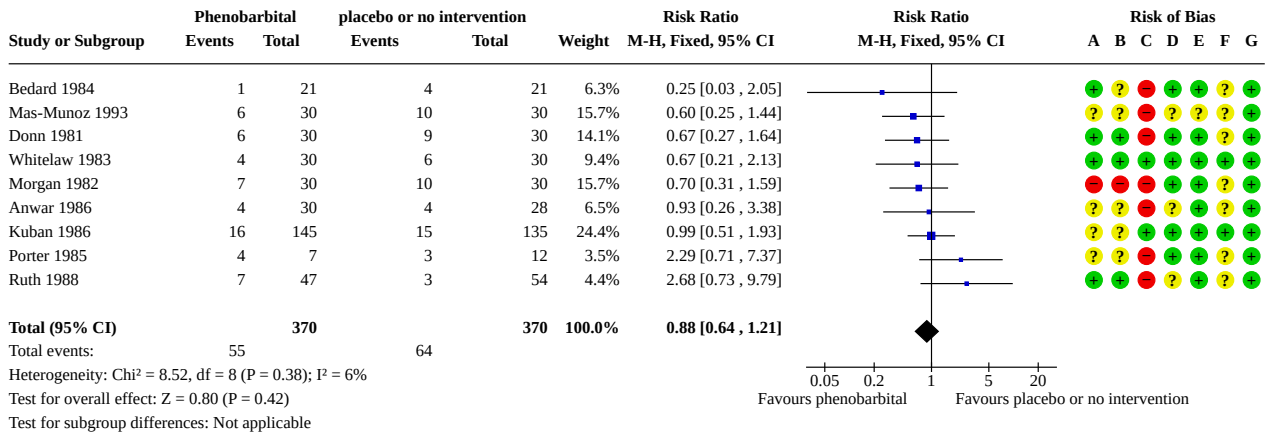
**Analysis 1.10. Comparison 1: Phenobarbital versus control, Outcome 10: Severe neurodevelopmental impairment**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

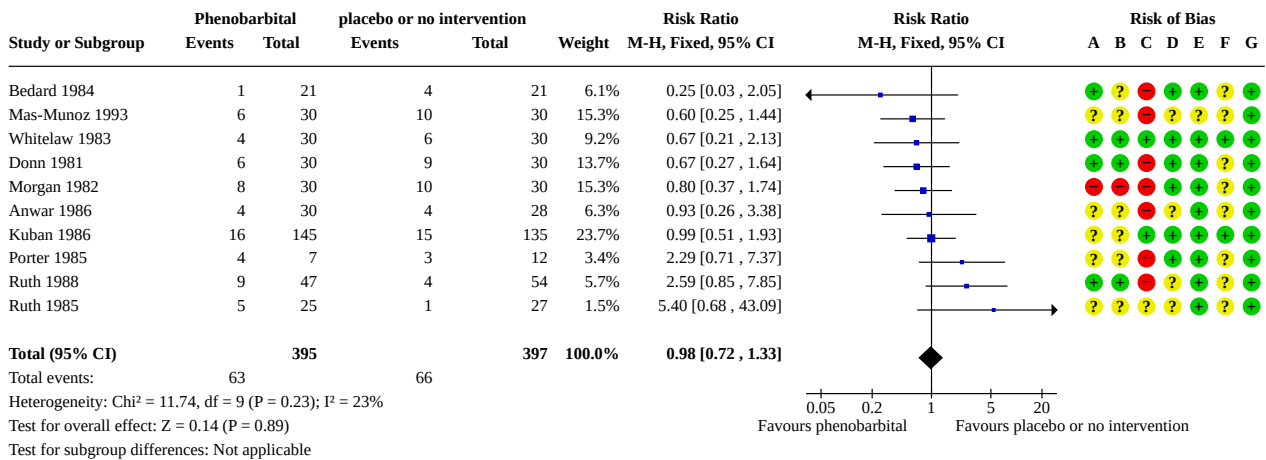
**Analysis 1.11. Comparison 1: Phenobarbital versus control, Outcome 11: Death before discharge**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Analysis 1.12. Comparison 1: Phenobarbital versus control, Outcome 12: All deaths during study**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**ADDITIONAL TABLES**
**Table 1. Overview of the included studies**

	Birthweight (g)		GA (weeks)		Study groups		Initiation (hours)
	Phenobarbital	Control	Phenobarbital	Control	Phenobarbital	Control	
Anwar 1986	1119 ± 264	1120 ± 218	NR	NR	LD 20 mg/kg, T12 MD 2.5 mg/kg, x12, UD	No intervention	6
Bedard 1984	1491 ± 421	1271 ± 422	31.1 ± 2.7	32.2 ± 1.7	LD 10 mg/kg, T12 MD 2.5 mg/kg, x12, for 6 days	No intervention	6
Donn 1981	1101 ± 243	1037 ± 208	28.9 ± 1.9	28.6 ± 1.9	LD 10 mg/kg, T12 MD 2.5 mg/kg, x12, for 7 days	No intervention	12
Kuban 1986	Reported as the number of newborns for four different weight groups: ≤ 1000, 1001 to 1250, 1251 to 1500, 1501 to 1750 g		Reported as the number of newborns for three different GA groups: < 28, ≥28 to < 32 and ≥ 32 to < 37 weeks		LD 10 mg/kg, T12 MD 2.5 mg/kg, x12, UD	Placebo	6
Mas-Munoz 1993	1544 ± 480	1394 ± 430	31.5 ± 2	31.0 ± 2.0	LD 20 mg/kg MD 2.5 mg/kg, x12, UD	No intervention	6
Morgan 1982	1150 ± 200	1070 ± 250	31.1 ± 2.7	28.8 ± 2.8	LD 20 mg/kg no MD	No intervention	24
Porter 1985	1058 ± 269	1061 ± 226	29.4 ± 2.8	28.8 ± 2.2	LD 30 mg/kg MD 5 mg/kg, x24, for 3 days	No intervention	6
Ruth 1985	1090 ± 247	1180 ± 222	28.7 ± 2.1	29.3 ± 1.8	LD 15 mg/kg, T4 MD 5 mg/kg, x24, for 5 days	No intervention	2
Ruth 1988	1160 ± 210	1120 ± 250	29.4 ± 1.7	29.2 ± 2.1	LD 15 mg/kg, T4	Glucose infusion	4

**Table 1. Overview of the included studies** (Continued)

					MD 5 mg/kg, x24, for 5 days		
Whitelaw 1983	1116 ± 215	1143 ± 238	29.7 ± 2.0	29.8 ± 2.1	LD 20 mg/kg no MD	Saline	4

Unless indicated otherwise, data are given as the mean±SD.

GA: gestational age

LD: loading dose

MD: maintenance dose

NR: not reported

SD: standard deviation

T4: twice 4 hours apart

T12: twice 12 hours apart

UD: unknown duration

x12: every 12 hours

x24: every 24 hours

## APPENDICES

### Appendix 1. Risk of bias tool

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

For each included study, we categorised 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.

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

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

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

#### **3. 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 categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

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

#### **4. 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 categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

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

#### **5. 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 described the completeness of data, including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion, where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk ( $\geq$  20% missing data); or
- unclear risk.

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

For each included study, we described 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 compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it is clear that all 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.

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

For each included study, we described 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 assessed 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 explored the impact of the level of bias by undertaking sensitivity analyses.

## Appendix 2. Search strategies

No publication date or language limitation was applied.

### MEDLINE (EbscoHost)

#### Date of search: 2022-01-18

[Premature infant terms, Cochrane standard filter for Medline]

#1 (MH "Infant, Newborn+")  
644,360 records

#2 (MH "Intensive Care, Neonatal+")  
16,716 records

#3 (MH "Intensive Care Units, Neonatal")  
6011 records

#4 TI ( infant OR infants OR infantile OR infancy OR newborn\* OR new born OR new borns OR newly born OR neonat\* OR baby\* OR babies OR premature OR prematures OR prematurity OR preterm OR preterms OR pre term OR preemie OR preemies OR premies OR low birth weight OR low birthweight OR VLBW OR LBW OR ELBW OR NICU ) OR AB ( infant OR infants OR infantile OR infancy OR newborn\* OR new born OR new borns OR newly born OR neonat\* OR baby\* OR babies OR premature OR prematures OR prematurity OR preterm OR preterms OR pre term OR preemie OR preemies OR premies OR low birth weight OR low birthweight OR VLBW OR LBW OR ELBW OR NICU )  
968,741 records

#5 #1 OR #2 OR #3 OR #4  
1,257,959 records

[Phenobarbital terms]

#6 (MH "Phenobarbital")  
18,097 records

#7 TI ( 5 ethyl 5 phenylbarbituric acid OR adonal OR aephenal OR agrypna OR alepsal OR amylofene OR andral OR aparoxal OR aphenylbarbit OR aphenyletten OR atofen OR austrominal OR barbapil OR barbellan OR barbenyl OR barbilettae OR barbilixir OR barbinal OR barbiphen OR barbiphenyl OR barbivis OR barbonal OR barbonalett OR barbophen OR bardorm OR bartol OR bialminal OR calmetten OR calminal OR carbonal OR cardenal OR cemalonal OR codibarbital OR coronaletta OR cratecil OR damoral OR dezibarbitur OR dormina OR dormiral OR dromural OR ensobarb OR ensodorm OR epanal OR epanal 2 OR epidorm OR epilol OR episedal OR epsylone OR eskabarb OR etilfen OR euneryl OR fenbital OR fenemal OR fenemal nm pharma OR fenobarbital OR fenolbarbital OR fenosed OR fenylettaa OR gardenal OR gardenal sodium OR gardenale OR gardepanyl OR glysoletten OR haplopan OR haplos OR helional OR hennoletten OR hypnaletten OR hypno tablinetten OR hypno-tablinetten OR hypnogen fragner OR hypnolone OR hypnotal OR hypnotalon OR hysteps OR lefebar OR leonal OR leonal leo OR lephebar OR lepinal OR lethyl OR linasen OR liquital OR lixophen OR lubergal OR lubrokal OR lumesettes OR lumesyn OR luminal OR luminal sodium OR luminal OR luminaletas OR luminalette OR luminaletten OR luminalettes OR luminalum OR lumofridetten OR luphenil OR luramin OR menobarb OR molinal OR neurobarb OR nirvonol OR noptil OR nova pheno OR nova-

pheno OR nunol OR parkotal OR pharmetten OR phen bar OR phenaemal OR phenemal OR phenethylbarbital sodium OR phenobal OR phenobarb OR phenobarbital 2 OR phenobarbital i OR phenobarbital sodium OR phenobarbitol OR phenobarbiton OR phenobarbitone OR phenobarbitone sodium OR phenobarbitural OR phenobarbyl OR phenonyl OR phenotal OR phenoturic OR phenoyl OR phenyl ethyl barbituric acid OR phenylethyl barbituric acid OR phenylethylbarbituric acid OR phenylethylmalonyl urea OR phenylethylmalonylurea OR phenyletten OR phenyral OR polcominal OR promptonal OR seda tablinen OR sedabar OR sedicat OR sediz ORin OR sedlyn OR sedofen OR sedonal OR sedonettes OR seneval OR sevenal OR sodium phenobarbital OR sodium phenobarbitone OR sombutol mcclung OR somnolens OR somnolette) ORAB (5 ethyl 5 phenylbarbituric acid OR adonal OR aephenal OR agrypna OR alepsal OR amylofene OR andral OR aparoal OR aphenylbarbit OR aphenyletten OR atrofen OR austrominal OR barbapil OR barbellen OR barbenyl OR barbilettae OR barbilixir OR barbinal OR barbiphen OR barbiphenyl OR barbivis OR barbonal OR barbonalett OR barbophen OR bardorm OR bartol OR bialminal OR calmetten OR calminal OR carbronal OR cardenal OR cemalonal OR codibarbital OR coronaletta OR cratecil OR damoral OR dezibarbitur OR dormina OR dormiral OR dromural OR ensobarb OR ensodorm OR epanal OR epanal 2 OR epidorm OR epilol OR episedal OR epsylone OR eskabarb OR etilfen OR euneryl OR fenbital OR fenemal nm pharma OR fenobarbital OR fenolbarbital OR fenosed OR fenylettaa OR gardenal OR gardenal sodium OR gardenale OR gardepanyl OR glysoletten OR haplopan OR haplos OR helional OR hennoletten OR hypnaletten OR hypno tablinetten OR hypno-tablinetten OR hypnogen fragner OR hypnolone OR hypnotal OR hypnotalon OR hysteps OR lefebar OR leonal OR leonal leo OR lephebar OR lepinal OR lethyl OR linasen OR liquital OR lixophen OR lubergal OR lubrokal OR lumesettes OR lumesyn OR luminal OR luminal sodium OR luminale OR luminaletas OR luminalette OR luminaletten OR luminalettes OR luminalum OR lumofridetten OR luphenil OR luramin OR menobarb OR molinal OR neurobarb OR nirvonal OR noptil OR nova pheno OR nova-pheno OR nunol OR parkotal OR pharmetten OR phen bar OR phenaemal OR phenemal OR phenethylbarbital sodium OR phenobal OR phenobarb OR phenobarbital 2 OR phenobarbital i OR phenobarbital sodium OR phenobarbitol OR phenobarbiton OR phenobarbitone OR phenobarbitone sodium OR phenobarbitural OR phenobarbyl OR phenonyl OR phenotal OR phenoturic OR phenoyl OR phenyl ethyl barbituric acid OR phenylethyl barbituric acid OR phenylethylbarbituric acid OR phenylethylmalonyl urea OR phenylethylmalonylurea OR phenyletten OR phenyral OR polcominal OR promptonal OR seda tablinen OR sedabar OR sedicat OR sediz ORin OR sedlyn OR sedofen OR sedonal OR sedonettes OR seneval OR sevenal OR sodium phenobarbital OR sodium phenobarbitone OR sombutol mcclung OR somnolens OR somnolette)

57,630 records

#8 #6 OR #7

71,829 records

[Cochrane standard RCT filter]

#9 PT randomized controlled trial

555,218 records

#10 PT controlled clinical trial

94,616 records

#11 TI ( (randomized OR randomised) ) OR AB ( (randomized OR randomised) )

704,138 records

#12 TI placebo OR AB placebo

230,819 records

#13 TI drug therapy OR AB drug therapy

340,735 records

#14 TI randomly OR AB randomly

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373,286 records

#15 TI trial OR AB trial

1,140,170 records

#16 TI groups OR AB groups

4,020,880 records

#17 TI ( quasirandom\* OR quasi-random\* ) OR AB ( quasirandom\* OR quasi-random\* )

5267 records

#18 MH animals NOT MH humans

4,904,489 records

#19 #9 OR #10 OR #11 OR #12 # OR #13 OR #14 OR #15 OR #16 OR #17

7,204,932 records

#20 #19 NOT #18

6,273,649 records

[Premature infants AND Phenobarbital AND RCTs]

#21 #5 AND #8 AND #20

1334 records

### **Embase (Elsevier)**

Date of search: 2022-01-18

[Premature infant terms, Cochrane standard filter]

#1 'prematurity'/exp

122,488 records

#2 'infant'/exp

1,210,696 records

#3 'newborn intensive care'/exp

26,884 records

#4 'newborn care'/exp

45,292 records



#5 infant:ab,ti OR infants:ab,ti OR infantile:ab,ti OR infancy:ab,ti OR newborn\*:ab,ti OR 'new born':ab,ti OR 'new borns':ab,ti OR 'newly born':ab,ti OR neonat\*:ab,ti OR baby\*:ab,ti OR babies:ab,ti OR premature:ab,ti OR prematures:ab,ti OR prematurity:ab,ti OR preterm:ab,ti OR preterms:ab,ti OR 'pre term':ab,ti OR preemie:ab,ti OR preemies:ab,ti OR premies:ab,ti OR 'low birth weight':ab,ti OR 'low birthweight':ab,ti OR vlbw:ab,ti OR lbw:ab,ti OR elbw:ab,ti OR nicu:ab,ti  
 1,168,165 records

#6 #1 OR #2 OR #3 OR #4 OR #5  
 1,770,539 records

[Phenobarbital terms]

#7 'phenobarbital'/exp  
 64,993 records

#8 '5 ethyl 5 phenylbarbituric acid'/exp OR 'adonal'/exp OR 'aephenal'/exp OR 'agrypnaal'/exp OR 'alepsal'/exp OR 'amylofene'/exp OR 'andral'/exp OR 'aparoxal'/exp OR 'aphenylbarbit'/exp OR 'aphenyletten'/exp OR 'atrofen'/exp OR 'austrominal'/exp OR 'barbapil'/exp OR 'barbellen'/exp OR 'barbenyl'/exp OR 'barbilettae'/exp OR 'barbilixir'/exp OR 'barbinal'/exp OR 'barbiphen'/exp OR 'barbiphenyl'/exp OR 'barbivis'/exp OR 'barbonal'/exp OR 'barbonalett'/exp OR 'barbophen'/exp OR 'bardorm'/exp OR 'bartol'/exp OR 'bialminal'/exp OR 'calmetten'/exp OR 'calminal'/exp OR 'carbronal'/exp OR 'cardenal'/exp OR 'cemalonal'/exp OR 'codibarbital'/exp OR 'coronaletta'/exp OR 'cratecil'/exp OR 'damoral'/exp OR 'dezibarbitur'/exp OR 'dormina'/exp OR 'dormiral'/exp OR 'dromural'/exp OR 'ensobarb'/exp OR 'ensodorm'/exp OR 'epanal'/exp OR 'epanal 2'/exp OR 'epidorm'/exp OR 'epilol'/exp OR 'episedal'/exp OR 'epsylone'/exp OR 'eskabarb'/exp OR 'etilfen'/exp OR 'euneryl'/exp OR 'fenbital'/exp OR 'fenemal'/exp OR 'fenemal nm pharma'/exp OR 'fenobarbital'/exp OR 'fenolbarbital'/exp OR 'fenosed'/exp OR 'fenylettaa'/exp OR 'gardenal'/exp OR 'gardenal sodium'/exp OR 'gardenale'/exp OR 'gardepanyl'/exp OR 'glysoletten'/exp OR 'haplopan'/exp OR 'haplos'/exp OR 'helional'/exp OR 'hennoletten'/exp OR 'hypnaletten'/exp OR 'hypno tablinetten'/exp OR 'hypnogen fragner'/exp OR 'hypnolone'/exp OR 'hypnotal'/exp OR 'hypnotalon'/exp OR 'hysteps'/exp OR 'lefebar'/exp OR 'leonal'/exp OR 'leonal leo'/exp OR 'lephebar'/exp OR 'lepinal'/exp OR 'lethyl'/exp OR 'linasen'/exp OR 'liquital'/exp OR 'lixophen'/exp OR 'lubergal'/exp OR 'lubrokal'/exp OR 'lumesettes'/exp OR 'lumesyn'/exp OR 'luminal'/exp OR 'luminal sodium'/exp OR 'luminala'/exp OR 'luminaletas'/exp OR 'luminalette'/exp OR 'luminaletten'/exp OR 'luminalettes'/exp OR 'luminalum'/exp OR 'lumofridetten'/exp OR 'luphenil'/exp OR 'luramin'/exp OR 'menobarb'/exp OR 'molinal'/exp OR 'neurobarb'/exp OR 'nirvonol'/exp OR 'noptil'/exp OR 'nova pheno'/exp OR 'nunol'/exp OR 'parkotal'/exp OR 'pharmetten'/exp OR 'phen bar'/exp OR 'phenaemal'/exp OR 'phenemal'/exp OR 'phenethylbarbital sodium'/exp OR 'phenobal'/exp OR 'phenobarb'/exp OR 'phenobarbital 2'/exp OR 'phenobarbital i'/exp OR 'phenobarbital sodium'/exp OR 'phenobarbitol'/exp OR 'phenobarbiton'/exp OR 'phenobarbitone'/exp OR 'phenobarbitone sodium'/exp OR 'phenobarbitural'/exp OR 'phenobarbyl'/exp OR 'phenonyl'/exp OR 'phenotal'/exp OR 'phenoturic'/exp OR 'phenoyl'/exp OR 'phenyl ethyl barbituric acid'/exp OR 'phenylethyl barbituric acid'/exp OR 'phenylethylbarbituric acid'/exp OR 'phenylethylmalonyl urea'/exp OR 'phenylethylmalonylurea'/exp OR 'phenyletten'/exp OR 'phenyral'/exp OR 'polcominal'/exp OR 'promptonal'/exp OR 'seda tablinen'/exp OR 'sedabar'/exp OR 'sedicat'/exp OR 'sediz orin'/exp OR 'sedlyn'/exp OR 'sedofen'/exp OR 'sedonal'/exp OR 'sedonettes'/exp OR 'seneval'/exp OR 'sevenal'/exp OR 'sodium phenobarbital'/exp OR 'sodium phenobarbitone'/exp OR 'sombutol mcclung'/exp OR 'somnolens'/exp OR somnolette/exp

64,994 records

#9 '5 ethyl 5 phenylbarbituric acid':ab,ti OR adonal:ab,ti OR aephenal:ab,ti OR agrypnaal:ab,ti OR alepsal:ab,ti OR amylofene:ab,ti OR andral:ab,ti OR aparoxal:ab,ti OR aphenylbarbit:ab,ti OR aphenyletten:ab,ti OR atrofen:ab,ti OR austrominal:ab,ti OR barbapil:ab,ti OR barbellen:ab,ti OR barbenyl:ab,ti OR barbilettae:ab,ti OR barbilixir:ab,ti OR barbinal:ab,ti OR barbiphen:ab,ti OR barbiphenyl:ab,ti OR barbivis:ab,ti OR barbonal:ab,ti OR barbonalett:ab,ti OR barbophen:ab,ti OR bardorm:ab,ti OR bartol:ab,ti OR bialminal:ab,ti OR calmetten:ab,ti OR calminal:ab,ti OR carbronal:ab,ti OR cardenal:ab,ti OR cemalonal:ab,ti OR codibarbital:ab,ti OR coronaletta:ab,ti OR cratecil:ab,ti OR damoral:ab,ti OR dezibarbitur:ab,ti OR dormina:ab,ti OR dormiral:ab,ti OR dromural:ab,ti OR ensobarb:ab,ti OR ensodorm:ab,ti OR epanal:ab,ti OR 'epanal 2':ab,ti OR epidorm:ab,ti OR epilol:ab,ti OR episedal:ab,ti OR epsylone:ab,ti OR eskabarb:ab,ti OR etilfen:ab,ti OR euneryl:ab,ti OR fenbital:ab,ti OR fenemal:ab,ti OR 'fenemal nm pharma':ab,ti OR fenobarbital:ab,ti OR fenolbarbital:ab,ti OR fenosed:ab,ti OR fenylettaa:ab,ti OR gardenal:ab,ti OR 'gardenal sodium':ab,ti OR gardenale:ab,ti OR gardepanyl:ab,ti OR glysoletten:ab,ti OR haplopan:ab,ti OR haplos:ab,ti OR helional:ab,ti OR hennoletten:ab,ti OR hypnaletten:ab,ti OR 'hypno tablinetten':ab,ti OR 'hypnogen fragner':ab,ti OR hypnolone:ab,ti OR hypnotal:ab,ti OR hypnotalon:ab,ti OR hysteps:ab,ti OR lefebar:ab,ti OR leonal:ab,ti OR 'leonal leo':ab,ti OR lephebar:ab,ti OR lepinal:ab,ti OR lethyl:ab,ti OR linasen:ab,ti OR liquital:ab,ti OR lixophen:ab,ti OR lubergal:ab,ti OR lubrokal:ab,ti OR lumesettes:ab,ti OR lumesyn:ab,ti OR luminal:ab,ti OR 'luminal sodium':ab,ti OR luminala:ab,ti OR luminaletas:ab,ti OR luminalette:ab,ti OR luminaletten:ab,ti OR luminalettes:ab,ti OR luminalum:ab,ti OR lumofridetten:ab,ti OR luphenil:ab,ti OR luramin:ab,ti OR menobarb:ab,ti OR molinal:ab,ti OR neurobarb:ab,ti OR nirvonol:ab,ti OR noptil:ab,ti OR 'nova pheno':ab,ti OR nunol:ab,ti OR parkotal:ab,ti OR pharmetten:ab,ti OR 'phen bar':ab,ti OR phenaemal:ab,ti OR phenemal:ab,ti OR 'phenethylbarbital sodium':ab,ti OR phenobal:ab,ti OR phenobarb:ab,ti OR 'phenobarbital 2':ab,ti OR 'phenobarbital i':ab,ti OR 'phenobarbital sodium':ab,ti OR phenobarbitol:ab,ti OR phenobarbiton:ab,ti OR phenobarbitone:ab,ti OR 'phenobarbitone sodium':ab,ti OR phenobarbitural:ab,ti OR phenobarbyl:ab,ti OR phenonyl:ab,ti OR phenotal:ab,ti OR phenoturic:ab,ti OR phenoyl:ab,ti OR 'phenyl ethyl barbituric acid':ab,ti OR 'phenylethyl barbituric acid':ab,ti OR 'phenylethylbarbituric acid':ab,ti OR 'phenylethylmalonyl urea':ab,ti OR 'phenylethylmalonylurea':ab,ti OR phenyletten:ab,ti OR phenyral:ab,ti OR polcominal:ab,ti OR promptonal:ab,ti OR 'seda tablinen':ab,ti OR sedabar:ab,ti OR sedicat:ab,ti OR 'sediz orin':ab,ti OR sedlyn:ab,ti OR sedofen:ab,ti OR sedonal:ab,ti OR sedonettes:ab,ti

OR seneval:ab,ti OR sevenal:ab,ti OR 'sodium phenobarbital':ab,ti OR 'sodium phenobarbitone':ab,ti OR 'sombutol mcclung':ab,ti OR somnolens:ab,ti OR somnolette:ab,ti

74,055 records

#10 #7 OR #8 OR #9

131,246 records

[Cochrane standard RCT filter]

#11 'randomized controlled trial'/de OR 'controlled clinical trial'/de  
868,883 records

#12 random\*:ti,ab  
1,742,040 records

#13 'randomization'/de  
92,815 records

#14 placebo:ti,ab,kw  
336,138 records

#15 ((double OR single OR doubly OR singly) NEAR/2 (blind OR blinded OR blindly)):ti,ab  
255,461 records

#16 'double blind procedure'/de  
190,931

#17 (controlled NEAR/7 (study OR design OR trial)):ti,ab  
398,623 records

#18 'parallel group\$:ti,ab  
28,641 records

#19 crossover:ti,ab OR 'cross over':ti,ab  
114,398 records

#10 ((assign\* OR match OR matched OR allocation) NEAR/5 (alternate OR group\$ OR intervention\$ OR patient\$ OR subject\$ OR participant \$)):ti,ab  
367,802

#21 (open NEAR/2 label):ti,ab  
93,640 records

#22 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21  
2,494,295

#23 ('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'animal cell'/de OR 'nonhuman'/de) AND ('human'/de OR 'normal human'/de OR 'human cell'/de)  
24,289,798 records

#24 'animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'animal cell'/de OR 'nonhuman'/de  
31,695,867 records

#25 #23 NOT #24  
7,406,069 records

#26 #22 NOT #25  
2,225,115 records

[Premature infants AND Phenobarbital AND RCTs]

#27 #6 AND #10 AND #26  
573 records

#28 #27 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)  
133 records

**CENTRAL (via Cochrane Library, Wiley)**

Date of search: 2022- 01-18

#1 MeSH descriptor: [Infant, Newborn] explode all trees  
17,052 records

#2 MeSH descriptor: [Intensive Care, Neonatal] explode all trees  
349 records

#3 MeSH descriptor: [Intensive Care Units, Neonatal] explode all trees  
824 records

#4 (baby\* OR babies OR infant OR infants OR infant s OR infant's OR infantile OR infancy OR low birth weight OR low birthweight OR neonat\*OR newborn\* OR new born OR new borns OR newly born OR premature OR prematures OR prematurity OR preterm OR preterms OR pre term OR preemie OR preemies OR premies OR premie OR VLBW OR LBW OR ELBW OR NICU):ti,ab  
75,489 records

#5 #1 OR #2 OR #3 OR #4  
80,434 records

#6 MeSH descriptor: [Phenobarbital] explode all trees  
499 records

#7 (5 ethyl 5 phenylbarbituric acid OR adonal OR aephenal OR agrypna OR alepsal OR amylofene OR andral OR apoxal OR aphenylbarbit OR aphenyletten OR atrofen OR austrominal OR barbapil OR barbellin OR barbenyl OR barbilettae OR barbilixir OR barbinal OR barbiphen OR barbiphenyl OR barbivis OR barbonal OR barbonalett OR barbophen OR bardorm OR bartol OR bialminal OR calmetten OR calminal OR carbromal OR cardenal OR cernalonal OR codibarbital OR coronaletta OR cratecil OR damoral OR dezibarbitur OR dormina OR dormiral OR dromural OR ensobarb OR ensodorm OR epanal OR epanal 2 OR epidorm OR epilol OR episedal OR epsylone OR eskabarb OR etilfen OR euneryl OR fenbital OR fenemal OR fenemal nm pharma OR fenobarbital OR fenolbarbital OR fenosed OR fenylettaa OR gardenal OR gardenal sodium OR gardenale OR gardepanyl OR glysoletten OR haplopan OR haplos OR helional OR hennoletten OR hypnaletten OR hypno tablinetten OR hypno-tablinetten OR hypnogen fragner OR hypnolone OR hypnotal OR hypnotalon OR hysteps OR lefebar OR leonal OR leonal leo OR lephebar OR lepinal OR lethyl OR linasen OR liquital OR lixophen OR lubergal OR lubrokal OR lumesettes OR lumesyn OR luminal OR luminal sodium OR luminale OR luminaletas OR luminalette OR luminaletten OR luminalettes OR luminalum OR lumofridetten OR luphenil OR luramin OR menobarb OR molinal OR neurobarb OR nirvonol OR noptil OR nova pheno OR nova-pheno OR nunol OR parkotal OR pharmetten OR phen bar OR phenaemal OR phenemal OR phenethylbarbital sodium OR phenobal OR phenobarb OR phenobarbital 2 OR phenobarbital i OR phenobarbital sodium OR phenobarbitol OR phenobarbiton OR phenobarbitone OR phenobarbitone sodium OR phenobarbitural OR phenobarbyl OR phenonyl OR phenotal OR phenoturic OR phenoyl OR phenyl ethyl barbituric acid OR phenylethyl barbituric acid OR phenylethylbarbituric acid OR phenylethylmalonyl urea OR phenylethylmalonylurea OR phenyletten OR phenylal OR polcominal OR promptonal OR seda tablinen OR sedabar OR sedicat OR sediz ORin OR sedlyn OR sedofen OR sedonal OR sedonettes OR seneval OR sevenal OR sodium phenobarbital OR sodium phenobarbitone OR sombutol mcclung OR somnolens OR somnolette):ti,ab

2645 records

#8 #6 OR #7  
2941 records

#9 #5 AND 8  
278 records of which 265 are trials

**Cinahl Complete (EbscoHost)**

Date of search: 2022-01-18

[Premature infant terms, Cochrane standard filter adapted from Medline]

#1 (MH "Infant, Newborn+")  
152,151 records

#2 (MH "Intensive Care, Neonatal+")  
6289 records

#3 (MH "Intensive Care Units, Neonatal")  
14,774 records

#4 TI ( infant OR infants OR infantile OR infancy OR newborn\* OR new born OR new borns OR newly born OR neonat\* OR baby\* OR babies OR premature OR prematures OR prematurity OR preterm OR preterms OR pre term OR preemie OR preemies OR premies OR low birth weight OR low birthweight OR VLBW OR LBW OR ELBW OR NICU ) OR AB ( infant OR infants OR infantile OR infancy OR newborn\* OR new born OR new borns OR newly born OR neonat\* OR baby\* OR babies OR premature OR prematures OR prematurity OR preterm OR preterms OR pre term OR preemie OR preemies OR premies OR low birth weight OR low birthweight OR VLBW OR LBW OR ELBW OR NICU )  
259983 records

#5 #1 OR #2 OR #3 OR #4  
318,505 records

[Phenobarbital terms]

#6 (MH "Phenobarbital")  
705 records

#7 TI (5 ethyl 5 phenylbarbituric acid OR adonal OR aephenal OR agrypna OR alepsal OR amylofene OR andral OR aparoxal OR aphenylbarbit OR aphenyletten OR atrofene OR austrominal OR barbapil OR barbellene OR barbenyl OR barbilettae OR barbilixir OR barbinal OR barbiphen OR barbiphenyl OR barbivis OR barbonal OR barbonalett OR barbophen OR bardorm OR bartol OR bialminal OR calmetten OR calminal OR carbronal OR cardenal OR cemalonal OR codibarbital OR coronaletta OR cratecil OR damoral OR dezibarbitur OR dormina OR dormiral OR dromural OR ensobarb OR ensodorm OR epanal OR epanal 2 OR epidorm OR epilol OR episedal OR epsylone OR eskabarb OR etilfen OR euneryl OR fenbital OR fenemal OR fenemal nm pharma OR fenobarbital OR fenolbarbital OR fenosed OR fenylettaa OR gardenal OR gardenal sodium OR gardenale OR gardepanyl OR glysoletten OR haplopan OR haplos OR helional OR hennoletten OR hypnaletten OR hypno tablinetten OR hypno-tablinetten OR hypnogen fragner OR hypnolone OR hypnotal OR hypnotalon OR hysteps OR lefebar OR leonal OR leonal leo OR lephebar OR lepinal OR lethyl OR linasen OR liquital OR lixophen OR lubergal OR lubrokal OR lumesettes OR lumesyn OR luminal OR luminal sodium OR luminale OR luminaletas OR luminalette OR luminaletten OR luminalettes OR luminalum OR lumofridetten OR luphenil OR luramin OR menobarb OR molinal OR neurobarb OR nirvonol OR noptil OR nova pheno OR novapheno OR nunol OR parkotal OR pharmetten OR phen bar OR phenaemal OR phenemal OR phenethylbarbital sodium OR phenobarb OR phenobarb OR phenobarbital 2 OR phenobarbital i OR phenobarbital sodium OR phenobarbitol OR phenobarbiton OR phenobarbitone OR phenobarbitone sodium OR phenobarbitural OR phenobarbyl OR phenonyl OR phenotal OR phenoturic OR phenoyl OR phenyl ethyl barbituric acid OR phenylethyl barbituric acid OR phenylethylbarbituric acid OR phenylethylmalonyl urea OR phenylethylmalonylurea OR phenyletten OR phenylal OR polcominal OR promptonal OR seda tablinen OR sedabar OR sedicat OR sediz OR in OR sedlyn OR sedofen OR sedonal OR sedonettes OR seneval OR sevenal OR sodium phenobarbital OR sodium phenobarbitone OR sombutol mcclung OR sommolens OR somnolette) OR AB (5 ethyl 5 phenylbarbituric acid OR adonal OR aephenal OR agrypna OR alepsal OR amylofene OR andral OR aparoxal OR aphenylbarbit OR aphenyletten OR atrofene OR austrominal OR barbapil OR barbellene OR barbenyl OR barbilettae OR barbilixir OR barbinal OR barbiphen OR barbiphenyl OR barbivis OR barbonal OR barbonalett OR barbophen OR bardorm OR bartol OR bialminal OR calmetten OR calminal OR carbronal OR cardenal OR cemalonal OR codibarbital OR coronaletta OR cratecil OR damoral OR dezibarbitur OR dormina OR dormiral OR dromural OR ensobarb OR ensodorm OR epanal OR epanal 2 OR epidorm OR epilol OR episedal OR epsylone OR eskabarb OR etilfen OR euneryl OR fenbital OR fenemal OR fenemal nm pharma OR fenobarbital OR fenolbarbital OR fenosed OR fenylettaa OR gardenal OR gardenal sodium OR gardenale OR gardepanyl OR glysoletten OR haplopan OR haplos OR helional OR hennoletten OR hypnaletten OR hypno tablinetten OR hypno-tablinetten OR hypnogen fragner OR hypnolone OR hypnotal OR hypnotalon OR hysteps OR lefebar OR leonal OR leonal leo OR lephebar OR lepinal OR lethyl OR linasen OR liquital OR lixophen OR lubergal OR lubrokal OR lumesettes OR lumesyn OR luminal OR luminal sodium OR luminale OR luminaletas OR luminalette OR luminaletten OR luminalettes OR luminalum

luminalum OR lumofridetten OR luphenil OR luramin OR menobarb OR molinal OR neurobarb OR nirvonol OR noptil OR nova pheno OR nova-pheno OR nunol OR parkotal OR pharmetten OR phen bar OR phenaemal OR phenemal OR phenethylbarbital sodium OR phenobal OR phenobarb OR phenobarbital 2 OR phenobarbital i OR phenobarbital sodium OR phenobarbitol OR phenobarbiton OR phenobarbitone OR phenobarbitone sodium OR phenobarbitural OR phenobarbyl OR phenonyl OR phenotal OR phenoturic OR phenoyl OR phenyl ethyl barbituric acid OR phenylethyl barbituric acid OR phenylethylbarbituric acid OR phenylethylmalonyl urea OR phenylethylmalonylurea OR phenyletten OR phenyral OR polcominal OR promptonal OR seda tablinen OR sedabar OR sedicat OR sediz ORin OR sedlyn OR sedofen OR sedonal OR sedonettes OR seneval OR sevenal OR sodium phenobarbital OR sodium phenobarbitone OR sombutol mcclung OR somnolens OR somnolette)

5184 records

#8 #6 OR #7

5680 records

[Cochrane standard RCT filter]

#9 PT randomized controlled trial

139,227 records

#10 (MH "Clinical Trials+")

333,021 records

#11 TI ( (randomized OR randomised) ) OR AB ( (randomized OR randomised) )

279,633 records

#12 TI placebo OR AB placebo

68,713 records

#13 TI drug therapy OR AB drug therapy

59,675 records

#14 TI randomly OR AB randomly

101,399 records

#15 TI trial OR AB trial

389,544 records

#16 TI groups OR AB groups

869,271 records

#17 TI ( quasirandom\* OR quasi-random\* ) OR AB ( quasirandom\* OR quasi-random\* )

2159 records

#18 MH animals NOT MH humans  
94,007 records

#19 #9 OR #10 OR #11 OR #12 # OR #13 OR #14 OR #15 OR #16 OR #17  
1,740,007 records

#20 #19 NOT #18  
1,710,499 records

[Premature infants AND Phenobarbital AND RCTs]

#21 #5 AND #8 AND #20

250 records

### ***Trial registry strategies***

#### **Clinicaltrials.gov**

Date of search: 2022-01-18

Advanced search, Other terms

(premature OR preterm OR neonat\* OR newborn OR infant) AND (phenobarbital OR phenylbarbital OR phenobarb\*)

30 records

#### **ICTRP (World Health Organization)**

Date of search: 2022-01-18

Simple search

(premature OR preterm OR neonat\* OR newborn OR infant) AND (phenobarbital OR phenylbarbital OR phenobarb\*)

48 records

2060 records in total from all databases and registries (before deduplication)

### **WHAT'S NEW**

Date	Event	Description
7 March 2023	New citation required and conclusions have changed	In this update, we report that the certainty of the evidence for the main outcomes ranged from low to very low; the evidence suggests that the use of phenobarbital results in little to no difference in the incidence of intraventricular haemorrhage (any grade; grade III and IV) compared with control. The previous version of this Cochrane Review concluded that postnatal pheno-

**Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants (Review)**

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Date	Event	Description
		barbital could not be recommended for prophylaxis against IVH in preterm infants.
7 March 2023	New search has been performed	<p>New authorship.</p> <p>Methods have been updated to meet MECIR standards and address the risk of bias.</p> <p>GRADE recommendations and a summary of findings have now been included.</p> <p>We updated searches in 2022. We included one new study (<a href="#">Ruth 1985</a>); this is an older study, but it was identified after search strategies had been revised to increase sensitivity and searches were conducted without date limits. We excluded two new studies (<a href="#">Cooke 1982</a>; <a href="#">Saliba 1991</a>).</p> <p>Three previously included studies have been moved to Additional References because they were not randomised – as was clear from the study titles (<a href="#">Liang 2009</a>; <a href="#">Zhang 2009</a>) or abstract (<a href="#">Sluncheva 2006</a>). According to Cochrane methods, only RCTs and quasi-RCTs are included in Cochrane Reviews, and the full text of these studies should not have been assessed.</p> <p>Three previously excluded studies have been moved to Additional References: two of these studies were not randomised or quasi-randomised studies, as was clear from the titles/abstracts (<a href="#">Chen 2008</a>; <a href="#">Hope 1982</a>), and one did not meet the gestational age inclusion criteria, as was clear from the abstract (<a href="#">Liu 2010</a>).</p>

## HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 3, 1999

Date	Event	Description
17 December 2012	New citation required but conclusions have not changed	<p>New authorship.</p> <p>A repeat search on October 31, 2012 identified four more studies, of which two were eligible for inclusion in this review update. One was excluded in view of lack of randomisation, one was excluded as it failed to meet the inclusion criteria.</p>
31 October 2012	New search has been performed	This review updates the original review "Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants", published in the Cochrane Library, Issue 4, 2007 ( <a href="#">Whitelaw 2007</a> ).
10 June 2008	Amended	Converted to new review format
31 May 2007	New search has been performed	This review updates the existing review "Postnatal phenobarbitone for the prevention of intraventricular hemorrhage in preterm infants", published in The Cochrane Library, Issue 3, 1999 ( <a href="#">Whitelaw 1999</a> ).

Date	Event	Description
		A repeat search 18th April 2007 identified one further eligible study.
31 May 2007	New citation required but conclusions have not changed	Substantive amendment

## CONTRIBUTIONS OF AUTHORS

### For the 2022 update of this review

MB and OR revised the Methods section, screened studies for inclusion, conducted the GRADE assessment and drafted a first version of the review.

ES and DO reviewed and commented on the manuscript.

### For the previous versions of this review

AW conducted a literature search and wrote the first draft of the protocol and the full review.

DO conducted a literature search in 2007 and updated the review and analysis.

ES conducted a literature search in 2012 and updated the review and analysis.

OR and MB conducted a literature search in 2018 and updated the review and analysis.

## DECLARATIONS OF INTEREST

OR has no interests to declare.

ES has no interests to declare.

DO has no interest to declare.

MB has no interest to declare but is an Associate Editor with the Cochrane Neonatal Group; he was not involved in the editorial process for this review.

## SOURCES OF SUPPORT

### Internal sources

- University of Bristol, UK
  - to ES
- Institute for Clinical Sciences, Lund University, Lund, Sweden
  - to OR and MB

### External sources

- Region Skåne, Skåne University Hospital, Lund University and Region Västra Götaland, Sweden
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- Vermont Oxford Network, USA

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2023 update, most of the Methods section has been updated according to the latest version of the Cochrane Handbook, including a description of Screen4Me and the section on 'Summary of findings and assessment of the certainty of the evidence'; the search strategy has been completed revised ([Appendix 2](#)).



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**INDEX TERMS****Medical Subject Headings (MeSH)**

Cerebral Hemorrhage [\*prevention & control]; Cerebral Ventricles; Excitatory Amino Acid Antagonists [\*therapeutic use]; Infant, Premature; Infant, Premature, Diseases [\*prevention & control]; Phenobarbital [\*therapeutic use]; Randomized Controlled Trials as Topic

**MeSH check words**

Humans; Infant, Newborn