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# Early erythropoiesis-stimulating agents in preterm or low birth weight infants (Review)

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# Early erythropoiesis-stimulating agents in preterm or low birth weight infants

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## A B S T R A C T

**Background**

Preterm infants have low plasma levels of erythropoietin (EPO), providing a rationale for the use of erythropoiesis-stimulating agents (ESAs) to prevent or treat anaemia and to provide neuro protection and protection against necrotising enterocolitis (NEC). Darbepoetin (Darbe) and EPO are currently available ESAs.

**Objectives**

To assess the effectiveness and safety of ESAs (erythropoietin (EPO) and/or Darbe) initiated early (before eight days after birth) compared with placebo or no intervention in reducing red blood cell (RBC) transfusions, adverse neurological outcomes, and feeding intolerance including necrotising enterocolitis (NEC) in preterm and/or low birth weight infants.

**Primary objective for studies that primarily investigate the effectiveness and safety of ESAs administered early in reducing red blood cell transfusions:**

To assess the effectiveness and safety of ESAs initiated early in reducing red blood cell transfusions in preterm infants.

**Secondary objectives:**

Review authors performed subgroup analyses of low (≤ 500 IU/kg/week) and high (> 500 IU/kg/week) doses of EPO and the amount of iron supplementation provided: none, low (≤ 5 mg/kg/d), and high (> 5 mg/kg/d).

**Primary objective for studies that primarily investigate the neuro protective effectiveness of ESAs:**

To assess the effectiveness and safety of ESAs initiated early in reducing adverse neurological outcomes in preterm infants.

**Primary objective for studies that primarily investigate the effectiveness of EPO or Darbe administered early in reducing feeding intolerance:**

To assess the effectiveness and safety of ESAs administered early in reducing feeding intolerance (and NEC) in preterm infants.

**Other secondary objectives:**

To compare the effectiveness of ESAs in reducing the incidence of adverse events and improving long-term neurodevelopmental outcomes.

## Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2), MEDLINE via PubMed (1966 to 10 March 2017), Embase (1980 to 10 March 2017), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 10 March 2017). We searched clinical trials databases, conference proceedings, and reference lists of retrieved articles for randomised and quasi-randomised controlled trials.

## Selection criteria

Randomised and quasi-randomised controlled trials of early initiation of EAS treatment versus placebo or no intervention in preterm or low birth weight infants.

## Data collection and analysis

We used the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* and the GRADE approach to assess the quality of evidence.

## Main results

This updated review includes 34 studies enrolling 3643 infants. All analyses compared ESAs versus a control consisting of placebo or no treatment.

Early ESAs reduced the risk of 'use of one or more [red blood cell] RBC transfusions' (typical risk ratio (RR) 0.79, 95% confidence interval (CI) 0.74 to 0.85; typical risk difference (RD) -0.14, 95% CI -0.18 to -0.10; $I^2$ = 69% for RR and 62% for RD (moderate heterogeneity); number needed to treat for an additional beneficial outcome (NNTB) 7, 95% CI 6 to 10; 19 studies, 1750 infants). The quality of the evidence was low.

Necrotising enterocolitis was significantly reduced in the ESA group compared with the placebo group (typical RR 0.69, 95% CI 0.52 to 0.91; typical RD -0.03, 95% CI -0.05 to -0.01; $I^2$ = 0% for RR and 22% for RD (low heterogeneity); NNTB 33, 95% CI 20 to 100; 15 studies, 2639 infants). The quality of the evidence was moderate.

Data show a reduction in 'Any neurodevelopmental impairment at 18 to 22 months' corrected age in the ESA group (typical RR 0.62, 95% CI 0.48 to 0.80; typical RD -0.08, 95% CI -0.12 to -0.04; NNTB 13, 95% CI 8 to 25. $I^2$ = 76% for RR (high heterogeneity) and 66% for RD (moderate); 4 studies, 1130 infants). The quality of the evidence was low.

Results reveal increased scores on the Bayley-II Mental Development Index (MDI) at 18 to 24 months in the ESA group (weighted mean difference (WMD) 8.22, 95% CI 6.52 to 9.92; $I^2$ = 97% (high heterogeneity); 3 studies, 981 children). The quality of the evidence was low.

The total volume of RBCs transfused per infant was reduced by 7 mL/kg. The number of RBC transfusions per infant was minimally reduced, but the number of donors to whom infants who were transfused were exposed was not significantly reduced. Data show no significant difference in risk of stage ≥ 3 retinopathy of prematurity (ROP) with early EPO (typical RR 1.24, 95% CI 0.81 to 1.90; typical RD 0.01, 95% CI -0.02 to 0.04; $I^2$ = 0% (no heterogeneity) for RR; $I^2$ = 34% (low heterogeneity) for RD; 8 studies, 1283 infants). Mortality was not affected, but results show significant reductions in the incidence of intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL).

## Authors' conclusions

Early administration of ESAs reduces the use of red blood cell (RBC) transfusions, the volume of RBCs transfused, and donor exposure after study entry. Small reductions are likely to be of limited clinical importance. Donor exposure probably is not avoided, given that all but one study included infants who had received RBC transfusions before trial entry. This update found no significant difference in the rate of ROP (stage ≥ 3) for studies that initiated EPO treatment at less than eight days of age, which has been a topic of concern in earlier versions of this review. Early EPO treatment significantly decreased rates of IVH, PVL, and NEC. Neurodevelopmental outcomes at 18 to 22 months and later varied in published studies. Ongoing research should evaluate current clinical practices that will limit donor exposure. Promising but conflicting results related to the neuro protective effect of early EPO require further study. Very different results from the two largest published trials and high heterogeneity in the analyses indicate that we should wait for the results of two ongoing large trials before drawing firm conclusions. Administration of EPO is not currently recommended because limited benefits have been identified to date. Use of darbepoetin requires further study.

## PLAIN LANGUAGE SUMMARY

**Early erythropoiesis-stimulating agents in preterm or low birth weight infants**

**Review questions:** Is early initiation of erythropoietin or darbepoetin (initiated before eight days after birth) effective and safe in reducing red blood cell transfusions among preterm and/or low birth weight infants? Does early initiation of erythropoietin or darbepoetin serve a neuro protective function? Do these agents protect against necrotising enterocolitis?

**Background:** In newborn infants, the number of red blood cells in the circulation decreases after birth. In infants born before term, this decrease is exaggerated by frequent withdrawal of blood, which may be necessary to monitor the infant's clinical condition. Therefore, infants born before term are likely to require transfusions of red blood cells. Low levels of erythropoietin (EPO), a substance in the blood that stimulates red blood cell production in preterm infants, provide a rationale for use of EPO to prevent or treat anaemia. EPO can be given 'early' (before the infant reaches eight days of age) to prevent or decrease the use of red blood cell transfusions. Increasing evidence suggests that EPO may protect against neurological damage and damage to the gut.

**Study characteristics:** We identified 34 studies that used this approach and enrolled a total of 3643 infants born before term. Studies of variable quality have been conducted in many different countries.

**Key results:** Early EPO treatment reduced the numbers of red blood cell transfusions and donor exposures following its use. However, the overall benefit of EPO may not be clinically important, as many of these infants had been exposed to red blood cell transfusions before trial entry. Early treatment with EPO does not alter the risk of death or retinopathy of prematurity and may decrease the risk of neurological damage and damage to the gut. It may also improve long-term outcomes.

**Quality of evidence:** According to GRADE, the quality of the main outcomes ranged from high to low.

**Conclusions:** On the basis of our findings, we do not currently recommend routine early use of erythropoietin in preterm infants. Ongoing studies might shed light on the possibility that erythropoietin may reduce risks of adverse neurodevelopmental outcomes and necrotising enterocolitis.

# SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

**Erythropoietin compared with placebo or no treatment for complications of preterm birth - primary outcomes**

**Patient or population:** preterm infants with low birth weight
**Settings:** NICU
**Intervention:** EPO
**Comparison:** placebo or no treatment

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or no treatment | EPO | | | | |
| Use of 1 or more red blood cell transfusions (low and high doses of EPO) | High-risk population | | RR: 0.79 (95% CI 0.74 to 0.85) | 1750 (19) | ⊕⊕◯◯ low | Bias: We had concerns about performance bias and detection bias in 10 of the studies. We downgraded the quality of the evidence by 1 step<br>Heterogeneity/ Consistency: I$^2$ for the typical RR was 69% and for the typical RD 62% (both moderate quality). We downgraded the quality of the evidence by 1 step<br>Directness of evidence: Studies were conducted in the target population |

| | | | | |
|---|---|---|---|---|
| | | | | Precision: Because of the large sample size (n = 1750), the point estimate was precise with a narrow 95% CI |
| | 694 per 1000 | 522 per 1000 (0 to 1000) | | Presence of publication bias: The funnel plot was symmetrical for all larger studies |
| Any neurodevelopmental impairment at 18 to 22 months' corrected age (in children examined) | High-risk population | RR: 0.62 (95% CI 0.48 to 0.80) | 1130 (4) | ⊕⊕○○ low | Bias: We had concerns about performance bias and detection bias in 1 of the studies, the largest (n = 613) (Song 2016). This study carried a weight of 48.7% in the analysis. We downgraded the quality of the evidence by 1 step |
| | | | | | Heterogeneity/Consistency: $I^2$ for the typical RR was 76% (high) and for the typical RD 66% (moderate). We downgraded the quality of the evidence by 1 step |
| | | | | | Directness of evidence: Studies were conducted in the target population |
| | | | | | Precision: Because of the large sample size (n |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | = 1130), the point estimate was precise with a narrow 95% CI Presence of publication bias: Although only 4 studies were included in the funnel plot, the funnel plot was symmetrical |
| | 210 per 1000 | 128 per 1000 (71 to 438) | | | |
| Bayley-II MDI at 18 to 24 months Bayley Scales of Infant Development, Second Edition, yields 2 single age-standardised composite scores (range 50 to 150): a Mental Development Index (MDI), which measures cognition through sensory perception, knowledge, memory, problem-solving and early language abilities; and a Psychomotor Development Index (PDI), which assesses fine and gross motor skills | Mean Bayley-II MDI ranged across control groups from 84.1 to 94.5 | Mean Bayley-II MDI at 18 to 24 months in the intervention groups was 8.22 higher (95% CI 6.52 to 9.92) | WMD: 8.22 (95% CI 6.52 to 9.92) | 981 (3) | ⊕⊕○○ low | Bias: We had concerns about performance bias and detection bias in one of the studies (Song 2016). We downgraded the quality of the evidence by 1 step. Song 2016 carried a weight in the analysis of 76.2%. Heterogeneity/Consistency: $I^2$ for the WMD was 97% (high). We downgraded the quality of the evidence by 1 step Directness of evidence: Studies were conducted in the target population Precision: Because of the large sample size (n = 981), the point estimate was precise with a narrow 95% CI |

| | | | | |
|---|---|---|---|---|
| | | | | Presence of publication bias: As only 3 studies were included, we did not prepare a funnel plot |
| Necrotising enterocolitis (stage not reported) | High-risk population | RR: 0.69 (95% CI 0.52 to 0.91) | 2639 (15) | ⊕⊕⊕◯ moderate | Bias: We had concerns about performance bias and detection bias in 6 of the studies, especially for Song 2016, the only study that showed a significant reduction in NEC. It carried a weight in the analysis of 47.8%. We downgraded the quality of the evidence by 1 step |
| | | | | | Heterogeneity/ Consistency: $I^2$ for the typical RR was 0% and for the typical RD 22% (both low) |
| | | | | | Directness of evidence: Studies were conducted in the target population |
| | | | | | Precision: Because of the large sample size (n = 2639), the point estimate was precise with a narrow 95% CI |
| | | | | | Presence of publication bias: The funnel plot was symmetrical |

| 84 per 1000 | 57 per 1000 |
| | (0 to 143) |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; EPO: erythropoietin; MDI: Mental Development Index; NICU: neonatal intensive care unit; NEC: necrotising enterocolitis; PDI: Psychomotor Development Index; RD: risk difference; RR: risk ratio; WMD: weighted mean difference

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

# BACKGROUND

## Description of the condition

After birth, the haemoglobin concentration of newborn infants normally falls to minimal levels of 11 g/dL in term infants by 8 to 12 weeks of age, and to 7.0 to 10.0 g/dL in preterm infants by 6 weeks of age (Stockman 1978). This process is called 'physiological anaemia of infancy' (Strauss 1986). In very low birth weight (VLBW) infants, hematocrit falls to approximately 24% in infants weighing 1.0 to 1.5 kg, and to 21% in infants weighing less than 1.0 kg, at birth (Stockman 1986). In extremely low birth weight (ELBW) infants, this decline in hematocrit to levels below 7.0 to 10.0 g/dL is called 'anaemia of prematurity' and is associated with clinical findings such as pallor, poor weight gain, decreased activity, tachypnoea, tachycardia, and feeding problems that prompt red blood cell (RBC) transfusions. Repeated blood draws, shortened RBC survival, rapid growth, and attenuated erythropoietin (EPO) response all contribute to anaemia of prematurity. To our knowledge, the diagnostic accuracy of different clinical signs and laboratory findings has not been studied (Cohen 1998). It is still unknown how low hematocrit levels can fall before clinical signs of anaemia of prematurity occur, and what minimal hematocrit level is acceptable in infants requiring supplemental oxygen (Ohls 2002). A rational guide for transfusion therapy for all anaemic neonates, whether ventilated or not, is not available (Cohen 1998). Nevertheless, 'top-up' transfusions are frequently used to treat low haemoglobin or low hematocrit levels. As many as 80% of VLBW infants and 95% of ELBW infants receive blood transfusions during hospitalisation (Widness 1996). A Cochrane review titled 'Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants' concludes, "The use of restrictive as compared to liberal haemoglobin thresholds in infants of very low birth weight results in modest reductions in exposure to transfusion and in haemoglobin levels. Restrictive practice does not appear to have a significant impact on death or major morbidities at first hospital discharge or at follow-up" (Whyte 2011).

Preterm birth and hypoxic Ischaemic encephalopathy (HIE) are conditions that frequently result in death or mental or physical impairment among survivors (Juul 2012). Several reviews examining the neuro protective and neurodegenerative effects of EPO/darbepoetin (Darbe) in the brain have been published, and evidence of its effectiveness is growing (Limperopoulos 2010; Kumral 2011; Juul 2012; Messier 2014; Rangarajan 2014; Patel 2015).

The intestinal barrier is maintained by tight junctions formed between adjacent intestinal epithelial cells. Disruption of tight junctions and loss of barrier function are associated with various gastrointestinal diseases, including neonatal necrotising enterocolitis (NEC) - the leading cause of death from gastrointestinal disease in preterm infants (Shiou 2011).

## Description of the intervention

The primary goal of EPO therapy is to reduce the number of transfusions. Most transfusions are given during the first three to four weeks of life. The larger or stable preterm infants, who respond best to EPO, receive few transfusions. ELBW infants, who are sick and have the greatest need for RBC transfusions shortly after birth, have not consistently responded to EPO. This suggests that EPO is a more effective erythropoietic stimulator in more mature neonates. ELBW neonates are more likely to need transfusions even if their erythropoiesis is stimulated by EPO (Kotto-Kome 2004). In addition, ELBW neonates have a smaller blood volume, and the relatively larger phlebotomy volumes that are required during hospital stay often necessitate 'early' transfusions. In contrast, 'late' transfusions more often are given because of anaemia of prematurity (Garcia 2002). Most preterm infants who require blood transfusions receive their first transfusion in the first two weeks of life (Zipursky 2000). Reducing the number of RBC transfusions reduces the risk of transmission of viral infections and may reduce costs. Frequent RBC transfusions may be associated with retinopathy of prematurity (ROP) (Hesse 1997) and bronchopulmonary dysplasia (BPD).

Preterm infants need iron for erythropoiesis. As neonatal blood volume expands with rapid growth, infants produce large amounts of haemoglobin. Several studies have observed a decrease in serum ferritin concentration during EPO treatment - an indication of iron deficiency (Finch 1982). Use of higher, more effective doses of EPO might be expected to increase iron demand and risk of iron deficiency. Iron supplementation during EPO treatment has been observed to reduce the risk of development of iron deficiency (Shannon 1995a). Iron doses are given to EPO-treated infants at dosages between 1 mg/kg/d and 10 mg/kg/d (Kotto-Kome 2004).

## How the intervention might work

EPO, with the addition of iron, effectively stimulates erythropoiesis. Plasma EPO levels in neonates are lower than those in older children and adults. Brown and colleagues reported that at between 2 and 30 days of life, the mean EPO concentration was 10 mIU/mL as compared with 15 mIU/mL in concurrently studied adults (Brown 1983). A low plasma EPO level is an important reason that nadir hematocrit values of preterm infants are lower than those of term infants (Dallman 1981; Stockman 1986). Low plasma EPO levels provide a rationale for use of EPO in prevention or treatment of anaemia of prematurity. Studies in newborn monkeys and sheep have demonstrated that neonates have a large volume of distribution and more rapid elimination of EPO, necessitating the use of higher doses than those required for adults. A systematic review of EPO administration in VLBW infants noted a wide range of doses used - from 90 to 1400 IU/kg/week (Kotto-Kome 2004). Side effects following EPO use in adults include hypertension, bone pain, rash, and, rarely, seizures.

Only transient neutropenia has been reported in neonates (Ohls 2000).

"Mechanisms of Epo neuro protection include receptor-mediated, cell-specific effects that occur both early and late in the healing process, and non-specific effects that also modulate the response to injury. EPO has anti-inflammatory, anti-excitotoxic, antioxidant and anti-apoptotic effects on neurons and oligodendrocytes, and promotes neurogenesis and angiogenesis, which are essential for injury repair and normal neurodevelopment. EPO effects are dose dependent, and multiple doses are more effective than single doses" (Juul 2012).

Human milk is protective against NEC, and the human milk factor EPO has been shown to protect endothelial cell-cell barriers (Shiou 2011). In a rat NEC model, oral administration of EPO statistically significantly lowered the incidence of NEC from 45% to 23% (Shiou 2011).

## Why it is important to do this review

The efficacy of EPO in anaemia of prematurity has been systematically reviewed (Vamvakas 2001; Garcia 2002; Kotto-Kome 2004). Vamvakas and coworkers concluded that variation in results of EPO studies is extreme, and stated that until this variation is better understood, it is too early to recommend EPO as standard treatment for anaemia of prematurity (Vamvakas 2001). Garcia 2002 concluded that administering EPO to VLBW neonates can result in a modest reduction in late erythrocyte transfusions, and that this effect is dependent on the dosage of EPO used. Kotto-Kome 2004 concluded that if EPO is begun during the first week of life, a moderate reduction can be expected in the proportion of VLBW neonates transfused. This reduction is less significant for early than for late transfusion.

EPO has been found to have important non-hematopoietic functions in the brain and other organs during development (Juul 2002). Administration of EPO could potentially have a neuro protective effect in preterm infants, especially among those with perinatal asphyxia (Dame 2001; Juul 2002). This aspect of EPO use in neonates with asphyxia will be systematically reviewed separately. In this update of the review, we include administration of EPO/Darbe early in life as neuro protective agents and for protection against NEC.

We therefore performed a series of Cochrane reviews on the use of EPO in preterm infants, including "Early erythropoietin (EPO) for preventing red blood cell transfusion in preterm or low birth weight infants" (starting in infants ≤ 7 days of age; < 8 days of age), versus placebo or no treatment (this review), "Late EPO (starting in infants > 7 days of age; ≥ 8 days of age) versus placebo/no treatment" (Aher 2006a) and "Early versus late EPO" (as per previous definitions) (Aher 2006b). These reviews were all updated in 2009 and 2012 (Aher 2012; Aher 2012a; Ohlsson 2012). We chose the cutoff of ≤ 7 days of age for early and > 7 days of age for late treatment with EPO, although somewhat arbitrary,

on the basis of previously published meta-analyses (Garcia 2002; Kotto-Kome 2004), to allow us to compare results of our reviews versus results of previously published reviews.

This review concerns early administration of EPO (starting in infants ≤ 7 days of age). The main rationale for such EPO therapy is to reduce exposure of neonates to red blood cell transfusion and its associated risks. Between 60% and 100% of preterm infants are transfused before three weeks of age (Shannon 1995a; Juul 1999; Zipursky 2000), and EPO administered during this period might decrease the need for RBC transfusions (Brown 1990; Kotto-Kome 2004). Several studies have concentrated on the effectiveness of EPO, beginning in the first week of life, in reducing or eliminating these 'early' transfusions. We conducted a systematic review to evaluate all available studies in which investigators started EPO treatment during the first week of life to assess its effect on erythrocyte transfusions. For this update, we include early use of EPO for neuro protection and for prevention of NEC.

A slightly modified long-acting version of EPO, darbepoetin alfa (Darbe), has been introduced (Egrie 2001). Darbepoetin was created by modifying five amino acids of the original EPO protein to generate two additional carbohydrate-binding sites, thereby significantly increasing circulating half-life and effectiveness. Compared with EPO, darbepoetin has an approximately three-fold longer serum half-life and greater in vivo potency, and can be administered less frequently to obtain the same biological response. A single subcutaneous dose of Darbe has been shown to accelerate erythropoiesis in preterm infants (Warwood 2005).

# O B J E C T I V E S

To assess the effectiveness and safety of erythropoiesis-stimulating agents (ESAs) (erythropoietin (EPO) and/or Darbe) initiated early (before eight days after birth) compared with placebo or no intervention in reducing red blood cell (RBC) transfusions, adverse neurological outcomes, and feeding intolerance and necrotising enterocolitis (NEC) in preterm and/or low birth weight infants.

## Primary objective for studies that primarily investigate the effectiveness and safety of EPO or Darbe administered early in reducing red blood cell transfusions

To assess the effectiveness and safety of EPO or Darbe initiated early (before eight days after birth) in reducing red blood cell transfusions in preterm and/or low birth weight infants.

## Secondary objectives

Review authors performed subgroup analyses of low (≤ 500 IU/kg/week) and high (> 500 IU/kg/week) doses of EPO and the

amount of iron supplementation provided: none, low ($\leq$ 5 mg/kg/d), and high (> 5 mg/kg/d).

## Primary objective for studies that primarily investigate the neuro protective effectiveness of EPO or Darbe

To assess the effectiveness and safety of EPO or Darbe initiated early (before eight days after birth) in reducing adverse neurological outcomes in preterm and/or low birth weight infants.

## Primary objective for studies that primarily investigate the effectiveness of EPO or Darbe administered early in reducing feeding intolerance

To assess the effectiveness and safety of EPO or Darbe administered early (before eight days after birth) in reducing feeding intolerance (and NEC) in preterm and/or low birth weight infants.

## Other secondary objectives

To compare the effectiveness of ESAs in reducing the incidence of adverse events and improving long-term neurodevelopmental outcomes.

# M E T H O D S

## Criteria for considering studies for this review

### Types of studies
Randomised and quasi-randomised controlled trials.

### Types of participants
Preterm (< 37 weeks' gestation) and/or low birth weight (< 2500 grams) neonates at less than eight days of age.

### Types of interventions
EPO initiated early (before eight days of age, using any dose, route, or duration of treatment) versus placebo or no intervention.
For the update in 2013, we included studies that used Darbe, a novel erythropoiesis-stimulating agent (ESA) (Egrie 2001; Warwood 2005). We kept analyses for EPO and Darbe separate, and we reported on studies that combined EPO and Darbe in combined analyses of ESAs.

For the update in 2017, we included studies that were designed to study the effectiveness of EPO/Darbe administered for neuro protection and for improved feeding intolerance. We included short-term outcomes in the same analyses, irrespective of the primary objective of the study.

## Types of outcome measures

### Primary outcomes

- Proportion of infants exposed to one or more red blood cell (RBC) transfusions
- Necrotising enterocolitis (NEC) (Bell's stage II or higher, or stage not reported)
- Any neurodevelopmental impairment at 18 to 22 months' corrected age (in children examined)
- Bayley-II Mental Development Index (MDI) at 18 to 24 months' corrected age

### Secondary outcomes

- Total volume (mL/kg) of blood transfused per infant
- Number of transfusions per infant
- Number of donors to whom the infant was exposed
- Mortality during initial hospital stay (all causes of mortality)
- Retinopathy of prematurity (ROP) (any stage and stage $\geq$ 3)
- Proven sepsis (clinical symptoms, signs of sepsis, and positive blood culture for bacteria or fungi)
- Intraventricular haemorrhage (IVH), all grades (we included in this group results from studies that did not define the grade) and grades III and IV
- Periventricular leukomalacia (PVL), cystic changes in periventricular areas (Note: For this updated review, we included persistent increased echogenicity in this outcome)
- Length of hospital stay (days)
- Bronchopulmonary dysplasia (BPD) (supplementary oxygen at 28 days of age or at 36 weeks' postmenstrual age (PMA) with or without compatible X-ray; we included an additional group in which age at BPD was not stated)
- Neutropenia
- Hypertension (not a prespecified outcome)
- Long-term outcomes assessed at any age at or beyond 12 months by a validated cognitive, motor, language, or behavioural, school, or a social interaction adaptation test (Note: We reported results of Bayley Scales of Infant Development (BSID) versions II and III separately)
- Cerebral palsy
- Post hoc analysis: any side effects reported by trial investigators (it is not possible to predict every side effect that can occur with a certain intervention; however, it is important that 'new side effects' are reported)

## Search methods for identification of studies

We used the standard search method of the Cochrane Neonatal Review Group.

### Electronic searches

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register).

For the 2017 update, we conducted a comprehensive search that included the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) in the Cochrane Library; MEDLINE via PubMed (1966 to 10 March 2017); Embase (1980 to 10 March 2017); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 10 March 2017), using the following search terms: (Erythropoietin OR rhuepo OR rhepo OR darbepoetin), plus database-specific limiters for RCTs and neonates (see Appendix 1 for full search strategies for each database). We did not apply language restrictions. The scope of this review has been broadened to include darbepoetin as an intervention and neuro protection as an outcome; therefore, we ran this search in all databases without date limits.

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the International Trials Registry and Platform of the World Health Organization ( www.whoint/ictrp/search/en/); and the ISRCTN Registry).

See Appendix 2 for previous search strategies.

### Searching other resources

We performed manual searches of bibliographies and personal files. We applied no language restrictions. We handsearched abstracts published from the Pediatric Academic Societies' Meetings and the European Society of Pediatric Research Meetings (published in *Pediatric Research*) from 1980 to April 2005.

For this update in 2017, in April 2017 we electronically searched the Pediatric Academic Societies' Annual Meetings from 2000 to 2017 (Abstracts2View™).

## Data collection and analysis

We used the standard review methods of the Cochrane Neonatal Review Group to assess the methodological quality of studies. We used the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1 (Higgins 2011).

### Selection of studies

The two review authors (AO, SMA) assessed all abstracts and published studies identified as potentially relevant by the literature search for inclusion in the review. For studies identified as abstracts, we contacted the primary authors, when possible, to obtain further information if the full publication was not available.

### Data extraction and management

For the original version of this review, both review authors extracted data separately and recorded data on a data abstraction form. We compared information and resolved differences by consensus. One review author (AO) entered data into RevMan (RevMan 2014); the other (SA) cross-checked the printout against his own data abstraction forms and corrected errors. One review author (AO) conducted the updates in 2009 and 2012. Both review authors (AO, SMA) performed the updates in 2013 and 2017.

### Assessment of risk of bias in included studies

Two review authors (AO, SMA) independently assessed risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- 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.

We resolved disagreements by discussion or by consultation with a third assessor. See Appendix 3 for a more detailed description of risk of bias for each domain.

### Measures of treatment effect

We performed statistical analyses using Review Manager software (RevMan 2014). We analysed categorical data using typical risk ratio (RR), typical risk difference (RD), and number needed to treat for an additional beneficial (NNTB) or harmful outcome (NNTH). We analysed continuous data using weighted mean difference (WMD) and reported the 95% confidence interval (CI) on all estimates.

### Unit of analysis issues

In all studies, the individual infant was the unit of analysis.

### Dealing with missing data

We approached several trial authors for additional data or for clarification of data.

### Assessment of heterogeneity

We performed heterogeneity tests including the $I^2$ statistic to assess the appropriateness of pooling data (Higgins 2003). We used the following criteria in describing the percentages of heterogeneity: < 25% no heterogeneity, 25% to 49% low heterogeneity, 50% to 74% moderate heterogeneity, and ≥ 75% high heterogeneity.

### Assessment of reporting biases

We prepared a funnel plot for the primary outcome in Comparison 1 - Erythropoietin versus placebo or no treatment, outcome 1.1. Use of one or more RBC transfusions (low and high doses of EPO).

### Data synthesis

We performed meta-analysis using RevMan 5.3, as supplied by Cochrane (RevMan 2014). For estimates of typical RR and RD, we used the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. If the RD was statistically significant, we calculated the NNTB or the NNTH. We performed all meta-analyses by using the fixed-effect model.

### Quality of evidence

We used the GRADE approach, as outlined in the *GRADE Handbook* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) primary outcomes in infants exposed to early EPO versus placebo or sham injection.

- Use of one or more red blood cell transfusions (low and high doses of EPO).
- NEC (stage not reported).
- Any neurodevelopmental impairment at 18 to 22 months' corrected age (in children examined).
- Bayley-II MDI at 18 to 24 months' corrected age.

We assessed the quality of evidence for the following short-term clinically relevant secondary outcomes.

- Mortality during initial hospital stay (all causes of mortality).
- Retinopathy of prematurity (ROP) (any stage and stage ≥ 3).
- Intraventricular haemorrhage (IVH), all grades (we included in this group results from studies that did not define the grade) and grades III and IV.
- Periventricular leukomalacia (PVL), cystic changes in periventricular areas. (Note: For this updated review, we included persistent increased echogenicity in this outcome.)
- Survivors to discharge from hospital without severe IVH, PVL, or ROP.
- Time to achieve full enteral feeding (days).

We assessed the quality of evidence for the following long-term clinically relevant secondary outcomes. (Note: We report results of BSID versions II and III separately.)

- Bayley-II MDI at 18 to 24 months (included as a primary outcome above).
- Cerebral palsy at 18 to 24 months' corrected age.

We assessed the quality of evidence for the following long-term clinically relevant secondary outcomes in infants exposed to early Darbe or EPO (ESA) versus placebo or sham injection.

- Bayley Scales of Infant Development - version III (BSID-III) composite cognitive scores at 18 to 22 months.
- Wechsler Preschool and Primary Scale of Intelligence - Third Edition (WPPSI-III) Full-Scale Intelligence Quotient (FSIQ) at 3.5 to 4 years of age.

Two review authors independently assessed the quality of evidence for each of the outcomes above. We considered evidence from randomised controlled trials (RCTs) as high quality but downgraded evidence quality by one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of evidence.
The GRADE approach results in an assessment of the quality of a body of evidence according to one of four grades.

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

### Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed for low (≤ 500 IU/kg/week) and high (> 500 IU/kg/week) doses of EPO and for low (≤ 5 mg/kg/d) and high (> 5 mg/kg/d) doses of supplemental iron by any route (co-intervention). Any amount of iron given intravenously (IV) was classified as high-dose iron.

### Sensitivity analysis

For the previous update, we conducted two post hoc analyses to try to explain between-study heterogeneity for the primary outcome 'use of one or more RBC transfusions'. In the first post hoc analysis, we divided studies into two groups: 'high-quality studies' and 'studies of uncertain quality'. In the second post hoc analysis, we analysed results for the four studies in which most of the neonatal intensive care units (NICUs) enrolling patients used satellite units of RBCs for transfusion. In a third post hoc analysis, we included results for ROP ≥ 3 for all available studies, regardless of the age of the infant at initiation of treatment with EPO. These additional analyses did not explain heterogeneity, and we deleted them from this update in 2017.

# R E S U L T S

## Description of studies

### Results of the search

We have presented results of our searches in the 'Study flow diagram' (Figure 1). Two studies reported on two separate populations in the same study; we treated these reports as separate studies for purposes of analysis (Kremenopoulos 1997A; Kremenopoulos 1997B; and Ohls 2001A; Ohls 2001B). We included seven new studies in the 2017 update (Kremenopoulos 1997A; Kremenopoulos 1997B; El-Ganzoury 2014; Fauchère 2015; Song 2016; Peltoniemi 2017; Qiao 2017). We identified six new long-term follow-up reports from previously published original studies. They are listed under the primary study reports (Fauchère 2015; Ohls 2013). Song 2016 included long-term follow-up in the primary report.

**Figure 1.   Study flow diagram: review update.**
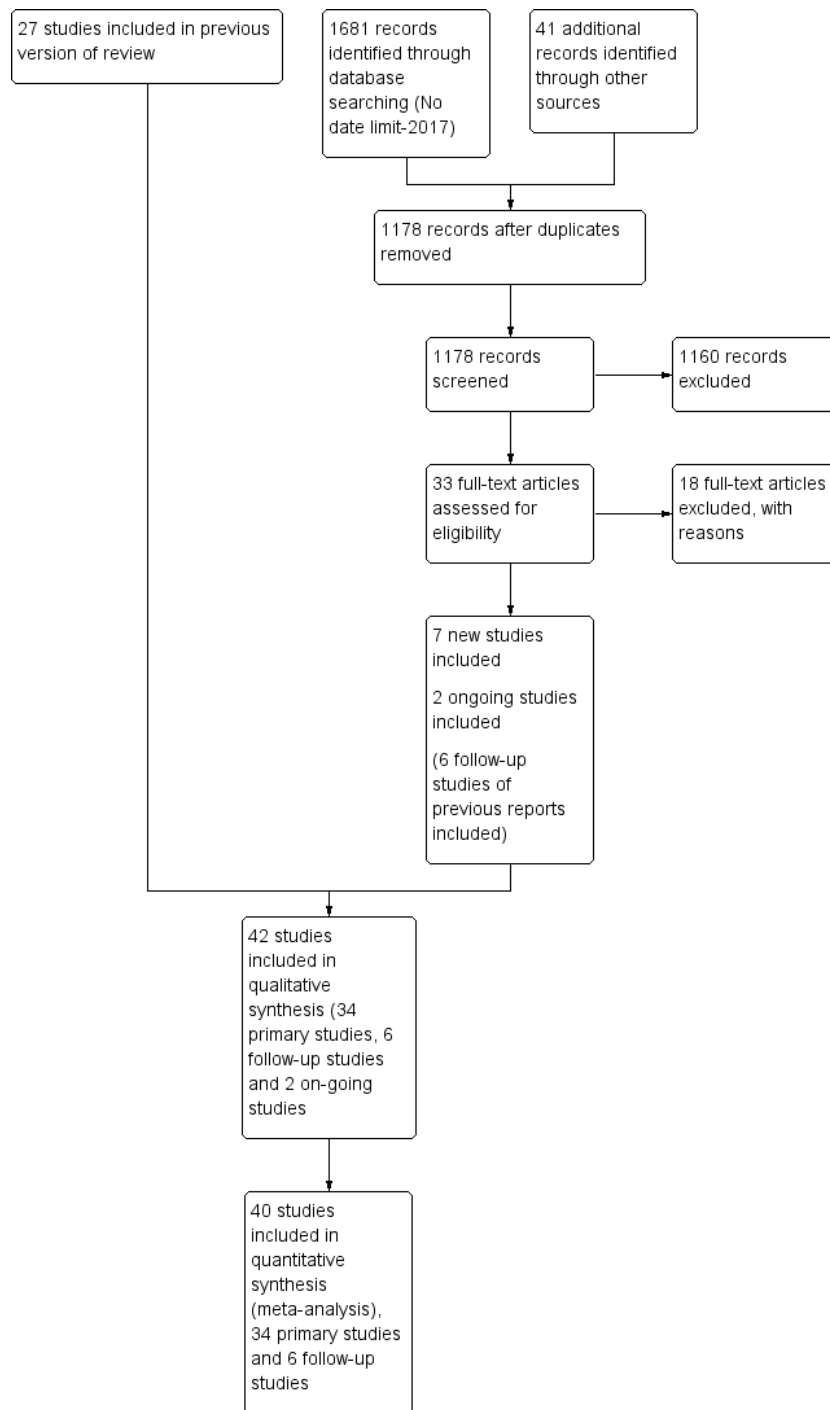
We included in this update 34 studies randomising 3643 infants, representing an increase of 1434 participants from the 2014 update. Studies were performed in 22 countries (Austria, Bangladesh, Belgium, Chile, China, Egypt, Finland, France, Germany, Greece, Iran, Italy, Mexico, Netherlands, New Zealand, Poland, Singapore, South Africa, Switzerland, Turkey, UK, and USA). Ohls 2013 randomised 102 infants to darebpoetin alfa (Darbe), EPO, or sham injection. This was the first study conducted to assess the effectiveness and safety of Darbe. We report separately on three comparisons in that study: Darbe versus no treatment, EPO versus no treatment, and EPO and Darbe (ESA) versus no treatment.

We excluded three additional studies from this 2017 update (Al Mofada 1994; Basiri 2015; López-Catzín 2015). Al Mofada 1994 reported the volume of RBC transfusions in mL/week averaged over the study period - not as total volume (mL/kg) of blood transfused per infant. In Basiri 2015, infants were > 6 days old at enrolment, and we will include this study in the update of the 'Late EPO' review. When contacted, one of the trial authors confirmed that López-Catzín 2015 was not an RCT.

All included studies fulfilled our inclusion criteria of gestational age < 37 weeks and/or birth weight < 2500 grams. Inclusion of infants in the studies was based on postmenstrual age (PMA) or birth weight or a combination of the two. The highest cutoff for birth weight was 1800 grams, and the highest cutoff for PMA was 35 weeks (Chang 1998). The lowest cutoff for birth weight was 401 grams (Ohls 2001A). Most studies used an upper cutoff for birth weight of 1500 grams and a PMA of 32 to 33 weeks.

EPO was administered subcutaneously (SC) or intravenously (IV), or IV then SC, when intravenous access was no longer available. Dosage ranged from 70 IU/kg/week in Obladen 1991 to 2100 IU/kg/week in Haiden 2005. The duration of EPO treatment ranged from two weeks in Ohls 1995 and Ohls 1997 to nine weeks in Maier 2002 or to discharge from hospital (several studies). Fauchère 2008 and Fauchère 2015 were designed to ascertain whether IV administration of high-dose EPO (3000 IU rhEPO/kg body weight) at three to six, 12 to 18, and 36 to 42 hours after birth would have a neuro protective effect. In those studies, no infant was treated at a later time with EPO.

Researchers used many different EPO preparations: EPREX 2000, Santa-Farma-Gurel, Istanbul (Arif 2005); Eprex, Cilag, Italy (Carnielli 1998); Cilag A.G., Zug, Switzerland (Kremenopoulos 1997A; Kremenopoulos 1997B; Soubasi 1993; Soubasi 1995; Soubasi 2000); Eprex 4000, Cilag de Mexico S.A. de C.V. (Lima-Rogel 1998); Eprex, Janssen-Cilag, Auckland, New Zealand (Meyer 2003); Eprex, Cilag comp (Khatami 2008); Eprex (Peltoniemi 2017); Recormon, Boehringer (Lauterbach 1995; Avent 2002); NeoRecormon, F. Hoffman-La Roche, Basel, Switzerland (Maier 2002); Epoetin beta, Boehringer-Mannheim, GmbH, Germany (Obladen 1991; Maier 1994); Kirin Brewery, Co., Ltd., Japan (Chang 1998); unnamed product (Carnielli 1992;

Ohls 1995; Ohls 1997; Yeo 2001; Ohls 2001A; Ohls 2001B; He 2008; Yasmeen 2012; Ohls 2013; Song 2016; Qiao 2017); Erypo, Janssen-Cilag Pharmaceuticals, Vienna, Austria (Meister 1997; Haiden 2005); Eritropoyetina del Laboratorio Andromaco, Penalolen, Chile (Salvado 2000); Epoietin beta, Roche, Basel, Switzerland (Fauchère 2008; Fauchère 2015); Epoetin, SEDICO Pharmaceuticals, 6th of October City, Egypt (El-Ganzoury 2014). One study stated previous donor exposure as an exclusion criterion (Arif 2005). Maier 1994 included 28 infants (23%) in the EPO group and 17 (14%) in the control group, who had received RBC transfusions before study entry. Maier 2002 reported that 24 (32%) of the infants in the early EPO group and 22 (31%) in the control group were exposed to donor blood before they entered the study. Ohls 2013 reported that 17% of infants were transfused before study entry. Authors of the remaining studies reported their specific exclusion criteria but did not list prior transfusion as an exclusion criterion. We assumed that infants who had received prior RBC transfusions were included.

We have provided details of the transfusion guidelines in the Additional tables (Table 1. Transfusion guidelines). As noted in the table, transfusion guidelines were based on various hematocrit (Hct) or haemoglobin (Hgb) levels. In addition, researchers used many other criteria, such as need for assisted ventilation, supplemental oxygen, age of the infant, weight gain, clinical condition, and physiological or biochemical signs thought to be associated with anaemia. For a few studies, we were unable to categorise different guidelines that could be used meaningfully for secondary analyses. We excluded from this update analyses based on transfusion information.

All but six studies reported that transfusion guidelines were in place (Chang 1998; Fauchère 2008; He 2008; El-Ganzoury 2014; Fauchère 2015; Qiao 2017). Lima-Rogel 1998 referred to the third Spanish edition of 'Care of the high-risk neonate' by Klaus and Fanaroff for the guidelines they adhered to (Klaus 1987). We were not able to locate that book, but in the third English edition of the book, we could not find transfusion guidelines for preterm infants (Klaus 1986).

In Carnielli 1998, all infants received dedicated units of RBCs. Ohls 1997 stated, "In some instances a new donor would be used each day for the newborn intensive care unit (University of Florida) and in other instances a unit would be dedicated to a single infant for the life of the unit (University of New Mexico and University of Utah)". These two studies did not report on our primary outcome of 'use of one or more RBC transfusions'. In Maier 2002, 12 of the 14 centres used satellite packs of the original red cell pack to reduce donor exposure. In Ohls 2001A and Ohls 2001B), study authors noted, "Whenever possible designated donor units that were capable of providing at least four transfusions were assigned to each infant (available in six of the eight participating centres)".

In a secondary (post hoc) analysis, we combined the results of these three studies. Ohls 2013 assigned each infant a matched, leuko-reduced, citrate-phosphate-dextrose adenine anticoagulant-preserved donor unit, made available in a sterile docking device capable of 50 mL aliquots of packed red blood cells (PRBCs) with four or more transfusions per unit, and a shelf life of 28 days. Three studies did not administer iron (Fauchère 2008; Fauchère 2015; Peltoniemi 2017). We are awaiting information from He 2008, as the abstract did not mention use of iron. In most studies, both EPO and control groups received iron, but often the dosage given to the control groups was lower. In Carnielli 1992 and Carnielli 1998, infants in the control groups did not receive iron.

### Included studies

For details, see the Characteristics of included studies table.

**Studies primarily designed to assess the effectiveness and safety of EPO or Darbe initiated early (before eight days after birth) in reducing red blood cell transfusions in preterm and/or low birth weight infants**

Arif 2005 was a single-centre study performed in Istanbul, Turkey.
- Objective: to determine whether EPO would prevent anaemia of prematurity and reduce the need for transfusion.
- Population: preterm infants < 33 weeks' gestational age (GA), birth weight < 1500 grams, seven days old, with no previous blood transfusion.
- Intervention: The EPO group received EPO 200 IU/kg SC from the seventh day of life and continued twice weekly (low dose) for six weeks. Placebo was not given to the control group. Both groups received iron (3 to 5 mg/kg/d orally) (low dose).
- Outcomes assessed: use of one or more RBC transfusions, mortality, NEC, ROP, BPD, neutropenia, side effects.

Avent 2002 was a two-centre study performed in South Africa.
- Objective: to evaluate the effectiveness of early treatment with EPO (both high and low doses) in comparison with conventional treatment with packed RBC transfusions for management of anaemia of prematurity in a country with limited resources.
- Population: preterm infants < seven days of age, in room air or requiring up to 30% oxygen at study entry, with birth weight between 900 and 1500 grams. Infants were stratified by weight ≤ 1250 grams and > 1250 grams.
- Intervention: One group received EPO 400 IU/kg SC three times a week (high dose), and a second group received EPO 250 IU/kg SC three times a week (high dose). All infants received a therapeutic dose of 6 mg/kg (high dose) elemental iron orally every day; this dosage was increased to 8 to 10 mg/kg (high-dose iron) if the hypochromic cells became 20% or more of the total cell population.

- Outcomes assessed: use of one or more RBC transfusions, total volume (mL/kg) of blood transfused per infant, number of blood transfusions per infant, mortality, sepsis.

Carnielli 1992 was a single-centre study performed in Italy.
- Objective: to determine whether early administration of a high dose of recombinant human erythropoietin (rHuEPO) and iron to premature infants would be well tolerated and would reduce the need for blood transfusions.
- Population: preterm infants with birth weight ≤ 1750 grams and GA ≤ 32 weeks, two days old.
- Intervention: The EPO group received EPO 400 IU, three times weekly (high dose) IV or SC, and iron 20 mg/kg once a week IV (high-dose iron) from second day of life until discharge. The control group did not receive either EPO or iron.
- Outcomes assessed: number and volume of transfusions, number of donor exposures, mortality during hospital stay, neutropenia, hospital stay in days.

Carnielli 1998 was a single-centre study performed in Italy.
- Objective: to determine whether iron supplementation would enhance erythropoiesis in preterm infants treated with EPO.
- Population: birth weight ≤ 1750 grams and gestational age ≤ 32 weeks, two days old.
- Intervention: The EPO + iron group received 400 IU/kg EPO three times a week (high dose) and 20 mg/kg/week of IV iron (high dose). The EPO + no iron group received EPO 400 IU/kg three times a week (high dose) without iron (no iron); infants in the control group received either no treatment or placebo.
- Outcomes assessed: number of donor exposures, BPD, IVH, sepsis, ROP, days on ventilator, days of oxygen, days in hospital, days to regain birth weight, weight gain from birth to eight weeks.

Chang 1998 was a single-centre study performed in China.
- Objective: to assess the efficacy and optimum dose of EPO for anaemia of prematurity.
- Population: infants with GA ≤ 35 weeks, birth weight ≤ 1800 grams, age one day, and no rhesus (Rh) or ABO (blood group) incompatibility.
- Intervention: Infants in EPO group 1 received EPO 150 IU/kg three times a week for six weeks (low dose). Infants in EPO group 2 received EPO 250 IU/kg three times a week for six weeks (high dose). Infants in the control group (group 3) received no EPO treatment. Infants in all three treatment groups received oral iron 20 mg/kg/d (high dose) from day seven after birth

- Outcomes assessed: use of one or more RBC transfusions, hypertension, side effects.

Haiden 2005 was a multi-centre study performed at NICUs of the Department of Pediatrics, University of Vienna, Austria.

- Objective: to evaluate effects of EPO therapy on platelet reactivity and thrombopoiesis in ELBW infants.
- Population: preterm infants with BW ≤ 800 grams and GA ≤ 32 weeks, < 8 days old.
- Intervention: The EPO group received 300 IU/kg/d of EPO IV (as long as IV access was available) or 700 IU/kg three times per week (2100 IU/kg/week, high dose), and iron dextran 1.5 mg/kg/d IV or iron polymerase complex 9 mg/kg/d orally (high dose).
- Outcomes assessed: use of one or more RBC transfusions, number of donors, mortality, NEC, PVL, IVH (grade I to II), IVH (grade III to IV), hospital stay, BPD (age not stated), ROP (stage I to II), ROP (stage III to IV).

Khatami 2008 was a single-centre study performed at Ghaem Medical Center in Tehran, Iran.
- Objective: to evaluate whether EPO therapy would decrease the need for RBC transfusions and prevent anaemia of prematurity.
- Population: preterm infants with BW > 1000 grams but < 1750 grams and GA > 28 weeks but < 34 weeks, and between 48 and 96 hours old at the time of study entry.
- Intervention: The EPO group received 500 IU/kg/d of EPO SC twice weekly (1000 IU/kg/week, high dose) and iron (ferrous sulphate) 3 mg/kg/d enterally (low dose).
- Outcomes assessed: number of RBC transfusions per participant, weight gain, hospital stay.

Kremenopoulos 1997A; & Kremenopoulos 1997B
- Objective: to determine the best timing of EPO administration in infants with anaemia of prematurity.
- Population: 50 neonates with BW ≤ 1500 grams, PMA ≤ 31 weeks. Infants who had received transfusion before enrolment were included.
- Intervention: The EPO group received rHuEPO (Cilag A.G., Zug, Switzerland) 3 × 250 U/kg/week SC (750 U/kg/week - high dose) (n = 24). Treatment was given for 6 weeks. The control group (n = 26) received no intervention. All infants received elemental iron 3 mg/kg/d. Treatment was initiated at three to seven days.
- Outcomes assessed: transfusions/patient, patients receiving transfusions.
- Retrospectively, infants were divided into those without complications (without or with minimal signs of respiratory distress and no signs of sepsis) and those with complications requiring mechanical ventilation (respiratory distress syndrome (RDS) and sepsis with positive blood culture) for longer than three days (were characterized as having complications). Outcomes were reported separately for infants without complications (we listed those outcomes under Kremenopoulos 1997A) and for infants with complications (we listed those outcomes under Kremenopoulos 1997B). An additional group of 35 infants (Group B) were enrolled at three to eight weeks and

will be included in the 'Late EPO' review. No information was provided regarding transfusion guidelines for either group.

Lauterbach 1995 was a single-centre study conducted in Poland.
- Objective: to evaluate the role of EPO for treatment of infants with anaemia of prematurity.
- Population: preterm infants with GA < 35 weeks and birth weight ≤ 1500 grams, seven days old.
- Interventions: Infants in EPO group 1 received EPO 100 IU/kg twice a week between days seven and 37 (low dose), and infants in EPO group 2 received 400 IU/kg twice weekly (high dose) during the same time period; the control group received no treatment or placebo. Both EPO groups and the control group received 10 mg/kg/week of iron IV (high dose).
- Outcomes assessed: total volume (mL/kg) of blood transfused between days seven and 37.

Lima-Rogel 1998 was a single-centre study performed in Mexico.
- Objective: to determine the efficacy of EPO in VLBW newborns at less than 72 hours of age.
- Population: infants with birth weight between 750 and 1500 grams, < 72 hours old.
- Intervention: Infants in the EPO group received EPO 150 IU/kg/d (high dose) during the first six weeks, and infants in the control group received placebo. Both groups received iron 4 mg/kg/d (low dose).
- Outcomes assessed: number of transfusions per group, sepsis, NEC, IVH, BPD.

Maier 1994 was a multi-centre trial conducted at 12 centres in six European countries (Belgium, France, Germany, Netherlands, Switzerland, UK).
- Objective: to determine whether EPO would prevent anaemia and reduce the need for transfusion in infants with VLBW.
- Population: infants with birth weight 750 to 1499 grams, and three days old.
- Intervention: The EPO group received 250 IU of EPO/kg IM three times per week (750 IU/kg/week, high dose). Treatment continued until day 40 to 42 for a total of 17 doses. Infants in the control group did not receive placebo, but adhesive tape was placed on both thighs and remained there until the next visit. Oral iron 2 mg/kg/d was started on day 14 for all infants (low dose).
- Outcomes assessed: use of one or more RBC transfusions, number of transfusions per infant, mortality, ROP, sepsis, NEC, IVH all grades, neutropenia, hypertension, side effects, weight gain, costs.

Maier 2002 was a multi-centre trial conducted at 14 centres in four European countries (Belgium, France, Germany, Switzerland).
- Objective: to investigate whether EPO reduced the need for transfusion in ELBW infants and to determine the optimal time for treatment.

• Population: infants with birth weight between 500 and 999 grams, three to five days old.
• Intervention: The EPO group received EPO 250 IU/kg, IV or SC, three times a week (high dose) starting on day three to five of life, for nine weeks. The control group received sham injections. Enteral iron 3 mg/kg was given to all infants from days three to five (low dose) and was increased at days 12 to 14 to 6 mg/kg/d (high dose) and to 9 mg/kg/d (high dose) at days 24 to 26 of life.
• Outcomes assessed: use of one or more RBC transfusions, number of donors the infant was exposed to, number of transfusions per infant, mortality during hospital stay, NEC, IVH, PVL, ROP, BPD, growth, days in oxygen, days in NICU, and days in hospital.

Meister 1997 was a single-centre trial conducted in Austria.
• Objective: to evaluate effects of EPO on circulating hematopoietic progenitor cells in anaemic premature infants.
• Population: preterm infants with birth weight of 750 to 1499 grams, at the age of 5 to 10 days.
• Intervention: The EPO group received EPO 300 IU/kg SC three times a week (high dose) for four weeks. The control group did not receive the drug and did not receive placebo. Oral iron administration was started with a dose of 6 mg/kg/d (high dose) and was increased after two weeks to 8 mg/kg/d (high dose). The control group received iron alone.
• Outcomes assessed: cumulative volume of blood transfused/kg.

Meyer 2003 was a single-centre trial conducted in New Zealand.
• Objective: to comprehensively identify preterm infants likely to require blood transfusion, and to investigate the effectiveness of EPO in this high-risk subgroup.
• Population: preterm infants with gestation < 33 weeks and birth weight < 1700 grams, at the age of 48 hours.
• Intervention: Infants in the treatment group received EPO 1200 IU/kg/week SC in three divided doses (high dose) until three weeks of age, then the dose was reduced to 600 IU/kg/week until 34 weeks' corrected GA, or for a minimum of three weeks. Infants in the control group received sham treatment. Both groups received elemental iron. Twenty-one infants in the control group received sham treatment to avoid subcutaneous injection. Iron at a dose of 6 mg/kg/d (high dose) was given to the EPO group once they had attained a postnatal age of two weeks and were receiving at least 50% energy intake orally. Those in the control group received 2 mg/kg/d iron (low dose) from the same age in a more dilute preparation, so that an equivalent volume was given.
• Outcomes assessed: use of one or more RBC transfusions, number of donors the infant was exposed to.

Obladen 1991 was a multi-centre study conducted at five centres in three European countries (Germany (FRG), Germany (GDR), UK).

• Objective: to investigate whether treatment with EPO reduced anaemia of prematurity and thus the need for transfusion by one-third in preterm infants.
• Population: preterm infants with GA 28 to 32 completed weeks, three days old.
• Intervention: The EPO group received EPO 30 IU/kg (low dose) every third day from the fourth to 25th day of life. The control group did not receive study drug and did not receive placebo. Iron treatment 2 mg/kg (low dose) orally was started on day 14 if there was no feeding intolerance.
• Outcomes assessed: use of one or more RBC transfusions, total volume of blood transfused per infant, mortality, chronic lung disease, IVH, NEC, BPD, hypertension.

Ohls 1995 was a single-centre trial conducted in the USA.
• Objective: to determine whether administering EPO to ill VLBW infants, beginning on the first or second day of life, would reduce blood transfusions and would be cost-effective.
• Population: infants at less than 48 hours of age with birth weight 750 and 1500 grams and GA > 27 weeks.
• Intervention: The EPO group received EPO 200 IU/kg/d (high dose) IV for 14 consecutive days. The control group received a similar volume of 0.9% saline solution in similar fashion as placebo. Infants in both groups received iron 2 mg/kg/d (low dose) orally when they were taking 70 mL/kg/d enterally, which was increased to 6 mg/kg/day (high dose) when infants were receiving more than 100 mL/kg per day of feeds.
• Outcomes assessed: use of one or more RBC transfusions, total volume of blood transfused per infant, number of transfusions per infant, neutropenia, thrombocytopenia, neutrophilia, NEC, IVH.

Ohls 1997 was a multi-centre trial conducted in the USA.
• Objective: to evaluate effects of EPO on the transfusion requirements of preterm infants weighing 750 grams or less.
• Population: infants with birth weight 750 grams or less at 72 hours of age or younger.
• Intervention: The EPO group received EPO 200 IU/kg/d (high dose) IV, for 14 consecutive days. The control group received placebo as an equivalent volume of diluent in similar fashion. All infants received 1 mg/kg/d iron dextran in total parenteral nutrition (TPN) solution during treatment period (high dose).
• Outcomes assessed: total volume of blood transfused per infant, number of transfusions per infant, mortality, sepsis, IVH, BPD, ROP.

Ohls 2001A was a multi-centre trial conducted in the USA.
• Objective: to evaluate effects of early EPO therapy on the transfusion requirements of preterm infants weighing less than 1000 grams.
• Population: infants with birth weight 401 to 1000 grams, GA < 32 weeks, between 24 and 96 hours of age at the time of study entry.

- Intervention: The EPO group received 400 IU/kg EPO three times weekly (high dose) IV or SC when IV access was not available. The placebo or control group received sham SC injections when IV access was not available. Treatment was continued until discharge, transfer, death, or 35 completed weeks' corrected gestational age. EPO-treated infants received a weekly IV infusion of 5 mg/kg iron dextran (high dose) until they had an enteral intake of 60 mL/kg/d. Placebo or control infants received 1 mg/kg iron dextran (high dose) once a week, administered in a similar manner. Once infants in both groups had an enteral intake of 60 mg/kg/d, they were given iron at a dose of 3 mg/kg/d (low dose). The dose was gradually increased to 6 mg/kg/d (high dose) depending on enteral intake.
- Outcomes assessed: use of one or more RBC transfusions, mean number of erythrocyte transfusions per infant, number of donors to whom the infant was exposed, total volume of blood transfused per infant, late-onset sepsis, mortality, chronic lung disease, ROP, severe IVH, NEC > Bell's stage II, BPD, neutropenia, hypertension. In a follow-up study of the 72 EPO-treated and 70 placebo control infants surviving to discharge, follow-up data at 18 to 22 months' corrected age were collected on 51 EPO -treated infants (71%) and 51 placebo controls (73%). Outcomes assessed were growth, psychomotor development, rehospitalization, and transfusions.

Ohls 2001B was a multi-centre trial conducted in the USA.
- Objective: to evaluate effects of early EPO therapy on the transfusion requirements of preterm infants weighing less than 1250 grams.
- Population: infants with birth weight between 1001 grams and 1250 grams, GA < 32 weeks, between 24 and 96 hours of age at the time of study entry.
- Intervention: The EPO group received 400 IU/kg EPO three times weekly (high dose) IV or SC when IV access was not available. The placebo control group received sham SC injections when IV access was not available. Treatment was continued until discharge, transfer, death, or 35 completed weeks' corrected GA. EPO-treated infants received a weekly IV infusion of 5 mg/kg iron dextran (high dose) until they had an enteral intake of 60 mL/kg/d. Placebo control infants received 1 mg/kg iron dextran (high dose) once a week, administered in a similar manner. Once infants in both groups had enteral intake of 60 mg/kg/d, they were given iron at a dose of 3 mg/kg/d (low dose). The dose was gradually increased to 6 mg/kg/d (high dose) depending on enteral intake.
- Outcomes assessed: use of one or more RBC transfusions, mean number of erythrocyte transfusions per infant, number of donors to whom the infant was exposed, total volume of blood transfused per infant, late-onset sepsis, mortality, chronic lung disease, ROP, severe IVH, NEC > Bell's stage II, BPD, neutropenia, hypertension.

Ohls 2013 was a multi-centre study conducted in the USA.

- Objective: to assess whether infants would respond to Darbe by reducing transfusion needs compared with no treatment, with less frequent dosing than erythropoietin.
- Population: preterm infants with birth weight of 500 to 1250 grams at < 48 hours of age.I
- Intervention: The Darbe group received 10 µg/kg one time per week SC. The EPO group received 400 U/kg three times per week SC. The control group received sham dosing. Injections continued through 35 weeks' PMA. All infants (regardless of treatment arm) received supplemental iron, folate (50 mg per day oral), and vitamin E (15 IU per day oral). Iron dextran 3 mg/kg once a week was added to parenteral nutrition while infants were receiving 60 mL/kg/d enteral feedings. Oral iron 3 mg/kg/d was started when feedings were ≥ 60 mL/kg/d, and was increased to 6 mg/kg/d when feedings reached 120 mL/kg/day (high dose).
- Outcomes assessed: use of one or more RBC transfusions, total volume (mL/kg) of blood transfused per infant, number of blood transfusions per infant, number of donors the infant was exposed to, mortality during initial hospital stay, ROP all stages and stages ≥ 3, late-onset sepsis, NEC stage > 2, IVH grade ≥ 3, PVL, length of hospital stay, BPD (oxygen dependency at 36 weeks' PMA), neutropenia, hypertension. In supplementary studies, long-term neurodevelopmental outcomes were reported until the age of 3.5 to 4 years in limited samples.

Peltoniemi 2017 was a single-centre study conducted in Finland.
- Objective: to determine whether administration of EPO without iron supplementation decreases iron load and morbidity.
- Population: 39 preterm infants (BW 700 to 1500 grams, PMA ≤ 30.0 weeks).
- Intervention: EPO 250 IU/kg daily during the first 6 days of life (high dose). The control group received a similar volume of isotonic saline solution in similar fashion. Iron was not administered in either of the two groups.
- Outcomes assessed: Primary outcome was the oxygen index (OI) calculated from the need for supplemental oxygen and mechanical ventilation during the first six days of life (OI = mean airway pressure × $FiO_2$ × $100/PaO_2$). Secondary outcomes included requirement for red blood cell transfusions during the first two weeks of life. The incidence of mild BPD was defined as the need for supplementary oxygen at 28 days. The incidence of moderate to severe BPD was defined as the need for supplementary oxygen at 28 days and at 36 postconceptional weeks. For the diagnosis of retinopathy of prematurity (ROP), the ophthalmoscopic examination was repeated until retinas were mature and the highest stage of retinopathy was reported. Severity of ROP was graded according to the international classification. IVH grades III and IV and periventricular leukomalacia (PVL). Number of days on assisted ventilation, use of supplemental oxygen, use of postnatal corticosteroid treatment for prevention of BPD and treatment of hypotension, length of hospital stay. Nosocomial sepsis was defined as a positive blood culture after day 3 of life. Diagnostic data on

hyperglycaemia, hypotension, or hypertension requiring therapy, patent ductus arteriosus (PDA) treated with prostaglandin inhibitor therapy or surgery, NEC, and intestinal perforations. Follow-up at 2 years' corrected age. Overall development was evaluated using the Griffiths Developmental Score. Cerebral palsy was defined as described by Rosenbaum 2002. The child's growth characteristics were reported.

● Notes: We received clarifying information from Dr. Peltoniemi regarding this study and its results.

Qiao 2017 was a single-centre study conducted in China.

● Objective: to evaluate effects of early parenteral iron supplementation combined with EPO for prevention of anaemia in preterm infants.

● Population: 96 preterm infants, PMA 28 to 34 weeks.

● Intervention: A control group receiving standard parenteral nutrition (group 1: n = 31), an iron-supplemented group (iron sucrose IS) (group 2: IS, n = 33), and an iron-supplemented combined erythropoietin group (group 3: IS + EPO, n = 32). The IS + EPO group received EPO 400 IU/kg twice a week for two weeks; total dose 800 IU/kg/week (1600 IU/kg in two weeks) (high dose). The IS group and the IS + EPO group received iron 200 µg/kg/d until 2 weeks after birth.

● Outcomes assessed: mortality, NEC, ROP.

● Notes: For outcome analyses, we included the IS group and the IS + EPO group.

Salvado 2000 was a single-centre trial conducted in Chile.

● Objective: to assess benefits of early EPO administration to reduce the requirement for blood transfusion in VLBW infants.

● Population: newborn infants with birth weight less than 1500 grams. Treatment started before 12 days of age (mean age EPO group 7.75 days, control group 7.96 days).

● Intervention: The EPO group received EPO 200 IU/kg SC three times a week (high dose) over four weeks. The control group received a similar volume of isotonic saline solution in similar fashion. All infants received oral iron at a dose of 3 mg/kg/d (low dose).

● Outcomes assessed: number of transfusions per infant, sepsis, IVH, days on ventilator.

Soubasi 1993 was a single-centre study conducted in Greece.

● Objective: to assess whether EPO treatment is safe and reduces the need for transfusion.

● Population: infants with GA ≤ 31 weeks, birth weight ≤ 1500 grams, age one to seven days, no history of haemolytic disease, who were clinically stable.

● Intervention: The EPO group received 150 IU/kg/dose of EPO twice a week (low dose) during four weeks. The control group received no placebo. From the 15th day of life, iron was started at 3 mg/kg/d (low dose) for all infants.

● Outcomes assessed: use of one or more RBC transfusions, number of transfusions per infant, mortality, sepsis, neutropenia, weight gain, hospital stay.

Soubasi 1995 was a single-centre study conducted in Greece.

● Objective: to follow up with VLBW infants after EPO treatment.

● Population: infants with GA ≤ 31 weeks, birth weight ≤ 1500 grams, age one to seven days, no history of haemolytic disease, who were clinically stable.

● Intervention: The EPO 300 group received EPO 150 IU/kg twice weekly (low dose), and the EPO 750 group received EPO 250 IU/kg three times a week (high dose). The control group did not receive any study drug and did not receive placebo. All infants received oral elemental iron 3 mg/kg/d from day 15 of life (low dose).

● Outcomes assessed: use of one or more RBC transfusions, number of blood transfusions per infant, mortality, follow-up to one year of age, weight gain, hospital stay.

Soubasi 2000 was a single-centre trial conducted in Greece.

● Objective: to investigate effects of EPO on oxygen affinity and adequate oxygen delivery to the tissues of stable preterm infants.

● Population: infants with GA ≤ 31 weeks and birth weight ≤ 1300 grams with clinical stability at the time of entry. Although trial authors did not state age at entry, we assumed from a graph (Figure 6) in the publication that age was seven days.

● Intervention: The EPO group received 200 IU/kg every alternate day (high dose) SC. The control group did not receive EPO and did not receive placebo. Infants received oral iron at a dose of 12 mg/kg/d (high dose) in the EPO group and 4 mg/kg/d (low dose) in the control group.

● Outcomes assessed: use of one or more RBC transfusions, number of transfusions per infant.

Yasmeen 2012 was a single-centre study conducted in Dhaka, Bangladesh.

● Objective: to investigate effects of short-term administration of EPO with iron and folic acid in prevention of anaemia of prematurity and reduction in the number of transfusions in preterm VLBW infants.

● Population: infants with GA < 35 weeks, birth weight < 1500 grams, and age < 7 days.

● Intervention: The EPO group received 200 IU/kg three times/week (high dose) SC. The control group did not receive EPO and did not receive placebo. All infants received oral iron at a dose of 6 mg/kg/d (high dose) and 0.5 mg of folic acid every alternate day up to 12 weeks of life. Administration of both iron and folic acid started from day 14 of life, or as soon as enteral feeding was initiated after day 14.

● Outcome assessed: mortality.

Yeo 2001 was a single-centre study conducted in Singapore.

● Objective: to study the efficacy, safety, and cost-effectiveness of EPO in reducing transfusion needs among VLBW infants.

- Population: VLBW infants with GA ≤ 33 weeks, age five days.
- Intervention: The EPO group received EPO 250 IU/kg/dose SC three times a week (high dose) from day 5 to day 40. Infants in the control group did not receive placebo. Infants in both groups received elemental iron 3 mg/kg/d (low dose) orally from day 10, increased to 6 mg/kg/d (high dose) when full feeds were well tolerated.
- Outcomes assessed: use of one or more RBC transfusions, mean number of erythrocyte transfusions per infant, total volume of blood transfused per infant, mortality, ROP, sepsis, NEC, BPD, hypertension, BPD, costs.

**Studies designed to primarily assess the effectiveness of EPO administered early as a neuro protective agent**

He 2008 was a single-centre study performed in the Department of Neonatology, Zhangzhou Municipal Hospital, Zhangzhou, Fujian, China.
- Objective: to evaluate effects of early EPO therapy on neuro behavioural development in preterm infants.
- Population: preterm infants, seven days old.
- Intervention: The EPO group received 250 IU/kg/d three times weekly IV for four weeks (750 IU/kg/week, high dose). The use of iron was not stated.
- Outcomes assessed: Neonatal Behavioral Neurological Assessment at 40 weeks PMA, Gesell Developmental Schedule at 6 and 12 months after birth.

Fauchère 2008 was a single-centre study performed in Switzerland.
- Objective: to investigate whether high-dose EPO administered to very preterm infants shortly after birth and subsequently during the first two days was safe in terms of short-term outcomes and may reduce perinatal brain injury (IVH and PVL).
- Population: preterm infants with GA 24 0/7 to 31 6/7 weeks.
- Intervention: Infants in EPO group received 3000 IU rhEpo/kg IV 3 to 6, 12 to 18, and 36 to 42 hours after birth. The placebo group received an equal volume of normal saline. Iron was not administered.
- Outcomes assessed: mortality, IVH (all grades and grades III to IV), persistent periventricular echodensity (included in the analysis for periventricular leukomalacia (PVL)), ROP (at all stages and at stages 3 to 4), sepsis, NEC (stage not reported), BPD (36 weeks' PMA), side effects.
- Notes: All infants who were born at 26 weeks' PMA or later were reported on in Fauchère 2015. From the 2008 study, we reported only on infants who were < 26 weeks' PMA. We received additional information on these eight infants from Dr. Fauchère.

Fauchère 2015 was a multi-centre study performed in Switzerland.

- Objective: to investigate the safety and short-term outcome of high-dose EPO given shortly after birth and subsequently over the first two days for neuro protection to very preterm infants.
- Population: preterm infants with PMA of 26 0/7 to 31 6/7 weeks.
- Intervention: infants in EPO group received 3000 IU rhEpo/kg IV 3 to 6, 12 to 18, and 36 to 42 hours after birth. The placebo group received an equal volume of normal saline. Iron was not administered.
- Outcomes assessed: mortality, IVH (all grades and grades III to IV), persistent periventricular echodensity (included in the analysis for periventricular leukomalacia (PVL)), ROP (at all stages and at stage 3 to 4), sepsis, NEC (stage not reported), BPD (36 weeks' PMA), side effects. Brain MRI abnormalities at term-equivalent age and long-term outcomes at two years of age reported separately.

Song 2016 was a single-centre study conducted in Zhengzhou, China.
- Objective: to evaluate the efficacy and safety of repeated low-dose EPO for improvement of neurological outcomes in very preterm infants.
- Population: preterm infants with GA ≤ 32 weeks, enrolled within 72 hours after birth.
- Intervention: The EPO group received rhEPO at 500 U/kg IV every other day for 2 weeks. Cumulative dose of 3500 U/kg. First dose within 72 hours after birth. Placebo group received an equivalent volume of normal saline.
- Outcomes assessed: Primary outcome was death or moderate to severe neurological disability assessed at 18 months' corrected age. Moderate or severe disabilities were defined as survival with at least 1 of the following complications: cerebral palsy, MDI < 70, deafness (defined as a hearing disability that required amplification, or blindness defined as visual corrected acuity of, 20/200). Secondary outcomes at 18 months' corrected age were individual components of the composite outcome. Short-term outcomes included intraventricular haemorrhage grade III to IV, PVL, ROP (grade not stated), NEC, BPD (at 36 weeks' PMA), sepsis.

**Studies designed to primarily assess the effectiveness of EPO administered early in improving feeding tolerance**

El-Ganzoury 2014 was a single-centre study conducted in Cairo, Egypt.
- Objective: to evaluate the efficacy and safety of enteral recombinant granulocyte colony-stimulating factor (rh-CSF) and recombinant human erythropoietin (rhEPO) in preventing feeding intolerance.

- Population: preterm infants with PMA ≤ 33 weeks.
- Intervention: Neonates were assigned to four groups: 20 received rhG-CSF, 20 received rhEPO, 20 received both, and 30 received distilled water (placebo control).

• Outcomes assessed: time to achieve full enteral feeding (150 mL/kg/d), mortality, NEC, duration of hospital stay.

• Notes: We included in analyses the 20 infants who received EPO and the 30 infants who received placebo.

## Excluded studies

We excluded 22 studies (see Characteristics of excluded studies table).

## Risk of bias in included studies

The risk of bias graph (Figure 2) shows our evaluations of individual studies, which are summarised in the 'Risk of bias' summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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

## Allocation

Information regarding whether the allocation was concealed was often missing. Twelve studies reported proper random sequence generation (Soubasi 1993; Soubasi 1995; Meister 1997; Soubasi 2000; Meyer 2003; Arif 2005; Fauchère 2008; Ohls 2013; El-Ganzoury 2014; Fauchère 2015; Song 2016; Peltoniemi 2017). We interpreted allocation to study groups as concealed in 17 studies (Obladen 1991; Soubasi 1993; Maier 1994; Ohls 1997; Ohls 2001A; Ohls 2001B; Maier 2002; Meyer 2003; Haiden 2005; Fauchère 2008; Khatami 2008; Ohls 2013; El-Ganzoury 2014; Fauchère 2015; Song 2016; Peltoniemi 2017; Qiao 2017). Fourteen studies used placebo or sham injections (Soubasi 1993; Maier 1994; Ohls 1995; Ohls 1997; Lima-Rogel 1998; Ohls 2001A; Ohls 2001B; Maier 2002; Meyer 2003; Fauchère 2008; Ohls 2013; Fauchère 2015; Peltoniemi 2017; Qiao 2017).

## Blinding

Fourteen studies blinded personnel (Soubasi 1993; Maier 1994; Ohls 1995; Ohls 1997; Lima-Rogel 1998; Ohls 2001A; Ohls 2001B; Maier 2002; Meyer 2003; Fauchère 2008; Ohls 2013; Fauchère 2015; Peltoniemi 2017; Qiao 2017). We interpreted that blinding of outcome assessment was appropriate in 14 studies (Soubasi 1993; Maier 1994; Ohls 1995; Ohls 1997; Lima-Rogel 1998; Ohls 2001A; Ohls 2001B; Maier 2002; Meyer 2003; Fauchère 2008; Ohls 2013; Fauchère 2015; Peltoniemi 2017; Qiao 2017).

## Incomplete outcome data

Risk of attrition bias was clear in two studies (Maier 1994; Yasmeen 2012). Six studies reported long-term (18 to 22/24 months' corrected age) outcomes (Ohls 2001A; Ohls 2013; Fauchère 2008; Fauchère 2015; Peltoniemi 2017; Song 2016). In Ohls 2001A, follow-up rates were low; among 72 EPO-treated and 70 placebo control infants surviving to discharge, follow-up data at 18 to 22 months' corrected age were collected on 51 of 72 EPO-treated infants (71%) and 51 of 70 placebo/controls (73%). Ohls 2013 enrolled 102 infants and at the end of hospitalisation evaluated 94 infants. These investigators evaluated 80 children at follow-up at corrected age of 18 to 22 months (Darbe n = 27 (84%), EPO n = 29 (91%), placebo/sham injection n = 24 (80%)). A report of preschool assessment (at age 3.5 to 4 years) was published in 2016 (Ohls 2016, follow up to Ohls 2013). This study assessed 53 children (Darbe n = 15 (47%), EPO n = 24 (75%), placebo n =14 (47%)). In 2017, Lowe 2017 (follow up to Ohls 2013) reported on behavioural measures in 49 children (Darbe or EPO n = 35 (55%), placebo n = 14 (47%)). The two groups given Darbe and EPO were combined and were referred to as the erythropoiesis-stimulating agents (ESA) group. Percentages are based on the number

of infants evaluated at the end of hospitalisation. Follow-up rates beyond 18 to 22 months were low. For Fauchère 2008, we obtained information from the first author on outcomes of eight infants born at < 26 weeks' PMA; five deaths and long-term follow-up were reported on three surviving infants. In Fauchère 2015, long-term outcomes were reported for 365 infants (81%): 191 infants (83%) assigned to the EPO group and 174 infants (79%) assigned to the placebo group. In Peltoniemi 2017, of 20 surviving children at two years of age, 19 were enrolled and 10 (50%) were evaluated by Griffiths Developmental Scale. Of 16 surviving placebo group children at 2 years of age, all were enrolled and 9 (56%) were evaluated by Griffiths Developmental Scale. Follow-up rates for Griffiths Developmental Scale were low. In the large study Song 2016, all 743 randomised infants were accounted for in short-term outcomes. For outcomes at 18 months, 309 children in the EPO group and 304 in the placebo group were assessed. In the EPO group, 36 children had been lost to follow-up, as were 39 children in the control group. Twenty-one infants in the EPO group had died, as had 34 children in the control group. Follow-up rate at 18 months was 90% in the EPO group and 87% in the control group.

## Selective reporting

For most included studies, the study protocol was not available to us. Therefore we could not ascertain whether deviations from the protocol occurred. We were able to locate study protocols for Ohls 2013; El-Ganzoury 2014; Fauchère 2015; Song 2016; and Peltoniemi 2017. Ohls 2013 was registered as NCT00334737 in June 2006 and showed no major deviations from the protocol, except that primary outcomes included MDI at 18 to 22 months and Psychomotor Development Index (PDI) as a secondary outcome. MDI and PDI are not reported in the primary publication. Fauchère 2008 was registered as NCT00413946 in December 2006 after the last patient had been enrolled in November 2006. Registration applies to the larger study published in 2015 (Fauchère 2015). The protocol for the early part of the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred. We noted no deviations from the protocol in Fauchère 2015. Song 2016 was registered as NCT02036073 in December 2013, after recruitment had been completed. This study started to recruit patients in January 2009. Therefore, we were unable to detect any deviations from a study protocol established before the start of the study. In the protocol, the primary outcome measured was incidence of MDI < 70 at corrected age of 18 months, and secondary outcome measures were incidence of ROP at corrected age 42 weeks. In the full report, primary outcomes are listed as death, disability, or death + disability at 18 months' corrected age. ROP is listed as a neonatal

complication. The protocol for Peltoniemi 2017 was written in Finnish. We contacted Dr. Peltoniemi, who contacted Dr. Antilla, a co-author, who assured us that no deviations from the protocol occurred.

All studies accounted for all enrolled infants.

### Other potential sources of bias

We did not identify any other sources of potential bias. Sample sizes were generally small, ranging from 19 infants enrolled in Lauterbach 1995 to 743 in Song 2016. Three original studies (Fauchère 2015; Song 2016; Peltoniemi 2017) reported study details as required by the CONSORT statement (Begg 1996).

### Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**; **Summary of findings 3**; **Summary of findings 4**

### Studies designed to primarily investigate the effectiveness and safety of EPO or Darbe administered early in reducing red blood cell transfusions or providing neuro protection or protection against necrotising enterocolitis

### Erythropoietin versus placebo or no treatment (Comparison 1)

All analyses reported for Comparison 1 compared EPO versus placebo or no intervention (sham injection).

We indicated the primary outcomes and noted that those not indicated as such were secondary outcomes. For outcomes included in 'Summary of findings' tables, we included our assessments of evidence quality according to GRADE.

### Use of one or more red blood cell transfusions (low (< 500 IU/kg/week) and high (> 500 IU/kg/week) doses of EPO) - Primary outcome (Outcome 1.1)

A total of 19 studies enrolling 1750 infants reported on the use of one or more RBC transfusions. Early EPO significantly reduced the proportion of infants who received one or more RBC transfusions (typical risk ratio (RR) 0.79, 95% confidence interval (CI) 0.74 to 0.85; typical risk difference (RD) -0.14, 95% CI -0.18 to -0.10; number needed to treat for an additional beneficial outcome (NNTB) 7, 95% CI 6 to 10). Heterogeneity for this outcome was moderate (RR: $I^2$ = 69%; RD: $I^2$ = 62%) (Analysis 1.1; Figure 4). The funnel plot was asymmetrical with relative absence of smaller studies not having a protective effect (Figure 5). The quality of the evidence was low.

**Figure 4. Forest plot of comparison: 1 Erythropoietin versus placebo or no treatment, outcome: 1.1 Use of 1 or more red blood cell transfusions (low and high doses of EPO).**
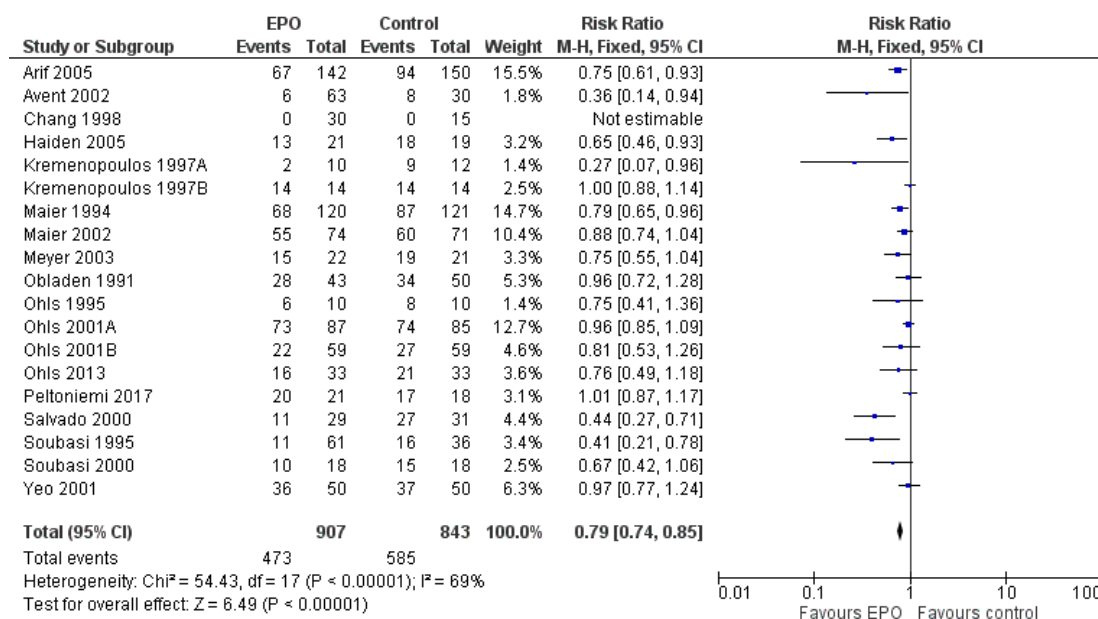
**Figure 5. Funnel plot of comparison: 1 Erythropoietin versus placebo or no treatment, outcome: 1.1 Use of 1 or more red blood cell transfusions (low and high doses of EPO).**
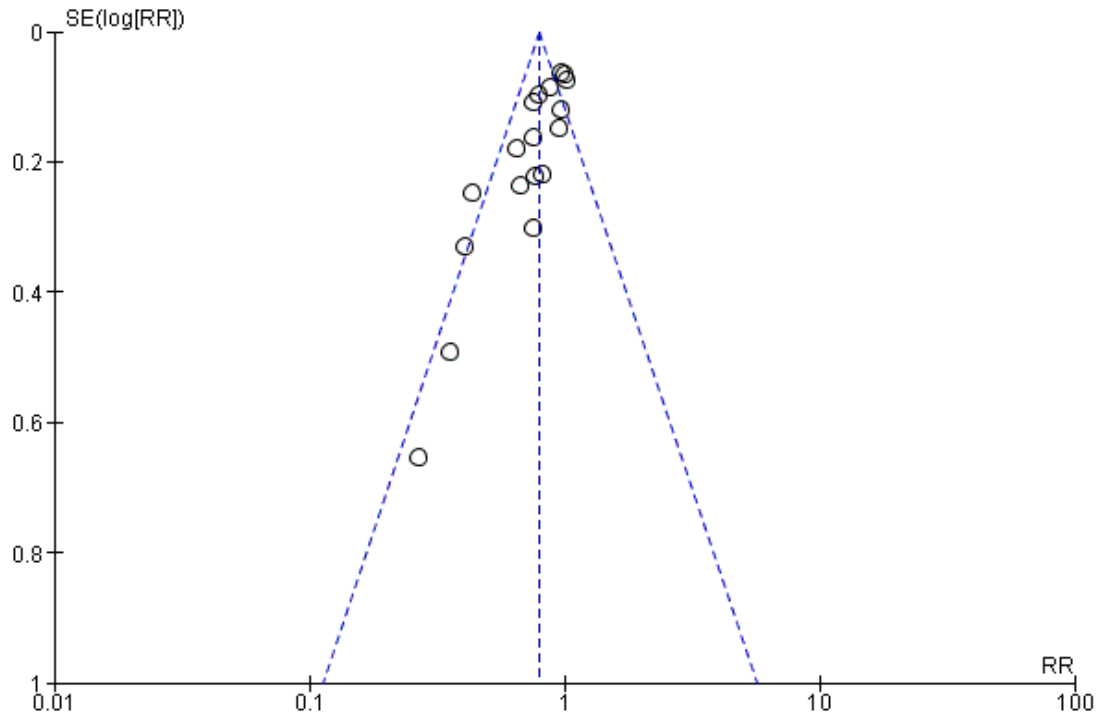


We conducted further analyses by including studies that used a high dose of EPO (> 500 U/kg/week) or a low dose of EPO ($\leq$ 500 U/kg/week).

**Use of one or more red blood cell transfusions (high dose of EPO (> 500 U/kg/week)) (Outcome 1.2)**

A total of 17 studies enrolling 1317 patients testing a high dose of EPO reported on this outcome. A high dose of EPO significantly reduced the proportion of infants who received one or more RBC transfusions (typical RR 0.79, 95% CI 0.74 to 0.86; typical RD -0.15, 95% CI -0.19 to -0.10; NNTB 7, 95% CI 5 to 10). Heterogeneity for this outcome was moderate (RR: $I^2$ = 71%; RD: $I^2$ = 64%) (Analysis 1.2).

We conducted a subgroup analysis for a high dose of EPO in combination with a high dose of iron (Outcome Table 1.2.1). A total of 11 studies enrolling 863 infants reported on this outcome. A high dose of EPO given with a high dose of iron significantly reduced the proportion of infants who received one or more RBC transfusions (typical RR 0.84, 95% CI 0.77 to 0.92; typical RD -0.11, 95% CI -0.16 to -0.05; NNTB 9, 95% CI 6 to 20). We noted low or no heterogeneity for this outcome (RR: $I^2$ = 32%; RD: $I^2$ = 22%).

A total of six studies enrolling 454 infants testing a high dose

of EPO and a low dose of iron (Outcome Table 1.2.2) reported on this outcome. A high dose of EPO and a low dose of iron significantly reduced the proportion of infants who received one or more RBC transfusions (typical RR 0.71, 95% CI 0.62 to 0.82; typical RD -0.21, 95% CI -0.29 to -0.14; NNTB 5, 95% CI 3 to 7). Heterogeneity for this outcome was high for RR ($I^2$ = 91%) and RD ($I^2$ = 84%).

**Use of one or more red blood cell transfusions (low dose of EPO (< 500 U/kg/week)) (Outcome 1.3)**

A total of four studies including 484 participants testing a low dose of EPO reported on this outcome. A low dose of EPO resulted in a significant reduction in the proportion of infants who received one or more RBC transfusions (typical RR 0.77, 95% CI 0.65 to 0.91; typical RD -0.13, 95% CI -0.22 to -0.05; NNTB 8, 95% CI 5 to 20). Heterogeneity was low and moderate for this outcome (RR: $I^2$ = 47%; RD: $I^2$ = 55%) (Analysis 1.3).

We conducted a subgroup analysis for a low dose of EPO in combination with a high dose of iron (Outcome Table 1.3.1). Two studies enrolling 322 infants reported on this outcome. One of these studies reported no outcomes for either group. The signifi-

cant RR was 0.75 (95% CI 0.61 to 0.93); the test for heterogeneity was not applicable. The significant typical RD was -0.14 (95% CI -0.24 to -0.04). Heterogeneity was not applicable for RR and was high for RD ($I^2$ = 81%). The NNTB was 7 (95% CI 4 to 25).

Two studies enrolling 162 infants tested the effectiveness of a low dose of EPO in combination with a low dose of iron (Outcome Table 1.3.2) and reported on this outcome. A low dose of EPO combined with a low dose of iron did not significantly reduce the proportion of infants who received one or more RBC transfusions (typical RR 0.80, 95% CI 0.60 to 1.07; typical RD -0.12, 95% CI -0.26 to 0.03). Heterogeneity was moderate ($I^2$ = 70%) for RR and low for RD ($I^2$ = 48%).

Only one study included a group that received no iron (Carnielli 1998); however, this study did not report on the primary outcome of interest: 'use of one or more RBC transfusions'. In Fauchère 2008 and Fauchère 2015, no group received iron. These studies did not report on the primary outcome of interest: 'use of one or more RBC transfusions'.

### Total volume (mL/kg) of red blood cells transfused per infant (Outcome 1.4)

Seven studies enrolling 581 infants reported on the total volume of RBCs transfused per infant. The significant weighted difference (WMD) was a reduction of 6.8 mL/kg of blood transfused per infant (95% CI -11.5 to - 2.1). Heterogeneity was moderate for this outcome ($I^2$ = 63%) (Analysis 1.4).

Carnielli 1998 reported on the mean volume of blood (mL/kg) transfused for the three groups: EPO + iron 16.7 (95% CI 4.9 to 28.6); EPO only 20.1 (95% CI 6.2 to 34.2), and control 44.4 (95% CI 29.0 to 59.7) (EPO vs control P = 0.028; EPO + iron vs control P = 0.009) (P values according to trial authors).

Lauterbach 1995 reported that infants treated with 800 IU of EPO/kg/week required a statistically significantly lower volume (mL/kg) of packed erythrocytes in comparison with untreated infants both between days 7 and 37 of life (18.6 mL vs 46.8 mL) and between day seven of life and the day of discharge (35.8 mL vs 94.2 mL) (P < 0.04 for both comparisons).

Maier 2002 reported on the mean (SD) volume of blood transfused as mL/kg/d: early EPO group 0.7 (1.2) and control group 1.1 (1.2) (P value not provided). Meister 1997 reported on the median (first and third quartile) volume of blood transfused as mL/kg/d: EPO group 0 (0 to 0.47) and control group 0.86 (0.5 to 1.1).

### Number of red blood cell transfusions per infant (Outcome 1.5)

A total of 16 studies enrolling 1744 infants reported on the number of RBC transfusions per infant. The significant weighted mean difference (WMD) for the number of RBC transfusions per infant was -0.57 (95% CI -0.68 to -0.45). Heterogeneity was high for this outcome ($I^2$ = 80%) (Analysis 1.5).

Carnielli 1998 reported on the mean number of RBC transfusions

for three groups: EPO + iron 1.0 (95% CI 0.28 to 1.18); EPO only 1.3 (95% CI 0.54 to 2.06); and control 2.9 (95% CI 1.84 to 3.88) (control vs EPO P = 0.065; control vs EPO + iron P = 0.035) (P values according to trial authors).

Avent 2002 reported the median and range of number of transfusions across three groups: low-dose EPO 0 (0 to 1); high-dose EPO 0 (0 to 2); and control 0 (0 to 4) (P = 0.03 across the three groups). Haiden 2005 reported the number of transfusions: EPO 2 (0 to 15) and control 4.5 (0 to 12) (not statistically significant according to trial authors).

### Number of donors to whom the infant was exposed (Outcome 1.6)

#### Number of donors the infant was exposed to among all randomised infants (Outcome 1.6.1)

Three studies enrolling 254 infants reported on this outcome as means and standard deviations (SDs). The significant WMD for the number of donors to whom the infant was exposed was -0.54 (95% CI -0.89 to -0.20). We noted no heterogeneity for this outcome ($I^2$ = 0%) (Analysis 1.6).

#### Number of donors the infant was exposed to among infants who were transfused (Outcome 1.6.2)

Two studies enrolling 290 infants reported on this outcome. The non-significant WMD for the number of donors the infant was exposed to among infants who were transfused was 0.05 (95% CI -0.33 to 0.42). Heterogeneity was moderate for this outcome ($I^2$ = 63%) (Analysis 1.6).

Carnielli 1992 reported that the number of donor exposures ranged from zero to five in the EPO group and from zero to six in the control group (P value not provided). Haiden 2005 reported on this outcome in a similar fashion: EPO group 1 donor (0 to 10), control group 3 donors (0 to 5) (not statistically significant according to trial authors).

### Mortality during initial hospital stay (all causes of mortality) (Outcome 1.7)

A total of 20 studies enrolling 2212 infants reported on this outcome. Mortality was not significantly altered by the use of EPO (typical RR 0.89, 95% CI 0.68 to 1.16; typical RD -0.01, 95% CI -0.03 to 0.01). We noted no heterogeneity for this outcome (RR and RD: $I^2$ = 0%) (Analysis 1.7). The quality of the evidence was high.

### Retinopathy of prematurity (ROP) (all stages or stage not stated by trial authors) (Outcome 1.8)

A total of 11 studies enrolling 2185 infants reported on ROP. We obtained unpublished data from Maier 2002 on the highest grade of ROP recorded during the study among examined survivors. Data show no significant difference in the incidence of ROP (all stages or stage not stated by trial authors) (typical RR 0.92, 95% CI 0.79 to 1.08; typical RD -0.02, 95% CI -0.05 to 0.02). We noted no heterogeneity for this outcome (RR and RD: $I^2$ = 0%) (Analysis 1.8).

### Retinopathy of prematurity (ROP) (stage ≥ 3) (Outcome 1.9)

A total of eight studies enrolling 1283 infants reported on severe ROP (stage ≥ 3). Data show no significant differences in ROP (stage ≥ 3) between groups (typical RR 1.24, 94% CI 0.81 to 1.90; typical RD 0.01, 95% CI -0.01 to 0.04). We noted no heterogeneity for this outcome for RR ($I^2$ = 0%) and low heterogeneity for RD ($I^2$ = 34%) (Analysis 1.9). The quality of the evidence was high.

Ohls 1997 reported no differences in ROP (stage ≥ 3) rates between groups (data not provided).

### Proven sepsis (clinical symptoms and signs of sepsis and positive blood culture for bacteria or fungi) (Outcome 1.10)

Twelve studies including 2180 infants reported on this outcome. EPO did not significantly change rates of proven sepsis (typical RR 0.87, 95% CI 0.74 to 1.02; typical RD -0.03, 95% CI -0.06 to 0.00). We noted no heterogeneity (RR and RD: $I^2$ = 0%) (Analysis 1.10).

### Necrotising enterocolitis (NEC) (stage > 2 or stage not reported) (Outcome 1.11)

We included in this analysis any outcome stated as NEC. We include 15 studies reporting on 2639 infants. EPO significantly reduced the rate of NEC (typical RR 0.69, 95% CI 0.52 to 0.91; typical RD -0.03, 95% CI -0.05 to -0.01). We noted no heterogeneity for this outcome (RR: $I^2$ = 0%, RD: $I^2$ = 22%; NNTB 33, 95% CI 20 to 100) (Analysis 1.11). The quality of evidence was moderate.

Ohls 1995 reported no differences in NEC rates between groups (data not provided). The quality of the evidence was low.

### Intraventricular haemorrhage (IVH); all grades (Outcome 1.12)

Many trial authors did not state the grade of IVH. We included in this outcome studies in which authors did not state the grade and excluded IVH grades III and IV when known. A total of ten studies including 1226 infants reported on this outcome. EPO did not significantly change the rate of IVH (all grades) (typical RR 0.98, 95% CI 0.76 to 1.26; typical RD -0.00, 95% CI -0.04 to 0.04) (Analysis 1.12). We noted no heterogeneity for this outcome for RR and RD ($I^2$ = 0%). Ohls 1995 and Ohls 1997 reported no differences in IVH rates between groups (data not provided).

### Intraventricular haemorrhage (IVH); grades III and IV (Outcome 1.13)

Eight studies enrolling 1460 infants reported on this outcome. EPO significantly reduced the rate of IVH (grades III and IV) (typical RR 0.60, 95% CI 0.43 to 0.85; typical RD -0.04, 95% CI -0.07 to -0.02; NNTB 25, 95% CI 14 to 50). Heterogeneity was low for this outcome for RR ($I^2$ = 45%) but high for RD ($I^2$ = 79%) (Analysis 1.13). The quality of the evidence was moderate.

### Periventricular leukomalacia (PVL); cystic changes in periventricular areas (Outcome 1.14)

Six studies enrolling 1469 infants reported on PVL. EPO significantly reduced the rate of PVL (typical RR 0.66, 95% CI 0.48 to 0.92; typical RD -0.04, 95% CI -0.07 to -0.01; NNTB 25, 95% CI 14 to 100). We noted no heterogeneity for this outcome for RR ($I^2$ = 5%) but high heterogeneity for RD ($I^2$ = 79%) (Analysis 1.14). The quality of the evidence was moderate.

### Length of hospital stay (days) (Outcome 1.15)

Eight studies enrolling 970 infants reported on length of hospital stay. EPO significantly reduced length of hospital stay (typical MD -3.20 days, 95% CI -5.34 to -1.06). Heterogeneity was moderate for this outcome ($I^2$ = 58%) (Analysis 1.15).

Avent 2002 reported the median and range (days) for hospital stay across three groups: low-dose EPO 32 (5 to 54), high-dose EPO 32 (16 to 74), and control 30 (14 to 46) (P = 0.10 across the three groups). Haiden 2005 reported on hospital stay (days, median and range): EPO group 97 (59 to 162) and control group 89 (77 to157) (not statistically significant according to trial authors). Maier 2002 reported on the median (quartiles) for hospital stay: early EPO 87 (73 to 107), control 87 (69 to 108).

### Bronchopulmonary dysplasia (BPD) (Outcome 1.16)

#### *Bronchopulmonary dysplasia (BPD) (supplemental oxygen at 28 days of age) (Outcomes Table 1.16.1)*

Two studies enrolling 136 infants reported on use of supplemental oxygen at 28 days. EPO did not significantly change the rate of BPD (supplemental oxygen at 28 days of age) (RR 0.86, 95% CI 0.50 to 1.47; RD -0.04, 95% CI -0.19 to 0.10). We noted no

heterogeneity for this outcome (RR and RD: $I^2$ = 0%) (Analysis 1.16).

Ohls 1995 and Ohls 1997 reported no differences in BPD rates between groups (data not provided).

### *Bronchopulmonary dysplasia (BPD) (supplemental oxygen at 36 weeks' postmenstrual age (PMA)) (Outcomes Table 1.16.2)*

Seven studies enrolling 1719 infants reported on use of supplemental oxygen at 36 weeks' PMA. EPO did not significantly change the rate of BPD (supplementary oxygen at 36 weeks' PMA) (typical RR 0.95, 95% CI 0.81 to 1.11; typical RD -0.01, 95% CI -0.05 to 0.02). We noted no heterogeneity for this outcome (RR and RD: $I^2$ = 0%) (Analysis 1.16).

### *Bronchopulmonary dysplasia (BPD) (age at diagnosis not stated) (Outcomes Table 1.16.3)*

A total of five studies enrolling 528 infants reported on this outcome. EPO did not significantly change the rate of BPD (age at diagnosis not stated) (typical RR 0.98, 95% CI 0.61 to 1.56; typical RD -0.00, 95% CI -0.05 to 0.05). We noted no heterogeneity for this outcome (RR and RD: $I^2$ = 0%) (Analysis 1.16).

### Neutropenia (Outcome 1.17)

Ten studies including 966 infants reported on neutropenia. The non-significant typical RR was 0.81 (95% CI 0.53 to 1.24); the typical RD was -0.01 (95% CI -0.05 to 0.02). We noted no heterogeneity for this outcome (RR and RD: $I^2$ = 0%) (Analysis 1.17).

### Hypertension (Outcome 1.18)

A total of six studies enrolling 706 infants reported on hypertension. Five studies reported no outcomes in treatment or control groups. Therefore, these five studies did not provide information for the typical RR estimate. The typical RR was 0.97 (95% CI 0.14 to 6.69). All six studies were included in the typical RD of -0.00 (95% CI -0.02 to 0.02). We noted no heterogeneity for this outcome (RR: $I^2$ = 0%; RD: $I^2$ = 0%) (Analysis 1.18).

### Hemangioma (Outcome 1.19)

One study reported on hemangioma among 443 infants. The RR was 1.33 (95% CI 0.79 to 2.26), and the RD was 0.03 (95% CI -0.03 to 0.09). Tests for heterogeneity were not applicable (Analysis 1.19).

### Neonatal Behavioural Neurological Assessment (NBNA) at 40 weeks' PMA (Outcome 1.20)

One study reported on NBNA at 40 weeks' PMA in 44 infants. The significant MD was 1.80 (95% CI 1.26 to 2.34) favouring the EPO group. Tests for heterogeneity were not applicable (Analysis 1.20).

### Infants with white matter injury at term-corrected PMA (Outcome 1.21)

One study reported on 165 infants. Data show a non-significant reduction in white matter injury in the EPO group compared with the control group (RR 0.61, 95% CI 0.37 to 1.00; NS) but significant reduction in the RD (-0.14, 95% CI -0.28 to -0.01; NNTB 7, 95% CI 4 to 100; tests for heterogeneity N/A) (Analysis 1.21).

### Infants with white matter signal abnormality injury at term-corrected PMA (Outcome 1.22)

One study reported on 165 infants. Study authors described a non-significant reduction in white matter signal abnormality in the EPO group compared with the control group (RR 0.23, 95% CI 0.05 to 1.01; NS) but a significant reduction in the RD (-0.09, 95% CI -0.16 to -0.01; NNTB 11, 95% CI 6 to 100; tests for heterogeneity N/A) (Analysis 1.22).

### Infants with periventricular white matter loss at term-corrected PMA (Outcome 1.23)

One study reported on 165 infants and noted a significant reduction in periventricular white matter loss in the EPO group compared with the control group (RR 0.55, 95% CI 0.32 to 0.97; RD -0.15, 95% CI -0.28 to -0.02; NNTB 7, 95% CI 4 to 50; tests for heterogeneity N/A) (Analysis 1.23).

### Infants with grey matter injury at term-corrected PMA (Outcome 1.24)

One study reported on 165 infants and noted a significant reduction in grey matter injury in the EPO group compared with the control group (RR 0.34, 95% CI 0.13 to 0.87; RD -0.13, 95% CI -0.23 to -0.03; NNTB 8, 95% CI 4 to 33; tests for heterogeneity N/A) (Analysis 1.24).

### Survivors at discharge from hospital without severe IVH, PVL, or ROP (Outcome 1.25)

One study reported on 443 infants and noted no significant differences between groups for the outcome 'Survivors at discharge from hospital without severe IVH, PVL, or ROP' (RR 1.00, 95%

CI 0.93 to 1.08; RD 0.00, 95% CI -0.06 to 0.07). Tests for heterogeneity were not applicable (Analysis 1.25). The quality of the evidence was high.

**Long-term outcomes assessed at any age beyond one year of age by a validated cognitive, motor, language, or behavioural, school, and social interaction adaptation test**

**Bayley-II Mental Development Index (MDI) < 70 at 18 to 24 months' corrected age (Outcome 1.26)**

Four studies reported on 1071 children. Data show a significant reduction in infants with MDI < 70 at 18 to 24 months' corrected age (typical RR 0.55, 95% CI 0.39 to 0.77; typical RD -0.07, 95% CI -0.11 to - 0.03; NNTB 14, 95% CI 9 to 33). Heterogeneity was moderate for RR ($I^2$ = 60%) and low for RD ($I^2$ = 31%) (Analysis 1.26).

**Psychomotor Developmental Index (PDI) < 70 at 18 to 22 months' corrected age (Outcome 1.27)**

Three studies reported on this outcome in 458 children following EPO treatment, noting no significant effects of EPO compared with control. The typical RR was 1.43 (95% CI 0.88 to 2.33); the typical RD was 0.04 (95% CI -0.02 to 0.11). Heterogeneity was low for RR ($I^2$ = 46%) and for RD ($I^2$ = 42%) (Analysis 1.27).

**Bayley-II MDI at 18 to 24 months (Outcome 1.28)**

Three studies reported on this outcome in 981 children following EPO treatment. Data show a significant increase in Bayley-II MDI at 18 to 24 months in the EPO group compared with the control group. The WMD was 8.22 (95% CI 6.52 to 9.92). Heterogeneity was high for this outcome ($I^2$ = 97%) (Analysis 1.28). The quality of the evidence was low.

**Bayley-II PDI at 18 to 24 months (Outcome 1.29)**

Fauchère 2008 reported on this outcome in three infants. We obtained unpublished data from the trial author and were not able to use the data in RevMan (RevMan 2014; Analysis 1.29).

**Cerebral palsy at 18 to 22 months' corrected age (Outcome 1.30)**

Six studies reported on this outcome in 1172 children following EPO treatment. The non-significant typical RR was 0.72 (95% CI 0.46 to 1.13); RD was -0.02 (95% CI -0.05 to 0.01). Heterogeneity was low (RR: $I^2$ = 48%; RD: $I^2$ = 41%) (Analysis 1.30). The quality of the evidence was high.

**Any neurodevelopmental impairment at 18 to 22 months' corrected age (Outcome 1.31)**

Four studies reported on this outcome in 1130 children following EPO treatment. The typical RR was 0.62 (95% CI 0.48 to 0.80); typical RD was -0.08 (95% CI -0.12 to -0.04); NNTB was 13 (95% CI 8 to 25). Heterogeneity was high for RR ($I^2$ = 76%) and moderate for RD ($I^2$ = 66%) (Analysis 1.31). The quality of the evidence was low.

**Visual impairment at 18 to 22 months' corrected age (Outcome 1.32)**

Five studies reported on this outcome in 1132 children following EPO treatment. Data show no significant differences between groups (typical RR 0.80, 95% CI 0.26 to 2.49; RD -0.00, 95% CI -0.01 to 0.01). We noted no heterogeneity for this outcome ($I^2$ = 0% for both RR and RD) (Analysis 1.32).

**Hearing impairment at 18 to 22 months' corrected age (Outcome 1.33)**

Five studies reported on this outcome in 1132 children following EPO treatment. Data show no significant differences between groups (typical RR 0.41, 95% CI 0.13 to 1.23; RD -0.01, 95% CI -0.02 to 0.00). We noted no heterogeneity for RR ($I^2$ = 11%) and low heterogeneity for RD ($I^2$ = 38%) (Analysis 1.33).

**Bayley Scales of Infant Development (BSID-III) cognitive scores at 18 to 22 months (Outcome 1.34)**

One study reported on this outcome in 53 infants. Scores were significantly higher in the group that received EPO (mean difference (MD) 9.2, 95% CI 1.70 to 16.70). Tests for heterogeneity were not applicable (Analysis 1.34).

Ohls 2013, with small sample sizes at both times of follow-up, reported secondary outcomes (53 and 38 children, respectively) for which none of the results reached statistical significance. Results are presented in the analyses: BSID-III composite language score (Analysis 1.35), BSID-III composite social/emotional score (Analysis 1.36), BSID-III object performance (OP) score (Analysis 1.37), Wechsler Preschool and Primary Scale of Intelligence - Third Edition Full-Scale Intelligence Quotient (WPPSI-III FSIQ) at 3.5 to 4 years of age (Analysis 1.38), WPPSI-III Verbal Intelligence Quotient (VIQ) at 3.5 to 4 years of age (Analysis 1.39), WPPSI-III Performance Intelligence Quotient (PIQ) at 3.5 to 4 years of age (Analysis 1.40), WPPSI-III General Language Composite score (GLC) at 3.5 to 4 years of age (Analysis 1.41), Executive function at 3.5 to 4 years of age (Analysis 1.42), Working memory at 3.5 to 4 years of age (Analysis 1.43), and Inhibition at 3.5 to 4 years of age (Analysis 1.44). In addition, Peltoniemi 2017 reported on the Griffiths Developmental Scale at two years of age for 19 infants, noting no statistical differences between groups (Analysis 1.45).

**Survival without major neurological or neurodevelopmental disorders at two years of age (Outcome 1.46)**

Two studies reported on this outcome in 404 children. Data show no statistically significant differences between EPO and control groups (typical RR 0.99, 95% CI 0.91 to 1.08; RD -0.01, 95% CI -0.08 to 0.06). We noted no heterogeneity for this outcome (RR: $I^2$ = 20%, RD: $I^2$ = 22%) (Analysis 1.46).

**Death or moderate/severe neurological disability at 18 to 24 months (Outcome 1.47)**

One study reported on this outcome in 668 children. Data show a significantly reduced rate of this outcome in the EPO group (RR 0.48, 95% CI 0.35 to 0.67; RD -0.14, 95% CI -0.20 to -0.08; NNTB 7, 95% CI 5 to 13). Tests for heterogeneity were not applicable (Analysis 1.47).

**Moderate/severe neurological disability at 18 to 24 months (Outcome 1.48)**

One study reported on this outcome in 613 children, noting a significantly reduced rate of this outcome in the EPO group (RR 0.38, 95% CI 0.24 to 0.60; RD -0.12, 95% CI -0.17 to -0.06; NNTB 8, 95% CI 6 to 17). Tests for heterogeneity were not applicable (Analysis 1.48).

**Any side effects reported in these trials (no outcomes table)**

Nine trials specifically reported that side effects did not occur ( Carnielli 1992; Maier 1994; Lauterbach 1995; Ohls 1995; Meister 1997; Chang 1998; Lima-Rogel 1998; Fauchère 2008; Khatami 2008). Ohls 2013 reported that side effects were minimal and were not different between groups.

**Darbepoetin alfa versus placebo or no treatment (Comparison 2)**

We identified only one study for this comparison (Ohls 2013); therefore tests for heterogeneity were not applicable for any of the analyses.

We indicate the primary outcome. All other analyses were performed for secondary outcomes.

**Use of one or more red blood cell transfusions (Outcome 2.1) - Primary outcome**

One study including 66 infants reported on this outcome. The RR of 0.62 (95% CI 0.38 to 1.02) was not significantly reduced, but the RD of -0.24 was significantly reduced (95% CI -0.48 to -0.01; NNTB 4, 95% CI 2 to 100) (Analysis 2.1).

Ohls 2013 reported the following secondary outcomes, which were not statistically significantly different between Darbe and no

treatment groups: Total volume (mL/kg) of blood transfused per infant (all infants) (Outcome 2.2) (Analysis 2.2); Total volume (mL/kg) of blood transfused in transfused infants only (Outcome 2.3) (Analysis 2.3); Number of blood transfusions per infant (Outcome 2.4) (Analysis 2.4); Number of donors the infant was exposed to (Outcome 2.5) (Analysis 2.5); Mortality during initial hospital stay (all causes of mortality) (Outcome 2.6) (Analysis 2.6); Retinopathy of prematurity (all stages) (Outcome 2.7) (Analysis 2.7); Retinopathy of prematurity (stage ≥ 3) (Outcome 2.8) (Analysis 2.8); Necrotising enterocolitis (stage > 2) (Outcome 2.9) (Analysis 2.9); Proven sepsis (Outcome 2.10) (Analysis 2.10); Intraventricular haemorrhage (grades III and IV) (Outcome 2.11) (Analysis 2.11); Periventricular leukomalacia (Outcome 2.12) (Analysis 2.12); Bronchopulmonary dysplasia (supplemental oxygen at 36 weeks' PMA) (Outcome 2.13) (Analysis 2.13); Length of hospital stay (days) (Outcome 2.14) (Analysis 2.14); Neutropenia (Outcome 2.15) (Analysis 2.15); and Hypertension (Outcome 2.16) (Analysis 2.16).

**Cerebral palsy (CP) at 18 to 22 months (Outcome 2.17)**

One study including 51 infants reported on this outcome. The non-significant RR was 0.08 (95% CI 0.00 to 1.40; P = 0.08), and the significantly reduced RD in favour of Darbe was -0.21 (95% CI -0.38 to -0.04; P = 0.02); the NNTB was 5 (95% CI 3 to 25) (Analysis 2.17).

**Neurodevelopmental impairment (NDI) (having CP, visual defect, or cognitive score < 85) at 18 to 22 months (Outcome 2.18)**

One study including 51 infants reported on this outcome. The significantly reduced RR was 0.27 (95% CI 0.08 to 0.86), and the significantly reduced RD was -0.31 (95% CI -0.54 to -0.08); the NNTB was 3 (95% CI 2 to 13) in favour of Darbe (Analysis 2.18).

**BSID-III composite cognitive scores at 18 to 22 months (Outcome 2.19)**

One study including 51 infants reported on this outcome. The significantly increased MD in favour of Darbe was 7.50 (95% CI 1.44 to 13.56) (Analysis 2.19).

**BSID-III composite language score at 18 to 22 months (Outcome 2.20)**

One study including 51 infants reported on this outcome. The significantly increased MD in favour of Darbe was 8.80 (95% CI 1.57 to 16.03) (Analysis 2.20).

**BSID-III social/emotional score at 18 to 22 months (Outcome 2.21)**

One study including 51 infants reported on this outcome. The non-significant MD was 6.80 (95% CI -3.82 to 17.42) (Analysis 2.21).

**Object performance (OP) score at 18 to 22 months (Outcome 2.22)**

One study including 51 infants reported on this outcome. The significant MD in favour of Darbe was 0.60 (95% CI 0.17 to 1.03) (Analysis 2.22).

**WPPSI-III FSIQ at 3.5 to 4 years of age (Outcome 2.23)**

One study reported on this outcome in 29 infants. The significant MD in favour of Darbe was 15.27 (95% CI 2.60 to 27.94) (Analysis 2.23).

**WPPSI-III VIQ at 3.5 to 4 years of age (Outcome 2.24)**

One study reported on this outcome in 29 infants. The non-significant MD was 9.17 (95% CI -2.86 to 21.20) (Analysis 2.24).

**WPPSI-III PIQ at 3.5 to 4 years of age (Outcome 2.25)**

One study reported on this outcome in 29 infants. The significant MD in favour of Darbe was 14.97 (95% CI 1.89 to 28.05) (Analysis 2.25).

**WPPSI-III GLC at 3.5 to 4 years of age (Outcome 2.26)**

One study reported on this outcome in 29 infants. The non-significant MD was 7.94 (95% CI -4.18 to 20.06) (Analysis 2.26).

**Executive function at 3.5 to 4 years (Outcome 2.27)**

One study reported on this outcome in 29 infants. The significant MD in favour of Darbe was 10.81 (95% CI 2.83 to 18.79) (Analysis 2.27).

**Working memory at 3.5 to 4 years (Outcome 2.27)**

One study reported on this outcome in 29 infants. The significant MD in favour of Darbe was 12.77 (95% CI 2.68 to 22.86) (Analysis 2.28).

**Inhibition at 3.5 to 4 years of age (Outcome 2.28)**

One study reported on this outcome in 29 infants. The non-significant MD was 8.77 (95% CI -2.47 to 20.01) (Analysis 2.28).

**Darbepoietin alfa or erythropoietin (ESA) versus placebo or no treatment (Comparison 3)**

We identified only one study for this comparison (Ohls 2013); therefore tests for heterogeneity were not applicable for any of these analyses.

We indicate the primary outcome. All other analyses were performed for secondary outcomes.

**BSID-III composite cognitive scores at 18 to 22 months (Outcome 3.1) - Primary outcome**

One study including 80 infants reported on this outcome. The significantly increased MD in favour of ESA was 7.80 (95% CI 1.65 to 13.95) (Analysis 3.1). The quality of the evidence was moderate.

**BSID-III composite language score at 18 to 22 months (Outcome 3.2)**

One study including 80 infants reported on this outcome. The significantly increased MD in favour of ESA was 7.10 (95% CI 0.49 to 13.71) (Analysis 3.2).

**BSID-III social/emotional score at 18 to 22 months (Outcome 3.3)**

One study including 80 infants reported on this outcome. The non-significant MD was 4.20 (95% CI -5.06 to 13.46) (Analysis 3.3).

**OP score at 18 to 22 months (Outcome 3.4)**

One study including 80 infants reported on this outcome. The non-significant MD was 0.40 (95% CI -0.04 to 0.84) (Analysis 3.4).

**Behavior Assessment System for Children (BASC-2) composite scores at 3.5 to 4 years - Adaptive skills (Outcome 3.5)**

One study including 49 infants reported on this outcome. The non-significant MD was 2.54 (95% CI -3.58 to 8.66) (Analysis 3.5).

**BASC-2 composite scores at 3.5 to 4 years - Behaviour symptoms (Outcome 3.6)**

One study including 49 infants reported on this outcome. The non-significant MD was -8.66 (95% CI -18.01 to 0.69) (Analysis 3.6).

**BASC-2 composite scores at 3.5 to 4 years - Externalising problems (Outcome 3.7)**

One study including 49 infants reported on this outcome. The significantly reduced MD in favour of ESA was -8.00 (95% CI -15.94 to -0.06) (Analysis 3.7).

**BASC-2 composite scores at 3.5 to 4 years - Internalising problems (Outcome 3.8)**

One study including 49 infants reported on this outcome. The non-significant MD was -2.56 (95% CI -9.25 to 4.13) (Analysis 3.8).

**WPPSI-III FSIQ at 3.5 to 4 years of age (Outcome 3.9) - Primary outcome**

One study reported on this outcome in 53 infants. The significantly increased MD in favour of ESA was 11.90 (95% CI 0.76 to 23.04) (Analysis 3.9). The quality of the evidence was low.

**WPPSI-III VIQ at 3.5 to 4 years of age (Outcome 3.10)**

One study reported on this outcome in 53 infants. The non-significant MD in favour of ESA was 8.80 (95% CI -1.75 to 19.35) (Analysis 3.10).

**WPPSI-III PIQ at 3.5 to 4 years of age (Outcome 3.11)**

One study reported on this outcome in 53 infants. The significant MD in favour of ESA was 13.50 (95% CI 1.98 to 25.02) (Analysis 3.11).

**WPPSI-III GLC at 3.5 to 4 years of age (Outcome 3.12)**

One study reported on this outcome in 53 infants. The significant MD in favour of ESA was 5.13 (95% CI -5.30 to 15.56) (Analysis 3.12).

**Executive function at 3.5 to 4 years (Outcome 3.13)**

One study reported on this outcome in 53 infants. The significant MD n favour of ESA was 8.36 (95% CI 0.51 to 16.21) (Analysis 3.13).

**Working memory at 3.5 to 4 years (Outcome 3.14)**

One study reported on this outcome in 53 infants. The non-significant MD was 9.06 (95% CI -1.06 to 19.18) (Analysis 3.14).

**Inhibition at 3.5 to 4 years of age (Outcome 3.15)**

One study reported on this outcome in 53 infants. The non-significant MD was 7.60 (95% CI -2.79 to 17.99) (Analysis 3.15).

**Effectiveness of EPO administered early versus placebo in improving feeding tolerance and decreasing NEC**

**Erythropoietin versus placebo or no treatment (Comparison 4)**

**Time to achieve full enteral feeding (days) (Outcome 4.1) - Primary outcome**

One study (El-Ganzoury 2014) reported on this outcome in 50 infants. EPO significantly reduced the time (days) to achieve full enteral feeding (MD -2.90 days, 95% CI -5.77 to -0.03). Testing for heterogeneity was not applicable. The quality of the evidence was low.

The outcome of NEC in this study is reported in Analysis 1.11, the outcome of mortality in Analysis 1.7, and the outcome of length of hospital stay in Analysis 1.15.

# ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

**Erythropoietin compared with placebo or no treatment for complications of preterm birth**

**Patient or population:** preterm infants with low birth weight
**Settings:** NICU
**Intervention:** EPO
**Comparison:** placebo or no treatment

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | **Assumed risk** | **Corresponding risk** | | | | |
| | **Placebo or no treatment** | **EPO** | | | | |
| Mortality during initial hospital stay (all causes of mortality) | High-risk population | | RR: 0.89 (95% CI 0.68 to 1.16) | 2212 (20) | ⊕⊕⊕⊕ high | Bias: We had concerns about bias (lack of blinding) in 10 of the included studies, but the outcome of mortality is not likely to be affected by researchers knowing the treatment assignment. We did not downgrade the quality of evidence on this item Heterogeneity/ Consistency: We noted no heterogeneity ($I^2$ = 0%). Directness of evidence: Studies were conducted in the target population |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Precision: Because of the large sample size (2212), the point estimate was precise with a narrow 95% CI |
| | 92 per 1000 | 82 per 1000 (0 to 172) | | | Presence of publication bias: The funnel plot was symmetrical |
| Retinopathy of prematurity (stage ≥ 3) | High-risk population | | RR: 1.24 (95% CI 0.81 to 1.90) | 1283 (8) | ⊕⊕⊕⊕ high | Bias: We found no risk of bias in any of the studies, except in the smallest study that enrolled 40 neonates. We did not downgrade the quality of evidence Heterogeneity/ Consistency: We noted no heterogeneity for RR ($I^2$ = 0%) and low ($I^2$ = 34%) heterogeneity for RD. Directness of evidence: Studies were conducted in the target population Precision: Because of the large sample size (n = 1283), the point estimate was precise with a narrow 95% CI Presence of publication bias: The funnel plot, which included 8 studies, was symmetrical |

| | | | | |
|---|---|---|---|---|
| | 53 per 1000 | 65 per 1000 (0 to 195) | | | |
| Intraventricular haemorrhage (grades III and IV) | High-risk population | | RR: 0.60 (95% CI 0.43 to 0.85) 1460 (8) | ⊕⊕⊕◯ moderate | Bias:The intervention was not blinded in the largest study, Song 2016 (n= 743). That study carried a weight of 72.8% in the analysis and was the only individual study that showed a significant reduction in IVH (grades III and IV). We downgraded the quality of the evidence by 1 step Heterogeneity/Consistency: Heterogeneity was low ($I^2$ = 45%). Directness of evidence: Studies were conducted in the target population Precision: Because of the large sample size (n = 1460), the point estimate was precise with a narrow 95% CI Presence of publication bias: The funnel plot, which included 8 studies, was symmetrical |
| | 111 per 1000 | 67 per 1000 (0 to 126) | | | |
| Periventricular leukomalacia | High-risk population | | RR: 0.66 (95% CI 0.48 to 0.92) 1469 (6) | ⊕⊕⊕◯ moderate | Bias: The intervention was not blinded in the largest study, Song 2016 (n = 743). That |

| | | | | |
|---|---|---|---|---|
| | | | | study carried a weight of 89.2% in the analysis and was the only individual study that showed a significant reduction in PVL. We downgraded the quality of the evidence by 1 step. Heterogeneity/ Consistency: We noted no heterogeneity ($I^2$ = 5%). Directness of evidence: Studies were conducted in the target population Precision: Because of the large sample size (n = 1469), the point estimate was precise with a narrow 95% CI Presence of publication bias: The funnel plot, which included 6 studies, was symmetrical |
| | 111 per 1000 | 71 per 1000 (0 to 150) | | |
| Survivors at discharge from hospital without severe IVH, PVL, ROP | High-risk population | RR: 1.00 (95% CI 0.93 to 1.08) | 443 (1) | ⊕⊕⊕⊕ high | Bias: We noted low risk of bias. Heterogeneity/ Consistency: N/A, as only 1 study. Directness of evidence: The study was conducted in the target population |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Precision: Because of the relatively large sample size (n = 443), the point estimate was precise with a narrow 95% CI<br>Presence of publication bias: As only 1 study was included, we did not develop a funnel plot |
| | 855 per 1000 | 856 per 1000 | | | |
| Time to achieve full enteral feeding (days) | Mean time to achieve full enteral feeding was 16.3 days (SD 5.3) in the control group | Mean time to achieve full enteral feeding in the intervention groups was 2.90 days shorter | MD: -2.90 (95% CI -5.77 to -0.03) | 50 (1) | ⊕⊕◯◯ low | Bias: We had concerns about blinding of the intervention and outcome assessments. We downgraded the quality of evidence by 1 step<br>Heterogeneity/Consistency: N/A, as only 1 study.<br>Directness of evidence: The study was conducted in the target population<br>Precision: Because of the small sample size (n = 50), the 95% CI around the point estimate was wide<br>Presence of publication bias: As only 1 study was included, we did not prepare a funnel plot |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; EPO: erythropoietin; IVH: intraventricular haemorrhage; MD: mean difference; N/A: not applicable; NICU: neonatal intensive care unit; PVL: periventricular leukomalacia; RD: risk difference; ROP: retinopathy of prematurity; RR: risk ratio; SD: standard deviation

GRADE Working Group grades of evidence.

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

**Erythropoietin compared with placebo or no treatment for complications of preterm birth - long-term outcomes**

**Patient or population:** preterm infants with low birth weight
**Settings:** NICU
**Intervention:** EPO
**Comparison:** placebo or no treatment

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | EPO | | | | |
| Cerebral palsy at 18 to 24 months' corrected age | High-risk population | | RR: 0.72 (95% CI 0.46 to 1.13) | 1172 (6) | ⊕⊕⊕⊕ high | Bias: Low risk of bias. All assessors of long-term outcomes were blinded in all trials. In Song 2016, treatment allocation was known to caregivers and probably parents, who could have possibly disclosed that information to assessors at long-term follow-up. We did not downgrade the quality of the evidence Heterogeneity/Consistency: Heterogeneity was low for this outcome ($I^2 = 48\%$). We did not downgraded the evidence. Directness of evidence: |

Studies were conducted in the target population

Precision: Because of the large sample size (n = 1172), the point estimate was precise with a narrow 95% CI

Presence of publication bias: We included 6 studies in the analysis; we did prepare a funnel plot, which was symmetrical

70 per 1000

50 per 1000 (0 to 285)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; EPO: erythropoietin; NICU: neonatal intensive care unit; RR: risk ratio; WMD: weighted mean difference

GRADE Working Group grades of evidence.

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

**Darbe or EPO (ESA) compared with sham injection for neuro protection - long-term outcomes**

**Patient or population:** neonates born preterm with low birth weight
**Settings:** NICU
**Intervention:** Darbe or EPO (ESA)
**Comparison:** sham injection

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | **Assumed risk** | **Corresponding risk** | | | | |
| | **Sham injection** | **ESA** | | | | |
| BSID-III composite cognitive scores at 18 to 22 months The Bayley-III has 3 main sub tests: the Cognitive Scale, which includes items such as attention to familiar and unfamiliar objects, looking for a fallen object, and pretend play; the Language Scale, which taps understanding and expression of language, for example, recognising objects and people, following directions, and naming objects and pictures; and the Motor Scale, which assesses gross and fine motor skills such as grasping, sit- | Mean BSID-III in the control group was 88.7 units (SD 13.5). | Mean BSID-III in the intervention group was 7.80 units higher | MD 7.80 (95% CI 1.65 to 13.95) | 80 (1) | ⊕⊕⊕◯ moderate | Bias: Risk of bias was low, but the sample followed was small. We did not reduce the quality of evidence Heterogeneity/Consistency: Only 1 study was included, so the test for heterogeneity was N/A Directness of evidence: The study was conducted in the target population Precision: Because of the small sample size (n = 80), the point estimate had a wide 95% CI. We downgraded the quality of evidence by 1 step Presence of publication |

| | | | | | | |
|---|---|---|---|---|---|---|
| ting, stacking blocks, and climbing stairs | | | | | | bias: N/A, as only 1 study was included |
| WPPSI-III FSIQ at 3.5 to 4 years of age Composite scores have a mean of 100 and a standard deviation of 15 Average is 90 to 109. | Mean WPPSI-III FSIQ in the control group was 79.2 units (SD 18,5) | Mean WPPSI-III FSIQ in the intervention group was 11.90 units higher | MD 11.90 (95% CI 0.76 to 23.04) | 53 (1) | ⊕⊕◯◯ low | Bias: Risk of bias was low, but the sample followed was even smaller than at 18 to 22 months of age (n = 53). We did reduce the quality of evidence by 1 step Heterogeneity/Consistency: Only 1 study was included, so the test for heterogeneity was N/A Directness of evidence: The study was conducted in the target population Precision: Because of the small sample size (n = 53), the point estimate had a large 95% CI. We downgraded the quality of evidence by 1 step Presence of publication bias: N/A, as only 1 study was included, |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BSID-III: Bayley Scales of Infant Development - Third Edition; CI: confidence interval; EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; MD: mean difference; N/A: not applicable; NICU: neonatal intensive care unit; RR: risk ratio; SD: standard deviation; WPPSI-III FSIQ: Wechsler Preschool and Primary Scale of Intelligence - Third Edition

GRADE Working Group grades of evidence.

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

# DISCUSSION

## Summary of main results

### Short-term outcomes

We included in this update 34 studies reporting on 3643 infants, representing an increase of 1434 trial participants from the 2014 update. Studies were performed in 22 countries. We excluded 22 studies. The quality of evidence ranged from high to low, according to GRADE (for specifics, see Quality of the evidence below).

Evidence from 19 of these 34 studies (n = 1750) indicates that early initiation of low or high doses of erythropoietin (EPO) administered at less than eight days of age reduced the need for one or more red blood cell transfusions. The total volume (mL/kg) of blood transfused per infant was reduced, as was the number of donors to whom the infant was exposed, among all randomised infants - but not among infants who were transfused. Most studies included infants who had received transfusions before study entry. Many studies followed guidelines (with tremendous variation between studies) for red blood cell transfusions (see Additional tables, Table 1).

Mortality during initial hospital stay was not affected by EPO treatment (n = 2212).

Most important, good evidence now shows that early EPO does not increase the risk of retinopathy of prematurity (ROP) (stage ≥ 3) (n = 1165), which was a matter of concern in previous versions of this review.

This update of the review reports a significant reduction in the incidence of necrotising enterocolitis (NEC) in a very large sample (n = 2639). In a single small study (n = 50), mean time to achieve full enteral feeds was significantly reduced.

The incidence of intraventricular haemorrhage (IVH) (grades III and IV) (n = 1460) was significantly reduced, as was the incidence of periventricular leukomalacia (PVL) (n = 1469). It has been postulated that early red blood cell transfusions may increase the risk of extension of IVH grade I to higher grades (Baer 2011), and that late red blood cell transfusions may be associated with NEC (Blau 2011). It has been suggested that even small reductions in the number of transfusions given to neonates could have an impact on the occurrence of IVH and NEC (Ohls 2013; Ohls 2013a). As most IVHs and extensions of IVHs occur within the first 72 hours of life (Dolfin 1983), it is difficult to imagine that early EPO treatment with a very small reduction in transfusions over the whole study period (< 1) could have an impact on the incidence of IVH and on extension from a grade I to a grade III or IV haemorrhage. Previously (before the use of EPO for neuro protection), most studies had started the intervention beyond 72 hours of age. Our previous EPO review found no significant reductions in IVH or NEC (Ohlsson 2014). Results showing a possible association between transfusions in neonates and occurrence of transfusion-associated NEC vary depending on study design (Kirpalani 2012).

A lower incidence of NEC was found to be associated with more transfusions in randomised controlled trials - an effect opposite to that seen in observational studies (transfusions are associated with NEC) (Kirpalani 2012).

Length of hospital stay was significantly reduced in the EPO group (n = 970).

Investigators reported no significant differences between EPO and control groups in the incidence of bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age (PMA) (n = 1719), nor in the incidence of proven sepsis (n = 2180).

Ultrasonographic signs of brain injury (IVH, PVL), BPD, severe ROP, and infection strongly predict risk of later death or neurosensory impairment as 18-month outcomes of extremely low birth weight infants (Schmidt 2003; Bassler 2009). As evidence now suggests that EPO reduces the incidence of IVH and PVL - although not of BPD, ROP, or sepsis - it is possible that early treatment with EPO could have a neuro protective effect among preterm infants. However, data show no significant differences in 'Survivors at discharge from hospital without severe IVH, PVL, or ROP' in a high-quality study including 443 infants.

### Neuroprotection

This aspect of EPO use in neonates has been systematically reviewed outside of Cochrane (see the section Agreements and disagreements with other studies or reviews). Four studies included in this review were designed to assess EPO as a neuro protective agent (Fauchère 2008; He 2008; Fauchère 2015; Song 2016). In addition, Ohls 2013 reported on possible neuro protective effects of EPO and Darbe in follow-up reports of the original cohort, although the objective of her primary study was to assess whether infants would respond to Darbe with reduced transfusion needs compared with no treatment, with less frequent dosing than with EPO. Fauchère 2008 used early EPO with the goal of providing neuro protection to very preterm infants. The primary hypothesis of this pilot study was that "the rate of survivors without brain injury (IVH and PVL) including ROP [is] not affected by administration of three high doses of EPO early after birth". The percentage of infants who survived without brain injury or ROP was 53% in the EPO group and 60% in the placebo group. However, five infants in the EPO group versus none in the placebo group died. The risk ratio (RR) for mortality was higher in this study when compared with results of other trials.

The purpose of He 2008 was to evaluate the effect of early EPO therapy on neuro behavioural development in preterm seven-day-old infants. This study was written in Chinese, and we were able to understand only the abstract, which was available in English (we have contacted trial authors to request additional information but have not received an answer). Neonatal Behavioral Neurological Assessment at 40 weeks' PMA and Gesell Developmental Schedule at 6 and 12 months after birth were used to assess infant participants. Results favoured the EPO group.

In our meta-analyses, we identified conflicting results for short- and long-term neurological outcomes. Data show significant reductions in white matter injury, signal abnormality, periventricular white matter loss, and grey matter injury among infants at term. At 18 to 24 months of age, incidences of Bayley-II Mental Development Index (MDI) < 70, but not of Bayley-II Psychomotor Development Index (PDI) < 70, were reduced. The Bayley-II MDI at 18 to 24 months (n = 981) was significantly increased in the EPO group compared with the placebo group, but heterogeneity was high ($I^2$ = 97%). The Bayley Scales of Infant Development - Third Edition (BSID-III) composite cognitive scores at 18 to 22 months were increased in favour of EPO in a small study (n = 53). In the same single study, the BSID-III composite cognitive score at 18 to 22 months was increased in favour of erythropoiesis-stimulating agents (ESAs) (n = 80), as was the Wechsler Preschool and Primary Scale of Intelligence - Third Edition Full-Scale Intelligence Quotient (WPPSI-III FSIQ) score at 3.5 to 4 years of age (n = 53).

We found no significant difference in the incidence of 'Cerebral palsy at 18 to 24 months' corrected age' between EPO and placebo groups (n = 1172) but a significant reduction in 'Any neurodevelopmental impairment at 18 to 22 months' in the EPO group compared with the placebo group (n = 1130). 'Survival without major neurological or neurodevelopmental disorders at 2 years of age' was not reduced in the EPO group compared with the placebo group (n = 404). Death or moderate/severe neurological disability at 18 to 24 months was significantly reduced in the EPO group in a single study (n = 668), as was 'Moderate/severe disability at 18 to 24 months' (n = 613). The Darbe versus no treatment study (n = 51) reported a significant reduction for risk difference (RD) but not for risk ratio (RR) in 'Cerebral palsy at 18 to 22 months' in favour of Darbe. The same comparison revealed reduced risk of neurological developmental impairment (having cerebral palsy (CP), visual defect, hearing defect, or cognitive score < 85) at 18 to 22 months (n = 51). In the same study, BSID-III composite cognitive scores, language scores, and objective permanence (OP) scores were significantly increased (n = 51), and in a smaller sample (n = 29), results were significantly better in the Darbe group compared with the no treatment group for WPPSI-III Full-Scale Intelligence Quotient (FSIQ), Performance Intelligence Quotient (PIQ), Executive function, and Working memory at 3.5 to 4 years of age.

## Overall completeness and applicability of evidence

This review provides evidence that early administration of EPO significantly reduces the 'use of one or more blood transfusions' following study entry with a low number needed to treat for an additional beneficial outcome (NNTB) of 7 and a narrow 95% confidence interval (CI) of 6 to 10. From our results, we cannot make a recommendation with regard to the best combination of a high or low dose of EPO and a high or low dose of iron. We had arbitrarily set a cutoff of ≤ 5 mg/kg/d of oral intake for low and high doses of iron. When we conducted the review, we discovered that several studies started with intravenous administration of iron in variable doses, and we considered any intravenous dose of iron as a high dose. Early EPO significantly reduces the total volume of red blood cells transfused, the number of red blood cell transfusions per infant, and the number of donor exposures. For these outcomes, effect sizes were small and are likely to be of limited clinical importance. Overall, early EPO provides very limited clinical benefit with regards to a reduction in the use of red blood cell transfusion; therefore, its use for this purpose is not recommended.

Good evidence suggests that early use of EPO does not have a statistically significant effect on mortality. This update of the review provides high-quality evidence obtained by GRADE to show that early EPO does not increase the risk of ROP (stage ≥ 3).

In this update of the review, some important short-term outcomes are now statistically significantly reduced: IVH (grades III and IV) (Analysis 1.13), PVL (Analysis 1.14), and NEC (Analysis 1.11) (all moderate-quality evidence by GRADE). In these analyses, the only study that showed a significant reduction in the incidence of these outcomes was Song 2016 - a large study (n = 743) - and in the analyses, this study carried weights of 72.8% for IVH, 89.2% for PVL, and 47.8% for NEC. The second largest included study - Fauchère 2015 (n = 443) - did not show significant differences among these three outcomes. It is expected that results of the two ongoing large studies (NCT01378273; NCT02550054) will shed light on these conflicting results. Until that time, early EPO is not recommended to reduce IVH, PVL, or NEC.

As noted above, results of long-term follow-up studies are conflicting; Song 2016 (n = 613) reported a marked increase in the Bayley-II MDI at 18 to 24 months by 11 points (Analysis 1.28), whereas Fauchère 2015 (n = 365) showed a non-significant decrease of one point. Heterogeneity for this outcome was extreme ($I^2$ = 97%). For the outcome 'Any neurodevelopmental impairment at 18 to 22 months' corrected age', evidence shows large differences between the two largest studies: Song 2016 (n = 613) showed a highly statistically significant reduction in the outcome, whereas Fauchère 2015 (n = 365) did not.

Again, it is hoped that the ongoing studies referenced above will resolve these conflicting results; until that time, early EPO is not recommended for neuro protection or for improved long-term neurodevelopmental outcomes.

## Quality of the evidence

Evidence shows statistically significant (moderate) heterogeneity for the primary outcome ('use of one or more blood transfusions') as well as for two important secondary outcomes ('total volume of blood transfused per infant' and 'number of transfusions per infant'). In previous versions of this review, we have tried to ex-

plain heterogeneity by performing secondary analyses based on perceived study quality and different transfusion practices. As we were not able to present an explanation, we excluded those analyses from this update. We have presented our concerns about heterogeneity both above and in the 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4).

We have presented in the 'Summary of findings' tables our judgements according to GRADE, regarding quality of the evidence for important primary and secondary outcomes (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4).

We rated the quality of evidence (GRADE) as high for 'Mortality during initial hospital stay', 'ROP (stage ≥ 3)', 'Survivors at discharge from hospital without severe IVH, PVL, ROP', and 'Cerebral palsy at 18 to 24 months'. We rated the quality of evidence (GRADE) as moderate for 'NEC', 'IVH', 'PVL', and 'BSID-III composite cognitive scores at 18 to 22 months'. We rated the quality of evidence (GRADE) as low for 'Use of one or more red blood cell transfusions (low and high doses of EPO)', 'Any neurodevelopmental impairment at 18 to 22 months' corrected age', 'Bayley-II MDI at 18 to 24 months', 'Time to achieve full enteral feeding', and 'WPPSI-III FSIQ at 3.5 to 4 years of age'.

Among the few infants studied to date, Darbe appears to have effectiveness similar to that of EPO. Too few infants have been studied for assessment of its safety. Darbepoetin does offer the advantage of fewer injections required, thus reducing painful stimuli for this vulnerable population.

A funnel plot for the primary outcome 'use of one or more red blood cell transfusions' was asymmetrical, with relative absence of smaller studies not having a protective effect (Figure 5). This may indicate that smaller studies with 'negative' results have not been published.

## Potential biases in the review process

We are not aware of any potential biases in our review process.

## Agreements and disagreements with other studies or reviews

Early systematic reviews (which included fewer studies than were included in our reviews) have not included ROP or other common neonatal outcomes as outcome measures (Vamvakas 2001; Garcia 2002; Kotto-Kome 2004). Those reviews noted similar effect sizes for transfusion needs and reported on statistically significant between-study heterogeneity.

Xu 2014 performed a meta-analysis of EPO and ROP. Review authors included randomised controlled trials (RCTs), observational cohort studies, and retrospective case-control studies. They concluded that EPO treatment is not associated with development of ROP in preterm infants, but this conclusion should be confirmed by further high-quality research. Chou 2017 performed a systematic review of early and late EPO administration and risk of ROP in preterm infants. These review authors included unpublished data from Maier 2002, which we had obtained from trial authors and had included in our Cochrane review. Results provided in Chou 2017 for the early EPO group correspond to those of our current updated review, except that we included two additional studies (Fauchère 2015; Peltoniemi 2017), thereby increasing the power of our analysis. Their conclusions that EPO administration did not increase the risk of ROP of any stage reported or of stage ≥ 3 are consistent with our findings in this update.

Zhang 2013 performed a review titled "Neuroprotection with erythropoietin in preterm and/or low birth weight infants". These review authors included four studies for the primary outcome of neurodevelopmental disability and concluded that use of EPO, to some extent, is associated with a reduction in neurodevelopmental disability in preterm infants. They included the Bierer 2006 report. One of the authors of this study, Dr. R.K. Ohls, informed us that this study reported on a subgroup of the Ohls 2001A study. All outcomes of Bierer 2006 are included in the 2004 follow-up publication of the Ohls 2001A study. Thus analyses that include results from both Ohls 2001A (follow-up, Ohls 2004) and Bierer 2006 are incorrect, as they include the same children twice. Under '2.6. Data extraction' review authors write, "All abstracts and published studies identified as potentially relevant by the literature search were assessed for inclusion by two review authors. Each author extracted data separately on a data extraction form. The information was then compared, and differences were resolved by consensus. One review author (A.O.) entered data into RevMan 5.1 Software (Cochrane Collaboration, Oxford, UK), and the other (S.A.) cross-checked the printout against his own data extraction forms and any errors were corrected. For the studies identified in abstract form, the primary author was contacted to obtain further information". This paragraph has been directly copied from our previous review, including our initials (A.O. and S.A.). That review included results of the Newton 1999 report. Trial authors followed up to seven years of age 40 infants who had been enrolled in two pilot studies and one multi-centre study at the University of California, San Francisco. The three included studies enrolled infants at eight or more days, at 10 to 35 days, and at 23 to 24 days of age. Those infants do not meet our inclusion criterion of age less than eight days. One included study was an observational study (Neubauer 2010). Owing to the concerns raised above, the results of this review are not valid.

Wang 2015 performed a meta-analysis of the protective effect of EPO for neurodevelopment in preterm infants. Review authors concluded that EPO treatment has beneficial effects on neurodevelopmental outcomes without severe adverse side effects. They included two RCTs and three quasi-randomised trials. They included the Bierer 2006 report, which we know from Dr. Ohls is a duplicate publication of her follow-up study from 2004 (listed

under Ohls 2001A). Thus the seven analyses that include results from both Ohls 2001A (follow-up of Ohls 2004) and Bierer 2006 are incorrect, and results of this review are not valid.

Fischer 2017 presented a meta-analysis of prophylactic early EPO in preterm infants. Review authors included four RCTs and referred to follow-up studies (Ohls 2004, Ohls 2014, Natalucci 2016) of the original reports - not the report of the primary study, except for Song 2016, which included long-term follow-up in the original report. We included follow-up reports under the original studies (Ohls 2001A; Ohls 2013; Fauchère 2015; Song 2016). In addition, we included unpublished information from Fauchère 2008, along with one new study (Peltoniemi 2017). The primary outcome of the meta-analysis by Fischer 2017 was the number of infants with a Mental Developmental Index (MDI) < 70 on the Bayley Scales of Infant Development - Second Edition (BSID-II) at 18 to 24 months' corrected age. If infants were assessed according to the Third Edition (BSID-III), review authors used cognitive scores < 85 as the primary outcome. We kept analyses for BSID-II and BSID-III separate. Sharp 2017 in a randomised cross-over study found that when severity of delay was classified via standardised cut-points for moderate and severe developmental delay (1 and 2 SDs below reference norm), 40% of children were classified as less severely delayed with the Bayley-III cognitive composite score than with the BSID-II MDI, whereas only one child (< 2%) was classified as more severely delayed with the Bayley-III. Sharp 2017 concluded that "these findings have critical implications for both the interpretation of clinical research studies and determination of eligibility for services in high-risk children". Fischer 2017 found that prophylactic EPO improved the cognitive development of very preterm infants as assessed by the MDI at corrected age of 18 to 24 months. However, review authors did not report on the MDI at that age, but on MDI < 70 at corrected age of 18 to 24 months. We found a similar reduction in this outcome and an increase in the WMD in Bayley-II at 18 to 24 months. Authors of the review state that they followed standard methods of the Cochrane Neonatal Review Group but made two deviations from the Cochrane Neonatal standard method, that is, they used the odds ratio and the random-effects model when performing these analyses. Review authors concluded that "prophylactic rhEPO improved the cognitive development of very preterm infants, as assessed by the MDI at a corrected age of 18 to 24 months, without affecting other neurodevelopmental outcomes. Current and future RCTs should investigate optimal dosing and timing of prophylactic rhEPO and plan for long-term neurodevelopmental follow-up" (Fischer 2017). Like us, Fischer 2017 raised concerns about lack of blinding, late registration, and differences in primary outcomes between the registration document and the final report in Song 2016 (high risk). We found significant results for several neurodevelopmentally related outcomes in infants treated with EPO; and reduced rates of IVH, PVL, white and grey matter injury at term, any neurodevelopmental impairment at 18 to 22 months' corrected age, moderate/severe neurological disability at 18 to 24 months, and death or moderate/severe neurological disability at 18 to 24 months. Many of these results were strongly influenced by results from Song 2016, for which both Fischer 2017 and we were concerned about high risk of bias. It is important that ongoing trials such as NCT01378273 and NCT02550054 are conducted and completed, with long-term follow-up provided in a timely fashion.

# AUTHORS' CONCLUSIONS

## Implications for practice

Early administration of erythropoietin (EPO) reduces the use of one or more red blood cell transfusions, the volume of red blood cells transfused, and the numbers of donors and transfusions the infant is exposed to following study entry (low quality of evidence according to GRADE). Donor exposure probably is not avoidable, as most studies included infants who had received red cell transfusions before trial entry. Although statistically significant, these reductions are of limited clinical importance. For the present, it is important that neonatal intensive care units (NICUs) develop practice guidelines to limit blood losses and donor exposure among neonates. Use of satellite packs and adherence to conservative transfusion guidelines reduce exposure to multiple donors during the hospital stay. The need for red blood cell transfusions is linked to loss of blood associated with sampling for laboratory testing. In the current update of this review, evidence of high quality according to GRADE shows no significant increase in the rate of retinopathy of prematurity (ROP) (stage ≥ 3) with early use of EPO. Increasing evidence suggests that EPO reduces several important adverse outcomes, including intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), and necrotising enterocolitis (NEC) (all with moderate quality of evidence according to GRADE). Early EPO used for neuro protection may reduce neurodevelopmental impairment at 18 to 22 months' corrected age (low quality of evidence according to GRADE) and may increase Bayley-II Mental Development Index (MDI) scores at 18 to 24 months (low quality of evidence according to GRADE). In view of limited clinical benefit, early administration of EPO outside of randomised controlled trials (RCTs) is not currently recommended. Evidence showing the effectiveness of Darbe is lacking because small samples have been studied and followed.

## Implications for research

Future research should focus on strategies to minimise red blood cell donor exposure during the first week of life, when the likelihood of the need for red blood cell transfusion is at its peak. Such strategies, which include use of satellite packs in combination with late EPO treatment, may reduce further donor exposure. Currently, trialists have expressed no concern that early EPO

exposure increases risk of ROP, but this should be included as an outcome in future trials. Early EPO may improve feeding intolerance and reduce the incidence of NEC; additional studies are needed in both developed and developing countries. Based on our 'Quality of evidence assessments according to GRADE', we have concerns about current evidence for the neuro protective effects of early EPO. Studies of the highest quality showed no significant reduction in adverse outcomes. One study with high risk of bias showed large significant effects of the intervention in favour of early EPO. Two currently ongoing large trials could shed light on these differences. New studies should include long-term follow-up.

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* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

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

### Arif 2005

| Methods | Randomised open controlled study<br>Study location: single-centre study performed in Istanbul, Turkey<br>Study period: 1993 to 2002 |
|---|---|
| Participants | 292 preterm infants < 33 weeks' GA, birth weight < 1500 grams, no blood sampling > 10 mL in the first 7 days after birth, no previous blood transfusion, no IVH > grade 1, no history of hematological disease, no urinary tract infection or sepsis |
| Interventions | 142 infants in EPO group received EPO (EPREX 2000, Santa-Farma-Gurel, Istanbul) 200 IU/kg SC from the seventh day of life and continued twice weekly (400 IU/kg/week, low dose) for 6 weeks. 150 infants in the control group did not receive a placebo. Both groups received iron (3 to 5 mg/kg/d orally) (high dose) |
| Outcomes | Use of 1 or more red blood cell transfusions<br>Mortality<br>NEC<br>ROP (stage not reported)<br>BP |
| Notes | Infants who had received red blood cell transfusion before study entry were excluded. Transfusion guidelines were in place.<br>The iron dose varied from 3 to 5 mg/kg/d, but we included this as a high dose in our subgroup analyses |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-assisted randomisation scheme |
| Allocation concealment (selection bias) | Unclear risk | No information provided |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | No placebo used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | No placebo used |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up: yes |

**Arif 2005** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Avent 2002**

| | |
|---|---|
| Methods | Randomised open controlled study<br>Study location: 2 centres in South Africa<br>Study period: not stated |
| Participants | 93 infants < 7 days of life, in room air or requiring 30% oxygen at study entry with birth weight between 900 and 1500 grams<br>Infants were stratified by weight < 1250 grams and > 1250 grams, then were randomised to 3 treatment groups |
| Interventions | 32 infants (low-dose group) received EPO (Recormon) SC, 250 IU/kg 3 times a week (high dose).<br>31 infants (high-dose group) received EPO (Recormon) SC, 400 IU/kg 3 times a week (high dose).<br>30 infants (control group) received standard care.<br>The endpoint of therapy was reached when the infant was discharged from the hospital.<br>All infants received a therapeutic dose of 6 mg/kg (high dose) elemental iron orally every day; this was increased to 8 to 10 mg/kg (high-dose iron) if hypochromic cells accounted for 20% or more.<br>All infants subsequently received blood transfusions if they met the transfusion criteria |
| Outcomes | Use of 1 or more red blood cell transfusions<br>Total volume (mL/kg) of blood transfused per infant<br>Number of blood transfusions per infant<br>Mortality<br>Sepsis<br>Hypertension<br>Length of hospital stay |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included. Transfusion guidelines were in place |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Blinding of randomisation unclear |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | No placebo was given to the control group. Personnel were aware of treatments |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | No placebo was given to the control group. Outcome assessors were aware of treatments |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Carnielli 1992**

| | |
|---|---|
| Methods | Randomised controlled trial Study location: single centre in Italy Study period: not stated |
| Participants | 22 preterm infants with gestational age < 32 weeks, birth weight < 1750 grams, and age > 2 days |
| Interventions | 11 infants in the EPO group received EPO (unnamed product), 400 IU, 3 times weekly, IV (400 IU/mL saline solution for 1 to 2 minutes) if IV line in place (1200 IU/kg/week, high dose), then continued SC, plus iron (h) 20 mg/kg once a week IV (high-dose iron) from second day of life until discharge. 11 infants in the control group did not receive EPO or iron. |
| Outcomes | Number of transfusions Number of donor exposures (range) Mortality Neutropenia Hospital stay in days Side effects |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included. Transfusion guidelines were in place. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | Infants randomly assigned |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Control group received no placebo. Personnel were not blinded |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Control group received no placebo. Personnel were not blinded |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

## Carnielli 1998

| | |
|---|---|
| Methods | Randomised controlled trial Study location: single centre in Italy Study period: not stated |
| Participants | 63 preterm infants with birth weight < 1750 grams and gestational age < 32 weeks, between the second day and 8 weeks of life |
| Interventions | 22 infants in EPO + iron group received 400 IU EPO (Eprex, Cilag, Italy) per kg 3 times a week (high dose) + 20 mg/kg/week of IV iron (high dose). 20 infants in EPO group received EPO 400 IU/kg 3 times a week (high dose) without iron (low dose). 21 infants in the control group received no treatment or placebo. Treatment was continued to the eighth week of life (or until hospital discharge). EPO was administered IV if the participant had an IV line, then was continued SC at the same dose. All infants were fed the same preterm formula and received 80 mcg/kg of folic acid and 25 IU/d of vitamin E during the study period. No oral iron supplements were given during the study period |

| Outcomes | Mean number of blood transfusions (95% CI) BPD (age not stated) IVH (grade not stated) Sepsis ROP (stage not stated) Days in hospital |
|---|---|
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included. Transfusion guidelines were in place. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | Infants randomly allocated |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | No placebo was administered. Personnel were aware of treatments |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | No placebo was administered. Outcome assessors were aware of treatments |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

Chang 1998

| Methods | Randomised controlled trial Study location: single centre in China Study period: March 1996 to March 1998 |
|---|---|
| Participants | 45 preterm infants with BW ≤ 1800 grams and GA ≤ 35 weeks, age 1 day |

| Interventions | 15 infants in group 1 received EPO (Kirin Brewery, Co., Ltd., Japan) 150 IU/kg (450 IU/kg/week, low dose) SC 3 times a week for 6 weeks.<br>15 infants in group 2 received EPO 250 IU/kg (750 IU/kg/week, high dose) SC 3 times a week for 6 weeks.<br>15 infants in group 3 did not receive any treatment.<br>All infants received oral iron 20 mg (high dose) from day 7 after birth |
|---|---|
| Outcomes | Use of 1 or more red blood cell transfusions<br>Sepsis<br>Neutropenia<br>Hypertension<br>Side effects |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included.<br>It is not stated whether transfusion guidelines were in place |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Unclear |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment unclear |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | No placebo was given. Personnel were aware of group assignments |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | No placebo was given. Outcome assessors were aware of group assignments |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**El-Ganzoury 2014**

| Methods | Double-blind randomised controlled trial<br>Study location: neonatal intensive care units of Ain-Shams Univeristy Hospital, Cairo, Egypt<br>Study period: March 2013 to March 2014 |
|---|---|
| Participants | Preterm infants, PMA ≤ 33 weeks |
| Interventions | 20 infants received enteral rhG-CSF, 20 received enteral rhEPO, 20 received both enteral rhG-CSF and rhEPO, and 30 received distilled water as placebo. This regimen was started on the day the neonatologist chose to start feedings. Study drugs were given enterally. The daily dose of enteral rhG-CSF and/or rhEPO was diluted in sterile distilled water and was kept in a separate opaque aliquot before administration through the orogastric/nasogastric tube with milk feedings for 7 days. rhEPO was given as 88 IU/kg (total dose 616 IU/kg - high dose). The placebo group was given 1 mL of distilled water once daily. It is not clear whether all infants received the same volume/kg of drug for the 3 interventions |
| Outcomes | Death<br>NEC<br>Time to achieve full enteral feeding (days)<br>Duration of hospital stay (days) |
| Notes | We included the outcome of Time to achieve full enteral feeding (days) under a separate comparison |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation sequence generated by computer |
| Allocation concealment (selection bias) | Low risk | Opaque sequentially numbered sealed envelopes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Study drugs were kept in separate opaque aliquots before administration through the orogastric/nasogastric tube with milk feedings for 7 days. Control group was given 1 mL of distilled water (placebo). Placebo must have looked different from the opaque study drugs |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | See above. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised infants were accounted for. |

| Selective reporting (reporting bias) | Low risk | Trial was registered as NCT01441427, on September 18, 2011, before the trial started. No deviations from the protocol are apparent |
| --- | --- | --- |
| Other bias | Low risk | Appears free of other bias |

### Fauchère 2008

| Methods | Randomised controlled trial<br>Study location: single centre in Switzerland<br>Study period: September 2005 through November 2006 |
| --- | --- |
| Participants | 45 preterm infants born between 24 6/7 and 31 6/7 weeks' gestation |
| Interventions | 30 infants in the EPO group received 3000 IU rhEPO/kg (Epoietin Beta, Roche, Basel Switzerland) IV 3 to 6, 12 to 18, and 36 to 42 hours after birth (high dose). No infant was treated later with rhEPO for anaemia of prematurity. 15 infants in the placebo group received the same volume of 0.9% NaCl (indistinguishable from rhEPO). Use of iron was not mentioned |
| Outcomes | Mortality<br>IVH (all grades and grades III to IV)<br>Persistent periventricular echodensity<br>ROP (all stages and stages 3 to 4)<br>Sepsis<br>NEC (stage not reported)<br>BPD at 36 weeks' PMA |
| Notes | Study was supported by Roche Foundation for Anemia Research. Infants who were 26 0/7 to 31 6/7 weeks' PMA at birth were included in another study by the same group (Fauchère 2015). The first author - Dr. Fauchère - informed us with that the study included 8 infants who were < 26 weeks' PMA at enrolment (6 infants in the EPO group and 2 in the placebo group). 3 survivors were included in the < 26 weeks' PMA group (1 infant in the EPO group and 2 in the placebo group). We report on mortality for these 8 infants under Fauchère 2008.<br>We report on MDI, PDI, CP, vision, and hearing for the 3 survivors under Fauchère 2008. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
| --- | --- | --- |
| Random sequence generation (selection bias) | Low risk | Computer-based random-number generator |
| Allocation concealment (selection bias) | Low risk | Assignment was made by the hospital pharmacy. |

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Normal saline was given as the placebo intervention; it was indistinguishable from the rhEPO solution |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Normal saline was given as the placebo intervention; it was indistinguishable from the rhEPO solution |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Outcomes reported for all randomised infants |
| Selective reporting (reporting bias) | Unclear risk | Study was registered at www.clinicaltrials. gov (NCT00413946) in December 2006, after the last participant had been enrolled in November 2006. Registration was for the larger study published in 2015 (Fauchère 2015). The protocol for the early part of the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Fauchère 2015**

| | |
|---|---|
| Methods | Randomised controlled trial Study location: multi-centre trial in Switzerland Study period: September 2005 to December 2012 |
| Participants | Preterm infants with PMA 26 0/7 to 31 6/7 weeks |
| Interventions | Experimental intervention: EPO (Epoietin Beta, Roche Basel, Switzerland) (3000 IU/ kg BW), equal to 1 mL solution/kg BW, was given IV at < 3, 12 to 18, and 36 to 42 hours after birth over a period of 10 minutes - total dose 9000 IU/kg during first week of life - high dose. Total number randomised: n = 229 infants (1 infant in the EPO group was excluded because the infant did not get the full medication dose as allocated - 229 infants analysed) Control intervention: 1 mL solution/kg BW of NaCl 0.9% IV at < 3, 12 to 18, and 36 to 42 hours after birth over a period of 10 minutes Total number randomised: n = 214 infants (6 infants in the placebo group excluded because they did not receive the full medication dose as allocated - 214 infants analysed) |
| Outcomes | Mortality ROP IVH Sepsis NEC BPD |

| | Survivors without any severe IVH and ROP, IVH, ventricular dilatation, cystic or non-cystic PVL, ROP, sepsis, NEC, persistent PDA, BPD, hemangioma, ROP grade 4, or need for laser/cryotherapy<br>Length of hospital stay, weight and head circumference at discharge<br>In a separate report by Leuchter R H-V et al in 2014, a subset of 165 infants (77 assigned to EPO and 88 to placebo) were assessed for brain abnormalities on MRI performed at term-equivalent age. Infants with abnormal scores for white matter injury, white matter signal intensity, periventricular white matter loss, and grey matter injury were reported. Outcomes at 2 years of age were reported in a separate study by Natalucci G et al in 2016. Outcomes reported included BSID-II (MDI and PDI), cerebral palsy, severe hearing impairment, severe visual impairment, survival without severe neurodevelopmental impairment, MDI < 70, and PDI < 70. Long-term outcomes were reported for 365 infants (81%); 191 infants were assigned to EPO, and 174 infants to placebo |
|---|---|
| Notes | This study includes infants ≥ 26 weeks from Fauchère 2008. The 2008 study included 6 infants in the EPO group and 2 in the placebo group who were < 26 weeks' PMA. In the EPO group, 5 died and 1 survived. In the placebo group, both infants survived. We report the outcomes of these infants under Fauchère 2008. We received additional information on these 8 infants at < 26 weeks' PMA from Dr. Fauchère |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-based random-number generator |
| Allocation concealment (selection bias) | Low risk | Assignment by hospital pharmacy |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Normal saline given as the placebo intervention and indistinguishable from the rhEPO solution |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Normal saline given as the placebo intervention and indistinguishable from the rhEPO solution |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Outcomes reported for all randomised infants |
| Selective reporting (reporting bias) | Low risk | Study was registered at www.clinicaltrials.gov (NCT00413946) in December 2006 |
| Other bias | Low risk | Appears free of other bias |

**Haiden 2005**

| Methods | Randomised controlled trial<br>Study location: neonatal intensive care units in Vienna, Austria<br>Study period: October 2000 to November 2002 |
|---|---|
| Participants | 40 preterm infants with BW < 800 grams and GA < 32 weeks' gestation |
| Interventions | EPO group (n = 21) received 300 IU/kg/d of EPO (Erypo, Janssen-Cilag Pharma, Vienna, Austria) IV (as long as IV access was available), or 700 IU/kg 3 times/week (2100 IU/kg/week, high dose) and iron dextran 1.5 mg/kg/d IV or iron polymerase complex 9 mg/kg/d orally (high dose).<br>Therapy was given until 40 weeks' GA or discharge.<br>Control group (n = 19) did not receive IV iron. Iron was started orally from the 15th day of life, or when infant tolerated 60 mL/kg of enteral feeding, whichever came first<br>Placebo was not used. |
| Outcomes | Use of 1 or more red blood cell transfusions<br>Number of donors<br>Mortality<br>NEC<br>PVL<br>IVH (grades I to II)<br>IVH (grades III and IV)<br>Hospital stay<br>BPD (age not stated)<br>ROP (stages I and II)<br>ROP (stages III and IV) |
| Notes | 47 infants were eligible for enrolment in the study. Four infants were excluded because of parental refusal (n = 2) or IVH grade IV (n = 2).<br>Three infants died before randomisation.<br>The final cohort included 40 infants.<br>It is not stated whether infants who had received blood transfusions before study entry were included.<br>Transfusion guidelines were in place. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Low risk | Sealed opaque envelopes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | No placebo was administered to the control group. Personnel were aware of group assignments |

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | High risk | No placebo was administered to the control group. Outcome assessors were aware of group assignments |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Complete follow-up: 47 infants were eligible for enrolment in the study. Four infants were excluded because of parental refusal (n = 2) or IVH grade IV (n = 2). Three infants died before randomisation. The final cohort included 40 infants. |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**He 2008**

| | |
|---|---|
| Methods | Randomised controlled trial Study location: Department of Neonatology, Zangzhou Municipal Hospital, Fujian, China Study period: not stated |
| Participants | Population: 44 preterm infants, 7 days old |
| Interventions | Intervention: EPO group received 250 IU/kg/d 3 times weekly IV for 4 weeks (750 IU/kg/week, high dose). Use of iron is not stated, nor is it stated what the control group received |
| Outcomes | Neonatal Behavioral Neurological Assessment at 40 weeks' PMA Gesell Developmental Schedule at 6 and 12 months after birth |
| Notes | This study has been published as a full report in Chinese. Only the abstract was written in English. We requested the full paper and if possible an English translation from the first author (2009-08-08). The only data provided with means and SDs were scores for the Neonatal Behavioral Neurological Assessment at 40 weeks' PMA |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | 44 preterm infants randomly divided into 2 groups |

| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | As we have not been able to obtain an English translation of the full article, this item cannot be assessed |
| --- | --- | --- |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | As we have not been able to obtain an English translation of the full article, this item cannot be assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Complete follow-up: unclear |
| Selective reporting (reporting bias) | Unclear risk | As we have not been able to obtain an English translation of the full article, this item cannot be assessed |
| Other bias | Unclear risk | As we have not been able to obtain an English translation of the full article, this item cannot be assessed |

**Khatami 2008**

| Methods | Randomised controlled trial<br>Study location: Newborn Services at Ghaem Medical Center, Tehran, Iran<br>Study period: 6 months from May 2003 |
| --- | --- |
| Participants | Population: 40 preterm infants with BW > 1000 grams but < 1750 grams and GA > 28 weeks but < 34 weeks, who were between 48 and 96 hours old at the time of study entry |
| Interventions | EPO group received 500 IU/kg/d of EPO SC twice weekly (1000 IU/kg/week, high dose) and iron (ferrous sulphate) 3 mg/kg/d enterally (low dose). Control infants received iron (ferrous sulphate) 3 mg/kg/d enterally (low dose) at second week of life. Parenteral iron was not administered throughout the study |
| Outcomes | Number of red blood cell transfusions per patient<br>Weight gain<br>Hospital stay |
| Notes | "Guidelines for red-cell transfusions were based on the relatively strict existing policy in the nursery which was used to administer transfusions during the study period" |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
| --- | --- | --- |
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Low risk | Numbered sealed envelopes |

| Blinding of participants and personnel (performance bias) All outcomes | High risk | No placebo was used. Personnel were aware of group assignments |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | High risk | No placebo was used. Outcome assessors were aware of group assignments |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete follow-up: yes. 18 infants were excluded owing to parents' refusal and un-availability |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Kremenopoulos 1997A**

| Methods | Randomised controlled study Study location: Department of Neonatology, University of Thessaloniki, Hippokratio Hospital, Thessaloniki, Greece Study period: not stated |
|---|---|
| Participants | 50 neonates with BW ≤ 1500 grams, PMA ≤ 31 weeks Infants who had received transfusion before enrolment were included |
| Interventions | EPO group received rhEPO (Cilag A.G., Zug, Switzerland) 3 × 250 U/kg/week SC (750 U/kg/week - high dose) (n = 24). Treatment was given for 6 weeks. Control group (n = 26) received no intervention All infants received elemental iron 3 mg/kg/d. Treatment was initiated at 3 to 7 days - early EPO. |
| Outcomes | Transfusions/patient Patients receiving transfusions |
| Notes | Retrospectively, infants were divided into those without complications (without or with minimal signs of respiratory distress and no signs of sepsis) and those with complications requiring mechanical ventilation (RDS and sepsis with positive blood culture) for longer than 3 days, who were characterised as having complications. Outcomes were reported separately for infants without complications (we listed those outcomes under Kremenopoulos 1997A) and for infants with complications (we listed those outcomes under Kremenopoulos 1997B). An additional group of 35 infants (Group B) were enrolled at 3 to 8 weeks and will be included in the late EPO review. No information was provided regarding transfusion guidelines for either group |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | "In group A 50 infants were randomly assigned". |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | No placebo was used. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | No placebo was used. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Outcomes were reported for all enrolled infants. |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us, so we cannot judge if whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Kremenopoulos 1997B**

| | |
|---|---|
| Methods | Randomised controlled study<br>Study location: Department of Neonatology, Univeristy of Thessaloniki, Hippokratio Hospital, Thessaloniki, Greece<br>Study period: not stated |
| Participants | 50 neonates with BW ≤ 1500 grams, PMA ≤ 31 weeks<br>Infants who had received transfusion before enrolment were included |
| Interventions | EPO group received rhEPO (Cilag A.G., Zug, Switzerland) 3 × 250 U/kg/week SC (750 U/kg/week - high dose) (n = 24). Treatment was given for 6 weeks. Control group (n = 26) received no intervention<br>All infants received elemental iron 3 mg/kg/d.<br>Treatment was initiated at 3 to 7 days - early EPO. |
| Outcomes | Transfusions/patient<br>Patients receiving transfusions |

**Kremenopoulos 1997B**  (*Continued*)

| | |
|---|---|
| Notes | Retrospectively, infants were divided into those without complications (without or with minimal signs of respiratory distress and no signs of sepsis) and those with complications requiring mechanical ventilation (RDS and sepsis with positive blood culture) for longer than 3 days, who were characterised as having complications. Outcomes were reported separately for infants without complications (we listed those outcomes under Kremenopoulos 1997A) and for infants with complications (we listed those outcomes under Kremenopoulos 1997B). An additional group of 35 infants (Group B) were enrolled at 3 to 8 weeks and will be included in the late EPO review. No information was provided regarding transfusion guidelines for either group |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | "In group B 50 infants were randomly assigned". |
| Blinding of participants and personnel (performance bias) <br> All outcomes | High risk | No placebo was used. |
| Blinding of outcome assessment (detection bias) <br> All outcomes | High risk | No placebo was used. |
| Incomplete outcome data (attrition bias) <br> All outcomes | Low risk | Outcomes were reported for all enrolled infants. |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us, so we cannot judge whether any deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Lauterbach 1995**

| | |
|---|---|
| Methods | Randomised controlled trial <br> Study location: single-centre study conducted in Krakow, Poland <br> Study period: not stated |
| Participants | 19 preterm infants with GA < 35 weeks' gestation and birth weight ≤ 1500 grams |
| Interventions | Infants in EPO group I (n = 6) received EPO (Recormon, Boehringer Mannheim) 100 IU/kg twice a week IV (200 IU/kg/week, low dose) between days 7 and 37, and infants in EPO group II (n = 6) received 400 IU/kg twice weekly (800 IU/kg/week, high dose) |

**Lauterbach 1995**   (*Continued*)

| | | |
|---|---|---|
| | during the same time period. Control group (n = 7) received no treatment or placebo. Both EPO groups received 10 mg/kg/week of iron IV (high dose). Control group did not receive iron | |
| Outcomes | Total volume (mL/kg) of blood transfused between days 7 and 37<br>Side effects | |
| Notes | Transfusion guidelines were in place.<br>We could not ascertain whether infants who had received blood transfusions before study entry were included | |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | Randomly selected preterm infants |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Control group received no placebo or iron. Personnel were aware of treatment groups |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Control group received no placebo or iron. Outcome assessors were aware of treatment groups |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Lima-Rogel 1998**

| | |
|---|---|
| Methods | Double-blind randomised controlled trial<br>Study location: single centre, Mexico<br>Study period: 1995 to 1996 |
| Participants | 40 VLBW infants with birth weight between 750 and 1500 grams at < 26 weeks' gestation |
| Interventions | 21 infants in the EPO group received EPO (Eprex 4000, Cilag de Mexico SA de CV) 150 units/kg/d (during first 6 weeks of life), 1050 IU/kg/week (high dose), and 19 infants |

|  | in the control group received placebo.<br>Iron 4 mg/kg/d (low dose) |
|---|---|
| Outcomes | Number of transfusions per group<br>Sepsis<br>NEC<br>IVH (grade not reported)<br>BPD (age not stated) |
| Notes | We could not ascertain whether transfusion guidelines were in place, and if infants who had received blood transfusions before study entry were included |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Unclear |
| Allocation concealment (selection bias) | Unclear risk | Infants were randomly assigned. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Observers were unaware of treatment assignments. Placebo was used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Observers were unaware of treatment assignments. Placebo was used |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Maier 1994**

| Methods | Double-blind randomised controlled trial<br>Study location: 12 centres in 6 European countries<br>Study period: September 1991 to December 1992 |
|---|---|
| Participants | 244 infants with birth weight of 750 to 1499 grams; 3 infants excluded after randomisation |

| Interventions | 120 infants in the EPO group received 250 IU of epoetin beta (Boehringer-Mannheim, Germany) per kilogram; injections on Monday, Wednesday, and Friday (750 IU/kg/week, high dose). Treatment continued until day 40 to 42, for a total of 17 doses. 121 infants in the control group did not receive placebo, but adhesive tape was placed on both thighs and remained there until the next visit. Oral iron supplementation 2 mg/kg/d was started on day 14 in all infants (low dose). Vitamin E supplementation was not part of the protocol. |
|---|---|
| Outcomes | Use of 1 or more red blood cell transfusions Number of transfusions per infant Mortality ROP Sepsis NEC IVH all grades IVH grades III and IV Neutropenia Hypertension Side effects |
| Notes | Infants who had received transfusions before study entry were included (28 in the EPO group and 17 in the control group). Transfusion guidelines were in place. 33 infants in the EPO group and 28 in the control group were withdrawn. Results are reported as per ITT. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Low risk | Numbered sealed envelopes |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Most participating doctors were reluctant to administer repeated subcutaneous injections of placebo to low birth weight infants. Therefoere, 2 teams were formed at each centre: Treating physicians determined whether infants could be enrolled or withdrawn from the study, decided whether they should receive transfusions, and monitored them without knowing their treatment group; "dosing investigators" performed randomisation and administered epoetin beta but were not involved in the infants' care. When treatment |

|  |  | was to be given, a dosing investigator carrying a "black box" containing appropriate equipment visited each infant, administered study medication, and placed adhesive strips on both thighs (of both epoetin recipients and controls), which remained there until the next visit. During this procedure, staff and parents had to leave. A treating physician or a dosing investigator assigned to an infant had to serve in that capacity as long as the infant was studied |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | See information in the box above. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Complete follow-up: no<br>33 infants in the EPO group and 28 in the control group were withdrawn.<br>Results are reported as per ITT.<br>Three of the 244 infants who underwent randomisation were excluded; all data on 2 infants were lost, and treatment (EPO) was inadvertently omitted for 1 infant, whose records were not completed. The remaining 241 infants were evaluated in an ITT analysis |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

## Maier 2002

| Methods | Double-blind randomised controlled trial<br>Study location: 14 centres in 4 European countries<br>Study period: May 1998 to June 1999 |
|---|---|
| Participants | 219 ELBW infants were randomly assigned to early EPO, late EPO, or control on day 3 of life |
| Interventions | 74 infants in the early EPO group received EPO (NeoRecor-mon, F. Hoffman-La Roche, Basel, Switzerland) 250 IU/kg, IV or SC, 3 times a week (750 IU/kg/week, high dose), starting from day 3 of life, for 9 weeks.<br>74 infants in the late EPO group received EPO 250 IU/kg IV or SC, 3 times a week, starting from the fourth week of life, for 6 weeks. |

|  |  |
|---|---|
|  | 71 infants in the control group received sham injections.<br>Enteral iron 3 mg/kg was given to all infants from days 3 to 5 and was increased at days 12 to 14 to 6 mg/kg/d, and to 9 mg/kg/d at days 24 to 26 of life (high dose) |
| Outcomes | Use of 1 or more red blood cell transfusions<br>Number of donors the infant was exposed to (median, quartiles)<br>Number of transfusions per infant (mean)<br>Mortality during hospital stay<br>NEC<br>IVH (grade not stated)<br>PVL<br>ROP (stage not stated)<br>BPD (at 36 weeks' postmenstrual age)<br>Growth<br>Days in hospital (median, quartiles) |
| Notes | Sample size calculation was performed.<br>24 (32%) infants in the early EPO group and 22 (31%) in the control group were exposed to donor blood before study entry.<br>Transfusion guidelines were followed.<br>Study was industry funded (F. Hoffman-La Roche, Basel Switzerland).<br>One infant was excluded from all evaluations because parents withdrew consent a few hours after randomisation before the start of the treatment phase |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Low risk | Numbered sealed envelopes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Treating physicians determined whether infants could be enrolled or withdrawn from the study, and whether infants should receive transfusions, and monitored them without knowing their treatment group. Dosing investigators performed randomisation and administered rhEPO but were not involved in the infants' care. When treatment was to be given, a dosing investigator carrying a "black box" containing appropriate equipment visited each infant, gave or simulated administration of study medication, and placed adhesive strips on both thighs (of rhEPO recipients and controls), which remained there until the next |

|  |  | visit. During this procedure, staff and parents had to leave. A treating physician or a dosing investigator assigned to an infant served in that function as long as the infant was studied |
| --- | --- | --- |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | See the information in the box above. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete follow-up: yes; 1 of the 220 randomised infants (control group) was excluded from all evaluations because parents withdrew consent a few hours after randomisation before the start of the treatment phase |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Meister 1997**

| Methods | Randomised controlled trial Study location: single centre, Austria Study period: not stated |
| --- | --- |
| Participants | 30 preterm infants with birth weight of 750 to 1499 grams and 5 to 10 days old |
| Interventions | 15 infants in the EPO group received epoetin alpha (Janssen-Cilag Pharmaceuticals, Vienna, Austria) 300 IU/kg SC 3 times a week for 4 weeks. 15 infants in the control group did not receive the drug. Oral iron administration was started with a dose of 6 mg/kg/d and was increased after 2 weeks to 8 mg/kg/d. Control group participants received iron alone |
| Outcomes | Study gives results as cumulative volume of blood transfused per kg with first and third quartiles |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included. Transfusion guidelines were in place. One infant in the control group was withdrawn from the study because of development of IVH grade IV |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computerised random number generator |
| Allocation concealment (selection bias) | Unclear risk | 30 preterm infants were randomly assigned. |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Control group did not receive placebo. Personnel were aware of group assignments |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Control group did not receive placebo. Outcome assessors were aware of group assignments |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete follow-up: yes One infant in the control group was withdrawn from the study because of development of IVH grade IV |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Meyer 2003**

| | |
|---|---|
| Methods | Double-blind randomised controlled trial Study location: single centre, Auckland, New Zealand Study period: 2-year period 1995 to 1996 |
| Participants | 43 preterm infants < 33 weeks' gestation and < 1700 grams |
| Interventions | 22 infants in EPO group received erythropoietin (Eprex; Janssen-Cilag, Auckland, New Zealand) at a dose of 1200 IU/kg/week (high dose) SC in 3 divided doses until the age of 3 weeks, when the dose was reduced to 600 IU/kg/week. Treatment continued until 34 weeks' completed gestation, or for a minimum of 3 weeks. 21 infants in the control group received sham treatment, to avoid SC injection. Ferrous gluconate at a dose of 6 mg of elemental iron/kg/d (high dose) was given to the EPO group once they had attained a postnatal age of 2 weeks and were receiving at least 50% energy intake orally. Those in the control group received 2 mg/kg/d iron from the same age, in a more dilute preparation, so that an equivalent volume was given. All infants received a multi-vitamin preparation and vitamin E (25 IU/d) |

| Outcomes | Use of 1 or more red blood cell transfusions<br>Number of donors the infant was exposed to<br>Number of transfusions per infant |
|---|---|
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included.<br>Transfusion guidelines were in place. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer generated |
| Allocation concealment (selection bias) | Low risk | Infants were randomised by the hospital pharmacist to receive EPO or no treatment (control group) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Treatment was administered by a designated study nurse who was not involved in clinical management decisions related to the infants. On each of the treatment days, the nurse collected vials of EPO and saline, and 1-mL syringes were prepared in a side room. The syringes were labelled with the patient's name. A screen was placed around the bedside; those on EPO received SC injection, and adhesive plaster was placed over the injection site. Those in the control group had plaster applied to a similar site as those on EPO; the sites in both groups were then left covered until the next treatment day |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | See above, under 'Blinding of participants and personnel'. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Obladen 1991** *(Continued)*

| Methods | Randomised controlled trial<br>Study location: 5 centres in Europe<br>Study period: April 1989 to February 1990 |
|---|---|
| Participants | 93 infants with PMA of 28 to 32 completed weeks' gestation |
| Interventions | 43 infants in the EPO group received EPO (Boehringer Mannheim GmbH) 30 IU/kg SC every third day (70 IU/kg/week, low dose) from the fourth to the 25th day of life.<br>50 control infants did not receive SC injections of placebo but were managed identically.<br>Elemental iron treatment was started on day 14 with 2 mg/d orally |
| Outcomes | Use of 1 or more red blood cell transfusions<br>Total volume of blood transfused per infant<br>Mortality<br>Chronic lung disease<br>ROP (infants were followed for ROP, but results were not reported)<br>IVH<br>NEC<br>BPD<br>Hypertension<br>Renal failure<br>PDA |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included.<br>Transfusion guidelines were in place. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Low risk | Prenumbered sealed envelopes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Control infants were not given subcutaneous injections of placebo. Personnel were not blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Control infants were not given subcutaneous injections of placebo. Assessors were not blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain |

| | | whether deviations from the protocol occurred |
|---|---|---|
| Other bias | Low risk | Appears free of other bias |

## Ohls 1995

| Methods | Randomised controlled trial<br>Study location: single centre, USA<br>Study period: not stated |
|---|---|
| Participants | 20 ill newborn VLBW infants, less than 48 hours of age, weighing between 750 and 1500 grams at birth with GA > 27 weeks |
| Interventions | 10 infants in the EPO group received EPO (unnamed product), 200 IU/kg/d (1400 IU/kg/week, high dose) IV for 14 consecutive days.<br>10 infants in the control group received similar volume of 0.9% saline solution in similar fashion as placebo.<br>Infants in both groups received iron, 2 mg/kg per day orally, when they were taking 70 mL/kg/d enterally, which was increased to 6 mg/kg per day (high dose) when infants were receiving more than 100 mL/kg per day of feeds |
| Outcomes | Use of 1 or more red blood cell transfusions<br>Total volume of blood transfused per infant<br>Number of transfusions per infant<br>BPD<br>Neutropenia<br>NEC<br>IVH<br>Side effects |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included.<br>Transfusion guidelines were in place. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | Infants were randomly selected. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | All caregivers and investigators were masked to treatment groups |

**Ohls 1995**  (*Continued*)

| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | All caregivers and investigators were masked to treatment groups |
| --- | --- | --- |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up: yes<br>Investigators found no differences in the number of infants with BPD, IVH, or NEC (data not shown) |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred. After the interim analysis, the study was discontinued because of significant differences between groups in numbers of transfusions |
| Other bias | Low risk | Appears free of other bias |

**Ohls 1997**

| Methods | Double-blind randomised controlled trial<br>Study location: 3 centres, USA<br>Study period: not stated |
| --- | --- |
| Participants | 28 ELBW infants with birth weight ≤ 750 grams who were 72 hours of age or younger |
| Interventions | 15 infants received EPO (unnamed product) 200 IU/kg/d (1400 IU/kg/week, high dose) IV, for 14 consecutive days.<br>13 infants received placebo as an equivalent volume of diluent in similar fashion.<br>All infants received 1 mg/kg/d iron dextran in TPN solution during the treatment period (high dose).<br>All infants received vitamin E 25 IU/d when they tolerated 60 mL/kg/d feeds enterally |
| Outcomes | Total volume of blood transfused per infant<br>Number of transfusions per infant<br>Mortality<br>Sepsis<br>IVH<br>BPD<br>ROP<br>Neutropenia |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included, but numbers of transfusions from birth to day 1 are reported; thus infants who had received transfusions were included.<br>Transfusion guidelines were in place. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Low risk | Infants were randomly assigned in a double-blind fashion. |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Study is described as a double-blind placebo-controlled study, and a placebo was used |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Study is described as a double-blind placebo-controlled trial, and a placebo was used |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete follow-up: yes. Two infants in each group died before the 21-day study period |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Ohls 2001A**

| | |
|---|---|
| Methods | Double-blind randomised controlled trial Study location: multi-centre trial, USA Trial period not stated The study was performed concurrently, as 2 parallel trials based on birth weight, because different primary outcomes were evaluated in each trial. We report under Ohls 2001A on infants with birth weight 401 to 100 grams, and under Ohls 2001B on infants with birth weight 1001 to 1250 grams. |
| Participants | 172 infants with birth weight between 401 grams and 1000 grams, PMA < 32 weeks, and between 24 and 96 hours old at the time of study entry, who were likely to survive > 72 hours |
| Interventions | 87 infants in the EPO group received 400 U/kg EPO (unnamed product) 3 times weekly (1200 IU/kg/week, high dose) IV, or SC when IV access was not available. 85 infants in the placebo/control group received sham SC injections when IV access was not available. An adhesive bandage covered the true and sham injection sites. Treatment was continued until discharge, transfer, death, or 35 completed weeks' corrected GA. |

| | |
|---|---|
| | Treated infants received a weekly IV infusion of 5 mg/kg iron dextran (high dose) until they had an enteral intake of 60 mL/kg/d. Iron dextran was added to the TPN solution and was administered over 24 hours or was diluted in 10% dextrose in water or normal saline and was administered over 4 to 6 hours. Placebo/control infants received 1 mg/kg iron dextran once a week, administered in a similar manner. Once infants in both groups had enteral intake of 60 mg/kg/d, they were given iron a dose of 3 mg/kg/d. The dose was gradually increased to 6 mg/kg/d, depending on enteral intake. Study infants received enteral vitamin E 15 to 25 IU/d, and enteral folate supplements 25 to 50 mcg/d were provided according to centre practice |
| Outcomes | Use of 1 or more red blood cell transfusions Mean number of erythrocyte transfusions per infant (primary outcome) Number of donors the infant was exposed to Total volume of blood transfused per infant Late-onset sepsis Mortality Chronic lung disease (at 36 weeks' postmenstrual age) ROP Severe IVH (stage ≥ 3) NEC BPD Neutropenia Hypertension Hospital stay At follow-up (see notes), growth, development, rehospitalization, transfusions |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included. Strict protocol was used to administer transfusions during the study period. Of 72 EPO-treated and 70 placebo-control infants surviving to discharge, follow-up data at 18 to 22 months' corrected age were collected on 51 of 72 EPO-treated infants (71%) and 51 of 70 placebo/controls (73%) Study was supported by grants from Ortho-Biotech and Schein Pharmaceuticals |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Low risk | Blinding of randomisation: yes. All caregivers and investigators (except research nurses) were masked to treatment assignment |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | All caregivers and investigators (except research nurses) were masked to treatment assignment |

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | All caregivers and investigators (except research nurses) were masked to treatment assignment |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | All infants were followed through their hospital stay up to 120 days. Of 72 EPO-treated and 70 placebo-control infants surviving to discharge, follow-up data at 18 to 22 months' corrected age were collected on 51 of 72 EPO-treated infants (71%) and 51 of 70 placebo/controls (73%). Follow-up rates were low |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias. Study was supported by grants from Ortho-Biotech and Schein Pharmaceuticals |

**Ohls 2001B**

| | |
|---|---|
| Methods | Double-blind randomised controlled trial<br>Study location: multi-centre trial, USA<br>Trial period not stated<br>The study was performed concurrently as 2 parallel trials based on birth weight, because different primary outcomes were evaluated in each trial. We report under Ohls 2001A on infants with birth weight 401 to 1000 grams, and under Ohls 2001B on infants with birth weight 1001 to 1250 grams. |
| Participants | 118 infants with birth weight 1001 to 1250 grams, PMA ≤ 32 weeks, and between 24 and 96 hours old at the time of study entry who were likely to survive > 72 hours |
| Interventions | 59 infants in the EPO group received 400 U/kg EPO (unnamed product) 3 times weekly (1200 IU/kg/week, high dose) IV or SC when IV access was not available. 59 infants in the placebo/control group received sham SC injections when IV access was not available. An adhesive bandage covered true and sham injection sites. Treatment was continued until discharge, transfer, death, or 35 completed weeks' corrected PMA |
| Outcomes | Numer of infants who received any transfusion (primary outcome)<br>Use of 1 or more red blood cell transfusions<br>Mean number of erythrocyte transfusions per infant<br>Number of donors the infant was exposed to<br>Total volume of blood transfused per infant<br>Late-onset sepsis<br>Mortality |

| | Chronic lung disease (at 36 weeks' postmenstrual age) |
|---|---|
| | ROP stage ≥ 3 |
| | Severe IVH (stage ≥ 3) |
| | NEC |
| | BPD |
| | Neutropenia |
| | Hypertension |
| | Hospital stay |
| | At follow-up (see notes), growth, development, rehospitalization, transfusions |
| Notes | Infants in Ohls 2001B were not examined at 18 to 22 months' corrected age. Only infants in Ohls 2001A were examined at follow-up (see notes under Ohls 2001A). |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Low risk | Blinding of randomisation: yes. All caregivers and investigators (except research nurses) were masked to treatment assignment |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | All caregivers and investigators (except research nurses) were masked to treatment assignment |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | All caregivers and investigators (except research nurses) were masked to treatment assignment |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | All infants were followed through their hospital stay up to 120 days |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias. Study was supported by grants from Ortho-Biotech and Schein Pharmaceuticals |

**Ohls 2013**

| | |
|---|---|
| Methods | Randomised masked controlled clinical trial<br>Study location: University of New Mexico, Albuquerque, New Mexico, University of Colorado, Aurora, Colorado and Intermountin Health Care, Salt Lake City, Utah, USA<br>Study period: July 2006 to May 2010 |
| Participants | 102 infants with BW 500 to 1250 grams and ≤ 48 hours of age. Infants with trisomies, significant congenital anomalies, hypertension, seizures, thromboses, haemolytic disease, or receiving EPO clinically were ineligible for the study |
| Interventions | Infants were randomised in masked fashion to 1 of 3 groups: EPO, 400 U/kg (1200 U/kg/week - high dose), given subcutaneously 3 times a week (Monday, Wednesday, and Friday); Darbe, 10 μg/kg, given subcutaneously once a week, with sham dosing 2 other times per week; or placebo, consisting of 3 sham doses per week. Dosing continued until 35 completed weeks' gestation, discharge, transfer to another hospital, or death. Doses of Darbe and EPO were initially based on study entry weight and were adjusted weekly. Study drug concentrations were chosen to give equivalent volumes (0.1 mL/kg body weight) of Darbe or EPO. All infants (regardless of treatment arm) received supplemental iron, folate (50 mg per day oral), and vitamin E (15 IU per day oral). Iron dextran, 3 mg/kg once a week, was added to parenteral nutrition while infants were receiving, 60 mL/kg per day enteral feedings. Oral iron 3 mg/kg per day was started when feedings were ≥ 60 mL/kg per day, and was increased to 6 mg/kg per day when feedings reached 120 mL/kg per day (high dose). Serum ferritin concentrations were used to adjust iron dosing. For infants in whom ferritin concentrations were > 400 ng/mL, the parenteral or enteral dose of iron was decreased by 50%; for infants in whom ferritin concentrations were < 50 ng/mL, the parenteral or enteral dose was doubled |
| Outcomes | Use of 1 or more red blood cell transfusions<br>Total volume (mL/kg) of blood transfused per infant<br>Number of blood transfusions per infant<br>Number of donors the infant was exposed to<br>Mortality during initial hospital stay<br>ROP all stages and stages ≥ 3<br>Late-onset sepsis<br>NEC stage > 2<br>IVH grade ≥ 3<br>PVL<br>Length of hospital stay<br>BPD (oxygen dependency at 36 weeks' PMA)<br>Neutropenia<br>Hypertension<br>Cognitive scores on Bayley Scales of Infant Development (BSID-III) at 18 to 22 months were reported initially in abstract form, but later in a full publication, in which cognitive, language, social/emotional, and OP scores were reported, as were CP, visual deficit, and NDI or death. We used the numbers reported in the 2014 report for these outcomes. Some infants (n = 53) were again assessed at 3.5 years of age (24 EPO-treated infants, 15 Darbe-treated infants, and 14 placebo-treated infants). They were assessed by Wechsler Preschool and Primary Scale of Intelligence, Third Edition, and by an overall measure of executive function, on the basis of tests evaluating inhibitory control and spatial working memory. Rates of neurodevelopmental impairment were reported. A further reduced |

| | | |
|---|---|---|
| | sample (n = 45 infants) was assessed via behavioural measures at an approximate mean age of 48 months | |
| Notes | In the previous version of the review, we obtained additional information from Dr. Ohls regarding several outcomes; this explains why some of the data we have entered in RevMan 5.3 differ from the original publication. 17 infants (17%) were transfused before treatment was initiated | |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation lists for each pharmacist were computer generated |
| Allocation concealment (selection bias) | Low risk | All caregivers were blinded to treatment groups, except research pharmacists at each site, who drew up study medications to be administered by the research nurse |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | All caregivers were blinded to treatment groups, except research pharmacists at each site, who drew up study medications to be administered by the research nurse. The placebo group received sham injections |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | All caregivers were blinded to treatment groups, except research pharmacists at each site, who drew up study medications to be administered by the research nurse. The placebo group received sham injection |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Three participants (1 who had the study drug mistakenly held at the start of the study and subsequently never received any study drug; 1 who was found to be in-eligible based on congenital neurological anomaly on head ultrasound noted before receiving study drug; and 1 who died of a pulmonary haemorrhage before receiving study drug) were excluded from analysis. One infant had the study drug stopped at 34 weeks' corrected gestation at the request of parents. All infants who received at least 1 dose of study drug were included in the analysis (n = 33 in each group). Bayley Scales of Infant Development (BSID-III) cognitive scores at 18 to 22 months are |

| | | reported in E-PAS2013:2924, but not PDI scores. A full report was published in 2014 (Ohls 2014). At the end of hospitalisation, 94 infants were evaluated. Five hospital deaths occurred, and 14 children did not return for follow-up. Eighty children were evaluated at follow-up at a corrected age of 18 to 22 months (Darbe n = 27 (84%), EPO n = 29 (91%), placebo/sham injection n = 24 (80%)). A report of preschool assessment (at age 3.5 to 4 years) was published in 2016 (Ohls 2016), and the study assessed 53 children (Darbe n = 15 (47%), EPO n = 24 (75%), placebo n =14 (47%)). In 2017, an additional study (Lowe 2017) reported on behavioural measures in 49 children (Darbe or EPO n = 35 (55%), placebo n = 14 (47%)). The 2 groups of Darbe and EPO were combined to create an erythropoiesis-stimulating agent (ESA) group. Percentages are based on the number of infants evaluated at the end of hospitalisation. Follow-up rates beyond 18 to 22 months were low |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | Study was registered as NCT00334737 in June 2006. No major deviations from the protocol are apparent, except that primary outcomes included MDI at 18 to 22 months and PDI as a secondary outcome. MDI and PDI are not reported in the primary publication |
| Other bias | Low risk | Appears free of other bias |

**Peltoniemi 2017**

| Methods | Randomised controlled trial<br>Study location: neonatal intensive care unit at Oulu University Hospital, Finland<br>Study period: March 1998 to May 2000 |
|---|---|
| Participants | 39 infants (BW 700 to 1500 grams, PMA $\leq$ 30.0 weeks) |
| Interventions | 21 infants received EPO (EPO 250 IU/kg/d during the first 6 days of life IV for a period of 30 minutes) (total dose 1500 IU/kg/week). 18 infants received placebo (isotonic saline as placebo for a period of 30 minutes). None of the infants received iron during the first week of life |

| Outcomes | Iron status<br>Postnatal morbidities and follow-up at the age of 2 years |
|---|---|
| Notes | We received additional information from Dr. Peltoniemi. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table |
| Allocation concealment (selection bias) | Low risk | Allocation was concealed, but details are not provided. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Study drug and placebo were put into identical syringes. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Nurses, doctors, and study investigators were blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Outcomes during initial hospital stay reported for all randomised infants. Of 20 surviving children at 2 years of age, 19 were enrolled and 10 were evaluated on Griffiths Developmental Scale. Of 16 surviving placebo group children at 2 years of age, all were enrolled and 9 were evaluated at on Griffiths Developmental Scale. Follow-up rates for Griffiths Developmental Scale were low (thus unclear risk) |
| Selective reporting (reporting bias) | Low risk | The protocol for the study was not available to us. The protocol was written in Finnish, and Dr. Antilla assured Dr. Peltoniemi that no deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Qiao 2017**

| Methods | Single-blind randomised controlled trial<br>Study location: NICU of the First People's Hospital in Kunshan, Jiangsu Univeristy, People's Republic of China<br>Study period: February 2014 to June 2014 |
|---|---|
| Participants | 96 preterm infants, PMA 28 to 34 weeks' gestation |
| Interventions | Control group receiving standard parenteral nutrition (group 1: n = 31), iron-supplemented group (iron sucrose (IS)) (group 2: IS, n = 33), and iron-supplemented combined erythropoietin group (group 3: IS + EPO, n = 32). IS + EPO group received EPO 400 IU/kg twice a week for 2 weeks; total dose 800 IU/kg per week (1600 IU/kg in 2 weeks) (high dose). IS group and IS + EPO group received iron 200 µg/kg/d until 2 weeks after birth |
| Outcomes | NEC<br>ROP<br>Mortality |
| Notes | For outcomes, we included the IS group and the IS + EPO group |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Low risk | Participants were randomly assigned to 1 of 3 groups in the following manner: Treatment cards were imprinted with a unique randomisation code and were placed in sequentially numbered opaque envelopes. At the study site, treatment cards were taken out in sequential order, and participants were assigned to the corresponding treatment group on the basis of the randomisation number |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | All investigators, physicians, and nurses involved in participant care and parents were blinded to group assignment<br>The randomisation process was made available only to the pharmacist, who supervised the quality of iron sucrose and the parenteral nutrition preparation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | All investigators, physicians, and nurses involved in participant care and parents were blinded to this assignment |

|  |  | The randomisation process was made available only to the pharmacist, who supervised the quality of iron sucrose and the parenteral nutrition preparation |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Of 96 preterm infants enrolled, 91 infants completed the study; 30 belonged to the control group, 31 to the iron-supplemented (IS) group, and 30 to the iron-supplemented (IS) + EPO group. Five infants could not complete the study. One infant in the IS group died from respiratory failure, and 4 infants (1 in the control group, 1 in the IS group, and 2 in the IS + EPO group) were discharged because treatments were discontinued by their parents |
| Selective reporting (reporting bias) | Unclear risk | Study protocol was not available to us, and we cannot judge whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias. |

**Salvado 2000**

| Methods | Randomised double-blind controlled clinical trial Study location: single centre, Chile Study period: April 1998 to December 1999 |
|---|---|
| Participants | 60 newborn infants under 1500 grams birth weight; mean age at entry in the EPO group 7.75 ± 2.42 days, and mean age at entry in the control group 7.96 ± 2.44 days |
| Interventions | 29 infants in the EPO group received r-EPO (Eritropoyetina del Laboraorio Andromaco) 200 IU/kg SC, 3 times a week (600 IU/kg/week, high dose), during 4 weeks. 31 infants in the control group received similar volume of isotonic saline solution in similar fashion. All infants received oral iron at a dose of 3 mg/kg/d (low dose) |
| Outcomes | Number of transfusions per infant Sepsis IVH |
| Notes |  |
| *Risk of bias* |  |

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

| Random sequence generation (selection bias) | Unclear risk | No information presented |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | "were randomised in a double-blind fashion" - but no specific information provided |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | No specific information provided |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | No specific information provided |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Song 2016**

| Methods | Randomised controlled trial<br>Study location: 2 NICUs in China: Third Affiliated Hospital of Zhengzhaou University and Zhengzhou Children's Hospital<br>Study period: January 2009 to June 2013 |
|---|---|
| Participants | Preterm infants, PMA $\leq$ 32 weeks' gestation, and < 72 hours of age |
| Interventions | EPO group (n = 366) received EPO at 500 IU/kg IV every other day for 2 weeks. Cumulative dose of 3500 IU/kg. First dose within 72 hours after birth. Placebo group (n = 377) received an equivalent volume of normal saline IV |
| Outcomes | Head U/S within 3 days after birth, then weekly until discharge<br>MRI at 49 weeks' PMA<br>ICH<br>PVL<br>BPD<br>NEC<br>Sepsis<br>ROP graded according to the international classification of ROP<br>At 18 months' corrected age, neurological exam and Mental Developmental Index (Bayley Scales - Second Edition)<br>Hearing test,- Deafness defined as a hearing disability that required amplification. Blind- |

|  | | ness defined as corrected visual acuity < 20/200<br>Moderate or severe disability defined as survival with at least 1 of the following complications: cerebral palsy, MDI < 70, deafness, or blindness |
| --- | --- | --- |
| Notes | | ROP grades are not reported. We wrote in March 2017 to the corresponding author, but we had not received a response as of 11 June 2017 |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
| --- | --- | --- |
| Random sequence generation (selection bias) | Low risk | Computer-based random number generator |
| Allocation concealment (selection bias) | Low risk | Group assignment for each consecutive participant was concealed in a sealed envelope before participants were included |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Doctors and nurses responsible for treatment were not blinded according to the rules of medical procedure in China |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | According to trial authors, "The investigators performing the short-term and long-term outcome assessments and the parents were blinded to patients' group allocation". It is difficult to understand this statement, as doctors and nurses were not blinded to treatments. Final evaluation at 18 months' corrected age was performed by doctors from the Child Growth and Development Department, who were blinded to the treatment protocol and were not allowed to have access to the treatment history of infants |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | All 743 randomised infants were accounted for in short-term outcomes. For outcomes at 18 months, 309 children in the EPO group (36 infants were lost to follow-up) and 304 in the placebo group (39 children were lost to follow-up) were assessed (90% in both groups) |
| Selective reporting (reporting bias) | High risk | Study was registered as NCT02036073 but was registered in December 2013, after recruitment had been completed. Study started to recruit patients in January 2009. Therefore we are unable to tell whether any deviations occurred from the study proto- |

| | | col that was established before the study start. In the protocol, the primary outcome measure was: Incidence of MDI < 70 at corrected age of 18 months, and secondary outcome measures were Incidence of ROP at corrected age 42 weeks. In the full report, primary outcomes are listed as death, disability, or death + disability at 18 months' corrected age. ROP is listed as a neonatal complication |
|---|---|---|
| Other bias | Low risk | Appears free of other bias |

**Soubasi 1993**

| Methods | Randomised double-blind controlled trial<br>Study location: single centre in Thessaloniki, Greece<br>Study period: not stated |
|---|---|
| Participants | 44 newborn infants with birth weight under 1500 grams, age 1 to 7 days |
| Interventions | EPO group (n = 25) received 150 IU/kg/dose of EPO (Cilag AG, Zug, Switzerland) twice a week (300 IU/kg/week, low dose) during 4 weeks. Control group (n = 19) received no placebo. From the 15th day of life, iron was started at 3 mg/kg/d (low dose) in all infants |
| Outcomes | Number of transfusions per infant<br>Sepsis<br>IVH<br>Days on ventilator |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included.<br>Transfusion guidelines were in place. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table |
| Allocation concealment (selection bias) | Low risk | Blinding of randomisation: yes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "The doctors in clinical charge were unaware of the treatment or control status of the babies" |

| Blinding of outcome assessment (detection bias) All outcomes | Low risk | "The doctors in clinical charge were unaware of the treatment or control status of the babies" |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Soubasi 1995**

| Methods | Randomised controlled trial Study location: single centre, Greece Study period: not stated |
|---|---|
| Participants | 97 VLBW infants with GA ≤ 31 weeks, birth weight 1500 grams or less, and age 1 to 7 days |
| Interventions | 33 infants received rHuEPO (Cilag AG, Zug, Switzerland) 150 IU/kg twice weekly (300 IU/kg/week, low dose). 28 infants received rHuEPO 250 U/kg 3 times per week (750 IU/kg/week, high dose). EPO was administered from first week of life for 6 weeks. 36 infants (control) did not receive any treatment. All infants received oral elemental iron 3 mg/kg/d from day 15 of life (low dose). After discontinuation of EPO therapy, 75 infants were followed weekly until discharge, and thereafter at 3, 6, and 12 months of age |
| Outcomes | Use of 1 or more red blood cell transfusions Number of blood transfusions per infant Mortality Follow-up to 1 year of age Hospital stay After discontinuation of EPO therapy, 75 infants were followed weekly until discharge, and thereafter at 3, 6, and 12 months of age (no neurodevelopmental outcomes reported) |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included. Transfusion guidelines were in place. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

| Random sequence generation (selection bias) | Low risk | Random number table |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Infants were randomly assigned. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Control group received no placebo. Personnel were not blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Control group received no placebo. Outcome assessors were not blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Soubasi 2000**

| Methods | Randomised controlled clinical trial<br>Study location: single centre, Thessaloniki, Greece<br>Study period: not stated |
|---|---|
| Participants | 36 VLBW infants with gestational age < 31 weeks and birth weight < 1300 grams with clinical stability at the time of entry |
| Interventions | 18 infants in the treatment group received rHuEPO (Cilag AG, Zug, Switzerland) 200 IU/kg every alternate day (700 units/kg/week, high dose) SC.<br>18 infants in the control group did not receive EPO or placebo.<br>Duration of EPO treatment is not stated.<br>Additionally, infants received oral iron at a dose of 12 mg/kg/d (high dose) in the EPO group and 4 mg/kg/d in the control group.<br>Both groups were supplemented with 500 mcg of oral folate every other day, 10 IU of vitamin E every day, and multivitamins, when enteral feeding reached 75% of total fluid intake, until discharge |
| Outcomes | Use of 1 or more red blood cell transfusions<br>Number of transfusions per infant |
| Notes | This study does not mention the exact day when treatment was started.<br>It is not stated whether infants who had received blood transfusions before study entry were included. |

| | | Transfusion guidelines were in place. |
|---|---|---|

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table |
| Allocation concealment (selection bias) | Unclear risk | Infants were randomly assigned to receive EPO or not. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | No placebo was administered. Personnel were not blinded. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | No placebo was administered. Outcome assessors were not blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Completeness follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Yasmeen 2012**

| Methods | Randomised controlled trial<br>Study location: single centre, Dhaka, Bangladesh<br>Study period: April 2007 to May 2008 |
|---|---|
| Participants | 60 VLBW infants, < 7 days of age, < 35 weeks' PMA, and weighing < 1500 grams |
| Interventions | 30 infants were supplemented with rHuEPO 200 IU/kg/dose SC 3 times/week for 2 weeks, started on day 7 of life. EPO group and control group (n = 30) received oral iron 6 mg/kg/d and folic acid 0.5 mg every alternate day up to 12 weeks of age. Administration of both iron and folic acid started from day 14 of life, or as soon as enteral feeding was initiated after day 14 |
| Outcomes | Mortality is the only outcome that can be ascertained from this study |
| Notes | Mortality is the only outcome that can be ascertained from this study. For all other outcomes of interest, including neonates requiring blood transfusion while in hospital, trial authors excluded 13 infants; in the EPO group, 4 infants died during hospital stay, 1 |

| | | |
|---|---|---|
| | participant did not come in for first follow-up, and 1 did not come in for second follow-up. In the control group, 5 infants died during hospital stay and 2 did not come in for second follow-up. Finally, 24 infants in group 1 and 23 infants in group 2 completed follow-up until 10 weeks of age. These 13 infants who dropped out were excluded from the analysis. We suggest that infants who died should have been included in both the nominator and the denominator for the outcomes of need for blood transfusion and number of blood transfusions (ITT analysis). A total of 13 infants dropped out of the study, which represents 22% - a very high percentage | |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Lottery method |
| Allocation concealment (selection bias) | Unclear risk | Lottery method |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | No placebo was used, so personnel could not be blinded. |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Outcome assessors were not blinded. |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 22% of the infants dropped out. In-hospital outcome data did not include deaths. Lack of ITT analysis |
| Selective reporting (reporting bias) | Unclear risk | The protocol for this study was not available to us, so we are not able to tell whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

**Yeo 2001**

| | |
|---|---|
| Methods | Non-blind randomised controlled trial Study location: single centre, Singapore Study period: January 1997 to March 2000 |
| Participants | 00 VLBW infants, < 33 weeks' GA, hematocrit 40% to 60% at birth |
| Interventions | 50 infants in the EPO group received EPO (unnamed product) 250 IU/kg/dose SC 3 times a week (750 IU/kg/week, high dose) from day 5 to day 40. 50 infants in the control group did not receive any treatment. Infants in both groups received elemental iron 3 mg/kg/d orally from day 10, increased |

| | |
|---|---|
| | to 6 mg/kg/d (high dose) when full feeds were well tolerated |
| Outcomes | Exposure of a proportion of infants to 1 or more red blood cell transfusions<br>Mean number of erythrocyte transfusions per infant<br>Total volume of blood transfused per infant<br>Mortality<br>ROP (stage not stated)<br>Sepsis<br>NEC<br>BPD (age not stated)<br>Hypertension |
| Notes | It is not stated whether infants who had received blood transfusions before study entry were included.<br>Transfusion guidelines were in place. |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | Infants were randomised to receive EPO or no drug. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | No placebo drug was given to the control group. Personnel were not blinded to study group |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | No placebo drug was given to the control group. Outcome assessors were not blinded to study group |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up: yes |
| Selective reporting (reporting bias) | Unclear risk | The protocol for the study was not available to us; therefore we cannot ascertain whether deviations from the protocol occurred |
| Other bias | Low risk | Appears free of other bias |

BP: blood pressure.
BPD: bronchopulmonary dysplasia.
BSID: Bayley Scales of Infant Development.
BW: birth weight.

CI: confidence interval.
CP: cerebral palsy.
ELBW: extremely low birth weight.
EPO: erythropoietin.
GA: gestational age.
g: grams.
Hct: hematocrit.
IS: iron sucrose.
ITT: intention-to-treat.
IU: international units.
IV: intravenous/intravenously.
IVH: intraventricular haemorrhage.
MDI: Mental Development Index.
MRI: magnetic resonance imaging.
NEC: necrotising enterocolitis.
PDI: Psychomotor Development Index.
PMA: postmenstrual age.
PVL: periventricular leukomalacia.
RDS: respiratory depression syndrome.
rhEPO: recombinant human EPO.
rhG-CSF: recombinant human granulocyte colony-stimulating factor.
ROP: retinopathy of prematurity.
SC: subcutaneous/subcutaneously.
TPN: total parenteral nutrition.
u/s: ultrasound.
VLBW: very low birth weight.

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

| Study | Reason for exclusion |
|---|---|
| Al Mofada 1994 | Patients were enrolled immediately after birth. The volume of RBC transfusions was reported as mL/week over the study period. We could not use this information in our outcome of total volume (mL/kg) of blood transfused per infant |
| Amin 2002 | This study was not a randomised controlled trial. |
| Basiri 2015 | Infants were > 6 days old. Will be included in the 'Late EPO' review |
| Bierer 2006 | One of the authors of this study, Dr. R.K. Ohls, informed us that this study reported on a subgroup of Ohls 2001A. All outcomes of Bierer 2006 were included in the 2004 follow-up publication of Ohls 2001A. |
| Brown 1999 | This study compared 2 different dosing regimens for the same total weekly dose of EPO. The trial included no control or placebo group |
| Costa 2013 | This study assessed the effectiveness of IV vs SC administration of EPO and included no non-treated group |

*(Continued)*

| | |
|---|---|
| Fearing 2002 | This study did not reveal the number of infants allocated to treatment and control groups, nor the age at which the infants entered into the study |
| Haiden 2006a | This study reported the same findings as Haiden 2005. |
| Haiden 2006b | Both study groups received erythropoietin. |
| Juul 2008 | This was not a randomised controlled trial. |
| Klipp 2007 | This was a randomised controlled trial, but results showed no clinical outcomes of interest for this review |
| Krallis 1999 | No outcomes of interest for this review were reported. |
| López-Catzín 2015 | Upon consultation with one of the trial authors (Bolado-Garcia PB), it was clarified that this was not a randomised controlled trial |
| Maggio 2007 | This randomised controlled trial compared the effectiveness of EPO administered by continuous intravenous vs subcutaneous route |
| Maier 1998 | This randomised controlled trial compared 2 doses of EPO: 750 IU/kg/week vs 1500 IU/kg/week without a non-treated control group |
| Ohls 1996 | This study compared different routes of administration (SC EPO vs EPO added to the total parenteral nutrition fluid). This study included no untreated control group |
| Saeidi 2012 | This was a randomised controlled trial in which one group received oral EPO, and the other group SC EPO. The trial included no untreated control group |
| Soubasi 2005 | 128 infants were randomised early (first week of life) to EPO group (n = 66) or control group (n = 62). The dose of EPO is not stated in the abstract. Infants randomised to EPO received significantly fewer transfusions and had less IVH |
| Soubasi 2009 | Not a randomised controlled trial (20 study participants and 20 concurrent controls) |
| Turker 2005 | This study was labelled by trial authors as a quasi-randomised (assignment on an alternating basis) trial. Study authors reported on uneven numbers in the 2 groups (42 infants in the EPO group and 51 in the control group). On request, the principal author provided the following information. "In the study period 112 premature infants < 1500 grams were followed in the NICU. Informed consents were obtained from the parents of 97 babies, but only 93 babies completed the study because 3 patients were lost to follow-up after discharge and one baby died of bronchopulmonary dysplasia before completing the 12 week monitoring period. These 4 babies were omitted from the study group (r-Hu EPO+enteral iron). These infants are included in the result section. At the end of the study r-Hu EPO was not available, and 2 more patients had only iron supplementation. Then the study was closed and these 2 babies were also added to the control group". 97 participants (48 in EPO group; 3 lost-to follow-up; 1 death; -2 rHuEPO unavailable; 49 controls; +2) Based on this information, we excluded the study, as it was not a quasi-randomised trial |

| Vázquez López 2011 | This randomised controlled trial compared 2 different dosing schedules of EPO. Group 1 (60 infants; mean postnatal age at entry 6 ± 3.1 days) received SC EPO at 250 units per kg per dose, 3 times weekly for 6 weeks. Group 2 (59 infants; mean postnatal age at entry 7 ± 3.9 days) received SC EPO at 750 units per kg per dose once weekly for 6 weeks. No untreated group was included |
|---|---|
| Zhu 2009 | Trial population consisted of infants > 37 weeks' PMA. |

EPO: erythropoietin.
IV: intravenous.
IVH: intraventricular haemorrhage.
RBC: red blood cell.
SC: subcutaneous.

## Characteristics of ongoing studies  *[ordered by study ID]*

### NCT01378273

| Trial name or title | Preterm Erythropoietin Neuroprotection Trial (PENUT Trial) (PENUT) |
|---|---|
| Methods | Randomised controlled trial |
| Participants | Preterm infants 24 0/7 to 27 6/7 weeks' gestation, beginning in the first 24 hours after birth |
| Interventions | Experimental: EPO 1000 U/kg followed by 400 U/kg. Participants will receive 6 doses of intravenous EPO 1000 U/kg/dose at 48-hour intervals from the time of enrolment. Following the high-dose period, participants will receive subcutaneous EPO 400 U/kg/dose 3 times a week until 32 6/7 weeks' postmenstrual age |
| Outcomes | Primary outcome measures: neurodevelopmental outcome [Time Frame: 24 to 26 months' corrected age], neurodevelopmental exam Bayley-III: MDI and PDI<br>Secondary outcome measures: safety [Time Frame: term PMA]. Safety of EPO treatment will be assessed by comparing adverse events and co morbidities between groups.<br>Imaging [Time Frame: 24 to 26 months] MRI at 36 weeks' PMA will be used as a biomarker of long-term outcomes.<br>Biomarkers [Time Frame: 24 to 26 months of age] Circulating bio markers of inflammation and brain injury will be evaluated and correlated with neurodevelopmental outcomes<br>Placebo comparator: Control participants will receive 6 doses of vehicle intravenously during the first 2 weeks of life. Doses will be administered at 48-hour intervals from the time of enrolment. Following high-dose administration, sham subcutaneous injections will be given 3 times a week through to 32 6/7 weeks' postmenstrual age |
| Starting date | December 2013 |
| Contact information | Sandra Juul, Professor of Pediatrics, University of Washington |
| Notes | NCT01378273 |

| | |
|---|---|
| Trial name or title | Erythropoietin in premature infants to prevent encephalopathy: a multi-centre randomised blinded controlled study of the efficacy of erythropoietin in China |
| Methods | Multi-centre randomised blinded controlled study |
| Participants | Preterm infants |
| Interventions | Experimental: Erythropoietin EPO is administered 1000 U/kg IV in 48 hours after preterm birth, and at 48-hour intervals for 3 doses per week. After 6 doses, subcutaneously 3 doses per week until at corrected age of 34 weeks. Placebo comparator: Normal saline is administered 5 mL IV at 3 to 6 hours after preterm birth, and at 48-hour intervals for 3 doses per week. After 6 doses, subcutaneously 3 doses per week until at corrected age of 34 weeks |
| Outcomes | Primary outcome measures: neurodevelopment (Bayley Scores) [Time Frame: At corrected age of 18 months]. To evaluate neurodevelopmental function via Bayley Scores of Infant Development Mental Development Index (BSID) and incidence of MDI < 70 (severe) or MDI < 85 (moderate). Neurological evaluation (GMFM-88 scores) [Time Frame: At corrected age of 18 months]. To gain changes in standardised gross motor function using GMFM (Gross Motor Function Measure) as a standardised measurement tool for assessing gross motor function consisting of sub scales, lying and rolling, sitting, crawling and kneeling, standing, walking, running and jumping (range: 0 to 100, higher value means better gross motor function). Secondary outcome measures: numerous |
| Starting date | September 2015 |
| Contact information | Wenhao Zhou, Doctor (+86)021-64931003; zwhchfu@126.com |
| Notes | NCT02550054 |

BSID: Bayley Scales of Infant Development.
EPO: erythropoietin.
GMFM: Gross Motor Function Measure.
MDI: Mental Development Index.
PDI: Psychomotor Development Index.
PMA: postmenstrual age.

# D A T A   A N D   A N A L Y S E S

## Comparison 1.   Erythropoietin versus placebo or no treatment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Use of 1 or more red blood cell transfusions (low and high doses of EPO) | 19 | 1750 | Risk Ratio (M-H, Fixed, 95% CI) | 0.79 [0.74, 0.85] |
| 2 Use of 1 or more blood transfusions (high dose of EPO) | 17 | 1317 | Risk Ratio (M-H, Fixed, 95% CI) | 0.79 [0.74, 0.86] |
| 2.1 High-dose iron | 11 | 863 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.77, 0.92] |
| 2.2 Low-dose iron | 6 | 454 | Risk Ratio (M-H, Fixed, 95% CI) | 0.71 [0.62, 0.82] |
| 3 Use of 1 or more red blood cell transfusions (low-dose EPO) | 4 | 484 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.65, 0.91] |
| 3.1 High-dose iron | 2 | 322 | Risk Ratio (M-H, Fixed, 95% CI) | 0.75 [0.61, 0.93] |
| 3.2 Low-dose iron | 2 | 162 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.60, 1.07] |
| 4 Total volume (mL/kg) of blood transfused per infant | 7 | 581 | Mean Difference (IV, Fixed, 95% CI) | -6.82 [-11.52, -2.11] |
| 5 Number of red blood transfusions per infant | 16 | 1744 | Mean Difference (IV, Fixed, 95% CI) | -0.57 [-0.68, -0.45] |
| 6 Number of donors to whom the infant was exposed | 5 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 6.1 Among all randomised infants | 3 | 254 | Mean Difference (IV, Fixed, 95% CI) | -0.54 [-0.89, -0.20] |
| 6.2 Among infants who were transfused | 2 | 290 | Mean Difference (IV, Fixed, 95% CI) | 0.05 [-0.33, 0.42] |
| 7 Mortality during initial hospital stay (all causes of mortality) | 20 | 2212 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.68, 1.16] |
| 8 Retinopathy of prematurity (all stages or stage not reported) | 11 | 2185 | Risk Ratio (M-H, Fixed, 95% CI) | 0.92 [0.79, 1.08] |
| 9 Retinopathy of prematurity (stage $\geq$ 3) | 8 | 1283 | Risk Ratio (M-H, Fixed, 95% CI) | 1.24 [0.81, 1.90] |
| 10 Proven sepsis | 12 | 2180 | Risk Ratio (M-H, Fixed, 95% CI) | 0.87 [0.74, 1.02] |
| 11 Necrotising enterocolitis (stage not reported) | 15 | 2639 | Risk Ratio (M-H, Fixed, 95% CI) | 0.69 [0.52, 0.91] |
| 12 Intraventricular haemorrhage (all grades) | 10 | 1226 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.76, 1.26] |
| 13 Intraventricular haemorrhage (grades III and IV) | 8 | 1460 | Risk Ratio (M-H, Fixed, 95% CI) | 0.60 [0.43, 0.85] |
| 14 Periventricular leukomalacia | 6 | 1469 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.48, 0.92] |
| 15 Length of hospital stay (days) | 8 | 970 | Mean Difference (IV, Fixed, 95% CI) | -3.20 [-5.34, -1.06] |
| 16 Bronchopulmonary dysplasia | 13 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 16.1 Supplemental oxygen at 28 days of age | 2 | 136 | Risk Ratio (M-H, Fixed, 95% CI) | 0.86 [0.50, 1.47] |
| 16.2 Supplemental oxygen at 36 weeks | 7 | 1719 | Risk Ratio (M-H, Fixed, 95% CI) | 0.95 [0.81, 1.11] |

| | | | | |
|---|---|---|---|---|
| 16.3 Age at diagnosis not stated | 5 | 528 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.61, 1.56] |
| 17 Neutropenia | 10 | 966 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.53, 1.24] |
| 18 Hypertension | 6 | 706 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.14, 6.69] |
| 19 Hemangioma | 1 | 443 | Risk Ratio (M-H, Fixed, 95% CI) | 1.33 [0.79, 2.26] |
| 20 Neonatal Behavioral Neurological Assessment at 40 weeks' PMA | 1 | 44 | Mean Difference (IV, Fixed, 95% CI) | 1.80 [1.26, 2.34] |
| 21 Infants with white matter injury at term-corrected PMA | 1 | 165 | Risk Ratio (M-H, Fixed, 95% CI) | 0.61 [0.37, 1.00] |
| 22 Infants with white matter signal abnormality at term-corrected PMA | 1 | 165 | Risk Ratio (M-H, Fixed, 95% CI) | 0.23 [0.05, 1.01] |
| 23 Infants with periventricular white matter loss at term-corrected PMA | 1 | 165 | Risk Ratio (M-H, Fixed, 95% CI) | 0.55 [0.32, 0.97] |
| 24 Infants with grey matter injury at term-corrected PMA | 1 | 165 | Risk Ratio (M-H, Fixed, 95% CI) | 0.34 [0.13, 0.87] |
| 25 Survivors at discharge from hospital without severe IVH, PVL, ROP | 1 | 443 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.93, 1.08] |
| 26 Bayley-II MDI < 70 at 18 to 24 months' corrected age | 4 | 1071 | Risk Ratio (M-H, Fixed, 95% CI) | 0.55 [0.39, 0.77] |
| 27 Bayley-II PDI < 70 at 18 to 22 months' corrected age (in children examined) | 3 | 458 | Risk Ratio (M-H, Fixed, 95% CI) | 1.43 [0.88, 2.33] |
| 28 Bayley-II MDI at 18 to 24 months | 3 | 981 | Mean Difference (IV, Fixed, 95% CI) | 8.22 [6.52, 9.92] |
| 29 Bayley-II PDI at 18 to 24 months | 1 | 3 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 30 Cerebral palsy at 18 to 24 months' corrected age | 6 | 1172 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.46, 1.13] |
| 31 Any neurodevelopmental impairment at 18 to 22 months' corrected age (in children examined) | 4 | 1130 | Risk Ratio (M-H, Fixed, 95% CI) | 0.62 [0.48, 0.80] |
| 32 Visual impairment at 18 to 24 months' corrected age | 5 | 1132 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.26, 2.49] |
| 33 Hearing impairment at 18 to 24 months' corrected age | 5 | 1132 | Risk Ratio (M-H, Fixed, 95% CI) | 0.41 [0.13, 1.23] |
| 34 BSID-III composite cognitive scores at 18 to 22 months | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 9.20 [1.70, 16.70] |
| 35 BSID-III composite language score | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 6.30 [-2.20, 14.80] |
| 36 BSID-III composite social/emotional score | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 2.90 [-7.84, 13.64] |
| 37 BSID-III object performance (OP) score | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 0.20 [-0.32, 0.72] |
| 38 WPPSI-III FSIQ at 3.5 to 4 years of age | 1 | 38 | Mean Difference (IV, Fixed, 95% CI) | 10.42 [-1.96, 22.80] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 39 WPPSI-III VIQ at 3.5 to 4 years of age | 1 | 38 | Mean Difference (IV, Fixed, 95% CI) | 10.64 [-0.73, 22.01] |
| 40 WPPSI-III PIQ at 3.5 to 4 years of age | 1 | 38 | Mean Difference (IV, Fixed, 95% CI) | 10.12 [-2.67, 22.91] |
| 41 WPPSI-III GLC at 3.5 to 4 years of age | 1 | 38 | Mean Difference (IV, Fixed, 95% CI) | 3.12 [-8.37, 14.61] |
| 42 Executive function at 3.5 to 4 years of age | 1 | 38 | Mean Difference (IV, Fixed, 95% CI) | 6.82 [-1.97, 15.61] |
| 43 Working memory at 3.5 to 4 years of age | 1 | 38 | Mean Difference (IV, Fixed, 95% CI) | 6.74 [-4.56, 18.04] |
| 44 Inhibition at 3.5 to 4 years of age | 1 | 38 | Mean Difference (IV, Fixed, 95% CI) | 6.86 [-4.56, 18.28] |
| 45 Griffiths Developmental Scale at 2 years of age | 1 | 19 | Mean Difference (IV, Fixed, 95% CI) | 3.0 [-3.75, 9.75] |
| 46 Survival without major neurological or neurodevelopmental disorders at 2 years of age | 2 | 404 | Risk Ratio (M-H, Fixed, 95% CI) | 0.99 [0.91, 1.08] |
| 47 Death or moderate/severe neurological disability at 18 to 24 months | 1 | 668 | Risk Ratio (M-H, Fixed, 95% CI) | 0.48 [0.35, 0.67] |
| 48 Moderate/severe neurological disability at 18 to 24 months | 1 | 613 | Risk Ratio (M-H, Fixed, 95% CI) | 0.38 [0.24, 0.60] |

## Comparison 2.   Darbepoetin alfa versus placebo or no treatment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Use of 1 or more red blood cell transfusions | 1 | 66 | Risk Ratio (M-H, Fixed, 95% CI) | 0.62 [0.38, 1.02] |
| 2 Total volume (mL/kg) of blood transfused per infant (all infants) | 1 | 66 | Mean Difference (IV, Fixed, 95% CI) | -21.0 [-50.72, 8.72] |
| 3 Total volume (mL/kg) of blood transfused in transfused infants only | 1 | 34 | Mean Difference (IV, Fixed, 95% CI) | -5.10 [-53.71, 43.51] |
| 4 Number of blood transfusions per infant | 1 | 66 | Mean Difference (IV, Fixed, 95% CI) | -1.2 [-2.48, 0.08] |
| 5 Number of donors the infant was exposed to | 1 | 66 | Mean Difference (IV, Fixed, 95% CI) | -0.5 [-1.10, 0.10] |
| 6 Mortality during initial hospital stay (all causes of mortality) | 1 | 66 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.12, 3.73] |
| 7 Retinopathy of prematurity (all stages) | 1 | 62 | Risk Ratio (M-H, Fixed, 95% CI) | 0.94 [0.50, 1.75] |
| 8 Retinopathy of prematurity (stage ≥ 3) | 1 | 62 | Risk Ratio (M-H, Fixed, 95% CI) | 0.47 [0.09, 2.37] |
| 9 Necrotising enterocolitis (> stage 2) | 1 | 62 | Risk Ratio (M-H, Fixed, 95% CI) | 0.94 [0.14, 6.24] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 10 Proven sepsis | 1 | 62 | Risk Ratio (M-H, Fixed, 95% CI) | 1.13 [0.38, 3.30] |
| 11 Intraventricular haemorrhage (grades III and IV) | 1 | 62 | Risk Ratio (M-H, Fixed, 95% CI) | 0.40 [0.11, 1.41] |
| 12 Periventricular leukomalacia | 1 | 62 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 13 Bronchopulmonary dysplasia (supplemental oxygen at 36 weeks' PMA) | 1 | 62 | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 [0.73, 1.46] |
| 14 Length of hospital stay (days) | 1 | 62 | Mean Difference (IV, Fixed, 95% CI) | 2.0 [-17.84, 21.84] |
| 15 Neutropenia | 1 | 62 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 16 Hypertension | 1 | 62 | Risk Ratio (M-H, Fixed, 95% CI) | 1.88 [0.18, 19.63] |
| 17 Cerebral palsy at 18 to 22 months | 1 | 51 | Risk Ratio (M-H, Fixed, 95% CI) | 0.08 [0.00, 1.40] |
| 18 NDI (with CP, visual defect, hearing defect, or cognitive score < 85) at 18 to 22 months | 1 | 51 | Risk Ratio (M-H, Fixed, 95% CI) | 0.27 [0.08, 0.86] |
| 19 BSID-III composite cognitive score at 18 to 22 months | 1 | 51 | Mean Difference (IV, Fixed, 95% CI) | 7.5 [1.44, 13.56] |
| 20 BSID-III composite language score at 18 to 22 months | 1 | 51 | Mean Difference (IV, Fixed, 95% CI) | 8.80 [1.57, 16.03] |
| 21 Bayley-III social/emotional score at 18 to 22 months | 1 | 51 | Mean Difference (IV, Fixed, 95% CI) | 6.80 [-3.82, 17.42] |
| 22 OP score at 18 to 22 months | 1 | 51 | Mean Difference (IV, Fixed, 95% CI) | 0.60 [0.17, 1.03] |
| 23 WPPSI-III FSIQ at 3.5 to 4 years of age | 1 | 29 | Mean Difference (IV, Fixed, 95% CI) | 15.27 [2.60, 27.94] |
| 24 WPPSI-III VIQ at 3.5 to 4 years of age | 1 | 29 | Mean Difference (IV, Fixed, 95% CI) | 9.17 [-2.86, 21.20] |
| 25 WPPSI-III PIQ at 3.5 to 4 years of age | 1 | 29 | Mean Difference (IV, Fixed, 95% CI) | 14.97 [1.89, 28.05] |
| 26 WPPSI-III GLC at 3.5 to 4 years of age | 1 | 29 | Mean Difference (IV, Fixed, 95% CI) | 7.94 [-4.18, 20.06] |
| 27 Executive function at 3.5 to 4 years of age | 1 | 29 | Mean Difference (IV, Fixed, 95% CI) | 10.81 [2.83, 18.79] |
| 28 Working memory at 3.5 to 4 years of age | 1 | 29 | Mean Difference (IV, Fixed, 95% CI) | 12.77 [2.68, 22.86] |
| 29 Inhibition at 3.5 to 4 years of age | 1 | 29 | Mean Difference (IV, Fixed, 95% CI) | 8.77 [-2.47, 20.01] |

## Comparison 3. Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 BSID-III composite cognitive score at 18 to 22 months | 1 | 80 | Mean Difference (IV, Fixed, 95% CI) | 7.80 [1.65, 13.95] |
| 2 BSID-III composite language score at 18 to 22 months | 1 | 80 | Mean Difference (IV, Fixed, 95% CI) | 7.10 [0.49, 13.71] |

| | | | | |
|---|---|---|---|---|
| 3 BSID-III composite social/emotional score at 18 to 22 months | 1 | 80 | Mean Difference (IV, Fixed, 95% CI) | 4.20 [-5.06, 13.46] |
| 4 OP score at 18 to 24 months | 1 | 80 | Mean Difference (IV, Fixed, 95% CI) | 0.40 [-0.04, 0.84] |
| 5 BASC-2 composite scores at 3.5 to 4 years - adaptive skills | 1 | 49 | Mean Difference (IV, Fixed, 95% CI) | 2.54 [-3.58, 8.66] |
| 6 BASC-2 composite scores at 3.5 to 4 years - behaviour symptoms | 1 | 49 | Mean Difference (IV, Fixed, 95% CI) | -8.66 [-18.01, 0.69] |
| 7 BASC-2 composite score at 3.5 to 4 years - externalising problems | 1 | 49 | Mean Difference (IV, Fixed, 95% CI) | -8.0 [-15.94, -0.06] |
| 8 BASC-2 composite scores at 3.5 to 4 years - internalising problems | 1 | 49 | Mean Difference (IV, Fixed, 95% CI) | -2.56 [-9.25, 4.13] |
| 9 WPPSI-III FSIQ at 3.5 to 4 years of age | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 11.90 [0.76, 23.04] |
| 10 WPPSI-III VIQ at 3.5 to 4 years of age | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 8.80 [-1.75, 19.35] |
| 11 WPPSI-III PIQ at 3.5 to 4 years of age | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 13.5 [1.98, 25.02] |
| 12 WPPSI-III GLC at 3.5 to 4 years of age | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 5.13 [-5.30, 15.56] |
| 13 Executive function at 3.5 to 4 years | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 8.36 [0.51, 16.21] |
| 14 Working memory at 3.5 to 4 years | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 9.06 [-1.06, 19.18] |
| 15 Inhibition at 3.5 to 4 years | 1 | 53 | Mean Difference (IV, Fixed, 95% CI) | 7.60 [-2.79, 17.99] |

## Comparison 4. Erythropoietin versus placebo to improve feeding intolerance

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Time to achieve full enteral feeding (days) | 1 | 50 | Mean Difference (IV, Fixed, 95% CI) | -2.90 [-5.77, -0.03] |

**Analysis 1.1. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 1 Use of 1 or more red blood cell transfusions (low and high doses of EPO).**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 1 Use of 1 or more red blood cell transfusions (low and high doses of EPO)

| Study or subgroup | EPO n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Arif 2005 | 67/142 | 94/150 | | 15.5 % | 0.75 [ 0.61, 0.93 ] |
| Avent 2002 | 6/63 | 8/30 | | 1.8 % | 0.36 [ 0.14, 0.94 ] |
| Chang 1998 | 0/30 | 0/15 | | | Not estimable |
| Haiden 2005 | 13/21 | 18/19 | | 3.2 % | 0.65 [ 0.46, 0.93 ] |
| Kremenopoulos 1997A | 2/10 | 9/12 | | 1.4 % | 0.27 [ 0.07, 0.96 ] |
| Kremenopoulos 1997B | 14/14 | 14/14 | | 2.5 % | 1.00 [ 0.88, 1.14 ] |
| Maier 1994 | 68/120 | 87/121 | | 14.7 % | 0.79 [ 0.65, 0.96 ] |
| Maier 2002 | 55/74 | 60/71 | | 10.4 % | 0.88 [ 0.74, 1.04 ] |
| Meyer 2003 | 15/22 | 19/21 | | 3.3 % | 0.75 [ 0.55, 1.04 ] |
| Obladen 1991 | 28/43 | 34/50 | | 5.3 % | 0.96 [ 0.72, 1.28 ] |
| Ohls 1995 | 6/10 | 8/10 | | 1.4 % | 0.75 [ 0.41, 1.36 ] |
| Ohls 2001A | 73/87 | 74/85 | | 12.7 % | 0.96 [ 0.85, 1.09 ] |
| Ohls 2001B | 22/59 | 27/59 | | 4.6 % | 0.81 [ 0.53, 1.26 ] |
| Ohls 2013 | 16/33 | 21/33 | | 3.6 % | 0.76 [ 0.49, 1.18 ] |
| Peltoniemi 2017 | 20/21 | 17/18 | | 3.1 % | 1.01 [ 0.87, 1.17 ] |
| Salvado 2000 | 11/29 | 27/31 | | 4.4 % | 0.44 [ 0.27, 0.71 ] |
| Soubasi 1995 | 11/61 | 16/36 | | 3.4 % | 0.41 [ 0.21, 0.78 ] |
| Soubasi 2000 | 10/18 | 15/18 | | 2.5 % | 0.67 [ 0.42, 1.06 ] |
| Yeo 2001 | 36/50 | 37/50 | | 6.3 % | 0.97 [ 0.77, 1.24 ] |
| **Total (95% CI)** | **907** | **843** | | **100.0 %** | **0.79 [ 0.74, 0.85 ]** |

Total events: 473 (EPO), 585 (Control)

Heterogeneity: Chi$^2$ = 54.43, df = 17 (P<0.00001); I$^2$ =69%

Test for overall effect: Z = 6.49 (P < 0.00001)

Test for subgroup differences: Not applicable

```
       0.01   0.1    1    10   100
         Favours EPO   Favours control
```

**Analysis 1.2. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 2 Use of 1 or more blood transfusions (high dose of EPO).**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 2 Use of 1 or more blood transfusions (high dose of EPO)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **1 High-dose iron** | | | | | |
| Avent 2002 | 6/63 | 8/30 | | 2.4 % | 0.36 [ 0.14, 0.94 ] |
| Chang 1998 | 0/15 | 0/15 | | | Not estimable |
| Haiden 2005 | 13/21 | 18/19 | | 4.1 % | 0.65 [ 0.46, 0.93 ] |
| Maier 2002 | 55/74 | 60/71 | | 13.3 % | 0.88 [ 0.74, 1.04 ] |
| Meyer 2003 | 15/22 | 19/21 | | 4.2 % | 0.75 [ 0.55, 1.04 ] |
| Ohls 1995 | 6/10 | 8/10 | | 1.7 % | 0.75 [ 0.41, 1.36 ] |
| Ohls 2001A | 73/87 | 74/85 | | 16.2 % | 0.96 [ 0.85, 1.09 ] |
| Ohls 2001B | 22/59 | 27/59 | | 5.9 % | 0.81 [ 0.53, 1.26 ] |
| Ohls 2013 | 16/33 | 21/33 | | 4.6 % | 0.76 [ 0.49, 1.18 ] |
| Soubasi 2000 | 10/18 | 15/18 | | 3.3 % | 0.67 [ 0.42, 1.06 ] |
| Yeo 2001 | 36/50 | 37/50 | | 8.0 % | 0.97 [ 0.77, 1.24 ] |
| **Subtotal (95% CI)** | **452** | **411** | | **63.6 %** | **0.84 [ 0.77, 0.92 ]** |
| Total events: 252 (Treatment), 287 (Control) | | | | | |
| Heterogeneity: Chi² = 13.15, df = 9 (P = 0.16); I² =32% | | | | | |
| Test for overall effect: Z = 3.80 (P = 0.00014) | | | | | |
| **2 Low-dose iron** | | | | | |
| Kremenopoulos 1997A | 2/10 | 9/12 | | 1.8 % | 0.27 [ 0.07, 0.96 ] |
| Kremenopoulos 1997B | 14/14 | 14/14 | | 3.1 % | 1.00 [ 0.88, 1.14 ] |
| Maier 1994 | 68/120 | 87/121 | | 18.8 % | 0.79 [ 0.65, 0.96 ] |
| Peltoniemi 2017 | 20/21 | 17/18 | | 4.0 % | 1.01 [ 0.87, 1.17 ] |
| Salvado 2000 | 11/29 | 27/31 | | 5.7 % | 0.44 [ 0.27, 0.71 ] |
| Soubasi 1995 | 4/28 | 16/36 | | 3.0 % | 0.32 [ 0.12, 0.85 ] |
| **Subtotal (95% CI)** | **222** | **232** | | **36.4 %** | **0.71 [ 0.62, 0.82 ]** |
| Total events: 119 (Treatment), 170 (Control) | | | | | |
| Heterogeneity: Chi² = 56.65, df = 5 (P<0.00001); I² =91% | | | | | |
| Test for overall effect: Z = 4.79 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **674** | **643** | | **100.0 %** | **0.79 [ 0.74, 0.86 ]** |

0.01   0.1   1   10   100

Favours EPO          Favours control

(*Continued* . . . )

| Study or subgroup | Treatment | Control | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |

Total events: 371 (Treatment), 457 (Control)

Heterogeneity: Chi$^2$ = 51.84, df = 15 (P<0.00001); I$^2$ =71%

Test for overall effect: Z = 5.99 (P < 0.00001)

Test for subgroup differences: Chi$^2$ = 4.00, df = 1 (P = 0.05), I$^2$ =75%

```
         0.01   0.1    1    10   100
              Favours EPO   Favours control
```

### Analysis 1.3.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 3 Use of 1 or more red blood cell transfusions (low-dose EPO).

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   3 Use of 1 or more red blood cell transfusions (low-dose EPO)

| Study or subgroup | Treatment | Control | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| 1 High-dose iron | | | | | |
| Arif 2005 | 67/142 | 94/150 | ■ | 66.2 % | 0.75 [ 0.61, 0.93 ] |
| Chang 1998 | 0/15 | 0/15 | | | Not estimable |
| **Subtotal (95% CI)** | **157** | **165** | ◆ | **66.2 %** | **0.75 [ 0.61, 0.93 ]** |
| Total events: 67 (Treatment), 94 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.61 (P = 0.0091) | | | | | |
| 2 Low-dose iron | | | | | |
| Obladen 1991 | 28/43 | 34/50 | ■ | 22.8 % | 0.96 [ 0.72, 1.28 ] |
| Soubasi 1995 | 7/33 | 16/36 | ■ | 11.1 % | 0.48 [ 0.22, 1.01 ] |
| **Subtotal (95% CI)** | **76** | **86** | ◆ | **33.8 %** | **0.80 [ 0.60, 1.07 ]** |
| Total events: 35 (Treatment), 50 (Control) | | | | | |
| Heterogeneity: Chi$^2$ = 3.29, df = 1 (P = 0.07); I$^2$ =70% | | | | | |
| Test for overall effect: Z = 1.53 (P = 0.13) | | | | | |
| **Total (95% CI)** | **233** | **251** | ◆ | **100.0 %** | **0.77 [ 0.65, 0.91 ]** |
| Total events: 102 (Treatment), 144 (Control) | | | | | |

```
         0.01   0.1    1    10   100
              Favours EPO   Favours control
```

| Study or subgroup | Treatment | Control | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |

Heterogeneity: Chi² = 3.78, df = 2 (P = 0.15); I² =47%

Test for overall effect: Z = 3.01 (P = 0.0026)

Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² =0.0%

```
        0.01   0.1    1    10   100
          Favours EPO    Favours control
```

## Analysis 1.4. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 4 Total volume (mL/kg) of blood transfused per infant.

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 4 Total volume (mL/kg) of blood transfused per infant

| Study or subgroup | Treatment | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Obladen 1991 | 43 | 14.1 (17.8) | 34 | 16.5 (20.8) | | 28.7 % | -2.40 [ -11.19, 6.39 ] |
| Ohls 1995 | 10 | 13.4 (2.85) | 10 | 28.7 (14.86) | | 25.2 % | -15.30 [ -24.68, -5.92 ] |
| Ohls 1997 | 15 | 70 (42.6) | 13 | 112 (61.3) | | 1.4 % | -42.00 [ -81.69, -2.31 ] |
| Ohls 2001A | 87 | 80 (53) | 85 | 95 (63) | | 7.3 % | -15.00 [ -32.42, 2.42 ] |
| Ohls 2001B | 59 | 39 (26) | 59 | 35 (24) | | 27.1 % | 4.00 [ -5.03, 13.03 ] |
| Ohls 2013 | 33 | 23 (33) | 33 | 51 (65) | | 3.6 % | -28.00 [ -52.87, -3.13 ] |
| Yeo 2001 | 50 | 36.1 (41.6) | 50 | 46.2 (50.4) | | 6.7 % | -10.10 [ -28.21, 8.01 ] |
| **Total (95% CI)** | **297** | | **284** | | | **100.0 %** | **-6.82 [ -11.52, -2.11 ]** |

Heterogeneity: Chi² = 16.41, df = 6 (P = 0.01); I² =63%

Test for overall effect: Z = 2.84 (P = 0.0045)

Test for subgroup differences: Not applicable

```
      -100   -50    0    50   100
          Favours EPO    Favours control
```

**Analysis 1.5.** Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 5 Number of red blood transfusions per infant.

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 5 Number of red blood transfusions per infant

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Carnielli 1992 | 11 | 0.8 (1.5) | 11 | 3.1 (2.1) | | 0.6 % | -2.30 [ -3.83, -0.77 ] |
| Kremenopoulos 1997A | 10 | 0.2 (0.4) | 12 | 1 (0.7) | | 6.4 % | -0.80 [ -1.27, -0.33 ] |
| Kremenopoulos 1997B | 14 | 5 (2.5) | 14 | 4.9 (2.4) | | 0.4 % | 0.10 [ -1.72, 1.92 ] |
| Maier 2002 | 74 | 2.3 (2.2) | 71 | 3.1 (2.6) | | 2.3 % | -0.80 [ -1.59, -0.01 ] |
| Meyer 2003 | 22 | 2.5 (2.3) | 21 | 3.2 (3.4) | | 0.5 % | -0.70 [ -2.44, 1.04 ] |
| Ohls 1995 | 10 | 1.9 (2.85) | 10 | 2.7 (3.48) | | 0.2 % | -0.80 [ -3.59, 1.99 ] |
| Ohls 1997 | 15 | 4.7 (2.71) | 13 | 7.5 (3.9) | | 0.2 % | -2.80 [ -5.32, -0.28 ] |
| Ohls 2001A | 87 | 4.3 (3.6) | 85 | 5.2 (4.2) | | 1.0 % | -0.90 [ -2.07, 0.27 ] |
| Ohls 2001B | 59 | 1 (1.6) | 59 | 1.1 (1.5) | | 4.5 % | -0.10 [ -0.66, 0.46 ] |
| Ohls 2013 | 33 | 1.2 (1.6) | 33 | 2.4 (2.9) | | 1.1 % | -1.20 [ -2.33, -0.07 ] |
| Salvado 2000 | 29 | 0.69 (1) | 31 | 1.41 (1.1) | | 5.0 % | -0.72 [ -1.25, -0.19 ] |
| Song 2016 | 366 | 1.1 (1.2) | 377 | 2.2 (1.7) | | 31.4 % | -1.10 [ -1.31, -0.89 ] |
| Soubasi 1993 | 25 | 5.44 (4.06) | 19 | 5.37 (3.01) | | 0.3 % | 0.07 [ -2.02, 2.16 ] |
| Soubasi 1995 | 61 | 0.31 (0.59) | 36 | 0.9 (1.1) | | 9.3 % | -0.59 [ -0.98, -0.20 ] |
| Soubasi 2000 | 18 | 1.05 (1.6) | 18 | 2.94 (3.19) | | 0.5 % | -1.89 [ -3.54, -0.24 ] |
| Yeo 2001 | 50 | 0.7 (0.5) | 50 | 0.7 (0.5) | | 36.4 % | 0.0 [ -0.20, 0.20 ] |
| **Total (95% CI)** | **884** | | **860** | | | **100.0 %** | **-0.57 [ -0.68, -0.45 ]** |

Heterogeneity: Chi² = 73.82, df = 15 (P<0.00001); I² =80%

Test for overall effect: Z = 9.37 (P < 0.00001)

Test for subgroup differences: Not applicable

-4  -2  0  2  4

Favours EPO        Favours control

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: I Erythropoietin versus placebo or no treatment

Outcome: 6 Number of donors to whom the infant was exposed

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| I Among all randomised infants | | | | | | | |
| Maier 2002 | 74 | 1.5 (1.3) | 71 | 2.1 (1.5) | | 57.5 % | -0.60 [ -1.06, -0.14 ] |
| Meyer 2003 | 22 | 1.86 (1.5) | 21 | 2.95 (3.8) | | 4.0 % | -1.09 [ -2.83, 0.65 ] |
| Ohls 2013 | 33 | 0.8 (1) | 33 | 1.2 (1.3) | | 38.5 % | -0.40 [ -0.96, 0.16 ] |
| **Subtotal (95% CI)** | **129** | | **125** | | | **100.0 %** | **-0.54 [ -0.89, -0.20 ]** |
| Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | | | | |
| 2 Among infants who were transfused | | | | | | | |
| Ohls 2001A | 87 | 3.2 (2.5) | 85 | 3.8 (3.2) | | 19.2 % | -0.60 [ -1.46, 0.26 ] |
| Ohls 2001B | 59 | 2.1 (1.3) | 59 | 1.9 (1) | | 80.8 % | 0.20 [ -0.22, 0.62 ] |
| **Subtotal (95% CI)** | **146** | | **144** | | | **100.0 %** | **0.05 [ -0.33, 0.42 ]** |
| Heterogeneity: Chi² = 2.69, df = I (P = 0.10); I² =63% | | | | | | | |
| Test for overall effect: Z = 0.24 (P = 0.81) | | | | | | | |
| Test for subgroup differences: Chi² = 5.09, df = I (P = 0.02), I² =80% | | | | | | | |

```
        -4   -2   0   2   4

     Favours EPO    Favours control
```

**Analysis 1.7. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 7 Mortality during initial hospital stay (all causes of mortality).**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 7 Mortality during initial hospital stay (all causes of mortality)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Arif 2005 | 19/142 | 22/150 | | 21.2 % | 0.91 [ 0.52, 1.61 ] |
| Avent 2002 | 2/63 | 1/30 | | 1.3 % | 0.95 [ 0.09, 10.09 ] |
| Carnielli 1992 | 0/11 | 0/11 | | | Not estimable |
| El-Ganzoury 2014 | 2/20 | 3/30 | | 2.4 % | 1.00 [ 0.18, 5.46 ] |
| Fauch re 2008 | 5/6 | 0/2 | | 0.7 % | 4.71 [ 0.36, 60.97 ] |
| Fauch re 2015 | 12/229 | 12/214 | | 12.3 % | 0.93 [ 0.43, 2.03 ] |
| Haiden 2005 | 3/21 | 4/19 | | 4.2 % | 0.68 [ 0.17, 2.65 ] |
| Maier 1994 | 3/120 | 3/121 | | 3.0 % | 1.01 [ 0.21, 4.90 ] |
| Maier 2002 | 6/74 | 9/71 | | 9.1 % | 0.64 [ 0.24, 1.70 ] |
| Obladen 1991 | 0/43 | 2/50 | | 2.3 % | 0.23 [ 0.01, 4.70 ] |
| Ohls 1997 | 6/15 | 4/13 | | 4.2 % | 1.30 [ 0.47, 3.62 ] |
| Ohls 2001A | 15/87 | 15/85 | | 15.0 % | 0.98 [ 0.51, 1.87 ] |
| Ohls 2001B | 1/59 | 4/59 | | 4.0 % | 0.25 [ 0.03, 2.17 ] |
| Ohls 2013 | 1/32 | 3/30 | | 3.1 % | 0.31 [ 0.03, 2.84 ] |
| Peltoniemi 2017 | 1/21 | 2/18 | | 2.1 % | 0.43 [ 0.04, 4.35 ] |
| Qiao 2017 | 0/32 | 1/33 | | 1.5 % | 0.34 [ 0.01, 8.13 ] |
| Soubasi 1993 | 2/25 | 1/19 | | 1.1 % | 1.52 [ 0.15, 15.55 ] |
| Soubasi 1995 | 7/61 | 3/36 | | 3.7 % | 1.38 [ 0.38, 4.99 ] |
| Yasmeen 2012 | 4/30 | 5/30 | | 4.9 % | 0.80 [ 0.24, 2.69 ] |
| Yeo 2001 | 5/50 | 4/50 | | 4.0 % | 1.25 [ 0.36, 4.38 ] |
| **Total (95% CI)** | **1141** | **1071** | | **100.0 %** | **0.89 [ 0.68, 1.16 ]** |

Total events: 94 (Treatment), 98 (Control)

Heterogeneity: Chi$^2$ = 7.53, df = 18 (P = 0.98); I$^2$ =0.0%

Test for overall effect: Z = 0.84 (P = 0.40)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours EPO     Favours control

**Analysis 1.8. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 8 Retinopathy of prematurity (all stages or stage not reported).**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 8 Retinopathy of prematurity (all stages or stage not reported)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Arif 2005 | 34/142 | 39/150 | | 15.3 % | 0.92 [ 0.62, 1.37 ] |
| Carnielli 1998 | 4/42 | 1/21 | | 0.5 % | 2.00 [ 0.24, 16.79 ] |
| Fauchère 2015 | 20/212 | 19/191 | | 8.0 % | 0.95 [ 0.52, 1.72 ] |
| Haiden 2005 | 2/21 | 2/19 | | 0.8 % | 0.90 [ 0.14, 5.81 ] |
| Maier 1994 | 19/120 | 20/121 | | 8.0 % | 0.96 [ 0.54, 1.70 ] |
| Maier 2002 | 42/74 | 38/71 | | 15.6 % | 1.06 [ 0.79, 1.42 ] |
| Ohls 2013 | 11/32 | 12/30 | | 5.0 % | 0.86 [ 0.45, 1.64 ] |
| Peltoniemi 2017 | 4/20 | 5/15 | | 2.3 % | 0.60 [ 0.19, 1.86 ] |
| Qiao 2017 | 0/30 | 0/31 | | | Not estimable |
| Song 2016 | 79/366 | 97/377 | | 38.4 % | 0.84 [ 0.65, 1.09 ] |
| Yeo 2001 | 17/50 | 15/50 | | 6.0 % | 1.13 [ 0.64, 2.01 ] |
| **Total (95% CI)** | **1109** | **1076** | | **100.0 %** | **0.92 [ 0.79, 1.08 ]** |

Total events: 232 (Treatment), 248 (Control)

Heterogeneity: Chi² = 3.00, df = 9 (P = 0.96); I² =0.0%

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours EPO          Favours control

**Analysis 1.9. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 9 Retinopathy of prematurity (stage ≥ 3).**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 9 Retinopathy of prematurity (stage ≥ 3)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 2/212 | 5/191 | | 15.4 % | 0.36 [ 0.07, 1.84 ] |
| Haiden 2005 | 1/21 | 0/19 | | 1.5 % | 2.73 [ 0.12, 63.19 ] |
| Maier 1994 | 1/120 | 1/121 | | 2.9 % | 1.01 [ 0.06, 15.94 ] |
| Maier 2002 | 12/67 | 5/62 | | 15.2 % | 2.22 [ 0.83, 5.94 ] |
| Ohls 2001A | 17/87 | 14/85 | | 41.3 % | 1.19 [ 0.62, 2.25 ] |
| Ohls 2001B | 4/59 | 2/59 | | 5.8 % | 2.00 [ 0.38, 10.50 ] |
| Ohls 2013 | 2/32 | 4/30 | | 12.1 % | 0.47 [ 0.09, 2.37 ] |
| Peltoniemi 2017 | 4/59 | 2/59 | | 5.8 % | 2.00 [ 0.38, 10.50 ] |
| **Total (95% CI)** | **657** | **626** | | **100.0 %** | **1.24 [ 0.81, 1.90 ]** |

Total events: 43 (Treatment), 33 (Control)

Heterogeneity: Chi² = 5.86, df = 7 (P = 0.56); I² =0.0%

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours EPO    Favours control
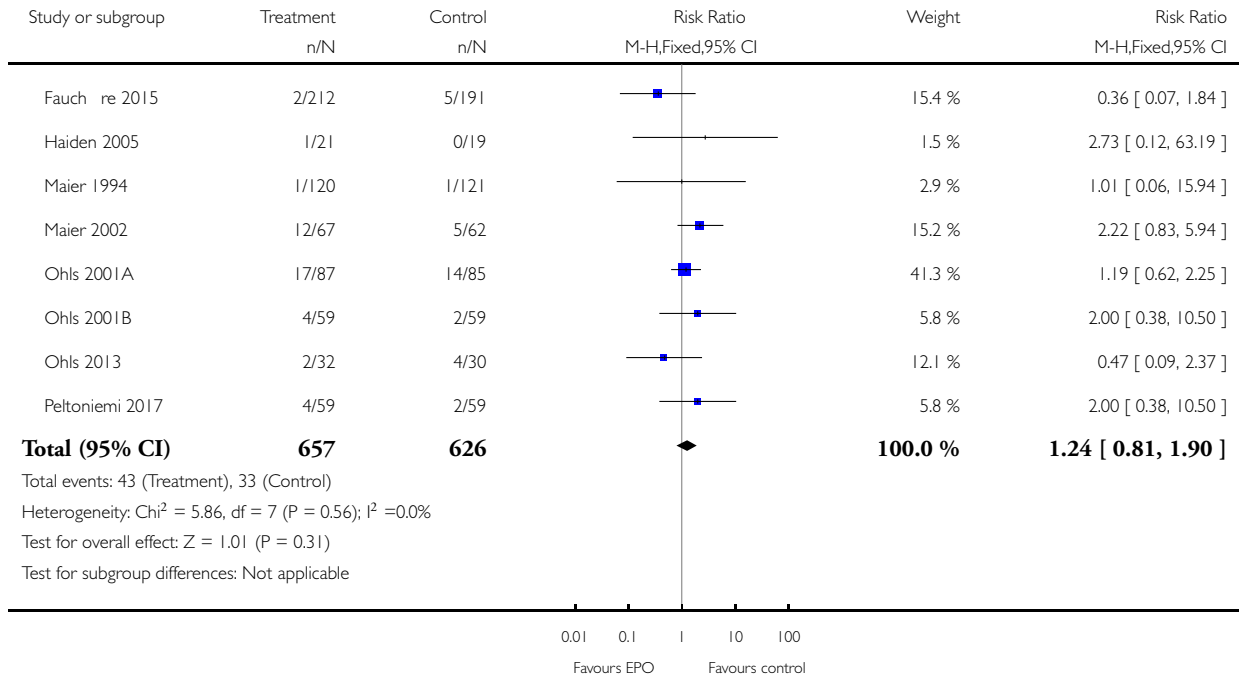
**Analysis 1.10.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 10 Proven sepsis.**

Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:    1 Erythropoietin versus placebo or no treatment

Outcome:    10 Proven sepsis

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Avent 2002 | 6/63 | 2/30 | | 1.2 % | 1.43 [ 0.31, 6.66 ] |
| Carnielli 1998 | 3/42 | 2/21 | | 1.2 % | 0.75 [ 0.14, 4.15 ] |
| Chang 1998 | 0/30 | 0/15 | | | Not estimable |
| Fauchère 2015 | 31/229 | 29/214 | | 13.2 % | 1.00 [ 0.62, 1.60 ] |
| Lima-Rogel 1998 | 6/21 | 5/19 | | 2.3 % | 1.09 [ 0.39, 2.99 ] |
| Maier 1994 | 14/120 | 7/121 | | 3.1 % | 2.02 [ 0.84, 4.82 ] |
| Ohls 2001A | 33/87 | 37/85 | | 16.5 % | 0.87 [ 0.61, 1.25 ] |
| Ohls 2001B | 9/59 | 12/59 | | 5.3 % | 0.75 [ 0.34, 1.64 ] |
| Ohls 2013 | 5/32 | 5/30 | | 2.3 % | 0.94 [ 0.30, 2.92 ] |
| Salvado 2000 | 18/29 | 21/31 | | 8.9 % | 0.92 [ 0.63, 1.33 ] |
| Song 2016 | 71/366 | 99/377 | | 43.0 % | 0.74 [ 0.56, 0.97 ] |
| Yeo 2001 | 4/50 | 7/50 | | 3.1 % | 0.57 [ 0.18, 1.83 ] |
| **Total (95% CI)** | **1128** | **1052** | | **100.0 %** | **0.87 [ 0.74, 1.02 ]** |

Total events: 200 (Treatment), 226 (Control)

Heterogeneity: Chi² = 6.66, df = 10 (P = 0.76); I² =0.0%

Test for overall effect: Z = 1.71 (P = 0.087)

Test for subgroup differences: Not applicable

```
        0.01    0.1     1      10    100
          Favours EPO        Favours control
```

## Analysis 1.11. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 11 Necrotising enterocolitis (stage not reported).

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 11 Necrotising enterocolitis (stage not reported)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Arif 2005 | 7/142 | 6/150 | | 5.2 % | 1.23 [ 0.42, 3.58 ] |
| El-Ganzoury 2014 | 0/20 | 3/30 | | 2.5 % | 0.21 [ 0.01, 3.87 ] |
| Fauchère 2015 | 6/229 | 10/214 | | 9.3 % | 0.56 [ 0.21, 1.52 ] |
| Haiden 2005 | 3/21 | 0/19 | | 0.5 % | 6.36 [ 0.35, 115.73 ] |
| Lima-Rogel 1998 | 2/21 | 0/19 | | 0.5 % | 4.55 [ 0.23, 89.08 ] |
| Maier 1994 | 6/120 | 8/121 | | 7.2 % | 0.76 [ 0.27, 2.11 ] |
| Maier 2002 | 7/74 | 8/71 | | 7.3 % | 0.84 [ 0.32, 2.19 ] |
| Obladen 1991 | 1/43 | 3/50 | | 2.5 % | 0.39 [ 0.04, 3.59 ] |
| Ohls 2001A | 9/87 | 10/85 | | 9.1 % | 0.88 [ 0.38, 2.06 ] |
| Ohls 2001B | 3/59 | 4/59 | | 3.6 % | 0.75 [ 0.18, 3.21 ] |
| Ohls 2013 | 1/32 | 2/30 | | 1.9 % | 0.47 [ 0.04, 4.91 ] |
| Peltoniemi 2017 | 1/21 | 1/18 | | 1.0 % | 0.86 [ 0.06, 12.75 ] |
| Qiao 2017 | 0/30 | 0/31 | | | Not estimable |
| Song 2016 | 25/366 | 54/377 | | 47.8 % | 0.48 [ 0.30, 0.75 ] |
| Yeo 2001 | 4/50 | 2/50 | | 1.8 % | 2.00 [ 0.38, 10.43 ] |
| **Total (95% CI)** | **1315** | **1324** | | **100.0 %** | **0.69 [ 0.52, 0.91 ]** |

Total events: 75 (Treatment), 111 (Control)

Heterogeneity: Chi² = 10.79, df = 13 (P = 0.63); I² =0.0%

Test for overall effect: Z = 2.63 (P = 0.0084)

Test for subgroup differences: Not applicable

0.01    0.1    1    10    100

Favours EPO          Favours control

**Analysis 1.12. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 12 Intraventricular haemorrhage (all grades).**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 12 Intraventricular haemorrhage (all grades)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Carnielli 1998 | 4/42 | 3/21 | | 4.1 % | 0.67 [ 0.16, 2.71 ] |
| Chang 1998 | 4/42 | 3/21 | | 4.1 % | 0.67 [ 0.16, 2.71 ] |
| Fauchère 2015 | 43/229 | 41/214 | | 43.5 % | 0.98 [ 0.67, 1.44 ] |
| Haiden 2005 | 7/21 | 7/19 | | 7.5 % | 0.90 [ 0.39, 2.10 ] |
| Lima-Rogel 1998 | 0/21 | 2/19 | | 2.7 % | 0.18 [ 0.01, 3.56 ] |
| Maier 1994 | 10/120 | 10/121 | | 10.2 % | 1.01 [ 0.44, 2.33 ] |
| Maier 2002 | 22/74 | 18/71 | | 18.8 % | 1.17 [ 0.69, 1.99 ] |
| Obladen 1991 | 5/43 | 5/50 | | 4.7 % | 1.16 [ 0.36, 3.75 ] |
| Peltoniemi 2017 | 3/21 | 3/18 | | 3.3 % | 0.86 [ 0.20, 3.73 ] |
| Salvado 2000 | 2/29 | 1/30 | | 1.0 % | 2.07 [ 0.20, 21.60 ] |
| **Total (95% CI)** | **642** | **584** | | **100.0 %** | **0.98 [ 0.76, 1.26 ]** |

Total events: 100 (Treatment), 93 (Control)

Heterogeneity: Chi² = 2.79, df = 9 (P = 0.97); I² =0.0%

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable

0.01  0.1  1  10  100

Favours EPO          Favours control

## Analysis 1.13.  Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 13 Intraventricular haemorrhage (grades III and IV).

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   13 Intraventricular haemorrhage (grades III and IV)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauch re 2008 | 4/30 | 0/15 | | 0.8 % | 4.65 [ 0.27, 81.01 ] |
| Haiden 2005 | 0/21 | 2/19 | | 3.2 % | 0.18 [ 0.01, 3.56 ] |
| Maier 1994 | 2/120 | 1/121 | | 1.2 % | 2.02 [ 0.19, 21.95 ] |
| Ohls 2001A | 11/87 | 8/85 | | 10.0 % | 1.34 [ 0.57, 3.18 ] |
| Ohls 2001B | 3/59 | 2/59 | | 2.5 % | 1.50 [ 0.26, 8.65 ] |
| Ohls 2013 | 3/32 | 7/30 | | 8.9 % | 0.40 [ 0.11, 1.41 ] |
| Peltoniemi 2017 | 2/21 | 0/18 | | 0.7 % | 4.32 [ 0.22, 84.48 ] |
| Song 2016 | 24/366 | 60/377 | | 72.8 % | 0.41 [ 0.26, 0.65 ] |
| **Total (95% CI)** | **736** | **724** | | **100.0 %** | **0.60 [ 0.43, 0.85 ]** |

Total events: 49 (Treatment), 80 (Control)

Heterogeneity: Chi$^2$ = 12.76, df = 7 (P = 0.08); I$^2$ =45%

Test for overall effect: Z = 2.92 (P = 0.0035)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
        Favours EPO      Favours control
```

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants
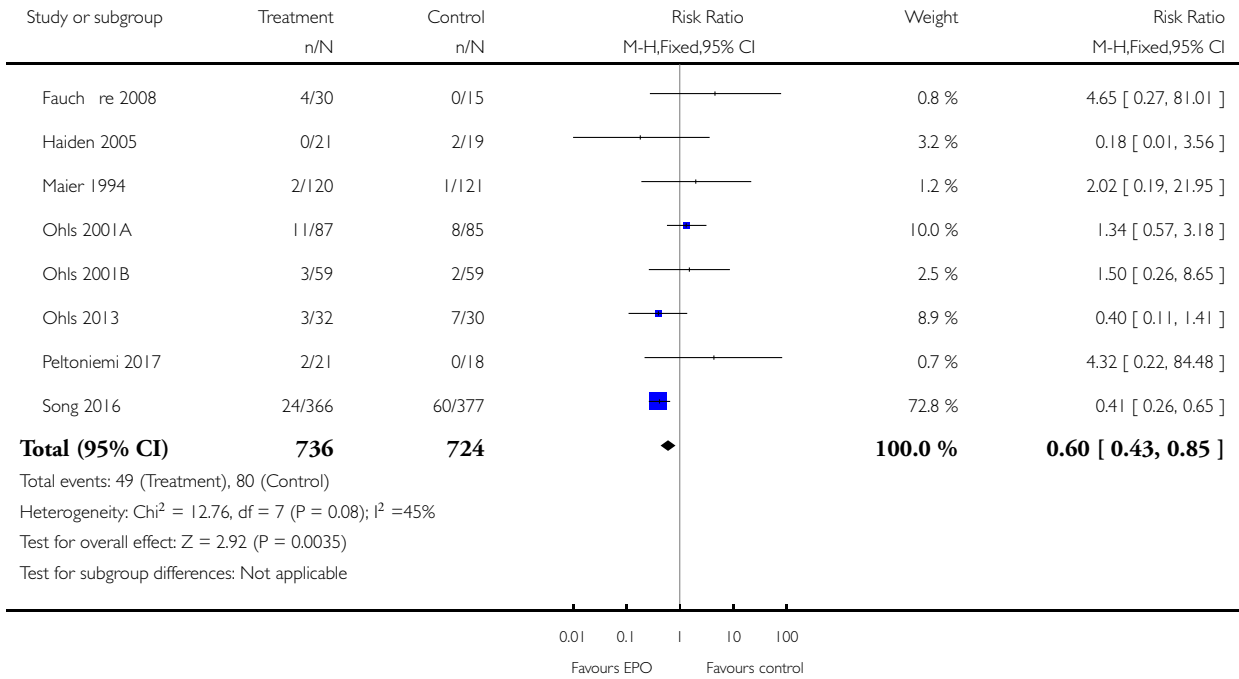
Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   14 Periventricular leukomalacia

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 4/229 | 3/214 | | 3.8 % | 1.25 [ 0.28, 5.50 ] |
| Haiden 2005 | 4/21 | 3/19 | | 3.9 % | 1.21 [ 0.31, 4.71 ] |
| Maier 2002 | 0/74 | 1/71 | | 1.9 % | 0.32 [ 0.01, 7.73 ] |
| Ohls 2013 | 1/32 | 0/30 | | 0.6 % | 2.82 [ 0.12, 66.62 ] |
| Peltoniemi 2017 | 3/20 | 0/16 | | 0.7 % | 5.67 [ 0.31, 102.31 ] |
| Song 2016 | 41/366 | 74/377 | | 89.2 % | 0.57 [ 0.40, 0.81 ] |
| **Total (95% CI)** | **742** | **727** | | **100.0 %** | **0.66 [ 0.48, 0.92 ]** |

Total events: 53 (Treatment), 81 (Control)

Heterogeneity: Chi$^2$ = 5.25, df = 5 (P = 0.39); I$^2$ =5%

Test for overall effect: Z = 2.50 (P = 0.013)

Test for subgroup differences: Not applicable

```
0.01    0.1      1      10     100
```

Favours EPO          Favours control

**Analysis 1.15. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 15 Length of hospital stay (days).**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 15 Length of hospital stay (days)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Carnielli 1992 | 11 | 49.2 (39.9) | 11 | 54 (28.1) | | 0.6 % | -4.80 [ -33.64, 24.04 ] |
| Carnielli 1998 | 42 | 51.34 (31.82) | 21 | 56 (30) | | 1.8 % | -4.66 [ -20.70, 11.38 ] |
| El-Ganzoury 2014 | 20 | 43.5 (11.1) | 30 | 57.9 (10.8) | | 11.9 % | -14.40 [ -20.61, -8.19 ] |
| Fauchère 2015 | 229 | 58.3 (35.2) | 214 | 58.6 (31.9) | | 11.7 % | -0.30 [ -6.55, 5.95 ] |
| Khatami 2008 | 20 | 13.63 (3.54) | 20 | 16.25 (5.3) | | 58.6 % | -2.62 [ -5.41, 0.17 ] |
| Ohls 2001A | 87 | 78 (33) | 85 | 79 (36) | | 4.3 % | -1.00 [ -11.33, 9.33 ] |
| Ohls 2001B | 59 | 57 (22) | 59 | 54 (17) | | 9.1 % | 3.00 [ -4.09, 10.09 ] |
| Ohls 2013 | 32 | 72 (26) | 30 | 74 (33) | | 2.1 % | -2.00 [ -16.85, 12.85 ] |
| **Total (95% CI)** | **500** | | **470** | | | **100.0 %** | **-3.20 [ -5.34, -1.06 ]** |

Heterogeneity: Chi² = 16.65, df = 7 (P = 0.02); I² =58%

Test for overall effect: Z = 2.93 (P = 0.0034)

Test for subgroup differences: Not applicable

-50    -25    0    25    50

Favours EPO        Favours control

**Analysis 1.16. Comparison I Erythropoietin versus placebo or no treatment, Outcome 16 Bronchopulmonary dysplasia.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 16 Bronchopulmonary dysplasia

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **1 Supplemental oxygen at 28 days of age** | | | | | |
| Peltoniemi 2017 | 9/20 | 7/16 | | 39.3 % | 1.03 [ 0.49, 2.15 ] |
| Yeo 2001 | 9/50 | 12/50 | | 60.7 % | 0.75 [ 0.35, 1.62 ] |
| **Subtotal (95% CI)** | **70** | **66** | | **100.0 %** | **0.86 [ 0.50, 1.47 ]** |
| Total events: 18 (Treatment), 19 (Control) | | | | | |
| Heterogeneity: Chi² = 0.35, df = 1 (P = 0.56); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.55 (P = 0.58) | | | | | |
| **2 Supplemental oxygen at 36 weeks** | | | | | |
| Fauch re 2015 | 71/229 | 67/214 | | 32.3 % | 0.99 [ 0.75, 1.31 ] |
| Maier 2002 | 19/74 | 16/71 | | 7.6 % | 1.14 [ 0.64, 2.03 ] |
| Ohls 2001A | 45/87 | 46/85 | | 21.7 % | 0.96 [ 0.72, 1.27 ] |
| Ohls 2001B | 9/59 | 9/59 | | 4.2 % | 1.00 [ 0.43, 2.34 ] |
| Ohls 2013 | 21/32 | 20/30 | | 9.6 % | 0.98 [ 0.69, 1.41 ] |
| Peltoniemi 2017 | 5/20 | 2/16 | | 1.0 % | 2.00 [ 0.45, 8.98 ] |
| Song 2016 | 37/366 | 51/377 | | 23.5 % | 0.75 [ 0.50, 1.11 ] |
| **Subtotal (95% CI)** | **867** | **852** | | **100.0 %** | **0.95 [ 0.81, 1.11 ]** |
| Total events: 207 (Treatment), 211 (Control) | | | | | |
| Heterogeneity: Chi² = 2.87, df = 6 (P = 0.83); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | |
| **3 Age at diagnosis not stated** | | | | | |
| Arif 2005 | 6/142 | 5/150 | | 17.5 % | 1.27 [ 0.40, 4.06 ] |
| Carnielli 1998 | 11/42 | 7/21 | | 33.6 % | 0.79 [ 0.36, 1.73 ] |
| Haiden 2005 | 6/21 | 8/19 | | 30.3 % | 0.68 [ 0.29, 1.60 ] |
| Lima-Rogel 1998 | 1/21 | 0/19 | | 1.9 % | 2.73 [ 0.12, 63.19 ] |
| Obladen 1991 | 6/43 | 5/50 | | 16.7 % | 1.40 [ 0.46, 4.25 ] |
| **Subtotal (95% CI)** | **269** | **259** | | **100.0 %** | **0.98 [ 0.61, 1.56 ]** |
| Total events: 30 (Treatment), 25 (Control) | | | | | |
| Heterogeneity: Chi² = 1.98, df = 4 (P = 0.74); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.10 (P = 0.92) | | | | | |

```
        0.01   0.1    1    10   100
        Favours EPO      Favours control
```

**Analysis 1.17. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 17 Neutropenia.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 17 Neutropenia

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Arif 2005 | 0/142 | 0/150 | | | Not estimable |
| Carnielli 1992 | 2/11 | 2/11 | | 5.3 % | 1.00 [ 0.17, 5.89 ] |
| Chang 1998 | 0/30 | 0/15 | | | Not estimable |
| Khatami 2008 | 0/20 | 0/20 | | | Not estimable |
| Maier 1994 | 25/120 | 29/121 | | 76.7 % | 0.87 [ 0.54, 1.39 ] |
| Ohls 1995 | 0/10 | 0/10 | | | Not estimable |
| Ohls 1997 | 0/15 | 3/13 | | 9.9 % | 0.13 [ 0.01, 2.22 ] |
| Ohls 2001A | 3/87 | 3/85 | | 8.1 % | 0.98 [ 0.20, 4.71 ] |
| Ohls 2013 | 0/32 | 0/30 | | | Not estimable |
| Soubasi 1993 | 0/25 | 0/19 | | | Not estimable |
| **Total (95% CI)** | **492** | **474** | | **100.0 %** | **0.81 [ 0.53, 1.24 ]** |

Total events: 30 (Treatment), 37 (Control)

Heterogeneity: Chi² = 1.82, df = 3 (P = 0.61); I² =0.0%

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Not applicable

0.01    0.1    1    10    100

Favours EPO        Favours control

**Analysis 1.18.  Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 18 Hypertension.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 18 Hypertension

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Avent 2002 | 0/63 | 0/30 | | | Not estimable |
| Chang 1998 | 0/30 | 0/15 | | | Not estimable |
| Maier 1994 | 1/120 | 0/121 | | 24.4 % | 3.02 [ 0.12, 73.52 ] |
| Obladen 1991 | 0/43 | 0/50 | | | Not estimable |
| Ohls 2001A | 0/87 | 0/85 | | | Not estimable |
| Ohls 2013 | 0/32 | 1/30 | | 75.6 % | 0.31 [ 0.01, 7.40 ] |
| **Total (95% CI)** | **375** | **331** | | **100.0 %** | **0.97 [ 0.14, 6.69 ]** |

Total events: 1 (Treatment), 1 (Control)

Heterogeneity: Chi² = 0.98, df = 1 (P = 0.32); I² =0.0%

Test for overall effect: Z = 0.03 (P = 0.98)

Test for subgroup differences: Not applicable

```
         0.01    0.1     1    10    100
            Favours EPO     Favours control
```

**Analysis 1.19. Comparison I Erythropoietin versus placebo or no treatment, Outcome 19 Hemangioma.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 19 Hemangioma

| Study or subgroup | EPO n/N | Placebo or no treatment n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 30/229 | 21/214 | | 100.0 % | 1.33 [ 0.79, 2.26 ] |
| **Total (95% CI)** | **229** | **214** | | **100.0 %** | **1.33 [ 0.79, 2.26 ]** |

Total events: 30 (EPO), 21 (Placebo or no treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable

```
       0.01   0.1    I    10   100
       Favours [EPO]        Favours [Placebo/control]
```

**Analysis 1.20. Comparison I Erythropoietin versus placebo or no treatment, Outcome 20 Neonatal Behavioral Neurological Assessment at 40 weeks' PMA.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 20 Neonatal Behavioral Neurological Assessment at 40 weeks' PMA

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| He 2008 | 22 | 36.2 (0.75) | 22 | 34.4 (1.05) | | 100.0 % | 1.80 [ 1.26, 2.34 ] |
| **Total (95% CI)** | **22** | | **22** | | | **100.0 %** | **1.80 [ 1.26, 2.34 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 6.54 (P < 0.00001)

Test for subgroup differences: Not applicable

```
       -20   -10    0    10   20
       Favours experimental    Favours control
```

**Analysis 1.21.** **Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 21 Infants with white matter injury at term-corrected PMA.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 21 Infants with white matter injury at term-corrected PMA

| Study or subgroup | EPO n/N | Placebo n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 17/77 | 32/88 | | 100.0 % | 0.61 [ 0.37, 1.00 ] |
| **Total (95% CI)** | **77** | **88** | | **100.0 %** | **0.61 [ 0.37, 1.00 ]** |
| Total events: 17 (EPO), 32 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.95 (P = 0.052) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

```
          0.01   0.1    1    10   100
         Favours [EPO]    Favours [Placebo]
```
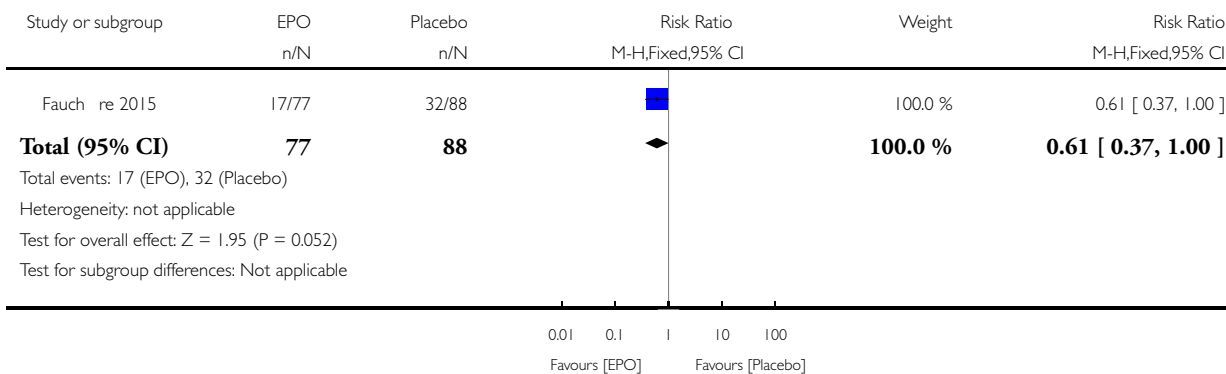
**Analysis 1.22.** **Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 22 Infants with white matter signal abnormality at term-corrected PMA.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 22 Infants with white matter signal abnormality at term-corrected PMA

| Study or subgroup | EPO n/N | Placebo n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 2/77 | 10/88 | | 100.0 % | 0.23 [ 0.05, 1.01 ] |
| **Total (95% CI)** | **77** | **88** | | **100.0 %** | **0.23 [ 0.05, 1.01 ]** |
| Total events: 2 (EPO), 10 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.95 (P = 0.052) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

```
          0.01   0.1    1    10   100
         Favours [EPO]    Favours [Placebo]
```
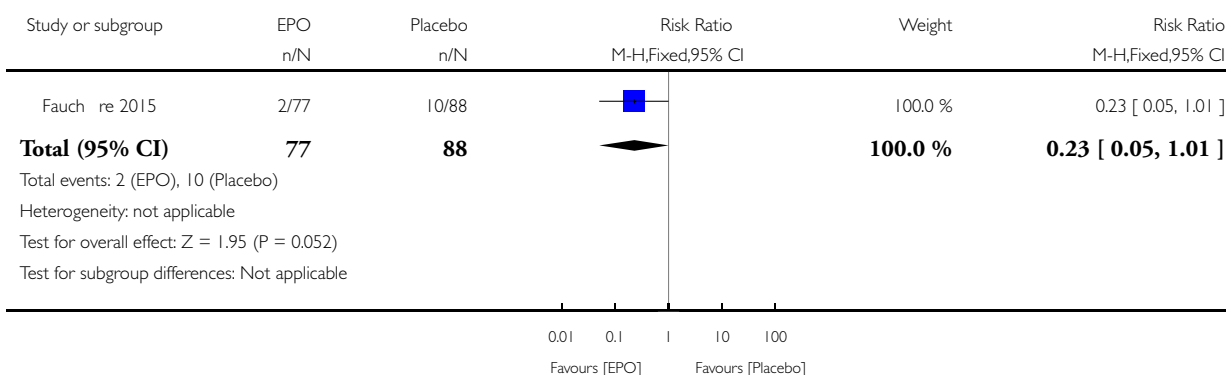
**Analysis 1.23. Comparison I Erythropoietin versus placebo or no treatment, Outcome 23 Infants with periventricular white matter loss at term-corrected PMA.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: I Erythropoietin versus placebo or no treatment

Outcome: 23 Infants with periventricular white matter loss at term-corrected PMA

| Study or subgroup | EPO n/N | Placebo n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 14/77 | 29/88 | | 100.0 % | 0.55 [ 0.32, 0.97 ] |
| **Total (95% CI)** | **77** | **88** | | **100.0 %** | **0.55 [ 0.32, 0.97 ]** |

Total events: 14 (EPO), 29 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 2.08 (P = 0.037)
Test for subgroup differences: Not applicable

```
      0.01   0.1    I    10   100
        Favours [EPO]   Favours [Placebo]
```
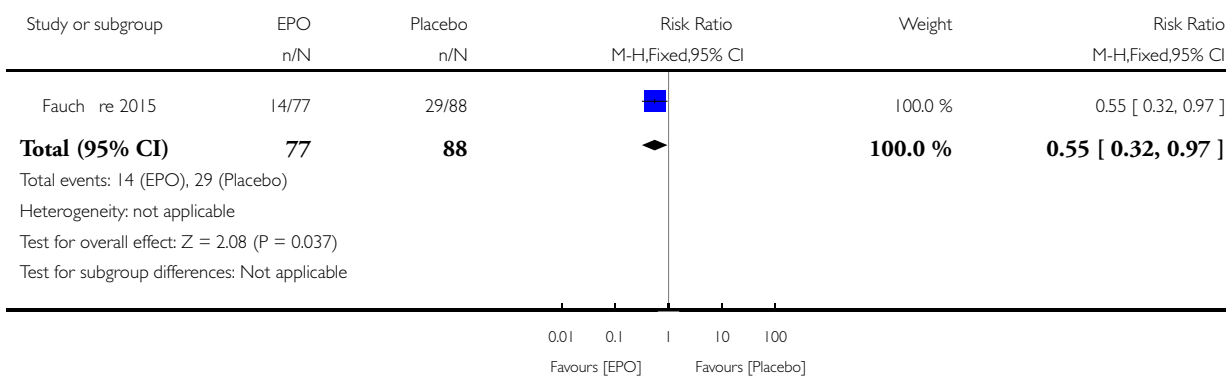
**Analysis 1.24. Comparison I Erythropoietin versus placebo or no treatment, Outcome 24 Infants with grey matter injury at term-corrected PMA.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: I Erythropoietin versus placebo or no treatment

Outcome: 24 Infants with grey matter injury at term-corrected PMA

| Study or subgroup | EPO n/N | Placebo n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 5/77 | 17/88 | | 100.0 % | 0.34 [ 0.13, 0.87 ] |
| **Total (95% CI)** | **77** | **88** | | **100.0 %** | **0.34 [ 0.13, 0.87 ]** |

Total events: 5 (EPO), 17 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 2.25 (P = 0.024)
Test for subgroup differences: Not applicable

```
      0.01   0.1    I    10   100
        Favours [EPO]   Favours [Placebo]
```
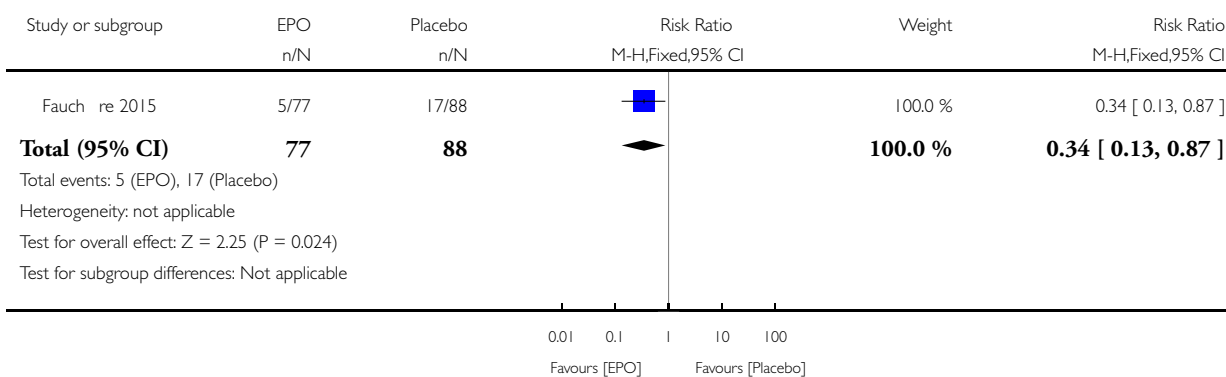
**Analysis 1.25. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 25 Survivors at discharge from hospital without severe IVH, PVL, ROP.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 25 Survivors at discharge from hospital without severe IVH, PVL, ROP

| Study or subgroup | EPO n/N | Placebo n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 196/229 | 183/214 | | 100.0 % | 1.00 [ 0.93, 1.08 ] |
| **Total (95% CI)** | **229** | **214** | | **100.0 %** | **1.00 [ 0.93, 1.08 ]** |

Total events: 196 (EPO), 183 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable

```
        0.01    0.1     1     10    100
          Favours [EPO]    Favours [Placebo]
```
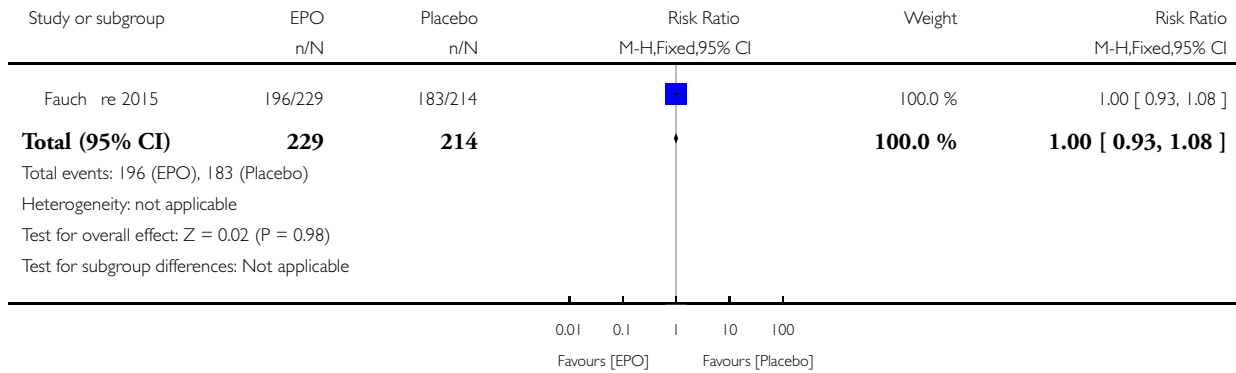
**Analysis 1.26. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 26 Bayley-II MDI < 70 at 18 to 24 months' corrected age.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 26 Bayley-II MDI < 70 at 18 to 24 months' corrected age

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2008 | 0/1 | 0/2 | | | Not estimable |
| Fauchère 2015 | 12/191 | 15/174 | | 19.4 % | 0.73 [ 0.35, 1.51 ] |
| Ohls 2001A | 14/45 | 16/45 | | 19.7 % | 0.88 [ 0.49, 1.57 ] |
| Song 2016 | 19/309 | 49/304 | | 60.9 % | 0.38 [ 0.23, 0.63 ] |
| **Total (95% CI)** | **546** | **525** | | **100.0 %** | **0.55 [ 0.39, 0.77 ]** |

Total events: 45 (Treatment), 80 (Control)
Heterogeneity: Chi² = 5.02, df = 2 (P = 0.08); I² =60%
Test for overall effect: Z = 3.51 (P = 0.00045)
Test for subgroup differences: Not applicable

```
        0.01    0.1     1     10    100
          Favours EPO      Favours control
```
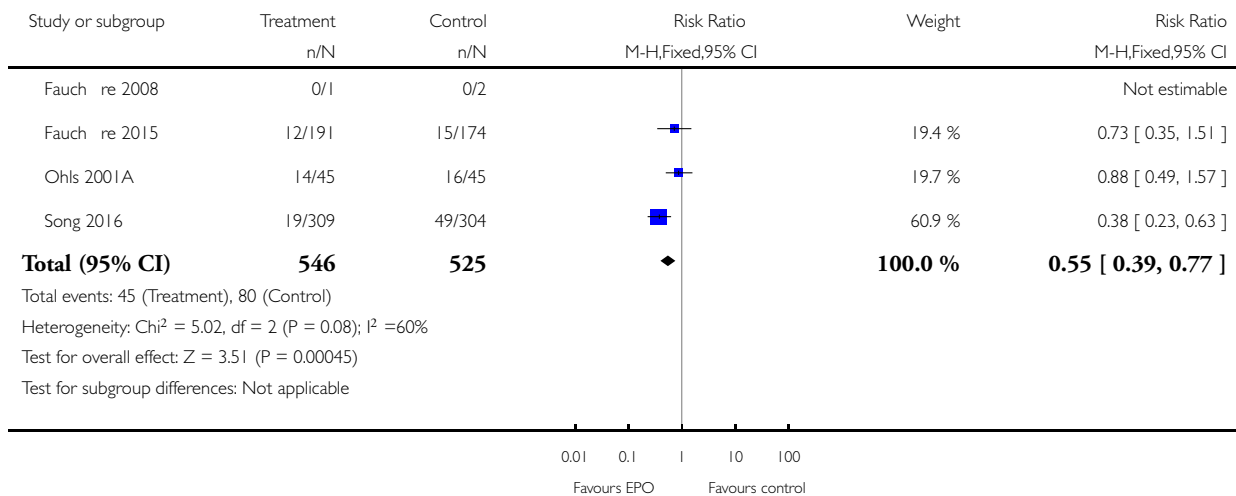
**Analysis 1.27.   Comparison I Erythropoietin versus placebo or no treatment, Outcome 27 Bayley-II PDI <
70 at 18 to 22 months' corrected age (in children examined).**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   I Erythropoietin versus placebo or no treatment

Outcome:   27 Bayley-II PDI < 70 at 18 to 22 months' corrected age (in children examined)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauch  re 2008 | 0/1 | 0/2 | | | Not estimable |
| Fauch  re 2015 | 21/191 | 17/174 | | 74.8 % | 1.13 [ 0.61, 2.06 ] |
| Ohls 2001A | 14/45 | 6/45 | | 25.2 % | 2.33 [ 0.98, 5.53 ] |
| **Total (95% CI)** | **237** | **221** | | **100.0 %** | **1.43 [ 0.88, 2.33 ]** |

Total events: 35 (Treatment), 23 (Control)

Heterogeneity: Chi² = 1.84, df = 1 (P = 0.18); I² =46%

Test for overall effect: Z = 1.44 (P = 0.15)

Test for subgroup differences: Not applicable

```
        0.01    0.1      1      10    100

        Favours EPO        Favours control
```
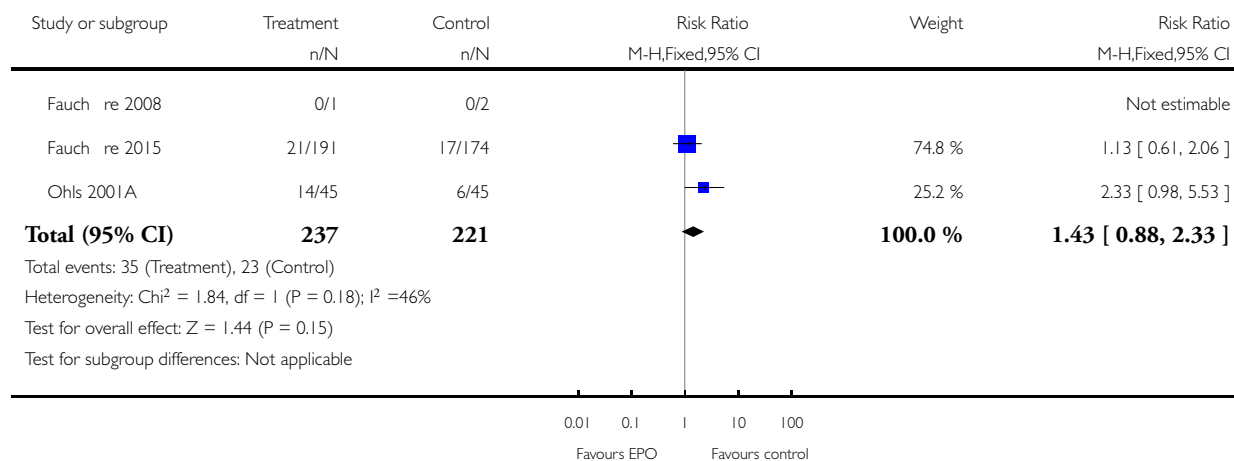
**Analysis 1.28.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 28 Bayley-II MDI at 18 to 24 months.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   28 Bayley-II MDI at 18 to 24 months

| Study or subgroup | EPO | | Control/Placebo | | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | | | |
| Fauch re 2008 | 1 | 96 (0) | 2 | 92 (2.83) | | | Not estimable |
| Fauch re 2015 | 191 | 93.5 (16) | 174 | 94.5 (17.8) | | 23.8 % | -1.00 [ -4.48, 2.48 ] |
| Song 2016 | 309 | 95.2 (12.5) | 304 | 84.1 (12.1) | | 76.2 % | 11.10 [ 9.15, 13.05 ] |
| **Total (95% CI)** | **501** | | **480** | | | **100.0 %** | **8.22 [ 6.52, 9.92 ]** |

Heterogeneity: Chi² = 35.29, df = 1 (P<0.00001); I² =97%

Test for overall effect: Z = 9.48 (P < 0.00001)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
        Favours [EPO]      Favours [control/placebo]
```
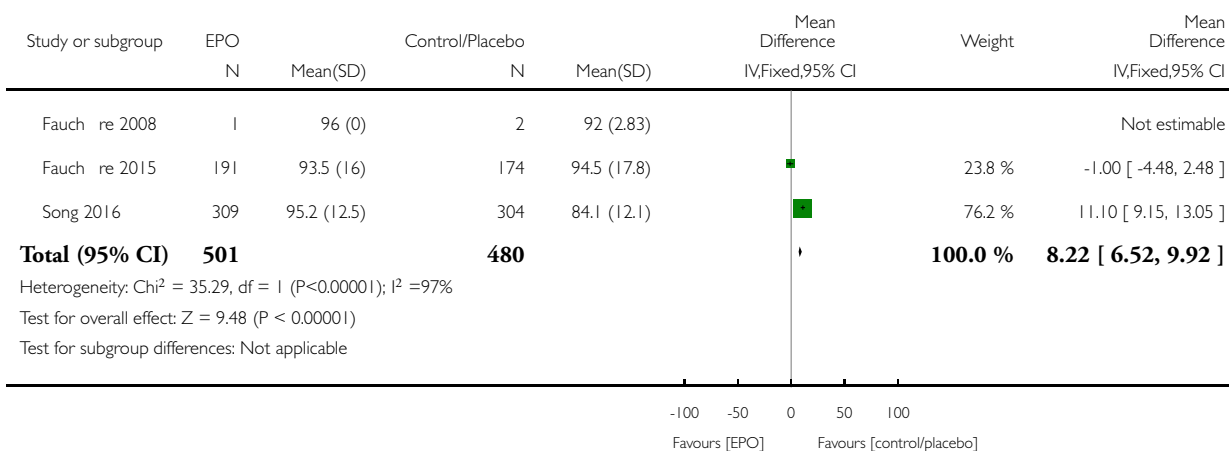
**Analysis 1.29.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 29 Bayley-II PDI at 18 to 24 months.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   29 Bayley-II PDI at 18 to 24 months

| Study or subgroup | EPO | | Placebo | | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | | | |
| Fauch re 2008 | 1 | 90 (0) | 2 | 83 (4.24) | | | Not estimable |
| **Total (95% CI)** | **1** | | **2** | | | | **Not estimable** |

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
        Favours [EPO]      Favours [Placebo]
```
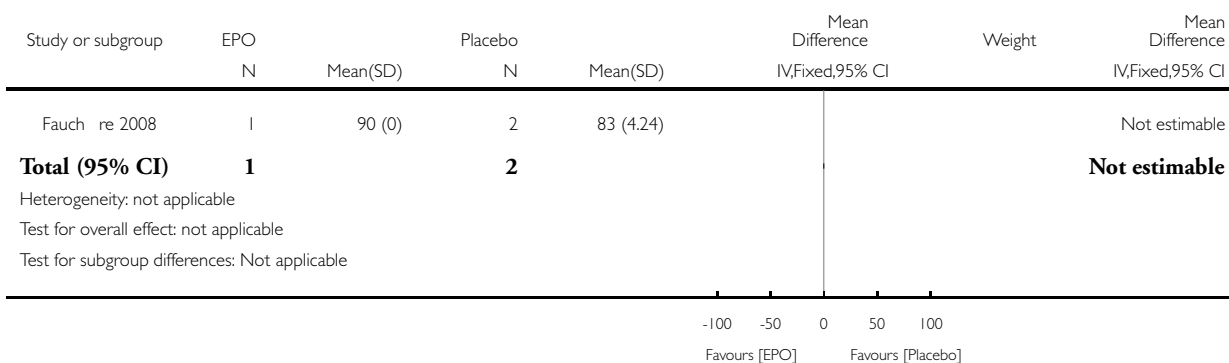
**Analysis 1.30. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 30 Cerebral palsy at 18 to 24 months' corrected age.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 30 Cerebral palsy at 18 to 24 months' corrected age

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauch re 2008 | 0/1 | 0/2 | | | Not estimable |
| Fauch re 2015 | 8/191 | 8/174 | | 20.2 % | 0.91 [ 0.35, 2.37 ] |
| Ohls 2001A | 9/48 | 9/51 | | 21.1 % | 1.06 [ 0.46, 2.45 ] |
| Ohls 2013 | 0/29 | 5/24 | | 14.5 % | 0.08 [ 0.00, 1.30 ] |
| Peltoniemi 2017 | 6/21 | 2/18 | | 5.2 % | 2.57 [ 0.59, 11.20 ] |
| Song 2016 | 7/309 | 16/304 | | 39.0 % | 0.43 [ 0.18, 1.03 ] |
| **Total (95% CI)** | **599** | **573** | | **100.0 %** | **0.72 [ 0.46, 1.13 ]** |

Total events: 30 (Treatment), 40 (Control)

Heterogeneity: Chi$^2$ = 7.67, df = 4 (P = 0.10); I$^2$ =48%

Test for overall effect: Z = 1.43 (P = 0.15)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours EPO     Favours control
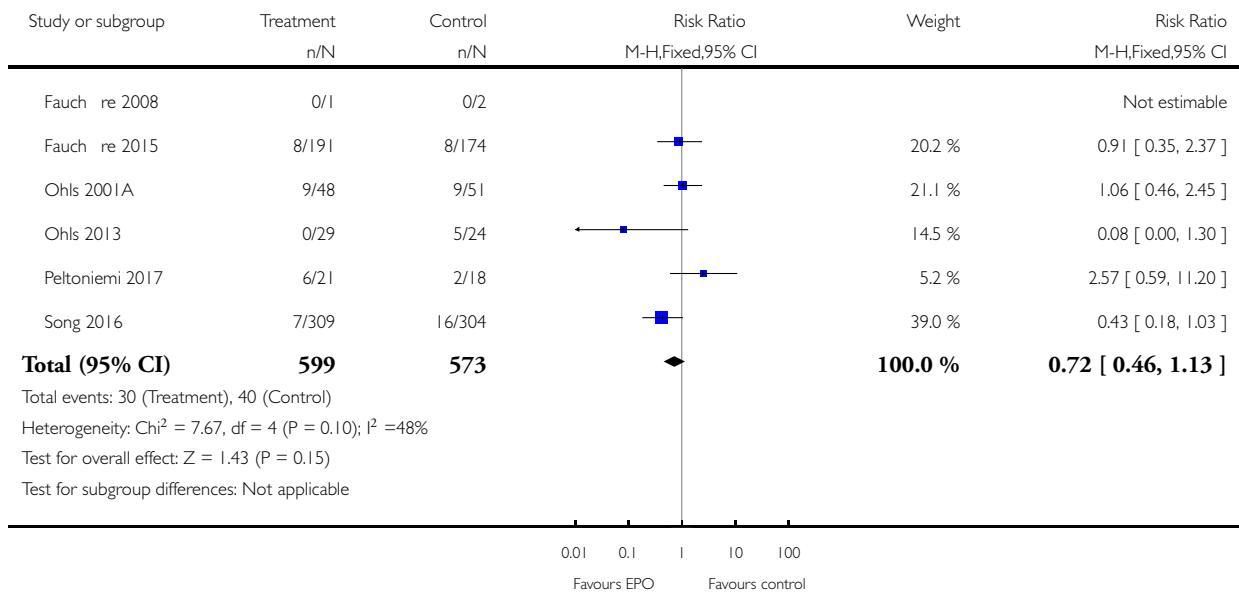
**Analysis 1.31.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 31 Any neurodevelopmental impairment at 18 to 22 months' corrected age (in children examined).**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   31 Any neurodevelopmental impairment at 18 to 22 months' corrected age (in children examined)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 27/191 | 26/174 | | 23.1 % | 0.95 [ 0.58, 1.56 ] |
| Ohls 2001A | 21/48 | 23/51 | | 18.9 % | 0.97 [ 0.62, 1.51 ] |
| Ohls 2013 | 4/29 | 10/24 | | 9.3 % | 0.33 [ 0.12, 0.92 ] |
| Song 2016 | 22/309 | 57/304 | | 48.7 % | 0.38 [ 0.24, 0.60 ] |
| **Total (95% CI)** | **577** | **553** | | **100.0 %** | **0.62 [ 0.48, 0.80 ]** |

Total events: 74 (Treatment), 116 (Control)

Heterogeneity: Chi² = 12.45, df = 3 (P = 0.01); I² =76%

Test for overall effect: Z = 3.63 (P = 0.00028)

Test for subgroup differences: Not applicable

0.01    0.1    1    10    100

Favours EPO          Favours control
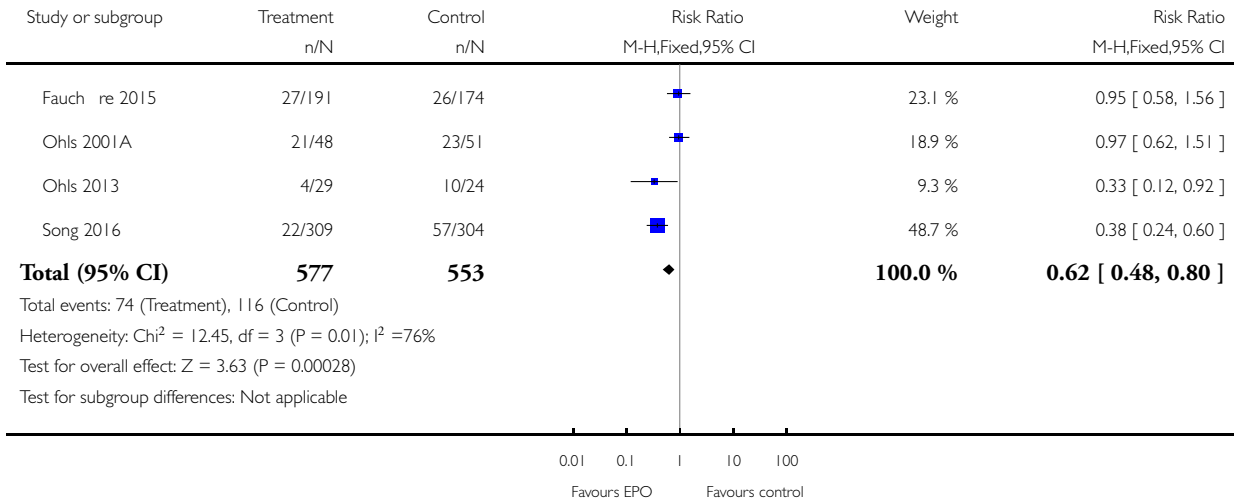
**Analysis 1.32.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 32 Visual impairment at 18 to 24 months' corrected age.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   32 Visual impairment at 18 to 24 months' corrected age

| Study or subgroup | Experimental n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2008 | 0/1 | 0/2 | | | Not estimable |
| Fauchère 2015 | 2/191 | 0/174 | | 7.9 % | 4.56 [ 0.22, 94.27 ] |
| Ohls 2001A | 0/48 | 1/50 | | 22.1 % | 0.35 [ 0.01, 8.31 ] |
| Ohls 2013 | 0/29 | 1/24 | | 24.6 % | 0.28 [ 0.01, 6.52 ] |
| Song 2016 | 2/309 | 3/304 | | 45.5 % | 0.66 [ 0.11, 3.90 ] |
| **Total (95% CI)** | **578** | **554** | | **100.0 %** | **0.80 [ 0.26, 2.49 ]** |

Total events: 4 (Experimental), 5 (Control)

Heterogeneity: Chi$^2$ = 2.01, df = 3 (P = 0.57); I$^2$ =0.0%

Test for overall effect: Z = 0.38 (P = 0.70)

Test for subgroup differences: Not applicable

0.01    0.1    1    10    100

Favours experimental          Favours control
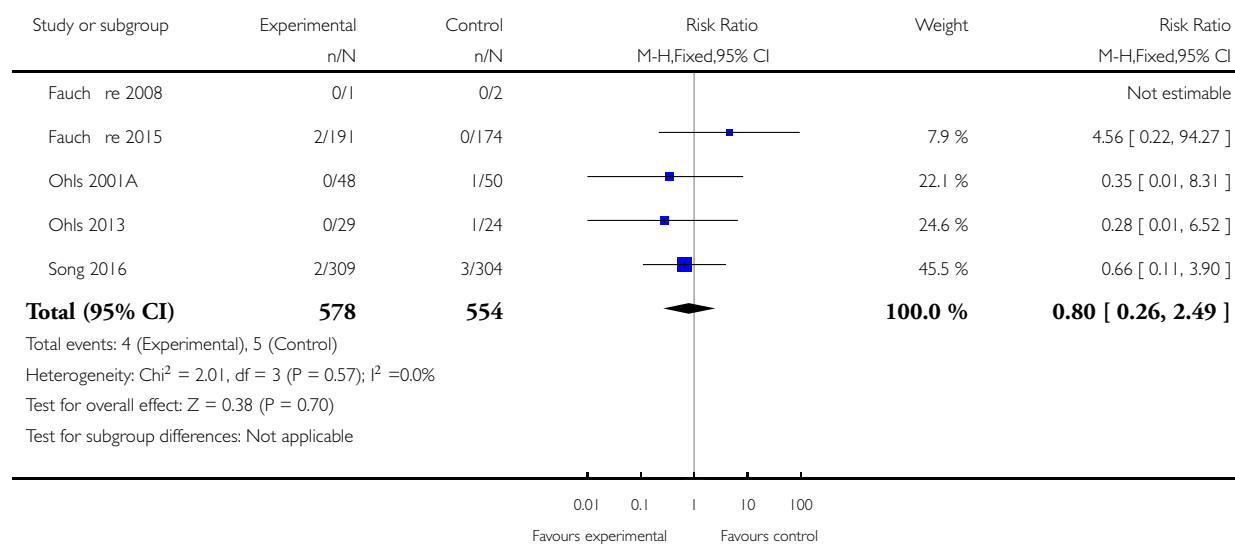
**Analysis 1.33.  Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 33 Hearing impairment at 18 to 24 months' corrected age.**
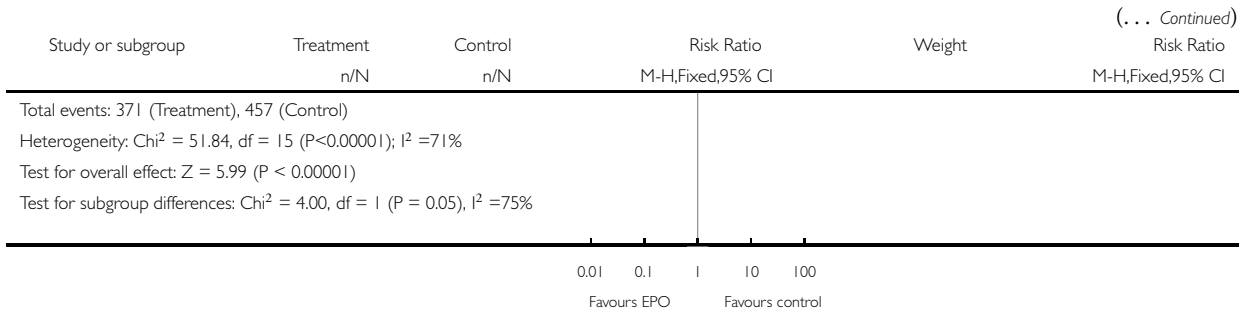
Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:    1 Erythropoietin versus placebo or no treatment

Outcome:    33 Hearing impairment at 18 to 24 months' corrected age

| Study or subgroup | Experimental | Control | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| Fauch  re 2008 | 0/1 | 0/2 | | | Not estimable |
| Fauch  re 2015 | 1/191 | 0/174 | | 4.9 % | 2.73 [ 0.11, 66.68 ] |
| Ohls 2001A | 1/48 | 1/50 | | 9.2 % | 1.04 [ 0.07, 16.19 ] |
| Ohls 2013 | 1/29 | 1/24 | | 10.3 % | 0.83 [ 0.05, 12.54 ] |
| Song 2016 | 1/309 | 8/304 | | 75.6 % | 0.12 [ 0.02, 0.98 ] |
| **Total (95% CI)** | **578** | **554** | | **100.0 %** | **0.41 [ 0.13, 1.23 ]** |

Total events: 4 (Experimental), 10 (Control)

Heterogeneity: Chi² = 3.36, df = 3 (P = 0.34); I² =11%

Test for overall effect: Z = 1.59 (P = 0.11)

Test for subgroup differences: Not applicable

```
         0.01   0.1    1    10   100
    Favours experimental    Favours control
```
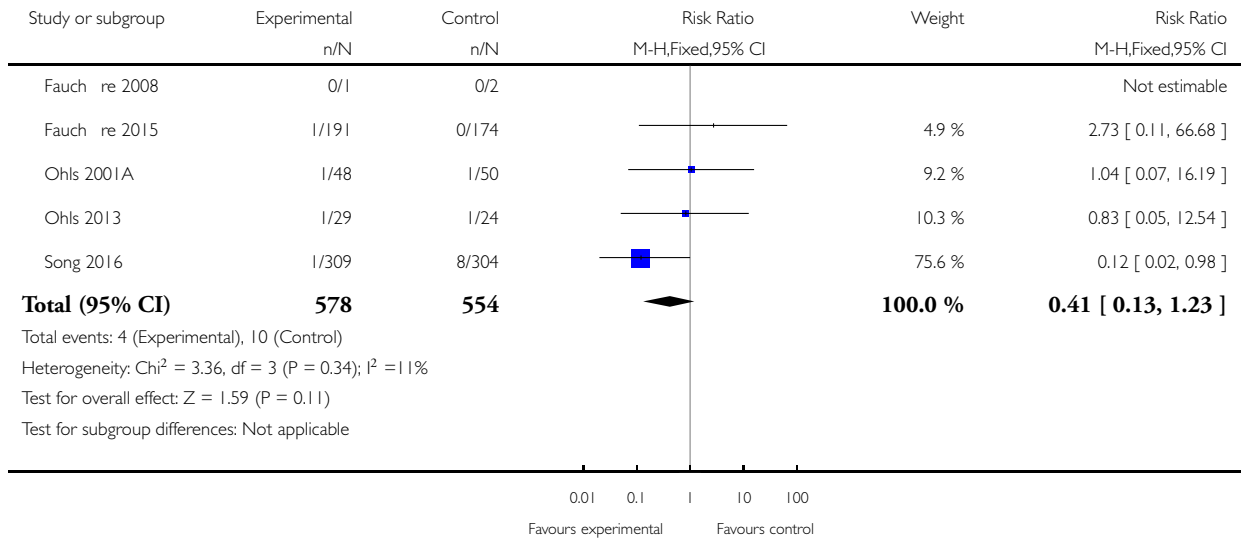
**Analysis 1.34. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 34 BSID-III composite cognitive scores at 18 to 22 months.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 34 BSID-III composite cognitive scores at 18 to 22 months

| Study or subgroup | EPO | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 29 | 97.9 (14.3) | 24 | 88.7 (13.5) | | 100.0 % | 9.20 [ 1.70, 16.70 ] |
| **Total (95% CI)** | **29** | | **24** | | | **100.0 %** | **9.20 [ 1.70, 16.70 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.40 (P = 0.016) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
        -20   -10    0    10    20
          Favours EPO    Favours control
```
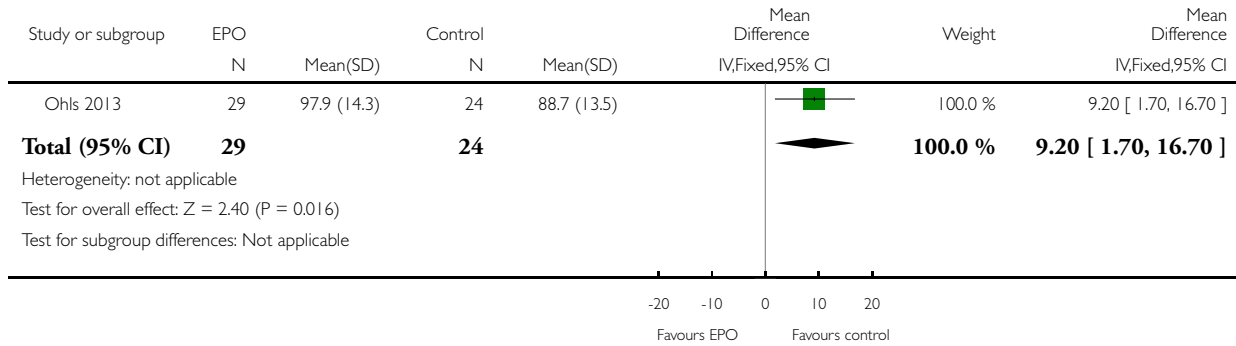
**Analysis 1.35. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 35 BSID-III composite language score.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 35 BSID-III composite language score

| Study or subgroup | EPO | | Placebo or None | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 29 | 89.9 (18.4) | 24 | 83.6 (13.1) | | 100.0 % | 6.30 [ -2.20, 14.80 ] |
| **Total (95% CI)** | **29** | | **24** | | | **100.0 %** | **6.30 [ -2.20, 14.80 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.45 (P = 0.15) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
        -100   -50    0    50    100
          Favours [EPO]    Favours [Placebo or None]
```
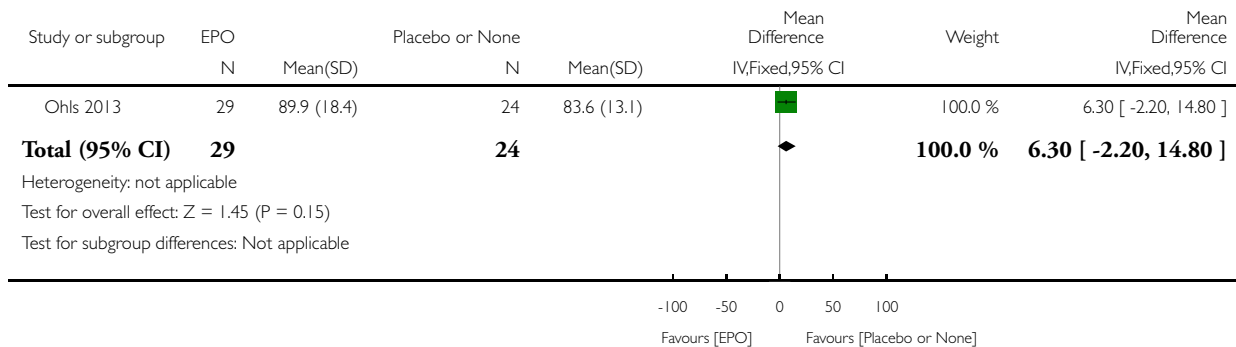
**Analysis 1.36.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 36 BSID-III composite social/emotional score.**

| Study or subgroup | EPO | | Placebo or None | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 29 | 99.6 (20.4) | 24 | 96.7 (19.4) | | 100.0 % | 2.90 [ -7.84, 13.64 ] |
| **Total (95% CI)** | **29** | | **24** | | | **100.0 %** | **2.90 [ -7.84, 13.64 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.53 (P = 0.60)

Test for subgroup differences: Not applicable

```
        -100    -50     0      50     100
        Favours [EPO]      Favours [Placebo or None]
```
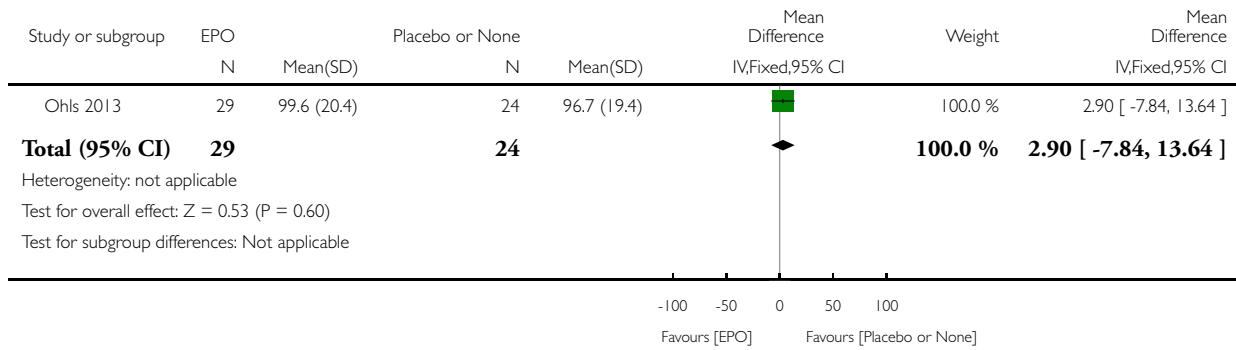
**Analysis 1.37.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 37 BSID-III object performance (OP) score.**

| Study or subgroup | EPO | | Placebo or None | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 29 | 2.4 (0.9) | 24 | 2.2 (1) | | 100.0 % | 0.20 [ -0.32, 0.72 ] |
| **Total (95% CI)** | **29** | | **24** | | | **100.0 %** | **0.20 [ -0.32, 0.72 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable

```
        -20    -10     0      10     20
        Favours [EPO]      Favours [No treatment]
```
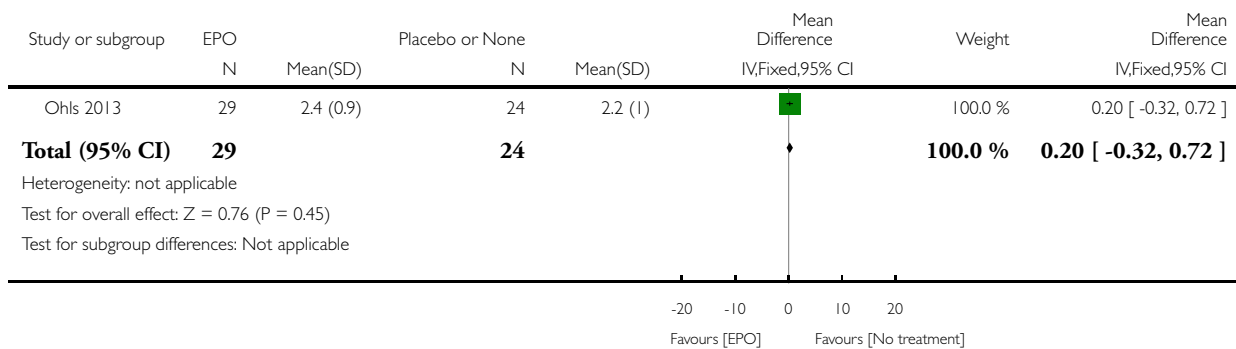
**Analysis 1.38.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 38 WPPSI-III FSIQ at 3.5 to 4 years of age.**

Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:    1 Erythropoietin versus placebo or no treatment
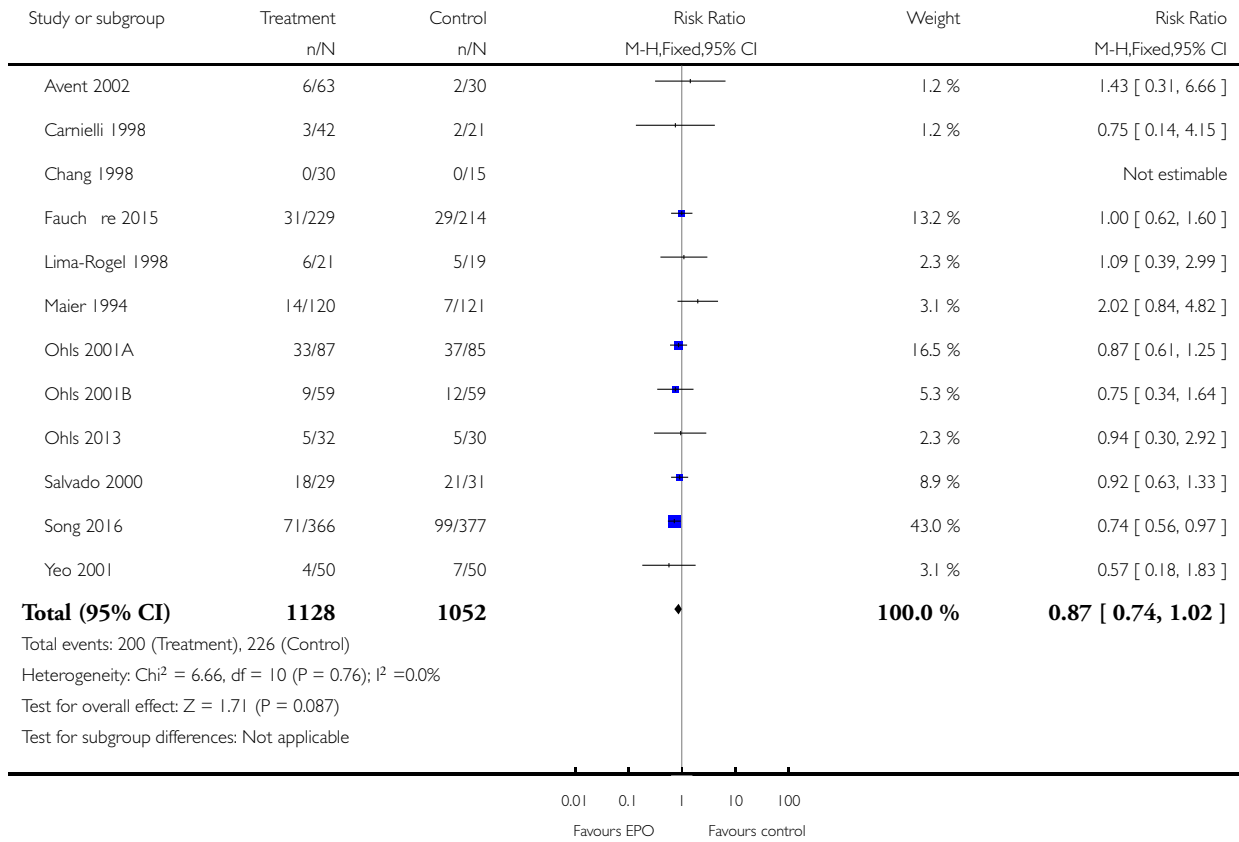
Outcome:    38 WPPSI-III FSIQ at 3.5 to 4 years of age

| Study or subgroup | EPO N | Mean(SD) | Placebo or None N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Ohls 2013 | 24 | 89.62 (19.24) | 14 | 79.2 (18.5) |  | 100.0 % | 10.42 [ -1.96, 22.80 ] |
| **Total (95% CI)** | **24** | | **14** | | | **100.0 %** | **10.42 [ -1.96, 22.80 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.65 (P = 0.099) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100    -50    0    50    100

Favours [EPO]          Favours [Placebo or None]
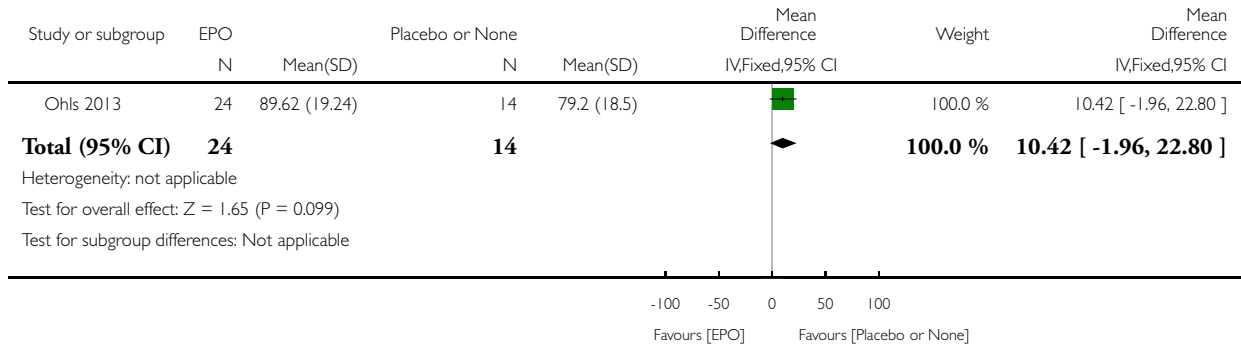
**Analysis 1.39.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 39 WPPSI-III VIQ at 3.5 to 4 years of age.**

Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

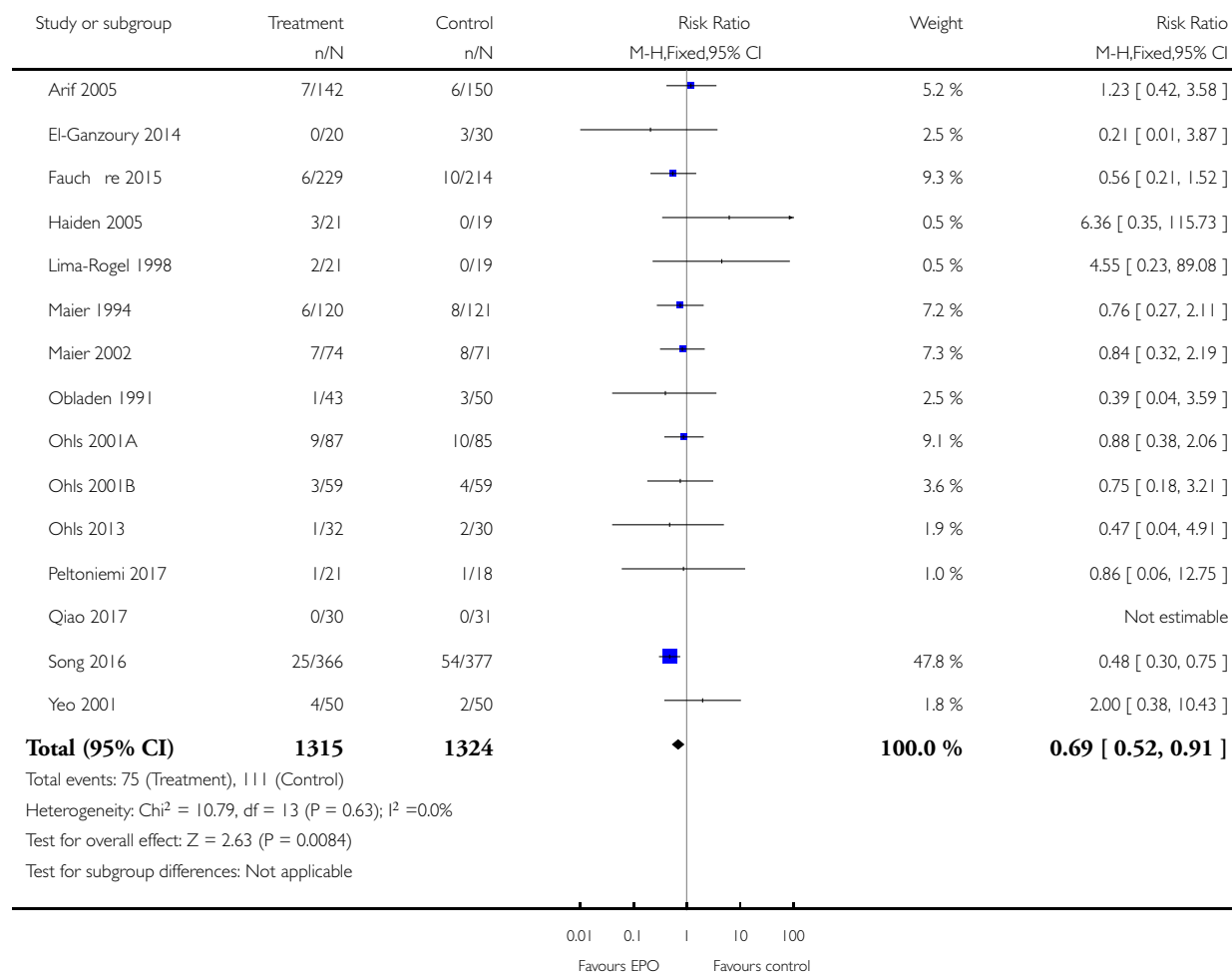Comparison:    1 Erythropoietin versus placebo or no treatment

Outcome:    39 WPPSI-III VIQ at 3.5 to 4 years of age

| Study or subgroup | EPO N | Mean(SD) | Placebo or None N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Ohls 2013 | 24 | 93.54 (17.85) | 14 | 82.9 (16.9) |  | 100.0 % | 10.64 [ -0.73, 22.01 ] |
| **Total (95% CI)** | **24** | | **14** | | | **100.0 %** | **10.64 [ -0.73, 22.01 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.83 (P = 0.067) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100    -50    0    50    100

Favours [EPO]          Favours [Placebo or None]
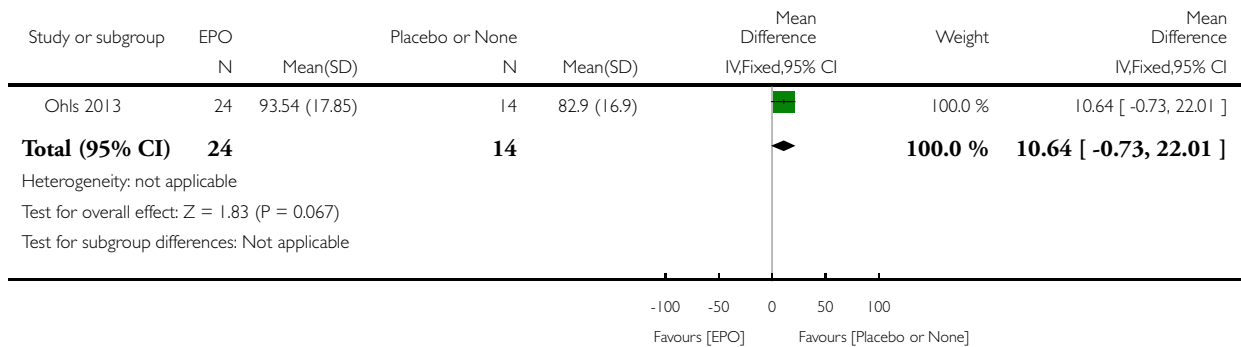
**Analysis 1.40.  Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 40 WPPSI-III PIQ at 3.5 to 4 years of age.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   40 WPPSI-III PIQ at 3.5 to 4 years of age

| Study or subgroup | EPO | | Placebo or None | | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | | | |
| Ohls 2013 | 24 | 89.62 (19.24) | 14 | 79.5 (19.5) | | 100.0 % | 10.12 [ -2.67, 22.91 ] |
| **Total (95% CI)** | **24** | | **14** | | | **100.0 %** | **10.12 [ -2.67, 22.91 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.55 (P = 0.12)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
       Favours [EPO]      Favours [Placebo]
```
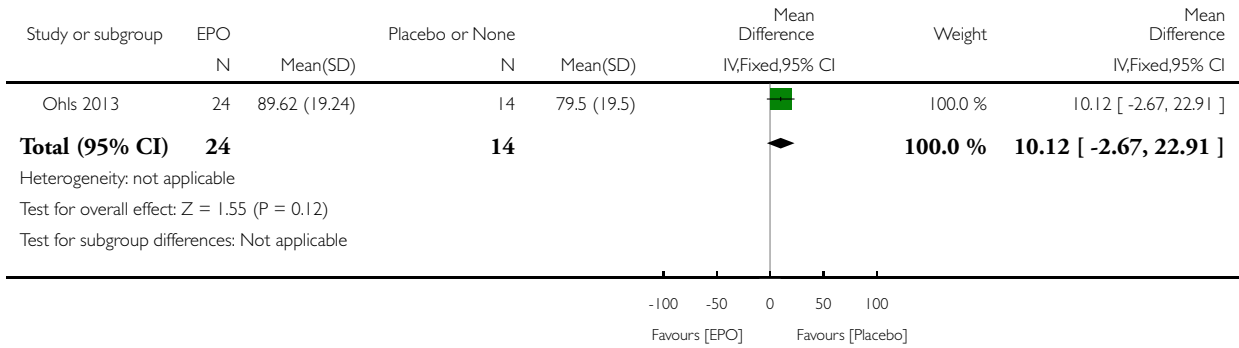
**Analysis 1.41.  Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 41 WPPSI-III GLC at 3.5 to 4 years of age.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

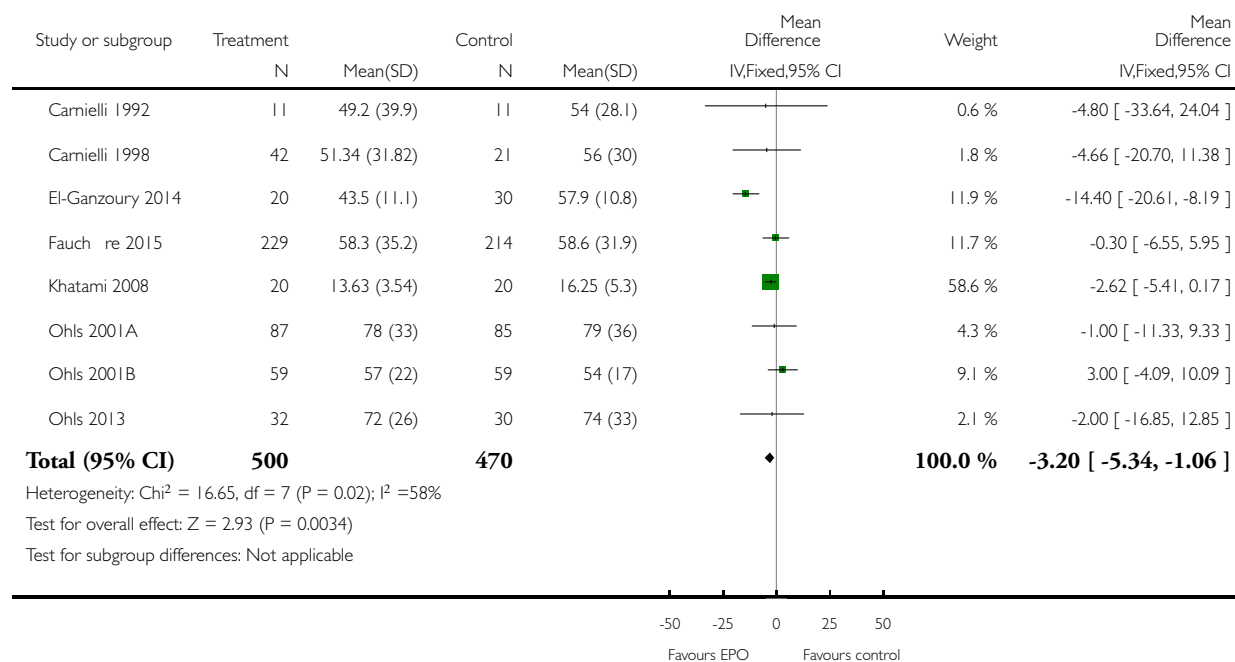Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   41 WPPSI-III GLC at 3.5 to 4 years of age

| Study or subgroup | EPO | | Placebo or None | | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | | | |
| Ohls 2013 | 24 | 87.91 (17.96) | 14 | 84.79 (17.11) | | 100.0 % | 3.12 [ -8.37, 14.61 ] |
| **Total (95% CI)** | **24** | | **14** | | | **100.0 %** | **3.12 [ -8.37, 14.61 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.53 (P = 0.59)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
       Favours [EPO]      Favours [Placebo or None]
```
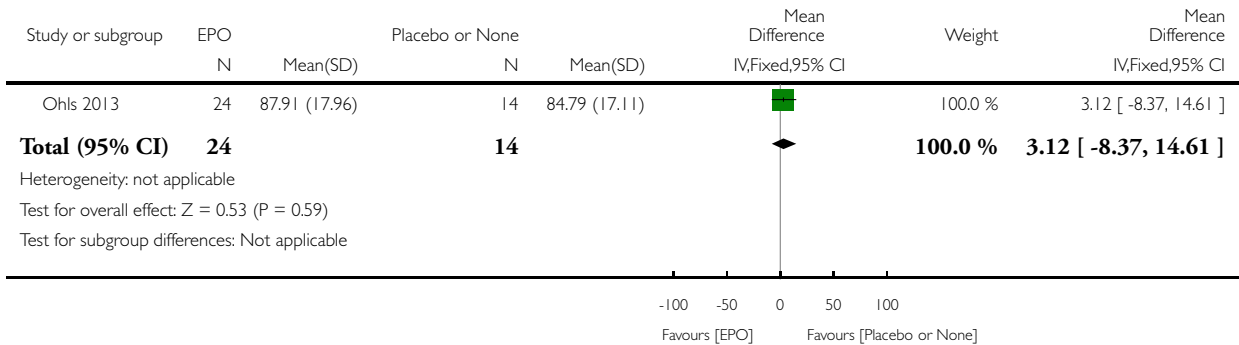
## Analysis 1.42. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 42 Executive function at 3.5 to 4 years of age.

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 42 Executive function at 3.5 to 4 years of age
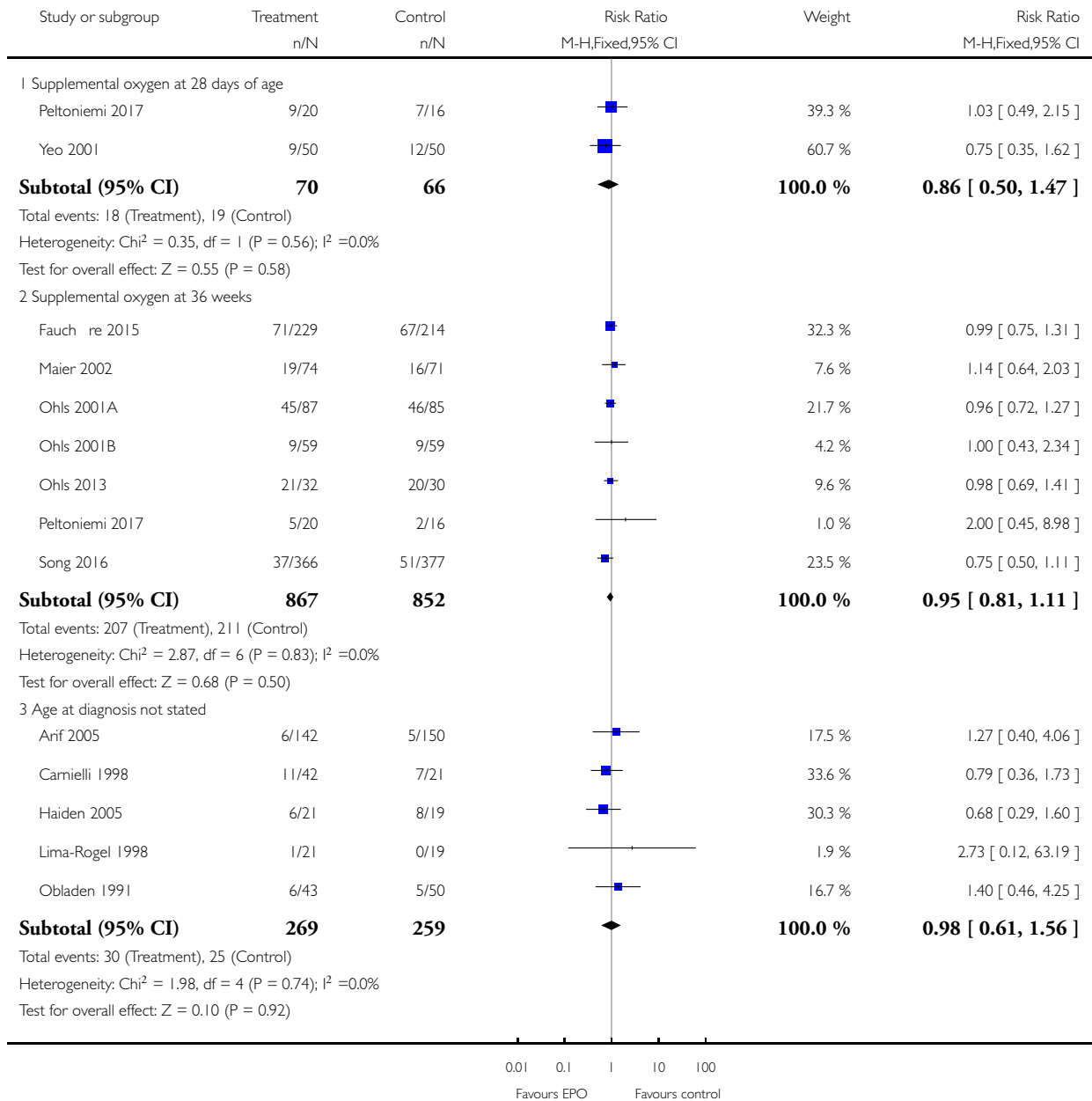
| Study or subgroup | EPO N | Mean(SD) | Placebo or None N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Ohls 2013 | 24 | 98.34 (13.47) | 14 | 91.52 (13.26) | | 100.0 % | 6.82 [ -1.97, 15.61 ] |
| **Total (95% CI)** | **24** | | **14** | | | **100.0 %** | **6.82 [ -1.97, 15.61 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.52 (P = 0.13) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
            -100   -50    0    50   100
          Favours [EPO]      Favours [Placebo or None]
```
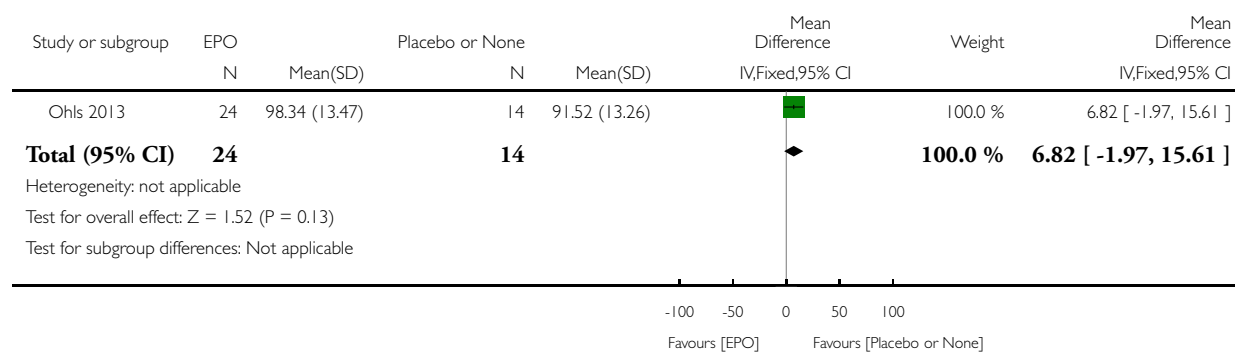
## Analysis 1.43. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 43 Working memory at 3.5 to 4 years of age.

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment
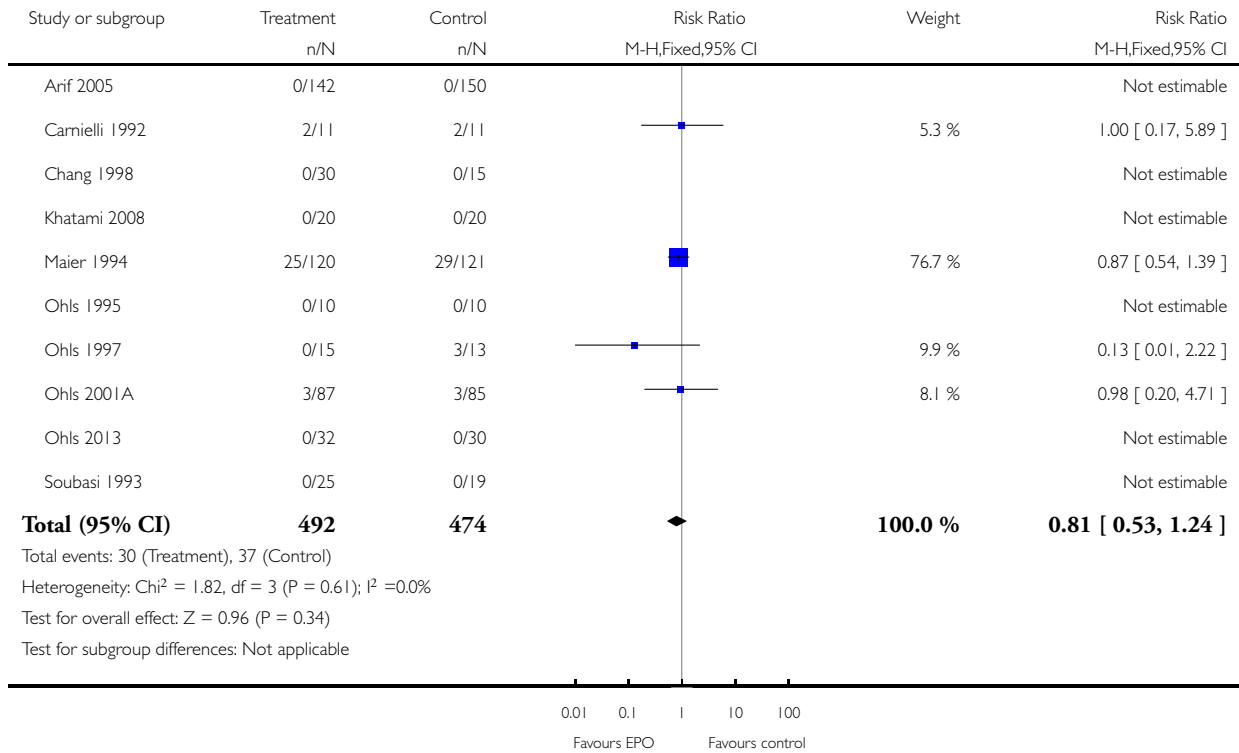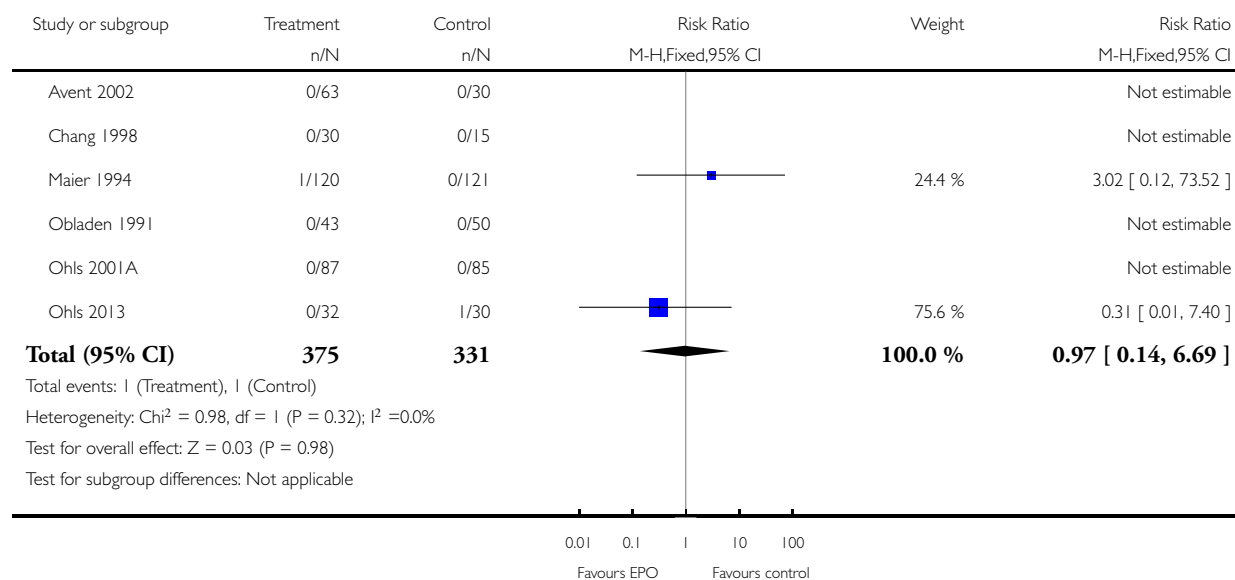
Outcome: 43 Working memory at 3.5 to 4 years of age

| Study or subgroup | EPO N | Mean(SD) | Placebo or None N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Ohls 2013 | 24 | 98.31 (16.98) | 14 | 91.57 (17.24) | | 100.0 % | 6.74 [ -4.56, 18.04 ] |
| **Total (95% CI)** | **24** | | **14** | | | **100.0 %** | **6.74 [ -4.56, 18.04 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
            -100   -50    0    50   100
          Favours [EPO]      Favours [Placebo or None]
```
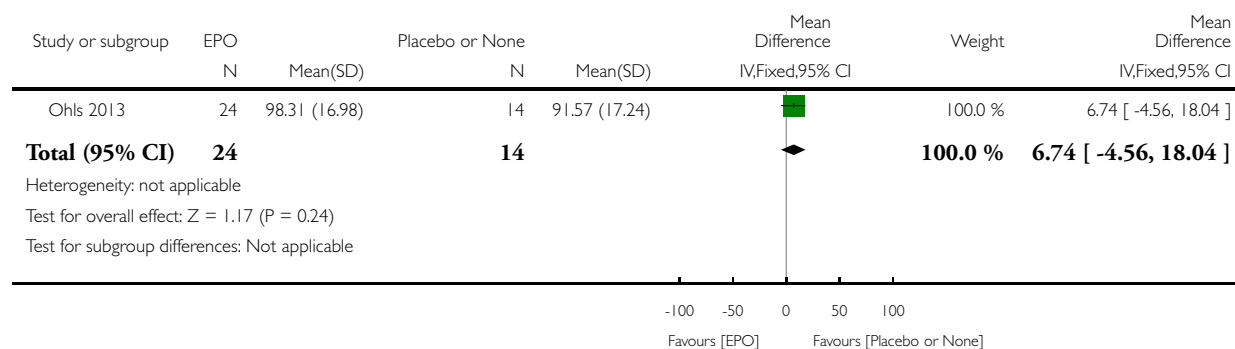
**Analysis 1.44. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 44 Inhibition at 3.5 to 4 years of age.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

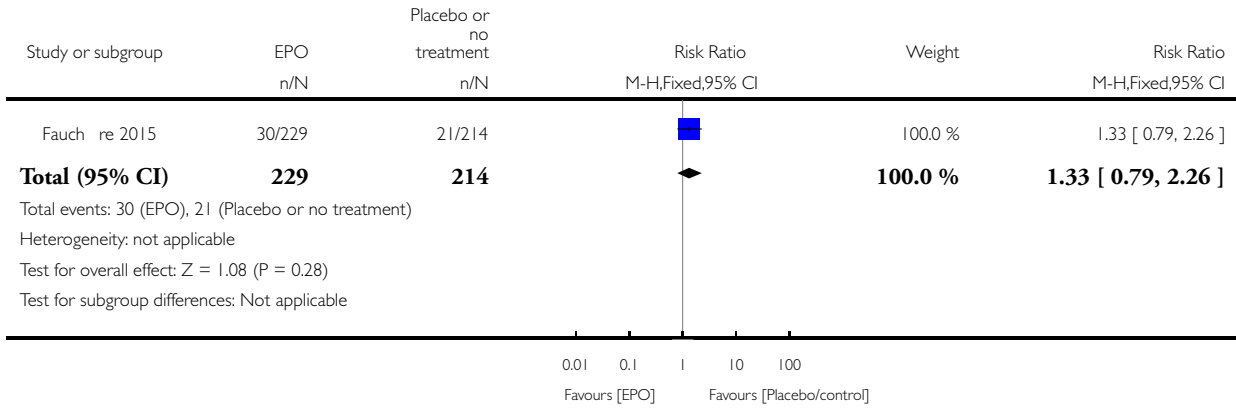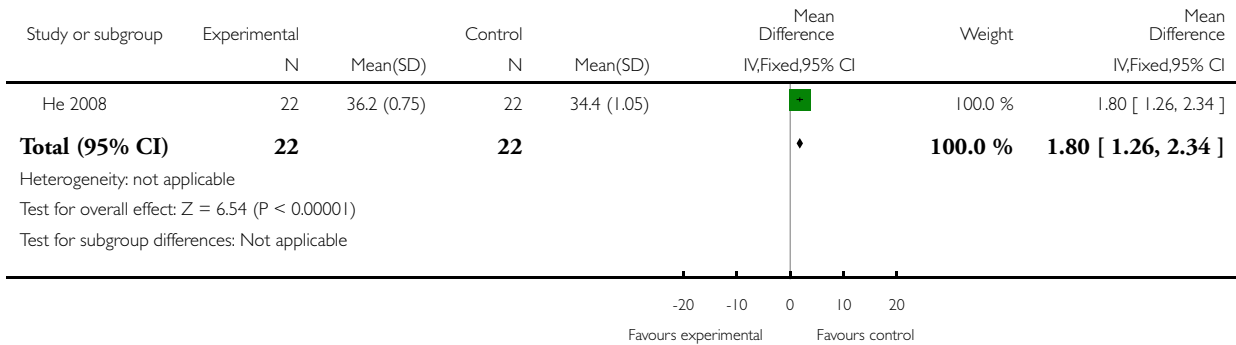Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 44 Inhibition at 3.5 to 4 years of age

| Study or subgroup | EPO | | Placebo or None | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 24 | 98.39 (16.81) | 14 | 91.53 (17.61) | | 100.0 % | 6.86 [ -4.56, 18.28 ] |
| **Total (95% CI)** | **24** | | **14** | | | **100.0 %** | **6.86 [ -4.56, 18.28 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.18 (P = 0.24) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100    -50    0    50    100

Favours [EPO]        Favours [Placebo or None]
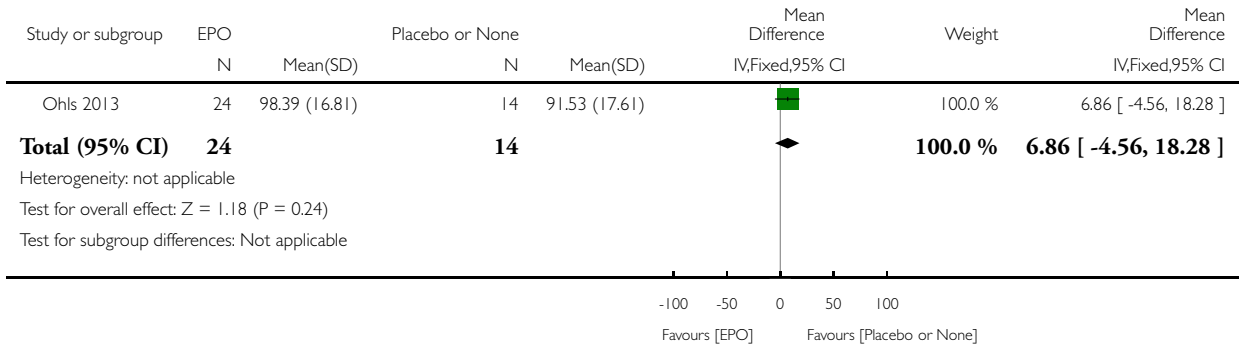
**Analysis 1.45. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 45 Griffiths Developmental Scale at 2 years of age.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 1 Erythropoietin versus placebo or no treatment

Outcome: 45 Griffiths Developmental Scale at 2 years of age

| Study or subgroup | EPO | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Peltoniemi 2017 | 10 | 109 (8) | 9 | 106 (7) | | 100.0 % | 3.00 [ -3.75, 9.75 ] |
| **Total (95% CI)** | **10** | | **9** | | | **100.0 %** | **3.00 [ -3.75, 9.75 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.87 (P = 0.38) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100    -50    0    50    100

Favours [EPO]        Favours [Placebo]
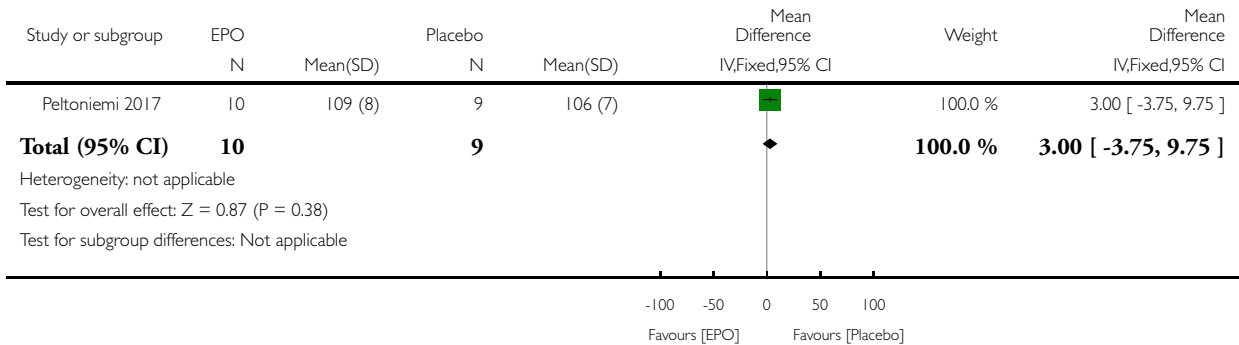
## Analysis 1.46. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 46 Survival without major neurological or neurodevelopmental disorders at 2 years of age.

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   46 Survival without major neurological or neurodevelopmental disorders at 2 years of age

| Study or subgroup | EPO<br>n/N | Placebo<br>n/N | Risk Ratio<br>M-H,Fixed,95% CI | Weight | Risk Ratio<br>M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Fauchère 2015 | 164/191 | 148/174 | | 91.1 % | 1.01 [ 0.93, 1.10 ] |
| Peltoniemi 2017 | 13/21 | 14/18 | | 8.9 % | 0.80 [ 0.52, 1.21 ] |
| **Total (95% CI)** | **212** | **192** | | **100.0 %** | **0.99 [ 0.91, 1.08 ]** |

Total events: 177 (EPO), 162 (Placebo)

Heterogeneity: Chi² = 1.25, df = 1 (P = 0.26); I² =20%

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable

```
0.01   0.1    1    10   100
Favours [Placebo]    Favours [EPO]
```
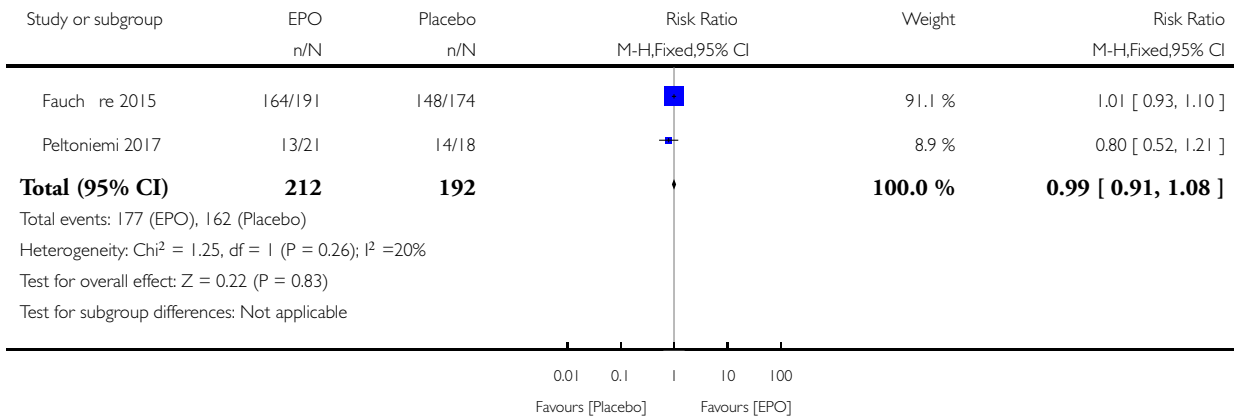
## Analysis 1.47. Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 47 Death or moderate/severe neurological disability at 18 to 24 months.

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   47 Death or moderate/severe neurological disability at 18 to 24 months

| Study or subgroup | EPO<br>n/N | Placebo<br>n/N | Risk Ratio<br>M-H,Fixed,95% CI | Weight | Risk Ratio<br>M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Song 2016 | 43/330 | 91/338 | | 100.0 % | 0.48 [ 0.35, 0.67 ] |
| **Total (95% CI)** | **330** | **338** | | **100.0 %** | **0.48 [ 0.35, 0.67 ]** |

Total events: 43 (EPO), 91 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 4.32 (P = 0.000016)

Test for subgroup differences: Not applicable

```
0.01   0.1    1    10   100
Favours [EPO]    Favours [Placebo]
```
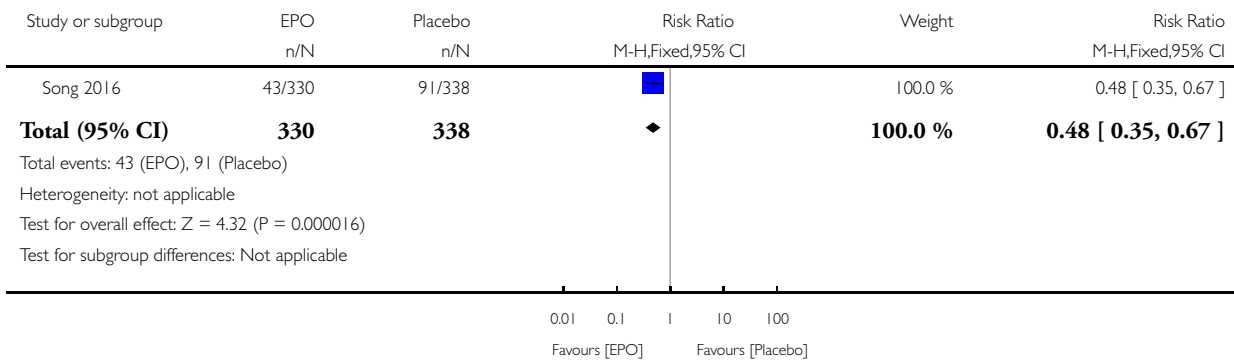
## Analysis 1.48.   Comparison 1 Erythropoietin versus placebo or no treatment, Outcome 48 Moderate/severe neurological disability at 18 to 24 months.

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   1 Erythropoietin versus placebo or no treatment

Outcome:   48 Moderate/severe neurological disability at 18 to 24 months

| Study or subgroup | EPO | Placebo | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| Song 2016 | 22/309 | 57/304 | | 100.0 % | 0.38 [ 0.24, 0.60 ] |
| **Total (95% CI)** | **309** | **304** | | **100.0 %** | **0.38 [ 0.24, 0.60 ]** |
| Total events: 22 (EPO), 57 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 4.07 (P = 0.000046) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

```
             0.01    0.1     1     10    100
           Favours [EPO]      Favours [Placebo]
```
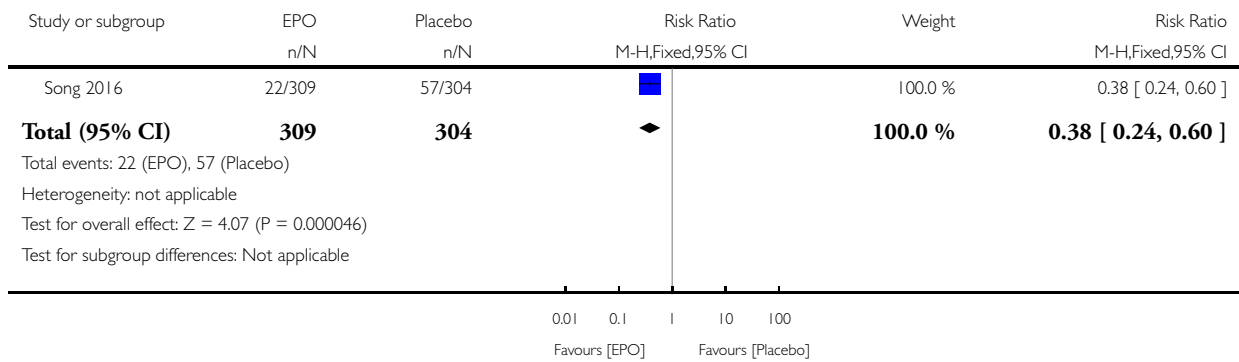
**Analysis 2.1.  Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 1 Use of 1 or more red blood cell transfusions.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   1 Use of 1 or more red blood cell transfusions

| Study or subgroup | Darbe<br>n/N | [Placebo or None]<br>n/N | Risk Ratio<br>M-H,Fixed,95% CI | Weight | Risk Ratio<br>M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Ohls 2013 | 13/33 | 21/33 | | 100.0 % | 0.62 [ 0.38, 1.02 ] |
| **Total (95% CI)** | **33** | **33** | | **100.0 %** | **0.62 [ 0.38, 1.02 ]** |

Total events: 13 (Darbe), 21 ([Placebo or None])

Heterogeneity: not applicable

Test for overall effect: Z = 1.90 (P = 0.058)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
            [Darbe]      [Placebo or None]
```
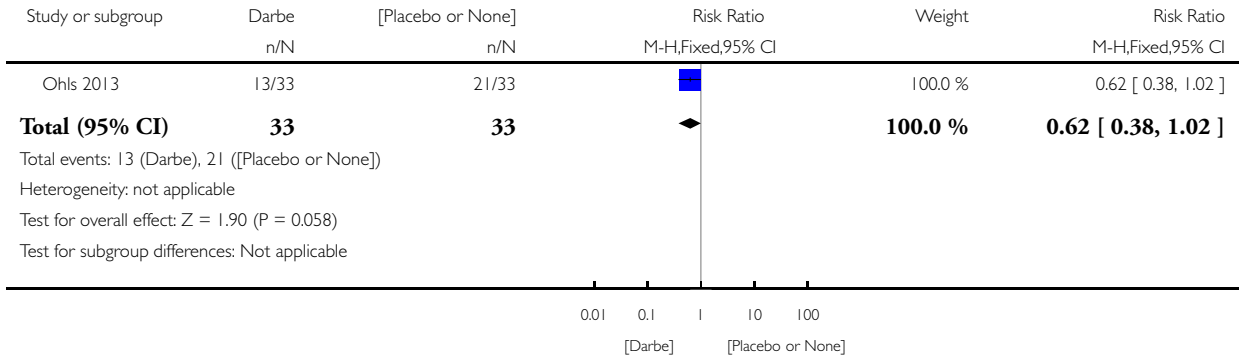
**Analysis 2.2.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 2 Total volume (mL/kg) of blood transfused per infant (all infants).**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   2 Total volume (mL/kg) of blood transfused per infant (all infants)

| Study or subgroup | Darbe<br>N | Mean(SD) | [Placebo or None]<br>N | Mean(SD) | Mean<br>Difference<br>IV,Fixed,95% CI | Weight | Mean<br>Difference<br>IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Ohls 2013 | 33 | 30 (58) | 33 | 51 (65) | | 100.0 % | -21.00 [ -50.72, 8.72 ] |
| **Total (95% CI)** | **33** | | **33** | | | **100.0 %** | **-21.00 [ -50.72, 8.72 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.38 (P = 0.17)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
            [Darbe]      [Placebo or None]
```
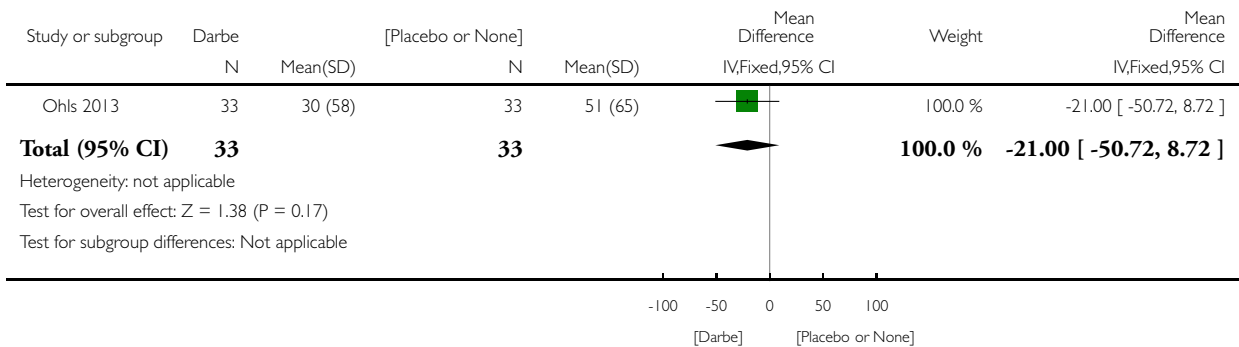
**Analysis 2.3. Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 3 Total volume (mL/kg) of blood transfused in transfused infants only.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 2 Darbepoetin alfa versus placebo or no treatment

Outcome: 3 Total volume (mL/kg) of blood transfused in transfused infants only

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | | | |
| Ohls 2013 | 13 | 75.6 (73.2) | 21 | 80.7 (65.3) | | 100.0 % | -5.10 [ -53.71, 43.51 ] |
| **Total (95% CI)** | **13** | | **21** | | | **100.0 %** | **-5.10 [ -53.71, 43.51 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.21 (P = 0.84) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100   -50   0   50   100

Favours [Darbe]       Favours [Placebo]
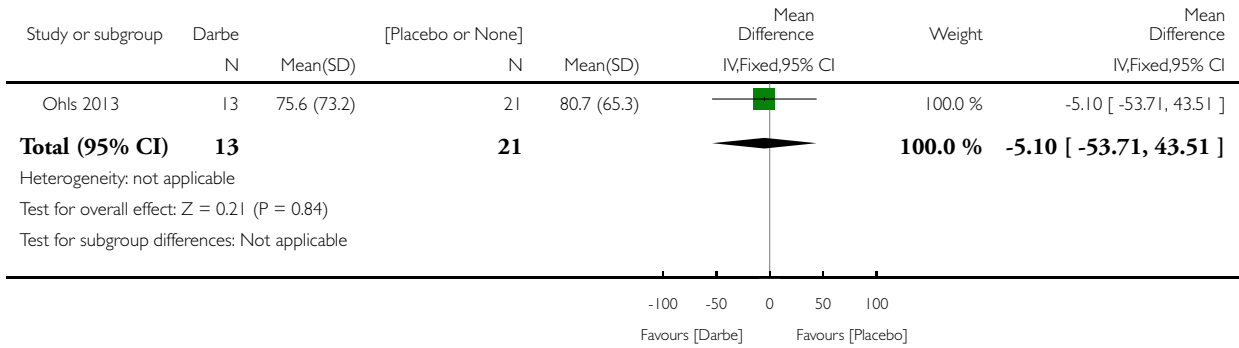
**Analysis 2.4. Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 4 Number of blood transfusions per infant.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 2 Darbepoetin alfa versus placebo or no treatment

Outcome: 4 Number of blood transfusions per infant

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | | | |
| Ohls 2013 | 33 | 1.2 (2.4) | 33 | 2.4 (2.9) | | 100.0 % | -1.20 [ -2.48, 0.08 ] |
| **Total (95% CI)** | **33** | | **33** | | | **100.0 %** | **-1.20 [ -2.48, 0.08 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.83 (P = 0.067) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100   -50   0   50   100

[Darbe]       [Placebo or None]
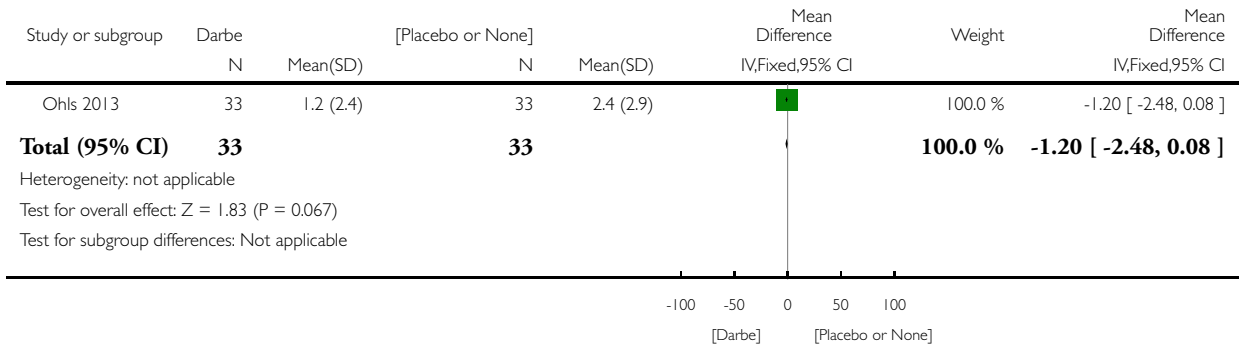
**Analysis 2.5.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 5 Number of donors the infant was exposed to.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   5 Number of donors the infant was exposed to

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 33 | 0.7 (1.2) | 33 | 1.2 (1.3) | | 100.0 % | -0.50 [ -1.10, 0.10 ] |
| **Total (95% CI)** | **33** | | **33** | | | **100.0 %** | **-0.50 [ -1.10, 0.10 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.62 (P = 0.10)

Test for subgroup differences: Not applicable

```
        -100    -50     0     50    100
             [Darbe]      [Placebo or None]
```

**Analysis 2.6.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 6 Mortality during initial hospital stay (all causes of mortality).**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   6 Mortality during initial hospital stay (all causes of mortality)

| Study or subgroup | Darbe | [Placebo or None] | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| Ohls 2013 | 2/33 | 3/33 | | 100.0 % | 0.67 [ 0.12, 3.73 ] |
| **Total (95% CI)** | **33** | **33** | | **100.0 %** | **0.67 [ 0.12, 3.73 ]** |

Total events: 2 (Darbe), 3 ([Placebo or None])

Heterogeneity: not applicable

Test for overall effect: Z = 0.46 (P = 0.64)

Test for subgroup differences: Not applicable

```
      0.01    0.1     1     10    100
             [Darbe]      [Placebo or None]
```
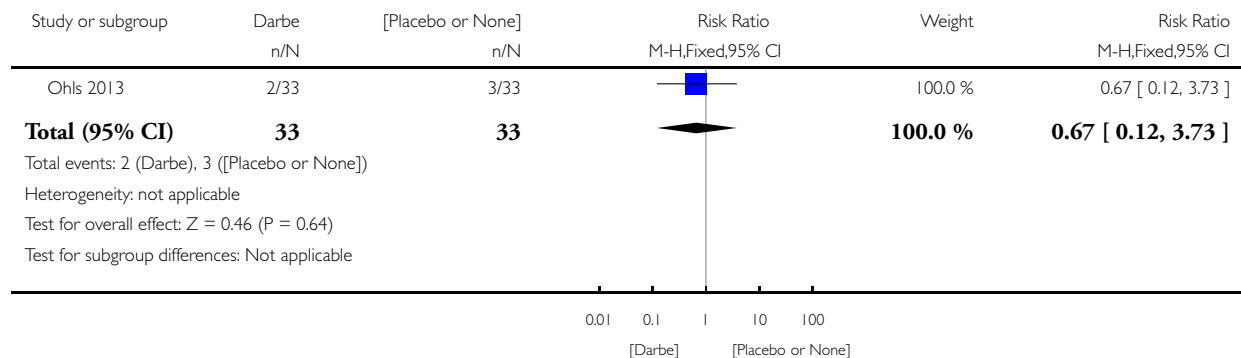
## Analysis 2.7. Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 7 Retinopathy of prematurity (all stages).

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 2 Darbepoetin alfa versus placebo or no treatment

Outcome: 7 Retinopathy of prematurity (all stages)

| Study or subgroup | Darbe n/N | [Placebo or None] n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Ohls 2013 | 12/32 | 12/30 | ■ | 100.0 % | 0.94 [ 0.50, 1.75 ] |
| **Total (95% CI)** | **32** | **30** | ◆ | **100.0 %** | **0.94 [ 0.50, 1.75 ]** |
| Total events: 12 (Darbe), 12 ([Placebo or None]) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.20 (P = 0.84) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

```
        0.01   0.1    1    10   100
            [Darbe]    [Placebo or None]
```
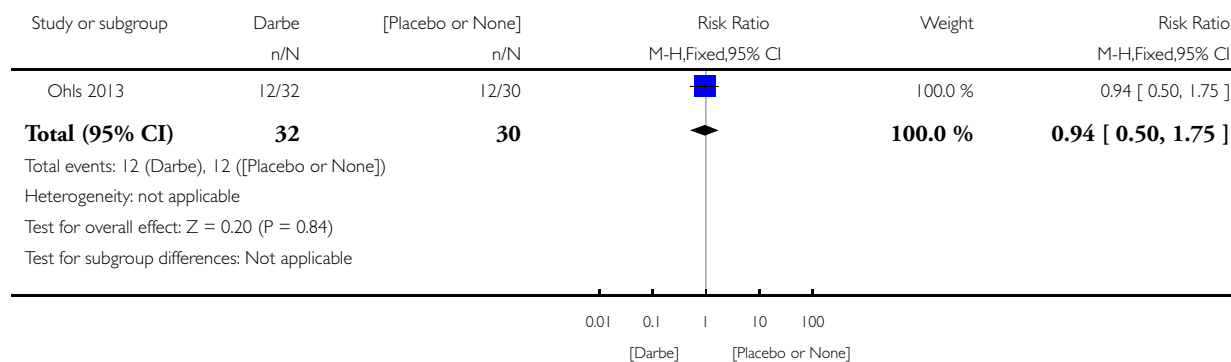
## Analysis 2.8. Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 8 Retinopathy of prematurity (stage ≥ 3).

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 2 Darbepoetin alfa versus placebo or no treatment

Outcome: 8 Retinopathy of prematurity (stage ≥ 3)

| Study or subgroup | Darbe n/N | [Placebo or None] n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Ohls 2013 | 2/32 | 4/30 | ■ | 100.0 % | 0.47 [ 0.09, 2.37 ] |
| **Total (95% CI)** | **32** | **30** | ◆ | **100.0 %** | **0.47 [ 0.09, 2.37 ]** |
| Total events: 2 (Darbe), 4 ([Placebo or None]) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.92 (P = 0.36) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

```
        0.01   0.1    1    10   100
            [Darbe]    [Placebo or None]
```
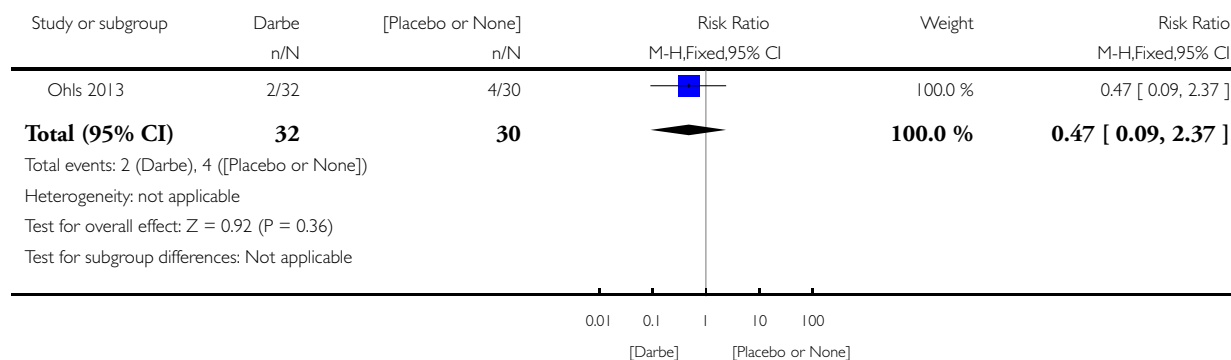
**Analysis 2.9.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 9 Necrotising enterocolitis (> stage 2).**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   9 Necrotising enterocolitis (> stage 2)

| Study or subgroup | Darbe | [Placebo or None] | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| Ohls 2013 | 2/32 | 2/30 | | 100.0 % | 0.94 [ 0.14, 6.24 ] |
| **Total (95% CI)** | **32** | **30** | | **100.0 %** | **0.94 [ 0.14, 6.24 ]** |

Total events: 2 (Darbe), 2 ([Placebo or None])

Heterogeneity: not applicable

Test for overall effect: Z = 0.07 (P = 0.95)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
         [Darbe]      [Placebo or None]
```

---
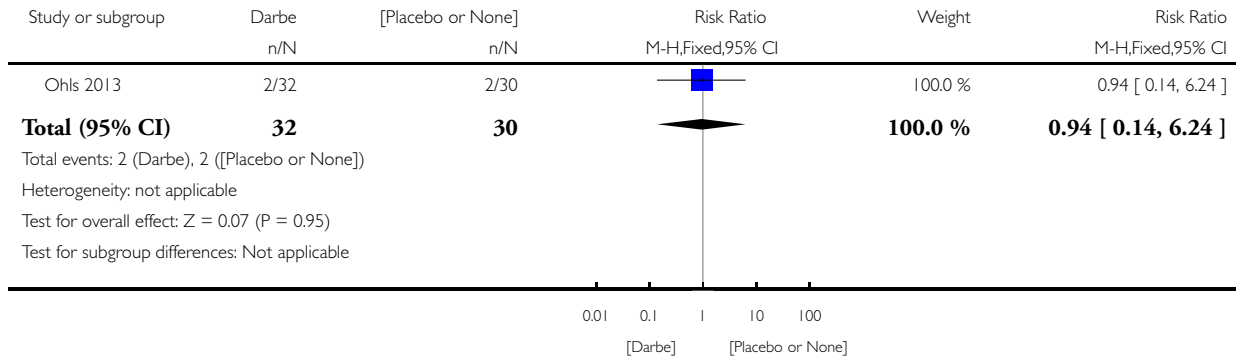
**Analysis 2.10.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 10 Proven sepsis.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   10 Proven sepsis

| Study or subgroup | Darbe | [Placebo or None] | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| Ohls 2013 | 6/32 | 5/30 | | 100.0 % | 1.13 [ 0.38, 3.30 ] |
| **Total (95% CI)** | **32** | **30** | | **100.0 %** | **1.13 [ 0.38, 3.30 ]** |

Total events: 6 (Darbe), 5 ([Placebo or None])

Heterogeneity: not applicable

Test for overall effect: Z = 0.21 (P = 0.83)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
         [Darbe]      [Placebo or None]
```

**Analysis 2.11.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 11 Intraventricular haemorrhage (grades III and IV).**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   11 Intraventricular haemorrhage (grades III and IV)

| Study or subgroup | Darbe | [Placebo or None] | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| Ohls 2013 | 3/32 | 7/30 | | 100.0 % | 0.40 [ 0.11, 1.41 ] |
| **Total (95% CI)** | **32** | **30** | | **100.0 %** | **0.40 [ 0.11, 1.41 ]** |
| Total events: 3 (Darbe), 7 ([Placebo or None]) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.42 (P = 0.16) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

```
         0.01   0.1    1    10    100
             [Darbe]      [Placebo or None]
```

**Analysis 2.12.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 12 Periventricular leukomalacia.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   12 Periventricular leukomalacia

| Study or subgroup | Darbe | [Placebo or None] | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| Ohls 2013 | 0/32 | 0/30 | | | Not estimable |
| **Total (95% CI)** | **32** | **30** | | | **Not estimable** |
| Total events: 0 (Darbe), 0 ([Placebo or None]) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

```
         0.01   0.1    1    10    100
             [Darbe]      [Placebo or None]
```
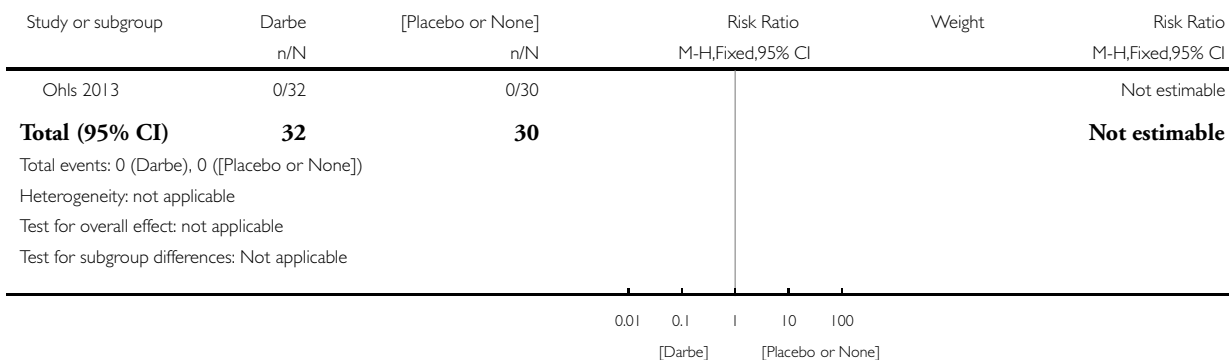
**Analysis 2.13.  Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 13 Bronchopulmonary dysplasia (supplemental oxygen at 36 weeks' PMA).**

Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:    2 Darbepoetin alfa versus placebo or no treatment

Outcome:    13 Bronchopulmonary dysplasia (supplemental oxygen at 36 weeks' PMA)

| Study or subgroup | Darbe | [Placebo or None] | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| Ohls 2013 | 22/32 | 20/30 | | 100.0 % | 1.03 [ 0.73, 1.46 ] |
| **Total (95% CI)** | **32** | **30** | | **100.0 %** | **1.03 [ 0.73, 1.46 ]** |

Total events: 22 (Darbe), 20 ([Placebo or None])

Heterogeneity: not applicable

Test for overall effect: Z = 0.18 (P = 0.86)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
            [Darbe]      [Placebo or None]
```

**Analysis 2.14.  Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 14 Length of hospital stay (days).**

Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:    2 Darbepoetin alfa versus placebo or no treatment

Outcome:    14 Length of hospital stay (days)

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 32 | 76 (46) | 30 | 74 (33) | | 100.0 % | 2.00 [ -17.84, 21.84 ] |
| **Total (95% CI)** | **32** | | **30** | | | **100.0 %** | **2.00 [ -17.84, 21.84 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
            [Darbe]      [Placebo or None]
```
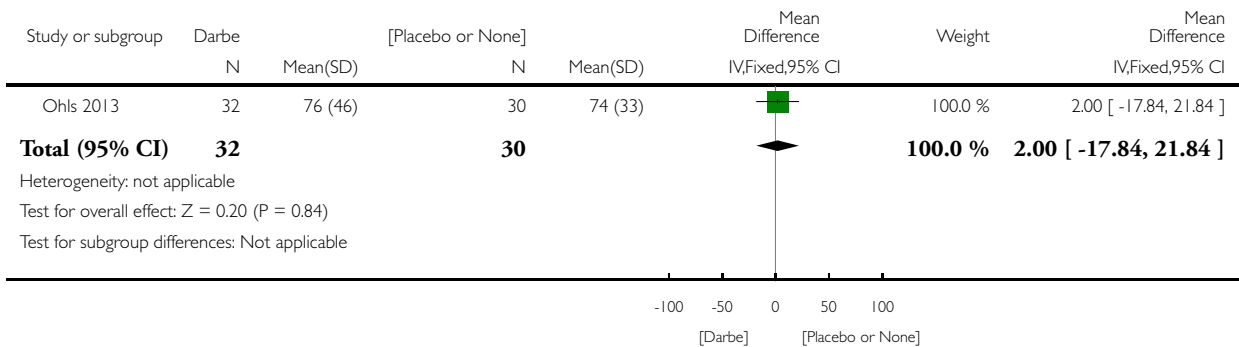
**Analysis 2.15.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 15 Neutropenia.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   15 Neutropenia

| Study or subgroup | Darbe | [Placebo or None] | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
|  | n/N | n/N | M-H,Fixed,95% CI |  | M-H,Fixed,95% CI |
| Ohls 2013 | 0/32 | 0/30 |  |  | Not estimable |
| **Total (95% CI)** | **32** | **30** |  |  | **Not estimable** |

Total events: 0 (Darbe), 0 ([Placebo or None])

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
            [Darbe]    [Placebo or None]
```

<br>

**Analysis 2.16.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 16 Hypertension.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   16 Hypertension

| Study or subgroup | Darbe | [Placebo or None] | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
|  | n/N | n/N | M-H,Fixed,95% CI |  | M-H,Fixed,95% CI |
| Ohls 2013 | 2/32 | 1/30 |  | 100.0 % | 1.88 [ 0.18, 19.63 ] |
| **Total (95% CI)** | **32** | **30** |  | **100.0 %** | **1.88 [ 0.18, 19.63 ]** |

Total events: 2 (Darbe), 1 ([Placebo or None])

Heterogeneity: not applicable

Test for overall effect: Z = 0.52 (P = 0.60)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
            [Darbe]    [Placebo or None]
```

**Analysis 2.17. Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 17 Cerebral palsy at 18 to 22 months.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 2 Darbepoetin alfa versus placebo or no treatment

Outcome: 17 Cerebral palsy at 18 to 22 months

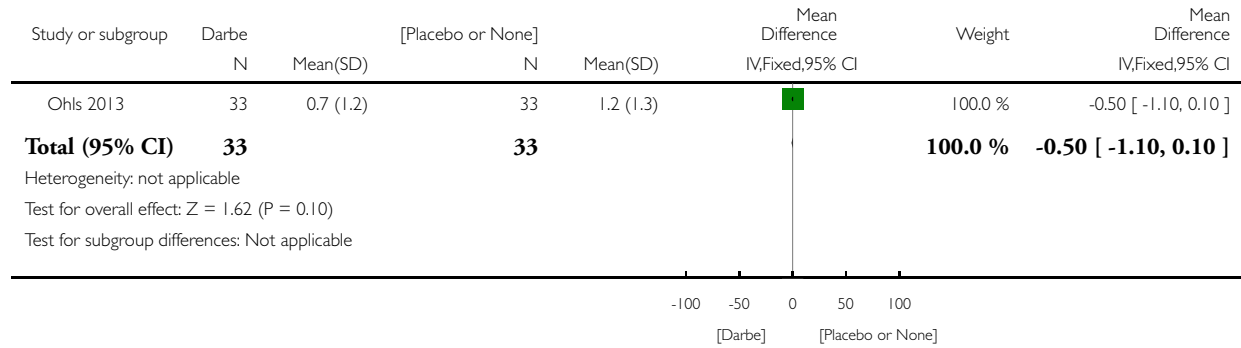| Study or subgroup | Darbe<br>n/N | [Placebo or None]<br>n/N | Risk Ratio<br>M-H,Fixed,95% CI | Weight | Risk Ratio<br>M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Ohls 2013 | 0/27 | 5/24 | | 100.0 % | 0.08 [ 0.00, 1.40 ] |
| **Total (95% CI)** | **27** | **24** | | **100.0 %** | **0.08 [ 0.00, 1.40 ]** |

Total events: 0 (Darbe), 5 ([Placebo or None])

Heterogeneity: not applicable

Test for overall effect: Z = 1.73 (P = 0.084)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10    100
            [Darbe]    [Placebo or None]
```

**Analysis 2.18. Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 18 NDI (with CP, visual defect, hearing defect, or cognitive score < 85) at 18 to 22 months.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 2 Darbepoetin alfa versus placebo or no treatment

Outcome: 18 NDI (with CP, visual defect, hearing defect, or cognitive score < 85) at 18 to 22 months

| Study or subgroup | Darbe<br>n/N | [Placebo or None]<br>n/N | Risk Ratio<br>M-H,Fixed,95% CI | Weight | Risk Ratio<br>M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Ohls 2013 | 3/27 | 10/24 | | 100.0 % | 0.27 [ 0.08, 0.86 ] |
| **Total (95% CI)** | **27** | **24** | | **100.0 %** | **0.27 [ 0.08, 0.86 ]** |

Total events: 3 (Darbe), 10 ([Placebo or None])

Heterogeneity: not applicable

Test for overall effect: Z = 2.22 (P = 0.026)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10    100
        Favours [Darbe]    Favours [Placebo or none]
```

**Analysis 2.19. Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 19 BSID-III composite cognitive score at 18 to 22 months.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 2 Darbepoetin alfa versus placebo or no treatment

Outcome: 19 BSID-III composite cognitive score at 18 to 22 months

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 27 | 96.2 (7.3) | 24 | 88.7 (13.5) | | 100.0 % | 7.50 [ 1.44, 13.56 ] |
| **Total (95% CI)** | **27** | | **24** | | | **100.0 %** | **7.50 [ 1.44, 13.56 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 2.42 (P = 0.015)

Test for subgroup differences: Not applicable

```
      -20   -10    0    10    20
           [Darbe]      [Placebo or None]
```
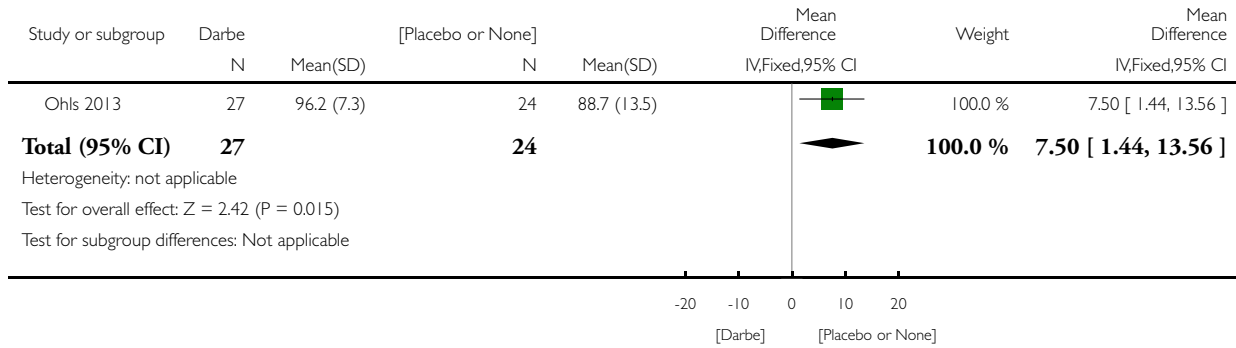
**Analysis 2.20. Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 20 BSID-III composite language score at 18 to 22 months.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

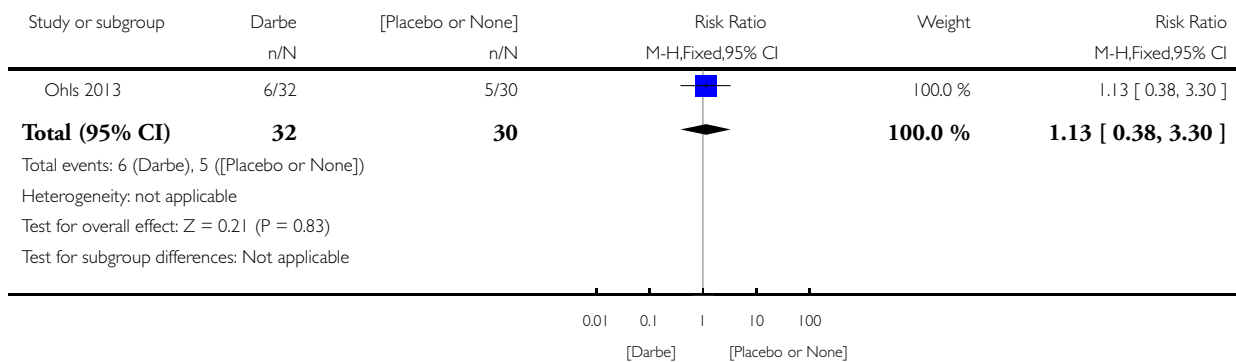Comparison: 2 Darbepoetin alfa versus placebo or no treatment

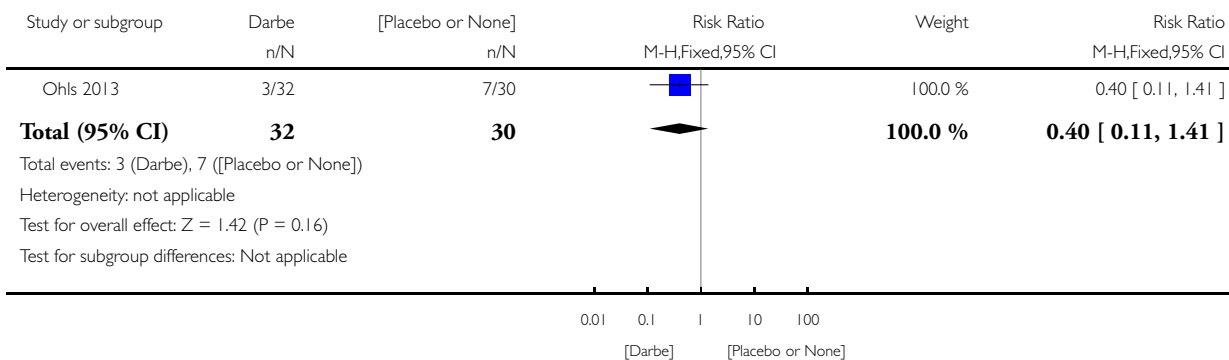Outcome: 20 BSID-III composite language score at 18 to 22 months

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 27 | 92.4 (13.2) | 24 | 83.6 (13.1) | | 100.0 % | 8.80 [ 1.57, 16.03 ] |
| **Total (95% CI)** | **27** | | **24** | | | **100.0 %** | **8.80 [ 1.57, 16.03 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 2.39 (P = 0.017)

Test for subgroup differences: Not applicable

```
      -100   -50    0    50    100
            [Darbe]      [Placebo or None]
```
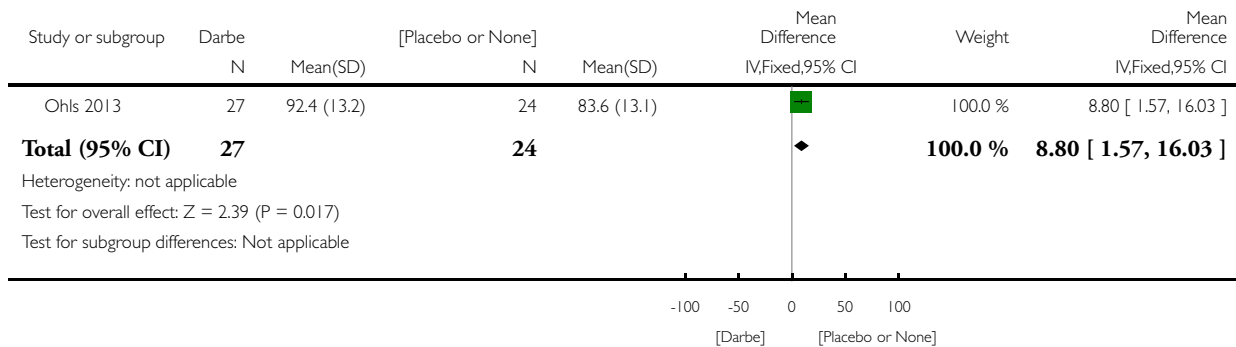
**Analysis 2.21.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 21 Bayley-III social/emotional score at 18 to 22 months.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   21 Bayley-III social/emotional score at 18 to 22 months

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 27 | 103.5 (19.2) | 24 | 96.7 (19.4) | | 100.0 % | 6.80 [ -3.82, 17.42 ] |
| **Total (95% CI)** | **27** | | **24** | | | **100.0 %** | **6.80 [ -3.82, 17.42 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.26 (P = 0.21) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
        -100   -50    0     50    100
              [Darbe]     [Placebo or None]
```
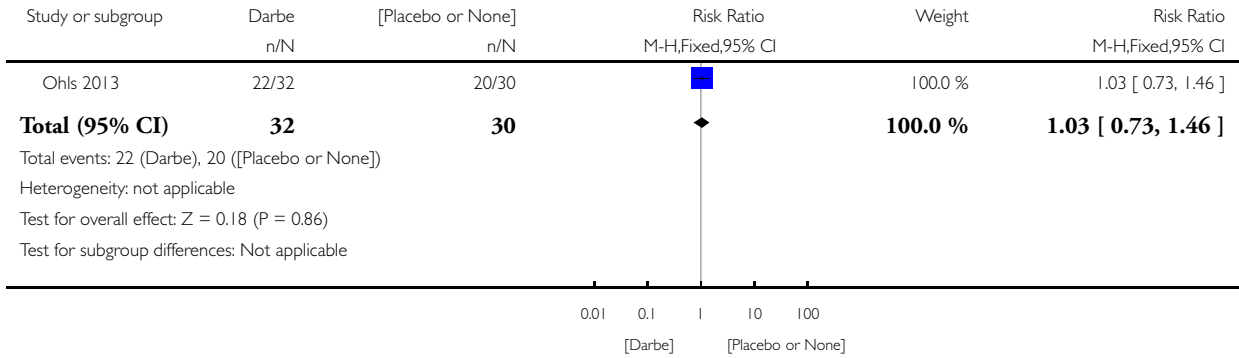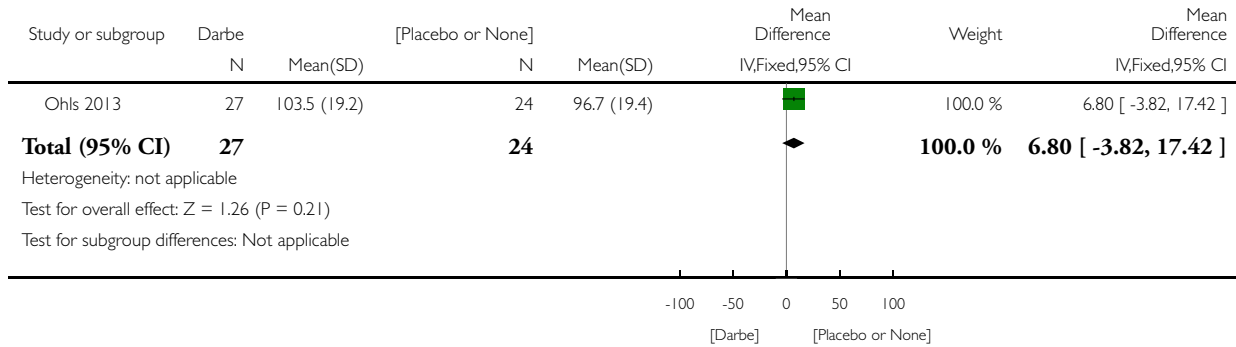
**Analysis 2.22.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 22 OP score at 18 to 22 months.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   22 OP score at 18 to 22 months
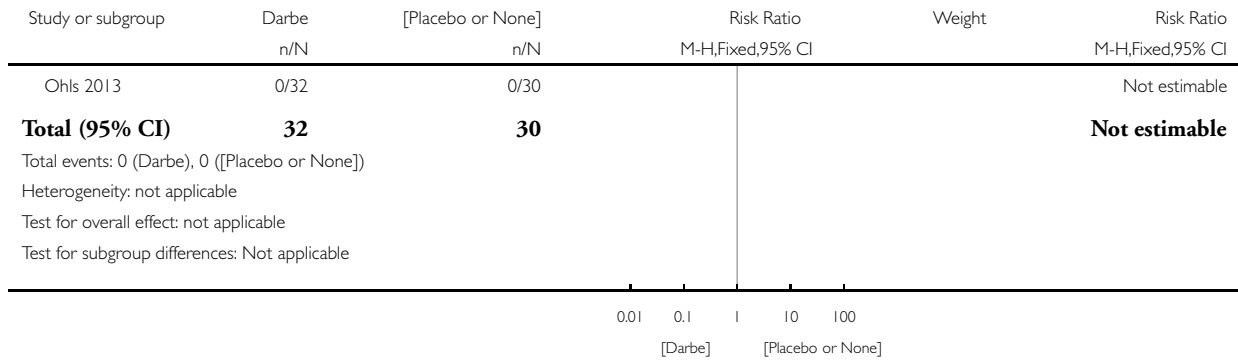
| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 27 | 2.8 (0.4) | 24 | 2.2 (1) | | 100.0 % | 0.60 [ 0.17, 1.03 ] |
| **Total (95% CI)** | **27** | | **24** | | | **100.0 %** | **0.60 [ 0.17, 1.03 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.75 (P = 0.0060) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
          -4    -2    0     2     4
              [Darbe]     [Placebo or None]
```
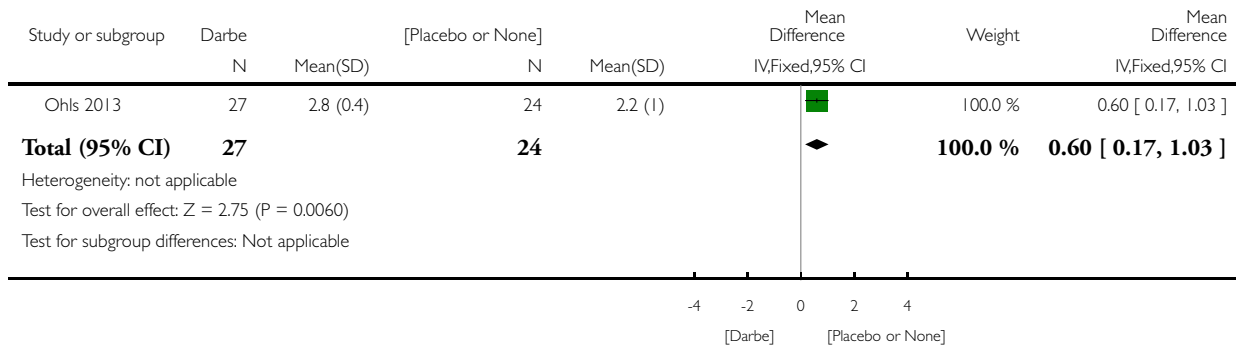
**Analysis 2.23.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 23 WPPSI-III FSIQ at 3.5 to 4 years of age.**

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 15 | 94.47 (16.14) | 14 | 79.2 (18.5) | | 100.0 % | 15.27 [ 2.60, 27.94 ] |
| **Total (95% CI)** | **15** | | **14** | | | **100.0 %** | **15.27 [ 2.60, 27.94 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 2.36 (P = 0.018)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50    100
        Favours [Darbe]   Favours [Placebo or None]
```

**Analysis 2.24.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 24 WPPSI-III VIQ at 3.5 to 4 years of age.**

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 15 | 92.07 (16.11) | 14 | 82.9 (16.9) | | 100.0 % | 9.17 [ -2.86, 21.20 ] |
| **Total (95% CI)** | **15** | | **14** | | | **100.0 %** | **9.17 [ -2.86, 21.20 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.49 (P = 0.14)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50    100
        Favours [Darbe]   Favours [Placebo or None]
```

**Analysis 2.25.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 25 WPPSI-III PIQ at 3.5 to 4 years of age.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

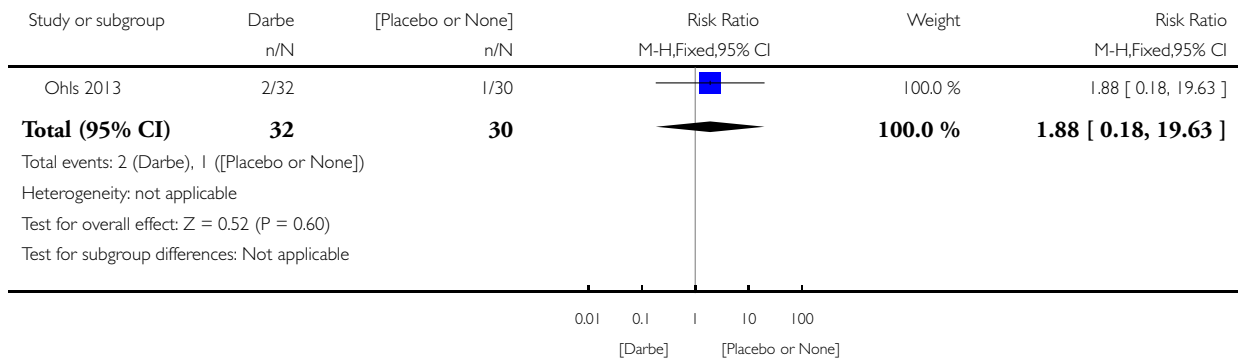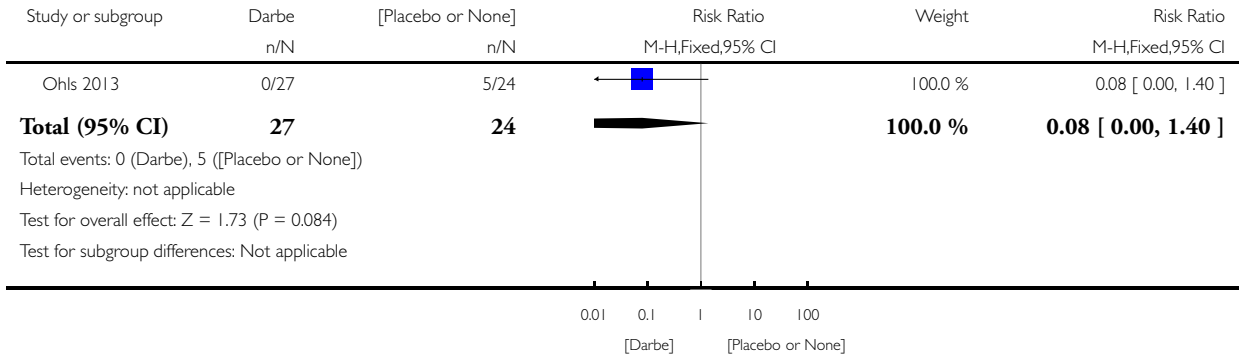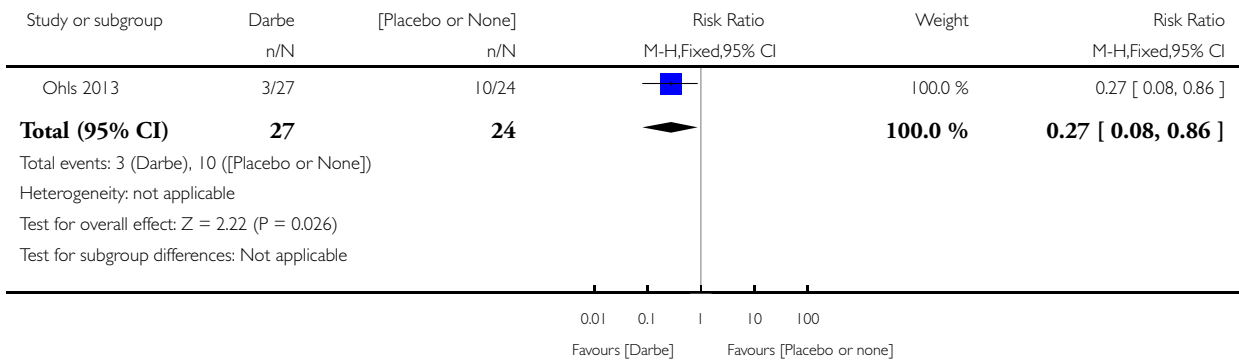Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   25 WPPSI-III PIQ at 3.5 to 4 years of age

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 15 | 94.47 (16.14) | 14 | 79.5 (19.5) | | 100.0 % | 14.97 [ 1.89, 28.05 ] |
| **Total (95% CI)** | **15** | | **14** | | | **100.0 %** | **14.97 [ 1.89, 28.05 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 2.24 (P = 0.025)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50    100
       Favours [Darbe]    Favours [Placebo or None]
```

**Analysis 2.26.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 26 WPPSI-III GLC at 3.5 to 4 years of age.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   26 WPPSI-III GLC at 3.5 to 4 years of age

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 15 | 92.73 (16.12) | 14 | 84.79 (17.11) | | 100.0 % | 7.94 [ -4.18, 20.06 ] |
| **Total (95% CI)** | **15** | | **14** | | | **100.0 %** | **7.94 [ -4.18, 20.06 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50    100
       Favours [No treatment]    Favours [Darbe]
```

**Analysis 2.27.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 27 Executive function at 3.5 to 4 years of age.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   27 Executive function at 3.5 to 4 years of age

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 15 | 102.33 (7.75) | 14 | 91.52 (13.26) | | 100.0 % | 10.81 [ 2.83, 18.79 ] |
| **Total (95% CI)** | **15** | | **14** | | | **100.0 %** | **10.81 [ 2.83, 18.79 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 2.66 (P = 0.0079)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
     Favours [Darbe]    Favours [Placebo or None]
```
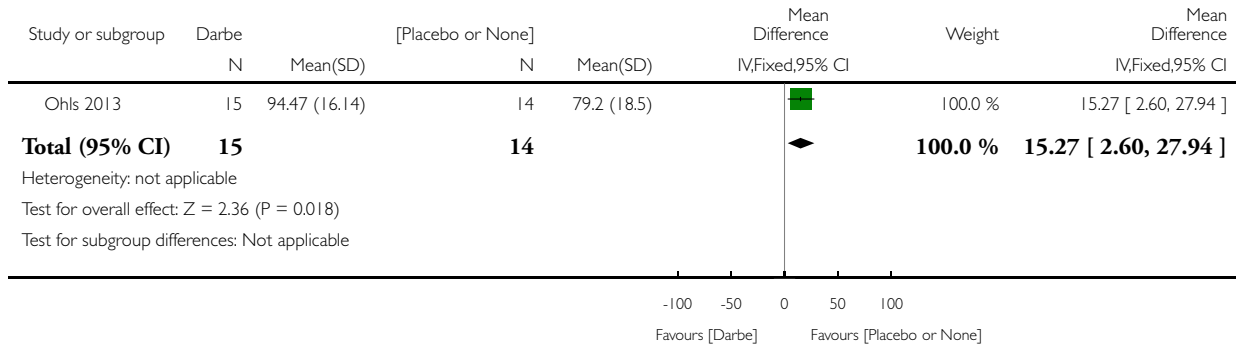
**Analysis 2.28.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 28 Working memory at 3.5 to 4 years of age.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment

Outcome:   28 Working memory at 3.5 to 4 years of age

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 15 | 104.34 (8.9) | 14 | 91.57 (17.24) | | 100.0 % | 12.77 [ 2.68, 22.86 ] |
| **Total (95% CI)** | **15** | | **14** | | | **100.0 %** | **12.77 [ 2.68, 22.86 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 2.48 (P = 0.013)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
     Favours [Darbe]    Favours [Placebo or None]
```

## Analysis 2.29.   Comparison 2 Darbepoetin alfa versus placebo or no treatment, Outcome 29 Inhibition at 3.5 to 4 years of age.

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   2 Darbepoetin alfa versus placebo or no treatment
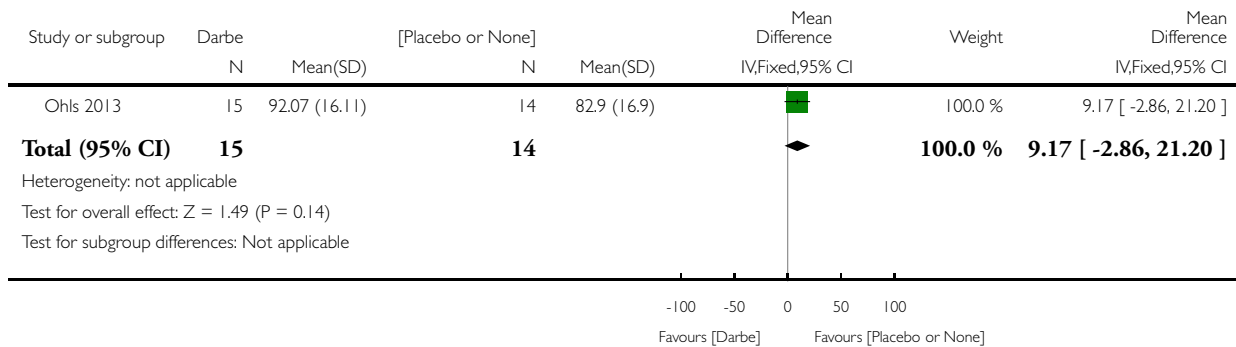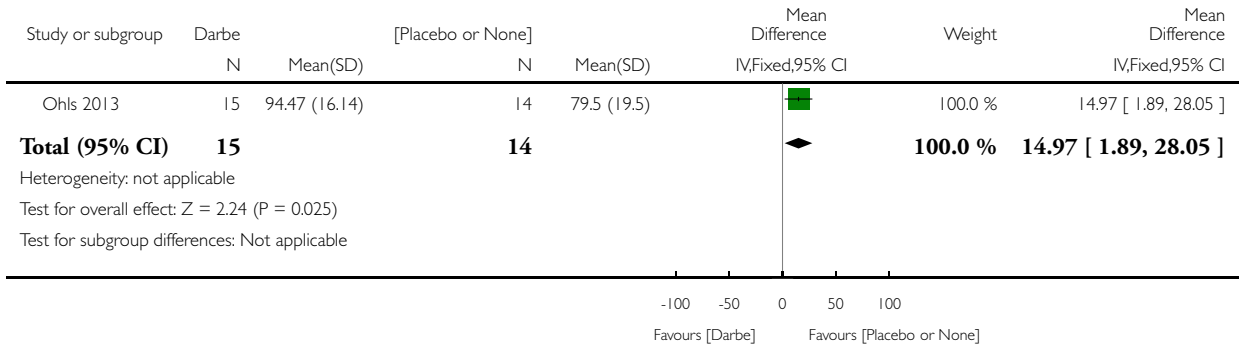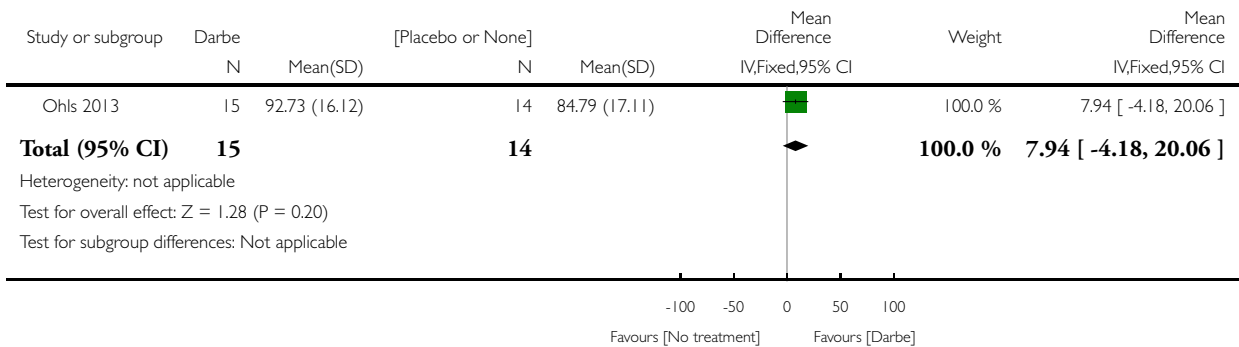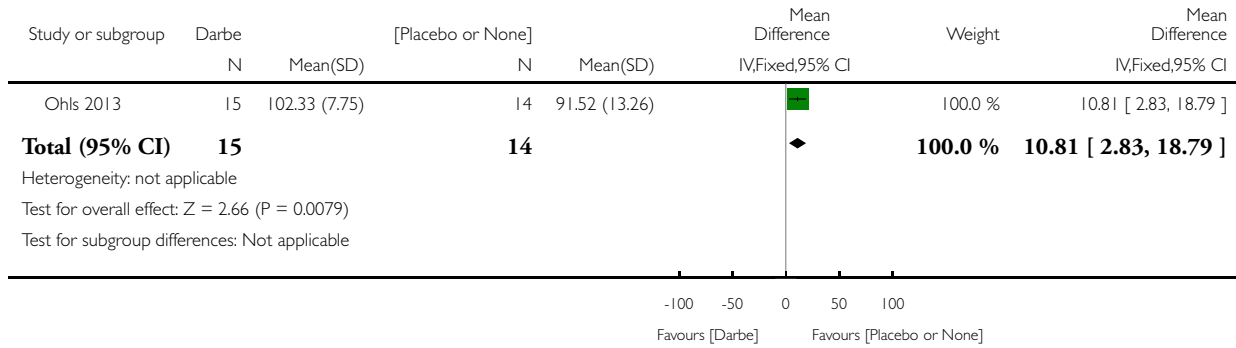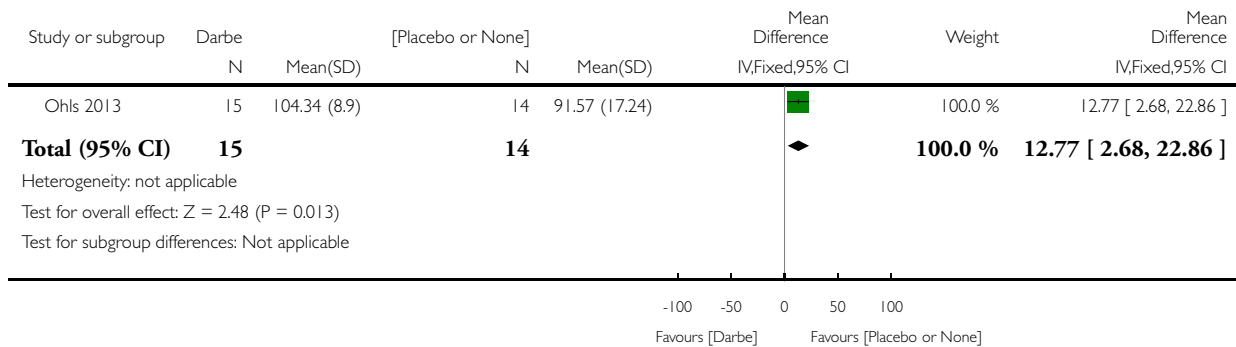
Outcome:   29 Inhibition at 3.5 to 4 years of age

| Study or subgroup | Darbe | | [Placebo or None] | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 15 | 100.3 (12.7) | 14 | 91.53 (17.61) | | 100.0 % | 8.77 [ -2.47, 20.01 ] |
| **Total (95% CI)** | **15** | | **14** | | | **100.0 %** | **8.77 [ -2.47, 20.01 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.53 (P = 0.13) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
        -100   -50    0    50   100
     Favours [Darbe]      Favours [Placebo or None]
```
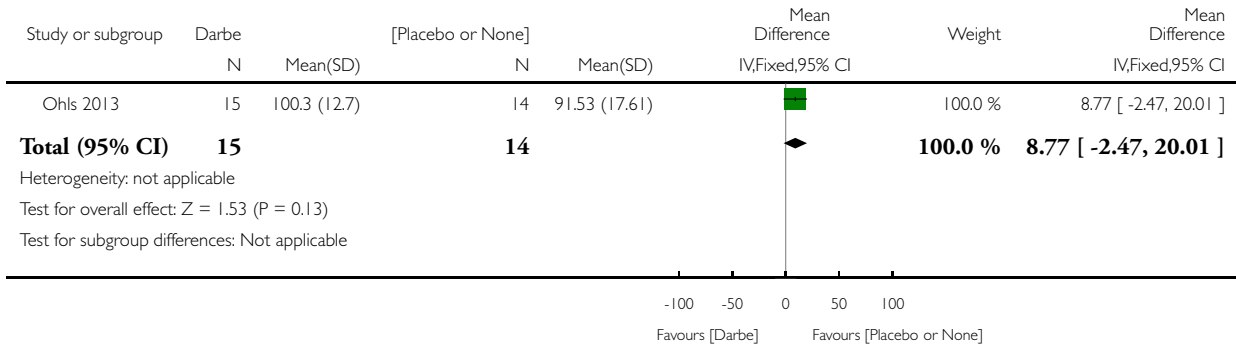
## Analysis 3.1.   Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 1 BSID-III composite cognitive score at 18 to 22 months.

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome:   1 BSID-III composite cognitive score at 18 to 22 months

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 56 | 96.5 (11.2) | 24 | 88.7 (13.5) | | 100.0 % | 7.80 [ 1.65, 13.95 ] |
| **Total (95% CI)** | **56** | | **24** | | | **100.0 %** | **7.80 [ 1.65, 13.95 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.49 (P = 0.013) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
        -20   -10    0    10   20
   Favours [Darbe % EPO]      Favours [Placebo or None]
```

**Analysis 3.2. Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 2 BSID-III composite language score at 18 to 22 months.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome: 2 BSID-III composite language score at 18 to 22 months

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 56 | 90.7 (15.4) | 24 | 83.6 (13.1) | | 100.0 % | 7.10 [ 0.49, 13.71 ] |
| **Total (95% CI)** | **56** | | **24** | | | **100.0 %** | **7.10 [ 0.49, 13.71 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.10 (P = 0.035) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-20  -10  0  10  20

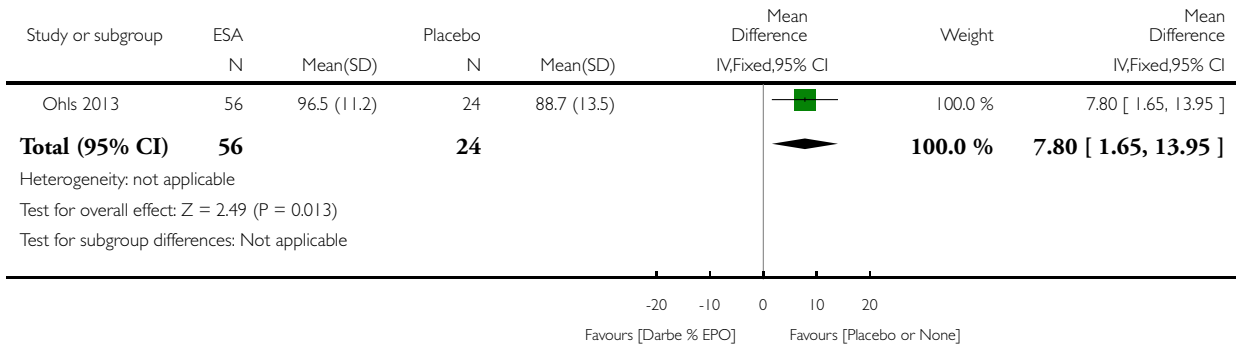Favours [Darbe % EPO]     Favours [Placebo or None]

**Analysis 3.3. Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 3 BSID-III composite social/emotional score at 18 to 22 months.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome: 3 BSID-III composite social/emotional score at 18 to 22 months

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 56 | 100.9 (19.3) | 24 | 96.7 (19.4) | | 100.0 % | 4.20 [ -5.06, 13.46 ] |
| **Total (95% CI)** | **56** | | **24** | | | **100.0 %** | **4.20 [ -5.06, 13.46 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.89 (P = 0.37) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100  -50  0  50  100
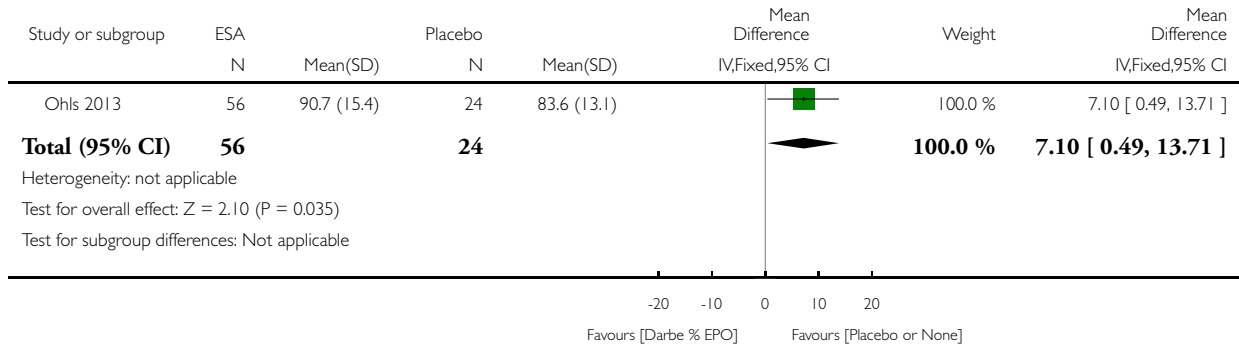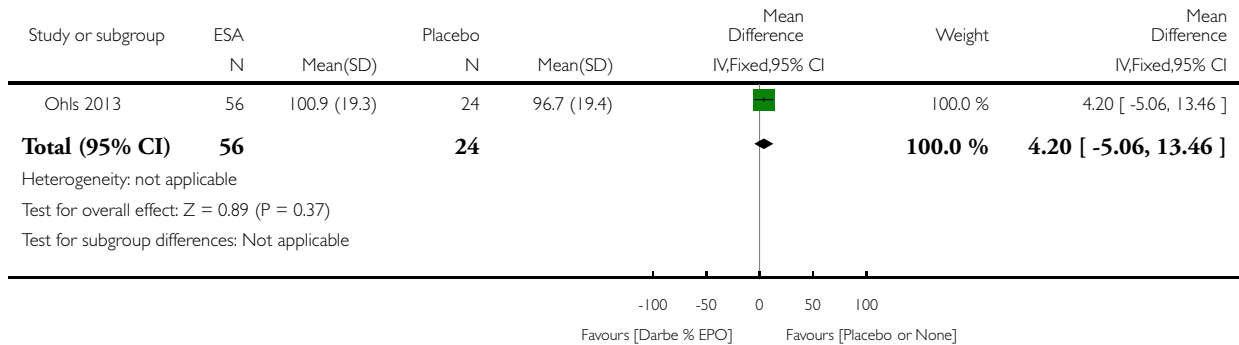
Favours [Darbe % EPO]     Favours [Placebo or None]

**Analysis 3.4. Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 4 OP score at 18 to 24 months.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome: 4 OP score at 18 to 24 months

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 56 | 2.6 (0.7) | 24 | 2.2 (1) | | 100.0 % | 0.40 [ -0.04, 0.84 ] |
| **Total (95% CI)** | **56** | | **24** | | | **100.0 %** | **0.40 [ -0.04, 0.84 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.78 (P = 0.075)

Test for subgroup differences: Not applicable

-4   -2   0   2   4
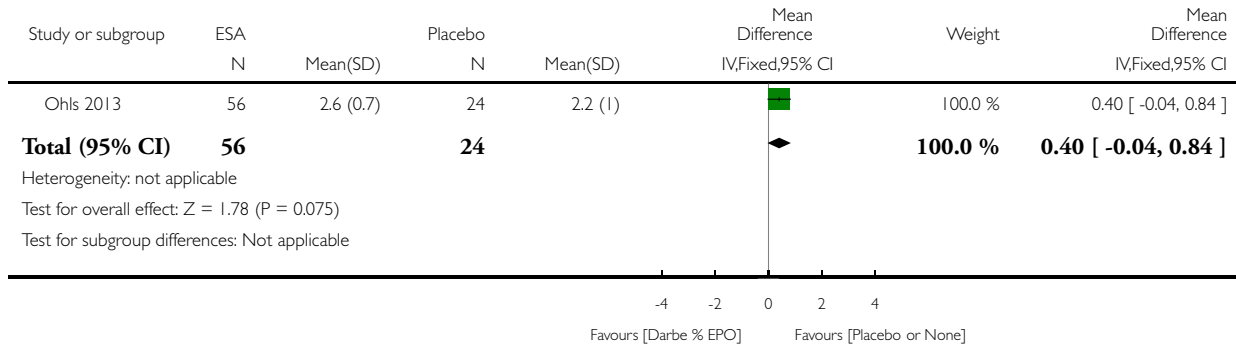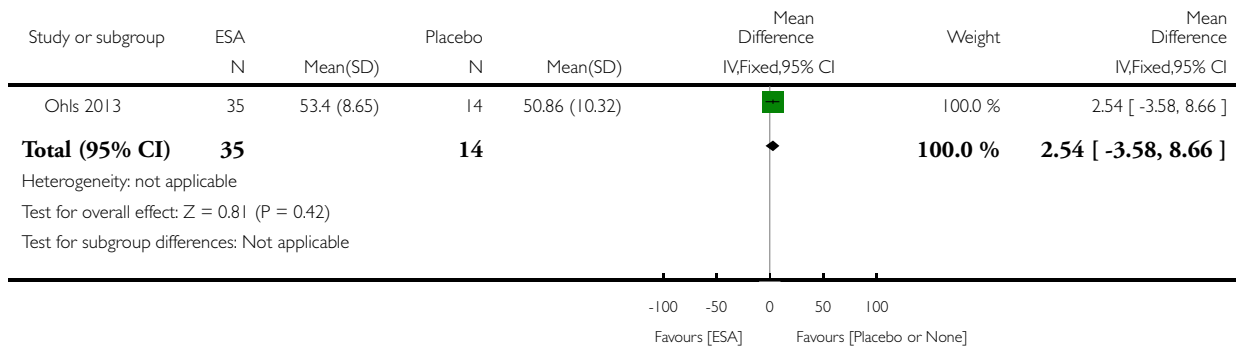
Favours [Darbe % EPO]          Favours [Placebo or None]

**Analysis 3.5. Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 5 BASC-2 composite scores at 3.5 to 4 years - adaptive skills.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome: 5 BASC-2 composite scores at 3.5 to 4 years - adaptive skills

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 35 | 53.4 (8.65) | 14 | 50.86 (10.32) | | 100.0 % | 2.54 [ -3.58, 8.66 ] |
| **Total (95% CI)** | **35** | | **14** | | | **100.0 %** | **2.54 [ -3.58, 8.66 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable

-100   -50   0   50   100

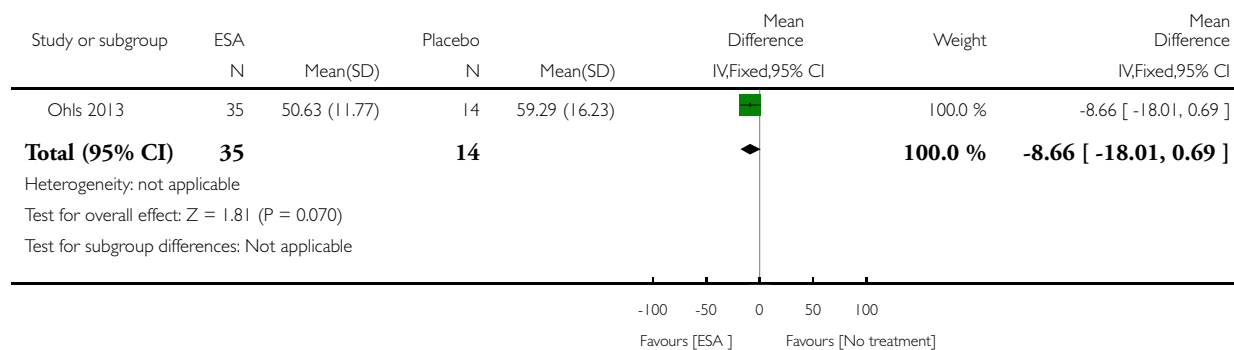Favours [ESA]          Favours [Placebo or None]

**Analysis 3.6.    Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 6 BASC-2 composite scores at 3.5 to 4 years - behaviour symptoms.**

Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:    3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome:    6 BASC-2 composite scores at 3.5 to 4 years - behaviour symptoms

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 35 | 50.63 (11.77) | 14 | 59.29 (16.23) | | 100.0 % | -8.66 [ -18.01, 0.69 ] |
| **Total (95% CI)** | **35** | | **14** | | | **100.0 %** | **-8.66 [ -18.01, 0.69 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.81 (P = 0.070) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100    -50    0    50    100

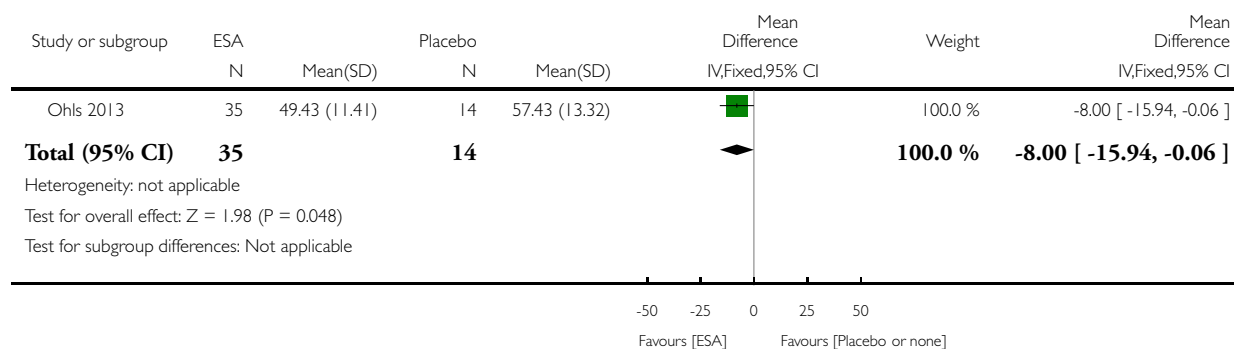Favours [ESA ]        Favours [No treatment]

**Analysis 3.7.    Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 7 BASC-2 composite score at 3.5 to 4 years - externalising problems.**

Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:    3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome:    7 BASC-2 composite score at 3.5 to 4 years - externalising problems

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 35 | 49.43 (11.41) | 14 | 57.43 (13.32) | | 100.0 % | -8.00 [ -15.94, -0.06 ] |
| **Total (95% CI)** | **35** | | **14** | | | **100.0 %** | **-8.00 [ -15.94, -0.06 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.98 (P = 0.048) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-50    -25    0    25    50

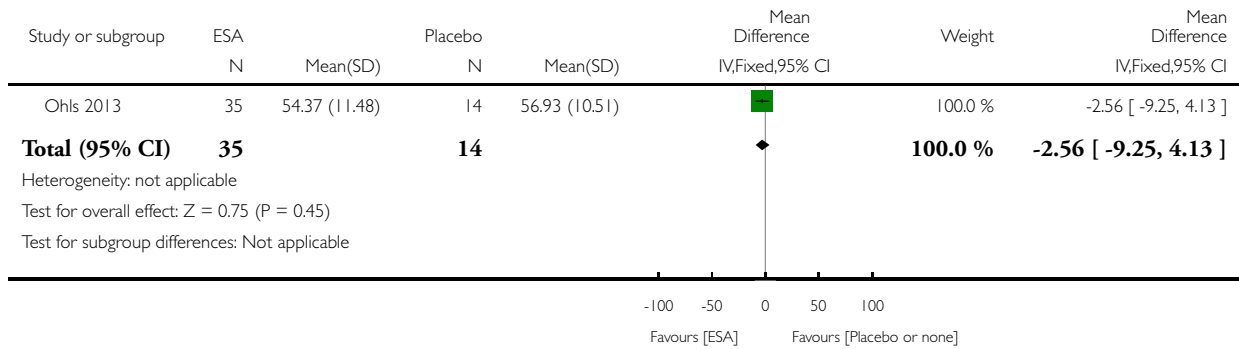Favours [ESA]        Favours [Placebo or none]

**Analysis 3.8.   Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 8 BASC-2 composite scores at 3.5 to 4 years - internalising problems.**

Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

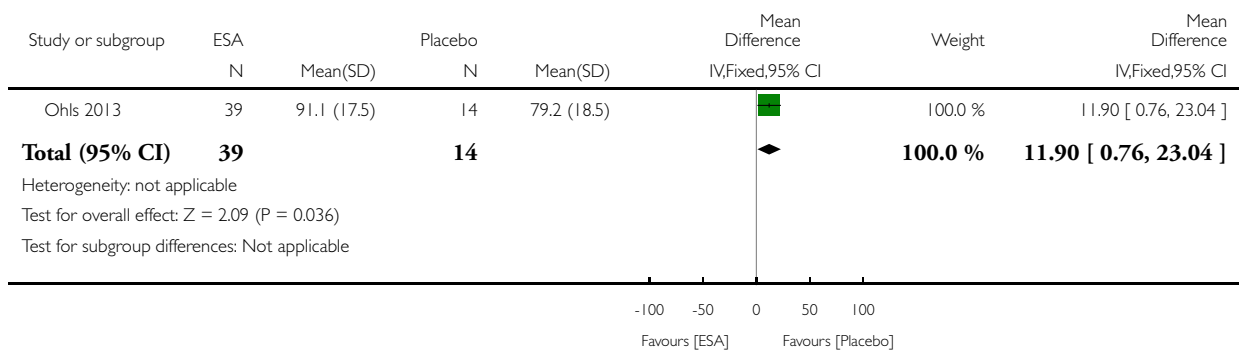Outcome:   8 BASC-2 composite scores at 3.5 to 4 years - internalising problems

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 35 | 54.37 (11.48) | 14 | 56.93 (10.51) | | 100.0 % | -2.56 [ -9.25, 4.13 ] |
| **Total (95% CI)** | **35** | | **14** | | | **100.0 %** | **-2.56 [ -9.25, 4.13 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.75 (P = 0.45) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100  -50  0  50  100

Favours [ESA]          Favours [Placebo or none]

---

**Analysis 3.9.   Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 9 WPPSI-III FSIQ at 3.5 to 4 years of age.**
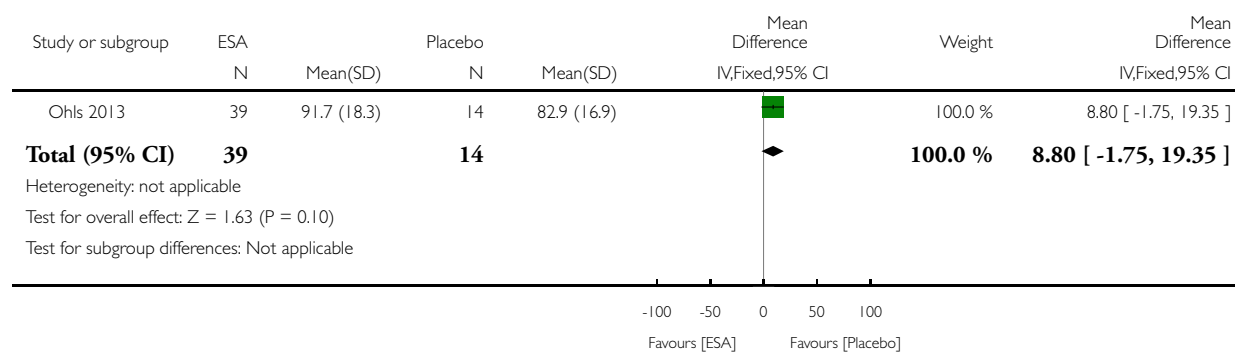
Review:   Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:   3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome:   9 WPPSI-III FSIQ at 3.5 to 4 years of age

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 39 | 91.1 (17.5) | 14 | 79.2 (18.5) | | 100.0 % | 11.90 [ 0.76, 23.04 ] |
| **Total (95% CI)** | **39** | | **14** | | | **100.0 %** | **11.90 [ 0.76, 23.04 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.09 (P = 0.036) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100  -50  0  50  100
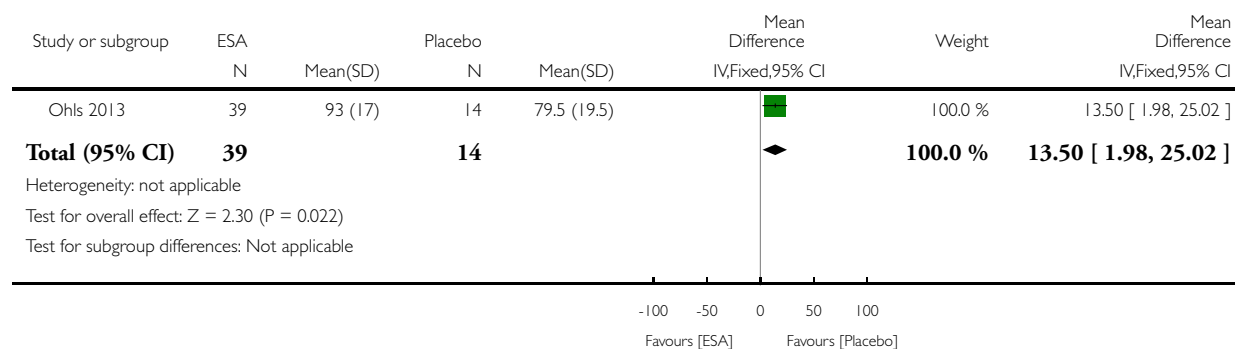
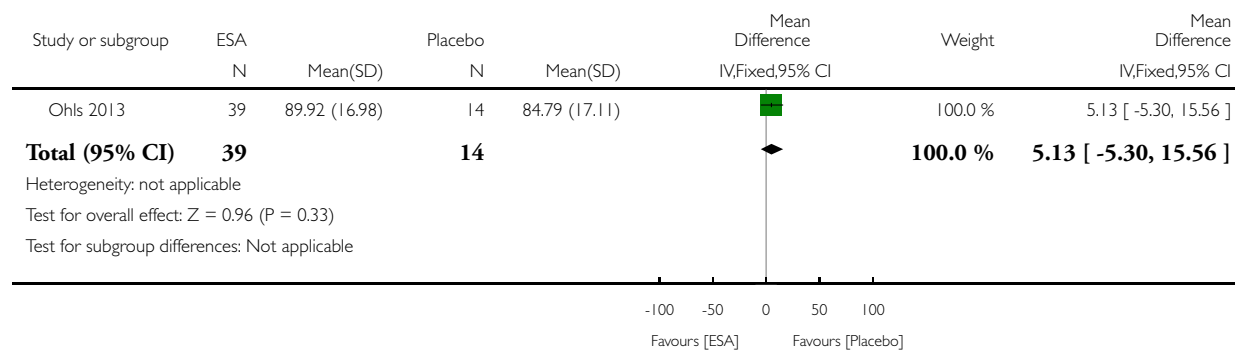Favours [ESA]          Favours [Placebo]

**Analysis 3.10. Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 10 WPPSI-III VIQ at 3.5 to 4 years of age.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome: 10 WPPSI-III VIQ at 3.5 to 4 years of age

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 39 | 91.7 (18.3) | 14 | 82.9 (16.9) | | 100.0 % | 8.80 [ -1.75, 19.35 ] |
| **Total (95% CI)** | **39** | | **14** | | | **100.0 %** | **8.80 [ -1.75, 19.35 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.63 (P = 0.10) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

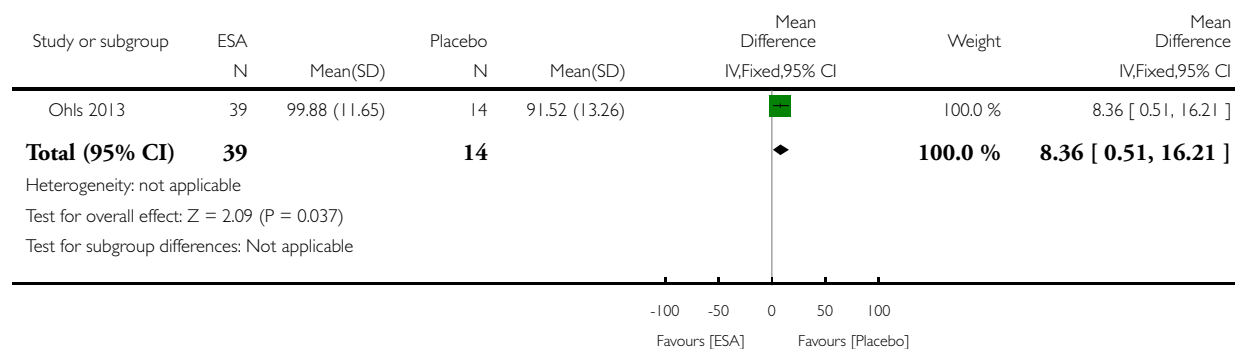-100    -50    0    50    100

Favours [ESA]    Favours [Placebo]

**Analysis 3.11. Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 11 WPPSI-III PIQ at 3.5 to 4 years of age.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome: 11 WPPSI-III PIQ at 3.5 to 4 years of age

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 39 | 93 (17) | 14 | 79.5 (19.5) | | 100.0 % | 13.50 [ 1.98, 25.02 ] |
| **Total (95% CI)** | **39** | | **14** | | | **100.0 %** | **13.50 [ 1.98, 25.02 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.30 (P = 0.022) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

-100    -50    0    50    100
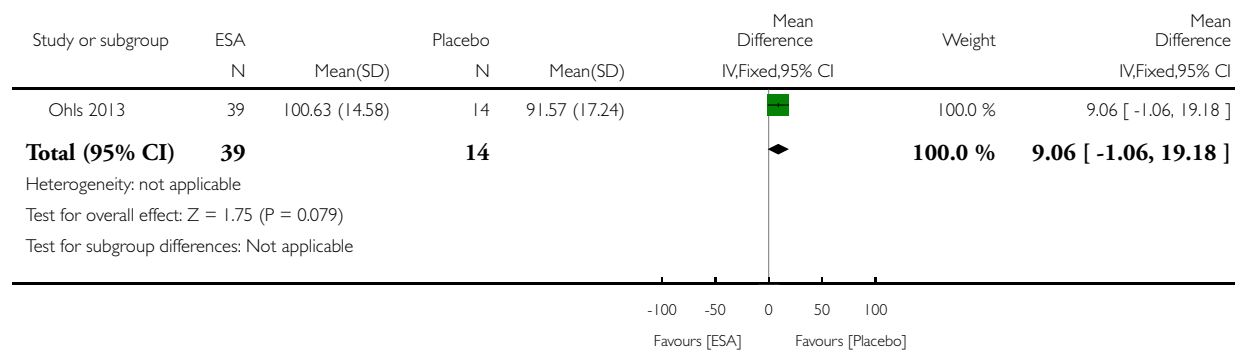
Favours [ESA]    Favours [Placebo]

**Analysis 3.12. Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 12 WPPSI-III GLC at 3.5 to 4 years of age.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome: 12 WPPSI-III GLC at 3.5 to 4 years of age

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 39 | 89.92 (16.98) | 14 | 84.79 (17.11) | | 100.0 % | 5.13 [ -5.30, 15.56 ] |
| **Total (95% CI)** | **39** | | **14** | | | **100.0 %** | **5.13 [ -5.30, 15.56 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.96 (P = 0.33)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
         Favours [ESA]   Favours [Placebo]
```

**Analysis 3.13. Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 13 Executive function at 3.5 to 4 years.**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome: 13 Executive function at 3.5 to 4 years

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 39 | 99.88 (11.65) | 14 | 91.52 (13.26) | | 100.0 % | 8.36 [ 0.51, 16.21 ] |
| **Total (95% CI)** | **39** | | **14** | | | **100.0 %** | **8.36 [ 0.51, 16.21 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 2.09 (P = 0.037)

Test for subgroup differences: Not applicable

```
        -100   -50    0    50   100
         Favours [ESA]   Favours [Placebo]
```

**Analysis 3.14.   Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 14 Working memory at 3.5 to 4 years.**
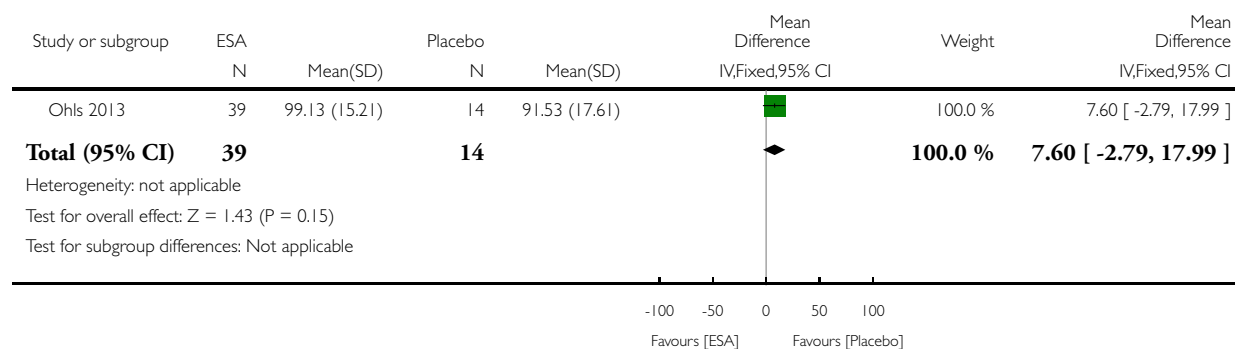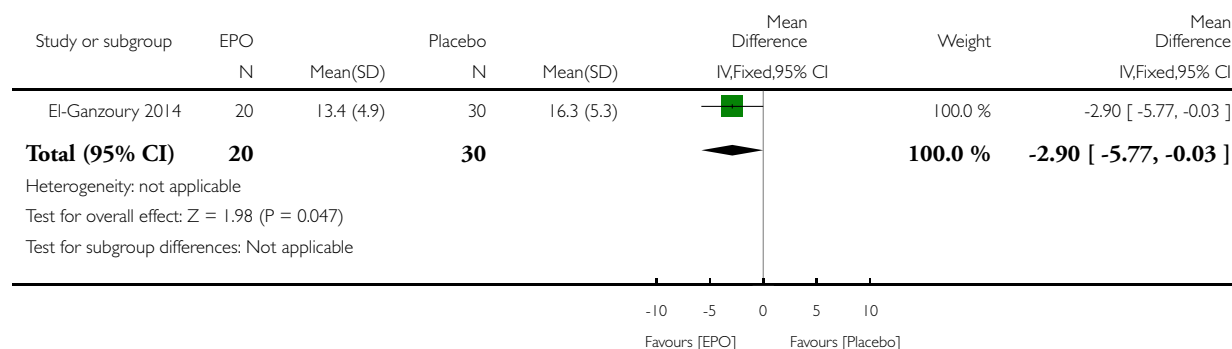
Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:    3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome:    14 Working memory at 3.5 to 4 years

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 39 | 100.63 (14.58) | 14 | 91.57 (17.24) | | 100.0 % | 9.06 [ -1.06, 19.18 ] |
| **Total (95% CI)** | **39** | | **14** | | | **100.0 %** | **9.06 [ -1.06, 19.18 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.75 (P = 0.079) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
                    -100   -50    0    50   100
                    Favours [ESA]    Favours [Placebo]
```

**Analysis 3.15.   Comparison 3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment, Outcome 15 Inhibition at 3.5 to 4 years.**

Review:    Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison:    3 Darbepoetin alfa or erythropoietin (erythropoiesis-stimulating agents - ESAs) versus placebo or no treatment

Outcome:    15 Inhibition at 3.5 to 4 years

| Study or subgroup | ESA | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Ohls 2013 | 39 | 99.13 (15.21) | 14 | 91.53 (17.61) | | 100.0 % | 7.60 [ -2.79, 17.99 ] |
| **Total (95% CI)** | **39** | | **14** | | | **100.0 %** | **7.60 [ -2.79, 17.99 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.43 (P = 0.15) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

```
                    -100   -50    0    50   100
                    Favours [ESA]    Favours [Placebo]
```

**Analysis 4.1. Comparison 4 Erythropoietin versus placebo to improve feeding intolerance, Outcome 1 Time to achieve full enteral feeding (days).**

Review: Early erythropoiesis-stimulating agents in preterm or low birth weight infants

Comparison: 4 Erythropoietin versus placebo to improve feeding intolerance

Outcome: 1 Time to achieve full enteral feeding (days)

| Study or subgroup | EPO | | Placebo | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| El-Ganzoury 2014 | 20 | 13.4 (4.9) | 30 | 16.3 (5.3) | ▣ | 100.0 % | -2.90 [ -5.77, -0.03 ] |
| **Total (95% CI)** | **20** | | **30** | | ◆ | **100.0 %** | **-2.90 [ -5.77, -0.03 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.98 (P = 0.047)

Test for subgroup differences: Not applicable

```
        -10    -5     0     5    10
     Favours [EPO]      Favours [Placebo]
```

# ADDITIONAL TABLES

**Table 1. Transfusion guidelines**

| Reference | Indications |
|---|---|
| Arif 2005 | Infants with Hgb concentrations < 7 g/dL and with a reticulocyte count lower than < 100,000/µL or Hgb concentrations < 8 g/dL having bradycardia, tachypnoea, or apnoea, or who were not able to gain weight despite adequate calorie intake, were chosen as candidates for blood transfusion |
| Avent 2002 | Infants received blood transfusions if they met the following criteria: 1. Hgb of 10 g/dL and 1 of the following: (i) an oxygen requirement greater than 30%; (ii) less than 1250 grams body weight 2. Hgb < 8 g/dL and 1 of the following: (i) 3 or more episodes of apnoea (respiration absent for 20 seconds) or bradycardia (heart rate < 100 beats/min) in a 24-hour period not due to other causes and not responsive to methylxanthine treatment; (ii) fractional inspired oxygen concentrations increasing by > 10% per week; and (iii) tachycardia (> 170 beats/min) or tachypnoea (> 70 breaths/min) sustained over a 24-hour period associated with acute cardiac decompression |
| Carnielli 1992 | Infants were transfused during the first week of life with packed erythrocytes if the Hct level was < 42% or 36%, depending on whether or not the patient was receiving supplemental oxygen. After the first week of life, indications for transfusions were Hct < 36% for oxygen-dependent patients and 32% if breathing room air. Anaemia was the only indication for giving packed erythrocytes to all infants |

**Table 1. Transfusion guidelines** (*Continued*)

| | |
|---|---|
| Carnielli 1998 | Infants received transfusions of packed cells during the first week of life if their peripheral Hct (heel stick) was < 42% or 36%, depending on whether or not the patient was receiving supplemental oxygen. After the first week of life, indications for transfusion were Hct < 36% for oxygen-dependent patients and 32% if in room air. Hct concentrations for red blood cell transfusions for blood obtained from venipuncture or arterial samples were 4% lower than the above mentioned values (38% and 32% for oxygen-dependent and non-oxygen-dependent patients in the first week, and 0.32 and 0.28 thereafter). All infants received dedicated units of red blood cells |
| Chang 1998 | Transfusion guidelines not provided |
| El-Ganzoury 2014 | Transfusion guidelines not provided |
| Fauchère 2008 | Transfusion guidelines not provided |
| Fauchère 2015 | Transfusion guidelines not provided |
| Haiden 2005 | Infants were transfused at Hct < 20%: 1. if asymptomatic with reticulocytes < 100,000/μL<br><br>Infants were transfused at Hct < 30%:<br>1. if receiving < 35% supplemental hood oxygen<br>2. if on CPAP or mechanical ventilation with mean air way pressure < 6 cmH$_2$O<br>3. if significant apnoea and bradycardia are noted (> 9 episodes in 12 hours or 2 episodes in 24 hours requiring bag and mask ventilation) while receiving therapeutic doses of methylxanthines<br>4. if heart rate > 180 beats/min or respiratory rate > 80 breaths/min persists for 24 hours<br>5. if weight gain < 10 g/d is observed over 4 days while receiving > 100 kcal/kg/d<br>6. if undergoing surgery<br><br>Transfuse for Hct < 35%<br>1. if receiving > 35% supplemental hood oxygen<br>2. if intubated on CPAP or mechanical ventilation with mean airway pressure > 6 to 8 cmH$_2$O<br>Do not transfuse:<br>1. to replace blood removed for laboratory tests alone<br>2. for low Hct alone |
| He 2008 | Transfusion guidelines are not reported in the English abstract of this study. We have requested the full text in Chinese from trial authors |
| Khatami 2008 | "Guidelines for red-cell transfusions were based on the relatively strict existing policy in the nursery which was used to administer transfusions during the study period" |
| Kremenopoulos 1997A | Transfusions were ordered by the clinicians caring for each infant without consulting the investigators, based on general guidelines for erythrocyte transfusions. According to these guidelines, neonates who were well received transfusions if their hematocrit was < 30% during the third week, < 25% during the fourth week, and < 23% after the first month of life, combined with signs referable to their anaemia, such as poor weight gain, episodes of persistent bradycardia or tachycardia, and apnoea. Neonates with severe respiratory disease (bronchopulmonary dysplasia), particularly those requiring oxygen and/or ventilator support, were given transfusions to maintain their hematocrit level at > 40% |

**Table 1. Transfusion guidelines**  (*Continued*)

| Kremenopoulos 1997B | See Kremenopoulos 1997A, |
|---|---|
| Lauterbach 1995 | Transfusion was given when the Hct level reached 28% and if clinical symptoms of tachypnoea, tachycardia, and bradycardia were present at Hct of 0.32 |
| Lima-Rogel 1998 | According to criteria published by Klaus and Fanaroff (see text for more info) |
| Maier 1994 | Infants who were receiving ventilation or who were less than 2 weeks old and had signs of anaemia were given transfusions if their Hct fell below 40%, their Hgb concentration fell below 14 g/dL (8.7 mmol/L), or blood samples totaling at least 9 mL/kg had been obtained from them since their previous transfusion. Spontaneously breathing infants, more than 2 weeks old, whose $FiO_2$ was < 0.40, were given transfusions if they had signs of anaemia and their Hct fell below 32% and their Hgb concentration below 11 g/dL (6.8 mmol/L); if they had signs of anaemia, corresponding cutoff values were 27% and 9 g/dL (5.6 mmol/L) |
| Maier 2002 | Infants with artificial ventilation or > 40% of inspired oxygen were not transfused unless Hct dropped below 0.40.<br>Spontaneously breathing infants were not transfused unless Hct dropped below 0.35 during the first 2 weeks of life, 0.30 during the third to fourth weeks, and 0.25 thereafter. Transfusion was allowed when life-threatening anaemia or hypovolaemia was assumed by the treating neonatologist, or surgery was planned. Twelve of the 14 centres used satellite packs of the original red cell pack to reduce donor exposure |
| Meister 1997 | Infants more than 2 weeks old who had been breathing spontaneously and whose $FiO_2$ was less than 0.40 were given transfusions if they had signs of anaemia and their Hct fell below 11 g/dL (6.8 mmol/L); if they had no signs of anaemia, corresponding cutoff values were 27% and 9 g/dL (5.6 mmol/L) |
| Meyer 2003 | Indications for transfusions were:<br>1. Hct of 36% to 40% and critically ill with requirement for oxygen > 45% via CPAP; ventilation (mean airway pressure > 10 cmH$_2$O); severe sepsis; active bleeding<br>2. Hct of 31% to 35% and requirement for oxygen (up to 45%) via CPAP; ventilation (mean airway pressure 7 to 10 cmH$_2$O)<br>3. Hct of 21% to 30% and gain less than 10 g/d averaged over 1 week; experienced at least 10 to 12 apneic or bradycardic episodes in 12 hours or 2 or more such episodes requiring bag and mask ventilation within a 24-hour period, not owing to other causes and not responsive to methylxanthine treatment; had a sustained tachycardia (> 170 beats/min) or tachypnoea (> 70/min) per 24 hours and not attributable to other causes; developed cardiac decompensation secondary to a clinically apparent patent ductus arteriosus; positive-pressure ventilation on low settings (mean airway pressure < 7 cmH$_2$O) or nasal CPAP; those requiring surgery<br>4. Hct 20% and reticulocyte count < $100 \times 10^9$/L |
| Obladen 1991 | Indications for transfusion of packed red cells:<br>1. If venous Hct < 42%, Hgb < 14 g/dL or > 9 mL/kg blood sampled since last transfusion transfuse if infant is ventilated or requires $FiO_2$ > 0.40<br>2. If age 1 to 2 weeks and symptoms of anaemia (apneic spells, distended abdomen, failure to thrive), transfuse if venous Hct < 36%, Hgb < 12 g/dL, or > 9 mL/kg blood sampled since last transfusion.<br>3. If age 3 to 5 weeks and symptoms of anaemia (apneic spells, distended abdomen, failure to thrive), transfuse if venous Hct < 30%, Hgb < 10 g/dL or > 9 mL/kg blood sampled since last transfusion.<br>4. If no symptoms of anaemia, transfuse at any age if venous Hct is < 27%, Hgb < 9 g/dL |

**Table 1. Transfusion guidelines** (*Continued*)

| | |
|---|---|
| Ohls 1995 | Transfusions were given during the first 3 weeks of life if Hct was < 33%, and if the infant had 1 or more symptoms thought to be due strictly to anaemia. Symptoms were defined as tachycardia (heart rate > 160 beats/min, calculated as the average of all heart rates recorded by the bedside nurse during the preceding 24-hour period), an increasing oxygen requirement (an increase in fraction of inspired oxygen of > 0.20 during a 24-hour period), "lethargy" as assessed by the primary caregiver, or an increase in the number of episodes of bradycardia requiring stimulation to increase the heart rate from less than 60 beats/min (an increase of such episodes by 3 or more per day). Infants in both groups whose Hct were > 33% and yet whose phlebotomy losses exceeded 10 mL/kg body weight received an infusion of 5% albumin, administered in aliquots of not less than 10 mL/kg. Infants were not given transfusions if they were free of symptoms, even if Hct fell to < 33% |
| Ohls 1997 | Transfusions were administered in both groups according to standardised transfusion criteria: For infants requiring mechanical ventilation, transfusions were given if Hct fell below 33%. For infants not receiving ventilatory support, transfusions were given if Hct fell below 28%, and if the infant was experiencing symptoms. Symptoms were defined as tachycardia (heart rate > 160 beats/min, calculated as the average of all heart rates recorded by the bedside nurse over the preceding 24-hour period), an increasing oxygen requirement (an increase in $FiO_2$ of > 0.20 over a 24-hour period, or an elevated lactate level (> 2.5 mmol/L). In some instances, a new donor would be used each day for the newborn intensive care unit (University of Florida), and in other instances, a unit would be dedicated to a single infant for the life of the unit (University of New Mexico and University of Utah) |
| Ohls 2001A | If Hct ≤ 35%/Hgb ≤ 11 g/dL, transfuse infants requiring moderate or significant mechanical ventilation (MAP > 8 $cmH_2O$ and $FiO_2$ > 0.4). <br> If Hct ≤ 30%/Hgb ≤ 10 g/dL, transfuse infants requiring minimal respiratory support (any mechanical ventilation or endotracheal/nasal CPAP > 6 $cmH_2O$ and $FiO_2$ ≤ 0.4). <br> If Hct ≤ 25%/Hgb ≤ 8 g/dL, transfuse infants not requiring mechanical ventilation but who are on supplemental $O_2$ or CPAP with an $FiO_2$ ≤ 0.4 and in whom 1 or more of the following is present: 24 hours of tachycardia (180 beats/min) or tachypnoea (>80 breaths/min), an increased oxygen requirement from the previous 48 hours, defined as 4-fold increase in nasal cannula flow (i.e. 0.25 L/min to 1 L/min), or an increase in nasal CPAP of 20% from the previous 48 hours (i.e. 5 cm to 6 $cmH_2O$), weight gain < 10 g/kg/d over the previous 4 days while receiving 100 kcal/kg/d, increase in episodes of apnoea and bradycardia (> 9 episodes in a 24-hour period or 2 episodes in 24 hours requiring bag-mask ventilation) while receiving therapeutic doses of methylxanthines, undergoing surgery. <br> If Hct ≤ 25%/Hgb ≤ 7 g/dL, transfuse asymptomatic infants with absolute reticulocyte count < 100,000 cells/μL |
| Ohls 2001B | See Ohls 2001A. |
| Ohls 2013 | The PRBC volume transfused was based on Hct/Hgb, respiratory support, and/or symptoms. <br> If Hct ≤ 30/Hgb ≤ 10 and the infant required moderate/significant ventilation (MAP > 8 $cmH_2O$ and $FiO_2$ > 0.4), the PRBC volume to be transfused was 15 to 20 mL/kg. <br> If Hct ≤ 25/Hgb ≤ 8 and the infant required minimal respiratory support (any mechanical ventilation with $FiO_2$ ≤ 0.4, or CPAP > 6 $cmH_2O$ and $FiO_2$ ≤ 0.4), the PRBC volume to be transfused was 20 mL/kg. <br> If Hct was ≤ 20/Hgb ≤ 7 and the infant required supplemental oxygen or CPAP with $FiO_2$ ≤ 0.4, and at least 1 of the following: <br> 1. ≥ 24 hours of tachycardia (heart rate > 180) or tachypnoea (RR > 60) <br> 2. doubling of the oxygen requirement from the previous 48 hours <br> 3. lactate ≥ 2.5 mEq/L or an acute metabolic acidosis (pH 7.20) |

**Table 1. Transfusion guidelines** *(Continued)*

| | |
|---|---|
| | 4. weight gain < 10 g/kg/d over the previous 4 days while receiving ≥ 120 kcal/kg/d<br>5. undergoing surgery within 24 hours<br>PRBC volume to be transfused was 20 mL/kg.<br>If Hct ≤18/Hgb ≤ 6 and the infant was asymptomatic and absolute reticulocyte count (ARC) was < 100, 000 cells/μL, the PRBC volume to be transfused was 20 mL/kg |
| Peltoniemi 2017 | Infants with the following respiratory needs received 10 to 15 mL/kg of RBC volume based on Hct:<br>1. < 0.40 mechanical ventilation, $FiO_2$ > 0.40<br>2. < 0.35 mechanical ventilation, $FiO_2$ < 0.40, or use of nasal CPAP at the age of < 2 weeks<br>3. < 0.30 supplemental oxygen, nasal CPAP, or apneas during later neonatal period<br>4. < 0.25 no symptoms during later neonatal period |
| Qiao 2017 | Transfusion guidelines not reported |
| Salvado 2000 | Preterm infants with Hct < 20%<br>Preterm infants with Hct < 30% when presenting with frequent apneas, or tachycardia > 180 beats/min, or requiring surgery |
| Song 2016 | Blood transfusion criteria followed strict clinical criteria as used by Vázquez López 2011. |
| Soubasi 1993 | Neonates who were well were transfused if their Hct was < 25% combined with signs referable to their anaemia, such as poor weight gain, persistent episodes of bradycardia or tachypnoea, and apnoea. Neonates with severe respiratory disease (BPD), particularly those requiring oxygen and/or ventilator support, received transfusions to maintain Hct level at > 40% |
| Soubasi 1995 | Infants who were receiving mechanical ventilation or who were less than 2 weeks old were given transfusion if their Hct fell below 40%. Spontaneously breathing infants more than 2 weeks old whose $FiO_2$ was less than 0.35 were given transfusion if they had signs of anaemia and their Hct fell below 30%; if they had no signs of anaemia, transfusion was given if Hct fell below 0.25. Growing, asymptomatic infants were transfused if Hct fell below 20%. Signs of anaemia included tachycardia, (> 170 beats/min) or tachypnoea (> 70/min) sustained over a 24-hour period or associated with acute cardiac decompensation; recurrent apnoea (respirations absent for 20 seconds) or bradycardia (heart rate < 100 beats/min) in a 24-hour period not due to other causes and not responsive to methylxanthine treatment; an increase in fractional oxygen requirement by 20% or more over a 24-hour period; or weight gain < 10 g/d averaged over a 1-week period while on adequate caloric intake |
| Soubasi 2000 | Neonates were transfused when Hct was < 20%, if they were asymptomatic, or < 30% if they were receiving $O_2$ < 0.35 and/or unexplained breathing disorders combined with signs referable to their anaemia, such as poor weight gain, episodes of persistent bradycardia or tachycardia |
| Yasmeen 2012 | After discharge from hospital, any patient with Hgb level ≤ 7 g/dL was readmitted to the hospital and managed with packed red cell transfusion |
| Yeo 2001 | Infants who were receiving mechanical ventilation or who were less than 2 weeks old were given transfusion if their Hct fell below 40%. Spontaneously breathing infants more than 2 weeks old whose $FiO_2$ was less than 35% were given transfusion if they had signs of anaemia and their Hct fell below 30%; if they had no signs of anaemia, transfusion was given if Hct fell below 25%. Growing, asymptomatic infants were transfused if Hct fell below 20%. Signs of anaemia included tachycardia, (> 170 beats/min) or tachypnoea (> 70/min) sustained over a 24-hour period or associated with acute cardiac decompression; recurrent apnoea |

Table 1. Transfusion guidelines  (*Continued*)

|  | (respirations absent for 20 seconds) or bradycardia (heart rate < 100 beats/min) in a 24-hour period not due to other causes and not responsive to methylxanthine treatment; increased fractional oxygen requirement by 20% or more over a 24-hour period; or weight gain < 10 g/d averaged over a 1-week period while on adequate caloric intake |
|---|---|

ARC: absolute reticulocyte count.
BPD: bronchopulmonary dysplasia.
CPAP: continuous positive airway pressure.
FiO$_2$: fraction of inspired oxygen.
Hct: hematocrit.
Hgb: haemoglobin.
MAP: mean airway pressure.
PRBC: packed red blood cells.
RBC: red blood cell.
RR: respiratory rate.

# A P P E N D I C E S

## Appendix 1. Standard search method

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)
CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
The Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

## Appendix 2. Previous search method

For previous versions of this review, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2013, Issue 7) was searched to identify relevant randomised and quasi-randomised controlled trials. MEDLINE was searched for relevant articles (from 1966 to July 2013) using the following MeSH terms or text words: (exp Erythropoietin/OR erythropoietin:.mp. OR rhuepo.mp.) AND (anaemia/OR exp anaemia, neonatal/) AND (blood transfusion/OR blood component transfusion/OR erythrocyte transfusion/) AND (infant, newborn/OR infant, low birth weight/OR infant, very low birth weight/OR infant, premature/OR exp Infant, Premature, Diseases) OR (neonate: OR prematur*: OR newborn:).mp. OR newborn infant [age limit]) AND (clinical trial.pt. OR Randomized Controlled Trials/OR (random: OR rct OR rcts OR blind OR blinded OR placebo:).mp. OR (review.pt. OR review, academic.pt.) AND human. Embase (from 1980 to July 2013) and CINAHL (1982 to July 2013) were searched using the following MeSH terms or text words: (Erythropoietin/OR erythropoietin: OR epo OR epogen OR epoetin: OR (rhuepo).mp. AND (anaemia/ OR exp anaemia, neonatal/) AND (blood transfusion/OR exp blood component transfusion/OR erythrocytes/) AND exp Infant,

Premature, Diseases/OR infant, newborn/OR infant, low birth weight/OR infant, very low birth weight/OR infant, premature/OR (neonate: OR newborn: OR prematur*:).mp. OR newborn infant [age limit]. No language restrictions were applied.

For this review update, the same search strategy was applied in July 2013.

**Appendix 3. Risk of bias tool**

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality (to meet the validity criteria) of trials. For each trial, we sought information regarding the method of randomisation, and blinding and reporting of all outcomes of all infants enrolled in the trial. We assessed each criterion as low, high, or unclear risk. Two review authors separately assessed each study. We resolved any disagreement by discussion. We added this information to the 'Characteristics of included studies' table. We evaluated the following issues and entered the findings into the risk of bias table.

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:

a. low risk (any truly random process, e.g. random number table; computer random number generator);

b. high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or

c. 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:

a. low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

b. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or

c. 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 classes of outcomes. We categorised the methods as:

a. low risk, high risk, or unclear risk for participants; and

b. 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 classes of outcomes. We categorised the methods as:

a. low risk for outcome assessors;

b. high risk for outcome assessors; or

c. 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 randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

a. low risk (< 20% missing data);

b. high risk (≥ 20% missing data); or

c. 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. We assessed the methods as:

a. low risk (when it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);

b. high risk (when not all the study's prespecified outcomes have been reported; when one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; when study fails to include results of a key outcome that would have been expected to have been reported); or

c. unclear risk.

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

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

a. low risk;

b. high risk; or

c. unclear risk.

If needed, we explored the impact of the level of bias by undertaking sensitivity analyses.

# FEEDBACK

## Feedback from Dr. Robin Ohls, 27 March 2013

### Summary

This unscheduled update was initiated following feedback from Dr. Robin Ohls. Our inclusion of the study by Dr. Romagnoli and coworkers (Romagnoli 2000) in this review (early EPO review) was questioned by Dr. Ohls (Ohls 2013a), who suggested the study should be included in the 'Late EPO' review (New Reference). In addition, Dr. Ohls informed us that Bierer 2006 was a report of a subgroup of the Ohls 2001A study.

### Reply

We contacted Dr. Romagnoli, who informed us that the mean (± SD) age of infants when EPO treatment was started was 10 ± 1 days. We therefore moved the study to the 'Late EPO' review. It could not be ascertained from the published report that Bierer 2006 was a duplicate publication. We excluded Bierer 2006, as all outcomes were reported in Ohls 2001A.

### Contributors

Ohls, Romagnoli, Ohlsson, Aher.

# WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 6 December 2017 | Amended | Amended to correct misspellings of darbepoetin. |

# H I S T O R Y

Protocol first published: Issue 3, 2004

Review first published: Issue 3, 2006

| Date | Event | Description |
|---|---|---|
| 25 March 2017 | New search has been performed | This review was updated in March 2017. |
| 25 March 2017 | New citation required and conclusions have changed | For this update, we included erythropoietin (EPO)/darepoetin (erythropoiesis-stimulating agents - ESAs) as possible neuro protective agents and as agents protecting against necrotising enterocolitis. We provided additional information in the Background section to justify these inclusions. We changed the review title to "Early erythropoiesis-stimulating agents in preterm or low birth weight infants"<br><br>In the previous update, we included a post hoc analysis that examined results for retinopathy of prematurity (ROP) $\geq$ 3 for all available studies, regardless of the age of the infant at initiation of treatment with EPO. For this update, we excluded that analysis and corresponding references to studies that initiated EPO treatment beyond 7 days' postnatal age. We excluded post hoc analyses on the basis of study quality. No current evidence suggests that early EPO increases the risk of ROP<br><br>Promising evidence indicates that early ESAs may prevent necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), and periventricular leukomalacia (PVL), while improving long-term neurodevelopmental outcomes. Ongoing trials will prove whether this is the case |
| 19 July 2016 | Amended | We made minor edits. |
| 9 September 2013 | New citation required and conclusions have changed | We initiated this unscheduled update after receiving feedback from Dr. Robin Ohls. Dr. Ohls questioned our inclusion of the study by Dr. Romagnoli and coworkers (Romagnoli 2000) in this review (early erythropoietin (EPO) review) and suggested that this study should be included in the late EPO review (New Reference; Ohls 2013a). We contacted Dr. Romagnoli, who informed us that the mean ($\pm$ SD) age of infants at the start of EPO treatment was 10 $\pm$ 1 days. We therefore moved the study to the late EPO review. In addition, Dr. Ohls informed us that Bierer 2006 was a report on a subgroup of the Ohls 2001A study. It could not be ascertained from the published report that it was a duplicate publication. As Ohls 2001A reported |

all outcomes, we excluded Bierer 2006.

We conducted literature searches on 1 July 2013. We identified 2 new studies for inclusion (Yasmeen 2012; Ohls 2013), as well as 2 new studies for exclusion ( Saeidi 2012; Costa 2013).

As expected, when we excluded 2 studies (Romagnoli 2000; Bierer 2006) and added the results of 2 new studies (Yasmeen 2012; Ohls 2013), almost all point estimates and confidence intervals changed

The major difference was that the outcome of retinopathy of prematurity (ROP) stage $\geq$ 3 was no longer statistically significantly increased but remained a matter of concern as the typical risk ratio (RR) was 1.37 (95% confidence interval (CI) 0.87 to 2.17) with no heterogeneity ($I^2$ = 0%); the typical risk difference (RD) was 0.03 (95% CI -0.01 to 0.06) with low heterogeneity ($I^2$ = 29%).

Our decision to divide the EPO studies into early and late studies was based on initiation of EPO treatment at the cutoff of $\leq$ 7 days of age for early and > 7 days for late treatment with EPO. Although arbitrary, we chose this cutoff on the basis of previously published meta-analyses (Garcia 2002; Kotto-Kome 2004) to allow us to compare results of our reviews with those of previously published reviews

Concerns about a possibly increased risk of ROP remain, and because of the arbitrary cutoff age for early versus late EPO, we decided post hoc to perform a secondary analysis of data from all studies that reported on ROP (stage $\geq$ 3), regardless of age at initiation of EPO treatment. We included 3 studies from the late EPO review: Shannon 1995; Al-Kharfy 1996; and Romagnoli 2000. In these studies, investigators initiated treatment with EPO at 10 to 17 days; 10 ± 1 (SD) days; and 23 to 24 days, respectively. The outcome of ROP $\geq$ 3 was statistically significantly increased following EPO treatment initiated at any age during the neonatal period (typical RR 1.48, 95% CI 1.02 to 2. 13, P = 0.04 with no heterogeneity ($I^2$ = 0%); typical RD 0.03, 95% CI 0.00 to 0.06, P = 0.03 with moderate heterogeneity ($I^2$ = 50%); number needed to treat for an additional harmful outcome 33, 95% CI 17 to infinity)

When the Romagnoli 2000 study was moved to the late EPO review, the risk for ROP stage $\geq$ 3 was not statistically significantly increased in the late EPO review, but results showed a trend in the direction of increased risk (RR 1.73, 95% CI 0.92 to 3.24; RD 0.05, 95%

| | | CI -0.01 to 0.10; 3 trials enrolling 442 infants) (New Reference)<br>In the latest study by the Romagnoli group (Costa 2013), trial authors compared the use of early intravenous EPO vs subcutaneous EPO and reported that the incidence of stage ≥ 3 was high in both groups, at 16% and 14%, respectively (overall 15%), similar to the incidence of 17% in the Romagnoli 2000 study<br>Thus our concerns about increased risk of ROP ≥ 3 following EPO treatment remain |
|---|---|---|
| 1 July 2013 | New search has been performed | We conducted literature searches on 1 July 2013. |
| 2 May 2012 | New citation required but conclusions have not changed | This update identified several randomised controlled studies that were excluded, as they compared one EPO dosing regimen vs another, did not provide numbers randomised to EPO and placebo groups, or did not state the dose of EPO. Review authors identified cohort/case-control studies reporting on possibly increased risk of ROP following treatment with EPO and ROP<br>Review authors did not change the review conclusions. Studies using EPO for neuroprotection will be reviewed separately (Yu 2010) |
| 2 May 2012 | New search has been performed | This updates the review "Early erythropoietin for preventing red blood cell transfusions in preterm and/or low birth weight infants", which was published in the *Cochrane Database of Systematic Reviews*, Issue 3, 2006 (Ohlsson 2006), and updated in August 2009. |
| 21 August 2009 | New search has been performed | This updates the review "Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants", which was published in the *Cochrane Database of Systematic Reviews*, Issue 3, 2006 (Ohlsson 2006).<br>We have included 4 additional studies (adding 145 additional infants) in this review update. Studies using EPO for neuroprotection are emerging |

## CONTRIBUTIONS OF AUTHORS

Sanjay Aher (SA) and Arne Ohlsson (AO) contributed equally to all sections of the protocol for this review.

The literature search of databases was conducted with the help of an experienced librarian. Both review authors identified potentially eligible studies from the printouts and agreed on which trials should be included. Data collection forms were designed and agreed upon by the two review authors. Quality assessments were conducted and data were abstracted by both review authors independently and were compared. One review author (AO) entered the data into RevMan 5.3, and the other review author (SA) checked the data for accuracy. One review author (AO) wrote sections of the full review, and the other review author (SA) read these sections and made changes. Both review authors made changes after receiving feedback from the editors of the review group.

One review author (AO) conducted the July 2009 update of the review.

One review author (AO) conducted the May 2012 update of the review.

Both review authors (AO, SMA) conducted the June 2013 update of the review.

Both review authors (AO, SMA) conducted the March 2017 update of the review.

## DECLARATIONS OF INTEREST

None.

## SOURCES OF SUPPORT

### Internal sources

- Mount Sinai Hospital, Toronto, Canada.

### External sources

- No sources of support supplied

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol was published in 2004.

In the 2013 update, we included one study that used Darbe in one of the two treatment arms. The other arms used EPO and sham injection.

In the same update in 2013, we included the results of three studies in a post hoc analysis of stage $\geq$ 3 ROP from the late EPO review (treatment initiated at $\geq$ 8 days) that reported on this outcome. From the 2017 update, we excluded that analysis and the post hoc analyses on the basis of perceived study quality.

In the 2017 update, we included studies that were used to study EPO/Darbe for neuro protection and for improved feeding tolerance and prevention of NEC.

For the 2017 update, we changed the review title to "Early erythropoiesis-stimulating agents in preterm or low birth weight infants".

# INDEX TERMS

## Medical Subject Headings (MeSH)

Anemia, Neonatal [*prevention & control]; Darbepoetin alfa [*administration & dosage]; Enterocolitis, Necrotizing [prevention & control]; Erythrocyte Transfusion [*utilization]; Erythropoietin [*administration & dosage]; Hematinics [*administration & dosage]; Infant, Low Birth Weight [*blood]; Infant, Premature [*blood]; Retinopathy of Prematurity [prevention & control]

## MeSH check words

Humans; Infant, Newborn