Supplemental Methods

Data sources and searches: We searched the Cochrane central register of controlled trials (www.thecochranelibrary.com,throughMay 2017), Pub Med (www.ncbi.nlm.nih.gov,1966-May 2017), EMBASE (Excerpta Medica database via Ovid (http://ovidsp.tx.ovid.com1980-May 2017), CINAHL (Cumulative Index of Nursing and Allied Health Literature) via Ovid(http://ovidsp.tx.ovid.com,1980-May 2017) databases, proceedings of Pediatric Academic Society meetings (www.abstracts2view.com/pasall, 2000-May 2017) for studies reported from the earliest available online year of indexing until May 2017 using the keywords/MeSH terms ["preterm" OR "premature" OR "infant" OR "very low birth weight" OR "extremely low birth weight"] AND ["erythropoietin" OR "recombinant erythropoietin" OR "EPO"] AND "necrotizing enterocolitis". No restrictions were applied on study design or language. References of the obtained studies were reviewed to identify additional studies. The international trial registries and Australian Clinical Trials Registry were checked for ongoing/registered trials in this area. Grey literature was searched through the national technical information services (http://www.ntis.gov/), Open Grey (http://www.opengrey.eu/), and Trove (http://trove.nla.gov.au/) for articles that might not have been cited in the standard medical databases. Reviewers AA, HB, SR and SP conducted the literature search independently.

Study selection process: Reviewers AA and HB independently assessed the eligibility for selection of all studies identified using the pre-specified search strategy. Any disagreements were resolved by discussion among all reviewers.

Data extraction: Reviewers AA and HB independently completed a pre-specified data extraction form for all included studies. For dichotomous outcomes, the number of participants with the event and the number of participants analysed in each treatment group of each study were entered into the form. For continuous outcomes, we entered the mean and standard deviations (SD). Information about the study design and outcomes was verified by all reviewers. Any disagreements were discussed until consensus was achieved. If required, we planned to contact the investigators for clarification and/or additional data for analysis.

Risk of bias (ROB) in individual studies: We used the Cochrane Neonatal Review Group guidelines to assess the methodological quality of the included RCTs (1). For each trial, information was sought regarding the method of randomization, allocation concealment and blinding and reporting of all outcomes of all participants enrolled in the trial. Reviewers AA and HB separately assessed each study. Any disagreement was resolved by discussion among all reviewers.

Assessment of publication bias: This was assessed by a funnel plot (1).

Data synthesis: Meta-analysis was conducted using the Review manager 5·3 (Cochrane collaboration, Nordic Cochrane Centre, Copenhagen, Denmark) if pooling of data was possible, and justified. A fixed effect model (FEM; Mantel-Haenszel) was used as it is the preferred meta-analytic method in CNRG reviews (http://neonatal.cochrane.org/resources-review-authors accessed on 23 May 2017). Meta-analysis using random effects model (REM; DerSimonian and Laird) (2) was conducted to check consistency of the results.

Effect size was expressed as relative risk (RR) and 95% confidence interval (CI). Continuous outcomes were expressed as mean difference (MD) and 95% CI, statistical heterogeneity was assessed with the χ^2 test, and I^2 statistic, and by visual inspection of the forest plot (overlap of CIs). A p value < 0·1 on the χ^2 statistic was considered to indicate heterogeneity. I^2 values were interpreted according to the Cochrane handbook guidelines (3).

Quality and strength of evidence: These conclusions were based on the GRADE (grading of recommendations, assessment, development, and evaluation) system**.**

Supplemental Table 1: The characteristics of the included studies[1]

Study number	Study authors, year (References)	Participants	Intervention and Control	Primary Outcomes[2]	Secondary Outcomes[3]	Conclusions	Comments
1	Arif et al., 2005 (48)	Preterm infants <33 weeks,<1500g (*n*=292)	rhEPO (*n*=142, Dose: 200U/kg) administered twice a week subcutaneously from day 7 to 6 weeks of life; control (*n*=150)	(EPO group before and after intervention): serum erythropoietin levels: 11.3 ±6.1mU/ml* and 38.3 ±19.1mU/ml* before and at the fourth week of the study**. Reticulocyte counts: 146 ×106±28 $\times10^6$/ml*, and 122 ×106±27 $\times10^6$/ml*, at the fourth and seventh week of the study**. (EPO vs. no EPO): Hematocrit values**:31.2 ± 1.8* vs. 33.5 ± 1.6*. The need for packed cell transfusions 47% vs. 62.6% **.	(EPO vs. no EPO): WBC count at 6 months:9.8 ± 0·9* vs. 9.3 ± 1.6*,*P*<0.001, reticulocyte count: 77 ± 14*x10^6/ ml* vs. 76 ± 12*, *P*=0.502; mortality rate:14.6% vs. 13.3%, *P*>0.05; CLD: 4.2% vs. 3.3%; nosocomial infection: 19% vs. 23.3%; NEC: 4.9% vs. 4%; ROP: 23.9% vs. 26%, *P*> 0.05 for all.	rhEPO stimulates erythropoiesis in low birth weight premature newborns and decreases the transfusion needs for anaemia of prematurity	short duration of treatment
2	Bierer et al., 2006 (38)	Preterm infants birth weight <1000g (*n*=16)	Intravenous rhEPO (*n*=7, Dose: 400U/kg 3 times/week); placebo (*n*=9, sham injections) from 96 hours of life till 35 weeks PMA	(EPO vs. placebo): MDI: 96±11* vs. 78±7*; PDI: 87±13* vs. 80±7*	(EPO vs. placebo): NEC: 0/7 vs. 0/8¥; BPD: 5/7 vs. 8/8¥; ROP: 1/7 vs. 2/8¥; PDA: 4/7 vs. 3/8¥; IVH: 0/7 vs1/8¥; mortality: 0/7 vs. 1/9	EPO concentrations did not correlate with PDI or overall neurodevelopmental impairment.	Small sample size

3	Fauchere et al. , 2008 (39)	Preterm infants 24 0/7- 31 6/7 weeks (*n*=45)	rhEPO (*n*=30, Dose: 3000 U/kg) intravenously; placebo: 0.9% NaCl (*n*=15) at 3 to 6,12 to 18 and 36 to 42 hours after birth during a period of 10 min.	(EPO vs. Placebo): IVH: OR: 1.2; 95% CI: 0·130, 4.600; PVL:OR:0.18; 95% CI: 0.008, 1.300; ROP:OR 0.64; 95% CI: 0.061, 6.800	(EPO vs. Placebo): sepsis: OR: 0.840; 95% CI: 0.200 ,3.900; NEC: OR: 0.00; 95% CI: 0.00, 1.700; PDA: OR: 2.600; 95% CI: 0.650, 11.000; AOP:OR:0.00; 95%CI: 0.000, 38.00; CLD: OR: 0.870; 95% CI: 0.240, 3.200; mortality: 5/30 vs. 0/15; weight at discharge (SD): 2567g (467) vs. 2653g (557)	rhEPO caused no significant adverse effects	Small sample size, short duration of treatment
4	Fauchere et al., 2015 (41)	Preterm infants 26-316/7weeks (*n*=443)	rhEPO intravenously (*n*=229, Dose: 3000U/kg); 0.9% NaCl (*n*=219) at 3, 12-18 and 36-42 hours of birth.	(EPO vs. Placebo): mortality rate: OR: 1.1; 95% CI: 0.5, 2.5; IVH: OR: 1; 95% CI: 0.6,1·6; ventricular dilatation: OR: 0.7; 95% CI: 0.2, 3.2; Cystic PVL: OR: 1.3; 95% CI: 0.3,5.7; ROP: OR: 0.9; 95% CI: 0.5,1.8; sepsis: OR: 1; 95% CI: 0.6,1.7; NEC: OR: 0.6; 95% CI:0.2,1.5; PDA: OR: 0.4; 95% CI: 0.1-1.2; BPD: OR: 1; 95% CI: 0.7,1.	(EPO vs. Placebo): Weight diff 102 (-0.2 to 204), Head circumference diff. 0.3 (-0.04 to 0.6),mortality: 12/214 vs12/229,OR: 1.1; 95% CI: 0.5-2.5; weight at discharge(SD): 2547 (484) vs. 2649 (572)	rhEPO is safe and cause no excess mortality or major adverse events.	Short duration of treatment
5	Ganzoury et al.,2014 (47)	Preterm infants ≤33 weeks (*n*=90)	Enteral rhG-CSF (*n*=20, Dose:4.5µg/kg); Enteral rhEPO (*n*=20, Dose: 88U/kg); Enteral rhG-CSF plus enteral rhEPO (*n*=20) for 7 days or normal saline as placebo control for 7 days	(EPO vs. Placebo): NEC: 0/40 vs. 3/30, *P*=0.165; Age at starting feeds: 2.3±1.75* vs. 1.7±1.4 *days, *P*=0.16; Time to reach 50% enteral feeds: 7.2±4·1* vs. 8.2±4.2* days, *P*=0.04; time to reach full enteral feeds:13.4 ±4.9 *vs. 16.3 ±5.3*, *P*=0.032	(EPO vs. Placebo): WBC count: 17.8±6.6* vs. 15.5±7.3*, *P*=0.25; Haemoglobin: 1.7±5.5* vs. 15.4±2.9*, *P*=0.27; Platelet count: 260±133* vs. 215±94*, *P*=0.19; mortality: 2/10 vs. 3/10, *P*=0.92	Enteral rhG-CSF and/or rhEPO improves feeding outcome and decreases the risk of NEC.	Small sample size, short duration of treatment
6	Gorman et al., 2015	Preterm infants 26-31	rhEPO intravenously (*n*=225, Dose: 3000U/Kg); 0·9% NaCl	(EPO vs. Placebo): white matter development: Fractional anisotropy:	(EPO vs. Placebo): ROP: 3/24vs 4/34, *P*=0.77; NEC: 0/24 vs. 1/34, *P*=0.58;	Early rhEPO administration improves	Short duration of treatment,

	(40)	weeks (*n*=440)	(*n*=215) at 3, 12-18, and 36-42 hours of birth.	coefficient 0.019; SE:0.004; **	sepsis:3/24 vs. 5/34, *P*=0.88; BPD: 2/24 vs. 5/34, *P*=0.38;birth weight: 0.27 ±0·71* vs. -0.19 ±0.95*, *P*= 0.72	white matter development in preterm infants	small sample size
7	Haiden et al., 2005 (56)	ELBW infants ≤32 weeks (*n*=40)	rhEPO intravenously/subcutaneously (*n*=21, Dose: 300U/kg/ 700U/kg); Control (*n*=19) during the first week of life	(EPO vs. Placebo): TRAP-6 induced expression of P-selectin, *P*<0·05	(EPO vs. no EPO): IVH: 7/21 vs. 5/19[¥] ; CLD: 6/21 vs. 8/19[¥]; NEC: 3/21 vs. 0/19[¥]; PDA: 3/21 vs. 2/19[¥]; ROP: 1/21 vs2/19[¥]; Death: 3/21 vs. 4/19**	EPO therapy has a short-lasting effect on platelet reactivity toTRAP-6 in ELBW infants during the first two weeks of life	Small sample size, short duration of treatment
8	Lima-Rogel et al., 1998 (60)	Preterm infants <26 weeks, birth weight 759g to 1500g (*n*=40)	Enteral rhEPO (*n*=21, Dose: 150U/kg/day); placebo (*n*=19) for four weeks	(EPO vs. Placebo): TRAP-6 induced expression of P-selectin, *P*<0·05	(EPO vs. no EPO): IVH: 7/21 vs. 5/19[¥]; CLD: 6/21 vs. 8/19[¥]; NEC: 3/21 vs. 0/19[¥]; PDA: 3/21 vs. 2/19[¥]; ROP: 1/21 vs. 2/19[¥]; Death: 3/21 vs. 4/19[¥].	rEPO is effective in reducing the transfusion in preterm very low birth weight infants	small sample size, short duration
9	Maier et al., 1994 (49)	Preterm infants ≤33 weeks; birth weight 750-1499g (*n*=241)	Subcutaneous rhEPO (*n*=120, Dose: 250U/kg 3 times/week); control (*n*=121) from day 3 to 42	(EPO vs. control): cumulative median volume transfused:0·09 vs. 0·41; *P*=0.044; mean no: of transfusions per infant:0.87 vs. 1.25, *P*=0.013	(EPO vs. control): NEC: 6/120 vs. 8/121[¥]; septicaemia: 14/120 vs.7/121[¥]; IVH: 8/120 vs. 9/121[¥]; mortality: 3/120 vs. 3/121[¥]	VLBW infants have lesser need of transfusions if EPO is given during the first six weeks of life	Small sample size, short duration of treatment
10	Maier et al., 2002 (42)	Preterm ELBW infants 500-999g (*n*=219)	early rhEPO: rhEPO intravenously from 1st to 9 weeks (*n*=74,Dose:750U/kg/week); late rhEPO: rhEPO iv during	(early EPO vs. control): no transfusion and hematocrit levels never below 30%: RR: 0.68; 95% CI: 0.48,0.96; *P*=0.03 (late EPO vs. control): no transfusion and hematocrit levels never below 30%: RR: 0.76; 95% CI:	(Early EPO vs. late EPO vs. control): PDA: 24/74 vs. 24/74 vs. 23/71, *P* =0.71; NEC: 7/74 vs7/74 vs. 8/71, *P*= 0.91; IVH: 22/74 vs. 16/74 vs. 18/71, *P*=0.58; PVL: 0/74 vs. 5/74 vs1/71, *P*=0.03; ROP: 42/74	Early rhEPO treatment effectively reduces the need for transfusion in ELBW infants.	Short duration in late EPO group

			4weeks-6weeks (*n*=74, Dose: 750U/Kg/week); control group: no rhEPO (*n*=71).All received enteral iron 3-9mg/kg/day from 1st week	0.54,1.07; *P*=0.12 (early EPO vs. late EPO vs. control): Transfusion volume 0.4 vs. 0.5 vs. 0.7, *P*=0.02; median donor exposure:1vs. 1 vs. 2, *P*=0.05	vs. 34/74 vs. 38/71, *P*=0.27		
11	Meyer et al.,1994 (50)	Preterm infants ≤32 weeks; (*n*=80)	Subcutaneous rhEPO (*n*=40, Dose: 600U/kg /week); placebo (*n*=40) for up to 6 weeks.	(EPO vs. placebo): Number of blood transfusions: 7/40 vs. 21/40; *P*=0.002; no: of infants transfused: 6/40 vs. 17/40, *P*=0.013; mean hematocrit:32.3±4*% vs. 29.3±6·2*%, *P*=0.014; absolute reticulocyte count**: 223±73* vs. 124.9±73x10^9*	(EPO vs. placebo): NEC: 0/40 vs.1/40¥;sepsis:1/40 vs.3/40¥; PDA: 2/40 vs.7/40¥	VLBW infants have lesser need of transfusions if EPO is given during the first six weeks of life	Small sample size, short duration of treatment
12	Natalucci et al. , 2016 (43)	Preterm infants 26 weeks to 31weeks 6 days (*n*=365)	intravenous rhEPO (*n*=228, Dose: 3000U/Kg); Placebo (isotonic saline *n*=220) within 3 hours, at 12 to 18 hours and at 36 to 42 hours after birth	(EPO vs. Placebo): mean mental Developmental Index: 93.5,SD 16.0,91.2 to 95.8 vs. 94.5 SD: 17.8, 90.8 to 98.5; *P*=0.56	(EPO vs. Placebo): BDP: 66/191 vs. 64/175; sepsis: 24/191 vs. 22/175; NEC: 4/191 vs. 5/175; ROP: 1/191 vs. 5/175; PDA: 55/191 vs. 44/175; PDI: mean: 89.5 vs. 92.1, *P*=0.15; cerebral palsy: 8/191 vs. 8/174, *P*>0.99; severe hearing impairment:1/191vs. 0/174, *P*>0.99; severe visual impairment: 2/191 vs. 0/174, *P*=0.50	No statistically significant difference was found among very preterm infants who received prophylactic high dose rhEPO for neuroprotection compared with placebo	**S**mall sample size, short duration of treatment
13	Obladen et al. , 1991 (51)	Preterm infants 28-32 weeks (*n*=93)	**S**ubcutaneous rhEPO (*n*=43, Dose: 30U/kg/ every third day); control (*n*=50) from day 4 to day 25	(EPO vs. control): Volume of red cells transfused (ml/kg): 14.1± 17.8*vs. 16.5 ± 20.8*¥; no: of infants with/without transfusion: 23/15 vs. 29/16¥; haematological values on day 25 (mean):	(EPO vs. control): NEC : 1/43 vs. 3/50¥; PDA: 1/43 vs. 3/50¥; IVH: 5/43 vs. 5/50**; BPD: 6/43 vs. 5/50¥ ; mortality: 0/43 vs. 1/50¥	rEPO given at this dose is not effective in reducing the transfusion in preterm	Small sample size, short duration

				Hct:36 vs. 38; Hb:11.8 vs12.3			
14	Ohls et al., 2001A (44)	Preterm infants ≤32 weeks, Birth weight ≥ 410g to≤ 1000g (*n*=172)	Intravenous EPO (*n*=87, Dose:400U/kg 3 times weekly); placebo/control (*n*=85) from 4th day to 35th week post menstrual age	(EPO vs. Placebo): Transfusion/patient: 4.3 ± 3.6* vs. 5.2 ± 4.2*; *P*=0.09; transfused: 84 vs. 87, *P*=0.56; Hematocrit (%): 38 ±8* vs. 40 ±7*, *P*<0.05; Reticulocyte count ($x10^3$/μL): 211 ±128* vs. 234 ± 127**.	(EPO vs. Placebo) : CLD (%): 52 vs. 54¥; ROP stage 3 (%): 19 vs. 16¥ ; IVH grade 3 (%):13 vs.9¥; NEC (%) :10 vs. 12**; PDA (%): 36 vs. 46¥; sepsis (%): 38 vs. 43**; Mortality (%) :17 vs. 18¥	EPO stimulated erythropoiesis in infants who were <1250 g at birth.	Small sample size
15	Ohls et al., 2001B (44)	Preterm infants ≤32 weeks, Birth weight ≥ 1001g to ≤ 1250g (*n*=118)	EPO (*n*=59, Dose: 400U/Kg thrice weekly); placebo/control (*n*=59) from 4th day to 35th week post menstrual age	(EPO vs. control): Volume of red cells transfused (ml/kg):14.1 ± 17.8*vs. 16·5 ± 20.8*; no: of infants with/without transfusion: 23/15 vs. 29/16, *P*=ns; haematological values on day 25(mean): Hct:36 vs. 38; Hb:11.8 v. s12.3	(EPO vs. control): NEC: 1/43 vs. 3/50¥; PDA: 1/43 vs. 3/50¥; IVH: 5/43 vs. 5/50**; BPD: 6/43 vs. 5/50¥ ; mortality: 0/43 vs. 1/50¥	EPO stimulated erythropoiesis in infants who were <1250 g at birth.	Small sample size
16	Ohls et al., 2004 (45)	Preterm ELBW infants <1000g birth weight (*n* =172)	EPO (*n*=87, Dose:400U/Kg 3 times weekly iv or s/c) started at 96 hours of life and continued till 35 weeks; placebo/control (*n*=85)	(EPO vs. Placebo): weight on discharge: 2237 ± 525*vs. 2164 ± 537*; weight on follow up: 10.1 ± 1.4* vs. 10.4 ± 1.5*¥; length on discharge: 43.5 ±2.3* vs. 42.8± 2.9*; length on follow up: 80.2 ±3.8* vs. 80.8 ±3.4*¥; discharge head circumference: 32.5 ±1.7*vs. 32.1 ± 1.8*; Head circumference on follow up: 47.0 ± 2.1*¥ vs46.6 ±1.7*¥; NDI: 42% vs. 44%¥.	(EPO vs. Placebo): NEC: 3/51 vs. 5/51¥; BPD 33/51 vs. 30/51¥; IVH 6/51 vs. 1/51¥; LOS: 61/51 vs. 19/51¥; ROP: 10/51 vs. 7/51¥; weight at discharge: 2237±525* vs. 2164±537*.	EPO does not significantly influence anthropometric measurements, transfusions after discharge, or developmental outcome at 18 to 22 months' corrected age. Enteral rhG-CSF and/or rhEPO improves feeding outcome and decreases	Small sample size

						the risk of NEC.	
17	Ohls et al., 2013 (52)	Preterm infants 500-1250g weeks (*n*=102)	**S**ubcutaneous Darbe (*n*=33, Dose:10µg/kg) once per week; Subcutaneous EPO (*n*=33, Dose: 400U/kg) three times per week; Placebo (*n*=33,3 sham doses per week) till 35 weeks of gestation	(Darbe vs. EPO vs. Placebo): transfusion per subject:1.2±2.4* vs. 1.2±1.6* vs. 2.4±2.9*; *P*=0.949	(Darbe vs.EPO vs. Placebo): CLD: 22/32 vs. 21/32 vs. 20/30¥; NEC:2/32 vs. 1/32 vs. 2/30¥; PDA:16/32 vs. 16 /32 vs. 15/30¥; mortality: 2/32 vs. 1/32 vs. 3/30¥; ROP 2/32 vs. 1/32 vs. 2/30¥	Infants receiving Darbe or EPO received fewer transfusions and fewer donor exposures	Small sample size.
18	Qiao et al., 2017 (59)	Preterm infants 28 to 34 weeks (*n*=96)	Intravenous rhEPO (*n*=32, Dose: 400U/kg twice a week); control (*n*=31); iron supplement (*n*=33) for two weeks	(EPO vs. control): reticulocyte: 2.5±0.3 vs. 1·7±0.3; *P*<0.001; total iron binding capacity (TIBC): 41.6±5.2* vs. 36.7±4.6*; *P*=0.006	(EPO vs. control): NEC : 0/32 vs. 0/31¥; ROP: 0/32 vs. 0/31¥	rEPO improves reticulocyte count, decreases TIBC and improves haemoglobin transfusion in preterm infants	Short duration
19	Romagnoli et al., 2000 (53)	Preterm infants ≤30 weeks and those of 31-34 weeks with RDS (*n*=230)	subcutaneous rhEPO (*n*=115,Dose: 300IU/kg 3times per week); control (*n*=115; no EPO), from 2nd to 7th week of life	(EPO vs. control): transfused infants: 60(52·2) vs. 64 (55·6)¥; number of transfusions: 3·2 ± 2·2* (1±10) vs. 3·7 ± 3·1* (1±15)¥; ROP: 50/115 vs. 25/115, P=0·0007, OR: 2·769; 95% CI: 1·556, 4·929)	(EPO vs. control): NEC:4/115 vs. 4 /115¥; PDA: 29 /115 vs. 41/115¥; IVH: 7/115 vs. 7/115¥; sepsis: 24/115 vs. 30/115¥	Combination of EPO and iron could be associated with increased incidence of ROP	Small sample size±
20	Samanci et al., 199(17)	Preterm infants ≤32 weeks, birth weight ≤1250g (*n*=24)	subcutaneous rhEPO (*n*=12, Dose: 200U thrice weekly); placebo (*n*=12) for four weeks	(EPO vs. placebo): no: of infants requiring transfusion: 3/12 vs. 8/12**; no: of red blood cell transfusion per infant: 0.4±0.7* vs. 1.1±0.6*	(EPO vs. placebo): NEC: 0/12 vs. 0/12¥; IVH: 0/12 vs. 0/12¥	rEPO is effective in reducing the transfusion in preterm very low birth weight infants	Small sample size, short duration
	Shannon et	Preterm infants	Intravenous rhEPO (n=10,	(EPO vs. placebo): number of infants	EPO vs. placebo): NEC:1/10vs 0/10¥;	rEPO given at this dose is	Small sample

21	al. ,1991 (58)	≤1250g (*n*=20)	Dose: 200U/kg/week); placebo(*n*=10) from day 8 to 6 weeks	required transfusion:6/10vs 8/10¥	mortality: 1/10 vs. 0/10¥; neutropenia: 1/10 vs. 3/10¥; hypertension: 0/10 vs. 0/10¥	safe and feasible in reducing the transfusion in preterm	size
22	Shannon et al., 1995 (54)	Preterm infants <31 weeks,<1250g (*n*=157)	rhEPO (n=77, Dose:100U/kg/day) administered subcutaneously 5 days a week 6 weeks; placebo (*n*=80)	(EPO vs. placebo): erythrocyte transfusion: 1·1± 1·5* per infant vs. 1·6± 1·7*,*P*=0·046; volume of packed cell transfusion: 16·5± 23*ml vs. 23·9± 25·9* ml, *P*=0·023; hematocrit: 32± 3·8*% 27·3± 4·9*%, *P*=0·0001	(EPO vs. placebo): erythrocyte transfusion: 1·1± 1·5* per infant vs. 1·6± 1·7*, P=0·046; volume of packed cell transfusion: 16·5± 23*ml vs. 23·9± 25·9* ml, P=0·023; hematocrit:32± 3·8*% 27·3± 4·9*%, *P*=0·0001	(EPO vs. placebo): NEC: 3/147 vs. 4/150¥; ROP: 1/147 vs. 3/150¥; death during treatment: 0/147 vs. 1/150¥; culture proven sepsis: 6/147 vs. 6/150¥; feed intolerance: 7/147 vs. 7/150¥	Small sample size, Short duration of treatment
23	Song et al., 2016 (46)	Preterm infants ≤32 weeks (*n*=743)	Intravenous rhEPO (*n*=366, Dose:500U/Kg); Placebo(*n*=377) every other day for 2 weeks	(EPO vs. Placebo): Death and moderate/severe neurological disability: 43/330 vs. 91/338**	(EPO vs. Placebo): ICH III-IV: 24/366 vs. 60/377, *P*<0·001; PVL: 41/366 vs. 74/377, *P*=0·002; ROP: 79/366 vs. 97/377, *P*=0·196; NEC: 25/366 vs. 54/377, *P*=0·001; BPD: 37/366 vs. 51/377, *P*= 0·168; sepsis: 71/366 vs. 99/377, *P*=0·015; mortality: 21/330 vs. 34/338, *P*= 0·077	Repeated low dose rhEPO treatment reduced the risk of long term neurological disability in very preterm infants with no obvious adverse effects	Short duration of treatment
24	Turker et al.,2005 (57)	Preterm infants <1500g (*n*=93)	subcutaneous rhEPO (*n*=42, Dose: 750U/Kg/week in 3 doses); control (*n*=51) from day 5 to day 40	(EPO vs. control): Number of transfusions per infant during study in <1000g infants:2/15 vs5/15; *P*=0·004,total PRC volume transfused in infants<1000g (mL/kg/infants): 40 vs. 98; *P*=0·004	(EPO vs. control): NEC:15/42 vs14/51, *P*=0·5; BPD: 6/42 vs. 10/51, *P*=0·3; ROP: 1/42 vs. 7/51, *P*=0·09; IVH: 15/42 vs. 20/51, *P*=0·6	rEPO do not increase the risk of ROP,BPD,NEC,IVH and reduce the need of transfusion in infants < 1000g	Small sample size
25	Yeo et al., 2001 (55)	Preterm infants <33 weeks (*n*=100)	Subcutaneous rhEPO (*n*=50, Dose: 750U/kg/week); Control	(EPO vs. control): mean no: of transfusion per patient: 2·1±1·9 vs3·5±1·6; *P*=0·04,	(EPO vs. control): Death:5/50 vs. 4/50¥; NEC: 4/50 vs. 2/50¥; Septicemia: 4/50 vs.	rhEPO stimulates erythropoiesis and	Small sample size, short

	(*n*=50) from day 5 to day 40	volume of blood transfused per patient (mL/kg): 34·9± 32 *vs. 56·6 ±2*; *P*=0·03	7/50[¥]; CLD: 9/50 vs. 12/50[¥]; ROP: 17/50 vs. 15/50[¥]	reduces the need for blood transfusion	duration of treatment

[1] BPD: bronchopulmonary dysplasia; CLD: Chronic lung disease; CI: Confidence interval; ELBW: Extremely low birth weight; ICH: Intra cranial hemorrhage; IVH: Intraventricular hemorrhage; LOS: Late onset sepsis; NEC: Necrotizing enterocolitis; OR: Odds ratio; PDA: Patent ductus arteriosus; PVL: Periventricular leukomalacia rhEPO: Recombinant human erythropoietin; rhG-CSF: Recombinant human Granulocyte colony stimulating factor; ROP: Retinopathy of prematurity; TRAP-6: Thrombin receptor activator peptide 6

[2, 3] for these columns,* mean±SD; ** *P*<0.01; [¥]*P*=NS (not significant)

Supplemental Table 2: Sensitivity analysis of the RCTs.

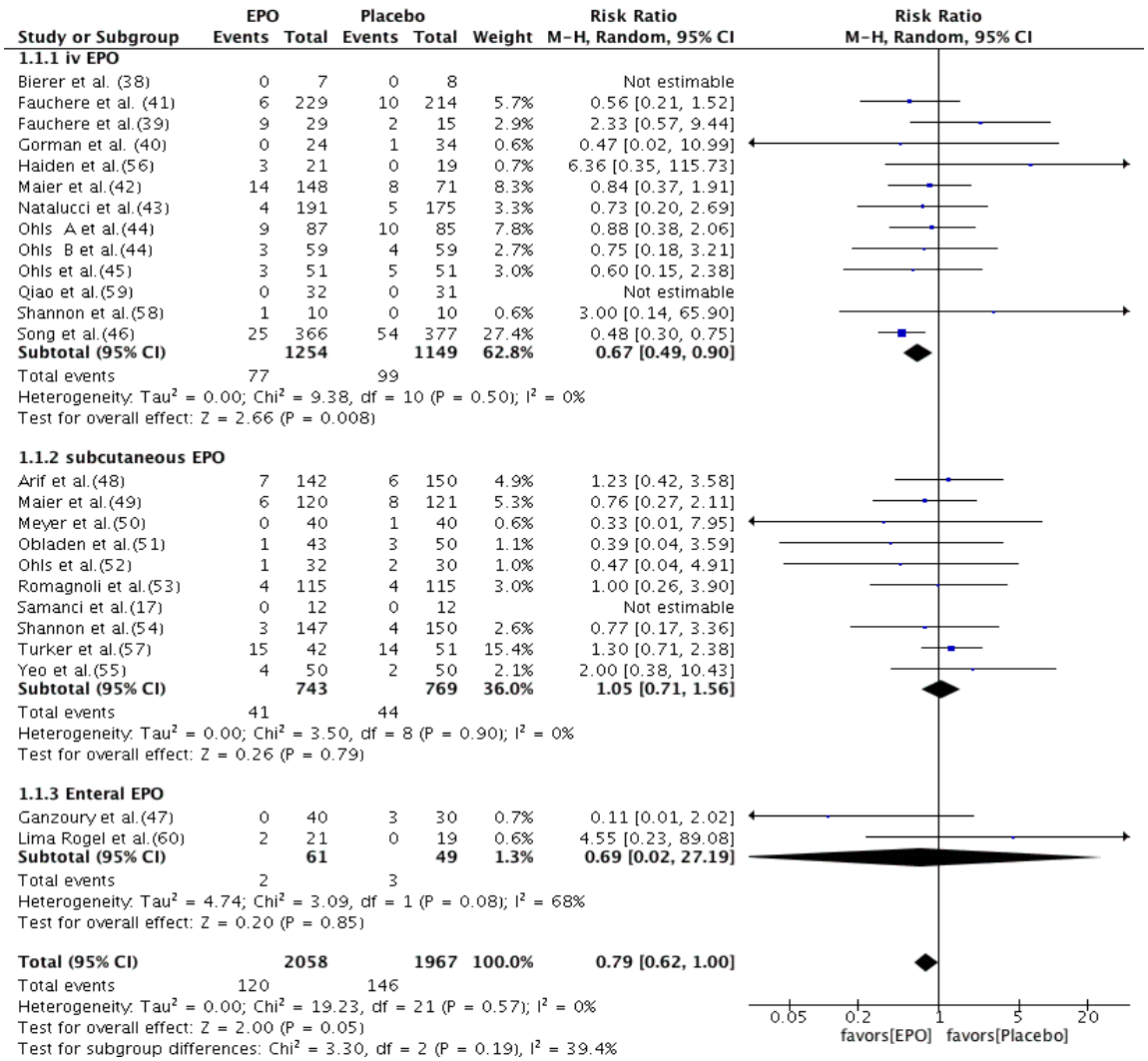
Item	Number of studies	Sample size	RR (95% CI) FEM
Studies with low ROB on random sequence generation	14	2592	0.61 (0.44,0.83); *P*=0.002
Studies with low ROB on allocation concealment	17	3243	0.66 (0.51,0.87); *P*=0.003
Studies where NEC was the primary outcome	2	493	0.49 (0.19,1.30); *P*=0.15
Studies where EPO was administered intravenously	13	2403	0.68 (0.51, 0.91); *P*=0.009
Studies where EPO was administered subcutaneously	10	1512	1.01 (0.68,1.50); *P*=0.95
Studies where EPO was administered enterally	2	110	0.62 (0.15,2.59); *P*=0.52

[1]ROB: ris of bias; NEC: necrotizing enterocolitis; EPO: erythropoietin

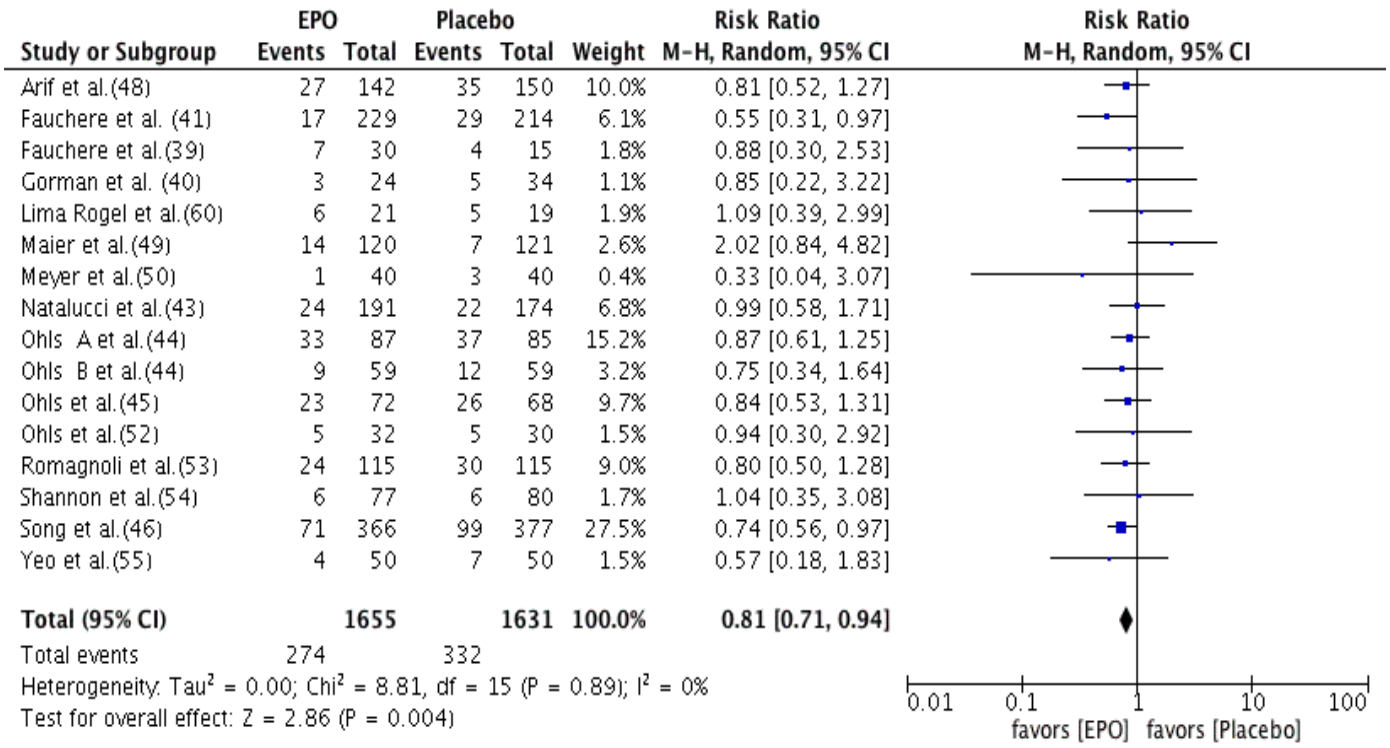
Supplemental Table 3: The evidence as per GRADE guidelines

Outcome	Absolute Risk		Relative effect, RR	Number of participants	Quality of evidence	Comment^
	Estimate without EPO administration	Corresponding Risk estimate with EPO administration	(95% CI)		GRADE	
NEC	146/1967 (7.42%)	120/2058 (5.83%)	0.77(0.61,0.97), *P*=0.03	4025	High	See below

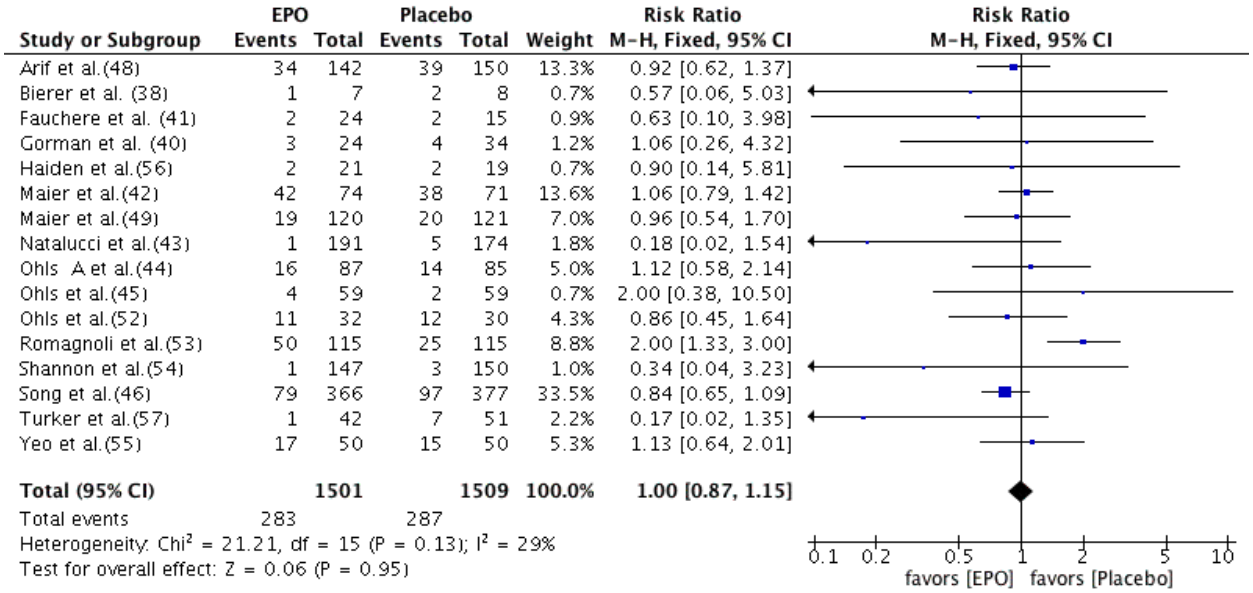
^The evidence was deemed high in view of low risk of bias in majority of the included studies, narrow CI around the effect size estimate, very low p value for effect size estimate and mild statistical heterogeneity



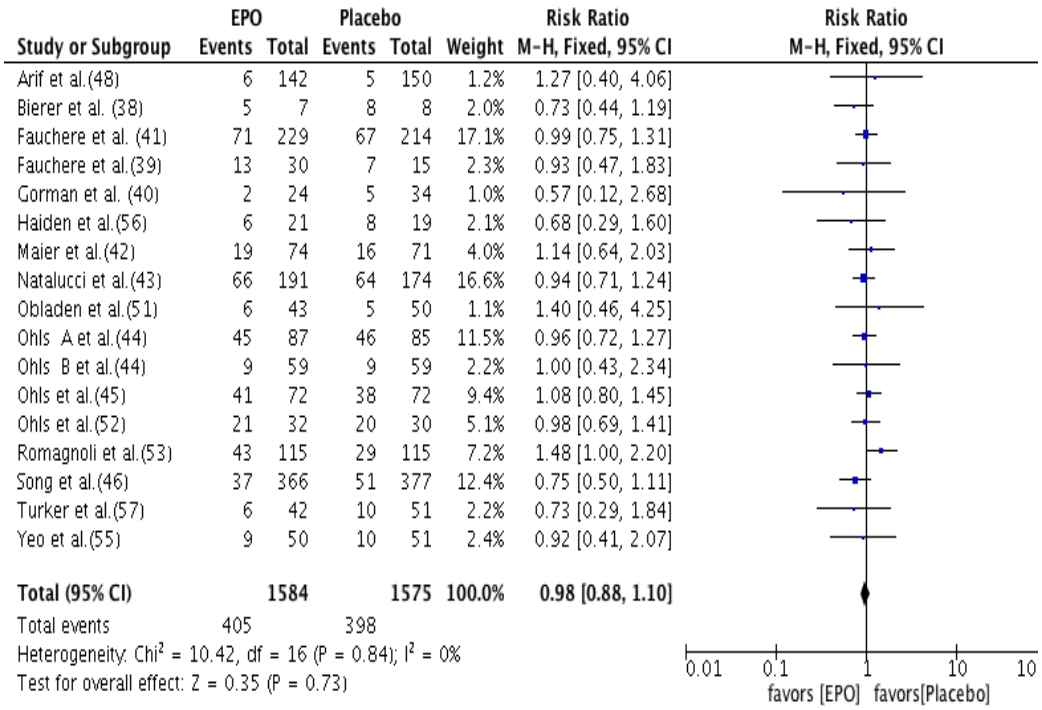
Supplemental Figure 1: Effect of recombinant erythropoietin (rEPO) on necrotizing enterocolitis in preterm neonates (random effect model)



Supplemental Figure 2: Effect of recombinant erythropoietin (rEPO) on sepsis in preterm neonates (random effect model)



Supplemental Figure 3: Effect of recombinant erythropoietin (rEPO) on Retinopathy of Prematurity (ROP) in preterm neonates (fixed effect model)



Supplemental Figure 4: Effect of recombinant erythropoietin (rEPO) on Bronchopulmonary Dysplasia (BPD) in preterm neonates (fixed effect model)

References

1. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011;343:d5928. Epub 2011/10/20.
2. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemporary clinical trials. 2015;45(Pt A):139-45.
3. Higgins J GS e. Cochrane Hadbook for Systematic Reviews of Interventions.version 5.10. In The Cochrane Collaboration; 2011. 2011; (updated March 2011).