Cochrane Library

Cochrane Database of Systematic Reviews

Intravenous iron versus oral iron versus no iron with or without erythropoiesis- stimulating agents (ESA) for cancer patients with anaemia: a systematic review and network meta-analysis (Review)

Adams A, Scheckel B, Habsaoui A, Haque M, Kuhr K, Monsef I, Bohlius J, Skoetz N

Adams A, Scheckel B, Habsaoui A, Haque M, Kuhr K, Monsef I, Bohlius J, Skoetz N.
Intravenous iron versus oral iron versus no iron with or without erythropoiesis- stimulating agents (ESA) for cancer patients with anaemia: a systematic review and network meta-analysis.
Cochrane Database of Systematic Reviews 2022, Issue 6. Art. No.: CD012633.
DOI: 10.1002/14651858.CD012633.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Intravenous iron versus oral iron versus no iron with or without erythropoiesis- stimulating agents (ESA) for cancer patients with anaemia: a systematic review and network meta-analysis

Anne Adams[1], Benjamin Scheckel[2], Anissa Habsaoui[3], Madhuri Haque[3], Kathrin Kuhr[1], Ina Monsef[3], Julia Bohlius[4], Nicole Skoetz[5]

[1]Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [2]Institute of Health Economics and Clinical Epidemiology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany. [3]Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [4]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [5]Cochrane Cancer, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

Contact: Nicole Skoetz, nicole.skoetz@uk-koeln.de.

Editorial group: Cochrane Haematology Group.
Publication status and date: New, published in Issue 6, 2022.

Citation: Adams A, Scheckel B, Habsaoui A, Haque M, Kuhr K, Monsef I, Bohlius J, Skoetz N. Intravenous iron versus oral iron versus no iron with or without erythropoiesis- stimulating agents (ESA) for cancer patients with anaemia: a systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews* 2022, Issue 6. Art. No.: CD012633. DOI: 10.1002/14651858.CD012633.pub2.

ABSTRACT

Background

Anaemia is common among cancer patients and they may require red blood cell transfusions. Erythropoiesis-stimulating agents (ESAs) and iron might help in reducing the need for red blood cell transfusions. However, it remains unclear whether the combination of both drugs is preferable compared to using one drug.

Objectives

To systematically review the effect of intravenous iron, oral iron or no iron in combination with or without ESAs to prevent or alleviate anaemia in cancer patients and to generate treatment rankings using network meta-analyses (NMAs).

Search methods

We identified studies by searching bibliographic databases (CENTRAL, MEDLINE, Embase; until June 2021). We also searched various registries, conference proceedings and reference lists of identified trials.

Selection criteria

We included randomised controlled trials comparing intravenous, oral or no iron, with or without ESAs for the prevention or alleviation of anaemia resulting from chemotherapy, radiotherapy, combination therapy or the underlying malignancy in cancer patients.

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias. Outcomes were on-study mortality, number of patients receiving red blood cell transfusions, number of red blood cell units, haematological response, overall mortality and adverse events. We conducted NMAs and generated treatment rankings. We assessed the certainty of the evidence using GRADE.

Main results

Ninety-six trials (25,157 participants) fulfilled our inclusion criteria; 62 trials (24,603 participants) could be considered in the NMA (12 different treatment options). Here we present the comparisons of ESA with or without iron and iron alone versus no treatment. Further results and subgroup analyses are described in the full text.

On-study mortality

We estimated that 92 of 1000 participants without treatment for anaemia died up to 30 days after the active study period. Evidence from NMA (55 trials; 15,074 participants) suggests that treatment with ESA and intravenous iron (12 of 1000; risk ratio (RR) 0.13, 95% confidence interval (CI) 0.01 to 2.29; low certainty) or oral iron (34 of 1000; RR 0.37, 95% CI 0.01 to 27.38; low certainty) may decrease or increase and ESA alone (103 of 1000; RR 1.12, 95% CI 0.92 to 1.35; moderate certainty) probably slightly increases on-study mortality. Additionally, treatment with intravenous iron alone (271 of 1000; RR 2.95, 95% CI 0.71 to 12.34; low certainty) may increase and oral iron alone (24 of 1000; RR 0.26, 95% CI 0.00 to 19.73; low certainty) may increase or decrease on-study mortality.

Haematological response

We estimated that 90 of 1000 participants without treatment for anaemia had a haematological response. Evidence from NMA (31 trials; 6985 participants) suggests that treatment with ESA and intravenous iron (604 of 1000; RR 6.71, 95% CI 4.93 to 9.14; moderate certainty), ESA and oral iron (527 of 1000; RR 5.85, 95% CI 4.06 to 8.42; moderate certainty), and ESA alone (467 of 1000; RR 5.19, 95% CI 4.02 to 6.71; moderate certainty) probably increases haematological response. Additionally, treatment with oral iron alone may increase haematological response (153 of 1000; RR 1.70, 95% CI 0.69 to 4.20; low certainty).

Red blood cell transfusions

We estimated that 360 of 1000 participants without treatment for anaemia needed at least one transfusion. Evidence from NMA (69 trials; 18,684 participants) suggests that treatment with ESA and intravenous iron (158 of 1000; RR 0.44, 95% CI 0.31 to 0.63; moderate certainty), ESA and oral iron (144 of 1000; RR 0.40, 95% CI 0.24 to 0.66; moderate certainty) and ESA alone (212 of 1000; RR 0.59, 95% CI 0.51 to 0.69; moderate certainty) probably decreases the need for transfusions. Additionally, treatment with intravenous iron alone (268 of 1000; RR 0.74, 95% CI 0.43 to 1.28; low certainty) and with oral iron alone (333 of 1000; RR 0.92, 95% CI 0.54 to 1.57; low certainty) may decrease or increase the need for transfusions.

Overall mortality

We estimated that 347 of 1000 participants without treatment for anaemia died overall. Low-certainty evidence from NMA (71 trials; 21,576 participants) suggests that treatment with ESA and intravenous iron (507 of 1000; RR 1.46, 95% CI 0.87 to 2.43) or oral iron (482 of 1000; RR 1.39, 95% CI 0.60 to 3.22) and intravenous iron alone (521 of 1000; RR 1.50, 95% CI 0.63 to 3.56) or oral iron alone (534 of 1000; RR 1.54, 95% CI 0.66 to 3.56) may decrease or increase overall mortality. Treatment with ESA alone may lead to little or no difference in overall mortality (357 of 1000; RR 1.03, 95% CI 0.97 to 1.10; low certainty).

Thromboembolic events

We estimated that 36 of 1000 participants without treatment for anaemia developed thromboembolic events. Evidence from NMA (50 trials; 15,408 participants) suggests that treatment with ESA and intravenous iron (66 of 1000; RR 1.82, 95% CI 0.98 to 3.41; moderate certainty) probably slightly increases and with ESA alone (66 of 1000; RR 1.82, 95% CI 1.34 to 2.47; high certainty) slightly increases the number of thromboembolic events. None of the trials reported results on the other comparisons.

Thrombocytopenia or haemorrhage

We estimated that 76 of 1000 participants without treatment for anaemia developed thrombocytopenia/haemorrhage. Evidence from NMA (13 trials, 2744 participants) suggests that treatment with ESA alone probably leads to little or no difference in thrombocytopenia/haemorrhage (76 of 1000; RR 1.00, 95% CI 0.67 to 1.48; moderate certainty). None of the trials reported results on other comparisons.

Hypertension

We estimated that 10 of 1000 participants without treatment for anaemia developed hypertension. Evidence from NMA (24 trials; 8383 participants) suggests that treatment with ESA alone probably increases the number of hypertensions (29 of 1000; RR 2.93, 95% CI 1.19 to 7.25; moderate certainty). None of the trials reported results on the other comparisons.

Authors' conclusions

When considering ESAs with iron as prevention for anaemia, one has to balance between efficacy and safety. Results suggest that treatment with ESA and iron probably decreases number of blood transfusions, but may increase mortality and the number of thromboembolic events. For most outcomes the different comparisons within the network were not fully connected, so ranking of all treatments together was not possible. More head-to-head comparisons including all evaluated treatment combinations are needed to fill the gaps and prove results of this review.

PLAIN LANGUAGE SUMMARY

Which combinations of medicines are best for the prevention and treatment of anaemia in people with cancer?

Key messages

• Giving medicines that stimulate the bone marrow to produce red blood cells (ESAs) with iron supplements probably decreases the number of blood transfusions, but may also cause more deaths and increase the number of unwanted effects, such as blood clots.

• Because of missing data from the studies we could not compare the different treatment options to each other and rank them.

• We need more studies that compare these medicines directly against each other.

What is anaemia and why do people with cancer develop it?

Anaemia develops when levels of red blood cells are too low. Red blood cells contain a protein called haemoglobin. Iron molecules in the haemoglobin bind to oxygen and carry it around the body. A lack of oxygen to the organs and tissues in the body makes people feel tired and lack energy, and they may be at greater risk of infections. People with cancer are particularly likely to suffer from anaemia. This might be because the cancers cause inflammation and prevent red blood cell production. Or it might be because treatments like chemotherapy slow down production of red blood cells in bone marrow.

People suffering from anaemia may need blood transfusions. However, treatment with medicines that stimulate the production of red blood cells in bone marrow (called erythropoiesis-stimulating agents or ESAs) and iron supplements may reduce the need for transfusions.

What did we want to find out?

We wanted to identify the most effective treatments for anaemia in people with cancer and whether they cause any unwanted effects. We were interested in whether iron supplements or ESAs given alone or together affect:

• deaths;

• haemoglobin levels;

• blood transfusions; and

• unwanted effects.

We also wanted to know the best way to give the medicines: by injection (intravenous), or swallowed (oral).

What did we do?

We searched for studies that compared intravenous, oral or no iron with or without ESAs for the prevention or treatment of anaemia resulting from chemotherapy, radiotherapy, combination therapy or the underlying malignancy in people with cancer. We compared and summarised their results, and rated our confidence in the evidence, based on factors such as study methods and numbers of participants. We used statistical methods to compare multiple treatments against each other and rank them in order of effectiveness and unwanted effects.

What did we find?

We found 96 relevant studies with 25,157 people. People in the studies were different ages and were receiving a mix of anti-cancer treatments or no treatment. They had different types of cancer.

Ninety-two studies reported data for our review. They included 24,603 people and compared 12 different treatment options for anaemia. The treatments included combinations of ESAs with intravenous or oral iron and placebo (something that looks, tastes and smells the same as the iron supplement or ESA but with no active ingredient).

Not every study reported everything we were interested in, so we did not have enough information to compare each treatment with each of the other treatments.

Treatment with ESAs when used on their own or with iron probably increases levels of red blood cells and reduces the need for red blood cell transfusions when compared with no treatment. We cannot rule out an increase in the risk of mortality with ESA in combination with iron, which also appeared to cause more deaths and lead to increased risk of harm caused by the formation of clots in the blood vessels.

Our confidence in the findings

Overall, we are moderately confident in the evidence that one treatment is better or worse than another. Our confidence is limited because we sometimes found very different results for the same treatments, meaning they could have been both good and bad for patients - we did not have enough evidence to reach firm conclusions. Also, due to a lack of evidence we could not rank the treatments.

How up to date is the evidence?

The evidence is up-to-date to June 2021.

SUMMARY OF FINDINGS

Summary of findings 1. ESA with or without iron versus no treatment

ESA with or without iron for cancer patients with anaemia

Patient or population: patients at any age with solid cancer or haematological malignancy

Settings: inpatient and outpatient care

Intervention: ESA + IV iron, ESA + oral iron, ESA without iron

Comparison: No treatment

Outcomes	Anticipated absolute effects (95% CI)[1]		Relative effects (95% CI)[2]	Certainty of the evidence (GRADE)	Interpretation of findings
	Comparator	Intervention			
On-study mortality[3] (Subnet based on 55 studies including 15,074 participants)	No treatment **92 per 1000**	ESA plus IV iron **12 per 1000** (1 to 211)	**RR 0.13** (0.01 to 2.29)	⊕⊕⊖⊖ **low**[d]	Treatment with ESA and IV iron may decrease or increase on-study mortality compared to no treatment.
		ESA plus oral iron **34 per 1000** (1 to 1000)	**RR 0.37** (0.01 to 27.38)	⊕⊕⊖⊖ **low**[d]	Treatment with ESA and oral iron may decrease or increase on-study mortality compared to no treatment.
		ESA without iron **103 per 1000** (85 to 124)	**RR 1.12** (0.92 to 1.35)	⊕⊕⊕⊖ **moderate**[a]	Treatment with ESA probably slightly increases on-study mortality compared to no treatment.
Haemoglobin response (Subnet based on 31 studies including 6985 participants)	No treatment **90 per 1000**	ESA plus IV iron **604 per 1000** (444 to 823)	**RR 6.71** (4.93 to 9.14)	⊕⊕⊕⊖ **moderate**[b]	Treatment with ESA and IV iron probably increases haemoglobin response compared to no treatment.
		ESA plus oral iron **527 per 1000** (365 to 758)	**RR 5.85** (4.06 to 8.42)	⊕⊕⊕⊖ **moderate**[b]	Treatment with ESA and oral iron probably increases haemoglobin response compared to no treatment.
		ESA without iron **467 per 1000** (362 to 604)	**RR 5.19** (4.02 to 6.71)	⊕⊕⊕⊖ **moderate**[b]	Treatment with ESA probably increases haemoglobin response compared to no treatment.

Red blood cell transfusions (Subnet based on 69 studies including 18,684 participants)	No treatment **360 per 1000**	ESA plus IV iron **158 per 1000** (112 to 227)	**RR 0.44** (0.31 to 0.63)	⊕⊕⊕⊖ **moderate**[b]	Treatment with ESA and IV iron probably decreases the need for red blood cell transfusions compared to no treatment.
		ESA plus oral iron **144 per 1000** (86 to 238)	**RR 0.40** (0.24 to 0.66)	⊕⊕⊕⊖ **moderate**[b]	Treatment with ESA and oral iron probably decreases the need for red blood cell transfusions compared to no treatment.
		ESA without iron **212 per 1000** (184 to 248)	**RR 0.59** (0.51 to 0.69)	⊕⊕⊕⊖ **moderate**[b]	Treatment with ESA probably decreases the need for red blood cell transfusions compared to no treatment.
Overall mortality[4] (Subnet based on 71 studies including 21,576 participants)	No treatment **347 per 1000**	ESA plus IV iron **507 per 1000** (302 to 843)	**RR 1.46** (0.87 to 2.43)	⊕⊕⊖⊖ **low**[a,c]	Treatment with ESA and IV iron may decrease or increase overall mortality compared to no treatment.
		ESA plus oral iron **482 per 1000** (208 to 1000)	**RR 1.39** (0.60 to 3.22)	⊕⊕⊖⊖ **low**[a,c]	Treatment with ESA and oral iron may decrease or increase overall mortality compared to no treatment.
		ESA without iron **357 per 1000** (337 to 382)	**RR 1.03** (0.97 to 1.10)	⊕⊕⊖⊖ **low**[a,c]	Treatment with ESA may lead to no or little difference in overall mortality compared to no treatment.
Thromboembolic events[5] (Subnet based on 50 studies including 15,408 participants)	No treatment **36 per 1000**	ESA plus IV iron **66 per 1000** (35 to 123)	**RR 1.82** (0.98 to 3.41)	⊕⊕⊕⊖ **moderate**[a]	Treatment with ESA and IV iron probably increases the number of thromboembolic events slightly compared to no treatment.
		ESA plus oral iron **n.r.**	-	-	-
		ESA without iron **66 per 1000** (48 to 89)	**RR 1.82** (1.34 to 2.47)	⊕⊕⊕⊕ **high**	Treatment with ESA slightly increases the number of thromboembolic events compared to no treatment.
Thrombocytopenia or haemorrhage[5] (Subnet based on 13 studies including 2744 participants)	No treatment **76 per 1000**	ESA plus IV iron **n.r.**	-	-	-
		ESA plus oral iron **n.r.**	-	-	-

		ESA without iron **76 per 1000** (51 to 112)	**RR 1.00** (0.67 to 1.48)	⊕⊕⊕⊖ **moderate**[a]	Treatment with ESA probably leads to little or no difference in thrombocytopenia or haemorrhage compared to no treatment.
Hypertension[5] (Subnet based on 24 studies including 8383 participants)	No treatment **10 per 1000**	ESA plus IV iron **n.r.**	-	-	-
		ESA plus oral iron **n.r.**	-	-	-
		ESA without iron **29 per 1000** (12 to 73)	**RR 2.93** (1.19 to 7.25)	⊕⊕⊕⊖ **moderate**[a]	Treatment with ESA probably increases the number of hypertensions compared to no treatment.

[1] Baseline risks obtained from the respective study population. Absolute risks in the intervention group result from product of control risk and risk ratio

[2] Results from network meta-analysis (random effects model). Network estimates are reported as risk ratios or mean difference with corresponding 95% confidence intervals.

[3]On-study mortality is defined as deaths occurring up to 30 days after the active study period.

[4]Overall mortality is defined as deaths occurring up to the longest follow-up available (median follow-up: 12 weeks).

[5]Events occurring during the whole study period.

[a]Downgraded one level for imprecision since 95% CI is wide and/or crosses unity

[b]Downgraded one level for inconsistency (heterogeneity)

[c]Downgraded one level for high risk of bias since exclusion of studies with overall high risk of bias changed results

[d]Downgraded two levels for imprecision since 95% CI is very wide and crosses unity

CI: confidence interval ;**ESA**: erythropoiesis-stimulating agent; **IV**: intravenous; **n.r.**: not reported **RR**: risk ratio

GRADE Working Group grades of evidence (or certainty in the evidence)

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

Summary of findings 2. IV or oral iron alone versus no treatment

IV or oral iron for cancer patients with anaemia

Patient or population: patients at any age with solid cancer or haematological malignancy

Settings: inpatient and outpatient care

Intervention: No ESA + IV iron, No ESA + oral iron

Comparison: No treatment

Outcomes	Anticipated absolute effects (95% CI)[1]		Relative effects (95% CI)[2]	Certainty of the evidence (GRADE)	Interpretation of findings
	Comparator	Intervention			
On-study mortality[3] (Subnet based on 55 studies including 15,074 participants)	No treatment **92 per 1000**	No ESA plus IV iron **271 per 1000** (65 to 1000)	**RR 2.95** (0.71 to 12.34)	⊕⊕⊖⊖ **low**[d]	Treatment with IV iron alone may increase on-study mortality compared to no treatment.
		No ESA plus oral iron **24 per 1000** (0 to 1000)	**RR 0.26** (0.00 to 19.73)	⊕⊕⊖⊖ **low**[d]	Treatment with oral iron alone may decrease or increase on-study mortality compared to no treatment.
Haemoglobin response (Subnet based on 31 studies including 6985 participants)	No treatment **90 per 1000**	No ESA plus IV iron **n.r.**	-	-	-
		No ESA plus oral iron **153 per 1000** (62 to 378)	**RR 1.70** (0.69 to 4.20)	⊕⊕⊖⊖ **low**[ab]	Treatment with oral iron alone may increase haemoglobin response compared to no treatment.
Red blood cell transfusions (Subnet based on 69 studies including 18,684 participants)	No treatment **362 per 1000**	No ESA plus IV iron **268 per 1000** (156 to 463)	**RR 0.74** (0.43 to 1.28)	⊕⊕⊖⊖ **low**[ab]	Treatment with IV iron alone may decrease or increase the need for red blood cell transfusions compared to no treatment.
		No ESA plus oral iron **333 per 1000** (195 to 568)	**RR 0.92** (0.54 to 1.57)	⊕⊕⊖⊖ **low**[ab]	Treatment with oral iron alone may decrease or increase the need for red blood cell transfusions compared to no treatment.
Overall mortality[4] (Subnet based on 71	No treatment **347 per 1000**	No ESA plus IV iron **521 per 1000** (219 to 1000)	**RR 1.50** (0.63 to 3.56)	⊕⊕⊖⊖ **low**[ac]	Treatment with IV iron alone may decrease or increase overall mortality compared to no treatment.

studies including 21,576 participants)		No ESA plus oral iron **534 per 1000** (229 to 1000)	**RR 1.54** (0.66 to 3.56)	⊕⊕⊖⊖ **low**[ac]	Treatment with oral iron alone may decrease or increase overall mortality compared to no treatment.
Thromboembolic events[5] (Subnet based on 50 studies including 15,408 participants)	No treatment **n.r.**	No ESA plus IV iron **n.r.**	-	-	-
		No ESA plus oral iron **n.r.**	-	-	-
Thrombocytopenia or haemorrhage[5] (Subnet based on 13 studies including 2744 participants)	No treatment **n.r.**	No ESA plus IV iron **n.r.**	-	-	-
		No ESA plus oral iron **n.r.**	-	-	-
Hypertension[5] (Subnet based on 24 studies including 8383 participants)	No treatment **n.r.**	No ESA plus IV iron **n.r.**	-	-	-
		No ESA plus oral iron **n.r.**	-	-	-

[1] Baseline risks obtained from the respective study population. Absolute risks in the intervention group result from product of control risk and risk ratio

[2] Results from network meta-analysis (random effects model). Network estimates are reported as risk ratios or mean difference with corresponding 95% confidence intervals.

[3]On-study mortality is defined as deaths occurring up to 30 days after the active study period.

[4]Overall mortality is defined as deaths occurring up to the longest follow-up available (median follow-up: 12 weeks).

[5]Events occurring during the whole study period.

[a] Downgraded one level for imprecision since 95% CI is wide and/or crosses unity

[b] Downgraded one level for inconsistency (heterogeneity)

[c] Downgraded one level for high risk of bias since exclusion of studies with overall high risk of bias changed results

[d]Downgraded two levels for imprecision since 95% CI is very wide and crosses unity

ESA: erythropoiesis-stimulating agent; **IV**: intravenous; **RR**: risk ratio; **CI**: confidence interval; **n.r.**: not reported

GRADE Working Group grades of evidence (or certainty in the evidence)

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

CI: confidence interval ;**ESA**: erythropoiesis-stimulating agent; **IV**: intravenous; **n.r.**: not reported **RR**: risk ratio

BACKGROUND

Description of the condition

A widely prevalent complication in patients suffering from cancer is the deficiency of haemoglobin-containing red blood cells (RBCs), referred to as anaemia (Knight 2004). The prevalence and incidence of anaemia in cancer patients is high, and it is an important contributor to morbidity and poor performance status (Ludwig 2004). The reported age-adjusted incidence rate of cancer in the USA in 2010 was 457.5 per 100,000 persons, with the age-adjusted death rate of 171.8 per 100,000 persons per year (Howlader 2014). The European prospective survey found a prevalence of anaemia in cancer patients of 39.3% at enrolment, increasing to 67% during the six months observation period (Ludwig 2004). Patients suffering from haematological malignancies frequently experience anaemia. This frequency ranges from 30% to 40% in patients diagnosed with Non-Hodgkin's Lymphomas (NHL) or Hodgkin's lymphoma (HL), up to 70% of patients with multiple myeloma, and higher in patients with myelodysplastic syndrome (Garton 1995; Tonia 2012). The intensity of anaemia has been classified, by the National Cancer Institute (NCI), based on the following haemoglobin (Hb) values (Groopman 1999):

- grade 0, within normal limits, Hb values are 12.0 g/dL to 16.0 g/dL for women and 14.0 g/dL to 18.0 g/dL for men;
- grade 1, mild (Hb 10 g/dL to normal limits);
- grade 2, moderate (Hb 8.0 g/dL to 10.0 g/dL);
- grade 3, serious/severe (Hb 6.5 g/dL to 8.0 g/dL); and
- grade 4, life-threatening (Hb less than 6.5 g/dL).

Anaemia of chronic disorders (ACD)

Due to an involvement of malignant bone marrow cells, the incidence rate of patients with symptomatic anaemia at the stage solid tumour diagnosis, prior to treatment, ranges from 31% to 50%. Furthermore, patients in advanced stages of haematological malignancies experience progressive anaemia with an incidence proportion of higher than 50% (Knight 2004; Ludwig 2004; Link 2013). With the exclusion of causes, such as iron or vitamin deficiencies, occult bleeding or pure RBC anaemia, progressive anaemia can be categorised as "anaemia of chronic disorders" (ACD). ACD is characterised by a close interaction of malignant cells and the patient's immune system, leading to inflammation. The severity of symptoms of anaemia varies among patients according to the progression of said disorder, including headaches, tachycardia, shortness of breath and palpitation. Chronic anaemia on the other hand may result in severe organ damage within the cardiovascular system, immune system and central nervous system (Nissenson 1992; Ludwig 2001).

Chemotherapy-induced anaemia (CIA)

The percentage of cancer patients, developing anaemia as a result of chemotherapy is estimated to be approximately 83% (Barrett-Lee 2006). CIA is most commonly reported in patients with gynaecological tumours, with a frequency of 81% to 88%, as well as patients with lung carcinoma (77% to 83%) (Ludwig 2004). CIA may manifest comparable to mild-to-moderate anaemia, with symptoms including dyspnoea, fatigue and weakness. These restrictive symptoms may lead to a decrease in quality of life and performance status of the patients (Littlewood 2001b; Stasi 2003; Mancuso 2006).

Radiotherapy-induced anaemia (RIA)

RIA is reported in 38% of all treated patients, with a repeating pattern of patients with gynaecological tumours and lung carcinoma showing the highest incidence proportion, with 54% and 51%, respectively. Moreover, the rate at which patients develop anaemia due to a combination of radiotherapy and chemotherapy is approximately 62% (Ludwig 2004).

Description of the intervention

Therapeutic alternatives are either treating the underlying cause or providing supportive care through RBC transfusions, recombinant human erythropoiesis-stimulating agents (ESAs), or iron (Rodgers 2012). Studies have shown a correlation of serious thromboembolic events and increased mortality of patients undergoing RBC transfusions (Bohlius 2006; Khorana 2008; Mercadante 2009).

Erythropoiesis-stimulating agents (ESAs)

ESAs contain proteins, which in response to a hypoxic environment stimulate the production of RBCs within the bone marrow. In the Cochrane Review evaluating ESAs versus no ESAs in cancer patients, Tonia and colleagues found that this interaction leads to a significant reduction of RBC transfusions (risk ratio (RR) 0.65 (95% confidence interval (CI) 0.62 to 0.68)) needed for the treatment of anaemic cancer patients and hence the potential to an increase in quality of life (QoL) (Tonia 2012). Even though, ESAs are thought to be an effective treatment in cancer patients suffering from chronic anaemia, ESAs have been shown to increase the risk of venous thromboembolisms by up to 57% (Bennett 2008). The risk ratio for thromboembolic complications was increased in patients receiving ESAs compared to controls (RR 1.52, 95% CI 1.33 to 1.73) (Tonia 2012). In addition, there is strong evidence for increased on-study mortality for patients receiving ESA (hazard ratio (HR) 1.17; 95% CI 1.06 to 1.29)(Tonia 2012).

Iron supplements

Iron supplements have been proposed as an adjunct to ESAs for the treatment of anaemic, as well as CIA/RIA patients. This is due to the fact that patients treated with ESAs alone have shown to produce iron-poor erythrocytes in the bone marrow, leading to a functional iron deficiency (FID) (Eschbach 2005). Mhaskar and colleagues reported iron supplementation to have a positive effect on the reduction in the risk for RBC transfusions (RR 0.74 (95% CI 0.60 to 0.92)) and increased Hb levels (mean difference (MD) 0.48 (95% CI 0.10 to 0.86)) when administered with ESAs (Mhaskar 2016). However, none of the eight included randomised controlled trials (RCTs) reported overall survival (Mhaskar 2016).

Both oral and intravenous (IV) iron therapy, including low-molecular weight iron dextran, iron sucrose and ferric gluconate, have shown adverse effects, such as constipation, nausea, emesis and diarrhoea (Fletes 2001; Mamula 2002; Chertow 2004; Chertow 2006). Intravenous iron might also lead to allergic reactions and pseudoanaphylaxis (anaphylactoid reactions), causing an anaphylaxis, in approximately 68 per 10,000 patients (Wang 2015).

ESAs plus iron supplements

Some evidence has been published, showing an increased response of ESAs, increased Hb levels, greater haematopoietic response and improved health-related quality of life in patients

being treated with both ESAs and IV iron Bastit 2008; Bellet 2007; Hedenus 2007; Pedrazzoli 2008).

How the intervention might work

ESAs contain an acidic glycoprotein-hormone, which facilitates the production of erythrocytes in the bone marrow. While the desired effect of an increase of Hb levels is achieved with the use of ESAs, the treatment without iron supplements often results in patients developing FID. FID is a result of ESAs reducing the amount of circulating iron molecules, hence yielding iron-poor erythrocytes in the bone marrow. Therefore, adjuvant iron is used to prevent the development of FID (Mhaskar 2016). Furthermore, iron supplements may reduce the required ESA dose to obtain desired Hb levels (Auerbach 2008).

Why it is important to do this review

Recommendations in guidelines are inconsistent regarding the usage of ESAs and iron, especially regarding IV iron. The guidelines by the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) do not consider the usage of IV iron as standard of care (Rizzo 2010). The European Organisation for Research and Treatment of Cancer (EORTC) (Bokemeyer 2007) guidelines found evidence for an improved response to ESA with IV iron, but point out that the doses and schedules for IV iron supplementation are not yet well-defined (Bokemeyer 2007). The guidelines by the European Society of Medical Oncology (ESMO) suggest additional iron to ESAs for iron-deficient patients (Schrijvers 2010), and the National Comprehensive Cancer Network (NCCN) guidelines consider IV iron supplementation for absolute or functional iron deficiency (Rodgers 2012).

In order to provide the highest level of evidence for treatment decisions in cancer patients, we conducted a network meta-analysis that summarises the direct and indirect evidence for different preventive and therapeutic strategies for anaemia due to chemotherapy, radiotherapy or chronic disorders in cancer patients.

OBJECTIVES

The objectives were to systematically review the effect of intravenous (IV) iron, oral iron or no iron in combination with or without erythropoiesis-stimulating agents (ESAs) on the prevention or alleviation of anaemia in cancer patients and to generate treatment rankings using network meta-analyses.

METHODS

Criteria for considering studies for this review

Types of studies

The protocol for this review was published as a Cochrane protocol and registered with PROSPERO (Weigl 2017). We considered only randomised controlled trials (RCTs). We included both full-text and abstract publications if sufficient information is available on study design, characteristics of participants and interventions provided.

Types of participants

We included trials on patients of any age with solid cancer and/or haematological malignancy undergoing chemotherapy, radiotherapy or no anti-cancer therapy. We applied no gender or ethnicity restrictions. We exclusively included studies in which participants were anaemic or at risk for anaemia from chemotherapy, radiotherapy or combination therapy, or the underlying malignant disease.

We excluded studies including patients with anaemia pre-planned for surgery or as a result of surgery, as well as patients suffering from anaemia due to haemolysis.

Types of interventions

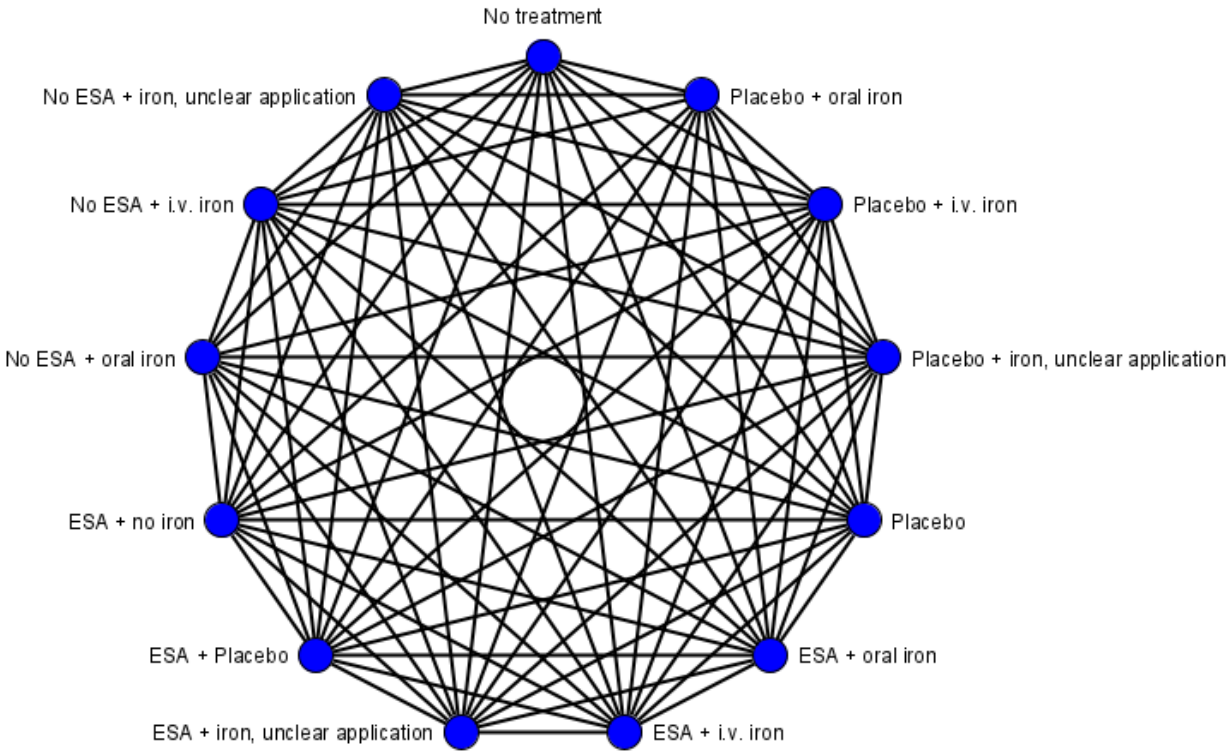
Included trials addressed one or multiple of the following interventions:

- ESA + IV iron;
- ESA + oral iron;
- ESA + no iron (including iron if necessary);
- ESA + iron, unclear application;
- ESA + placebo;
- no ESA + IV iron;
- no ESA + oral iron;
- no treatment (including iron if necessary);
- no ESA + iron, unclear application;
- placebo;
- placebo + IV iron;
- placebo + oral iron;
- placebo + iron, unclear application.

We used definitions from studies; most excluded administration of interventions of interest pre-randomisation.

All interventions were compared to each other using a network meta-analysis (Figure 1). We assumed that any patient that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the eligible interventions. We grouped interventions by merging doses and administration frequencies according to the product characteristics. Our main comparator *no treatment* means that patients received no treatment for anaemia while standard therapies for cancer could be given.

Figure 1. Overview of the ideal network (created with yEd)



We decided to combine the treatments *no iron* and *iron if necessary.*

To minimise the uncertainty in the network, we decided to exclude the treatment *iron unclear* because it is not known whether the patient has received iron or not.

Types of outcome measures

We estimated the relative ranking of the competing interventions according to the following outcomes:

- on-study mortality (deaths occurring up to 30 days after the active study period);
- haematological response (proportion of participants with an increase in haemoglobin (Hb) level of 2 g/dL or more, or increase in haematocrit (Hct) of six percentage points or more, unrelated to transfusion);
- number of patients with red blood cell transfusions;
- number of red blood cell (RBC) transfusions;
- overall mortality (longest follow-up available); and
- adverse events (AEs) during the whole study period.

Primary outcomes

As primary outcome we evaluated on-study mortality defined as deaths occurring up to 30 days after the active study period. This is due to the qualitatively low number of studies reporting long follow-up time periods. Long-term follow-up is prone to be less precise when it comes to recording the number of deaths, hence on-study mortality is more appropriate as a primary outcome measure.

Secondary outcomes

We analysed the following outcomes as secondary outcomes:

- haematological (Hb) response;
- number of patients with RBC transfusions;
- number of RBC transfusions;
- overall mortality; and
- AEs.

Search methods for identification of studies

We adapted search strategies as suggested in Chapter Four of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2021). We applied no language restrictions to reduce language bias. Only trials that compare at least two of the interventions were eligible. We searched for all possible comparisons formed by the interventions of interest.

Electronic searches

We searched the following databases and sources:

- databases of medical literature:
  - the Cochrane Central Register of Controlled Trials (CENTRAL, 2021, Issue 06) in the Cochrane Library (searched 16 June 2021) (Appendix 1);
  - MEDLINE (Ovid; Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions) (1946 to 15 June 2021) (searched 16 June 2021) (Appendix 2);
  - Embase (Ovid) (1972 to 15 June 2021) (searched 16 June 2021) (Appendix 3);

- conference proceedings of annual meetings of the following societies for abstracts, if not included in CENTRAL (2010 to June 2021):
  - American Society of Hematology;
  - American Society of Clinical Oncology;
  - European Hematology Association;
- databases of ongoing trials:
  - ClinicalTrials.gov (www.clinicaltrials.gov) (searched 16 June 2021) (Appendix 4);
  - World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch) (searched 16 June 2021) (Appendix 5);
- databases and websites of relevant institutions, and organisations (e.g. pharmaceutical industries).

Searching other resources

- Handsearching of references:
  - references of all identified trials and relevant review articles; current treatment guidelines as further literature.

We used the following sources to identify the studies for this network meta-analysis:

- previous Cochrane Reviews on the effect of ESAs on cancer patients with anaemia, as well as patients with CIA (Tonia 2012; Mhaskar 2016); and
- reference lists of other systematic reviews and meta-analyses.

Data collection and analysis

Selection of studies

Two of three review authors (AA, BS, NS) each independently screened results of search strategies for eligibility for this review by reading all abstracts. In cases of disagreement, we obtained the full-text publication. If no consensus could be reached, we consulted a third review author (Lefebvre 2021).

We documented the process of study selection in a flow chart, as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher 2009), showing total numbers of retrieved references and numbers of included and excluded studies.

Data extraction and management

Two of three review authors (AA, MH, NS) each extracted the data independently according to Chapter Five of the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2021). We contacted authors of individual studies to ask for additional information, if required. We used a standardised data extraction form containing the following items:

- general information:
  - author, title, source, publication date, country, language, duplicate publications;
- risk of bias assessment:
  - allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias;
- study characteristics:
  - trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, subgroup analysis, treatment cross-overs, compliance with assigned treatment, length of follow-up;
- participant characteristics:
  - patient's age, gender, number of participants recruited/allocated/evaluated, participants lost to follow-up, type of treatment, underlying disease, newly diagnosed or relapsed;
- interventions:
  - placebo use, ESA-dose, iron-dose, dosing regimen, duration, route of administration, RBC transfusion trigger, co-medications with dose, co-treatment, route and timing; and
- outcomes:
  - on-study mortality, haematological response, overall survival, AEs, number of RBC transfusions.

Data on potential effect modifiers

We extracted from each included study data on the following.

- Intervention and population characteristics that may act as effect modifiers (age, sex, haemoglobin value at baseline, cancer type, type of therapy, type of ESA)
- Year of publication

Assessment of risk of bias in included studies

Two of four review authors (AA, AH, MH, NS) each independently assessed risk of bias for each study using the following criteria, as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- sequence generation;
- allocation concealment;
- blinding (participants, personnel, outcome assessors);
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We made a judgement for each criterion, using one of the following categories:

- 'low risk': if the criterion is adequately fulfilled in the study (i.e. the study is at low risk of bias for the given criterion);
- 'high risk': if the criterion is not fulfilled in the study (i.e. the study is at high risk of bias for the given criterion); and
- 'unclear': if the study report does not provide sufficient information to allow a clear judgement, or if risk of bias is unknown for one of the criteria listed above.

Studies with two domains judged as high risk of bias were overall classified as having a high risk of bias.

Measures of treatment effect

We used intention-to-treat data. For binary outcomes, we used risk ratios (RRs) with 95% confidence intervals (CIs) as the measure of treatment effect. For time-to-event outcomes, we used hazard ratios (HRs) and their 95% CIs. Data were extracted from publications according to Parmar 1998 and Tierney 2007. We calculated continuous outcomes as mean differences (MDs) with 95% CIs. We did not expect continuous outcomes assessed with different instruments, so standardised mean difference (SMD) was not required.

Relative treatment ranking

We obtained a treatment hierarchy for each outcome using P scores (Rücker 2015). P scores allow ranking treatments on a continuous 0 to 1 scale in a frequentist network meta-analysis.

Unit of analysis issues

In the case of cross-over trials, only the first period of the trial was analysed.

Studies with multiple treatment groups

As recommended in Chapter 23.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b), for studies with multiple treatment groups, we combined arms as long as they could be regarded as subtypes of the same intervention.

When arms could not be pooled this way, we compared each arm with the common comparator separately. For pairwise meta-analysis, we split the 'shared' group into two or more groups with smaller sample size, and included two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, both the number of events and the total number of patients were divided up, and for continuous outcomes, the total number of participants was divided up with unchanged means and standard deviations. For network meta-analysis, instead of subdividing the common comparator, we used an approach that accounts for the within-study correlation between the effect sizes by re-weighting all comparisons of each multi-arm study (Rücker 2012; Rücker 2014).

Dealing with missing data

As suggested in Chapter 10.12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021), we took the following steps to deal with missing data.

If the number of patients evaluated for a given outcome was not reported, we used the number of patients randomised per treatment arm as denominator. If only percentages but no absolute number of events were reported for binary outcomes, we calculated numerators using percentages. If estimates for mean and standard deviations were missing, we calculated these statistics from reported data whenever possible, using approaches described in Chapter 5.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2021). If standard deviations were missing and we were not able to calculate them from reported data, we calculated values according to a validated imputation method (Furukwa 2006). If data were not reported in a numerical but graphical format, we estimated missing data from figures. We performed sensitivity analyses to assess how sensitive results were to imputing data in some way. We addressed the potential impact of missing data on findings of the review in the Discussion section.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

We evaluated the assumption of transitivity epidemiologically by comparing the distribution of the potential effect modifiers across the different pairwise comparisons. For each set of studies, grouped by treatment comparison, we created a table of important clinical and methodological characteristics. We visually inspected the similarity of these factors, including the inclusion and exclusion criteria of every trial in the network.

Assessment of transitivity across treatment comparisons

To infer about the assumption of transitivity, we assessed whether the included interventions are similar when they are evaluated in RCTs with different designs. Furthermore, we compared the distribution of the potential effect modifiers across the different pairwise comparisons.

Assessment of statistical heterogeneity and inconsistency

Pairwise meta-analyses

For each direct comparison, we visually inspected the forest plots as well as Cochran's Q based on a Chi^2 statistic and the I^2 statistic in order to detect the presence of heterogeneity. We interpreted I^2 values according to Chapter 10.10.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). We used the P value of the Chi^2 test only for describing the extent of heterogeneity and not for determining statistical significance. In addition, we reported τ^2, the between-study variance in random-effects meta-analysis.

Network meta-analysis

A very important pre-supposition for using network meta-analysis is to make sure that the network is consistent, meaning that direct and indirect evidence on the same comparisons agree. Inconsistency can be caused by incomparable inclusion and exclusion criteria of the trials in the network.

To evaluate the presence of inconsistency locally, we used the Bucher method for single loops of evidence (Bucher 1997), as described for example in Dias 2013. For each closed loop, we calculated the difference between direct and indirect evidence together with its 95% confidence interval (CI). We used loop-specific z-tests to infer about the presence of inconsistency in each loop. We used graphical representation of estimates of inconsistency together with 95% CIs and reported the percentage of inconsistent loops in the network. It should be noted that in a network of evidence there may be many loops and with multiple testing and there was an increased likelihood that we might find an inconsistent loop by chance. Therefore, we were cautious deriving conclusions from this approach.

To evaluate the presence of inconsistency in the entire network, we gave the generalised heterogeneity statistic Q_{total} and the generalised I^2 statistic, as described in Schwarzer 2015. We used the decomp.design command in the R package netmeta (R 2019; netmeta 2021) for decomposition of the heterogeneity statistic into a Q statistic for assessing the heterogeneity between studies with the same design and a Q statistic for assessing the design's inconsistency to identify the amount of heterogeneity/inconsistency within as well as between designs. Furthermore, we created a netheat plot (Krahn 2013), a graphical tool for locating inconsistency in network meta-analysis, using the command netheat in the R package netmeta. We gave Q_{total} and its components as well as net heat plots based on fixed-effect and random-effects models to identify differences between these approaches. For random-effects models, we reported τ^2.

If we found substantive heterogeneity and/or inconsistency, we explored possible sources by performing pre-specified sensitivity and subgroup analyses (see below). In addition, we reviewed the evidence base, reconsidered inclusion criteria as well as discussed the potential role of unmeasured effect modifiers to identify further sources.

Assessment of reporting biases

In pairwise comparisons with at least 10 trials, we examined the presence of small-study effects graphically by generating funnel plots. We used linear regression tests (Egger 1997) to test for funnel plot asymmetry. A P value less than 0.1 was considered significant for this test (Sterne 2011). We examined the presence of small-study effects for the primary outcome only.

Data synthesis

Methods for direct treatment comparisons

We performed analyses according to recommendations provided in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021), and used R (R 2019) for analyses.

If adequate, we performed standard pairwise meta-analyses using a random-effects model for every treatment comparison with at least two studies. We calculated corresponding 95% confidence intervals for all analyses. Since the focus of this review is on the network meta-analyses, and direct estimates are also reported in the league tables, we refrained from reporting forest plots of pairwise comparisons. When trials were clinically too heterogenous to be combined (e.g. various types of diseases), we performed only subgroup analyses without calculating an overall estimate.

Methods for indirect and mixed comparisons

If the data were considered sufficiently similar to be combined, we performed a network meta-analysis on all efficacy and safety outcomes using the frequentist weighted least squared approach described by Rücker 2012. We used a random-effects model, taking into account the correlated treatment effects in multi-arm studies. We assumed a common estimate for the heterogeneity variance across the different comparisons. To evaluate the extent to which treatments are connected, we gave a network plot for our primary and secondary outcomes. In the case of a network which is not fully connected, all existing subnetworks (subnets) are displayed. For each comparison, we evaluated the estimated treatment effect along with its 95% confidence interval. We graphically presented the results using forest plots, with placebo as reference. We used the R package netmeta (R 2019, netmeta 2021) for statistical analyses.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses for network meta-analyses were conducted on all efficacy and safety outcomes, if appropriate:

- type of iron (iron dextran, ferrous gluconate, ferrous sulphate, etc.);
- route of iron administration (IV versus oral);
- type of ESA (epoetin versus darbepoetin);
- type of anti-cancer therapy (chemotherapy, radiotherapy, no treatment);
- cancer type; and
- duration of follow-up.

Sensitivity analysis

To test the robustness of the results, we conducted fixed-effect pairwise and network meta-analyses. We reported the estimates of the fixed-effect only if they showed a difference to the random-effects model. We explored the influence of quality components with regard to low and high risk of bias for each outcome by excluding studies with at least two domains with high risk of bias. For overall mortality, blinding was always assessed as low, so for this outcome we excluded studies with at least one domain with high risk of bias.

Summary of findings and assessment of the certainty of the evidence

Review authors AA and NS independently rated the certainty of the evidence of each prioritised outcome. We used GRADEpro (Grades of Recommendation, Assessment, Development and Evaluation) software to rank the certainty of the evidence using the guidelines provided in Chapter 14.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schuenemann 2021) and specifically for network meta-analyses (Puhan 2014). The GRADE working group suggests to assess the certainty of the evidence of no more than seven outcomes, and for each outcome included in the summary of findings tables. Therefore, only for the outcomes that are the most critical or important for decision-making (Guyatt 2013).

The GRADE approach used five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty in the body of evidence for each outcome. The GRADE approach used the following criteria for assigning grade of evidence.

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

The GRADE system used the following criteria for assessing a certainty level to a body of evidence (Schuenemann 2021).

- High: randomised trials; or double-upgraded observational studies.
- Moderate: downgraded randomised trials; or upgraded observational studies.
- Low: double-downgraded randomised trials; or observational studies.
- Very low: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports.

We decreased grade if:

- serious (-1) or very serious (-2) risk of bias;
- important inconsistency (-1);

- some (-1) or major (-2) uncertainty about indirectness;
- imprecise data (-1) or very imprecise data (-2);
- high probability of reporting bias (-1).

We created summary of findings tables on absolute risks in each group, and in these tables, we summarised the evidence on on-study mortality, number of patients with RBC transfusions, haematological response, overall mortality, thromboembolic events, thrombocytopenia/haemorrhage and hypertension. In the summary of findings tables comparisons of ESA with IV iron, ESA with oral iron, ESA without iron, IV iron alone and oral iron alone against no treatment are displayed.

RESULTS

Description of studies

Results of the search

We identified 11,770 potentially relevant publications through database searches and handsearching. After we removed 4231 duplicates, we excluded a total of 7287 articles due to irrelevancy to our research question. The remaining 252 publications were screened in a full-text and abstract screening, depending on the availability of resources. Out of 252, we excluded 70 publications after a consensus on the ineligibility of the publication was reached by two review authors. Most of the 70 publications, of which 12 publications were ongoing and 18 were awaiting classification, were excluded because of the wrong intervention. Other reasons for exclusion include wrong comparator or wrong study design.

The total of 182 publications we identified as relevant for our research question, yielded 96 studies including 25,157 participants, which were included in our analysis. The overall numbers of references screened, identified, selected, excluded and included are documented according to the PRISMA flow diagram (Figure 2).

Figure 2. Study flow diagram.

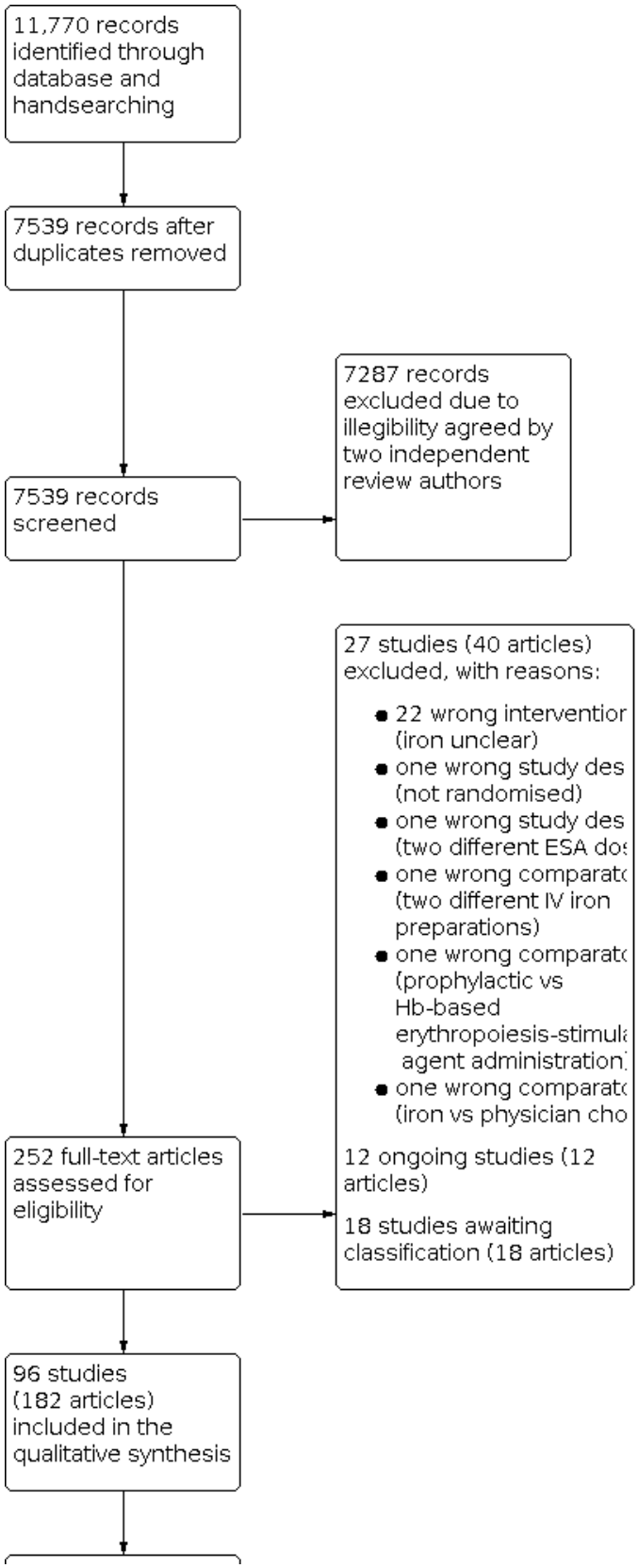
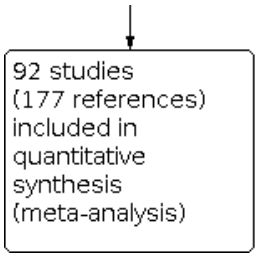


Figure 2. (Continued)



Included studies

All 96 included studies reported in 182 publications fit the inclusion criteria, set in our a-priori protocol (Weigl 2017). The time-line of recruitment ranged from late 1988 (Case 1993) to early 2020 (Hajigholami 2021), some studies did not provide information regarding time of recruitment. Detailed information on the included studies is summarised in the Characteristics of included studies table.

Design

All of the included studies consisted of randomised controlled trials (RCTs). Ninety-three trials were designed as two-armed RCTs, while three trials were designed as three-arm comparisons (Auerbach 2004; Henry 2007; Steensma 2011). A total of 31 studies were double-blinded, while 30 studies were not blinded (open-label); the remaining 35 studies did not report any information regarding blinding. Furthermore, only one study was conducted single centre (Aravantinos 2003), while 12 studies were multicentric. Most studies did not provide any information of whether they were single- or multicentric.

Sample sizes

Sample size among included trials varied from 19 randomised participants (Hedenus 2014) to 2549 participants (Gascon 2019). The average number of included participants among all included trials was 262.

Participants

Participants of any age, with a confirmed malignancy including myelodysplastic syndrome (MDS) were represented within the 96 included trials. Participants included in this analysis were undergoing chemotherapy, radiotherapy, radiochemotherapy, a mix of both therapies or received no anticancer therapy.

Among the included 96 studies, the included participants were diagnosed with haematological malignancy (11 trials), non-myeloid malignancy (one trial), MDS (two trials), mixed type of tumour (24 trials), and solid tumours (58 trials). The included participants were either female (19 studies), male (six studies) or both (56 trials). In the other 15 trials the gender distribution was not mentioned. In most studies, participants were older than 18 years. Only Ataollah Hiradfar 2018 and Razzouk 2006 included patients of younger age.

Interventions

Treatment groups were represented by any of the following intervention groups:

- ESA + IV iron;
- ESA + oral iron;
- ESA + no iron (including iron if necessary);
- ESA + iron, unclear application;
- ESA + placebo;
- no ESA + IV iron;
- no ESA + oral iron;
- no treatment (including iron if necessary);
- no ESA + iron, unclear application;
- placebo;
- placebo + IV iron;
- placebo + oral iron;
- placebo + iron, unclear application.

The network graph of the ideal network comparing all different interventions is represented in Figure 1. Control arms were most commonly represented by the intervention group of "ESA + no iron" (67/96). These studies had either mentioned an absence of iron supplementation in their methods section, or had no mention of iron supplementation throughout their publication, including those studies in which iron supplementation was given if necessary. Interventions with explicit mention of iron supplementation, in addition to ESA treatment, were classified as ESA + intravenous iron, oral iron or iron, unclear application. These intervention groups occurred to 10.4%, 14.6% and 7.3%,respectively. One out of 96 studies treated participants with "ESA + placebo". Seven trials were conducted in the absence of ESA (Ansari 2016; Athibovonsuk 2013; Birgegard 2015; Gilreath 2019; Hedenus 2014; Ng 2018; Noronha 2016). These studies analysed the impact of intravenous versus placebo, oral or no iron supplementation for the treatment of cancer-related anaemia.

Outcomes

Out of 96 trials, 66 trials reported our primary outcome of on-study mortality. Patients undergoing red blood cell (RBC) transfusions were reported by 77 trials, while only 21 trials reported the number of RBC-transfusions per patient. Moreover, 32 studies reported the haematological response (haemoglobin (Hb) response), while 80 trials reported overall survival (OS). Adverse events, including thromboembolic events, hypertension, haemorrhage, thrombocytopenia and rash were reported by 61, 28, 17, and 18 studies, respectively.

Ongoing studies

In total, there are 12 ongoing studies. Seven studies gave an exact date of the end of the study, which ranges from late 2017(ChiCTR-IPR-16009508; EUCTR2016-002021-11-PL) to mid 2022 (NCT03683810). No data regarding the end of study were available for four studies (ACTRN12620001105932p; ChiCTR-IPR-16009059;

CTRI/2019/05/019378; KCT0004311). Additionally, one study did not give an exact end date but reported an initial estimate of study duration of two years. It can therefore be assumed that the study most likely ended in 2020 (EUCTR2018-001669-17-GB). Chen 2016 and NCT02731378 had the most patients with 603 patients each and both ended in November 2019. All ongoing studies planned to enrol patients with cancer. However, only five studies gave more information regarding the type of malignancy. Furthermore, six studies investigate the effect of ESA + different forms of iron supplementation (Chen 2016; ChiCTR-IPR-16009059; ChiCTR-IPR-16009508; KCT0004311; NCT02731378; NCT03683810), while the remaining six studies compared the effect of different forms of iron supplementation without the use of ESA (ACTRN12620001105932p; CTRI/2019/05/019378; EUCTR2016-002021-11-PL; EUCTR2018-001669-17-GB; ISRCTN13370767; Zur Hausen 2016). Detailed information on the ongoing studies is summarised in the Characteristics of ongoing studies table.

Studies awaiting classification

In total, there are 18 studies awaiting classification. Eight studies were completed, but no results were available (CTRI/2011/12/002273; EUCTR2004-002176-42-IT; ISRCTN01957333; ISRCTN61345286; JPRN-JapicCTI-050013; JPRN-JapicCTI-080582; NCT03776032; NTR250). Another eight studies ended prematurely but no results were available (EUCTR2005-005658-37-DK; EUCTR2006-000137-35-LT; EUCTR2006-005965-20-SE; EUCTR2007-005777-57-GR; EUCTR2008-002723-85-IT; EUCTR2009-015766-56-GR; EUCTR2009-015767-14-SE; EUCTR2011-001664-22-AT). One trial was not started due to being cancelled (EUCTR2008-001721-34-BE) and for one trial there was insufficient information about the status of the trial (Anthony 2011).

Excluded studies

We excluded 27 full-texts studies for the following reasons:

- 22 wrong interventions (iron unclear) (Antonadou 2001; Bamias 2003; Cabanillas 2012; Carabantes 1999; EPO-GER-20 IPD; Fenaux 2017; Gebbia 2003; Hedenus 2002; Heidenreich 2015; Katakami 2008; Kunikane 2001; Leyland-Jones 2015; List 2016; OBE/EPO-INT-03 IPD; P-174 J&J 2004; Platzbecker 2017; Rosen 2003; Savonije 2005; Silvestris 1995; Suzuki 2008; Thompson 2000; Wurnig 1996);
- one wrong study design (not randomised) (Mafodda 2017);
- one wrong study design (two different ESA doses) (Vansteenkiste 2009);
- one wrong comparator (two different IV iron preparations) (Boccia 2019);
- one wrong comparator (prophylactic versus Hb-based erythropoiesis-stimulating agent administration) (Mountzios 2016);
- one wrong comparator (iron versus physician choice (no treatment, oral iron, ESA, or both)) (Tesch 2019).

Detailed information on the excluded studies is summarised in the Characteristics of excluded studies table.

Risk of bias in included studies

The risk of bias for the included studies was assessed and graded independently by two of four review authors (AA, AH, MH, NS) under the domains as specified by *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The risk of bias tables, which are part of the 'Characteristics of included studies' tables, addressed each domain for each study (Figure 3; Figure 4).

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

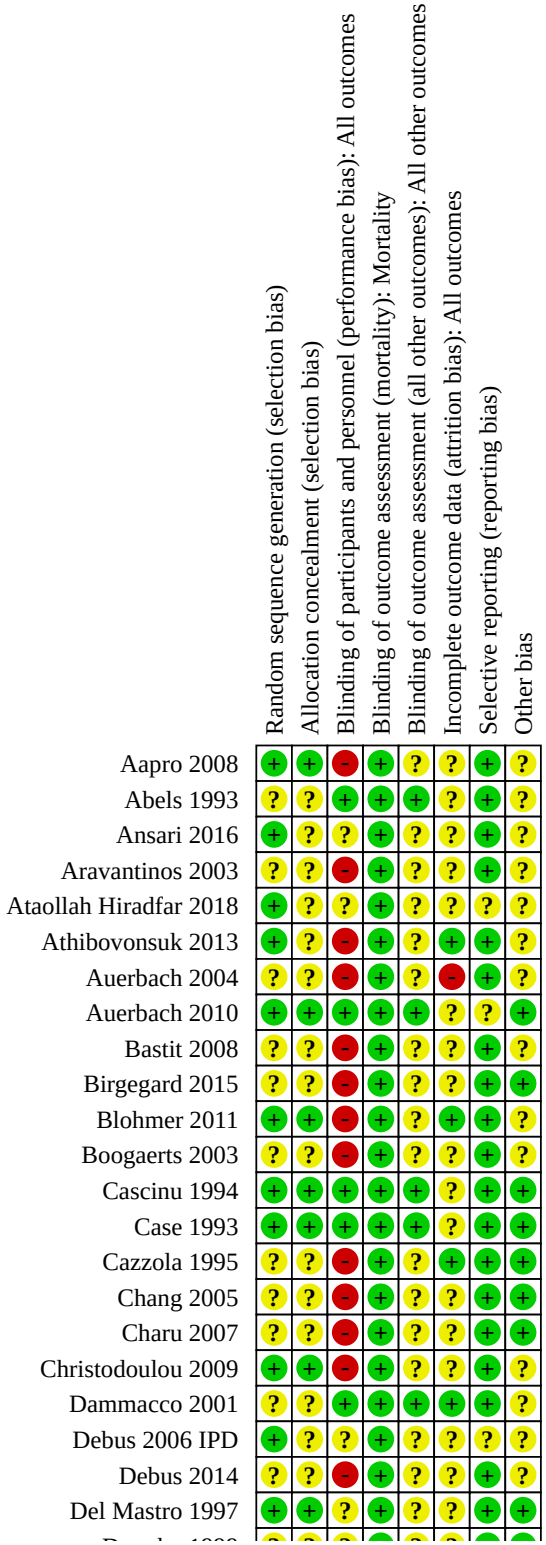


Figure 3. (Continued)

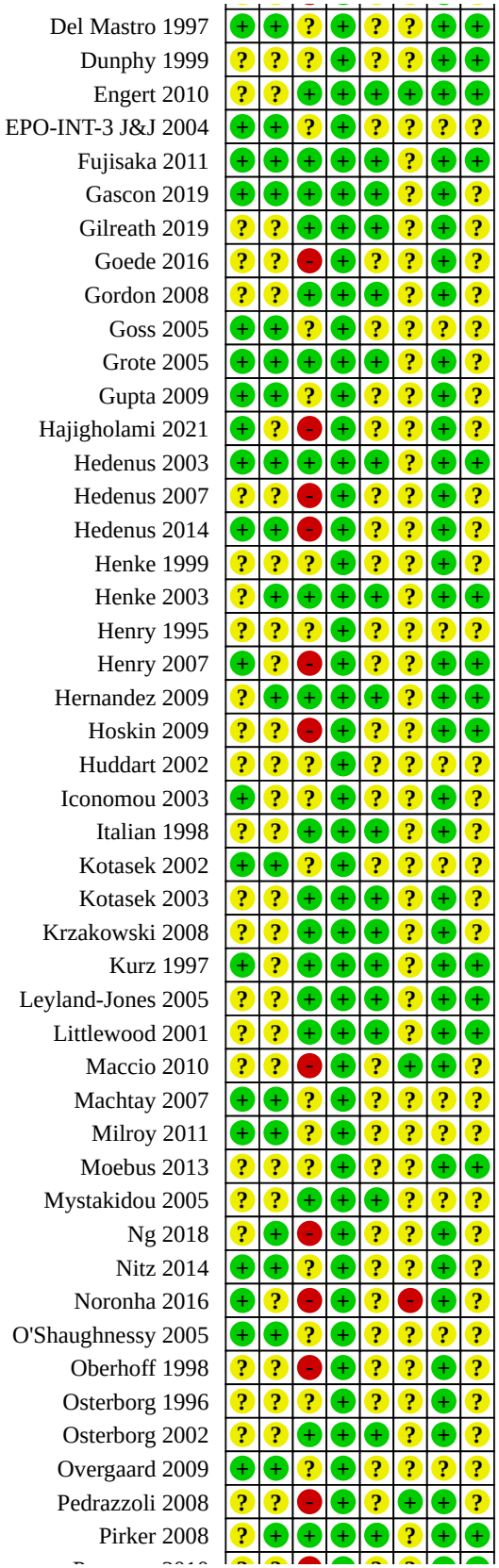


Figure 3. (Continued)

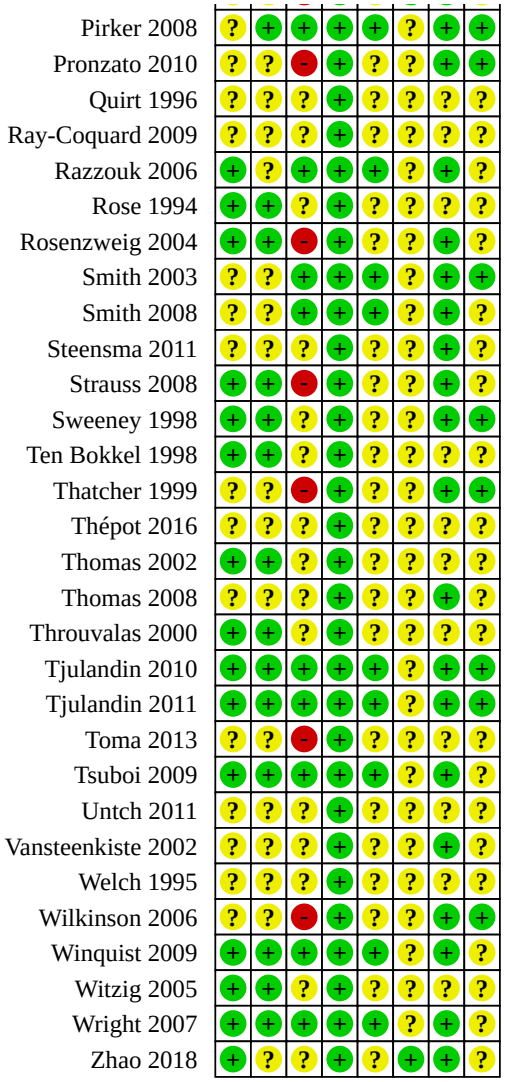
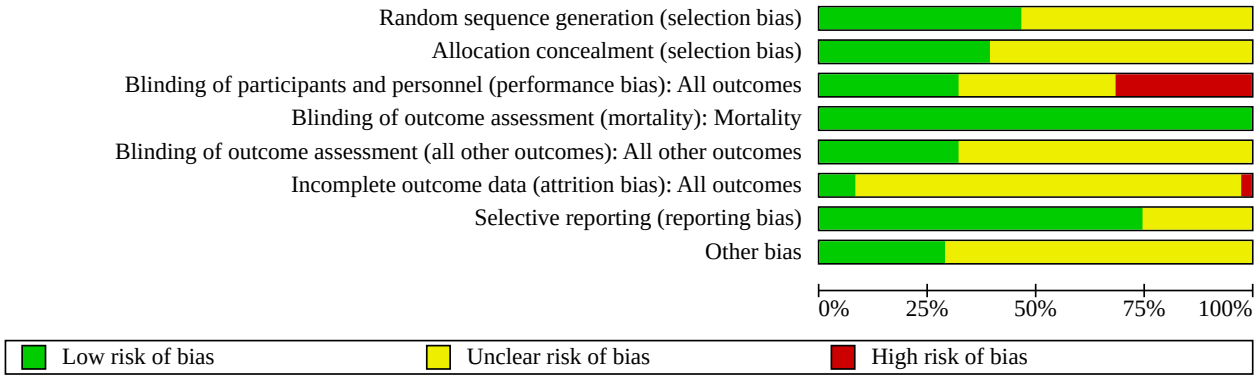


Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All 96 included studies reported that the trials were randomised. Forty-five studies (47%) described the method of randomisation and were therefore judged as low risk of bias. However, 51 of the 96 studies (53%) did not provide sufficient information concerning the method of randomisation used, and therefore they were judged as unclear risk of selection bias.

Furthermore, 40% (38/96) of the studies provided information regarding the allocation concealment and were therefore judged as having a low risk of bias. 60% (58/96) of the trials were judged as unclear risk of bias, due to insufficient information regarding allocation concealment. Due to being published in abstract form, Toma 2013 could not be evaluated regarding selection bias.

Blinding

Blinding of participants and personnel (performance bias)

Thirty-one studies (32%) were judged as having low risk of performance bias. Studies having a low risk rating most often reported their trial as being double-blinded. For 35 studies (37%) blinding of participants and personnel was not reported and we judged them as unclear risk of bias. The remaining 30 studies (31%) were judged as high risk for performance bias since participants and personnel were not blinded.

Blinding of outcome assessment (detection bias)

All included studies were judged as having low risk for blinding of outcome assessment (detection bias) regarding mortality. They were judged as having low risk because mortality is an objective outcome.

For the other outcomes, the outcome assessor was blinded in 31 studies (32%), resulting in low risk of bias. For the remaining 65 studies (68%) blinding of outcome assessment was not reported, we judged as unclear risk of bias.

Incomplete outcome data

Eight studies (8%) of the included studies were classified as having low risk for attrition bias because analysis was most commonly based on the evaluation of the intention-to-treat population. The larger part of the evaluated trials did not give information regarding attrition bias. Hence, 90% (86/96) of all included studies were judged as unclear risk of attrition bias. Two trials (2%) among the included studies were deemed to have high risk for attrition bias (Auerbach 2004; Noronha 2016), due to a modification of their intention-to-treat (ITT) population for efficacy analysis.

Selective reporting

For 75% (72/96) of the included studies, it was possible to evaluate reporting bias; for the remaining studies no study protocol or study registry entry was available (unclear risk of bias). Seventy-two out of the 96 trials were classified as having a low risk since there were no inconsistencies in the reported results. The remaining 25% (24/96) did not provide sufficient information to clarify any judgement regarding selective reporting and were therefore judged as unclear risk of bias.

Other potential sources of bias

We assessed 29% (28/96) as having a low risk of other bias, because we did not detect obvious reasons for bias. Due to insufficient information regarding other potential sources of bias, we judged the remaining 71% (68/96) as unclear risk of bias.

Effects of interventions

See: **Summary of findings 1** ESA with or without iron versus no treatment; **Summary of findings 2** IV or oral iron alone versus no treatment

The main findings are reported in the summary of findings tables (Summary of findings 1; Summary of findings 2). Since for most outcomes networks were not fully connected, we decided to report only treatments compared to our main comparator "no treatment" in the summary of findings tables. Results for other subnetworks (subnets) are reported in the text and additional tables.

For binary outcomes, studies with no events in both arms do not provide any indication of either direction or magnitude of the relative treatment effect and were therefore excluded from the analyses. In this section, our main comparator "No treatment" means that patients received no treatment for anaemia, while standard therapies for cancer could be given.

Since the focus of this review is on the network meta-analyses, and direct estimates are also reported in the league tables, we refrain from reporting forest plots of pairwise comparisons. Forest plots for pairwise comparisons can be found in Tonia 2012 and Mhaskar 2016.

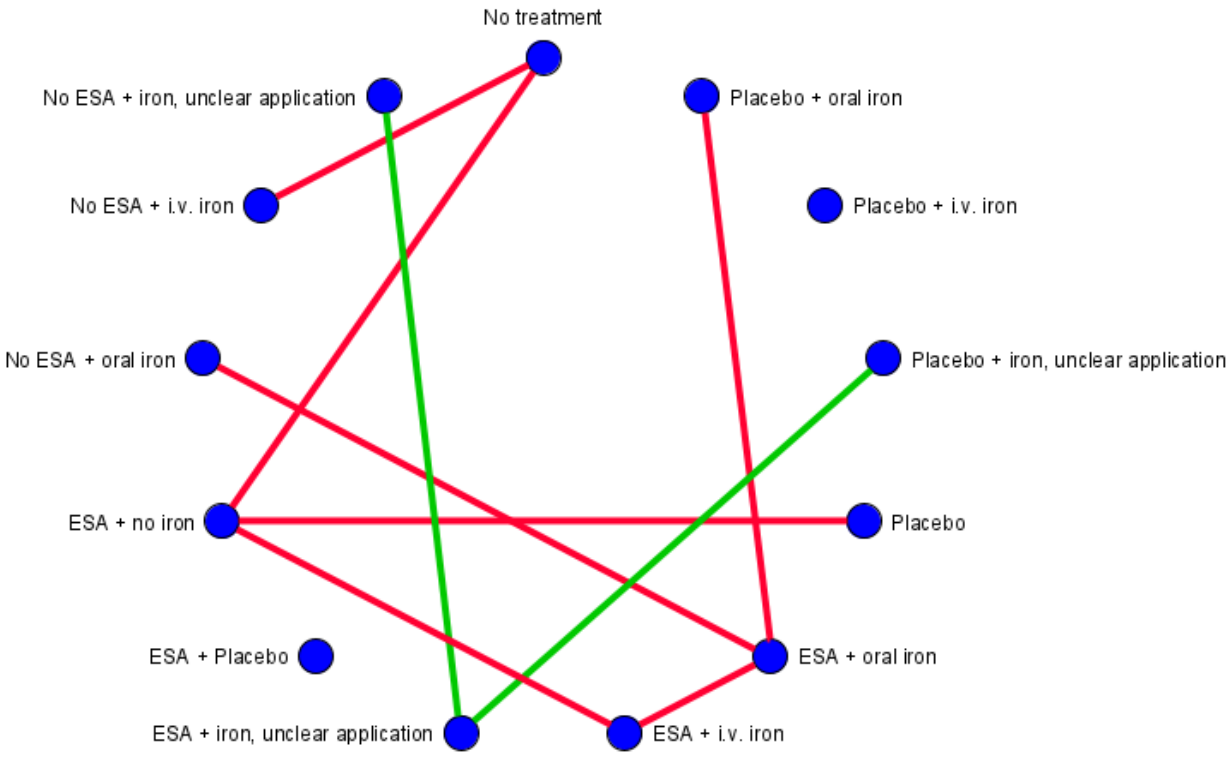
Transitivity

Included trials were similar in clinical and methodological characteristics that could potentially affect the relative treatment effects, thus we assumed the transitivity assumption holds. Distributions of potential effect modifiers across the different pairwise comparisons are displayed in Appendix 6. Since mechanisms and treatment strategies of anaemia in cancer patients are comparable between different cancer types, inclusion of different patient populations with different cancer types was considered unproblematic.

On-study mortality

Sixty-six RCTs (N = 17,688) reported on-study mortality of their participants. Eight studies (Cascinu 1994; Del Mastro 1997; Kurz 1997; Maccio 2010; Moebus 2013; Strauss 2008; Sweeney 1998; Untch 2011) including 1839 participants reported no events and were excluded from the analyses. The network, based on 58 pairwise comparisons, was not fully connected, but consisted of two subnets (Figure 5), with one subnetwork (subnet) consisting of 55 pairwise comparisons and one subnet consisting of only three pairwise comparisons. Eight treatment options could be compared in subnet 1 and three in subnet 2.

Figure 5. Network Graph for outcome on-study mortality (created with yEd). Red lines: Subnet 1. Green lines: Subnet 2. Orange lines: Subnet 3.



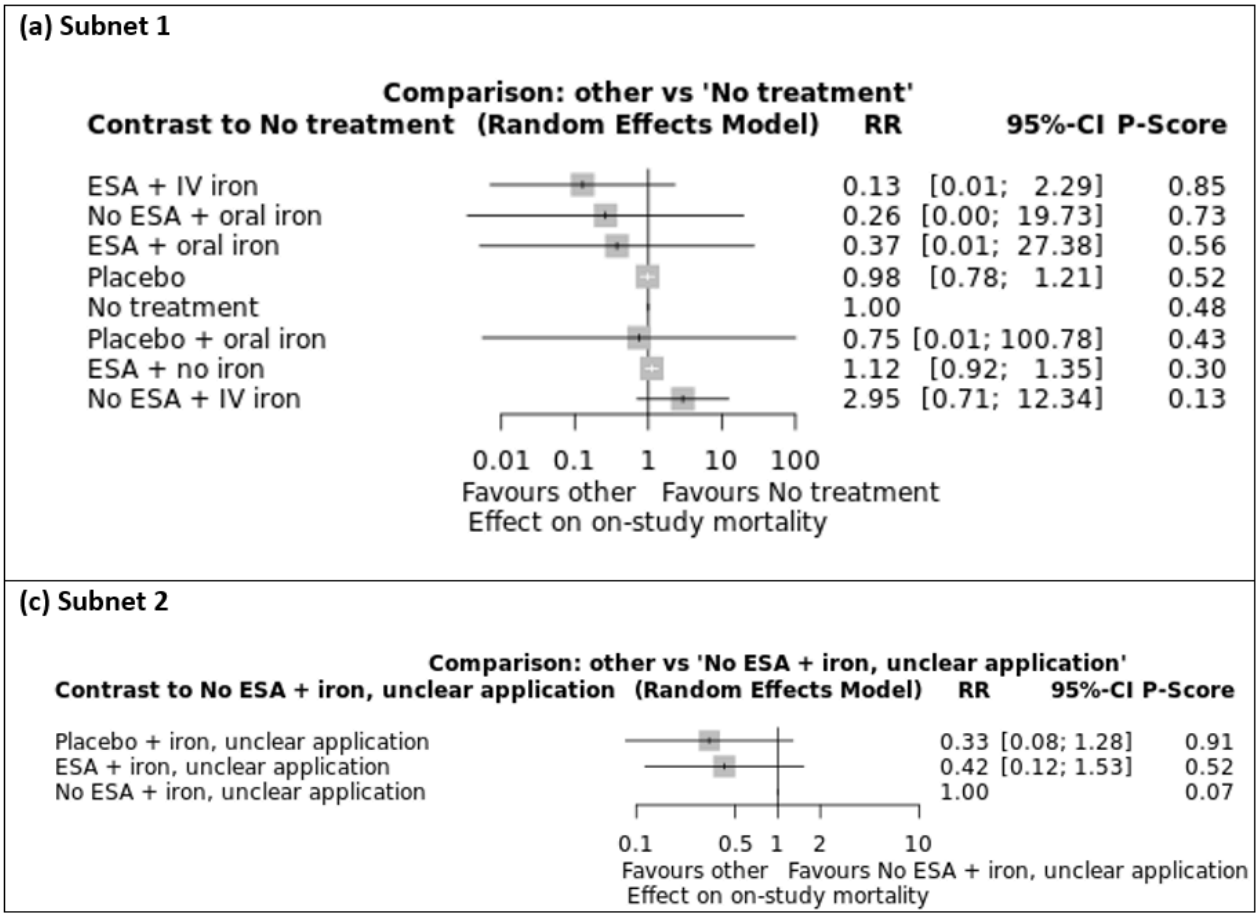
Pairwise comparisons

For five treatment comparisons only one study was included, therefore, no meta-analysis was performed, and individual study results were reported. For "ESA + no iron" vs. "Placebo," pairwise comparison showed increased on-study mortality for ESA administration (risk ratio (RR) 1.14, 95% confidence interval (CI) 1.03 to 1.26). Heterogeneity statistics showed no significant heterogeneity between the included studies, with I^2 = 0% for all pairwise comparisons. Pairwise meta-analysis showed no further meaningful results. Funnel plot analyses using linear regression tests were performed in pairwise comparisons with at least 10 trials. Analysis of funnel plot asymmetry for the comparisons of "ESA + no iron" with "Placebo", and "ESA + no iron" with "No treatment" did not identify evidence of small-study effects (P = 0.57, and P = 0.39, respectively) (data not shown).

Network meta-analysis

For both subnets a network meta-analysis was performed. A league table with results for all pairwise comparisons is shown in Table 1. In subnet 1, analysis resulted in increased on-study mortality for "ESA + no iron" compared to "Placebo" (RR 1.14, 95% CI 1.03 to 1.26) as already shown in pairwise meta-analysis. In subnet 2 no meaningful results were found. Cochran's Q-test and I^2 statistics showed no significant heterogeneity between studies (subnet 1: Q = 36.41, df = 48, P = 0.89, I^2 = 0%, Tau^2 = 0, subnet 2: Q = 0.24, df = 1, P = 0.62, I^2 = 0%, Tau^2 = 0). Ranking of treatments in both subnets showed no meaningful results since treatment effects had quite large confidence intervals (Figure 6).

Figure 6. Forest plot for outcome on-study mortality. (a) Subnet 1. Reference treatment: No treatment (b) Subnet 2: Reference treatment: No ESA + iron, unclear application. Treatments are ordered by P score (descending). RR: risk ratio. CI: confidence interval.



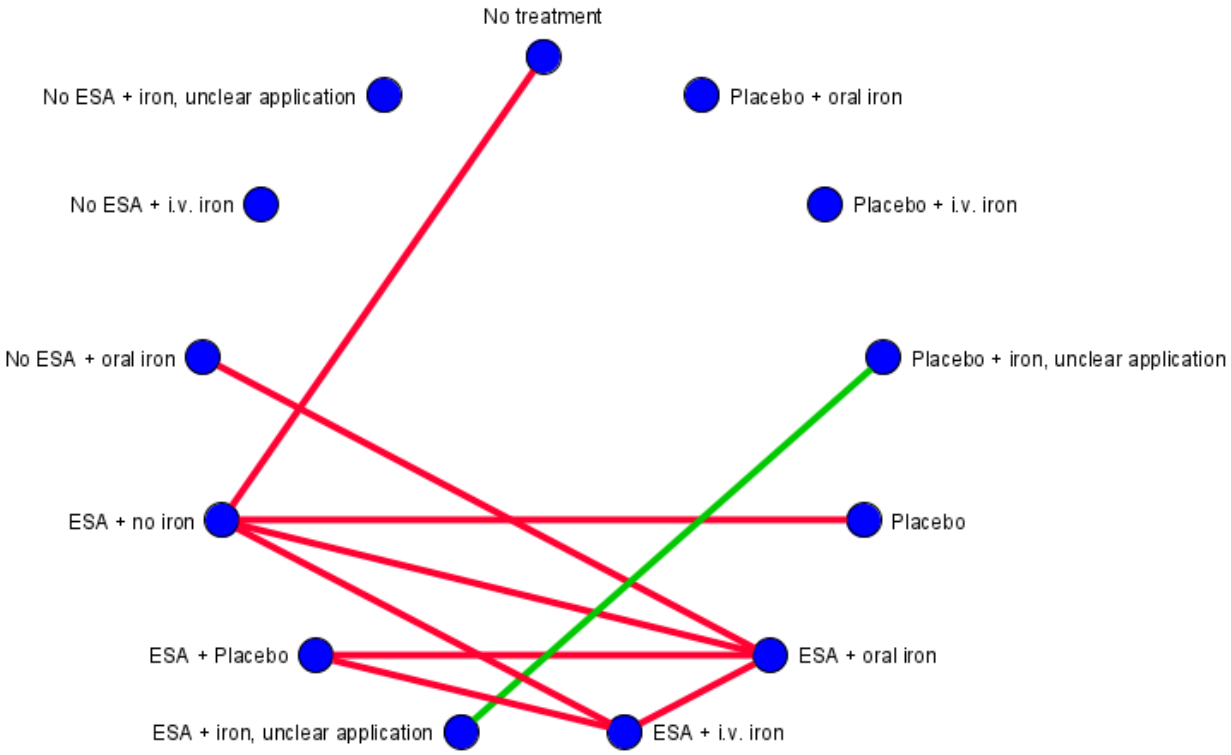
We rated the certainty of the evidence for on-study mortality according to the GRADE approach for "ESA + intravenous IV) iron", "ESA + oral iron", "ESA + no iron", "No ESA + Iv iron" and "No ESA + oral iron" compared to our main comparator "No treatment", respectively. We found that treatment with ESA and IV iron and treatment with ESA and oral iron may decrease or increase on-study mortality compared to no treatment (low certainty). We found that treatment with ESA alone probably slightly increases on-study mortality compared to no treatment (moderate certainty). Additionally, we found that treatment with IV iron alone may increase and treatment with oral iron alone may increase or decrease on-study mortality compared to no treatment (low certainty). Our main reason for downgrading was imprecision. Reasons for downgrading are provided in the summary of findings tables (Summary of findings 1; Summary of findings 2).

Since there were no closed loops in the networks, inconsistencies could not be statistically analysed.

Haematological response

Thirty-two studies (N = 7314) reported haematological response, including three three-arm studies. All studies reported at least one event and could be included in the analyses. The network was not fully connected, but consisted of two subnets (Figure 7) with one network consisting of 37 pairwise comparisons and one of only one pairwise comparison. Seven treatment options could be compared in subnet 1 and two in subnet 2.

Figure 7. Network graph for outcome Hb response (created with yEd). Red lines: Subnet 1. Green line: Subnet 2.



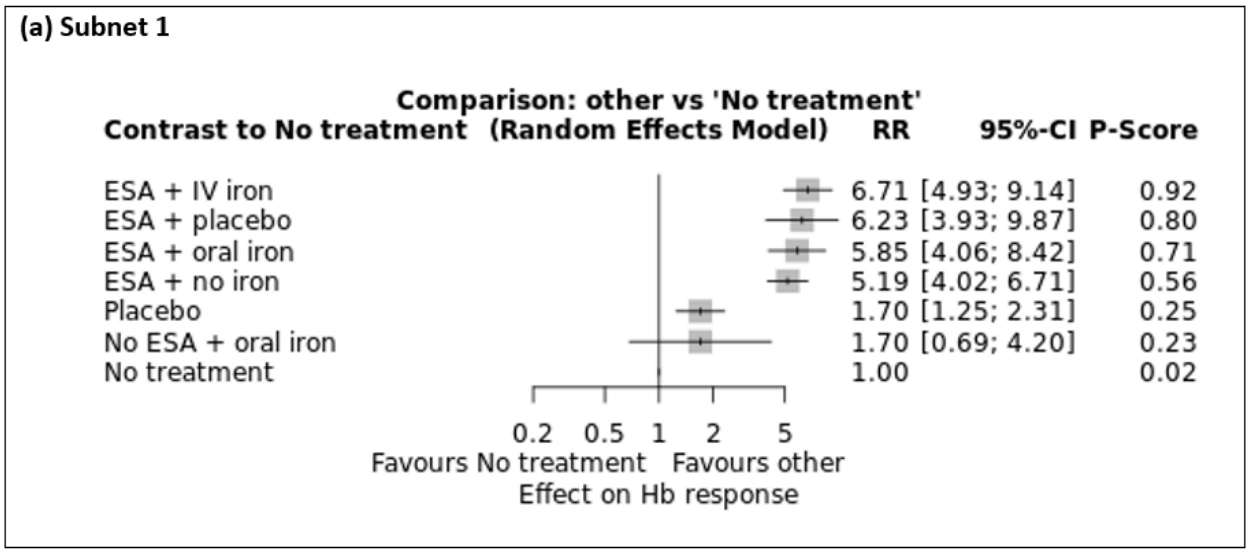
Pairwise comparisons

Pairwise comparisons showed a benefit for "ESA + no iron" compared to "Placebo" (RR 3.18, 95% CI 2.58 to 3.93) and to "No treatment" (RR 5.28, 95% CI 3.83 to 7.28). However, statistical tests suggest moderate heterogeneity for the studies comparing "ESA + no iron" and "No treatment" (I^2 = 44%, P = 0.09) and moderate to substantial heterogeneity for the studies comparing "ESA + no iron" and "Placebo" (I^2 = 57%, P < 0.01). "ESA + IV iron" showed a benefit compared to "ESA + no iron" (RR 1.25, 95% CI 1.17 to 1.36). Combination of ESA and oral iron also showed a beneficial effect compared to oral iron alone (RR 3.45, 95% CI 1.62 to 7.31). Furthermore, "ESA + iron, unclear application" showed a benefit compared to "Placebo + iron, unclear application" (RR 2.29, 95% CI 1.80 to 2.93) (data not shown).

Network meta-analysis

For this outcome, subnet 1 could be examined in network meta-analysis. The second network consisted only of one two-arm study (Witzig 2005). Results of network meta-analysis are illustrated in Table 2. "ESA + IV iron" resulted in higher Hb response compared to "ESA + no iron" (RR 1.29, 95% CI 1.09 to 1.54), "Placebo" (RR 3.95, 95% CI 3.10 to 5.04), "No ESA + oral iron" (RR 3.96, 95% CI 1.68 to 9.33) and "No treatment" (RR 6.71, 95% CI 4.93 to 9.14). Administration of "ESA + placebo" resulted in higher Hb response compared to "Placebo" (RR 3.67, 95% CI 2.42 to 5.58), "No ESA + oral iron" (RR 3.67, 95% CI 1.49 to 9.04) and "No treatment" (RR 6.23, 95% CI 3.93 to 9.87). Additionally, "ESA + oral iron" and "ESA + no iron" had a higher haemoglobin (Hb) response compared to "Placebo" (RR 3.45, 95% CI 2.53 to 4.70; RR 3.06, 95% CI 2.58 to 3.63), "No ESA + oral iron" (RR 3.45, 95% CI 1.50 to 7.90; RR 3.06, 95% CI 1.28 to 7.30) and "No treatment" (RR 5.85, 95% CI 4.06 to 8.42; RR 5.19, 95% CI 4.02 to 6.71). Finally, administration of "Placebo" resulted in higher Hb response compared to "No treatment" (RR 1.70, 95% CI 1.25 to 2.31). Cochran's Q-test and I^2 statistics showed moderate heterogeneity between studies (subnet 1: Q_{total} = 57.45, df = 28, P < 0.01 / Q_{within} = 51.30, df = 25, P < 0.01 / $Q_{between}$ = 6.14, df = 3, P = 0.10, I^2 = 51.3%, Tau^2 = 0.0321). For subnet 1 a treatment ranking could be conducted. In subnet 1 "ESA + IV iron" was ranked highest compared to "No treatment" (P score: 0.92) (Figure 8). The ranking also suggests higher efficacy for ESA administration compared to placebo and no administration of ESA.

Figure 8. Forest plot for outcome Hb response. (a) Subnet 1. Reference treatment: No treatment. Treatments are ordered by P-Score (descending). RR: risk ratio. CI: confidence interval.



We rated the certainty of the evidence for Hb response according to the GRADE approach for "ESA + IV iron", "ESA + oral iron", "ESA + no iron", "No ESA + IV iron" and "No ESA + oral iron" compared to our main comparator "No treatment", respectively. Nevertheless, we could not rate the certainty of the evidence for "No ESA + IV iron" as this treatment is not included in our network. We found that treatment with ESA and IV iron, ESA and oral iron and ESA without iron probably increases Hb response compared to no treatment (moderate certainty). Additionally, treatment with oral iron alone may increase Hb response compared to no treatment (low certainty). Our main reasons for downgrading were inconsistency and imprecision. Reasons for downgrading are provided in the summary of findings tables (Summary of findings 1; Summary of findings 2).

For the closed loops in subnet 1, inconsistencies could be analysed. For "ESA + IV iron" vs. "ESA + no iron" there is a clear difference between direct and indirect estimate, but the confidence intervals are overlapping. For all other comparisons, no noticeable disagreements between direct and indirect estimates were found (Table 3, Figure 9). The netheat plot also showed small signs of inconsistencies for the comparison "ESA + IV iron" vs. "ESA + no iron" (Figure 10).

Figure 9. Comparison of direct and indirect evidence (in closed loops) for outcome Hb response. RR: risk ratio. CI: confidence interval.

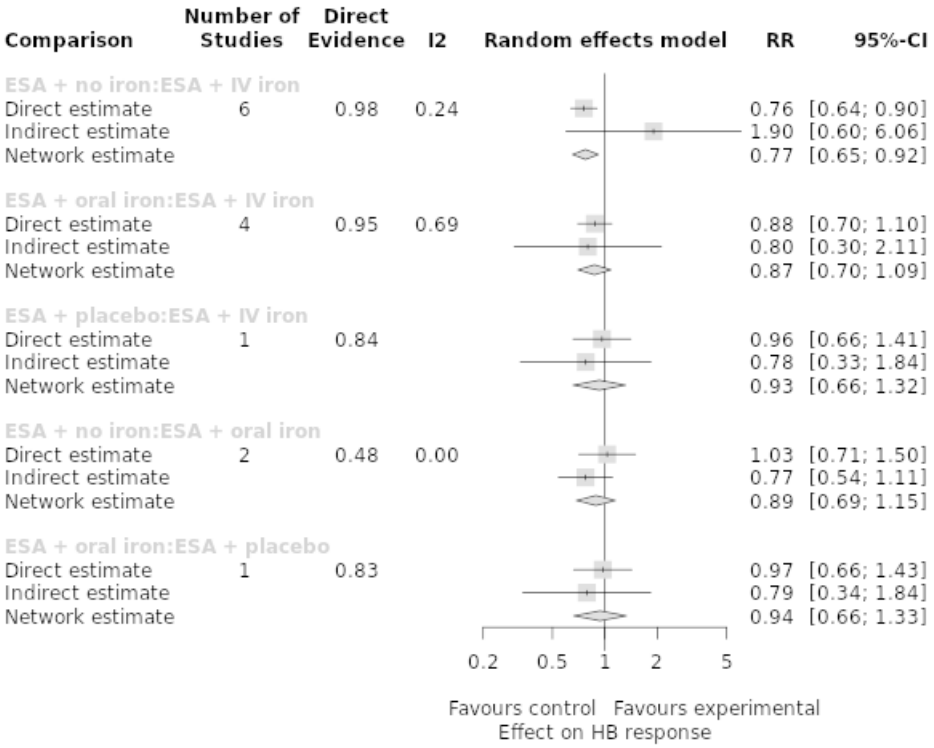
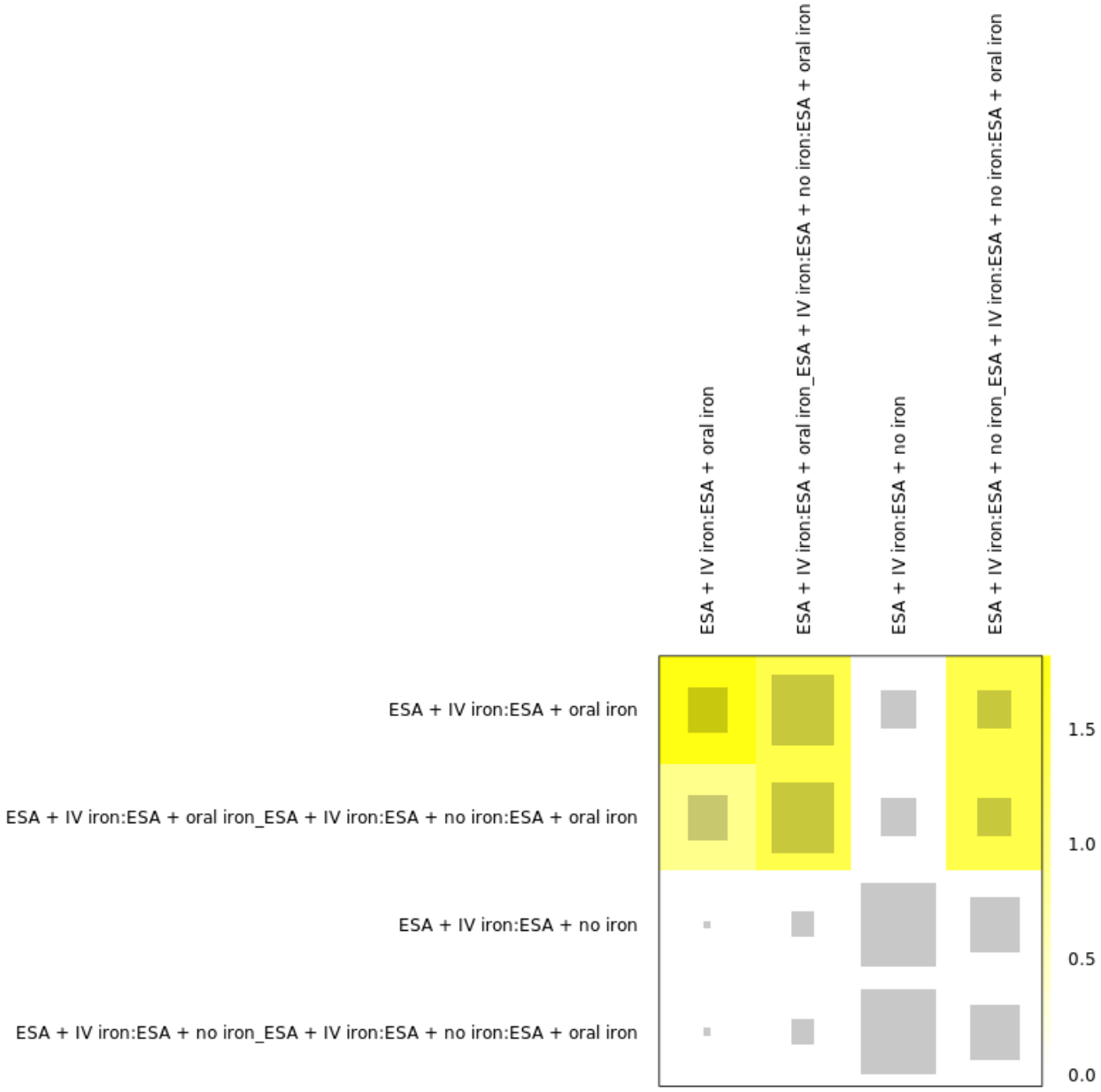


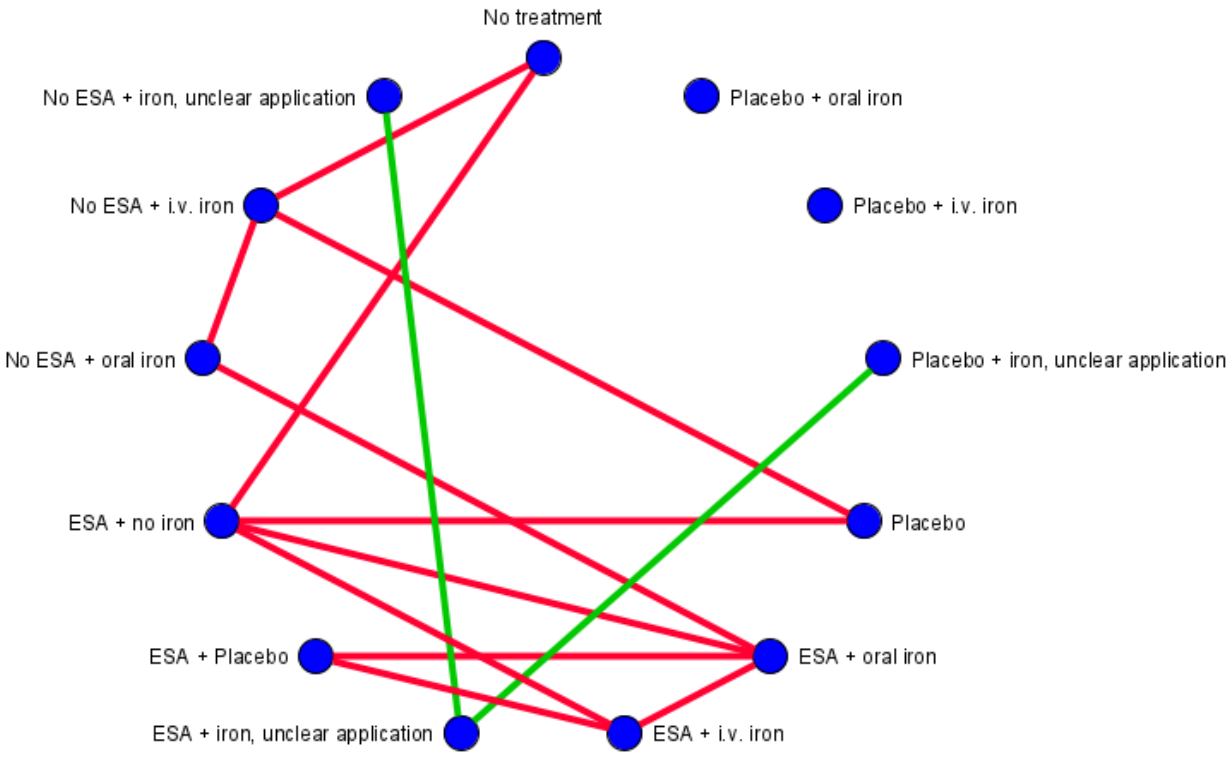
Figure 10. Netheat plot for outcome hb response (random effects model).



Red blood cell transfusions

Seventy-seven RCTs (N = 20,411) reported numbers of patients with red blood cell transfusions. Two studies (Hedenus 2014; Zhao 2018) including 99 participants reported no events and were therefore excluded from the analyses. The network, based on 81 pairwise comparisons, was not fully connected, but consisted of two subnets (Figure 11) with eight interventions in one network and three in the other one.

Figure 11. Network graph for outcome red blood cell transfusion (created with yEd). Red lines: Subnet 1. Green lines: Subnet 2.



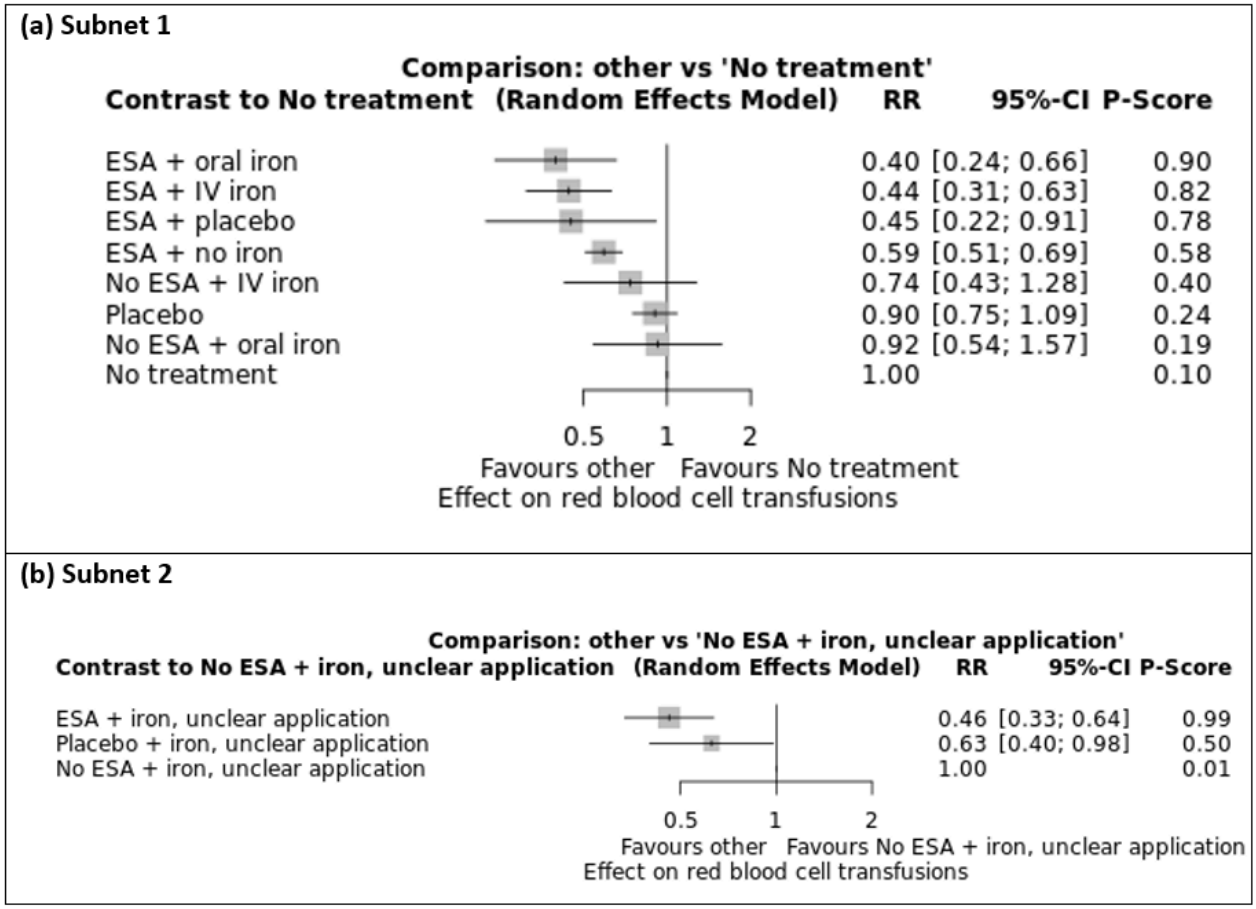
Pairwise comparisons

Pairwise comparisons showed a lower risk for red blood cell transfusions for "ESA + no iron" compared to "Placebo" (RR 0.66, 95% CI 0.60 to 0.73) and to "No treatment" (RR 0.56, 95% CI 0.46 to 0.68). However, statistical tests suggest substantial heterogeneity for both comparisons (I^2 = 62%, P < 0.01 and I^2 = 74%, P < 0.01). Combination of ESA and oral iron also showed a decreased need for red blood cell transfusions compared to oral iron alone (RR 0.45, 95% CI 0.36 to 0.55) and "ESA + no iron" (RR 0.43, 95% CI 0.19 to 0.99). Cochran's Q-test and I^2 statistics showed no significant heterogeneity for these pairwise comparisons (I^2 = 0%, P = 0.93 and I^2 = 0%, P = 0.97). Additionally, "ESA + IV iron" showed a lower risk for red blood cell transfusions compared to "ESA + no iron" (RR 0.75, 95% CI 0.58 to 0.96). Cochran's Q-test and I^2 statistics showed no significant heterogeneity for this pairwise comparison (I^2 = 0%, P = 0.67). Furthermore, "ESA + iron, unclear application" showed a decreased need for transfusions compared to "No ESA + iron, unclear application" (RR 0.46, 95% CI 0.34 to 0.63). Cochran's Q-test and I^2 statistics showed no significant heterogeneity for this pairwise comparison (I^2 = 12%, P = 0.33). (data not shown)

Network meta-analysis

For this outcome, both subnets could be examined in network meta-analyses. Results of network meta-analysis are illustrated in Table 4. "ESA + oral iron" resulted in lower need for red blood cell transfusions compared to "No ESA + IV iron" (RR 0.54, 95% CI 0.32 to 0.90), "Placebo" (RR 0.44, 95% CI 0.27 to 0.72), "No ESA + oral iron" (RR 0.43, 95% CI 0.33 to 0.57) and "No treatment" (RR 0.40, 95% CI 0.24 to 0.66). Administration of "ESA + IV iron" and "ESA + placebo" resulted in lower risk for need for red blood cell transfusions compared to "No ESA + oral iron" (RR 0.48, 95% CI 0.29 to 0.80; RR 0.49, 95% CI 0.25 to 0.97) and "No treatment" (RR 0.44, 95% CI 0.31 to 0.63; RR 0.45, 95% CI 0.22 to 0.91). Administration of "ESA + IV iron" further resulted in a lower risk for red blood cell transfusions compared to "Placebo" (RR 0.49, 95% CI 0.35 to 0.68). Additionally, "ESA + no iron" resulted in lower need for red blood cell transfusions compared to "Placebo" (RR 0.65, 95% CI 0.59 to 0.73) and "No treatment" (RR 0.59, 95% CI 0.51 to 0.69). In subnet 2, "ESA + iron, unclear application" and "Placebo + iron, unclear application" showed reduced need for red blood cell transfusions compared to "No ESA + iron, unclear application" (RR 0.46, 95% CI 0.33 to 0.64; RR 0.63, 95% CI 0.40 to 0.98). Cochran's Q-test and I^2 statistics showed moderate to substantial heterogeneity between studies for subnet 1 (Q_{total} = 162.04, df = 65, P < 0.01 / Q_{within} = 159.35, df = 61, P < 0.01 / $Q_{between}$ = 2.68, df = 4, P = 0.61, I^2 = 59.9%, Tau^2 = 0.0447) and no statistical meaningful heterogeneity for subnet 2 (Q = 5.00, df = 4, P = 0.29, I^2 = 19.9%, Tau^2 = 0.0168). For both subnets a treatment ranking could be conducted. In subnet 1 "ESA + oral iron" was ranked highest compared to "No treatment" (P score: 0.90) (Figure 12). The ranking also suggests higher efficacy for ESA administration compared to placebo and no administration of ESA. For subnet 2 "ESA + iron, unclear application" was ranked first compared to "No ESA + iron, unclear application" (P score: 0.99).

Figure 12. Forest plot for outcome red blood cell transfusions. (a) Subnet 1. Reference treatment: No treatment (b) Subnet 2. Reference treatment: No ESA + iron, unclear application. Treatments are ordered by P-Score (descending). RR: risk ratio. CI: confidence interval.



We rated the certainty of the evidence for red blood cell transfusions according to the GRADE approach for "ESA + IV iron", "ESA + oral iron", "ESA + no iron", "No ESA + IV iron" and "No ESA + oral iron" compared to our main comparator "No treatment", respectively. We found that treatment with ESA and IV iron, ESA and oral iron and ESA alone probably decreases the need for red blood cell transfusions compared to no treatment (moderate certainty). Additionally, treatment with IV iron alone and with oral iron alone may decrease or increase the need for red blood cell transfusions compared to no treatment (low certainty). Our main reasons for downgrading were inconsistency and imprecision. Reasons for downgrading are provided in the summary of findings tables (Summary of findings 1; Summary of findings 2).

For closed loops in subnet 1, inconsistencies could be analysed. Test for disagreement showed no significant disagreement between direct and indirect estimates in closed loops (Table 5, Figure 13). The netheat plot also showed no conspicuous signs of inconsistencies (Figure 14).

Figure 13. Comparison of direct and indirect evidence (in closed loops) for outcome red blood cell transfusions. RR: risk ratio. CI: confidence interval.

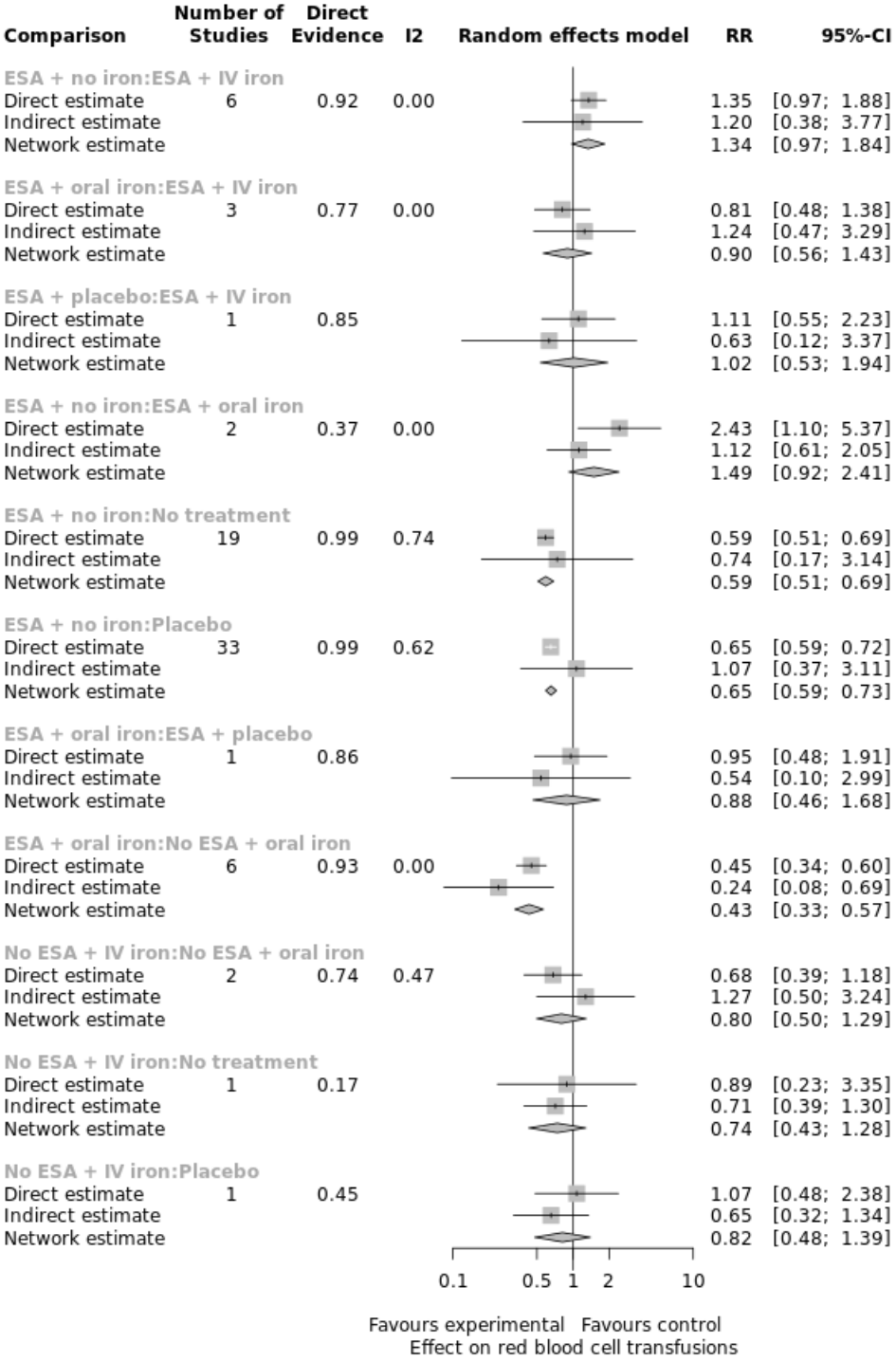
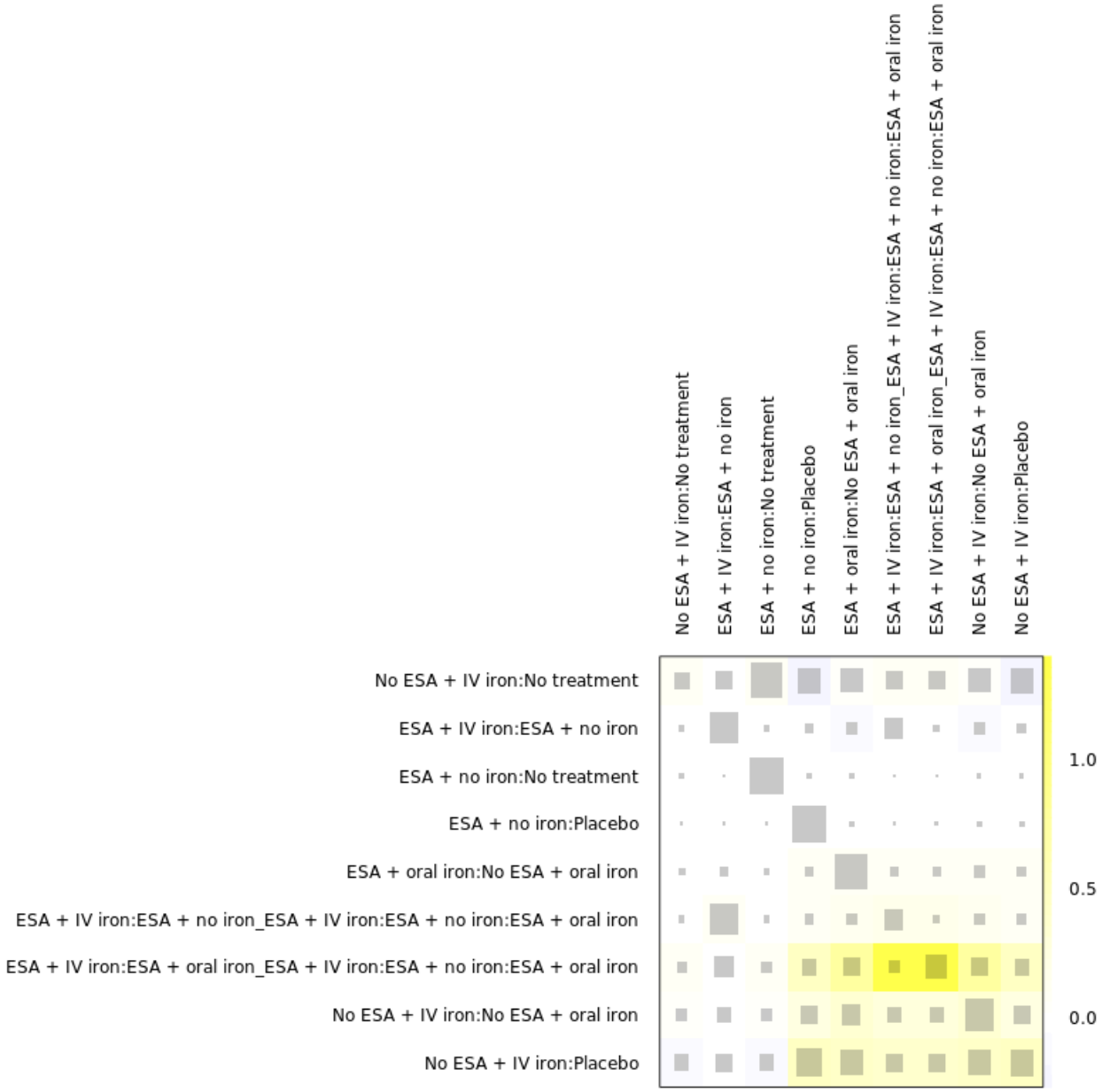


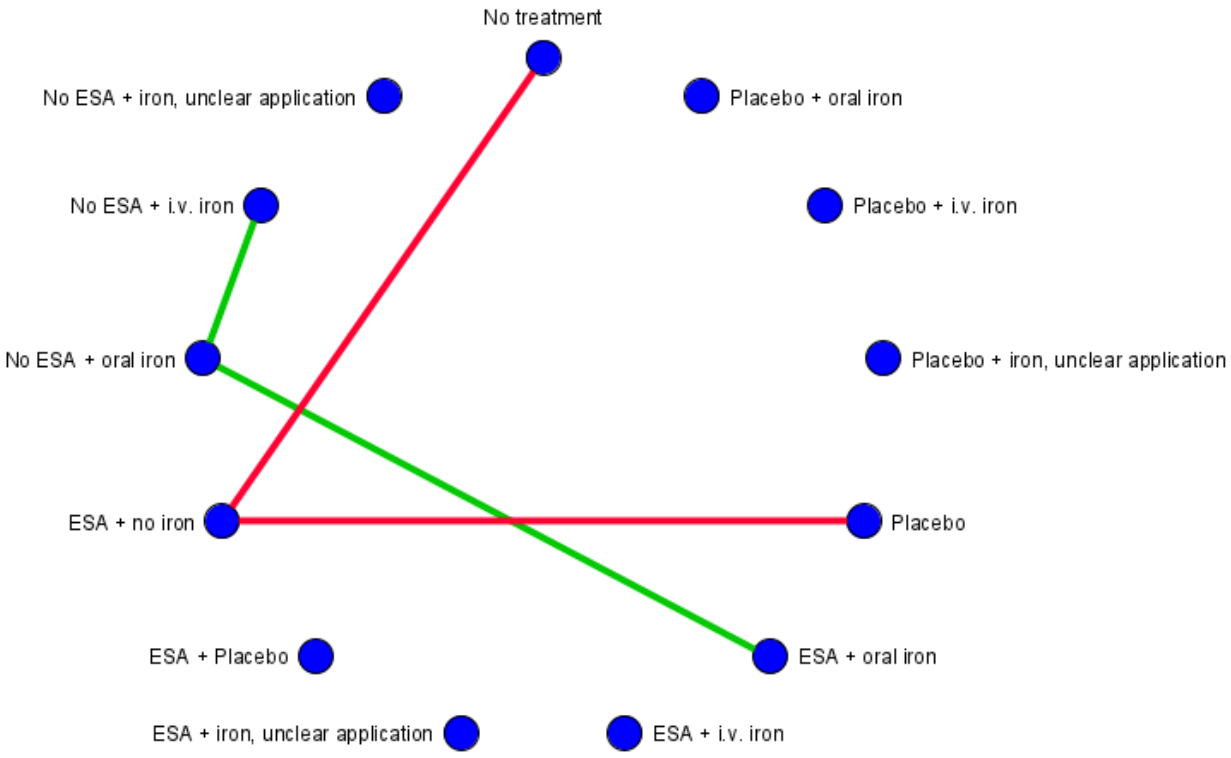
Figure 14. Net heat plot for outcome red blood cell transfusions (random effects model).



Number of red blood cell transfusions

Twenty-one studies (N = 4908) reported this outcome. All studies could be included in the analyses. In 19 studies no iron administration was given. The network was not fully connected, but consisted of two subnets, each with a maximum of three interventions studied (Figure 15).

Figure 15. Network graph for outcome number of red blood cell transfusions (created with yEd). Red lines: Subnet 1. Green lines: Subnet 2.



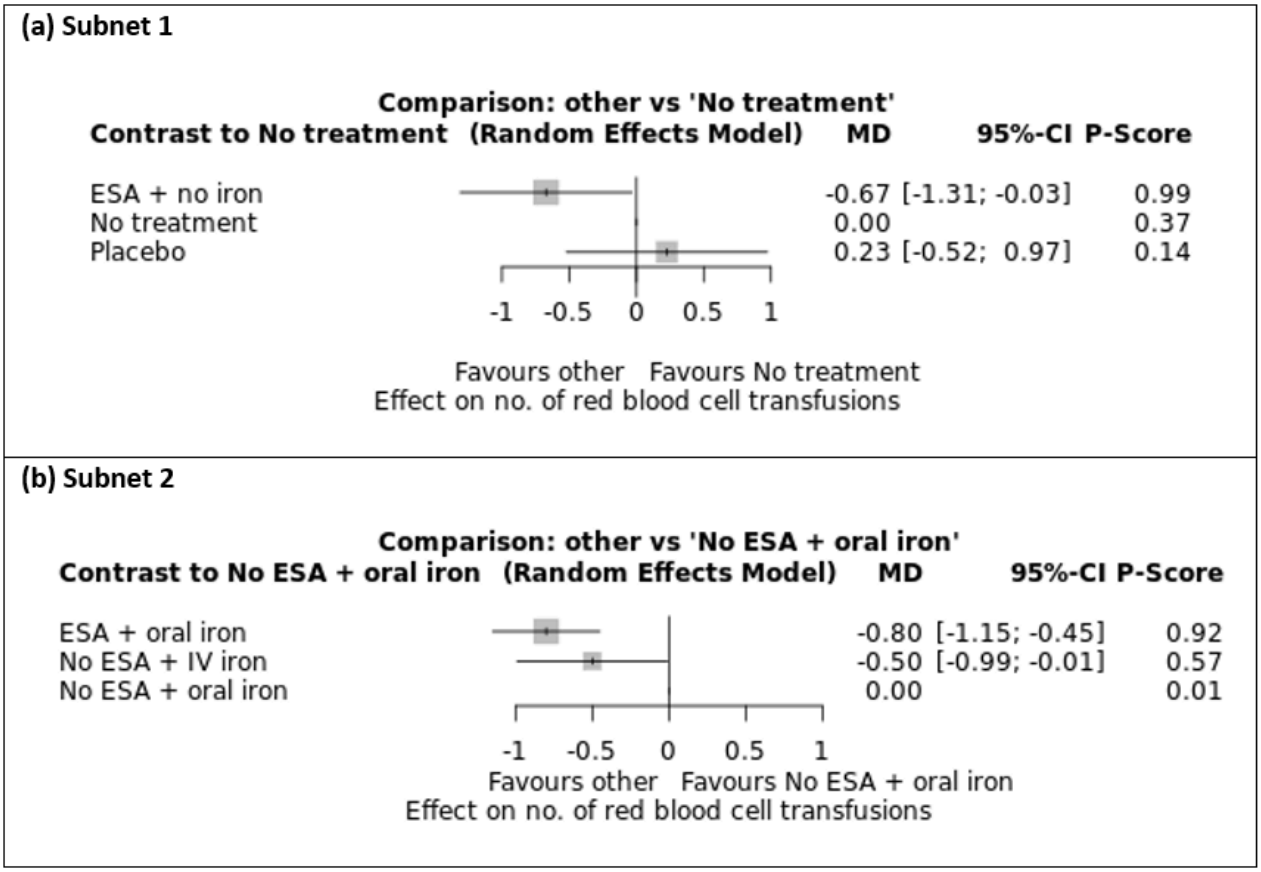
Pairwise comparisons

Pairwise comparisons favoured the interventions in which ESA is administered versus no ESA. Administration of "ESA + no iron" resulted in less transfusions compared to "No treatment" (mean difference (MD) -0.83, 95% CI -1.64 to -0.02) or "Placebo" (MD -0.90, 95% CI -1.25 to -0.55). Nevertheless, the fixed-effect model showed a different result for "ESA + no iron vs. no treatment" indicating no meaningful difference (RR -0.00, 95% CI -0.04 to 0.03). However, statistical tests suggest moderate heterogeneity for the studies comparing "ESA + no iron" and "Placebo" (I^2 = 51%, P = 0.02) and substantial heterogeneity for the studies comparing "ESA + no iron" and "No treatment" (I^2 = 67%, P < 0.01). Compared to "No ESA + oral iron", "ESA + oral iron" reduced number of transfusions (MD -0.80, 95% CI -1.15 to -0.45) as well as "No ESA + IV iron" (MD -0.50, 95% CI -0.99 to -0.01) (data not shown).

Network meta-analysis

Network meta-analyses confirmed results of pairwise comparisons (Table 6). Ranking in subnet 1 showed superiority of "ESA + no iron" compared to "No treatment" (P score: 0.99) (Figure 16). In subnet 2 "ESA + oral iron" reached highest P score when using "No ESA + oral iron" as reference treatment (P score: 0.92) (Figure 16).

Figure 16. Forest plot for outcome number of red blood cell transfusions. (a) Subnet 1. Reference treatment: No treatment (b) Subnet 2. Reference treatment: No ESA + oral iron. Treatments are ordered by P-Score (descending). MD: mean difference. CI: confidence interval.



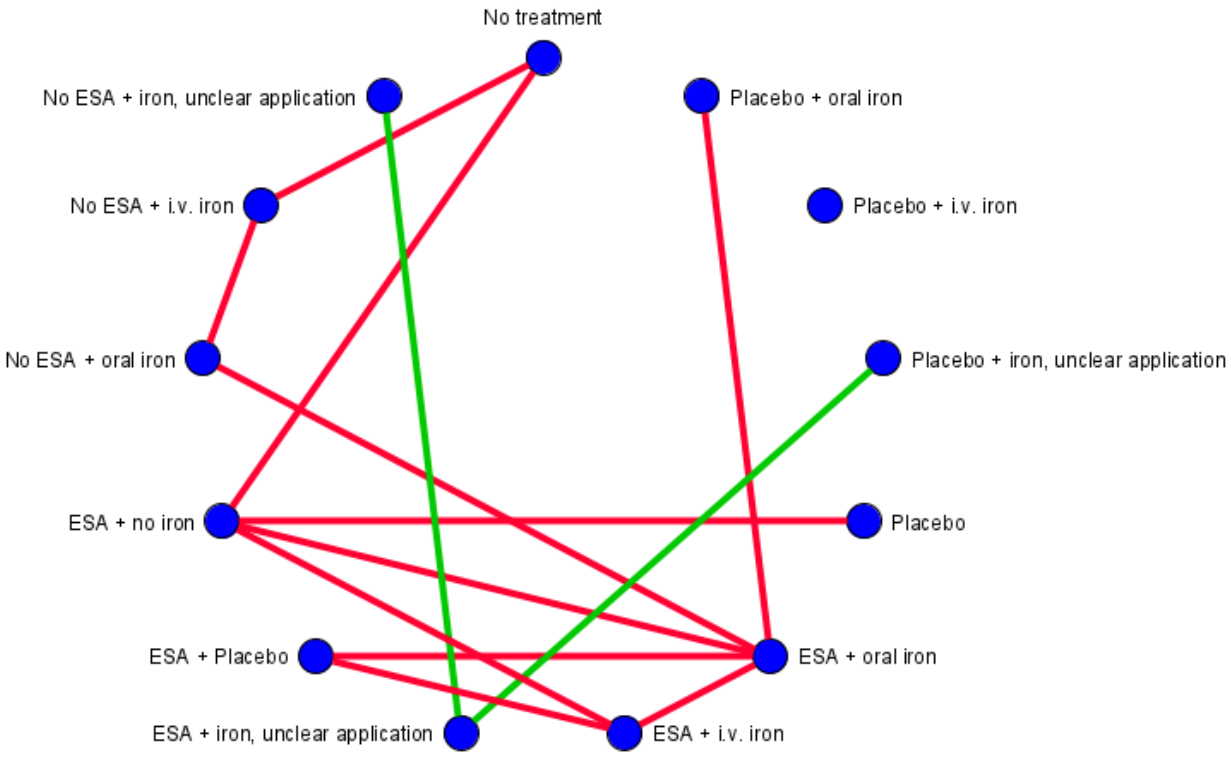
Since in the summary of findings table only seven outcomes can be displayed, the number of red blood cell transfusions was not included in the summary of findings table because numbers of patients with red blood cell transfusions were reported more often than numbers of red blood cell transfusions.

Inconsistencies could not be analysed since there were no closed loops.

Overall mortality

Since the intended outcome overall survival was reported heterogeneously in included studies, we used a different method to analyse the outcome from that reported in the protocol as binary outcome (overall mortality) to include as much study data as possible. 80 RCTs (N = 23,488) reported overall mortality of their participants. Four RCTs (Cascinu 1994; Kurz 1997; Maccio 2010; Sweeney 1998) including 331 participants reported no events and were therefore excluded from network meta-analysis. The network, based on 80 pairwise comparisons, was not fully connected (Figure 17), but consisted of two subnets with nine interventions in one network and three in the other one.

Figure 17. Network graph for outcome overall mortality (created with yEd). Red lines: Subnet 1. Green lines: Subnet 2.



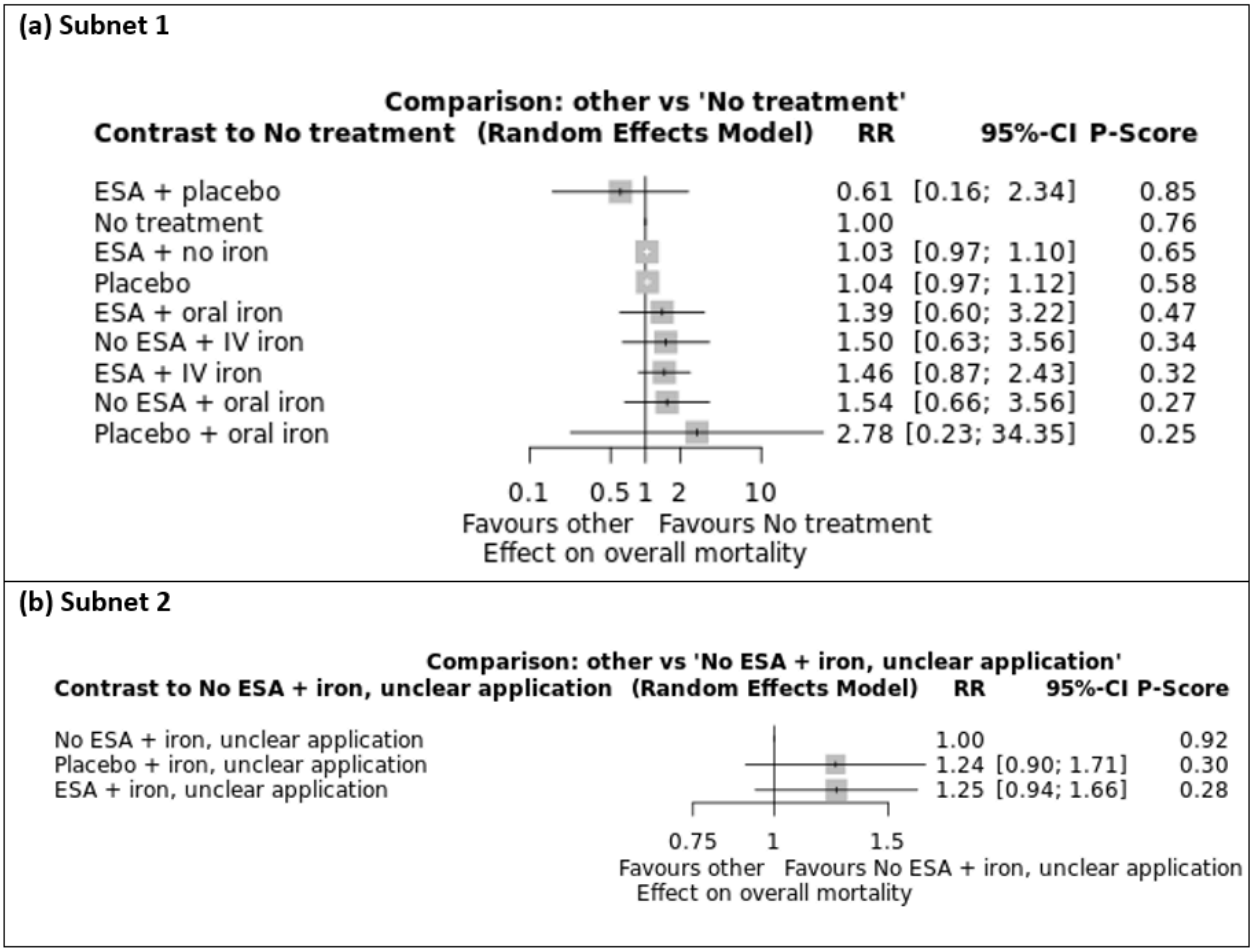
Pairwise comparisons

Pairwise comparison showed a benefit for“ESA + oral iron" compared to" No ESA + oral iron” indicating a lower mortality risk for "ESA + oral iron" (RR 0.91, 95% CI 0.84 to 0.98). Nevertheless, the fixed-effect model showed a different result indicating no benefit for "ESA + oral iron" (RR 0.92, 95% CI 0.84 to 1.02). None of the other pairwise comparisons in both subnets showed important benefits. Heterogeneity statistics showed no meaningful heterogeneity in pairwise comparisons, with an I^2 of 0-15% for all pairwise comparisons (data not shown).

Network meta-analysis

For each subnet we performed a network meta-analysis. Results for all network comparisons are shown in the league table in Table 7. "ESA + oral iron" resulted in lower overall mortality compared to "No ESA + oral iron" (RR 0.91, 95% CI 0.84 to 0.98). Cochran's Q-test and I^2 statistics showed no significant heterogeneity between studies (subnet 1: Q_{total} = 61.55, df = 65, P = 0.60 / Q_{within} = 59.02, df = 61, P = 0.55 / $Q_{between}$ = 2.53, df = 4, P = 0.64; I^2 = 0%, Tau^2 = 0; subnet 2: Q = 1.27, df = 3, P = 0.74; I^2 = 0%, Tau^2 = 0). For each subnet a treatment ranking was conducted (Figure 18). Rankings of treatments in both subnets showed no meaningful results since treatment effects had quite large confidence intervals.

Figure 18. Forest plot for outcome overall mortality. (a) Subnet 1. Reference treatment: No treatment (b) Subnet 2. Reference treatment: No ESA + iron, unclear application. Treatments are ordered by P-Score (descending). RR: risk ratio. CI: confidence interval.



We rated the certainty of the evidence for overall mortality according to the GRADE approach for "ESA + IV iron", "ESA + oral iron", "ESA + no iron", "No ESA + IV iron" and "No ESA + oral iron" compared to our main comparator "No treatment", respectively. We found that treatment with ESA with or without IV or oral iron may decrease or increase overall mortality compared to no treatment (low certainty). Additionally, treatment with ESA alone may lead to little or no difference in overall mortality compared to no treatment (low certainty). Our main reasons for downgrading were imprecision and high risk of bias since excluding studies with overall high risk of bias changed results. Reasons for downgrading are provided in the summary of findings tables (Summary of findings 1; Summary of findings 2).

For closed loops in subnet 1, inconsistencies could be analysed. Test for disagreement showed no significant disagreement between direct and indirect estimates in closed loops (Table 8, Figure 19). The netheat plot also showed no conspicuous signs of inconsistencies (Figure 20).

Figure 19. Comparison of direct and indirect evidence (in closed loops) for outcome overall mortality. RR: risk ratio. CI: confidence interval.

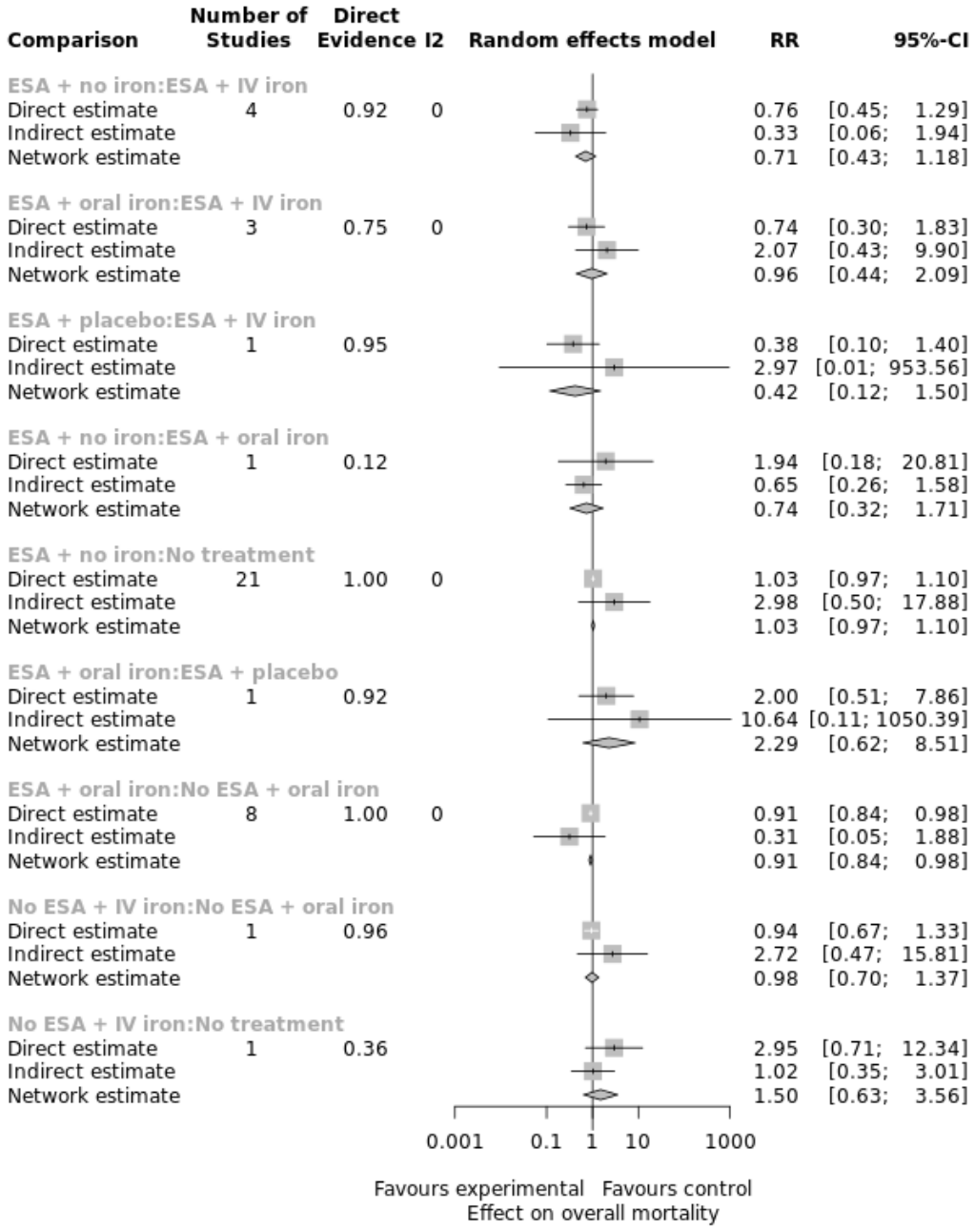
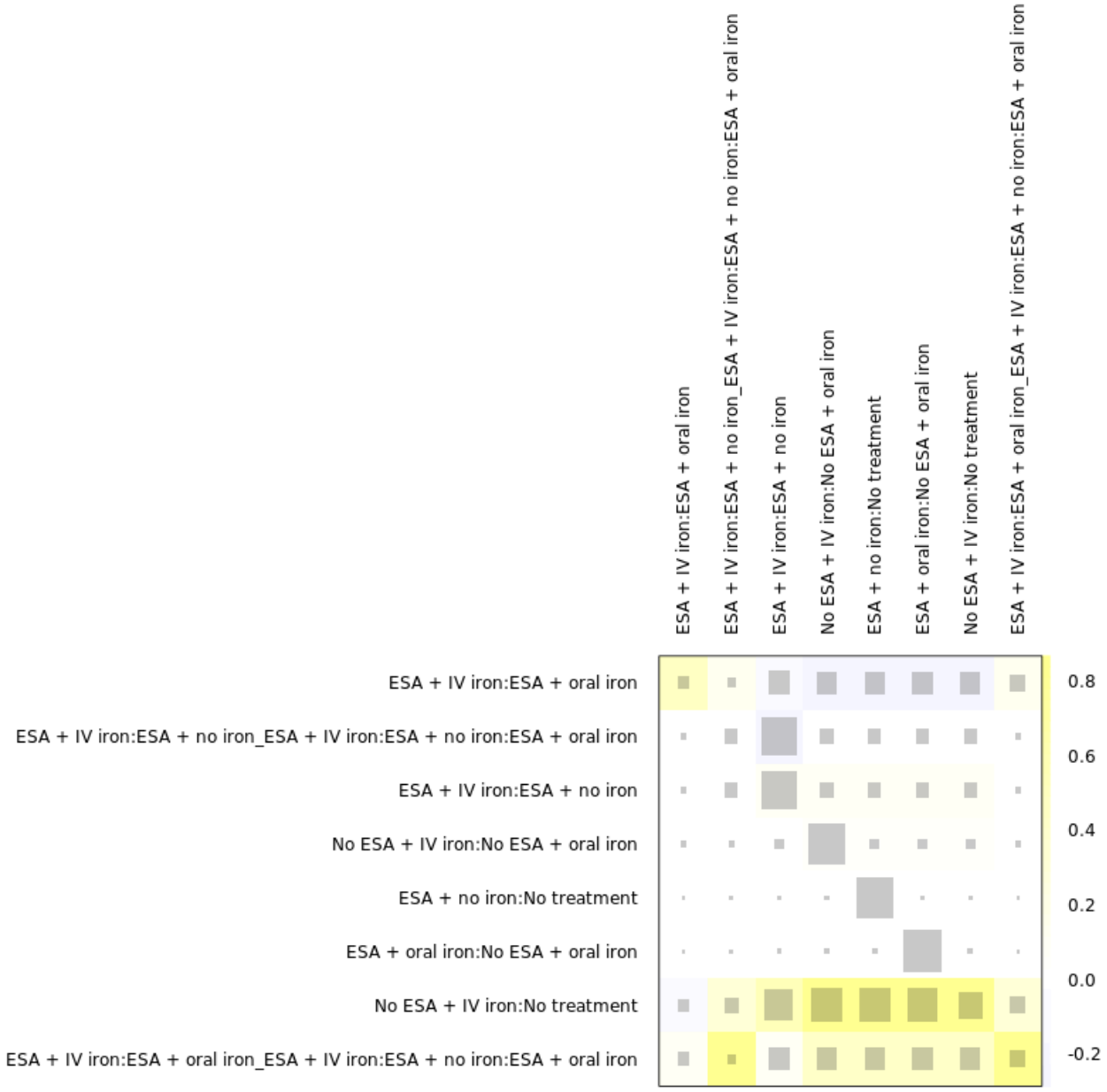


Figure 20. Net heat plot for outcome overall mortality (random effects model).

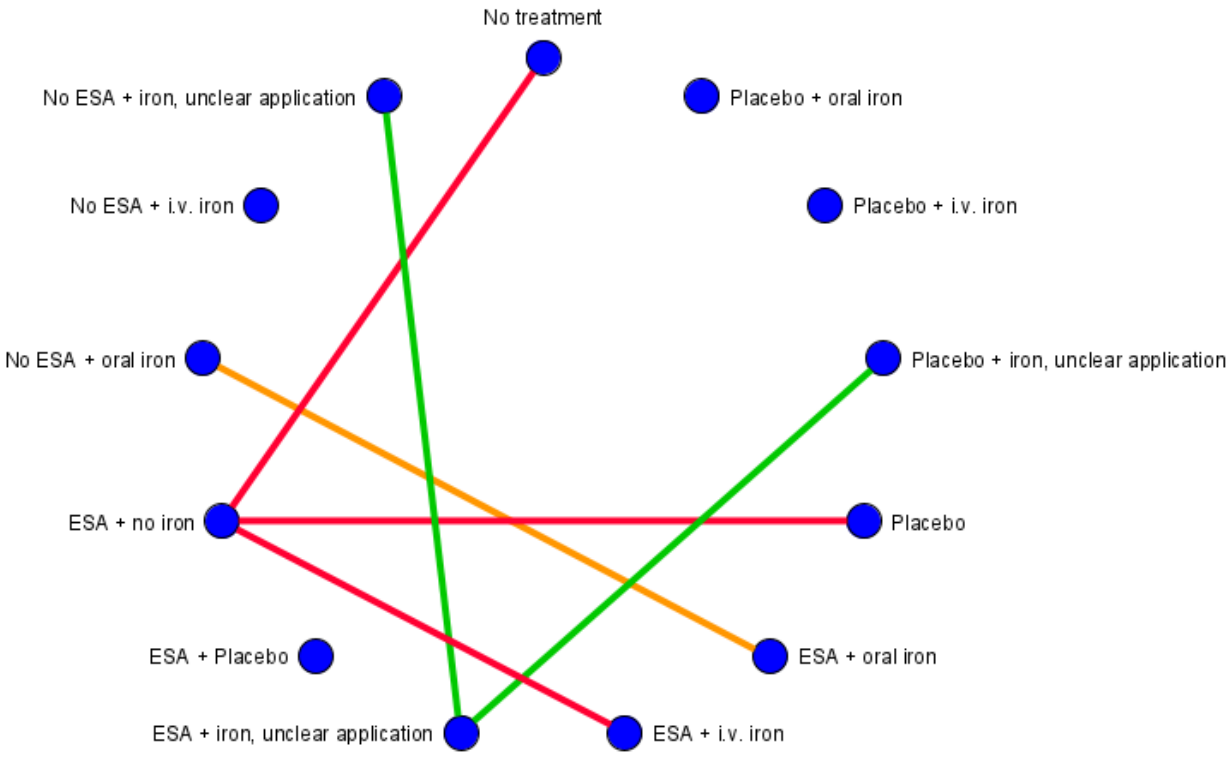


Adverse events

Thromboembolic events

Thromboembolic events were reported in 61 studies (N = 19,370). Three studies (Cascinu 1994; Gupta 2009; Maccio 2010) including 363 participants reported no events and were therefore excluded from network meta-analysis. The network, based on 58 pairwise comparisons, was not fully connected but consisted of three subnets (Figure 21), each with one to three pairwise comparisons. Four treatment options could be compared in subnet 1, three in subnet 2 and two in subnet 3.

Figure 21. Network graph for outcome thromboembolic events (created with yEd). Red lines: Subnet 1. Green lines: Subnet 2. Orange line: Subnet 3.



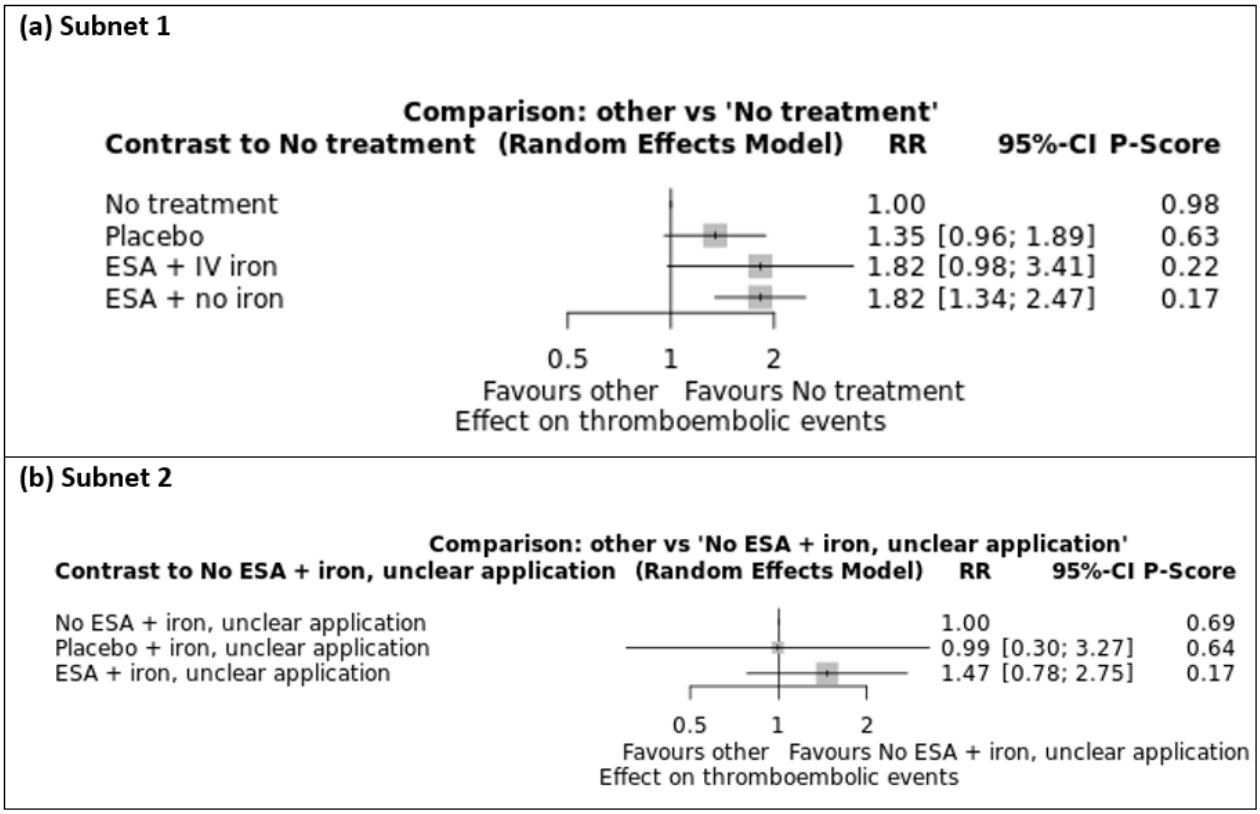
Pairwise comparisons

In subnet 1 the pairwise comparisons "ESA + no iron" vs. "No treatment" and "ESA + no iron" vs. "Placebo" showed a higher risk for "ESA + no iron" (RR 1.82, 95% CI 1.34 to 2.47; RR 1.35, 95% CI 1.16 to 1.58). In subnet 3, which only consists of one pairwise comparison, we also found a higher risk for thromboembolic events for ESA when added to oral iron compared to oral iron alone (RR 1.89, 95% CI 1.40 to 2.53). No meaningful statistical heterogeneity was found in these comparisons (I^2 = 0% for all comparisons) (data not shown).

Network meta-analysis

For subnets containing more than two treatments (subnets 1 and 2) a network meta-analysis was conducted. Results of all network comparisons are shown in the league table in Table 9 and confirmed results of pairwise comparisons. "No treatment" and "Placebo" resulted in fewer thromboembolic events compared to "ESA + no iron" (RR 0.55, 95% CI 0.41 to 0.74; RR 0.74, 95% CI 0.63 to 0.86). For subnet 1 Cochran's Q-test and I^2 statistics showed no significant heterogeneity between studies (Q = 31.54, df = 47, P = 0.96; I^2 = 0%, Tau^2 = 0), for subnet 2 heterogeneity could not be analysed as the network consisted of only two studies. For subnets 1 and 2 a treatment ranking was performed (Figure 22). In subnet 1 the reference treatment "No treatment" was ranked highest (P score: 0.98), since all other treatments were associated with increased risk of thromboembolic events. In subnet 2 reference treatment "No ESA + iron, unclear application" was ranked highest (P score: 0.69) compared to "Placebo + iron unclear application" and "ESA + unclear application", but confidence intervals are very large.

Figure 22. Forest plot for outcome thromboembolic events. (a) Subnet 1. Reference treatment: No treatment (b) Subnet 2. Reference treatment: No ESA + iron, unclear application. Treatments are ordered by P-Score (descending). RR: risk ratio. CI: confidence interval.



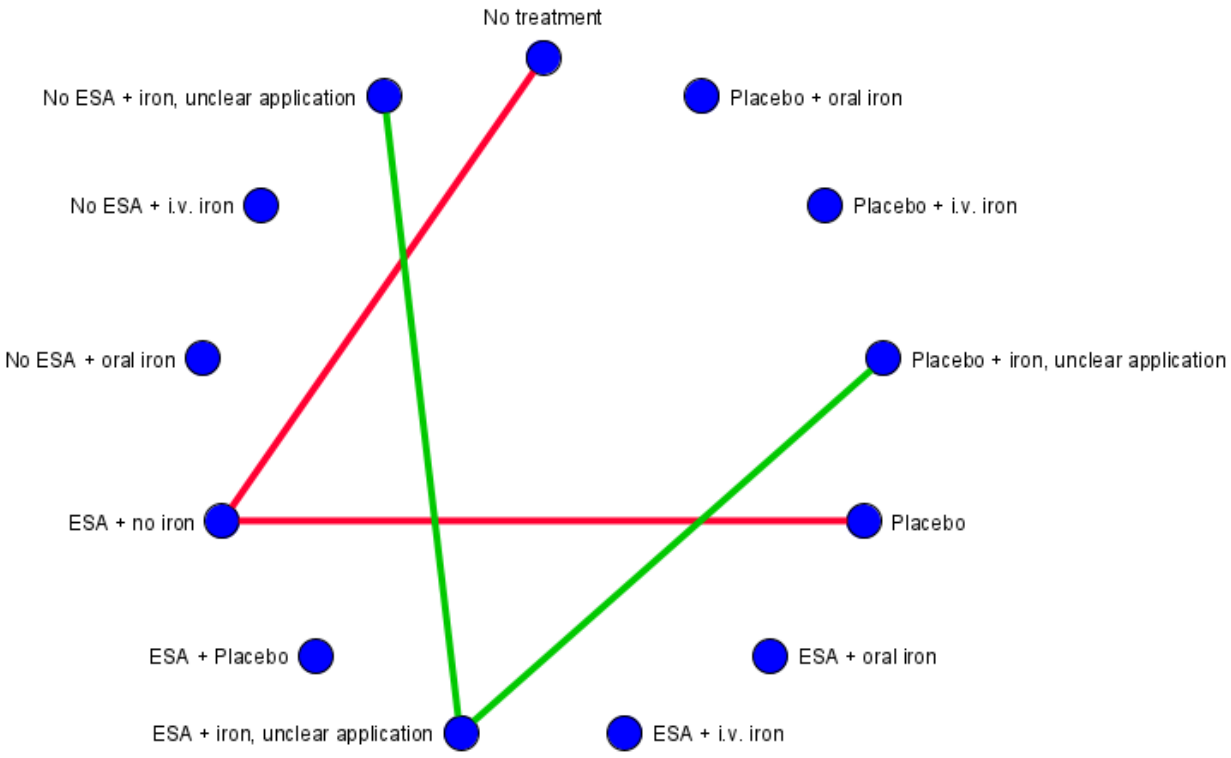
We rated the certainty of the evidence for thromboembolic events according to the GRADE approach for "ESA + IV iron", "ESA + oral iron", "ESA + no iron", "No ESA + IV iron" and "No ESA + oral iron" compared to our main comparator "No treatment", respectively. Nevertheless, we could only rate the certainty in the evidence for "ESA + IV iron" and "ESA + no iron" as the other treatments are not included in our network. We found that treatment with ESA and IV iron probably increases the number of thromboembolic events slightly compared to no treatment (moderate certainty). Additionally, treatment with ESA alone slightly increases the number of thromboembolic events compared to no treatment (high certainty). Our main reason for downgrading was imprecision. Reasons for downgrading are provided in the summary of findings tables (Summary of findings 1; Summary of findings 2).

Since there were no closed loops, inconsistencies could not be analysed.

Thrombocytopenia or haemorrhage

The outcome thrombocytopenia was reported in 17 studies (N = 4006). Two studies (Cascinu 1994; Gupta 2009) including 215 participants reported no events and were therefore excluded from network meta-analysis. The network, based on 15 pairwise comparisons, was not fully connected but consisted of two subnets (Figure 23) each with two pairwise comparisons and including three different treatments.

Figure 23. Network graph for outcome thrombocytopenia or haemorrhage (created with yEd). Red lines: Subnet 1. Green lines: Subnet 2.



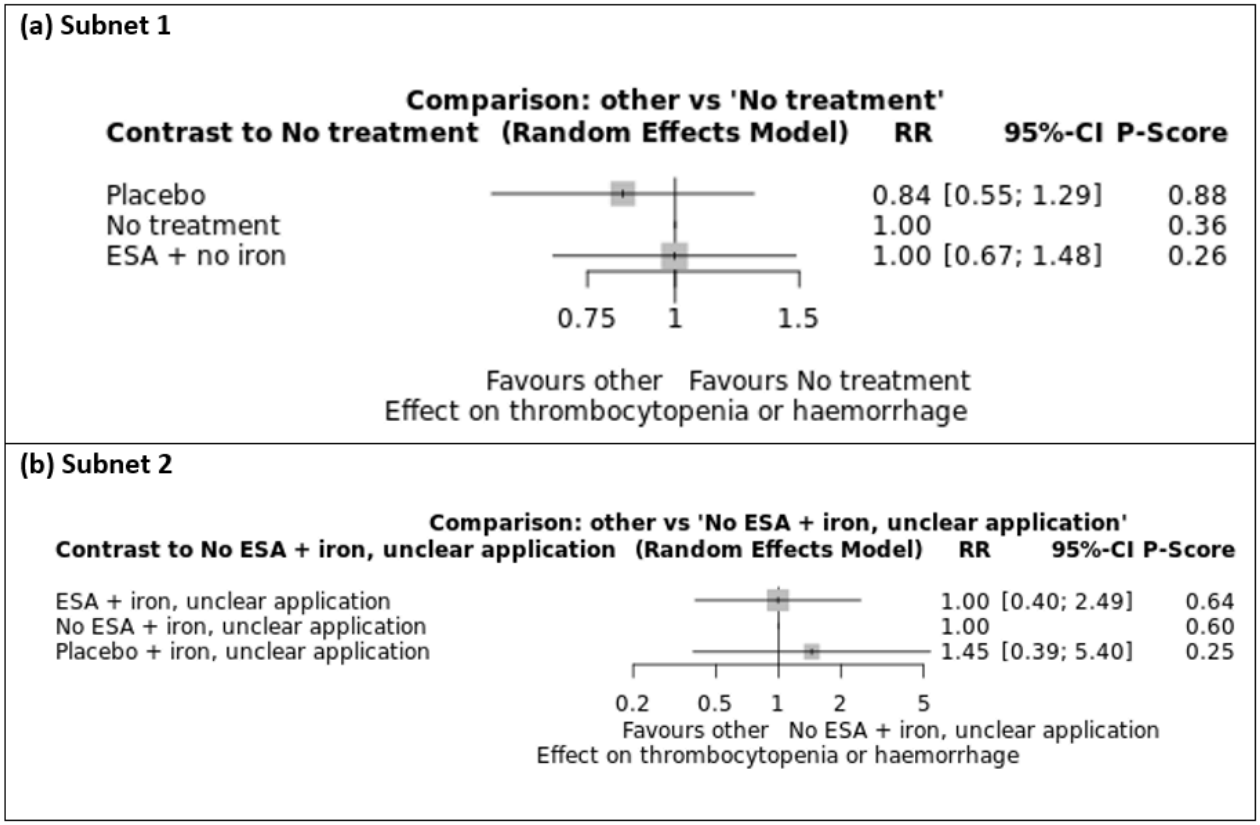
Pairwise comparisons

Pairwise comparisons showed in subnet 1 a higher risk of thrombocytopenia or haemorrhage for "ESA + no iron" compared to "Placebo" (RR 1.18, 95% CI 1.01 to 1.39). No meaningful statistical heterogeneity was found in pairwise comparisons (I^2 = 0% for all comparisons). (data not shown)

Network meta-analysis

For both subnets a network meta-analysis was conducted. Results are shown in the league table in Table 10. "Placebo" resulted in fewer events of thrombocytopenia or haemorrhage than "ESA + no iron" (RR 0.84, 95% CI 0.72 to 0.99). For subnet 1 Cochran's Q-test and I^2 statistics showed no significant heterogeneity between studies (Q = 7.84, df = 11, P = 0.73; I^2 = 0%, Tau^2 = 0); for subnet 2 heterogeneity could not be analysed as the network consisted of only two studies. For both subnets a treatment ranking was conducted (Figure 24). In subnet 1 "Placebo" was ranked highest compared to reference treatment "No treatment" (P score: 0.88). In subnet 2 "ESA + iron, unclear application" was ranked highest compared to reference treatment "No ESA + iron, unclear application" (P score: 0.64), but confidence intervals are very large.

Figure 24. Forest plot for outcome thrombocytopenia or haemorrhage. (a) Subnet 1. Reference treatment: No treatment (b) Subnet 2. Reference treatment: No ESA + iron, unclear application. Treatments are ordered by P-Score (descending). RR: risk ratio. CI: confidence interval.



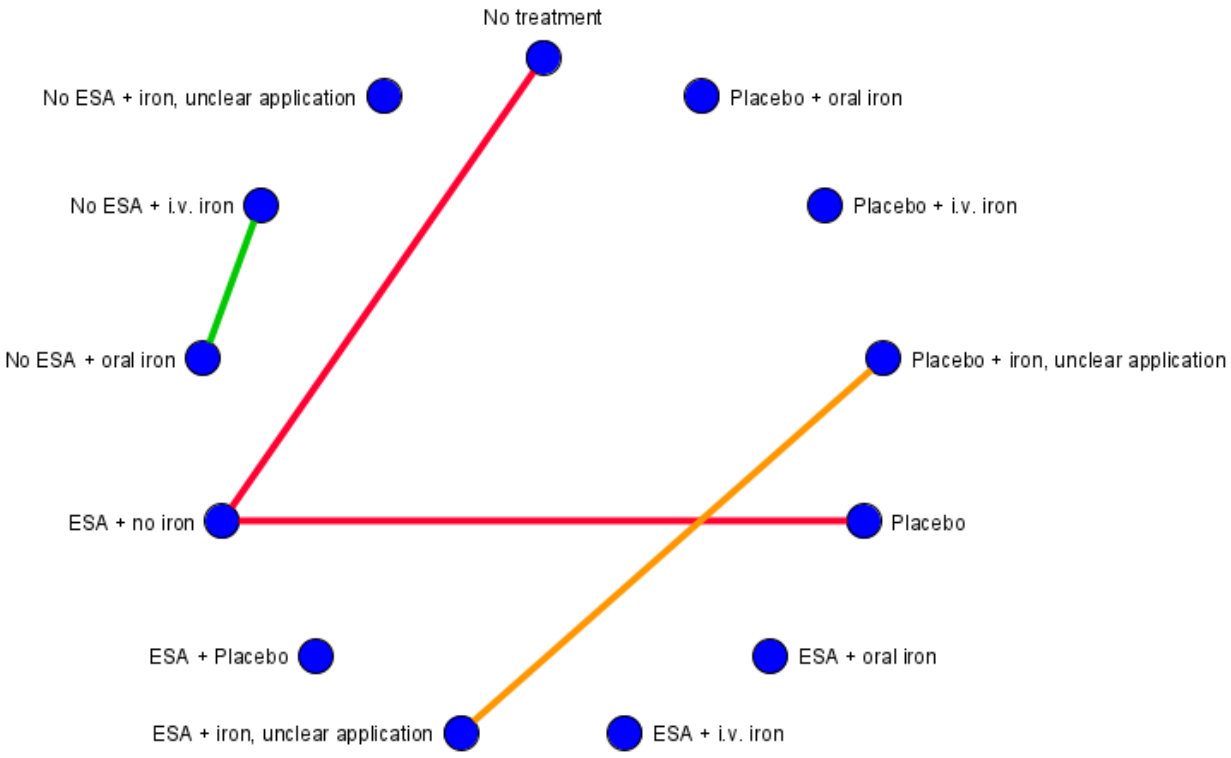
We rated the certainty of the evidence for thrombocytopenia or haemorrhage according to the GRADE approach for "ESA + IV iron", "ESA + oral iron", "ESA + no iron", "No ESA + IV iron" and "No ESA + oral iron" compared to our main comparator "No treatment", respectively. Nevertheless, we could only rate the certainty in the evidence for "ESA + no iron" as the other treatments are not included in our network. We found that treatment with ESA alone probably leads to little or no difference in number of patients with thrombocytopenia or haemorrhage compared to no treatment (moderate certainty). Our main reason for downgrading was imprecision. Reasons for downgrading are provided in the summary of findings tables (Summary of findings 1; Summary of findings 2).

Since there were no closed loops, inconsistencies could not be analysed.

Rash

The outcome rash was examined in 18 studies (N = 5245). Two studies (Gupta 2009; Kurz 1997) including 139 participants reported no events and were therefore excluded from network meta-analysis. The network, based on 16 pairwise comparisons, was not fully connected but consisted of three subnets (Figure 25) each with one or two pairwise comparisons. Three treatment options could be compared in subnet 1 and two in subnet 2 and 3.

Figure 25. Network graph for outcome rash (created with yEd). Red lines: Subnet 1. Green line: Subnet 2. Orange line: Subnet 3.



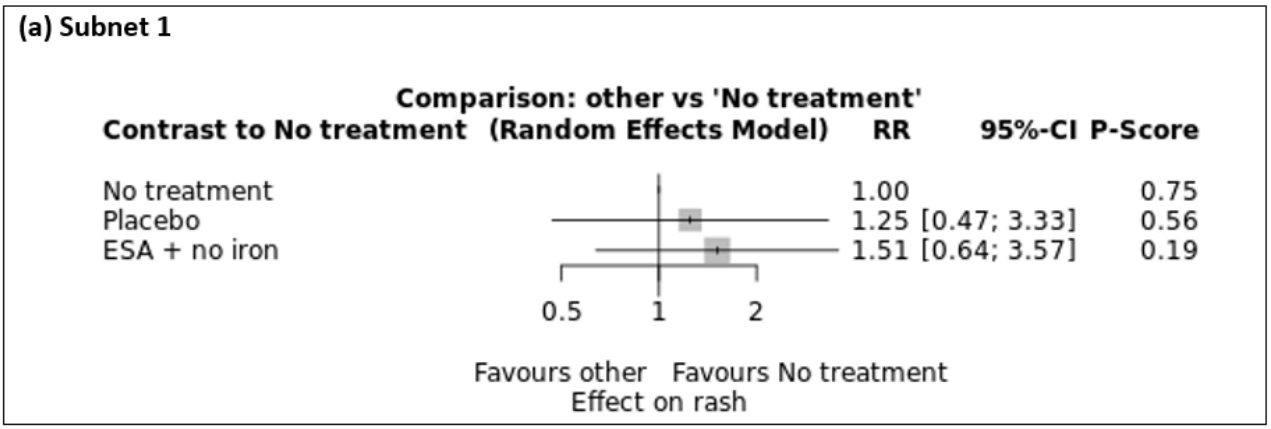
Pairwise comparisons

Pairwise comparisons showed no meaningful results. (data not shown)

Network meta-analysis

For subnet 1 a network meta-analysis was conducted. Results are shown in the league table in Table 11. Network meta-analysis even showed no meaningful results. For subnet 1 a treatment ranking was conducted (Figure 26). Reference treatment "No treatment" was ranked highest (P score: 0.75), but confidence intervals are very large.

Figure 26. Forest plot for outcome rash. (a) Subnet 1. Reference treatment: No treatment. Treatments are ordered by P-Score (descending). RR: risk ratio. CI: confidence interval.



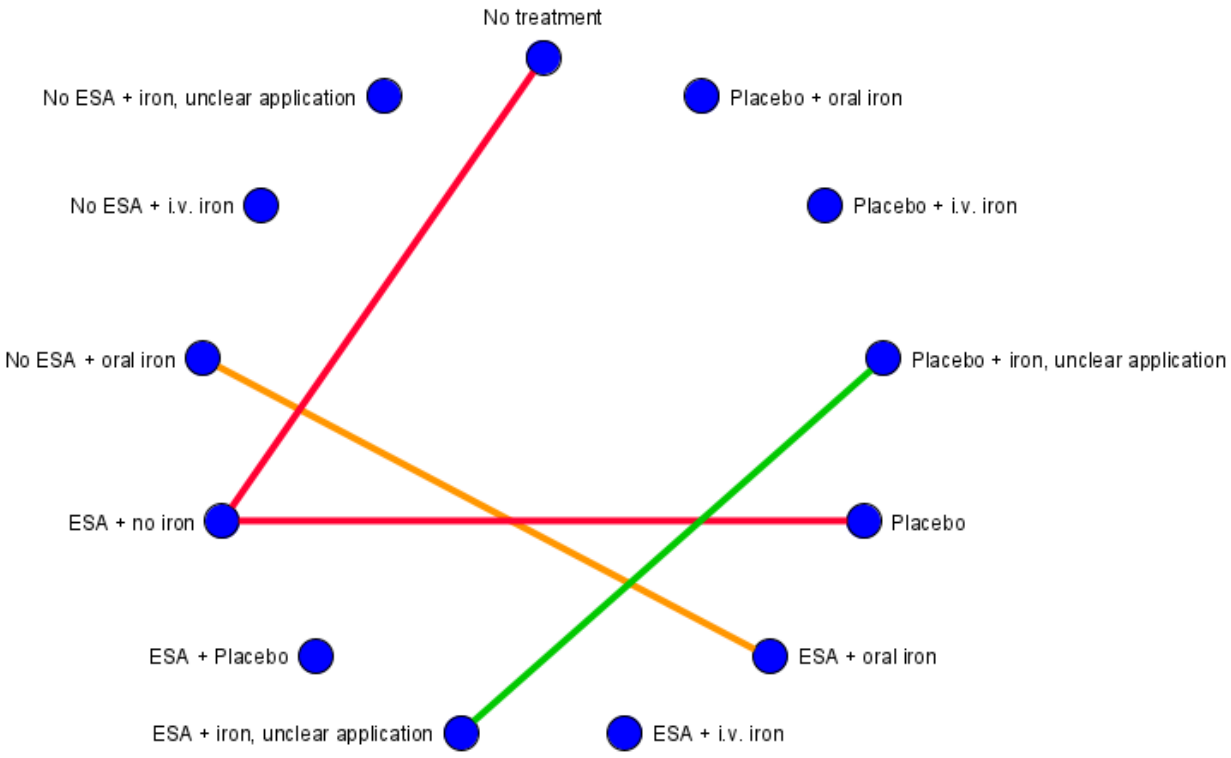
Since only seven outcomes can be displayed, rash is not reported in the summary of findings tables.

Since there were no closed loops, inconsistencies could not be analysed.

Hypertension

The outcome hypertension was evaluated in 28 studies (N = 9190). Two studies (Cascinu 1994; Iconomou 2003) including 212 participants reported no events and were therefore excluded from network meta-analysis. The network, based on 26 pairwise comparisons, was not fully connected and consisted of three subnets (Figure 27) each with one or two pairwise comparisons. Three treatment options could be compared in subnet 1 and two in subnet 2 and 3.

Figure 27. Network graph for outcome hypertension (created with yEd). Red lines: Subnet 1. Green line: Subnet 2. Orange line: Subnet 3.



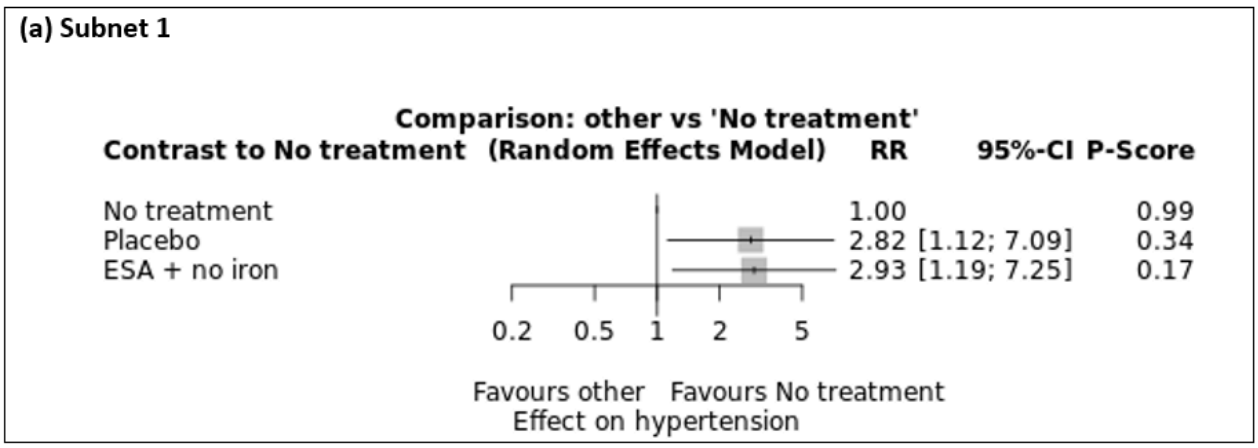
Pairwise comparisons

For "ESA + no iron" pairwise comparison showed a higher risk for hypertension compared to "No treatment" (RR 2.93, 95% CI 1.19 to 7.25). No other pairwise comparisons showed meaningful results. No meaningful statistical heterogeneity was found in pairwise comparisons (I^2 = 0-5% for all comparisons). (data not shown)

Network meta-analysis

For subnet 1 a network meta-analysis was performed. Results of network meta-analysis are shown in the league table in Table 12. "ESA + no iron" and "Placebo" resulted in higher risk for hypertension compared to "No treatment" (RR 2.93, 95% CI 1.19 to 7.25; RR 2.82, 95% CI 1.12 to 7.09). Cochran's Q-test and I^2 statistics showed no significant heterogeneity between studies (Q = 17.54, df = 22, P = 0.73; I^2 = 0%, Tau^2 = 0). For subnet 1 a treatment ranking was conducted (Figure 28). Reference treatment "No treatment" was ranked highest (P-score: 0.99), compared to "Placebo" and "ESA + no iron", which both showed an increased risk for hypertension compared to reference treatment "No treatment".

Figure 28. Forest plot for outcome hypertension. (a) Subnet 1. Reference treatment: No treatment. Treatments are ordered by P-Score (descending). RR: risk ratio. CI: confidence interval.



We rated the certainty of the evidence for hypertension according to the GRADE approach for "ESA + IV iron", "ESA + oral iron", "ESA + no iron", "No ESA + IV iron" and "No ESA + oral iron" compared to our main comparator "No treatment", respectively. Nevertheless, we could only rate the certainty in the evidence for "ESA + no iron" as the other treatments are not included in our network. We found that treatment with ESA alone probably increases the number of hypertensions compared to no treatment (moderate certainty). Our main reason for downgrading was imprecision. Reasons for downgrading are provided in the summary of findings tables (Summary of findings 1; Summary of findings 2).

Since there were no closed loops in any subnet, inconsistencies could not be analysed.

Subgroup analyses

Comparison of different routes of iron administrations (IV, oral) were included in network meta-analysis for each outcome.

Since trial data for type of iron and duration of follow-up were less reported, no subgroup analyses were conducted for these predefined subgroups. For cancer type most studies included participants with solid or mixed tumours, so no subgroup analyses were performed.

Finally, subgroup analyses could only be performed for type of ESA (epoetin vs. darbepoetin) and type of therapy (chemotherapy vs. no chemotherapy). In the following, for each outcome results of network,meta-analyses are described for each of the four subgroups (data not shown).

On-study mortality

Forty-six of the 58 studies, that reported at least one event, included participants treated with epoetin. "No ESA + IV iron" dropped out of subnet 1. Network meta-analysis for subnet 1 yielded similar results, except that the comparison "ESA + no iron" vs. "Placebo" no longer showed a meaningful benefit for "ESA + no iron" (RR 1.14, 95% CI 0.98 to 1.30), but confidence intervals are overlapping. For the other subnet, network meta-analyses yielded similar results.

Eleven of the 58 studies, that reported at least one event, included participants treated with darbepoetin instead. For this subgroup, only subnet 1 remained. For subnet 1, most treatments dropped out of the network, only "Placebo", "No treatment" and "ESA + no iron" remained in the network. Network meta-analysis of the remaining treatments yielded similar effect estimates but larger confidence intervals.

Forty-two of the 58 studies, that reported at least one event, included participants undergoing chemotherapy. "ESA + IV iron", "ESA + oral iron" and "No ESA + oral iron" dropped out of subnet 1. For this subnet, network meta-analysis of the remaining treatments yielded similar results, except that "ESA + no iron" no longer showed a meaningful benefit compared to "Placebo" (RR 1.09, 95% CI 0.96 to 1.23), but confidence intervals are overlapping. Additionally, in the ranking of treatments "No treatment" and "Placebo" swapped their ranks, but confidence intervals are overlapping. For subnet 2 results did not change.

Sixteen of the 58 studies, that reported at least one event, included participants not undergoing chemotherapy. "ESA + oral iron", "No ESA + oral iron" and "Placebo + oral iron" dropped out of subnet 1. Network meta-analysis on subnet 1 yielded similar effect estimates, but confidence intervals are partly a bit larger. Subnet 2 was completely omitted.

Haematological response

Twenty-five of the 32 studies, that reported at least one event, included participants treated with epoetin. "ESA + placebo" dropped out of subnet 1. Network meta-analysis for subnet 1 yielded slightly different effect estimates and larger confidence intervals.

Seven of the 32 studies, that reported at least one event, included participants treated with darbepoetin. "No ESA + oral iron" dropped out of subnet 1. Network meta-analysis for subnet 1 yielded slightly larger effect estimates, but even much larger confidence intervals. The comparison "Placebo" vs. "No treatment" no longer showed a meaningful benefit for "Placebo" (RR 2.19, 95% CI 0.90 to 5.36), but confidence intervals are overlapping. The ranking of treatments did not change.

Twenty-five of the 32 studies, that reported at least one event, included participants undergoing chemotherapy. Network meta-analysis for subnet 1 yielded very similar results with strongly overlapping confidence intervals, except that the comparison "ESA + IV iron" vs. "ESA + no iron" no longer showed a meaningful benefit for "ESA + IV iron" (RR 1.23, 95% CI 0.98 to 1.56), but confidence intervals are overlapping. The ranking of treatments did not change.

Seven of the 32 studies, that reported at least one event, included participants not undergoing chemotherapy. "ESA + placebo", "ESA + oral iron" and "No ESA + oral iron" dropped out of subnet 1. Network meta-analysis of the remaining treatments for subnet 1 yielded a bit larger effect estimates, but even much larger confidence intervals. The comparison "Placebo" vs. "No treatment" no longer showed a meaningful benefit for "Placebo" (RR 2.34, 95% CI 0.90 to 6.12), but confidence intervals are overlapping. The ranking of remaining treatments did not change.

Red blood cell transfusions

Fifty-seven of the 75 studies, that reported at least one event, included participants treated with epoetin. "ESA + placebo" and "No ESA + IV iron" dropped out of subnet 1. Network meta-analysis for subnet 1 yielded slightly different results. The comparison "ESA + IV iron" vs. "No ESA + oral iron" no longer showed a meaningful benefit for "ESA + IV iron" (RR 0.84, 95% CI 0.36 to 1.94). Instead, "ESA + oral iron" resulted in a lower need for red blood cell transfusions compared to "ESA + no iron" (RR 0.44, 95% CI 0.21 to 0.96). Additionally, the effect of "ESA + no iron" vs. "No ESA + oral iron" changed the direction, but confidence intervals are overlapping. In the ranking of treatments "No ESA + oral iron" and "Placebo" swapped their ranks, but confidence intervals are overlapping. For subnet 2, network meta-analysis yielded similar results, except that "ESA + iron, unclear application" resulted in a lower need for red blood cell transfusions compared to "Placebo + iron, unclear application" (RR 0.73, 95% 0.55 to 0.98).

Fourteen of the 75 studies, that reported at least one event, included participants treated with darbepoetin. "No ESA + IV iron" and "No ESA + oral iron" dropped out of subnet 1. Network meta-analysis for subnet 1 yielded slightly different results. The comparisons "ESA + oral iron", "ESA + placebo" and "ESA + no iron" vs. "No treatment" no longer showed a meaningful benefit compared to "No treatment" (RR 0.35, 95% CI 0.12 to 1.04; RR 0.37, 95% CI 0.13 to 1.08; RR 0.54, 95% CI 0.27 to 1.08). Additionally, the comparisons "ESA + oral iron" vs. "Placebo" and "ESA + placebo" vs. "Placebo" no longer showed a meaningful benefit compared to "Placebo" (RR 0.43, 95% CI 0.18 to 1.01; RR 0.45, 95% CI 0.19 to 1.05). In the ranking of treatments "ESA + IV iron" and "ESA + oral iron" swapped their ranks, but confidence intervals are overlapping. Subnet 2 consisted of only one study, so no further analyses could be performed.

Fifty-nine of the 75 studies, that reported at least one event, included participants undergoing chemotherapy. Network meta-analysis for subnet 1 yielded similar results, except that the comparison "ESA + placebo" vs. "No ESA + oral iron" no longer showed a meaningful benefit for "ESA + placebo" (RR 0.49, 95% CI 0.23 to 1.03). In the ranking of treatments "No ESA + oral iron" and "Placebo" swapped their ranks, but confidence intervals are overlapping. For subnet 2, network meta-analysis yielded similar results, except that "Placebo + iron, unclear application" vs. "No ESA+ iron, unclear application" no longer showed a meaningful benefit for "Placebo + iron, unclear application" (RR 0.67, 95% 0.40 to 1.11).

Sixteen of the 75 studies, that reported at least one event, included participants not undergoing chemotherapy. "ESA + oral iron", "ESA + placebo", "No ESA + IV iron" and "No ESA + oral iron" dropped out of subnet 1, resulting in a much sparser network. Network meta-analysis of the remaining treatments yielded slightly different effect estimates and a bit larger confidence intervals. The comparisons "ESA + IV iron" vs. "Placebo" and "No treatment" no longer showed a meaningful benefit for "ESA + IV iron" (RR 0.71, 95% CI 0.43 to 1.18; RR 0.54, 95% CI 0.28 to 1.06). Subnet 2 consisted of only one study, so no further analyses could be performed.

Number of red blood cell transfusions

Eighteen of the 21 studies included participants treated with epoetin. Network meta-analysis for subnet 1 yielded very similar results. Subnet 2 consisted of only one study, so no further analyses could be performed.

Two of the 21 studies included participants treated with darbepoetin. For subnet 1, only one pairwise comparison remained so no network meta-analysis was possible. Subnet 2 is completely omitted.

Eighteen of the 21 studies included participants undergoing chemotherapy. Network meta-analysis for subnet 1 yielded very similar results. Subnet 2 consisted of only one study, so no further analyses could be performed.

Two of the 21 studies included participants not undergoing chemotherapy. For subnet 1, only one pairwise comparison remained so no network meta-analysis was possible. Furthermore, subnet 2 consisted of only one study, so no further analyses could be performed.

Overall mortality

Fifty-eight of the 76 studies, that reported at least one event, included participants treated with epoetin. "ESA + placebo" and "No ESA + IV iron" dropped out of subnet 1. Network meta-analysis for subnet 1 yielded slightly different effect estimates and larger confidence intervals. For "ESA + oral iron", "Placebo" and "No ESA + oral iron" the direction of effect changed compared with "No treatment", but confidence intervals are overlapping. In the ranking of treatments "ESA + oral iron", "Placebo" and "No ESA + oral iron" are here better than "No treatment". For subnet 2, network meta-analysis yielded similar results.

Sixteen of the 76 studies, that reported at least one event, included participants treated with darbepoetin. "Placebo + oral iron" and "No ESA + IV iron" dropped out of subnet 1. Network meta-analysis for subnet 1 yielded slightly different results. The comparison "ESA + oral iron" vs. "No ESA + oral iron" no longer showed a meaningful benefit for "ESA + oral iron" and changed direction (RR 1.03 95% CI 0.67 to 1.60). Instead, "ESA + no iron" and "Placebo" resulted in a higher risk for overall mortality compared to "No treatment" (RR 1.23, 95% CI 1.04 to 1.45; RR 1.27, 95% CI 1.07 to 1.51). In the ranking of treatments "No ESA + oral iron" and "Placebo" swapped their ranks, but confidence intervals are overlapping. Subnet 2 consisted of only one study, so no further analyses could be performed.

Fifty-three of the 76 studies, that reported at least one event, included participants undergoing chemotherapy. "Placebo + oral iron" dropped out of subnet 1. Network meta-analysis for subnet 1 yielded similar results, except that the comparison "ESA + oral iron" vs. "No ESA + oral iron" no longer showed a meaningful benefit for "ESA + oral iron" (RR 0.90, 95% CI 0.76 to 1.07). In the ranking of treatments "No treatment" and "ESA + no iron" swapped their ranks, but confidence intervals are overlapping. For subnet 2, network meta-analysis yielded very similar results.

Twenty=three of the 76 studies, that reported at least one event, included participants not undergoing chemotherapy. For subnet 1, the network split into two smaller subnets. The first network consisted of "No treatment", "Placebo", "ESA + no iron" and "ESA + IV iron". Network meta-analysis for this network yielded similar results with a bit larger confidence intervals. Here, "ESA + no iron" resulted in a higher risk for overall mortality compared to "No treatment" (RR 1.16, 95% CI 1.02 to 1.31). In the ranking of treatments "ESA + no iron" here was ranked last, but confidence intervals are overlapping. "ESA + oral iron", "Placebo + oral iron" and "No ESA + oral iron" now form their own network. Here, results remained almost the same. Subnet 2 consisted of only one study, so no further analyses could be performed.

Thromboembolic events

Forty-four of the 58 studies, that reported at least one event, included participants treated with epoetin. Network meta-analysis for subnet 1 yielded similar results, but confidence intervals are partly a bit larger. For subnet 2, only one pairwise comparison remained so no network meta-analysis was possible.

Fourteen of the 58 studies, that reported at least one event, included participants treated with darbepoetin. Network meta-analysis for subnet 1 yielded a bit larger effect estimates, but even much larger confidence intervals. The comparison "ESA + no iron" vs. "No treatment" no longer showed a meaningful benefit for "ESA + no iron" (RR 2.28, 95% CI 0.74 to 7.02), but confidence intervals are overlapping. Subnet 2 consisted of only one study, so no further analyses could be performed.

Thirty-five of the 58 studies, that reported at least one event, included participants undergoing chemotherapy. Network meta-analysis for subnet 1 yielded similar results. For subnet 2, results did not change.

Twenty-three of the 58 studies, that reported at least one event, included participants not undergoing chemotherapy. Network meta-analysis for subnet 1 yielded partly a bit larger effect estimates, but even much larger confidence intervals. Subnet 2 is completely omitted.

Thrombocytopenia or haemorrhage

Thirteen of the 15 studies, that reported at least one event, included participants treated with epoetin. Network meta-analysis for subnet 1 yielded similar results, except that the comparison "ESA + no iron" vs. "Placebo" no longer showed a meaningful benefit for "ESA + no iron" (RR 0.90, 95% CI 0.75 to 1.08), but confidence intervals are overlapping. Subnet 2 consisted of only one study, so no further analyses could be performed.

Two of the 15 studies, that reported at least one event, included participants treated with darbepoetin. Subnets 1 and 2 consisted each of only one study, so no further analyses could be performed.

Thirteen of the 15 studies, that reported at least one event, included participants undergoing chemotherapy. Network meta-analysis for subnet 1 yielded very similar results. For subnet 2, results did not change.

Two of the 15 studies, that reported at least one event, included participants not undergoing chemotherapy. Network meta-analysis for subnet 1 yielded a bit larger effect estimates and confidence intervals. In the ranking of treatments "ESA + no iron" and "No treatment" swapped their ranks, but confidence intervals are overlapping. Subnet 2 is completely omitted.

Rash

Thirteen of the 16 studies, that reported at least one event, included participants treated with epoetin. Network meta-analysis for subnet 1 yielded slightly different results, but confidence intervals are overlapping. In the ranking of treatments "Placebo" and "No treatment" swapped their ranks, but confidence intervals are overlapping.

Two of the 16 studies, that reported at least one event, included participants treated with darbepoetin. For subnet 1, only one pairwise comparison remained so no network meta-analysis was possible.

Thirteen of the 16 studies, that reported at least one event, included participants undergoing chemotherapy. Network meta-analysis for subnet 1 yielded very similar results.

Two of the 16 studies, that reported at least one event, included participants not undergoing chemotherapy. Network meta-analysis for subnet 1 yielded larger effect estimates and much larger confidence intervals. In the ranking of treatments "ESA + no iron" and "Placebo" swapped their ranks, but confidence intervals are overlapping.

Hypertension

Twenty of the 26 studies, that reported at least one event, included participants treated with epoetin. Network meta-analysis for subnet 1 yielded very similar results.

Six of the 26 studies, that reported at least one event, included participants treated with darbepoetin. For subnet 1, only one pairwise comparison remained so no network meta-analysis was possible.

Twenty-one of the 26 studies, that reported at least one event, included participants undergoing chemotherapy. Network meta-analysis for subnet 1 yielded similar results, except that the comparison "Placebo" vs. "No treatment" no longer showed a meaningful benefit for "Placebo" (RR 2.35, 95% CI 0.88 to 6.30), but confidence intervals are overlapping.

Five of the 26 studies, that reported at least one event, included participants not undergoing chemotherapy. Network meta-analysis for subnet 1 yielded similar effect estimates, but confidence intervals are much larger and crossing unity. Additionally, in the ranking of treatments "ESA + no iron" and

"Placebo" swapped their ranks, but confidence intervals are overlapping.

Sensitivity analysis

For statistical analysis a fixed-effect model was compared to a random-effects model. For on-study mortality the comparison showed similar results (data not shown).

Furthermore, to explore the influence of quality components, studies rated as high overall risk of bias (Auerbach 2004; Noronha 2016) were excluded from sensitivity analyses.

For on-study mortality, number of red blood cell transfusions, hypertension, thromboembolic events and thrombocytopenia or haemorrhage, no sensitivity analyses were performed, because these outcomes included no studies with high overall risk of bias.

For haematological response, in subnet 1 the exclusion of Auerbach 2004 yielded similar results and the ranking of treatment did not change.

For red blood cell transfusions, in subnet 1 the exclusion of Auerbach 2004 and Noronha 2016 yielded similar effect estimates and confidence intervals. The ranking of treatments remained the same, except that "ESA + oral iron" and "ESA + IV iron" and "No treatment" and "No ESA + oral iron" changed their ranks, but effect estimates and confidence intervals are similar and overlapping. Additionally, the confidence intervals of "ESA + oral iron vs. No ESA + IV iron", "ESA + placebo vs. No treatment" and "ESA + no iron vs. No ESA + oral iron" are larger and crosses unity (data not shown).

For overall mortality, the exclusion of Noronha 2016 resulted in a different ranking of treatments, and for some comparisons the effects changed their direction. Nevertheless, confidence intervals are very large and overlapping (data not shown).

With regard to the outcome rash, after excluding Noronha 2016 subnet 2 is omitted completely.

DISCUSSION

Summary of main results

The objectives of this review were to systematically evaluate the effect of intravenous (IV), oral, or no iron in combination with erythropoiesis-stimulating agents (ESAs) on the prevention or alleviation of anaemia in cancer patients, and to collect further information on the safety and efficacy of these interventions. We identified 96 randomised controlled trials (RCTs) including 25,157 participants. We investigated 12 different treatment options in our analyses. The treatment options included combinations of ESAs with IV or oral iron and placebo. From the 96 studies included in our review, four studies (Ansari 2016; Birgegard 2015; Goede 2016; Henke 1999) could not be analysed in network meta-analyses as they did not report any of our studied outcomes. As there was no complete network for any outcome, we could not rank all treatments for each predefined outcome. The results and the certainty in the evidence for the main outcomes and comparisons are reported in Summary of findings 1 and Summary of findings 2 and are summarised below.

- Regarding on-study mortality, our network consisted of two subnets (subnet)s comparing 11 different treatment options. Evidence from network meta-analyses (NMA) (55 RCTS, 15,074 participants) suggests that treatment with ESA alone leads to increased on-study mortality compared to placebo alone. We found that administration of ESA with IV or oral iron may decrease or increase on-study mortality compared to no treatment (low-certainty evidence). Further, we found that treatment with ESA alone probably leads to slightly increased on-study mortality compared to no treatment (moderate certainty). Additionally, we found that treatment withIV iron alone may increase, and treatment with oral iron alone may increase or decrease on-study mortality compared to no treatment (low certainty).
- Regarding haematological response, our network consisted of two subnets comparing nine different treatment options. Evidence from NMA (31 RCTs, 6985 participants) suggests that the treatment with ESA andIV iron leads to higher haemoglobin response compared to ESA alone, placebo alone, oral iron alone, and no treatment. Additionally, ESA with placebo, ESA with oral iron and ESA without iron resulted in higher haemoglobin response than placebo alone, oral iron alone and no treatment. Furthermore, placebo alone resulted in higher haemoglobin response compared to no treatment. In the ranking of treatments, ESA with IV iron was ranked highest. The ranking also suggests higher efficacy for ESA administration compared to placebo or no administration of ESAs. We found that treatment with ESA and IV iron, ESA and oral iron, and ESA alone probably increases haemoglobin response compared to no treatment (moderate certainty). Additionally, treatment with oral iron alone may increase haemoglobin response compared to no treatment (low certainty).
- Regarding red blood cell transfusions, our network consisted of two subnets comparing 12 different treatment options. Evidence from NMA (69 RCTs, 18,684 participants) suggests that treatment with ESA and oral iron leads to a reduced need for red blood cell transfusions compared to IV iron alone, oral iron alone, placebo alone and no treatment. Additionally, administration of ESA withIV iron and ESA with placebo resulted in a reduced need for red blood cell transfusions compared to oral iron alone and no treatment. Administration of ESA with intravenous iron further resulted in reduced need for red blood cell transfusions compared to placebo alone. Finally, treatment with ESA alone resulted in a reduced need for red blood cell transfusions compared to placebo alone and no treatment. In the ranking of treatments ESA with oral iron was ranked highest compared to no treatment. Additionally, ranking suggests higher efficacy for ESA administration compared to placebo or no administration of ESA. In the second subnetwork, ESA with unclear application of iron and placebo with unclear application of iron resulted in a reduced need for red blood cell transfusions compared to unclear application of iron without ESAs. In the ranking of treatments, ESA with unclear application of iron was ranked first. We found that administration of ESA with IV or oral iron and ESA alone probably decreases the need for red blood cell transfusions compared to no treatment (moderate certainty). Additionally, treatment with intravenous iron alone and with oral iron alone may decrease or increase the need for red blood cell transfusions compared to no treatment (low certainty).
- Regarding number of red blood cell transfusions, our network consisted of two subnets comparing six different treatment options. Evidence from NMA (19 RCTs, 4459 participants) suggests that administration of ESA alone leads to less red blood cell transfusions compared to no treatment and placebo alone.

Additionally, administration of ESA with oral iron and IV alone resulted in less red blood cell transfusions than administration of oral iron alone.

- Regarding overall mortality, our network consisted of two subnets comparing 12 different treatment options. Evidence from NMA (71 RCTs, 21,576 participants) suggests that treatment with ESA and oral iron leads to lower overall mortality than oral iron alone. We found that administration of ESA with or without IV or oral iron may decrease or increase overall mortality compared to no treatment (low certainty,) and treatment with ESA alone may lead to little or no difference in overall mortality compared to no treatment (low certainty).
- Regarding thromboembolic events, our network consisted of three subnets comparing nine different treatment options. Evidence from NMA (50 RCTs, 15,408 participants) suggests that no treatment and treatment with placebo alone leads to fewer thromboembolic events compared to ESA alone. Additionally, pairwise comparison of ESA with oral iron and oral iron alone resulted in fewer thromboembolic events for oral iron alone. We found that treatment with ESA and intravenous iron probably increases the number of thromboembolic events slightly compared to no treatment (moderate certainty) and treatment with ESA alone slightly increases the number of thromboembolic events compared to no treatment (high certainty).
- Regarding thrombocytopenia or haemorrhage, our network consisted of two subnets comparing six different treatment options. Evidence from NMA (13 RCTs, 2744 participants) suggests that ESA alone leads to a higher risk for thrombocytopenia or haemorrhage than placebo alone. In the ranking of treatments, placebo was ranked as the best option (lowest risk of thrombocytopenia or haemorrhage) compared to no treatment. We found that treatment with ESA alone probably leads to little or no difference in number of patients with thrombocytopenia or haemorrhage compared to no treatment (moderate certainty).
- Regarding rash, our network consisted of three subnets comparing seven different treatment options. Evidence from NMA (14 RCTs, 4592 participants) showed no statistically meaningful results for this outcome.
- Regarding hypertension, our network consisted of three subnets comparing seven different treatment options. Evidence from NMA (24 RCTs, 8383) suggests that administration of ESA alone and placebo alone leads to a higher risk for hypertension compared to no treatment. In the ranking of treatments reference "no treatment" was ranked highest compared to ESA alone and placebo alone. We found that treatment with ESA alone probably increases the number of participants with hypertension compared to no treatment (moderate certainty).

Overall completeness and applicability of evidence

We were able to compare a total of 12 different treatment options, combining ESAs with intravenous (IV) or oral iron, for the prevention or alleviation of anaemia in cancer patients. The only treatment option from our ideal network, which is not included in any network, was "Placebo + IV iron".

Not all trials reported all the studied outcomes, resulting in very different graphical networks for each outcome. The definitions of efficacy outcomes within the trials did not all correspond with our definitions. For example, we defined haematological response as proportion of participants with an increase in haemoglobin (Hb) level of 2 g/dL or more, or increase in haematocrit of six percentage points or more, unrelated to transfusion. However, some studies reported the outcome haematological response differently.

A connected network could not be formed for any of the outcomes of interest. Instead, for each outcome, there was a minimum of two different subnetworks (subnets). In some studies, the iron application was not clearly reported, so treatments with unclear application form of iron formed their own network.

We detected moderate inconsistency within the network for haemoglobin response and substantial inconsistency for the outcome red blood cell transfusions, both indicating differences within pairwise comparisons. We found no signs of inconsistencies between direct and indirect evidence. However, this inconsistency within pairwise comparisons could not be statistically explained or resolved in sensitivity and subgroup analyses. It probably originates from the interplay of some effect modifiers, in which our included trials slightly differ (e.g. cancer types, study start date, and regions). These are only minor differences. From a clinical point of view, our included studies, therefore, remain largely comparable.

In addition to the studies included in this review, we are aware of a further 31 trials which may be eligible for inclusion in our review. Of these, 19 trials are still awaiting assessment as no results are available, and 12 trials are still ongoing. These studies may alter our results if included in our analyses.

However, despite all these limitations, we were able to identify an extensive number of trials comparing treatment combinations for multiple outcomes to each other. We were able to consider the experience of almost 25,000 individuals, emphasising the overall completeness and applicability of our findings.

Quality of the evidence

Risk of bias

We rated the risk of bias for each trial. We took into consideration if outcomes were objective or subjective to participants and outcome assessors. Overall, only two studies showed high risk of bias in more than one domain. The risk of bias of the included studies was mostly related to the blinding of participants and personnel and attrition bias. Reasons why risk of bias was unclear were often due to insufficient available information to clarify any judgement.

Certainty of the evidence

Overall, the certainty of the evidence for most of the outcomes was assessed as moderate. This includes the outcomes haemoglobin response and red blood cell transfusions as they showed inconsistency (mostly downgraded one point). For all other outcomes network meta-analysis showed no important inconsistencies. Furthermore, the outcomes hypertension, thrombocytopenia or haemorrhage and thromboembolic events were assessed as moderate as well. Here, we mostly downgraded one point due to imprecision since 95% confidence intervals (CIs) are wide and/or cross unity. Because sensitivity analyses for the outcome overall mortality showed differences in the effect size and direction if high risk of bias studies were excluded, we downgraded one point for study limitations. We additionally downgraded one point for imprecision since 95% CIs are wide and crosses unity as well, resulting in low-certainty evidence. We rated the outcome

on study mortality as low or moderate certainty of the evidence because we downgraded one to two points for imprecision for the different comparisons.

Potential biases in the review process

Review author IM is an information specialist experienced in medical terminology, who developed the sensitive search strategy. We searched all relevant databases, trial registries, conference proceedings, and reference lists and are therefore confident that we identified all relevant trials.

To minimise potential biases in the review process, we conducted the selection of studies, data extraction, risk of bias assessment and GRADE assessment in duplicate by two independent review authors and consulted a third review author in case no consensus could be reached. We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. However, comprehensive reporting of identified records was partially scarce which complicated correct allocation of the reports. In case we were uncertain whether two reports belonged to the same trial we considered them as individual trials.

We decided to pool the treatments *no iron* and *iron, if necessary*. By doing so, we gained networks, which are more connected and were able to compare most of our included treatment options directly.

It is important to clarify that many of the included studies used haemoglobin thresholds of >12 g/dL. Some people think that ESAs do not increase mortality when less aggressive doses are used with smaller haemoglobin thresholds. This distinction would certainly be interesting in future work.

There are some older studies included in this review that used higher dosing of ESAs than currently recommended. Nevertheless, the number of participants and therefore weight of these studies is very small, so the impact of these studies for the overall result is very limited.

To analyse the number of red blood cell transfusions given, we used the thresholds for transfusion of the individual studies, however, often the thresholds were not reported. Therefore, we cannot say whether thresholds differ across individual studies or whether red blood cell transfusions were given based on clinical considerations. As a result, it would be possible that studies with higher thresholds may not show evidence for a difference between study arms.

For our primary outcome, we created funnel plots for comparisons including at least 10 studies. Nevertheless, we could have also created comparison-adjusted funnel plots, which requires an assumption regarding the difference between small studies and large studies (e.g. newer treatments favoured in small trials, active treatment versus placebo, sponsored versus non-sponsored) (Chaimani 2013). However, the challenge in network meta-analysis is that we would need to take into account several comparisons, which means that we do not have one single line of reference. We therefore decided not to create comparison-adjusted funnel plots.

For a more comprehensive presentation of results, we estimated absolute treatment effects using the actual reported event rates for our chosen main comparator (no treatment). However, if we would choose another comparator to estimate absolute event rates, these effects could all change. Thus, when interpreting the results of our network meta-analysis, it must be considered that the reported absolute event rates are for illustrative purposes and do not reflect anticipated real-life event rates.

In our opinion, the summary of findings tables are not ideal to sum up such extensive analyses. Also, we surmise that the overall judgement of the risk of bias in included trials and the certainty in the evidence could diverge between different author teams. Both the risk of bias tool and the GRADE approach are sensitive to subjective assessments and can be done more or less stringent.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first comprehensive review with network meta-analysis comparing all possible treatment combinations of erythropoiesis-stimulating agents (ESAs) and iron for the prevention and alleviation of anaemia in cancer patients

Compared to a systematic review analysing the use of ESAs for prophylaxis or treatment of anaemia in cancer patients with or without concurrent antineoplastic therapy (Bohlius 2006), our results are in parallel regarding the use of ESAs leading to a reduction of the number of red blood cell transfusions and increasing the number of thromboembolic events. Regarding overall mortality, our results showed a slightly lower effect than Bohlius 2006 (in that review evaluated as overall survival, also based on number of patients who died), which found increased mortality in the ESA group. Regarding haematological response, our results showed an even higher effect of ESAs compared to no treatment than Bohlius 2006.

Compared to a Cochrane Review with meta-analysis based on individual patient data analysing the use of ESAs plus red blood cell transfusions (if necessary) versus red blood cell transfusions (if necessary) alone (Bohlius 2009), our results showed similar results regarding on-study mortality and overall mortality. Nevertheless, our results showed no clear effect for ESA alone compared to no treatment, but results indicate increased mortality for participants treated with ESA.

Compared to a systematic review with meta-analysis looking at the use of iron as a supplement to ESA and iron alone compared with ESA alone in the management of chemotherapy-induced anaemia (Mhaskar 2016), our results are in parallel regarding the use of intravenous or oral iron in combination with ESAs leading to a higher haematological response and a reduced need for red blood cell transfusions and showing no meaningful differences in the number of thromboembolic events.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of our systematic review and network meta-analyses might support clinicians and patients in decision-making regarding the use of erythropoiesis-stimulating agents (ESAs) and iron for the prevention or alleviation of anaemia in cancer patients. Our results provide a comprehensive overview of all possible treatment combinations of ESAs and intravenous or oral iron, including a treatment ranking for each outcome. However, these rankings should be interpreted with caution and the results of all outcomes should be taken into consideration before a decision is met. Because of missing data from the included trials and not fully connected networks, not all treatment combinations could be

compared to each other for every outcome. More trials with head-to-head comparisons including all potential agents are needed to draw the whole picture and proof the results of this analysis.

When interpreting the results of this systematic review, it is important to understand that network meta-analyses are no substitute for direct head-to-head comparisons. It is also important to consider that the results of our network meta-analysis do not necessarily rule out differences which could be clinically relevant for some individuals.

Implications for research

Even though direct and/or indirect comparisons of the different treatment options are possible through performing network meta-analysis, head-to-head trials are needed to be able to provide clear recommendations. Future trials should consider reporting all patient-relevant outcomes more consistently. The finding that for most outcomes a different graphical network emerged shows how the 96 included trials reported patient-relevant outcomes inconsistently, particularly our primary endpoint on-study mortality and adverse events. Due to the fact that for every single outcome the networks were not fully connected, the arising ranking of treatments included different sets of treatment options for each outcome, which makes an overall judgement impossible.

ACKNOWLEDGEMENTS

We would like to thank the following members of Cochrane Haematology for their comments and improving the review: Dr Guido Schwarzer, Prof. Benjamin Djulbegovic, Prof. Rahul Mhaskar and the consumer editor Anne Lyddiatt.

We would like to thank the Cochrane Member Yuan Chi for translating a Chinese paper.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Toby Lasserson, Deputy Editor in Chief, Cochrane
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Colleen Olveman, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Heather Maxwell, Cochrane Production Team
- Peer-reviewers (provided comments and recommended an editorial decision): Prof. Sunday Ocheni, Department of Haematology & Immunology, University of Nigeria (clinical review), Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review), Andrew Bäck, Statistical Editor, Methods Support Unit, Cochrane (methods review), Douglas M Salzwedel, Cochrane Hypertension (search review). Two additional peer reviewers provided clinical peer review but chose not to be publicly acknowledged.

REFERENCES

References to studies included in this review

Aapro 2008 *{published data only}*

Aapro M, Barnadas A, Leonard RC, Marangolo M, Untch M. Effects of epoetin beta treatment in patients with metastatic breast cancer receiving chemotherapy. Results of the BRAVE trial. In: Breast Cancer Research and Treatment. Vol. 100. 2006:Abstract 6095.

* Aapro M, Leonard RC, Barnadas A, Marangolo M, Untch M, Malamos N, et al. Effect of once-weekly epoetin beta on survival in patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy: results of the Breast Cancer-Anemia and the Value of Erythropoietin (BRAVE) Study. *Journal of Clinical Oncology* 2008;**26**(4):592-8.

Leonard RC, Aapro M, Chan S, Dirix LY, Mayordomo J, Reichert D, et al. Once weekly epoetin beta in patients with metastatic breast cancer receiving anthracycline- or taxane-based chemotherapy. In: Annals of Oncology. Vol. Vol. 15. 2004:iii.50 (Abstract 188p).

Abels 1993 *{published and unpublished data}*

* Abels R. Erythropoietin for anemia in cancer patients. In: European Journal of Cancer. Vol. 29A. 1993:2-8.

Abels R. Recombinant human erythropoietin in the treatment of the anaemia of cancer. In: Acta Haematologica. Vol. 87 (Suppl 1). 1992:4-11.

Abels RI, Larholt KM, Krantz KD, Bryant EC. Recombinant Human Erythropoietin (rHuEPO) for the treatment of the anemia of cancer. *Oncologist* 1996;**1**(3):140-50.

Ansari 2016 *{published data only}***IRCT2015092111560N9**

Ansari NN, Abbasi B, Fardad F, Mehrara M, Ramim T. Comparing the effectiveness of ferric carboxymaltose and oral iron in treatment of chronic iron deficiencyanemia in colon cancer patients. In: Supportive Care in Cancer. Vol. 24. 2016:S37-S38.

Aravantinos 2003 *{published data only}*

Aravantinos G, Linardou H, Makridaki D, Laiou E, Zafiropoulos A, Janninis J, et al. Recombinant human erythropoietin for platinum-based chemotherapy-induced anaemia: a single-centre randomised study. *Journal of Balkan Union of Oncology* 2003;**8**(2):127-32.

Ataollah Hiradfar 2018 *{published data only}***IRCT2015061822805N1**

Ataollah Hiradfar A, Rezamand A, Pourghasem M, Karkon SS, Ghamari B, Karkon SF. Recombinant human erythropoietin in children with solid tumors and chemotherapy-induced anemia. *Iranian Journal of Blood and Cancer* 2018;**10**(1):9-15.

Athibovonsuk 2013 *{published data only}*

Athibovonsuk P, Manchana T, Sirisabya N. Prevention of blood transfusion with intravenous iron in gynecologic cancer patients receiving platinum-based chemotherapy. *Gynecologic Oncology* 2013;**131**(3):679-82.

Auerbach 2004 *{published data only}*

Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. *Journal of Clinical Oncology* 2004;**22**(7):1301-7. [MEDLINE: 105]

Auerbach 2010 *{published data only}*

Auerbach M, Silberstein PT, Webb RT, Averyanova S, Ciuleanu T E, Shao J, et al. Darbepoetin alfa 300 or 500 µg once every 3 weeks with or without intravenous Iron in patients with chemotherapy-induced anemia. *American Journal of Hematology* 2010;**85**(9):655-63.

Bastit 2008 *{published data only}*

Bastit L, Vandebroek A, Altintas S, Gaede B, Pinter T, Suto TS, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *Journal of Clinical Oncology* 2008;**26**(10):1611-8.

Birgegard 2015 *{published data only}*

Birgegard G, Henry D, Glaspy J, Chopra R, Thomsen LL, Auerbach M. A randomized noninferiority trial of intravenous iron isomaltoside versus oral iron sulfate in patients with nonmyeloid malignancies and anemia receiving chemotherapy: the PROFOUNDTrial. *Pharmacotherapy* 2016;**36**(4):402-14.

Blohmer 2011 *{published data only}*

* Blohmer JU, Paepke S, Sehouli J, Boehmer D, Kolben M, Würschmidt F, et al. Randomized phase III trial of sequential adjuvant chemoradiotherapy with or without erythropoietin alfa in patients with high-risk cervical cancer: results of the NOGGO-AGO intergroup study. *Journal of Clinical Oncology* 2011;**29**(28):3791-7.

Blohmer JU, Wuerschmidt J, Petry K, Weise G, Sehouli J, Kimming R, et al. Results with sequential adjuvant chemo-radiotherapy with vs. without epoetin alfa for patients with high-risk cervical cancer: results of a prospective, randomized, open and controlled AGO and NOGGO-intergroup study. In: Annals of Oncology. Vol. 15 Suppl 3. 2004.

Boogaerts 2003 *{published data only}*

* Boogaerts M, Coiffier B, Kainz C, Epoetin beta QOL Working Group. Impact of epoetin beta on quality of life in patients with malignant disease. *British Journal of Cancer* 2003;**88**(7):988-95. [MEDLINE: 167]

Neorecormon (epoetin beta). Briefing package or the FDA Oncologic Advisory Committee Meeting, May 4, 2004;**RO 205-3859**.

Cascinu 1994 *{published data only}*

Cascinu S, Fedeli A, Del Ferro E, Fedeli SL, Catalano G. Recombinant human erythropoietin treatment in cisplatin-

associated anemia: a randomized, double-blind trial with placebo. *Journal of Clinical Oncology* 1994;**12**:1058-62.

Case 1993 *{published data only}*

Abels RI, Larholt KM, Krantz KD, Bryant EC. Recombinant Human Erythropoietin (rHuEPO) for the treatment of the anemia of cancer. *Oncologist* 1996;**1**(3):140-50.

* Case DC, Bukowski RM, Carey RW, Fishkin EH, Henry DH, Jacobson RJ, et al. Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *Journal of the National Cancer Institute* 1993;**85**(10):801-6.

Cazzola 1995 *{published data only}*

* Cazzola M, Messinger D, Battistel V, Bron D, Cimino R, Enller-Ziegler L, et al. Recombinant human erythropoietin in the anemia associated with multiple myeloma or non-Hodgkin's lymphoma: dose finding and identification of predictors of response. *Blood* 1995;**86**(12):4446-53.

Neorecormon (epoetin beta). Briefing package or the FDA Oncologic Advisory Committee Meeting, May 4, 2004;**RO 205-3859**.

Chang 2005 *{published data only}*

* Chang J, Couture F, Young S, McWatters KL, Lau CY. Once weekly epoetin alfa maintains hemoglobin, improves quality of life and reduces transfusion in breast cancer patients receiving chemotherapy. *Journal of Clinical Oncology* 2005;**23**(12):2597-605. [MEDLINE: 2]

Chang J, Couture FA, Young SD, Lau CY, Lee McWatters K. Weekly administration of epoetin alfa improves cognition and quality of life in patients with breast cancer receiving chemotherapy. *Supportive Cancer Therapy* 2004;**2**(1):52-8.

Charu 2007 *{published data only}*

Charu V, Belani CP, Gill AN, Bhatt M, Ben-Jacob A, Tomita D, et al. A controlled, randomized, open-label study to evaluate the effect of every-2-week darbepoetin alfa for anemia of cancer. In: Annual Meeting Proceedings of the American Society of Clinical Oncology. 2004:abstract 8084.

* Charu V, Belani CP, Gill AN, Bhatt M, Tomita D, Rossi G, et al. Efficacy and safety of every-2-week darbepoetin alfa in patients with anemia of cancer: a controlled, randomized, open-label phase II trial. *Oncologist* 2007;**12**(6):727-37.

Charu V, Saidman B, Ben-Jacob A, Justice GR, Maniam AS, Rearden T, et al. Improvements in fatigue are associated with early treatment with darbepoetin alfa every 3 weeks in anemic patients receiving chemotherapy. In: Journal of Supportive Oncology. Vol. 3. 2005:14-5.

Christodoulou 2009 *{published data only}*

* Christodoulou C, Dafni U, Aravantinos G, Koutras A, Samantas E, Metal K. Effects of epoetin-alpha on quality of life of cancer patients with solid tumors receiving chemotherapy. *Anticancer Research* 2009;**29**(2):693-702.

Janinis J, Dafni U, Aravantinos G, Kalofonos HP, Papakostas P, Tsavdaridis D, et al. Quality of life (QoL) outcome of epoietin-alfa (EPO-A) in anemic cancer patients undergoing platinum or non-platinum-based chemotherapy: a randomized study conducted by the Hellenic Cooperative Oncology Group. In: Proceedings of the American Society of Clinical Oncology. Vol. 22. 2003:789.

Dammacco 2001 *{published data only}*

* Dammacco F, Castoldi G, Rodjer S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. *British Journal of Haematology* 2001;**113**(1):172-9.

Dammacco F, Silvestris F, Castoldi GL, Grassi B, Bernasconi C, Nadali G, et al. The effectiveness and tolerability of epoetin alfa in patients with multiple myeloma refractory to chemotherapy. *International Journal of Clinical and Laboratory Research* 1998;**28**:127-34.

Debus 2006 IPD *{published data only}*

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer - meta-analysis based on individual patient data. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007303. [DOI: 10.1002/14651858.CD007303.pub2]

Debus 2014 *{published data only}*

Debus J, Drings P, Baurecht W, Angermund R. Prospective, randomized, controlled, and open study in primarily inoperable, stage III non-small cell lung cancer (NSCLC) patients given sequential radiochemotherapy with or without epoetin alfa. *Radiotherapy and Oncology* 2014;**112**(1):23-9.

Del Mastro 1997 *{published data only}*

Del Mastro L, Venturini M, Lionetto R, Garrone O, Melioli G, Pasquetti W, et al. Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. *Journal of Clinical Oncology* 1997;**15**(7):2715-21.

Dunphy 1999 *{published data only}*

Dunphy FR, Harrison BR, Dunleavy TL, Rodriguez JJ, Hilton JG, Boyd JH. Erythropoietin reduces anemia and transfusions. *Cancer* 1999;**86**:1362-7.

Engert 2010 *{published data only}*

Engert A, Josting A, Haverkamp H, Villalobos M, Lohri A, Sökler M, et al. Epoetin alfa in patients with advanced-stage Hodgkin's lymphoma: results of the randomized placebo-controlled GHSG HD15EPO trial. *Journal of Clinical Oncology* 2010;**28**(13):2239-45.

EPO-INT-3 J&J 2004 *{published data only}*

Johnson & JPR&D, LLC. Background information for Oncologic Drugs Advisory Committee Meeting, Safety of Erythropoietin Receptor Agonists (ERAs) in Patients with Cancer. Johnson and Johnson briefing document for FDA/ODAC hearing May 4, 2004; Gaithersburg, MD Report Date: 30 MARCH 2004.

Fujisaka 2011 *{published data only}*

* Fujisaka Y, Sugiyama T, Saito H, Nagase S, Kudoh S, Endo M, et al. Randomised, phase III trial of epoetin-B to treat chemotherapy-induced anaemia according to the EU regulation. *British Journal of Cancer* 2011;**105**(9):1267-72.

Yoshizaki A, Kumagai S, Sugiyama T, Goto I, Saito H, Ariyoshi Y, et al. A phase III, randomized, double-blind placebo-controlled study of epoetin beta in lung and gynecological cancer receiving platinum-based chemotherapy: Japan Erythropoietin Study Group. *Annals of Oncology* 2010;**21**(S8):viii385.

Gascon 2019 *{published data only}*

Gage J, Gascan P, Nagarkar R, Smakal M, Syrigos K, Barrios C, et al. Long-term safety and efficacy of darbepoetin alfa in subjects with advanced stage NSCLC receiving multi-cycle chemotherapy. In: Journal of Thoracic Oncology. Vol. 12. 2017:S1091-S1092.

Gascon P, Nagarkar R, Smakal M, Syrigos K, Barrios CH, Cardenas Sanchez J, et al. Long-term safety and efficacy of darbepoetin alfa in subjects with stage IV NSCLC receiving multi-cycle chemotherapy. In: Annals of Oncology. Vol. 28. 2017:iii48.

* Gascon P, Nagarkar R, Smakal M, Syrigos KN, Barrios CH, Sanchez JC, et al. A randomized, double-blind, placebo-controlled, phase III noninferiority study of the long-term safety and efficacy of darbepoetin alfa for chemotherapy-induced anemia in patients with advanced non-small cell lung cancer. *Journal of Thoracic Oncology* 2019;**15**(2):190-202.

Henry D, Hirsh V, Kubota K, Steinmetz T, Thomas G, Kang JH, et al. Randomized, double-blind, placebo (P)-controlled phase III noninferiority study of darbepoetin alfa (D) for anemia in patients (pts) with advanced NSCLC: an ad hoc subgroup analysis of pts with baseline hemoglobin (Hb) < 10.0 g/dL. In: Annals of Oncology. Vol. 29. 2018:viii499-viii500.

Nagarkar R, Gascon P, Smakal M, Syrigos K, Barrios C, Cardenas Sanchez J, et al. A double-blind, randomized, placebo-controlled phase 3 noninferiority study of darbepoetin alfa for anemia in advanced NSCLC. In: Journal of Thoracic Oncology. Vol. 13. 2018:S359.

Gilreath 2019 *{published data only}*

Gilreath JA, Makharadze T, Boccia RV, Krupa A, Henry DH. Efficacy and safety of ferric carboxymaltose injection in reducing anemia in patients receiving chemotherapy for non-myeloid malignancies: a phase 3, placebo-controlled study (Iron Clad). In: Blood. Vol. 134. 2019.

Goede 2016 *{published data only}*

Goede V, Busch R, Bahlo J, Chataline V, Kremers S, Muller L, et al. Low-dose fludarabine with or without darbepoetin alfa in patients with chronic lymphocytic leukemia and comorbidity: primary results of the CLL9 trial of the German CLL Study Group. *Leukaemia & Lymphoma* 2016;**57**(3):596-603.

Gordon 2008 *{published data only}*

* Gordon D, Nichols G, Ben-Jacob A, Tomita D, Lillie T, Miller C. Treating anemia of cancer with every-4-week darbepoetin alfa: Final efficacy and safety results from a phase II, randomized, double-blind, placebo-controlled study. *Oncologist* 2008;**13**(6):715-24.

Gordon DH, Nichols G, Ben-Jacob A, Lam H, Lillie T, Miller C. Treating anemia of cancer with darbepoetin alfa administered every 4 weeks: Final results from a phase 2, randomized, double-Blind, placebo-controlled study in cancer patients not receiving chemotherapy and/or radiotherapy. In: Blood. Vol. 108. 2006:abstract 1304.

Goss 2005 *{published data only}*

Goss G, Feld R, Bezjak A, Perry G, Melosky B, Smith C, et al. Impact of maintaining Hb with epoetin alfa on time to progression (TTP), overall survival (OS), quality of life (QOL) and transfusion reduction in limited disease SCLC patients. In: Lung Cancer. Vol. 49. 2005:S53.

Grote 2005 *{published data only}*

* Grote T, Yeilding AL, Castillo R, Butler D, Fishkin E, Henry DH, et al. Efficacy and safety analysis of epoetin alfa in patients with small-cell lung cancer: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Oncology* 2005;**23**(36):9377-86.

Luksenburg H, Weir A, Wager R. Safety Concerns Associated with Aranesp (darbepoetin alfa) Amgen, Inc. and Procrit(epoetin alfa) Ortho Biotech, L.P., for the Treatment of Anemia Associated with Cancer Chemotherapy. FDA Briefing Document May 4, 2004 Oncologic Drugs Advisory Committee.

Gupta 2009 *{published data only}*

Gupta S, Singh P, Bisht S, Bhatt M, Pant M, Gupta R, et al. Recombinant human erythropoietin in patients of advanced Cancer treated "by chemoradiotherapy". *Landes Bioscience* 2009;**8**(1):13-7.

Hajigholami 2021 *{published data only}*

Hajigholami A, Maghsoodi A , Ansari H, Kafeshani M. Treatment of chemotherapy induced anemia; a randomized clinical trial to compare quality of life in patients taking intravenous versus oral iron. *Immunopathologia Persa* 2021;**7**(2):e32.

Hedenus 2003 *{published data only}*

Amgen Inc. Aranesp® (darbepoetin alfa) safety. Oncologic Drugs Advisory Committee, 4 May 2004.

* Hedenus M, Adriansson M, San Miguel J, Kramer MH, Schipperus MR, Juvonen E, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. *British Journal of Haematology* 2003;**122**(3):394-403.

Hedenus M, Brandberg Y, Molostova V, Iosova G, Abdulkadyrov K, Messinger D, et al. Efficacy of epoetin beta in treating the anaemia of cancer in patients with haematological malignancies. In: Proceedings of the 6th Congress of the European Haematology Association. 2001:abstract 190.

Hedenus 2007 *{published data only}*

Hedenus M, Birgegard G, Nasman P, Ahlberg L, Karlsson T, Lauri B, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies, a rndomized multicenter study. *Leukemia* 2007;**21**(4):627-32.

Hedenus 2014 *{published data only}*

Hedenus M, Karlsson T, Ludwig H, Rzychon B, Felder M, Roubert B, et al. Intravenous iron alone resolves anemia in patients with functional iron deficiency and lymphoid malignancies undergoing chemotherapy. *Medical Oncology* 2014;**31**(12):302.

Henke 1999 *{published data only}*

Henke M, Guttenberger R, Barke A, Pajonk F, Potter R, Frommhold H. Erythropoietin for patients undergoing radiotherapy: a pilot study. *Radiotherapy and Oncology* 1999;**50**(2):185-90.

Henke 2003 *{published data only}*

* Henke M, Laszig R, Ruebe C, Schaefer U, Haase KD, Schilcher B, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003;**362**:1255-60.

Schipper J, Henke M. Erythropoietin in patients with head and neck carcinomas? [Erythropoetin bei Karzinomen im Kopf-/ Halsbereich?]. *Laryngorhinootologie* 2004;**83**(5):292-7.

Henry 1995 *{published data only}*

Abels RI, Larholt KM, Krantz KD, Bryant EC. Recombinant Human Erythropoietin (rHuEPO) for the treatment of the anemia of cancer. *Oncologist* 1996;**1**(3):140-50.

Henry DH, Abels RI. Recombinant human erythropoietin in the treatment of cancer and chemotherapy-induced anemia: results of double-blind and open-label follow-up studies. In: Seminars in Oncology. Vol. 21. 1994:21-8.

* Henry DH, Brooks BJ, Case DC, Fishkin E, Jacobson R, Keller AM, et al. Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy. *Cancer Journal from Scientific American* 1995;**1**:252-60.

Henry 2007 *{published data only}*

* Henry DH, Dahl NV, Auerbach M, Tchekmedyian S, Laufman LR. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. *Oncologist* 2007;**12**(2):231-42.

Henry DH, Dahl NV, Auerbach M. Is thromboembolism in cancer patients treated with erythropoietic stimulating agents related to thrombocytosis and iron restricted erythropoiesis? In: Blood. Vol. 110. 2007:abstract 1625.

Hernandez 2009 *{published data only}*

* Hernandez E, Ganly P, Charu V, Dibenedetto J, Tomita D, Lillie T, et al. Randomized, double-blind, placebo-controlled trial of every-3-week darbepoetin alfa 300 micrograms for treatment of chemotherapy-induced anemia. *Current Medical Research and Opinion* 2009;**25**(9):2109-20. [OTHER] [OTHER]

Taylor K, Ganly P, Charu V, DiBenedetto J, Kracht K, Rossi G, et al. Randomized, double-blind, placebo-controlled study of darbepoetin alfa every 3 weeks for the treatment of chemotherapy-induced anemia. In: Blood. Vol. 106. 2005:abstract 3556.

Hoskin 2009 *{published data only}*

* Hoskin P, Robinson M, Slevin N, Morgan D, Harrington K, Gaffney C. Effect of epoetin alfa on survival and cancer treatment-related anemia and fatigue in paatients receiving radical radiotherapy with curative intent for head and neck cancer. *Journal of Clinical Oncology* 2009;**27**(34):5751-6.

Johnson & JPR & D, LLC. Background information for Oncologic Drugs Advisory Committee Meeting, Safety of Erythropoietin Receptor Agonists (ERAs) in Patients with Cancer. Johnson and Johnson briefing document for FDA/ODAC hearing May 4, 2004; Gaithersburg, MD, Report Date: 30 MARCH 2004.

Huddart 2002 *{published data only}*

Huddart RA, Welch RS, Chan S, Perren T, Atkinson R. A prospective randomised comparative-group evaluation of epoetin alfa for the treatment of anaemia in UK cancer patients receiving platinum-based chemotherapy. In: Annals of Oncology. Vol. 13 (Suppl 5). 2002:177. [MEDLINE: 388]

Iconomou 2003 *{published data only}*

Iconomou G, Koutras A, Rigopoulos A, Vagenakis AG, Kalofonos HP. Effect of recombinant human erythropoietin on quality of life in cancer patients receiving chemotherapy: results of a randomized, controlled trial. *Journal of Pain & Symptom Management* 2003;**25**(6):512-8. [MEDLINE: 44]

Italian 1998 *{published data only}*

Ferrini PR, Grossi A, Vannucchi AM, Barosi G, Guarnone R, Piva N, et al. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. *British Journal of Haematology* 1998;**103**(4):1070-4.

Kotasek 2002 *{published data only}*

Kotasek D, Albertsson M, Mackey J, Darbepoetin A980291SG. Randomized, double-blind, placebo-controlled, dose-finding study of darbepoetin alfa administered once every 3 (Q3W) or 4 (Q4W) weeks in patients with solid tumors. Proceedings of the American Society of Clinical Oncology 2002;**21**:356a.

* Kotasek D, Albertsson M, Mackey J, Steger G, Rossi G, O'Byne J, et al. Once per cycle dosing of darbepoetin alfa is feasible in anemic cancer patients receiving chemotherapy. In: Annals of Oncology. Vol. 13. 2002:170.

Kotasek 2003 *{published data only}*

Kotasek D, Berg R, Poulsen E, Colowick A. Randomized, double-blind, placebo controlled, phase I/II dose finding study of ARANESP (TM) administered once every three weeks in solid tumor patients. In: Blood. Vol. 96. 2000:abstract 1268.

* Kotasek D, Steger G, Faught W, Underhill C, Poulsen E, Colowick AB, et al. Darbepoetin alfa administered every 3 weeks alleviates anaemia in patients with solid tumours receiving chemotherapy; results of a double-blind, placebo-controlled, randomised study. *European Journal of Cancer* 2003;**39**(14):2026-34. [MEDLINE: 17]

Krzakowski 2008 *{published data only}*

Krzakowski M, DYNEPO OSG. Epoetin delta: efficacy in the treatment of anaemia in cancer patients receiving chemotherapy. *Clinical Oncology* 2008;**20**:705-13.

Kurz 1997 *{published data only}*

Kurz C, Marth C, Windbichler G, Lahousen M, Medl M, Vavra N, et al. Erythropoietin treatment under polychemotherapy in patients with gynecologic malignancies: a prospective, randomized, double-blind placebo-controlled multicenter study. *Gynecologic Oncology* 1997;**65**(3):461-6.

Leyland-Jones 2005 *{published data only}*

* Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *Journal of Clinical Oncology* 2005;**23**(25):5865-8.

Leyland-Jones B. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncology* 2003;**4**:459-60.

Luksenburg H, Weir A, Wager R. Safety Concerns Associated with Aranesp (darbepoetin alfa) Amgen, Inc. and Procrit (epoetin alfa) Ortho Biotech, L.P., for the Treatment of Anemia Associated with Cancer Chemotherapy. FDA Briefing Document May 4, 2004 Oncologic Drugs Advisory Committee.

Littlewood 2001 *{published data only}*

Aapro MS, Cella D, Zagari M. Age, anemia, and fatigue. In: Seminars in Oncology. Vol. 29. 2002:55-9.

Fairclough DL, Gagnon DD, Zagari MJ, Marschner N, Dicato M. Evaluation of quality of life in a clinical trial with nonrandom dropout: the effect of epoetin alfa in anemic cancer patients. *Quality of Life Research* 2003;**12**(8):1013-27.

Fallowfield L, Gagnon D, Zagari M, Cella D, Bresnahan B, Littlewood TJ, et al. Multivariate regression analyses of data from a randomised, double-blind, placebo-controlled study confirm quality of life benefit of epoetin alfa in patients receiving non-platinum chemotherapy. *British Journal of Cancer* 2002;**87**(12):1341-53.

* Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving non-platinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Oncology* 2001;**19**(11):2865-74.

Littlewood TJ, Cella D, Nortier JW. Erythropoietin improves quality of life. *Lancet Oncology* 2002;**3**(8):459-60.

Littlewood TJ, Kallich JD, San Miguel J, Hendricks L, Hedenus M. Efficacy of darbepoetin alfa in alleviating fatigue and the effect of fatigue on quality of life in anemic patients with lymphoproliferative malignancies. *Journal of Pain & Symptom Management* 2006;**31**(4):317-25.

Littlewood TJ, Nortier J, Rapoport B, Pawlicki M, de Wasch G, Vercammen E, et al. Epoetin alfa corrects anemia and improves quality of life in patients with hematologic malignancies receiving non-platinum chemotherapy. *Hematological Oncology* 2003;**21**(4):169-80.

Littlewood TJ. Efficacy and quality of life outcomes of epoetin-alpha in a double-blind, placebo-controlled, multicentre study of cancer patients receiving non-platinum-containing chemotherapy. *Frontiers of Radiation Therapy and Oncology* 2002;**37**:34-7.

Martin SC, Gagnon DD, Zhang L, Bokemeyer C, Van Marwijk KM, Van Hout B. Cost-utility analysis of survival with epoetin-alfa versus placebo in stage IV breast cancer. *Pharmacoeconomics* 2003;**21**(16):1153-69.

Maccio 2010 *{published data only}*

Maccio A, Madeddu C, Gramignano G, Mulas C, Sanna E, Mantovani G. Efficacy and safety of oral lactoferrin supplementation in combination with rHuEPO-β for the treatment of anemia in advanced cancer patients undergoing chemotherapy: open-label, randomized controlled study. *Oncologist* 2010;**15**:894-902.

Machtay 2007 *{published data only}*

Johnson & JPR & D, LLC. Background information for Oncologic Drugs Advisory Committee Meeting, Safety of Erythropoietin Receptor Agonists (ERAs) in Patients with Cancer. Johnson and Johnson briefing document for FDA/ODAC hearing May 4, 2004; Gaithersburg, MD, Report Date: 30 MARCH 2004.

Luksenburg H, Weir A, Wager R. Safety Concerns Associated with Aranesp (darbepoetin alfa) Amgen, Inc. and Procrit (epoetin alfa) Ortho Biotech, L.P., for the Treatment of Anemia Associated with Cancer Chemotherapy. FDA Briefing Document May 4, 2004 Oncologic Drugs Advisory Committee.

Machtay M, Pajak T, Suntharalingam M, Hershock D, Stripp DC, Cmelak A, et al. Definitive radiotherpay +/- erythropoietin for squamous cell carcinoma of the head and neck: preliminary report of RTOG 99-03. In: International Journal of Radiation Oncology, Biology, Physics. Vol. 60 (Suppl 1). 2004:S132.

* Machtay M, Pajak TF, Suntharalingam M, Shenouda G, Hershock D, Stripp DC, et al. Radiotherapy with or without erythropoietin for anemic patients with head and neck cancer: a randomized trial of the Radiation Therapy Oncology Group (RTOG 99-03). *International Journal of Radiation Oncology, Biology, Physics* 2007;**69**(4):1008-17.

Shenouda G, Zhang Q, Ang K, Machtay M, Parliament M, Hershock D, et al. Long-term results of radiation therapy oncology group 9903: a randomized phase 3 trial to assess the effect of erythropoietin on local-regional control in anemic patients treated with radiation therapy for squamous cell carcinoma of the head and neck. *International Journal of Radiation Oncology Biology Physics* 2015;**91**(5):907-15.

Milroy 2011 *{published data only}*

Milroy R, Bajetta E, Van den Berg PM, O'Brien ME, Perez-Manga G, Georgoulias V, et al. Effects of epoetin alfa on anemia and patient-reported outcomes in patients with non-small cell lung cancer receiving chemotherapy: results of a European, multicenter, randomized, controlled study. *European Journal of Clinical and Medical Oncology* 2011;**3**(2):49-56.

Moebus 2013 *{published data only}*

Moebus V, Bastert G, Kreienberg R, Eidtmann H, Cierna M, Untch M, et al. Epoetin alpha prevents anemia and transfusions of rbcs in patients (pts) receiving dose-dense sequential chemotherapy [abstract]. In: Proceedings of the American Society of Clinical Oncology. Vol. 20 (Pt 1). 2001:10a, Abstract 36.

* Moebus V, Jackisch C, Schneeweiss A, Huober J, Lueck HJ, du Bois A, et al. Adding epoetin alfa to intense dose-dense adjuvant chemotherapy for breast cancer: randomized clinical trial. *Journal of the National Cancer Institute* 2013;**105**:1018-26.

Moebus V, Lueck H, Thomssen C, Harbeck N, Nitz U, Kreienberg R, et al. The impact of epoetin-alpha on anemia, red blood cell (RBC) transfusions, and survival in breast cancer patients (pts) treated with dose-dense sequential chemotherapy: Mature results of an AGO phase III study (ETC trial). In: Journal of Clinical Oncology. Vol. 25. 2007:569.

Moebus V, Untch M, du Bois A, Lueck H J, Thomssen C, Kuhn W, et al. Dose-dense sequential chemotherapy with epirubicin(E), paclitaxel (T) and cyclophosphamide (C) (ETC) is superior to conventional dosed chemotherapy in high-risk breast cancer patients (>= 4 +LN). First results of an AGO-trial. In: Journal of Clinical Oncology. Vol. 22. 2004:abstract 513.

Untch M, Jackisch C, Lenhard MS, du Bois A, Lueck HJ, Thomssen C, et al. Epoetin-alpha reduces red blood cell transfusions (RBC) in high-risk breast cancer patients with adjuvant dose-dense, sequential chemotherapy with epirubicin (E), paclitaxel (T) and cyclophosphamide (C) (ETC). In: Journal of Clinical Oncology. Vol. 23. 2005:613.

Mystakidou 2005 *{published data only}*

Mystakidou K, Kalaidopoulou O, Katsouda E, Parpa E, Kouskouni E, Chondros C, et al. Evaluation of epoetin supplemented with oral iron in patients with solid malignancies and chronic anemia not receiving anticancer treatment. *Anticancer Research* 2005;**25**(5):3495-500.

Ng 2018 *{published data only}*

* Ng O, Keeler B, Simpson JA, Madhusudan S, Brookes M, Acheson A. Feasibility of intravenous iron isomaltoside to improve anemia and quality of life during palliative chemotherapy for esophagogastric adenocarcinoma. *Nutrition and Cancer* 2018;**70**(7):1106-17.

Ng O, Keeler B, Simpson JA, Madhusudan S, Brookes MJ, Acheson AG. Iron isomaltoside to improve oesophagogastric adenocarcinoma related anaemia and quality of life during chemotherapy. In: Gut. Vol. 67. 2018:A177-A178.

Nitz 2014 *{published data only}*

Nitz U, Gluz O, Zuna I, Oberhoff C, Reimer T, Schumacher C, et al. Final results from the prospective phase III WSG-ARA trial: impact of adjuvant darbepoetin alfa on event-free survival in early breast cancer. *Annals of Oncology* 2014;**25**(1):75-80.

Noronha 2016 *{published data only}***CTRI/2016/01/006520**

Noronha V, Joshi A, Patil VM, Banavali SD, Gupta S, Parikh PM, et al. Phase III randomized trial comparing intravenous to oral iron in patients with cancer-related iron deficiency anemia not on erythropoiesis stimulating agents. *Asia-Pacific Journal of Clinical Oncology* 2018;**14**(2):e129-e137.

* Noronha V, Patil VM, Joshi A, More S, Goud S, Punatar S, et al. Phase III open label randomized controlled trial comparing intravenous iron sucrose to oral ferrous sulphate (without erythropoiesis stimulating agents) in the treatment of cancer related iron deficiency anemia. In: Journal of Clinical Oncology. Vol. 34. 2016.

O'Shaughnessy 2005 *{published and unpublished data}*

* O'Shaughnessy JA, Vukelja SJ, Holmes FA, Savin M, Jones M, Royall D, et al. Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. *Clinical Breast Cancer* 2005;**5**(6):439-46.

O'Shaugnessy J, Vukelja S, Savin M, Holmes FA, Jones M, Royall D, et al. Effects of epoetin alfa (Procrit) on cognitive function, mood, asthenia, and quality of life in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy: a double-blind, randomized, placebo-controlled trial. In: Proceedings of the American Society of Clinical Oncology. Vol. 3. 2002:abstract 1449:S116-S120.

Oberhoff 1998 *{published data only}*

Ehmer B, Schrenk U, Franks W, Quardor O, Messinger D. Clinical efficacy of epoetin beta (EPO) in the correction of chemotherapy (CT) induced anemia in patients with solid cancer: a randomized controlled clinical trial. In: Annals of Oncololgy. Vol. 7 (Suppl 5). 1996:A2960.

Neorecormon (epoetin beta). Briefing package or the FDA Oncologic Advisory Committee Meeting, May 4, 2004;**RO 205-3859**.

Oberhoff C, Krumeich B, Winkler UH, Hoffmann O, Schindler AE. Recombinant human erythropoietin (epoetin beta) in the treatment of chemotherapy - associated anaemia: effects on blood coagulation and fibrinolysis in patients with gynecological malignancies. Annals of Hematology 2000;**79 Suppl 3**:B16.

* Oberhoff C, Neri B, Amadori D, Petry KU, Gamucci T, Rebmann U, et al. Recombinant human erythropoietin in the treatment of chemotherapy- induced anemia and prevention of transfusion requirement associated with solid tumors: a randomized, controlled study. *Annals of Oncology* 1998;**9**(3):255-60.

Oberhoff C, Stauch M, Wilhelm G, Musch E, Heinrich B, Neise M, et al. Prevention and therapy of anemia in tumor patients with Epoetin beta (NeoRecormon). *Tumor Diagnostik und Therapie* 2005;**26**(4):166-71.

Osterborg 1996 *{published data only}*

Neorecormon (epoetin beta). Briefing package or the FDA Oncologic Advisory Committee Meeting, May 4, 2004;**RO 205-3859**.

* Osterborg A, Boogaerts MA, Cimino R, Essers U, Holowiecki J, Juliusson G, et al. Recombinant human erythropoietin in

transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma--a randomized multicenter study. *Blood* 1996;**87**(7):2675-82.

Osterborg 2002 *{published data only}*

Neorecormon (epoetin beta). Briefing package or the FDA Oncologic Advisory Committee Meeting, May 4, 2004;**RO 205-3859**.

Osterborg A, Brandberg Y, Hedenus M. Impact of epoetin-ß on survival of patients with lymphoproliferative malignancies: long-term follow up of a large randomized study. *British Journal of Haematology* 2005;**129**:206-9.

Osterborg A, Brandberg Y, Hedenus M. Impact of epoetin-ß on survival of patients with lymphoproliferative malignanices: long-term follow up of a large randomized study. *British Journal of Haematology* 2005;**129**:206-9.

* Osterborg A, Brandberg Y, Molostova V, Iosava G, Abdulkadyrov K, Hedenus M, et al. Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin Beta, in hematologic malignancies. *Journal of Clinical Oncology* 2002;**20**(10):2486-94.

Overgaard 2009 *{published data only}*

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer - meta-analysis based on individual patient data. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007303. [DOI: 10.1002/14651858.CD007303.pub2]

Lambin P, Ramaekers BLT, Van Mastrigt GAPG, Van den Ende P, De Jong J, De RDKM, et al. Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer. *Cochrane Database of Systematic Reviews* 2009, Issue 3, Art. No.: CD006158. Art. No: CD006158. [DOI: 10.1002/14651858.CD006158.pub2]

Overgaard J, Hoff C, Sand Hansen H, Specht L, Overgaard M, Grau C, et al. Randomized study of the importance of Novel Erythropoiesis Stimulating Protein (Aranesp®) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck (HNSCC) - the Danish Head and Neck Cancer Group DAHANCA 10 randomized trial. In: European Journal of Cancer Supplements. Vol. 5. 2007:abstract 6LB.

* Overgaard JS, Hoff CM, Hansen HS, Specht L, Overgaard M, Grau C, et al and Danish Head and Neck Cancer Group (DAHANCA). Randomized study of darbepoetin alfa as modifier of radiotherapy in patients with primary squamous cell carcinoma of the head and neck (HNSCC): Final outcome of the DAHANCA 10 trial. *ASCO Meeting Abstracts* 2009;**27**:6007.

Pedrazzoli 2008 *{published data only}*

Pedrazzoli P, Farris A, Del Prete S, Del Gaizo F, Ferrari D, Bianchessi C, et al. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. *Journal of Clinical Oncology* 2008;**26**(10):1619-25.

Pirker 2008 *{published data only}*

Pirker R, Ramlau RA, Schuette W, Zatloukal P, Ferreira I, Lillie T, et al. Safety and efficacy of darbepoetin alpha in previously untreated extensive-stage small-cell lung cancer treated with platinum plus etoposide. *Journal of Clinical Oncology* 2008;**26**(14):2342-9.

Pronzato 2010 *{published data only}*

Pronzato P, Cortesi E, Van der Rijt C, Moreno-Nogueria A, Raimundo D, Ostler P, et al. Early intervention with epoetin alfa in breast cancer (BC) patients (pts) undergoing chemotherapy (CT): results of a randomized, multicenter, phase IIIb study (EPO-INT-47 Study Group). In: Annals of Oncology. Vol. 13. 2002:168.

* Pronzato P, Cortesi E, Van der Rijt CC, Bols A, Moreno-Nogueira JA, de Oliveira CF, et al. Epoetin alfa improves anemia and anemia-related, patient-reported outcomes in patients with breast cancer receiving myelotoxic chemotherapy: results of a European, multicenter, randomized, controlled trial. *Oncologist* 2010;**15**(9):935-43. [22233]

Quirt 1996 *{published data only}*

Quirt I, Micucci S, Moran LA, Pater J, Browman G. The role of recombinant human erythropoietin (EPO) in reducing red blood cell transfusions and maintaining quality of life (QOL) in patients with lymphoma and solid tumors receiving cytotoxic chemotherapy. Results of a randomized, double-blind, placebo-controlled clinical trial. In: Blood. Vol. 88. 1996:347a.

Ray-Coquard 2009 *{published data only}*

* Ray-Coquard I, Dussart S, Goillot C, Mayeur D, Debourdeau P, Ghesquieres H, et al. A risk model for severe anemia to select cancer patients for primary prophylaxis with epoetin {alpha}: a prospective randomized controlled trial of the ELYPSE study group. Annals of Oncology 2009;(doi:10.1093/annonc/mdn750).

Ray-Coquard I, Perol D, Debourdeau P, Chabaud S, Chelghoum M, Mayeur D, et al. ELYPSE 4: a prospective randomized trial comparing Epo A in primary prophylaxis of severe anemia requiring red cells transfusion in high risk patients. In: Annals of Oncology. Vol. 17. 2006:ix294.

Razzouk 2006 *{published data only}*

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer - meta-analysis based on individual patient data. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007303. [DOI: 10.1002/14651858.CD007303.pub2]

Hinds PS, Hockenberry M, Feusner J, Hord JD, Rackoff W, Rozzouk BI. Hemoglobin response and improvements in quality of life in anemic children with cancer receiving myelosuppressive chemotherapy. In: Journal of Supportive Oncology. Vol. 3. 2005:10-1.

Razzouk BI, Hockenberry M, Hinds PS, Feusner J, Rackoff W, Hord JD. Influence of hemoglobin response to epoetin alfa on quality-of-life in anemic children with cancer receiving myelosuppressive chemotherapy. In: Blood. Vol. 104. 2004:abstract 221.

* Razzouk BI, Hord JD, Hockenberry M, Hinds PS, Feusner J, Williams D, et al. Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy. *Journal of Clinical Oncology* 2006;**24**(22):3583-9.

Rose 1994 *{published data only}*

Rose E, Rai K, Revicki D. Clinical and health status assessments in anemic chronic lymphocytic leukemia (CLL) patients treated with epoetin alfa (EPO). In: Blood. Vol. 84. 1994:526a.

Rosenzweig 2004 *{published data only}*

Rosenzweig MQ, Bender CM, Lucke JP, Yasko JM, Brufsky AM. The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. *Journal of Pain & Symptom Management* 2004;**27**(2):185-90. [MEDLINE: 90]

Smith 2003 *{published data only}*

Smith RE, Tchekmedyian NS, Chan D, Meza LA, Northfelt DW, Patel Retal. A dose- and schedule-finding study of darbepoetin alpha for the treatment of chronic anaemia of cancer. *British Journal of Cancer* 2003;**88**(12):1851-8. [MEDLINE: 955]

Smith 2008 *{published data only}*

Glaspy J, Smith RE, Aapro M, Ludwig H, Pinter T, Smakal M, et al. Results from a phase 3 randomized, double blind, placebo controlled study of darbepoetin alfa for the treatment of anemia in cancer patients not receiving chemotherapy or radiotherapy. In: Haematologica. Vol. 92. 2007:136.

* Smith RE, Aapro MS, Ludwig H, Pinter T, Smakal M, Ciuleanu TE, et al. Darbepoetin alpha for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Journal of Clinical Oncology* 2008;**26**(7):1040-50.

Steensma 2011 *{published data only}*

Steensma DP, Sloan JA, Dakhil SR, Dalton R, Kahanic SP, Prager DJ, et al. Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. *Journal of Clinical Oncology* 2011;**29**(1):97-105.

Strauss 2008 *{published data only}*

Strauss H, Haendgen G, Dunst J, Koelbl H. Effects of anaemia correction with epoetin beta in patients with advanced cervical cancer. In: Proceedings of the American Society of Clinical Oncology. 2003:abstract 5121.

* Strauss HG, Haendgen G, Dunst J, Haywrad CR, Burger HU, Scherhag A, etal. Effects of anemia correction with epoetin beta in patients receiving radiochemotherapy for advanced cervical cancer. In: International Journal of Gynecological Cancer. Vol. 18. 2008:515-24.

Sweeney 1998 *{published data only}*

* Sweeney PJ, Nicolae D, Ignacio L, Chen L, Roach M, Wara W, et al. Effect of subcutaneous recombinant human erythropoietin in cancer patients receiving radiotherapy: final report of a randomized, open- labelled, phase II trial. *British Journal of Cancer* 1998;**77**(11):1996-2002.

Vijayakumar S, Roach M, Wara W, Chan SK, Ewing C, Rubin S. Effect of subcutaneous recombinant human erythropoietin in cancer patients receiving radiotherapy: preliminary results of a randomized, open-labeled, phase II trial. *International Journal of Radiation Oncology, Biology and Physics* 1993;**26**:721-9.

Ten Bokkel 1998 *{published data only}*

Neorecormon (epoetin beta). Briefing package or the FDA Oncologic Advisory Committee Meeting, May 4, 2004;**RO 205-3859**.

Reed N, Rhan S, Hayward C, Burger H, Ten Bokkel Huinink W. Impact of epoetin beta on the survival of anemic patients with ovarian cancer receiving platinum-based chemotherapy. In: Proceedings of the American Society of Clinical Oncology. Vol. 23. 2003:abstract 5102.

* Ten Bokkel Huinink WW, De Swart CA, van Toorn DW, Morack G, Breed WP, Hillen HF, et al. Controlled multicentre study of the influence of subcutaneous recombinant human erythropoietin on anaemia and transfusion dependency in patients with ovarian carcinoma treated with platinum-based chemotherapy. *Medical Oncology* 1998;**15**(3):174-82.

Thatcher 1999 *{published data only}*

De Campos E, Radford J, Steward, Milroy R, Dougal M, Swindell R, et al. Clinical and and in vitro effects of recombinant human erythropoietin in patients receiving intensive chemotherapy for small-cell lung cancer. *Journal of Clinical Oncology* 1995;**13**(7):1623-31.

* Thatcher N, De Campos ES, Bell DR, Steward WP, Varghese G, Morant R, et al. Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer. *British Journal of Cancer* 1999;**80**(3-4):396-402.

Thépot 2016 *{published data only}*

Thépot S, Ben Abdelali R, Chevret S, Renneville A, Beyne-Rauzy O, Prébet T, et al. A randomized phase II trial of azacitidine +/- epoetin-β in lower-risk myelodysplastic syndromes resistant to erythropoietic stimulating agents. *Haematologica* 2016;**101**(8):918-925.

Thomas 2002 *{published data only}*

Thomas H, McAdam KF, Thomas RJ, Joffe JK, Sugden EM, Awwad ST, et al. Early intervention with epoetin alfa for treatment of anaemia and improvement of quality of life in cancer patients undergoing myelotoxic chemotherapy. In: Annals of Oncology. Vol. 13 (Suppl 5). 2002:177, #653P.

Thomas 2008 *{published data only}*

Johnson &JPR&D, LLC. Background information for Oncologic Drugs Advisory Committee Meeting, Safety of Erythropoietin Receptor Agonists (ERAs) in Patients with Cancer. Johnson and Johnson briefing document for FDA/ODAC hearing May 4, 2004; Gaithersburg, MD, Report Date: 30 MARCH 2004.

* Thomas G, Ali S, Hoebers FJP, Darcy KM, Rodgers WH Patel M, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecologic Oncology* 2008;**108**(2):317-25.

Throuvalas 2000 *{published data only}*

Throuvalas NA, Antonadou D, Boufi M, Lavey R Malamos N. Erythropoietin decreases transfusion requirements during radiochemotherapy. In: Proceedings of the American Society of Clinical Oncologists. Vol. 19. 2000:Abstract 1558.

Tjulandin 2010 *{published data only}*

Tjulandin SA, Bias P, Elsässer R, Gertz B, Kohler E, Buchner A. Epoetin theat in anaemic cancer patients receiving platinum-based chemotherapy: a randomised controlled trial. *Archives of Drug Information* 2010;**3**:45-53.

Tjulandin 2011 *{published data only}*

Buchner A, Bias P. Epoetin theta shows efficacy and safety in a placebo controlled, randomized phase III study in cancer patients receiving non-platinum chemotherapy. In: Onkologie. Vol. 32. 2009:88, Abstract V348.

* Tjulandin SA, Bias P, Elsässer R, Gertz B, Kohler E, Buchner A. Epoetin theta with a new dosing schedule in anaemic cancer patients receiving nonplatinum-based chemotherapy: a randomised controlled trial. *Archives of Drug Information* 2011;**4**(3):33-41.

Toma 2013 *{published data only}*

Toma A, Chevret S, Kosmider O, Delaunay J, Stamatoullas A, Rose C, et al. A randomized study of lenalidomide (LEN) with or without EPO in RBC transfusion dependent (TD) IPSS low and int-1 (lower risk) myelodysplastic syndromes (MDS) without del 5q resistant to EPO. In: Journal of Clinical Oncology. Vol. 31. 2013.

Tsuboi 2009 *{published data only}*

* Tsuboi M, Ezaki K, Tobinai K, Ohashi Y, Saijo N. Weekly administration of epoetin beta for chemotherapy-induced anemia in cancer patients: results of a multicenter, Phase III, randomized, double-blind, placebo-controlled study. *Japanese Journal of Clinical Oncology* 2009;**39**(3):163-8.

Watanabe M, Ezaki K, Tobinai K, Tsuboi M, Ohashi Y, Hirashima K, et al. A multicenter phase III randomized, double-blind placebo-controlled study of Epoetin beta administered once-weekly for chemotherapy induced anemia (CIA) in cancer patients: Japan Erythropoietin Study Group. In: Annals of Oncology. Vol. 17. 2006:294.

Untch 2011 *{published data only}*

* Untch M, Fasching PA, Konecny GE, von Koch F, Conrad U, Fett W, et al. PREPARE trial: A randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF versus a standard-dosed epirubicin/cyclophosphamide followed by paclitaxel (plus or minus) darbepoetin alfa in primary breast cancer-results at the time of surgery. *Annals of Oncology* 2011;**22**(9):1988-98.

Untch M, Fascing PA, Bauernfeind I, Conrad U, Camara O, Fett W, et al. PREPARE trial. A randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF with a standard dosed epirubicin/cyclophosphamide followed by paclitaxel +/- darbepoetin alfa in primary breast cancer: A preplanned interim analysis of efficacy at surgery. In: Journal of Clinical Oncology. Vol. 26. 2008:abstract 517.

Vansteenkiste 2002 *{published data only}*

Amgen I. Aranesp® (darbepoetin alfa) safety. Oncologic Drugs Advisory Committee, 4 May 2004.

Kallich JD, Tchekmedyian NS, Damiano AM, Shi J, Black JT, Erder MH. Psychological outcomes associated with anemia-related fatigue in cancer patients. In: Oncology (Huntingt). Vol. 16. 2002:117-24.

Pirker R, Vansteenkiste J, Gateley J, Yates P, Colowick A, Musil J. A phase 3, double-blind, placebo-controlled, randomized study of novel erythropoiesis stimulating protein (NESP) in patients undergoing platinum treatment for lung cancer. In: Proceedings of the American Society of Clinical Oncology. Vol. 20. 2001:abstract 1572.

Tchekmedyian NS, Kallich J, McDermott A, Fayers P, Erder MH. The relationship between psychologic distress and cancer-related fatigue. *Cancer* 2003;**98**(1):198-203.

Tchekmedyian S, Glaspy J, Colowick A, Tomita D, Rossi G. Effect of darbepoetin alfa and recombinant human erythropoietin (rHuEPO) on early hemoglobin (Hb) changes in anemic cancer patients (pts). Annals of Oncology 2002;**13**(Suppl 5):184.

* Vansteenkiste J, Pirker R, Massuti B, Barata F, Font A, Fiegl M, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy.[see comment]. *Journal of the National Cancer Institute* 2002;**94**(16):1211-20. [MEDLINE: 42]

Vansteenkiste J, Poulsen E, Rossi G, Glaspy J. Darbepoetin alfa: impact on treatment for chemotherapy-induced anemia and considerations in special populations. In: Oncology (Huntingt). Vol. 16. 2002:45-55.

Vansteenkiste J, Tomita D, Rossi G, Pirker R. Darbepoetin alfa in lung cancer patients on chemotherapy: a retrospective comparison of outcomes in patients with mild versus moderate-to-severe anaemia at baseline. *Supportive Care in Cancer* 2004;**12**(4):253-62.

Welch 1995 *{published data only}*

James RD, Wilkinson PM, Belli F, Welch R, Cowan R. Recombinant human erythropoietin in patients with ovarian carcinoma and anaemia secondary to cisplatin and carboplatin chemotherapy: preliminary results. In: Acta Haematologica. Vol. 87 (Suppl 1). 1992:12-5.

* Welch RS, James RD, Wilkinson PM, Belli F, Cowan RA. Recombinant human erythropoietin and platinum-based chemotherapy in advanced ovarian cancer. *Cancer Journal of the Scientific American* 1995;**1**(4):261-6.

Wilkinson 2006 *{published data only}*

Wilkinson PM, Antonopoulos M, Lahousen M, Lind M, Kosmidis P, EPO-INT-45 Study Group. Epoetin alfa in platinum-treated ovarian cancer patients: results of a multinational, multicentre, randomised trial. *British Journal of Cancer* 2006;**94**(7):947-54.

Winquist 2009 *{published data only}*

Winquist E, Julian JA, Moore MJ, Nabid A, Sathya J, Wood L, et al. Randomized, double-blind, placebo-controlled trial of epoetin alfa in men with castration-resistant prostate cancer and anemia. *Journal of Clinical Oncology* 2009;**27**(4):644-6.

Witzig 2005 *{published data only}*

Dicato M, Vercammen E, Liu KL, Xiu LX, Bowers P. Relationship of body weight to efficacy of a fixed-dose regimen of epoetin alfa vs placebo in anemic cancer patients. In: Haematologica. Vol. 90. 2005:abstract 0077.

* Witzig TE, Silberstein PT, Loprinzi CL, Sloan JA, Novotny PJ, Mailliard JA, et al. Phase III, randomized, double-blind study of epoetin alfa versus placebo in anemic patients with cancer undergoing chemotherapy. *Journal of Clinical Oncoogy* 2005;**23**(12):2606-17. [MEDLINE: 1]

Wright 2007 *{published data only}*

Wright JR, Ung YC, Julian JA, Pritchard KI, Whelan TJ, Smith C, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *Journal of Clinical Oncology* 2007;**25**(9):1027-32.

Zhao 2018 *{published data only}*

Zhao CM, Huang DF, Zhang LH, Cao YH, Che HL. Clinical observation of recombinant human erythropoietin on chemotherapy-induced anemia in patients with gastrointestinal cancer. *Chinese Journal of New Drugs* 2018;**27**(2):173-7.

References to studies excluded from this review

Antonadou 2001 *{published data only}*

Antonadou D, Cardamakis E, Puglisi M, Malamos N, Throuvalas N. Erythropoietin enhances radiation treatment efficacy in patients with pelvic malignancies. Final results of a randomized phase III study. In: European Journal of Cancer. Vol. 37. 2001:S144.

Bamias 2003 *{published data only}*

Bamias A, Aravantinos G, Kalofonos C, Timotheadou N, Siafaka V, Vlahou I, et al. Prevention of anemia in patients with solid tumors receiving platinum-based chemotherapy by recombinant human Erythropoietin (rHuEpo): a prospective, open label, randomized trial by the Hellenic Cooperative Oncology Group. *Oncology* 2003;**64**(2):102-10. [MEDLINE: 175]

Boccia 2019 *{published data only}*

Boccia RV, Dahl NV, Strauss WE. Severe hypophosphatemia in patients with cancer following IV iron treatment: results from a large comparative trial. In: Blood. Vol. 134. 2019.

Cabanillas 2012 *{published data only}*

Cabanillas ME, Kantarjian H, Thomas DA, Mattiuzzi GN, Rytting ME, Bruera E, et al. Epoetin alpha decreases the number of erythrocyte transfusions in patients with acute lymphoblastic leukemia, lymphoblastic lymphoma, and Burkitt leukemia/lymphoma: results of a randomized clinical trial. *Cancer* 2012;**118**(3):848-855.

Carabantes 1999 *{published data only}*

Carabantes FJ, Benavides M, Trujillo R, Cobo M, Hebrero ML, Garcia S, et al. Epoetin alfa in the prevention of anemia in cancer patients undergoing platinum-based chemotherapy (CT) (CT). A prospective randomized study. In: Proceedings of the American Society of Clinical Oncology. Vol. 18. 1999:596a. Abstract 2303.

EPO-GER-20 IPD *{published data only}*

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer - meta-analysis based on individual patient data. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007303. [DOI: 10.1002/14651858.CD007303.pub2]

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer - meta-analysis based on individual patient data. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007303. [DOI: 10.1002/14651858.CD007303.pub2]

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J. Erythropoietin or darbepoetin for patients with cancer - meta-analysis based on individual patient data. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007303. [DOI: 10.1002/14651858.CD007303.pub2]

Fenaux 2017 *{published data only}***EUCTR2010-022884-36-BG**

Fenaux P, Santini V, Aloe Spiriti M, Giagounidis A, Schlag R, Radinoff A, et al. Challenging IWG2006 response criteria: results of a randomized study of epoetin alfa versus placebo in anemic lower risk MDS patients. In: Leukemia Research. Vol. 55. 2017:S23.

Gebbia 2003 *{published data only}*

Gebbia V, Di Marco P, Citarrella P. Systemic chemotherapy in elderly patients with locally advanced and/or inoperable squamous cell carcinoma of the head and neck: impact of anemia and role of recombinant human erythropoietin. *Critical Reviews in Oncology/Hematology* 2003;**48**:49-55.

Hedenus 2002 *{published data only}*

Hedenus M, Hansen S, Taylor K, Arthur C, Emmerich B, Dewey C, et al. Randomized, dose-finding study of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies. *British Journal of Haematology* 2002;**119**(1):79-86. [MEDLINE: 37]

Heidenreich 2015 *{published data only}*

Heidenreich A, Miller K, Steiner U, Schostak M. Prospective clinical phase-II trial on docetaxel and estramustine with or without epoeitin-alpha in patients with metastatic castration-resistant prostate cancer (mCRPC). In: Journal of Clinical Oncology. 2015.

Katakami 2008 *{published data only}*

* Katakami N, Nishiwaki Y, Fujiwara Y, Tsuboi M, Takeda K, Nakanishi T, et al. Randomized, double-blind, placebo-controlled phase III study of weekly administration of darbepoetin alfa (DA) in anemic patients with lung or gynecologic cancer receiving platinum-containing chemotherapy. *Annals of Oncology* 2008;**19**(S8):viii277-8.

Katsumata N, Fujiwara Y, Katakami N, Nishiwaki Y, Tsuboi M, Takeda K, et al. Randomized, double-blind, placebo-controlled phase III study of weekly administration of darbepoetin alfa in anemic patients with lung or gynecologic cancer receiving platinum-containing chemotherapy. *Vox Sanguinis* 2009;**97**(S1):58.

Kunikane 2001 *{published data only}*

Kunikane H, Watanabe K, Fukuoka M, Saijo N, Furuse K, Ikegami H, et al. Double-blind randomized control trial of the effect of recombinant human erythropoietin on chemotherapy-induced anemia in patients with non-small cell lung cancer. *International Journal of Clinical Oncology* 2001;**6**:296-301.

Leyland-Jones 2015 *{published data only}*

Leyland-Jones B, Bondarenko I, Nemsadze G, Smirnov V, Litvin I, Kokhreidze I, et al. A randomized, open-label, multicenter, phase 3 study of epoetin alfa (EPO) plus standard supportive care versus standard supportive care in anemic patients with metastatic breast cancer (MBC) receiving standard chemotherapy. *Journal of Clinical Oncology* 2015;**34**(11):1197-207.

List 2016 *{published data only}*

List AF, Sun Z, Verma A, Bennett JM, Komrokji RS, McGraw K, et al. Lenalidomide-epoetin alfa versus lenalidomide monotherapy in myelodysplastic syndromes refractory to recombinant erythropoietin. *Journal of Clinical Oncology* 2021;**39**(9):1001-9.

List AF, Sun Z, Verma A, Bennett JM, McGraw KL, Nardelli LA, et al. Combined treatment with lenalidomide (LEN) and epoetin alfa (EA) is superior to lenalidomide alone in patients with erythropoietin (Epo)-refractory, lower risk (LR) non-deletion 5q myelodysplastic syndrome (MDS): results of the E2905 intergroup study-an. In: Blood. Vol. 128. 2016.

Mafodda 2017 *{published data only}*

Mafodda A, Giuffrida D, Prestifilippo A, Azzarello D, Giannicola R, Mare M, et al. Oral sucrosomial iron versus intravenous iron in anemic cancer patients without iron deficiency receiving darbepoetin alfa: a pilot study. *Supportive Care in Cancer* 2017;**25**(9):2779-86.

Mountzios 2016 *{published data only}***ACTRN12614001082695**

Mountzios G, Aravantinos G, Alexopoulou Z, Timotheadou E, Matsiakou F, Christodoulou C, et al. Lessons from the past: Long-term safety and survival outcomes of a prematurely terminated randomized controlled trial on prophylactic vs. hemoglobin-based administration of erythropoiesis-stimulating agents in patients with chemotherapy-induced anemia. *Molecular and Clinical Oncology* 2016;**4**(2):211-20.

OBE/EPO-INT-03 IPD *{published data only}*

Anonymous. A placebo-controlled study on the effect of epoetin alfa in patients with malignancy receiving chemotherapy. Raritan (NJ): Johnson and Johhnson Pharmaceutical Research and Development. Available at www.clinicaltrials.gov/ct2/show/NCT00270166 2005. (date of last access April 13, 2021).

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer - meta-analysis based on individual patient data. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007303. [DOI: 10.1002/14651858.CD007303.pub2]

P-174 J&J 2004 *{published and unpublished data}*

Johnson &JPR&D, LLC. Background information for Oncologic Drugs Advisory Committee Meeting, Safety of Erythropoietin Receptor Agonists (ERAs) in Patients with Cancer. Johnson and Johnson briefing document for FDA/ODAC hearing May 4, 2004; Gaithersburg, MD, Report Date: 30 MARCH 2004.

Pangalis GA, Poziopoulos C, Angelopoulou MK, Siakantaris MP, Panayiotidis P. Effective treatment of disease-related anaemia in B-chronic lymphocytic leukaemia patients with recombinant human erythropoietin. *British Journal of Haematology* 1995;**89**(3):627-9.

Platzbecker 2017 *{published data only}*

Gasal E, Pan C, Tankersley C. ARCADE (20090160): a randomized controlled trial of darbepoetin alpha in anemic patients with low or intermediate-1 risk myelodysplastic syndrome (MDS). In: Leukemia Research. Vol. 37. 2013:S166-S167.

Platzbecker U, Oliva EN, Symeonidis A, Delforge M, Mayer J, Goede JS, et al. A multicenter, randomized, double-blind placebocontrolled study of darbepoetin alfa for the treatment of anemic patients with low or intermediate-1 risk myelodysplastic syndrome. In: Hemasphere. Vol. 2. 2018:717.

Platzbecker U, Symeonidis A, Oliva E, Goede J, Delforge M, Mayer J, et al. A phase 3 randomized placebo (PBO)-controlled double-blind trial of darbepoetin alfa in low or intermediate-1 (INT-1) risk myelodysplastic syndromes (MDS). In: Haematologica. Vol. 102. 2017:484.

Platzbecker U, Symeonidis A, Oliva E, Goede JS, Delforge M, Mayer J, et al. Arcade (20090160): a phase 3 randomized placebo-controlled double-blind trial of darbepoetin alfa in the treatment of anemia in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS). In: Haematologica. Vol. 101. 2016:15.

Platzbecker U, Symeonidis A, Oliva EN, Goede JS, Delforge M, Mayer J, et al. A phase 3 randomized placebo (PBO)-controlled double-blind trial of darbepoetin alfa in the treatment of anemia in patients with low or intermediate-1 (Int-1) risk myelodysplastic syndromes (MDS). In: Blood. Vol. 128. 2016.

* Platzbecker U, Symeonidis A, Oliva EN, Goede JS, Delforge M, Mayer J, et al. A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes. *Leukemia* 2017;**31**(9):1944-50.

Rosen 2003 *{published data only}*

Rosen FR, Haraf DJ, Kies MS, Stenson K, Portugal L, List MA, et al. Multicenter randomized Phase II study of paclitaxel (1-hour infusion), fluorouracil, hydroxyurea, and concomitant twice daily radiation with or without erythropoietin for advanced head and neck cancer. *Clinical Cancer Research* 2003;**9**(5):1689-97. [MEDLINE: 139]

Savonije 2005 *{published data only}*

Savonije J, Van Groeningen C, Van Bochove A, Pinedo H, Giaccone G. Early intervention with epoetin-alfa during platinum-based chemotherapy. In: Journal of Clinical Oncology. Vol. 22. 2004:#8111.

* Savonije JH, Van Groeningen CJ, Van Bochove A, Honkoop AH, Van Felius CL, Wormhoudt LWetal. Effects of early intervention with epoetin alfa on transfusion requirement, hemoglobin level and survival during platinum-based chemotherapy: Results of a multicenter randomised controlled trial. *European Journal of Cancer* 2005;**41**(11):1560-9.

Savonije JH, van Groeningen CJ, Wormhoudt LW, Giaccone G. Early Intervention with epoetin alfa during platinum-based chemotherapy: an analysis of quality-of-life results of a multicenter, randomized, controlled trial compared with population normative data. *Oncologist* 2006;**11**(2):197-205.

Silvestris 1995 *{published data only}*

Silvestris F, Romito A, Fanelli P, Vacca A, Dammacco F. Long-term therapy with recombinant human erythropoietin (rHu-EPO) in progressing multiple myeloma. *Annals of Hematology* 1995;**70**:313-8.

Suzuki 2008 *{published data only}*

Suzuki Y, Tokuda Y, Okamoto R, Nakagawa K, Ando K, Iwata H, et al. Randomized, placebo-controlled phase II study of darbepoetin alfa (DA) administered every three weeks (Q3W) in patients with chemotherapy-induced anemia (CIA). *Annals of Oncology* 2008;**19**(S8):277.

Tesch 2019 *{published data only}*

Tesch H, Loibl S, Kast K, Jackisch C, Mobus V, Buchen S, et al. Chemotherapy (CT)-induced anaemia in patients (pts) treated with dose-dense regimen: results of the prospectively randomised anaemia substudy from the neoadjuvant GeparOcto study. In: Annals of Oncology. Vol. 30. 2019:v65-v66.

Thompson 2000 *{published data only}*

Thompson JA, Gilliland DG, Prchal JT, Bennett JM, Larholt K, Nelson RA, et al. Effect of recombinant human erythropoietin combined with granulocyte/macrophage colony-stimulating factor in the treatment of patients with myelodysplastic syndrome. *Blood* 2000;**95**:1175-9.

Vansteenkiste 2009 *{published data only}*

Vansteenkiste J, Hedenus M, Gascon P, Bokemeyer C, Ludwig H, Vermoken J, et al. Darbepoetin alfa for treating chemotherapy-induced anemia in patients with a baseline hemoglobin level < 10 g/dL versus ≥10 g/dL: an exploratory analysis from a randomized, double-blind, active-controlled trial. *BMC Cancer* 2009;**9**:311.

Wurnig 1996 *{published data only}*

Wurnig C, Windhager R, Schwameis E, Kotz R, Zoubek A, Stockenhuber F, et al. Prevention of chemotherapy-induced anemia by the use of erythropoietin in patients with primary malignant bone tumors (a double-blind, randomized, phase III study). *Transfusion* 1996;**36**(2):155-9.

References to studies awaiting assessment

Anthony 2011 *{published data only}*

Anthony L, Gabrail N, Ghazal H. IV iron sucrose for cancer and/or chemotherapy-induced anemia in patients treated with erythropoiesis-stimulating agents. https://www.mdedge.com/hematology-oncology/article/37193/patient-survivor-care/iv-iron-sucrose-cancer-and/or-chemotherapy 2011.

CTRI/2011/12/002273 *{published data only}*

CTRI/2011/12/002273. A clinical study to assess the absorption and distribution properties of iron isomaltoside 1000 (MonoferÂ®) administered by 500 mg IV bolus injection or 1000 mg intravenous infusion to subjects with non-haematological malignancies associated with chemotherapy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2011/12/002273 2011.

EUCTR2004-002176-42-IT *{published data only}*

EUCTR2004-002176-42-IT. Open randomized study to evaluate the efficacy of i.v. iron support (ferrum gluconate, 125 mg i.v. infusion weekly for 6 weeks) in primary solid tumour patients (breast, lung, colon-rectum and gynecological) treated with darbepoetin alfa (150 mcg once wee. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2004-002176-42-IT.

EUCTR2005-005658-37-DK *{published data only}*

EUCTR2005-005658-37-DK. A randomized, multi-center study to assess the effect of Darbepoetin alfa (Aranesp®) for the treatment of anemia in patients with advanced hormone independent prostate cancer and anaemia - DANCAPepo. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2005-005658-37-DK.

EUCTR2006-000137-35-LT *{published data only}*

EUCTR2006-000137-35-LT. Prospective controlled clinical trial of metastatic breast cancer treatment with capecitabine/docetaxel in combination with beta epoetin as compared with sole capecitabine/docetaxel treatment. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006-000137-35-LT.

EUCTR2006-005965-20-SE *{published data only}*

EUCTR2006-005965-20-SE. Effects of three treatment strategies on anemia and quality of life in patients with solid tumours or lymphoproliferative malignancies. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006-005965-20-SE.

EUCTR2007-005777-57-GR *{published data only}*

EUCTR2007-005777-57-GR. A comparative study of low molecular weight IV iron dextran (CosmoFer®) versus per os iron for the treatment of anaemia in patients with haematological malignancies receiving epoietin

treatment. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2007-005777-57-GR.

EUCTR2008-001721-34-BE *{published data only}*

EUCTR2008-001721-34-BE. A phase 2, randomised, double-blind, placebo-controlled, dose-finding study of Darbepoetin alfa for the treatment of anemia in paediatric subjects with solid tumours receiving cyclic chemotherapy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-001721-34-BE.

EUCTR2008-002723-85-IT *{published data only}*

EUCTR2008-002723-85-IT. A randomized, double-blind, placebo-controlled, multicenter study evaluating epoetin alfa initiated at 40,000 IU every week or 80,000 IU every week versus placebo in subjects with IPSS low- or intermediate-1 risk MDS. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-002723-85-IT.

EUCTR2009-015766-56-GR *{published data only}*

EUCTR2009-015766-56-GR. A randomised controlled parallel group open-label study to evaluate the efficacy and safety of intravenous ferric carboxymaltose versus no treatment in anaemic subjects with multiple myeloma and iron-restricted erythropoiesis receiving chemotherapy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-015766-56-GR.

EUCTR2009-015767-14-SE *{published data only}*

EUCTR2009-015767-14-SE. A randomised controlled parallel group open-label study to evaluate the efficacy and safety of intravenous ferric carboxymaltose versus no treatment in anaemic subjects with lymphoid malignancies and functional iron deficiency receiving chemotherapy - FER. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-015767-14-SE.

EUCTR2011-001664-22-AT *{published data only}*

EUCTR2011-001664-22-AT. A prospective, randomized, multicenter study to evaluate the impact of Darbepoetin alfa in combination with Ferric(III)-Carboxymaltose in comparison to Darbepoetin alfa and Ferric(III)-Carboxymaltose alone in patients with breast cancer and chemotherapy-i. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-001664-22-AT 2011.

ISRCTN01957333 *{published data only}*

ISRCTN01957333. Blood transfusion reduction with intravenous iron in gynaecological cancer patients receiving chemotherapy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN01957333.

ISRCTN61345286 *{published data only}*

ISRCTN61345286. Randomised study on haemoglobin response in iron-deficient anaemic patients with solid malignancies receiving epoetin alfa (rHuEPO) in combination with either oral or parental iron supplementation during treatment with non-platinum containing chemotherapy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN61345286.

JPRN-JapicCTI-050013 *{published data only}*

JPRN-JapicCTI-050013. A randomized, double-blind study of recombinant human erythropoietin in anemic cancer patients undergoing chemotherapy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-JapicCTI-050013.

JPRN-JapicCTI-080582 *{published data only}*

JPRN-JapicCTI-080582. A phase III randomized double-blind placebo-controlled study of epoetin beta for the treatment of chemotherapy-induced anemia in cancer patients. http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-JapicCTI-080582.

NCT03776032 *{published data only}*

NCT03776032. A novel erythropoiesis stimulating protein (NESP; Darbopoetin Alfa) for the treatment of anemia in lung cancer patients receiving multi-cycle platinum-containing chemotherapy. https://clinicaltrials.gov/show/NCT03776032.

NTR250 *{published data only}*

NTR250. Randomized study on hemoglobin response in iron-deficient anemic patients with solid maglignancies receiving epoetin alfa (rHuEPO) in combination with either oral or parental iron supplementation during treatment with non-platinum containing chemotherapy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=NTR250.

References to ongoing studies

ACTRN12620001105932p *{published data only}*

ACTRN12620001105932p. Women with breast cancer receiving adjuvant chemotherapy will receive intravenous iron to examine its effect on anaemia and anaemia-related symptoms during chemotherapy and up to 12 months after chemotherapy treatment.. https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620001105932.

Chen 2016 *{published data only}*

Chen L, Jiang H, Gao W, Tu Y, Zhou Y, Li X, et al. Combination with intravenous iron supplementation or doubling erythropoietin dose for patients with chemotherapy-induced anaemia inadequately responsive to initial erythropoietin treatment alone: study protocol for a randomised controlled trial. *BMJ Open* 2016;**6**(10):e012231.

ChiCTR-IPR-16009059 *{published data only}*

ChiCTR-IPR-16009059. The mechanism of gynecological cancer-related anemia and treatment strategies. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-IPR-16009059.

ChiCTR-IPR-16009508 *{published data only}*

ChiCTR-IPR-16009508. The mechanism and treatment strategies of gynecological cancer-related anemia. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-IPR-16009508.

CTRI/2019/05/019378 *{published data only}*

CTRI/2019/05/019378. Will intravenous iron reduce blood transfusion in patients undergoing treatment for ovarian cancer. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/05/019378.

EUCTR2016-002021-11-PL *{published data only}*

EUCTR2016-002021-11-PL. A study to investigate the efficacy and safety of Injectafer® (ferric carboxymaltose injection) in

anemia due to cancer and chemotherapy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-002021-11-PL.

EUCTR2018-001669-17-GB *{published data only}*

EUCTR2018-001669-17-GB. ICaRAS - A feasibility study of intravenous iron therapy for anaemia in palliative cancer care. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-001669-17-GB.

ISRCTN13370767 *{published data only}*

ISRCTN13370767. Intravenous iron for cancer-related anaemia symptoms. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN13370767.

KCT0004311 *{published data only}*

KCT0004311. Multicenter randomized study on the efficacy of intravenous iron injection in cancer patients with anemia. http://www.who.int/trialsearch/Trial2.aspx?TrialID=KCT0004311.

NCT02731378 *{published data only}*

NCT02731378. Erythropoietin and iron supplementation for patients with vhemotherapy-induced anaemia. https://clinicaltrials.gov/show/NCT02731378.

NCT03683810 *{published data only}*

NCT03683810. The effectiveness of lactoferrin in the management of treatment-induced anemia. https://clinicaltrials.gov/ct2/show/NCT03683810.

Zur Hausen 2016 *{published data only}*

Zur Hausen G, Rotzer I, Reichart A, Pauligk C, Hunfeld KP, Quidde J, et al. Intravenous ferric carboxymaltose vs. oral iron substitution in patients with metastatic colorectal cancer (mCRC) and iron deficiency anemia: a randomized multicenter treatment optimization study (A Study in Progress Report). *Oncology Research and Treatment* 2016;**39**:74.

Additional references

Auerbach 2008

Auerbach M. Should intravenous iron be the standard of care in oncology? *Journal of Clinical Oncology* 2008;**26**(10):1579-81.

Barrett-Lee 2006

Barrett-Lee PJ, Ludwig H, Birgegard G, Bokemeyer C, Gascon P, Kosmidis PA, et al. Independent risk factors for anemia in cancer patients receiving chemotherapy: results from the European Cancer Anaemia Survey. *Oncology* 2006;**70**(1):34-48.

Bellet 2007

Bellet RE, Ghazal H, Flam M, Drelichman A, Gabrail N, Woytowitz D, et al. A phase III randomized controlled study comparing iron sucrose intravenously (IV) to no iron treatment of anemia in cancer patients undergoing chemotherapy and erythropoietin stimulating agent (ESA) therapy. In: Journal of Clinical Oncology. Vol. 25. 2007:9109.

Bennett 2008

Bennett CL, Silver SM, Djulbegovic B, Samaras AT, Blau CA, Gleason KJ, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA* 2008;**299**(8):914-24.

Bohlius 2006

Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *Journal of the National Cancer Institute* 2006;**98**(10):708-14.

Bohlius 2009

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer - meta-analysis based on individual patient data. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007303. [DOI: 10.1002/14651858.CD007303.pub2]

Bokemeyer 2007

Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Osterborg A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. *European Journal of Cancer* 2007;**43**(2):258-70.

Bucher 1997

Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* 1997;**50**(6):683-91. [PMID: 9250266]

Chaimani 2013

Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLOS One* 2013;**8**(10):e76654. [DOI: https://doi.org/10.1371/journal.pone.0076654]

Chertow 2004

Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. On the relative safety of parenteral iron formulations. *European Dialysis and Transplant Association - European Renal Association* 2004;**19**(6):1571-5.

Chertow 2006

Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. *European Dialysis and Transplant Association - European Renal Association* 2006;**21**(2):378-82.

Cooper 2019

Cooper C, Varley-Campbell J, Carter P. Established search filters may miss studies when identifying randomized controlled trials. *Journal of Clinical Epidemiology* 2019;**112**:12-9. [DOI: 10.1016/j.jclinepi.2019.04.002] [PMID: 30986533]

Deeks 2021

Deeks JJ, Higgins JP, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors).

Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Dias 2013

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Medical Decision Making* 2013;**33**(5):641-56. [PMID: 23804508]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34. [PMID: 9310563]

Eschbach 2005

Eschbach JW. Iron requirements in erythropoietin therapy. *Best Practice & Research Clinical Haematology* 2005;**18**(2):347-61.

Fletes 2001

Fletes R, Lazarus JM, Gage J, Chertow GM. Suspected iron dextran-related adverse drug events in hemodialysis patients. *American Journal of Kidney Diseases* 2001;**37**(4):743-9.

Furukwa 2006

Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology* 2006;**59**(1):7-10. [PMID: 16360555]

Garton 1995

Garton JP, Gertz MA, Witzig TE, Greipp PR, Lust JA, Schroeder G, et al. Epoetin alfa for the treatment of the anemia of multiple myeloma. A prospective, randomized, placebo-controlled, double-blind trial. *Archives of Internal Medicine* 1995;**155**(19):2069-74. [PMID: 7575066]

Glanville 2019

Glanville J, Foxlee R, Wisniewski S, Noel-Storr A, Edwards M, Dooley G. Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study. *Health Information and Libraries Journal* 2019;**36**:264-77.

GRADEpro [Computer program]

Mc Master University GRADEpro. Version 3.2 for Windows. Hamilton, Ontario, Canada: Mc Master University, 2014.

Groopman 1999

Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *Journal of the National Cancer Institute* 1999;**91**(19):1616-34. [PMID: 10511589]

Guyatt 2013

Guyatt GH, Oxman AD, Satesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158-72.

Higgins 2011

HigginJP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Callaboration, 2011.

Higgins 2021b

Higgins JP, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Available from training.cochrane.org/handbook.

Howlader 2014

Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2010. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2010/ based on November 2012 SEER data submission, posted to the SEER web site, updated December 17, 2014, assessed 03 January 2015.

Khorana 2008

Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. *Archives of Internal Medicine* 2008;**168**(21):2377-81.

Knight 2004

Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *American Journal of Medicine* 2004;**116 Suppl 7A**:11S-26S. [PMID: 15050883]

Krahn 2013

Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Medical Research Methodology* 2013;**13**:35. [PMID: 23496991]

Lefebvre 2021

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Li 2021

Li T, Higgins JP, Deeks JJ (editors). Chapter 5: Collecting data. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Link 2013

Link H, Schmitz S. Treatment of cancer-associated anaemia: results from a two-day cross-sectional survey in Germany. *Onkologie* 2013;**36**(5):266-72. [PMID: 23689221]

Littlewood 2001b

Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy:

results of a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Oncology* 2001;**19**(11):2865-74.

Ludwig 2001

Ludwig H, Strasser K. Symptomatology of anemia. *Seminars in Oncology* 2001;**28**(2 Suppl 8):7-14.

Ludwig 2004

Ludwig H, Van Belle S, Barrett-Lee P, Birgegard G, Bokemeyer C, Gascon P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *European Journal of Cancer* 2004;**40**(15):2293-306. [PMID: 15454256]

Mamula 2002

Mamula P, Piccoli DA, Peck SN, Markowitz JE, Baldassano RN. Total dose intravenous infusion of iron dextran for iron-deficiency anemia in children with inflammatory bowel disease. *Journal of Pediatric Gastroenterology and Nutrition* 2002;**34**(3):286-90.

Mancuso 2006

Mancuso A, Migliorino M, De Santis S, Saponiero A, De Marinis F. Correlation between anemia and functional/cognitive capacity in elderly lung cancer patients treated with chemotherapy. *Annals of Oncology* 2006;**17**(1):146-50.

Mercadante 2009

Mercadante S, Ferrera P, Villari P, David F, Giarratano A, Riina S. Effects of red blood cell transfusion on anemia-related symptoms in patients with cancer. *Journal of Palliative Medicine* 2009;**12**(1):60-3.

Mhaskar 2016

Mhaskar R, Wao H, Miladinovic B, Kumar A, Djulbegovic B. The role of iron in the management of chemotherapy-induced anemia in cancer patients receiving erythropoiesis-stimulating agents. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No: CD009624. [DOI: 10.1002/14651858.CD009624.pub2]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006-12.

netmeta 2021 [Computer program]

http://CRAN.R-project.org/package=netmeta netmeta: Network Meta-Analysis using Frequentist Methods. R package version 1.3-0. Rücker G, Krahn U, König J, Efthimiou O, Schwarzer G. http://CRAN.R-project.org/package=netmeta, 2021.

Nissenson 1992

Nissenson AR. Epoetin and cognitive function. *American Journal of Kidney Diseases* 1992;**20**(1 Suppl 1):21-4.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

Puhan 2014

Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ (Clinical Research ed.)* 2014;**349**:g5630. [PMID: 25252733]

R 2019 [Computer program]

R Foundation for Statistical Computing R: A language and environment for statistical computing. R Core Team, Version 3.6.1. Vienna, Austria: R Foundation for Statistical Computing, 2019.

Rizzo 2010

Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, et al. clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Journal of Clinical Oncology* 2010;**28**(33):4996-5010.

Rodgers 2012

Rodgers GM, 3rd, Becker PS, Blinder M, Cella D, Chanan-Khan A, Cleeland C, et al. Cancer- and chemotherapy-induced anemia. *Journal of the National Comprehensive Cancer Network* 2012;**10**(5):628-53.

Rücker 2012

Rücker G. Network meta-analysis, electrical networks and graph theory. *Research Synthesis Methods* 2012;**3**(4):312-24. [PMID: 26053424]

Rücker 2014

Rücker G, Schwarzer G. Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis. *Statistics in Medicine* 2014;**33**(25):4353-69. [PMID: 24942211]

Rücker 2015

Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology* 2015;**15**:58. [PMID: 26227148]

Schrijvers 2010

Schrijvers D, De Samblanx H, Roila F. Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO Clinical Practice Guidelines for use. *Annals of Oncology* 2010;**21 Suppl 5**:244-7.

Schuenemann 2021

Schuenemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, Guyatt GH. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Cochrane Handbook for Systematic Reviews of Interventions Version 6.2. The Cochrane Collaboration, 2021.

Schwarzer 2015

Schwarzer G, Carpenter JR, Rücker G. Chapter 8: Network meta-analysis. In: Meta-Analysis with R. Springer International Publishing Switzerland, 2015.

Stasi 2003

Stasi R, Abriani L, Beccaglia P, Terzoli E, Amadori S. Cancer-related fatigue: evolving concepts in evaluation and treatment. *Cancer* 2003;**98**(9):1786-801.

Sterne 2011

Sterne JA, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16. [PMID: 17555582]

Tonia 2012

Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No: CD003407. [DOI: 10.1002/14651858.CD003407.pub5] [PMID: 23235597]

Wang 2015

Wang C, Graham DJ, Kane RC, Xie D, Wernecke M, Levenson M, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA* 2015;**314**(19):2062-8. [PMID: 26575062]

References to other published versions of this review

Weigl 2017

Weigl A, Köhler N, Monsef I, Bohlius J, Kuhr K, Becker I, et al. Intravenous iron versus oral iron versus no iron with or without erythropoiesis- stimulating agents (ESA) for cancer patients with anaemia: A systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No: CD012633. [DOI: 10.1002/14651858.CD012633]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aapro 2008

Study characteristics	
Methods	Randomised controlled trial, no placebo control
Participants	N = 463 randomised: ESA = 231; control = 232 Dropouts: 0% Disease: breast cancer (M1) Treatment: chemotherapy Mean age: 57.5/ 56.0 years Gender: female Mean/median baseline Hb: 11.4 g/dL
Interventions	Drug: epoetin beta Dose: 30,000 IU sc weekly Hb-target: 13 g/dL to15 g/dL Planned ESA duration: 24 weeks
Outcomes	Primary: overall survival Secondary: progression-free survival, tumour response rate, QoL
Notes	Ffull-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number 97413)
Risk of bias	

Aapro 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "....randomized, multicenter study in patients.....eligible patients were centrally randomized (1:1).... Random assignment using a block design....."
Allocation concealment (selection bias)	Low risk	Quote: "..patients were centrally randomized.."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "...an open-label,...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all of the primary and secondary efficacy outcomes have been reported in the result and discussion sections
Other bias	Unclear risk	'340 (73%) completed the study treatment period and 123 (27%) withdrew (epoetin beta, n = 69; control, n = 54; Fig 1).....The sponsor conducted all statistical analyses.'

Abels 1993

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 124 randomised: ESA = 65; control = 59 Dropouts: 0% Disease: haematological malignancies, genitourinary, gastrointestinal, and other cancer; except primary myeloid malignancy or acute leukaemia (category: mixed) Treatment: none Mean age: 61.2 / 62.5 years Gender: male + female Mean/median baseline Hb: 9.3 g/dL
Interventions	Drug: epoetin alpha Dose: 100 IU/kg three times per week sc

Abels 1993 *(Continued)*

	Hb-target: not reported Duration: 8 weeks
Outcomes	Primary: transfusion, Hct Secondary: QoL, safety
Notes	Full -ext publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number 98906)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " .....anemic cancer patients were randomized....." Comment: Description only includes the term 'randomized' and does not specify the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "....this paper will describe only the results of double-blind therapy."
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: the study was conducted to check the quality of life and addressed in the result and discussion section
Other bias	Unclear risk	Comment: there is no mention about the funding and insufficient information to address whether an important risk of bias exists

Ansari 2016

Study characteristics

Methods	Randomised controlled study, not placebo-controlled
Participants	N = 60 (n = 30 in each group) Dropouts: unclear

Ansari 2016 *(Continued)*

	Disease: colon cancer Treatment: unclear Mean age: 56.9 / 58.5 years Gender: male + female Baseline Hb: unclear
Interventions	Drug: Group 1= oral ferrous sulphate; Group 2 = IV ferric carboxymaltose Dose: Group 1= 65 mg 3 times a day; Group 2 = 1500 mg (body weight <70 kg), 2000 mg (body weight >70 kg) Hb-target: unclear Duration: 8 weeks
Outcomes	Comparing effectiveness
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were selected based on balanced block randomisation into two groups
Allocation concealment (selection bias)	Unclear risk	Balanced block randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in literature
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Not mentioned in literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of randomised and analysed patients not the same.
Selective reporting (reporting bias)	Low risk	All outcomes reported as intended
Other bias	Unclear risk	No description

Aravantinos 2003

Study characteristics	
Methods	Single-centre, non-blinded, randomised controlled trial
Participants	N = 47 randomised: ESA = 24; control = 23 Dropouts: 0% Disease: solid tumour (56% ovarian cancer Treatment: chemotherapy (36% cisplatin-based, 60% carboplatin-based, 4% combination) Mean age: unclear Gender: unclear Mean/median baseline Hb: N.R.
Interventions	drug: rHuEPO dose: 150 IU/kg, 3 times per week Hb-target: 13- dL to 15 g/dL planned ESA duration: N.R.
Outcomes	Primary: number of RBC transfusions secondary: correlation therapeutic outcome of rHuEPO with number of RBCs, Hb and Hct values
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 97413)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised; method of randomisation is not mentioned
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "... non-blinded ..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Quote: "... non-blinded ..."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No follow-up information available

Aravantinos 2003 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported as intended
Other bias	Unclear risk	Enrolment of patients at the end of different chemotherapy cycles

Ataollah Hiradfar 2018

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N= 57, rHuEPO = 29, no intervention = 28 Dropouts: 5% Disease: solid tumour Treatment: chemotherapy Mean age: 6.1 / 6.4 years Gender: male + female Baseline Hb: 8.85+/-1.01 and 8.98+/-0.11g
Interventions	Drug: rHuEPO Dose: 450 IU/kg Hb-target: unclear Duration: 12 weeks
Outcomes	Efficacy of recombinant human erythropoietin in reducing the need for blood transfusion
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Then, we randomly assigned the patients to two control and intervention groups using randomly permuted block method via an online software"
Allocation concealment (selection bias)	Unclear risk	Quote:"..randomly assigned the patients to two control and intervention groups using randomly permuted block method via an online software"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the literature
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is objective outcome

Ataollah Hiradfar 2018 *(Continued)*

Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of randomised and analysed patients not the same.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to clarify any judgement
Other bias	Unclear risk	No description

Athibovonsuk 2013

Study characteristics	
Methods	Open-label randomised study
Participants	N = 64 randomised: ESA = 32 ; control = 32 Dropouts: 0% Disease: gynaecological cancer (93.8% ovarian cancer) treatment: platin-chemotherapy Mean age: 49.7 / 52.1 years Gender: female Mean/median baseline Hb: 11.3-11.4 +- 1 g/dL
Interventions	Drug: IV iron sucrose (Venofer®, DKSH Limited, Bangkok, Thailand) Dose: 200 mg Hb-target: N/A g/dL Planned duration: N/A
Outcomes	Primary: requirement of RBC transfusions in each group Secondary: number of RBC transfusions, number of cycles requiring blood transfusion, AEs
Notes	Full-text publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote:"... Using a random table ..."
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was done using a random table with concealment."

Athibovonsuk 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow chart provided, ITT
Selective reporting (reporting bias)	Low risk	All intended outcomes reported
Other bias	Unclear risk	No description of statistical power analysis

Auerbach 2004

Study characteristics	
Methods	Randomised controlled study, no placebo control
Participants	N = 157 randomised: no-iron = 36; oral iron = 43; IV iron = 78 Dropouts: 0% Disease: histological diagnosis of cancer Treatment: chemotherapy Mean age: 53 / 46 /42 Gender: male +female Mean baseline Hb: <= 105 g/L;
Interventions	Drug: epoeitin alfa Dose: 40,000 U weekly Hb-target: >= 120 g/L Duration: 6 weeks
Outcomes	Hb response; QOL; safety; transfusions and treatment failures
Notes	Full-text publication
Risk of bias	

Auerbach 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "....randomized trial..." Comment: description only includes the term 'randomized' and does not specify the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "....open-label...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "..For safety data, the intent-to-treat (ITT) population was analyzed. For all efficacy analyses, a modified ITT population was analyzed" Comment: for efficacy analysis, the ITT population was being modified
Selective reporting (reporting bias)	Low risk	Comment: the purpose of the study was described in both result and discussion section
Other bias	Unclear risk	Quote: ".....this study was not statistically powered to detect differences between functional and absolute iron deficiency....."

Auerbach 2010

Study characteristics	
Methods	Randomised controlled trial, double-blinded, no placebo control
Participants	N = 238 randomised: EPO + IV iron = 116; EPO = 122 Dropouts: 0% Disease: active non myeloid malignancy anaemia Treatment: chemotherapy Mean age: 61.7 / 64.5 years Gender: unclear Mean baseline Hb: 9.4g/dL
Interventions	Drug: darbepoetin alfa dose: 300 µg; 500 µg

Auerbach 2010 *(Continued)*

	Hb-target: >= 11g/dL Duration: 15 weeks Iron: IV iron Dose: 400 µg
Outcomes	Haematopoietic response; RBC transfusions; time to haematopoietic response; QOL; treatment-related harms (thromboembolic events are not reported)
Notes	Full- ext publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "....randomization list was created and maintained by an independent randomization group at the study sponsor using permuted blocks."
Allocation concealment (selection bias)	Low risk	Quote: "A randomization list was created and maintained by an independent randomization group at the study sponsor using permuted blocks. The randomization list was transmitted to an IVRS vendor for execution. Enrollment and randomization were done by telephone and confirmed by facsimile. Patients were assigned blinded boxes of study medication using box numbers, which were recorded and reconciled."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient information to clarify any judgement
Selective reporting (reporting bias)	Unclear risk	Comment: The endpoints of the study were described in both result and discussion section
Other bias	Low risk	Quote: 'This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines.'

Bastit 2008

Study characteristics

Methods	Randomised controlled trial, open-label, no placebo control

Bastit 2008 *(Continued)*

Participants	N = 396 randomised: IV iron = 200; Standard practice = 196 Dropouts: 0% Disease: non myeloid malignancy Treatment: chemotherapy Mean age: 61.7 / 60.3 years Gender: male +female Mean base Hb: 10 g/dL
Interventions	Drug: darbepoetin alfa Dose: 500 µg Hb-target: >= 12 g/dL Duration: 16 weeks Iron: IV iron gluconate Dose: 200 mg
Outcomes	Haematopoietic response; RBC transfusions; QOL; safety
Notes	fFull-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "....randomized..." Comment: description only includes the term 'randomized' and does not specify the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "....open-label..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement

Bastit 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: all the endpoints are discussed in both result and discussion section
Other bias	Unclear risk	Quote: "Another study limitation was the use of a control arm with a mixed patient population....."

Birgegard 2015

Study characteristics	
Methods	Randomised controlled trial, open-label, no placebo control
Participants	N = 350 randomised: isomaltoside = 231; iron sulphate = 119 Dropouts: unclear Disease: non myeloid malignancies and anaemia Treatment: chemotherapy Mean age: 55 / 54 years Gender: male +female Mean base Hb: <= 12 g/dL
Interventions	Drug: iron isomaltoside 1000 mg; oral iron sulphate Dose: 1000 mg; 200 mg Hb-target: 13 g/dL Duration: a 24-weeks period
Outcomes	Hamatopoetic response; adverse drug reaction (ADR)
Notes	Full-text publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: " .....randomized in a 2:1 ratio...." Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "'.....open-label....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is objective outcome

Birgegard 2015 *(Continued)*

Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Quote: "……EudraCT number 2009-016727-53….." Comment: all the outcomes are discussed in both result and discussion section
Other bias	Low risk	Quote: "…..conducted in accordance with good clinical practice and the Declaration of Helsinki of 1975……"

Blohmer 2011

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 256, randomised: ESA = 127, control = 129 Dropouts: 0% Disease: cervical cancer Treatment: platinum-containing chemotherapy in all patients and radiotherapy (categorised as radiochemotherapy) Mean age: 41 / 42 years Gender: female Baseline Hb: 11.9 g/dL, ESA 12.0 g/dL, control 11.8 g/dL, categorised as 10-12 g/dL
Interventions	Drug: epoetin alfa Dose: 10, 000 IU sc, three times per week Hb-target: >14 g/dL Duration: >20 weeks
Outcomes	Primary: relapse-free survival
Notes	Full-text publication, additional unpublished data were obtained for the first Cochrane Review (1985 to 2001), Study ID number = 16218

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "….randomized….using a stratified random permuted block design…."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally according to the order in which information was received by fax.'

Blohmer 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote:".....open-label....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All efficacy analyses were performed from an intention-to-treat basis....."
Selective reporting (reporting bias)	Low risk	Comment: all of the primary and secondary efficacy outcomes have been reported in the result and discussion section
Other bias	Unclear risk	Quote: "Standards of care have changed since the trial was started....."

Boogaerts 2003

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 262 randomised: ESA = 133; control = 129 Dropouts: 1.15% Disease: multiple myeloma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, Hodgkin's disease, ovarian, bone, gastrointestinal, respiratory, other cancer Treatment: chemotherapy Mean age: 62 years Gender: male +female Baseline Hb: 9.0 g/dL
Interventions	Drug: epoetin beta Dose: 150 IU/kg sc, three times per week Hb-target: 12 g/dL to 14 g/dL Planned ESA duration: 12 weeks
Outcomes	Primary: QoL Secondary: haematological response, haematopoietic response, Hb change, transfusions, PS,Hct
Notes	Full-text publication of the study previously published as abstract Coiffier 2001, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 36158)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Boogaerts 2003 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "....randomised (1: 1, stratified according to centre)...."
Allocation concealment (selection bias)	Unclear risk	Stratified according to centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote:".....open-label....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting
Other bias	Unclear risk	Quote: "Although concurrent cisplatin-based CRT is now considered standard, at the time this trial was initiated, the role of chemotherapy had not been established for stage I to II cervical cancer. .....it is unclear whether different chemotherapy regimens and/or concurrent radiotherapy might have produced different results, limiting our ability to extrapolate our findings to current adjuvant CRT regimens."

Cascinu 1994

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 100, randomised: ESA = 50; control = 50 Dropouts: 0% Disease: various solid tumours Treatment: concomitant platinum-based chemotherapy; some patients received G-CSF (n = 27) Mean age: 58 / 57 years Gender: male + female Mean/median baseline Hb: 8.7 g/dL
Interventions	Drug: epoetin alpha Dose: 100 U/kg 3x/week sc Hb target: 10 g/dl to 12 g/dL Duration: 9 weeks

Cascinu 1994 *(Continued)*

Outcomes	Haematological response, change in Hb values, transfusion requirement, adverse events
Notes	Full-text publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001), Study ID number = 19,48

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly assigned.....Randomization, using cards from a computer-generated list in sealed envelopes..."
Allocation concealment (selection bias)	Low risk	Quote:"'Randomization, using cards from a computer-generated list in sealed envelopes, was performed by a person not involved with the care or evaluation of the patients."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ".....double-blind....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both result and discussion section
Other bias	Low risk	Quote: "No patient was removed from the study because of rHuEPO-related toxicity."

Case 1993

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 157, randomised: ESA = 81; control = 76 Dropouts: 0% Disease: non myeloid hematological malignancies, breast, lung, gynaecological, gastrointestinal, other cancer Treatment: non-cisplatin chemotherapy M age: 64 years gGnder: male + female

Case 1993 *(Continued)*

	Mean/median baseline Hct: 28.9%
Interventions	Drug: epoetin alpha Dose: 150 U/kg 3x/week sc Hb target: Hct 38% to 40% Duration: 12 weeks
Outcomes	Haematological response, change in Hct, transfusion requirement, QoL, adverse events
Notes	Full-text publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 34917)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "....patients were randomly assigned.....Randomization was performed according to a computer-generated randomization code at the Robert Wood Johnson Pharmaceutical Research Institute".
Allocation concealment (selection bias)	Low risk	Quote: "....Randomization was performed according to a computer-generated randomization code..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ".... double-blind....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both result and discussion section
Other bias	Low risk	Comment: no other bias has been found from the literature.

Cazzola 1995

Study characteristics

Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 146, randomised: control = 29 (IPD: control:30, EPO: 117), evaluated EPO:114 Control: 29 ESAa = 31; ESAb = 29; ESAc = 31; ESAd = 26; ESA total = 117

Cazzola 1995 *(Continued)*

	Dropouts: 2.05% Disease: multiple myeloma, non-Hodgkin lymphoma Treatment: chemotherapy, assumed without platinum because of hematological disease Mean age: 68 / 67 years Gender: male + female Mean/median baseline Hb: 9.4 g/dL
Interventions	Drug: Epoetin beta Dosages: a: 1000 IU sc 7x/week; b: 2000 IU sc 7x/week; c: 5000 IU sc 7x/ week; d:10,000 IU sc 7x/week Hb-target: 11-13 g/dL (MM), 11-15 g/dL (NHL) a: 1000 IU sc 7x/week, b: 2000 IU sc 7x/week; c: 5000 IU sc 7x/ week; d: 10,000 IU sc 7x/week Duration: 8 weeks
Outcomes	Primary: haematological response Secondary: Hb, Hct, transfusions, reticulocytes, iron, ferritin, safety
Notes	Full-text publication, additional unpublished data obtained for first Cochrane Review and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 37653)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...a randomized..." Comment: description does not specify the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "....open-dose-finding trial...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Randomized patients were evaluated according to an intention-to-treat analysis."
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both result and discussion section
Other bias	Low risk	Quote: "...no imbalance in the five treatment groups according to any of the following staging systems...."

Chang 2005

Study characteristics	
Methods	Rrandomised controlled trial, not placebo-controlled
Participants	N = 354, randomised: ESA = 176; control = 178 Dropouts: 0% Disease: breast cancer, stage I-IV Treatment: chemotherapy Mean age: 50.4 / 50.1 years Gender: female Baseline Hb: 11.3 g/dL
Interventions	Drug: epoetin alpha Dose: 40,000 IU qw sc Hb target: 14 g/dL Duration: 16 weeks, max 28 weeks
Outcomes	Primary: QoL Secondary: maintain Hb above 12 g/dL, tumour response, overall survival
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 99137)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: ".....randomly assigned in 1:1 ratio....."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: ".....open-label trial....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both result and discussion section
Other bias	Low risk	Quote:"' Baseline characteristics were well balanced between the two groups."

Charu 2007

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 287, randomised: ESA = 228, control = 59 Dropouts: 0% Disease: lymphoma, breast, lung, gastrointestinal, genitourinary, gynaecologic, other cancer Treatment: none Mean age: 71.7 / 67.2 years Gender: female Baseline Hb: 10.2 g/dL
Interventions	Drug: darbepoetin alpha Dose: 3.0 µg/kg sc Q2W Hb-target: 13-14 g/dL (women), 13-15 g/dL (men) Duration: 12 weeks
Outcomes	Primary: hospitalisation days Secondary: costs, QoL, transfusion, Hb, safety
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 53081)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "..... Patients were randomized in a 4:1 ratio....."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: ".....Open-Label....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: .all outcomes reported as intended

Charu 2007 *(Continued)*

Other bias	Low risk	Quote: "Patient demographics and baseline clinical characteristics were well balanced between groups."

Christodoulou 2009

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 337, randomised: NR, evaluated: ESA 167, control = 170 Dopouts: 0% Disease: solid tumours Treatment: chemotherapy, platinum and non-platinum containing Mean age: 61 / 63 years Gender: male + female Baseline Hb: 10.2 g/dL
Interventions	drug: epoetin alfa dose: 10'000 IU three times a week Hb-target: 12 g/dL to 14 g/dL Duration: minimum anticipated duration 12 weeks. categorised 12-16 weeks
Outcomes	Primary: QoL Secondary: transfusions, anaemia
Notes	Full-text publication, abstract in 2003 (Janinis), Study ID number = 22108

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Adaptive blocked stratified randomization balanced by center was performed centrally at the HeCOG data office....."
Allocation concealment (selection bias)	Low risk	Quote: "..randomization balanced by center was performed centrally.."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: ".....Open-Label....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias)	Unclear risk	Comment: insufficient information to clarify any judgement

Christodoulou 2009 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both result and discussion section
Other bias	Unclear risk	Quote: "...the inclusion of both patients on adjuvant and these on palliative cancer treatment is a conceptual problem when QOL is studied."

Dammacco 2001

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 145, randomised: ESA = 69; control = 76 Dropouts: 0% Disease: multiple myeloma Treatment: chemotherapy mean age: 67.3 / 65 years Dender: male + female Mean/median baseline Hb: 9.5 g/dL
Interventions	drug: Epoetin alpha dose: 150 U/kg 3x/week sc Hb target: 14 g/dL Duration: 12 weeks
Outcomes	Primary: transfusion Secondary: haematological response, Hb, Hct, reticulocytes, serum erythropoietin levels QoL, adverse events
Notes	Ful- text publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 11220)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…..randomized…." Comment: the method of randomisation is not described in the literature
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "…..double-blind….."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome

Dammacco 2001 *(Continued)*

Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Results for the primary efficacy evaluation of transfusion requirements and safety are reported for the intention-to-treat (ITT) population."
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both result and discussion section
Other bias	Unclear risk	Comment: insufficient information to clarify any judgement

Debus 2006 IPD

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 385, randomised: ESA = 195, control = 190 Dropouts: 0% Disease: NSCLC (stage III, primarily inoperable) Treatment: radiochemotherapy Mean age: 61.8 / 63.5 years Gender: male + female Baseline Hb: not reported, unclear
Interventions	drug: Epoetin alpha dose: 40,000 IU sc weekly Hb-target: 12 g/dL to14 g/dL, in November 2003 reduced to 12 g/dl to13 g/dL Duration: assumed to be 12-16 weeks
Outcomes	pPimary: 2-year-survival rate Secondary: tumour response, QoL, tolerance to epoetin alpha, Hb change, transfusion Safety
Notes	Only unpublished data available, were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 83322)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation code provided by Ortho Biotech
Allocation concealment (selection bias)	Unclear risk	Unclear - assigned envelopes, sequentially numbered, but it is unclear whether they were sealed and opaque
Blinding of participants and personnel (performance bias)	Unclear risk	No description

Debus 2006 IPD *(Continued)*

All outcomes		
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Debus 2014

Study characteristics	
Methods	Prospective, randomised, controlled trial not placebo-controlled
Participants	N = 385 Controll (RCHT)= 190 (RCHT + EPO) = 195 Dropouts: 0% Disease: primarily inoperable, stage III non-small cell lung cancer (NSCLC) treatment:: radiochemotherapy and EPO mean age: 63.5 / 61.8 gender: male + female baseline Hb:10–16 g/dL
Interventions	drug: Epoetin dose: 3 doses of 40,000 IU EPO duration: Over a 2-week period Hb-target:: Unclear
Outcomes	A statistically non-significant trend for 2-year OS was observed in a sub-group of EPO treated NSCLC-patients with baseline anaemia
Notes	'The sponsor has contributed to the study design, analysis, interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.'
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Debus 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: '....randomized....' Comment: Method of randomization is not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: '...open-label...'
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: All the outcomes are discussed in both result and discussion section
Other bias	Unclear risk	no description

Del Mastro 1997

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 62, randomised: ESA = 31, control = 31 Dropouts: 0% Disease: breast cancer Treatment: non-platinum based chemotherapy and G-CSF 5 µg/kg d4-d11 sc for all patients; radiotherapy and tamoxifen fore the majority Mean age: not mentioned Gender: female Mean/median baseline Hb: 13.1 g/dL
Interventions	Drug: epoetin dose: 150 U/kg 3x/week sc Hb target: 13 g/dL to 5 g/dL Duration: 14 weeks
Outcomes	Change in Hb values, transfusion requirement, QoL, adverse events

Del Mastro 1997 *(Continued)*

Notes	Full -ext publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001), Study ID number = 24367

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a telephone call to a central office. The randomization list was balanced with blocks of variable size."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by a telephone call to a central office.The randomization list was balanced with blocks of variable size."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: the literature does not address anything regarding blinding
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote: " The protocol was approved by the Protocol Review Committee and by Ethical Committee of the same Institute."

Dunphy 1999

Study characteristics

Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 30, randomised: ESA = 15, control = 15 Dsease: head and neck cancer, NSCLC Dropouts: 0% Treatment: platinum-based chemotherapy Mean age: 59 /67 years Gender: male + female Mean/median baseline Hb: 14.1 g/dL
Interventions	drug: Epoetin Dose: 150 U/kg 3x/week sc Hb target: 16 g/dL to 18 g/dL

Dunphy 1999 *(Continued)*

	Duration: 6 weeks
Outcomes	Change in Hb values, transfusion requirement
Notes	Full-text publication, study number = 25,455

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "'.....randomized ...." Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not described
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both result and discussion section
Other bias	Low risk	Quote: "The mean number of chemotherapy courses administered was three for each group."

Engert 2010

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 1283, randomised ESA: 640, placebo: 643 Dropouts: 0% Disease: advanced stage Hodgkin lymphoma Treatment: chemotherapy without platinum Mean age: 34 years Gender: male and female Baseline Hb: 12.5 g/dL

Engert 2010 *(Continued)*

Interventions	Drug: epoetin alpha Dose: 40,000 IU /week Hb target: 12 g/dL to 13 g/dL Duration: > 20 weeks
Outcomes	Primary: anaemia-related fatigue Secondary: other QoL, number of transfusions needed, Hb during and after treatment,safety, freedom from treatment failure, OS
Notes	Full-text publication, additional unpublished data, Study ID number = 27258

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly assigned...." Comment: method of randomisation is not described in the literature
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "......patients eligible for HD15EPO were randomly assigned to epoetin alfa or matched placebo, stratified by chemotherapy arm in a double blind setting."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The analysis set for clinical end points is based on the intention-to-treat (ITT) principle, only excluding nonqualified patients....."
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both results and discussion sections
Other bias	Low risk	Quote:"'...the questionnaires and instruments used in the present study had been shown to be relevant and reproducible before being applied in this trial."

EPO-INT-3 J&J 2004

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 201, randomised: ESA = 136, control = 65 Dropouts: 0.5% Disease: breast, NHL, MM, ovarian, SCLC, other cancer

EPO-INT-3 J&J 2004 *(Continued)*

	Treatment: chemotherapy, < 70% platinum containing Mean age: not mentioned Gender: male and female Baseline Hb: not reported, eligibility criterion Hb < 12 g/dL or Hb drop 1.5 g/dL Categorised as Hb 10 g/dL to 12 g/dL
Interventions	Drug: epoetin alpha Dose: 15 IU/kg to 300 IU/kg three times per week sc Hb-target: 14 g/dL for women and 16 g/dL for men Duration: 12 weeks
Outcomes	Primary: transfusions Secondary: mortality, disease progression, tumour response, adverse events, Hb, QoL
Notes	Data presented by J&J at FDA/ODAC hearing in May 2004, additional unpublished data were obtained for an individual patient datameta-analysis study (Bohlius 2009, Study ID number = 36274), clinicaltrials.gov

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes - central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

Fujisaka 2011

Study characteristics

Fujisaka 2011 *(Continued)*

Methods	Randomised controlled trial, placebo-controlled
Participants	Randomised N = 186, evaluated N = 181, ESA = 89, control = 92 Dropouts: 0% Disease: lung cancer, gynaecological cancer Treatment: platinum-based chemotherapy Mean age: 67 / 63.5 years gender: Male and fFemale Baseline Hb: 9.4 g/dL
Interventions	Drug: epoetin beta Dose: 36,000 IU/week Target Hb: 12.0 g/dL Duration: 12 weeks
Outcomes	Primary: proportion of patients receiving RBCs and/or Hb < 8.0 g/dL Secondary: need for transfusions, changes in Hb, QoL
Notes	Full-text publication, Study ID: 15478

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "....Patients were randomised 1: 1.....Randomisation was conducted by a contract research organisation (CRO) that was independent from the investigators."
Allocation concealment (selection bias)	Low risk	Quote: "Participants in the study and investigators (outcome assessors) were blinded toward treatment allocation. Randomisation was conducted by a contract research organisation (CRO) that was independent from the investigators. The randomisation was carried out by a central registration system....."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind...Participants in the study and investigators (outcome assessors) were blinded toward treatment allocation."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment:insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections

Fujisaka 2011 *(Continued)*

Other bias	Low risk	Quote: "The demographics and baseline characteristics of the FAS population were well balanced."

Gascon 2019

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled, double-blind, non-inferiority
Participants	N = 2549 (darbepoetin alpha = 1703, placebo = 846) Dropouts: 1.29% Disease: stage IV NSCLC Treatment: multi-cycle myelosuppressive chemotherapy Mean age: 62 / 63 years Gender: males and females Baseline Hb: ≤ 11.0 g/dL
Interventions	Drug: darbepoetin alpha Dose: 500 µg Hb-target: 12.0 g/dL Duration: unclear
Outcomes	Primary: overall survival Secondary: progression-free survival, incidence of one or more RBC transfusion, other safety and efficacy parameters
Notes	Quote: "The study was funded by Amgen Inc. Dr. Gascón has received honoraria from Amgen Inc., Sandoz, and Hospira (Pfizer); has received fees for a consulting or advisory role from Sandoz and Hospira (Pfizer)"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized 2:1...Randomization based on a schedule generated before the study start and was centrally executed by Interactive Voice Response System.."
Allocation concealment (selection bias)	Low risk	central randomisation: Quote: "Randomization was based on a schedule generated before the study start and was centrally executed by an Interactive Response System..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Patients, site personnel, and Amgen study personnel and designees were blinded to the randomized treatment group intervention” Darbepoetin alfa and placebo were provided in similar containers, packaged and stored in the same manner, and identified by a unique box number for assignment via IVRS/IWRS

Gascon 2019 *(Continued)*

Blinding of outcome assessment (mortality) Mortality	Low risk	Mmortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of randomised and analysed patients not the same.
Selective reporting (reporting bias)	Low risk	All outcomes are described in the literature
Other bias	Unclear risk	Study was terminated early because primary objective had been met with no new safety concerns

Gilreath 2019

Study characteristics	
Methods	Randomised study, placebo-controlled, double-blind, phase 3 study
Participants	N = 244 (n = 122, both groups) Dropouts: 0% Disease: non-myeloid malignancy Treatment: chemotherapy Mean age: not mentioned Gender: not mentioned Baseline Hb: 8 g/dL to 11 g/dL
Interventions	Drug: ferric carboxymaltose (FCM; Injectafer) Dose: 15 mg/kg (maximum single dose: 750 mg [total dose ≤1500 mg] diluted in ≤250 mL saline) Hb-target: unclear Duration: 18 weeks
Outcomes	Primary: percentage of patients with a decrease in Hb ≥0.5 g/dL from weeks 3 to 18 Secondary: change in Hb from baseline to end of treatment
Notes	Abstract

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Gilreath 2019 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Patients were randomised 1:1: but method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described in literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Outcomes reported in literature
Other bias	Unclear risk	No description

Goede 2016

Study characteristics	
Methods	Rrandomised controlled trials,open-label, no placebo control
Participants	N = 62 randomised: untreated = 31; pretreated = 31 Dropouts: not reported Disease: chronic lymphocytic leukaemia Treatment: chemotherapy Mean age: 75 / 73 years Gender: male Mean base Hb: < 12 g/dL
Interventions	Drug: fludarabine +/- darbepoietin alfa Dose: 300 µg Hb-target: unclear Duration: unclear
Outcomes	Event-free-survival; response rate; progression-free survival; OS; Aes

Goede 2016 *(Continued)*

Notes	Quote: ".... study was approved and overseen by institutional ethics committees and review boards, conducted according to the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and registered at www.clinicaltrials.gov (NCT00281892)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomized...." Comment: method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: ".....open-label...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Due to slow recruitment, study was terminated prematurely

Gordon 2008

Study characteristics

Methods	Rrandomised controlled trial, placebo-controlled
Participants	N = 220, randomised: ESA = 164, control = 56 Dropouts: 0% Disease: non-myeloid haematological malignancies, breast, gastrointestinal, genitourinary, lung, gynaecological, other cancer (stage I-IV) Therapy: none Mean age: 70 years Gender: female Baseline Hb: 10.2 g/dL

Gordon 2008 *(Continued)*

Interventions	Drug: darbepoetin alpha Dose: 6.75 µg/kg sc Q4W Hb-target: 12-13 g/dL Duration: 16 weeks
Outcomes	Primary: Hb response Secondary: transfusion, Hb change, QoL, safety
Notes	Full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius2009, Study ID number = 65772)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: ".....randomized.... randomly allocated in a 3:1 ratio....."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ".....double-blind....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: Aal the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Comment: not found

Goss 2005

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 104, randomised: ESA = 52, control = 52 Dropouts: 0% Disease:SCLC (limited disease) Treatment: radiochemotherapy

Goss 2005 *(Continued)*

	Mean age: not mentioned Gender: not mentioned Baseline Hb: 13.5 g/dL
Interventions	Drug: epoetin alpha Dose: 40,000 IU sc weekly Hb-target: 14 g/dL to 16 g/dL, in 10/2002 reduced to 12 g/d to 14 g/dL Duration: during chemotherapy and radiotherapy
Outcomes	Disease progression-free survival, tumour response, overall survival, local disease progression Hb, transfusion, QoL
Notes	Abstract publication, additional unpublished data obtained for an individual patient data meta-analysis study (Bohlius 2009,Study ID number = 55703)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	yes - computer-generated central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Grote 2005

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 224, randomised: ESA = 109, control = 115

Grote 2005 *(Continued)*

	Dropouts: 0% Disease: SCLC (limited and extensive disease) Treatment: chemotherapy Mean age: 64.4 / 63.2 years Gender: male and female Baseline Hb: 12.9 g/dL
Interventions	Drug: epoetin alpha Dose: 150 IU/kg sc to three times a week Hb-target: 14 g/dL to 16 g/dL Duration: NR, assumed to be 12 weeks (drug given during 3 x 3 weeks chemo plus 3 weeks)
Outcomes	Primary: assess possible stimulatory effects of ESA on solid tumour growth, tumour response Secondary: overall survival, Hb, transfusion, safety
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 73807)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "……randomly assigned 1:1 using a computer generated randomization schedule….."
Allocation concealment (selection bias)	Low risk	Quote: "…..computer generated randomization schedule..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "…..double-blind….."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both result and discussion section
Other bias	Unclear risk	Quote: " ...early study termination as a result of suboptimal enrollment..."

Gupta 2009

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 115, randomised: ESA = 58, control = 57 Dropouts: 0% Disease: cervical cancer Treatment: platinum-containing in all patients plus radiotherapy Mean age: 48.2 /48.3 years Gender: not mentioned Baseline Hb: 10.6 g/dL
Interventions	drug: Epoetin beta dose: 30,000 IU to three times a week Hb-target: unclear Duration: unclear
Outcomes	Primary: Hb, energy level, QoL Secondary: response rate, survival, toxicities, adverse events
Notes	Full-text publication, study number = 30,057

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: ". Randomization was carried out by drawing sealed envelopes."
Allocation concealment (selection bias)	Low risk	Quote: ". Randomization was carried out by drawing sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not described
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Not found

Hajigholami 2021

Study characteristics	
Methods	Randomised study, not placebo-controlled
Participants	n= 79 Dropout: 0% Disease: metastatic and non-metastatic carcinoma Treatment: chemotherapy Mean age: 50.9 / 41.8 years Gender: male and female Mean baseline Hb: Group 1: 10.1±1.3 g/dL; Group 2: 10.4±1.1 g/dL
Interventions	Drug: Group 1: EPO + Venofer; Group 2: EPO + ferrous sulphate Dose: Group 1: 150 units/kg subcutaneously three times a week and 100 mg, intravenously at each chemotherapy session; Group 2: 150 units/kg subcutaneously three times a week and one tablet every 8 hours Hb-target: unclear Duration: 6 weeks
Outcomes	QoL, Hb-levels
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned using random number table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "blindness was not performed due to differences in iron administration in the two groups."
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information to clarify any judgement

Hajigholami 2021 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All the outcomes are described in literature
Other bias	Unclear risk	Not reported

Hedenus 2003

Study characteristics		
Methods	Randomised controlled trial, placebo-controlled	
Participants	N = 349, randomised: ESA = 176, control = 173 Dropouts: 0% Disease: lymphoma: Hodgkin disease, NHL, MM, CLL, Waldenstrom´s disease Treatment: NR, assumed to be chemotherapy without platinum Mean age: 64.8 / 64.6 years Gender: male and female Hb baseline: 9.5 g/dL	
Interventions	Drug: Darbepoetin alpha dose: 2.25 mg/kg qw sc Hb target: 13 g/dL to14 g/dL (women), 13 g/dL to15 g/dL (men) Duration: 12 weeks	
Outcomes	Primary: Hb response Secondary: transfusion, Hb change, QoL, safety	
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 63455)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...randomized in a 1:1 allocation, by a central randomization service....."
Allocation concealment (selection bias)	Low risk	Quote: ".....a central randomization service."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ".....double-blind....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes)	Low risk	Comment: double-blind

Hedenus 2003 *(Continued)*

All other outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Comment: broad eligibility criteria, heterogenous population

Hedenus 2007

Study characteristics	
Methods	Randomised controlled trial, multicentre study, open-label
Participants	N= 67, (no iron = 34, iron = 3) Dropouts: 0% Disease: lymphoproliferative malignancy Treatment: no chemotherapy Mean age: 77/74 years gender: male and female Baseline Hb: 9 g/dL to 11 g/dL
Interventions	Drug: group 1: EPO + iv iron, group 2: EPO + no iron Dose: EPO: 30,000 IU once weekly or 60,000 once weekly if no increase of Hb >1g/dL after 4 weeks, iron: 100 mg once weekly Hb-target: 14 g/dL Duration: 16 weeks
Outcomes	Primary outcome: mean change in Hb concentration Secondary outcome: Hb response, time to Hb response, dose of epoetin and effect on iron variables
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized..." Comment: method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned in literature
Blinding of participants and personnel (performance bias)	High risk	Open-label

Hedenus 2007 *(Continued)*

All outcomes		
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no flow-chart provided
Selective reporting (reporting bias)	Low risk	Comment: all outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	No description

Hedenus 2014

Study characteristics	
Methods	Randomised controlled trial, multicentre, open-label
Participants	n = 19, (iron = 8, no iron = 11) Dropouts: 0% Disease: lymphoid malignancies Treatment: antineoplastic therapy Baseline Hb: 8.5 g/d to 10.5 g/dL Mean age: 69.5/71 years Gender: male and female
Interventions	Drug: Group 1: iv iron, Group 2: no iron Dose: 1,000 mg iron Hb-target: unclear Duration: 8 weeks
Outcomes	Primary outcome: mean Hb change from baseline to weeks 4, 6 and 8 without transfusions or ESA Secondary outcome: safety, Hb response and correction, median time to Hb response, changes in hematological variables
Notes	Premature termination of study due to difficulties with patient recruitment
Risk of bias	

Bias	Authors' judgement	Support for judgement

Hedenus 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Based on a predefined, computer-generated randomisation list, patients were randomized 1:1"
Allocation concealment (selection bias)	Low risk	Quote:Based on a predefined, computer-generated randomization list, patients were randomized 1:1"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment:flow-chart provided; 0 vs 2 patients excluded for analyses
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were discussed in the results and discussion sections
Other bias	Unclear risk	Comment: trial was early terminated due to poor recruitment

Henke 1999

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 72, randomised: control = 33; ESAa = 19; ESAb = 14; ESAc = 6; ESAtotal = 39 Dropouts: not reported Disease: various solid tumours Treatment: radiotherapy Mean age: not reported Gender: male and female Mean/median baseline Hb: 11.5 g/dL
Interventions	Drug: epoetin alpha or beta Dose: ESAa: 150 U/kg 3x/week i.v., ESAb: 300 U/kg 3x/week i.v., ESAc: 150 U/kg 3x/week sc Hb target: 14 g/dL to 16 g/dL (men) or 13 g/dL to 15 g/dL (women) Duration: 8 weeks
Outcomes	Haematological response, change in Hb values
Notes	Full-text publication, study number = 39,895
Risk of bias	

Henke 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "....weighted (2:4:3:1) randomization...."
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: the literature does not address anything regarding blinding
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the result and discussion sections
Other bias	Unclear risk	Not found

Henke 2003

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 351, randomised: ESA = 180, control = 171 Dropouts: 0% Disease: advanced (stage III, IV) head and neck cancer Treatment: radiotherapy Mean age: 57 / 58 years Gender: male and female Baseline Hb: 11.8 g/dL
Interventions	Drug: epoetin beta Dose: 300 IU/kg tiw sc Hb-target: 12 g/dL to14 g/dL (women), 13 g/dL to 15 g/dL (men) Duration: 7-9 weeks
Outcomes	Primary: efficacy of radiotherapy, measured as local progression-free survival Secondary: survival, progression-free survival, Hb, safety, tolerability

Henke 2003 *(Continued)*

Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 58106)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomised..." Comment: method of randomisation is not described in the literature
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelopes with the code for individual patients were provided to the treating physicians and all were recollected unopened."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment:aAll the outcomes are discussed in both result and discussion section
Other bias	Low risk	Quote: " ...stratified patients according to tumour resection status..."

Henry 1995

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 132, randomised: ESA = 67, control = 65 Dropouts: 0% Disease: any type of cancer except primary myeloid malignancy or acute leukaemia treatment: platinum-containing chemotherapy Mean age: not reported Gender: not reported Baseline Hb: 9.5 g/dL
Interventions	Drug: epoetin alpha Dose: 150 IU/kg sc to three times a week Hb-target: Hct 38% to 40%

Henry 1995 *(Continued)*

	Duration: 12 weeks
Outcomes	Primary: Hct, transfusion, haematological response Secondary: correction of anaemia, response, QoL, safety
Notes	fFll-text publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 70332)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised Comment: method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Henry 2007

Study characteristics

Methods	Randomised controlled trial, open-label, no placebo control
Participants	N = 187 randomised: oral iron = 61; no iron 63; iv iron = 63 Dropouts: 0% Disease: non myeloid malignancy Treatment: chemotherapy

Henry 2007 *(Continued)*

	Mean age: 63 / 65.4 / 67.4 years Gender: male and female Mean base Hb: 10.3 g/dL
Interventions	Drug: darbepoietin alfa Dose: unclear Iron: sodium ferric gluconate complex (FG); oral ferrous sulphate Dose: 125 mg IV weekly, 325 oral iron thrice daily Hb-target: >= 12 g/dL Duration: 8 weeks
Outcomes	Haematopoetic response; whole blood/RBC transfusion; study withdrawal
Notes	Fll-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "…..randomized in a 1:1:1 ratio…. conducted centrally…."
Allocation concealment (selection bias)	Unclear risk	Quote:"'…..randomized in a 1:1:1 ratio…. conducted centrally…."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote:"'…..open-label…"
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote: ".... the protocol and supporting documents were approved by the institutional review board at each participating institution...."

Hernandez 2009

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	n = 391, randomised: ESA = 196, control = 195 Dropouts: 0% Disease: non-myeloid haematological malignancies, breast, lung, gastrointestinal, genitourinary, gynaecological, other cancer (stage I-IV) Treatment: chemotherapy, 36% receiving platinum Mean age: 63.6 / 64.5 years Gender: male and female Baseline Hb:10.1 g/dL
Interventions	Drug: darbepoetin alpha Dose: 300 µg sc Q3W Hb-target: 12 g/d to13 g/dL Duration: 15 weeks
Outcomes	Primary: transfusion Secondary: Hb target achieved, number of transfusions, safety, QoL
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 37476, Taylor 2005)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "... randomly assigned in a 1:1 ratio...."; Comment: Method of randomisation not described
Allocation concealment (selection bias)	Low risk	Quote: "In this double-blind study, patients, investigators, and study personnel were unaware of the treatment group to which patients were assigned."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: 'In this double-blind study, patients, investigators, and study personnel were unaware of the treatment group to which patients were assigned."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Quote: "....patients, investigators, and study personnel were unaware of the treatment group to which patients were assigned."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections

Hernandez 2009 *(Continued)*

Other bias	Low risk	Quote: "...independent ethics committee or institutional review board for each site approved the protocol...."

Hoskin 2009

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 300, randomised: ESA = 151, control = 149 Dropouts: 0% Disease: head and neck cancer (stage I-IV) Treatment: radiotherapy, no chemotherapy Mean age: 58 / 60 years Gender: male and female Baseline Hb: 13.6 g/dL
Interventions	Drug: epoetin alpha Dose: if Hb < 12.5 10,000 IU sc three times a week; if Hb > 12.5 4000 IU sc three times a week Hb-target: 14.5 to 15 g/dL Duration: 12 weeks
Outcomes	Primary: local disease-free survival Secondary: overall survival, QoL, safety
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 81645)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly assigned in a ratio of 1:1....."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "...open-label, phase III study..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label

Hoskin 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both result and discussion section
Other bias	Low risk	Quote: "....protocol was reviewed by the United Kingdom Multicenter Research Ethics Committee and by local research ethics committees..."

Huddart 2002

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 95, randomised: ESA = 48, control = 47 Dropouts: 0% Disease: lung, gynaecological, genitourinary, other cancer Treatment: platinum-containing chemotherapy mean age: not reported Gender: not reported Baseline Hb: not reported, eligibility criterion Hb < 10.5 g/dL, categorised as Hb 10-12 g/dL
Interventions	Drug: epoetin alpha Dose: 10,000 IU three times a week Hb-target: 12 g/dL to 14 g/dL Duration: max 28 weeks
Outcomes	Hb response, reticulocyte numbers, survival, QoL, safety
Notes	Abstract, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 88443)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomizsd Comment: Method of Randomisation is not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (mortality)	Low risk	Comment: mortality is an objective outcome

Huddart 2002 *(Continued)*
Mortality

Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment:not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

Iconomou 2003

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 122, randomised: ESA = 57, control = 55 Dropouts: 0% Disease: lung, breast, colorectal, ovarian, unknown primary, kidney, stomach, other cancer Treatment: chemotherapy, platinum & non platinum Mean age: 60.6 / 62.6 years gender: male + female Baseline Hb: 10.1 g/dL
Interventions	Drug and dose: NR, assumed Epoetin alpha 10,000 IU three times a week sc Hb target: NR Duration: 12 weeks
Outcomes	Primary: QoL Secondary: Hb, transfusions
Notes	Full-text publication, study number = 40,799

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a telephone call to the Registry of the Department of Medicine, and no stratification was planned."
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was performed by a telephone call to the Registry of the Department of Medicine, and no stratification was planned."
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: There is no mention anything regarding blinding in the literature

Iconomou 2003 *(Continued)*

All outcomes		
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Quote:"'Furthermore, as expected, fewer patients were transfused in the rHuEPO arm than in the control arm, although the difference failed to reach significance."

Italian 1998

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 85, randomised: ESA = 43, control = 42 Dropouts: 0% Disease: myelodysplastic syndromes Treatment: none Mean age: 65 years Gender: male and female mMean/median baseline Hb: 8.2 g/dL
Interventions	Drug: epoetin alpha Dose: 150 U/kg three times a /week sc Hb target: not reported Duration: 8 weeks, thereafter Epo for all the patients
Outcomes	Haematological response, change in haemoglobin values, adverse events
Notes	Full-text publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001), Study ID number = 46703

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "....randomized to receive rHuEpo (epoetin a, Janssen-Cilag) or placebo in a 1:1 fashion."; Comment: method of randomisation not described

Italian 1998 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment:insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: Aal the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Not found

Kotasek 2002

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 161, randomised: ESA = 129, control = 32 Dropouts: 0% Disease: lung, breast, gastrointestinal, genitourinary, gynaecological, other cancer (stage I-IV) Treatment: chemotherapy Mean age: not reported Gender: female Baseline Hb: not reported, eligibility criterion Hb <= 11 g/dL, categorised as Hb 10 g/dL to 12 g/dL
Interventions	Drug: darbepoetin alpha Dose: a: 9 µg/kg sc Q4W, b: 12 µg/kg sc Q4W, c: 15 µg/kg sc Q4W, d: 18 µg/kg sc Q4W Hb-target: 13-14 g/dL (women), 13-15 g/dL (men) Duration: 12 weeks
Outcomes	Primary: safety Secondary: determine effective dose, effect of ESA, QoL feasibility
Notes	Additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 26117)
Risk of bias	

Kotasek 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

Kotasek 2003

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 259, randomised: ESA = 208, control = 51 Dropouts: 0% Disease: breast, gynaecological, gastrointestinal, lung, genitourinary, other cancer treatment: chemotherapy, not reported whether with or without platinum, interpreted as some patients receiving platinum Mean age: 56.2 / 58.3 years Gender: female Baseline Hb: 9.9 g/dL
Interventions	Drug = darbepoetin alpha Dose = a: 4.5 µg/kg sc Q3W, b: 6.75 µg/kg sc Q3W, c: 9 µg/kg sc Q3W, d: 12 µg/kg sc Q3W, e: 13.5 µg/kg sc Q3W, f: 15 µg/kg sc Q3W Hb-target = 13 g/dL to14 g/dL (women), 13 g/dL to 15 g/dL (men) Duration = 12 weeks
Outcomes	Primary: safety

Kotasek 2003 *(Continued)*

	Secondary: determine effective dose, effect of ESA, QoL feasibility
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 35466)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised in a 4:1 ratio.....'" Comment: method of randomization not described
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "'....double-blind...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Not found

Krzakowski 2008

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 313, randomised: ESA a = 104, ESA b = 105, control = 104 Dropouts: 0% Disease: lung cancer, gastrointestinal tumour, breast cancer, genitourinary, haematological and other cancer Treatment: platinum and non-platinum containing chemotherapy Mean age: not reported Gender: male and female Baseline Hb: 9.4 g/dL
Interventions	Drug: epoetin delta

Krzakowski 2008 *(Continued)*

	Dose: a: 150 IU/kg three times a week, b: 300 IU/kg three times a week Hb-target: 12 g/dL to 14 g/dL Duration: 12 weeks
Outcomes	Primary: Hb, RBC, transfusions Secondary: Hct, FACT-An, subgroup analysis for type of cancer/ chemotherapy
Notes	Full-text publication, study number = 49,839

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomised in a 2:2:1:1 ratio...."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "....double-blind...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Quote: "However, as with other studies in this area, the protocol did not stipulate that investigators must use the haemoglobin cut-off as an indication for transfusion; rather the decision to transfuse was at the discretion of the investigator. It seems that investigators chose not to transfuse patients receiving blinded placebo to the same extent as patients receiving blinded epoetin delta."

Kurz 1997

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 35, randomised: ESA = 23, control = 13 Dropouts: 0% Disease: gynaecological tumours

Kurz 1997 *(Continued)*

	Treatment: platinum-based chemotherapy Mean age: 52.7 / 54.4 years Gender: not reported Baseline Hb: 9.9 g/dL
Interventions	Drug: epoetin alpha dose: 150U/kg three times a week sc Hb-target: no upper target reported Duration: 12 weeks
Outcomes	Haematologic response, change inHb values, transfusion requirement, QoL, adverse events
Notes	Full -ext publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001), Study ID number = 54819

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... random permuted blocks and a corresponding randomization list was used in the randomization office...."
Allocation concealment (selection bias)	Unclear risk	Quote: "... random permuted blocks and a corresponding randomization list was used in the randomization office...."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: All the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Comment: patients with gynaecological malignancies

Leyland-Jones 2005

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 939, randomised: ESA = 469, control = 470

Leyland-Jones 2005 *(Continued)*

	Dropouts: 0% Disease: metastatic breast cancer (stage IV, M1) Treatment: chemotherapy Mean age: 55.8 / 55.1 years Gender: female Baseline Hb: 12.5 g/dL
Interventions	Drug: epoetin alpha Dose: 40,000 IU qw sc Hb-target = 12 g/dL to 14 g/dL Duration: 52 weeks
Outcomes	Primary: overall survival Secondary: Hb, transfusion, tumour control, QoL, time to progression
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 17100)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "....patients were randomly assigned...." Comment: method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Quote: "...double-blind..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote:"'Baseline disease characteristics were balanced between the two treatment groups."

Littlewood 2001

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 375, randomised: ESA = 251, control = 124 Dropouts: 0% Disease: NHL, MM, HD, CLL, gastrointestinal, other cancer Treatment: chemotherapy without platinum Mean age: 58.3 / 59.5 years Gender: male and female Baseline Hb: 9.8 g/dL
Interventions	Drug: epoetin alpha Dose: 150 IU/kg sc three times a week Hb-target: 12 g/dL to 15 g/dL Duration: 28 weeks
Outcomes	Primary: transfusion Secondary: haematological response, Hb, Hct, reticulocytes, predictors for response, QoL, adverse events, after protocol amendment also survival
Notes	Full -ext publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 17123)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "....patients were assigned randomly 2:1....."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ".....double-blind...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections

Littlewood 2001 *(Continued)*

Other bias	Low risk	Quote:'...the study protocol and amendments were reviewed by an independent ethics committee.

Maccio 2010

Study characteristics	
Methods	Randomised controlled study, not placebo-controlled
Participants	N= 148 (IV iron: 73; oral lactoferrin: 75) Dropouts: 0% Disease: solid tumor advanced stage Treatment: chemotherapy Mean age: 67.3 / 68.8 years Gender: male and female Baseline Hb: ≤10 g/dL
Interventions	dDug: rHuEPO-β + ferric gluconate IV or lactoferrin oral Dose: 30,000 IU sc weekly, 125 mg ferric gluconate IV, 200 mg/day oral lactoferrin Hb-target: >12 g/dL Duration: 12 weeks
Outcomes	primary: Hb-change from baseline secondary: haematopoietic response rate, time to haematopoietic response, time-adjusted Hb AUC between week 0 and week 12, change from baseline in other laboratory parameters (serum irom, serum ferritin, CRP, and ESR)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised in a 1:1 ratio; method not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is objective outcome
Blinding of outcome assessment (all other outcomes)	Unclear risk	Open-label

Maccio 2010 *(Continued)*
All other outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of randomised and analysed patients is the same
Selective reporting (reporting bias)	Low risk	All the outcomes are described in literature
Other bias	Unclear risk	Numbers per arm differ in text/tables and flow-chart

Machtay 2007

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 148, randomised: ESA = 77, control = 71 Dropouts: 0% Disease: head and neck cancer (stage I-IV) Treatment: radiotherapy, advanced stages received in addition platinum-based chemotherapy Mean age: 64 / 61 years Gender: male and female Baseline Hb: 12.1 g/dL
Interventions	Drug: epoetin alpha Dose: 40,000 IU sc weekly Hb-target: 12.5 g/dL to14 g/dL (women), 13.5 g/dL to16 g/dL (men) Duration: 8 to 10 weeks
Outcomes	Primary: local regional control tumour response Secondary: overall survival, patterns of failure, local-regional progression-free survival Hb, toxicity, QoL
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 87660), old publication was Machtay 2004

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Yes - central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description

Machtay 2007 *(Continued)*

Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Milroy 2011

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 424, randomised: ESA = 214, control = 210 Dropouts: 0% Disease: NSCLC (stage IIIb or IV, advanced) Treatment: platinum-based chemotherapy Mean age: 61.6 years Gender: male and female Baseline Hb: 12.7 g/dL
Interventions	Drug: epoetin alpha dose: if body weight > 45 kg 10,000 IU sc three times a week, if body weight < 45 kg 5000 IU sc three times a week Hb-target: 12.5-14 g/dL (women), 13.5-15 g/dL (men) duration = during chemotherapy
Outcomes	Primary: QoL Secondary: Hb, tumour response, survival, transfusion
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 67954)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes- central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation

Milroy 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Moebus 2013

Study characteristics	
Methods	Rrandomised controlled trial; no placebo control
Participants	N = 643 randomised: EPO alfa = 324; Control = 319 Dropouts: 0% Disease: primary breast cancer stage II to IIIa Treatment: chemotherapy Mean age: 52 / 50 years Gender: female Mean base Hb: 12.6 g/dL
Interventions	Drug: epoietin alfa Dose: 450 IU/kg Hb-target: 12.5 g/dL to 13 g/dL Duration: 18 weeks
Outcomes	Haematopoetic response; RBC transfusions; relapse-free survival; OS; intramammary relapse
Notes	Full-text publication
Risk of bias	

Moebus 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...Randomized Clinical Trial...." Comment: method of randomisation is not described in the literature
Allocation concealment (selection bias)	Unclear risk	Comment: there is no mention about the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: the literature does not mention anything regarding blinding
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: All the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Comment: homogenised study population.

Mystakidou 2005

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 100, treatment group: 50, control group: 50 Dropouts: 0% Disease: solid malignancy Treatment: no treatment, chemotherapy, radiotherapy Mean age: 64.5 / 63 years Gender: male and female Baseline Hb: ≤11 g/dL
Interventions	Drug: Group 1: oral iron + epoetin alfa; Group 2: oral iron + placebo Dose: Group 1: 200 mg oral iron once daily + 40,000 IU once weekly Group 2: 200 mg oral iron once daily + matching volume of placebo once weekly

Mystakidou 2005 *(Continued)*

	Hb-Target: at least 12 g/dL Duration: 24 weeks
Outcomes	Primary outcome: change in haemoglobin level Secondary outcome: change in QOL scores, proportion of patients who withdrew due to deterioration of their anaemia and/or had been transfused during the trial.
Notes	full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "....randomized...at a 1:1 ratio...."; Comment: Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Unclear risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Quote: "Patients enrolled in this study had various tumor types"

Ng 2018

Study characteristics

Methods	Randomised controlled trial, not placebo-controlled
Participants	N= 27 randomised: standard care = 13; IVI = 14 Dropouts: 11.11% Disease: oesophagogastric adenocarcinoma Treatment: chemotherapy

Ng 2018 *(Continued)*

	Mean age: 69 / 68 years Gender: male and female Baseline Hb: women <12 g/dL; men <13g/dL
Interventions	Drug: intravenous iron isomaltoside Dose: unclear Hb-target: unclear Duration: quote: "3 follow-up visits at the start of each 3-week cycle of chemotherapy"
Outcomes	Haemoglobin, ferritin, TSAT, blood transfusion rate, number of units transfused, mortality, FACT-An, EQ-5D quality of life scores
Notes	fFll-text publication, trial was terminated early due to poor recruitment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "Patients were randomized 1:1 to each group using random allocations" Method not described
Allocation concealment (selection bias)	Low risk	Random allocations concealed in opaque envelops
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: flowchart provided, 3 versus zero patients excluded; number of randomised and analysed patients not the same.
Selective reporting (reporting bias)	Low risk	Mentioned in the literature
Other bias	Unclear risk	Trial was terminated early due to poor recruitment; Quote:"... has received grant support from Syner-Med, UK and Vifor Pharma, Switzerland. AA has received honoraria .... None of the above companies have had any input or influence on the delivery or write up of this study"

Nitz 2014

Study characteristics	
Methods	Randomised controlled trial, no placebo control
Participants	N = 1234 randomised: DA+ = 615, DA- = 619 Dropouts: 0% Disease: breast cancer Treatment: chemotherapy Mean age: not reported Gender: not reported Mean base Hb: 13g/dL
Interventions	Drug: adjuvant epoietin alfa Dose: 500µg Hb-target: >14g/dL Duration: quote: "for the first 2 years, follow-up examinations were carried out every 3 months, thereafter twice yearly."
Outcomes	Event-free survival; toxicity; QoL; OS
Notes	Full-text publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized centrally....."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized centrally..."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: The literature does not mention anything regarding blinding
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement

Nitz 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: All the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Not found

Noronha 2016

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N= 192 (IV = 98; oral = 94) Dropouts: 0% Disease: cancer Treatment: chemotherapy Mean age: 55.5 / 50 years Gender: male and female Baseline Hb: ≤ 12 g/dL
Interventions	Drug: group 1= IV Iron sucrose; group 2= oral ferrous sulphate Dose: unclear Hb-target: unclear Duration: 6-week study period
Outcomes	Primary: change in Hb Secondary: included blood transfusion, QoL, toxicity, response rate and overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was by a computer generated schedule with block randomization, using a block size of 10."
Allocation concealment (selection bias)	Unclear risk	Quote: "...computer generated schedule with block randomization, using a block size of 10"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open label"
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is an objective outcome

Noronha 2016 *(Continued)*

Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "All patients randomized to each arm were included for analysis of the efficacy variables ... as per the modified intention-to treat principle. "
Selective reporting (reporting bias)	Low risk	All outcomes reported as intended.
Other bias	Unclear risk	Numbers per arm are reported different in text and flowchart/tables

O'Shaughnessy 2005

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled pilot trial
Participants	N= 100 N2= 51 N3= 49 Dropouts: 0% Disease: breast cancer treated with anthracycline-based adjuvant or neoadjuvant chemotherapy. Treatment: chemotherapy Mean age: 53.3 / 54.3 years gender: female Baseline Hb:
Interventions	Ddrug: epoetin alfa Dose 40,000 U Baseline Hb: Duration: epoetin alfa subcutaneously once weekly or placebo at the beginning of 4 cycles of chemotherapy administered over 12 weeks
Outcomes	Data suggest that epoetin alfa may have attenuated the cognitive impairment and fatigue that occurred during adjuvant breast cancer chemotherapy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes - computer generated
Allocation concealment (selection bias)	Low risk	Yes - computer generated; - coded drug packs of identical appearance

O'Shaughnessy 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Oberhoff 1998

Study characteristics	
Methods	Rrandomised controlled trial, not placebo-controlled
Participants	N = 227, randomised: ESA = 116, control = 111 Dropouts: 0% Disease: ovarian, breast, lung, genitourinary, gastrointestinal, other cancer treatment: platinum-containing chemotherapy Mean age: 53 years Gender: male and female Baseline Hb: ESA arm 9.6 g/dL, control 10.3 g/dL, categorised as < 10 g/dL
Interventions	Drug: epoetin beta dDse: 5,000 U daily sc Hb-target: 14 g/dL Duration: 12 weeks
Outcomes	Primary: transfusion Secondary: haematological response, Hb response, safety
Notes	Full -ext publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 45434)
Risk of bias	
Bias	**Authors' judgement**	**Support for judgement**

Oberhoff 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote:"'....randomized...." Comment: there is no mention of the method of randomisation in the literature
Allocation concealment (selection bias)	Unclear risk	Comment: there is no mention about the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "...open...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: All the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Quote: "Sample size was calculated for this trial to allow for 90% power to detect a difference in the volume of PRBC transfused per four weeks between the two treatment groups at a significance level of 5%."

Osterborg 1996

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 144, randomised: ESA 1 = 47, ESA 2 = 48, control = 49 Dropouts: 0% Disease: MM, NHL, chronic lymphocytic lymphoma treatment: chemotherapy, non-platinum containing Mean age: 65/66 years Gender: male and female Baseline Hb: 8.8 g/dL
Interventions	Drug: epoetin beta Dose: a: 10,000 IU sc 7x/week, b: 2000 U daily sc; increased to 50,00 U and 10,000 U daily if no response Hb-target: 12-13 g/dL (women), 13 g/dL to 14 g/dL (men) Duration: 24 weeks
Outcomes	Primary: transfusion Secondary: safety, Hb, haematological response

Osterborg 1996 *(Continued)*

Notes	Full-text publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 43680)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomly allocated....." Comment: the literature does not describe the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: there is no mention about the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment:tThe literature does not mention anything regarding blinding
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment:iInsufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Not found

Osterborg 2002

Study characteristics

Methods	Rrandomised controlled trial, placebo-controlled
Participants	N = 343, randomised: ESA = 170, control = 173 Dropouts: 0% Disease: MM, NHL, CLL; Treatment: chemotherapy, assumed without platinum because of haematological disease Mean age: 63/64 years Gender: male and female Baseline Hb: 9.3 10g/dL
Interventions	Drug: epoetin beta Dose: 150U/kg 3x/week sc

Osterborg 2002 *(Continued)*

	Hb-target = 13-14 g/dL duration: 16 weeks
Outcomes	primary: transfusion-free survival Secondary: haematological response, Hb change, time to response, number of blood transfusions, QoL, safety
Notes	Full-text publication, additional unpublished data were obtained for the first Cochrane Review and an individual patient data meta-analysis study (Bohlius 2009, StudyID number = 77914)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…..randomized…." Comment: the method of randomisation is not described in the literature
Allocation concealment (selection bias)	Unclear risk	Comment: there is no mention about allocation concealment in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	comment: patients with different tumour type (MM, NHL, CLL) included

Overgaard 2009

Study characteristics

Methods	randomised controlled trial, not placebo-controlled
Participants	N = 515, randomised: ESA = 255, control = 260 Dropouts: 0.19% Disease: head and neck cancer Treatment: radiotherapy Mean age: 59 years

Overgaard 2009 *(Continued)*

	Gender: male and female Baseline Hb: approximately 13 g/dL
Interventions	Drug: darbepoetin Dose: 150 mg sc weekly Hb target: > 15.5 g/dL Duration: 8 to 10 weeks
Outcomes	OS, DS, tumour control, adverse events
Notes	Abstract publication, study id number = 62913

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central allocation method
Allocation concealment (selection bias)	Low risk	Central allocation method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Pedrazzoli 2008

Study characteristics

Methods	Randomised, open-label, multicentre study Study length: 12 weeks Study conducted during: December 2004 to February 2006
Participants	Eligibility: Hb ≤ 11 g/dL within 24 hours of randomisation; participants were required not to harbour absolute or functional iron deficiency (i.e. serum ferritin level ≥100 ng/mL and TSAT ≥ 20%); ECOG ≤ 2 Age: ≥ 18 years; life expectancy ≥ 6 weeks

Pedrazzoli 2008 *(Continued)*

	Sex (number enrolled): female (104), male (45) Dropouts: 0% Mean age: not reported Experimental arm: ESAs + IV iron: enrolled 73, analysed 73 Control arm: ESAs only: enrolled 76, analysed 76 Mean baseline serum ferritin range (333 g/mL to 350.7 ng/mL); mean baseline TSAT range (27.6% to 30.6%)
Interventions	Experimental arm: ESAs + IV sodium ferric gluconate 125 mg/week for the first 6 weeks Control arm: ESAs only: SC darbepoetin 150 µg/week for 12 weeks (dose adjustments were done)
Outcomes	Haematopoietic response, RBC transfusions, time to haematopoietic response, treatment-related harms (thromboembolic events are reported)
Notes	Full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial authors described the study as “randomized trial,” Comment: method of Randomisation is not described
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding (study described as “open-label”), yet outcome measurement was likely to be influenced by lack of blinding
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were analysed using both ITT and per-protocol principle
Selective reporting (reporting bias)	Low risk	Benefits and harms were reported as indicated in a prespecified method
Other bias	Unclear risk	Not found

Pirker 2008

Study characteristics

Pirker 2008 *(Continued)*

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 600, randomised: ESA = 299, control = 301 Dropouts: 0% Disease: SCLC (untreated, extensive stage) Treatment: platinum-containing chemotherapy Mean age: 60.6/61.3 years Gender: male +female Baseline Hb: 11.9 g/dL, ESA arm 12.03 g/dL, control 11.86 g/dL, categorised as 10 g/dL to 12 g/dL
Interventions	Drug: darbepoetin alpha Dose: 300 µg sc weekly for weeks 1 to 4 then 300 µg Q3W starting week 5 onwards Hb-target: 13 g/dL to 14 g/dL Duration: 19 weeks
Outcomes	Primary: Hb change, survival Secondary: QoL, progression-free-survival, tumour response, time to progression, transfusion
Notes	Full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009,Study ID number = 89335)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "..randomly assigned (1:1)...." Comment: method of randomisation not described
Allocation concealment (selection bias)	Low risk	Quote:"'The randomized treatment assignment was obtained from the interactive voice-response system..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"...double-blind..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: All the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote: "Baseline demographics and clinical characteristics were similar between the two treatment groups."

Pronzato 2010

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 223, randomised ESA = 110, control = 113 Dropouts: 3.14% Disease: breast cancer (stage I-IV) Treatment: chemotherapy Mean age: 53.3/54.3 years Gender: female Baseline Hb: 10.7 g/dL
Interventions	Drug: epoetin alpha Dose: if body weight >45kg 10,000 IU sc three times a week, if body weight <45 kg 5,000 IU sc three times a week Hb target: 12-14 g/dL Duration: categorised: >20 weeks
Outcomes	Primary: QoL (anaemia) Secondary: haematological response, other QoL, tumour response, OS, number of patients transfusion
Notes	Full-text publication, unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 22233)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...patients were randomized 1:1....."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: the method of concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "......open-label...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement

Pronzato 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote: " Demographic and baseline characteristics of the mITT population were well balanced between the two groups."

Quirt 1996

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 56, randomised: ESA = 28, control = 28 Dropouts: 0% Disease: lung, gynaecological, hematological malignancies, other cancer treatment: chemotherapy Mean age: not reported Gender: not reported Baseline Hb: 10.8 g/dL
Interventions	Drug: epoetin alpha Dose: 150U/kg three times per week sc, Hb-target: 12.5 g/dL to 14 g/dL Duration: 16 weeks
Outcomes	Primary: transfusion, Hb change Secondary: QoL, costs from societal perspective, tumour response
Notes	Abstract publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study number = 80214)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Yes- randomised Comment: method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature

Quirt 1996 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Ray-Coquard 2009

Study characteristics	
Methods	Abstract publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 80214)
Participants	N = 218, randomised: ESA = 110, control = 108 Dropouts: 0% Disease: breast, sarcoma, lung, ovarian, other solid cancer and haematological malignancies Treatment: chemotherapy (IPD) full text: NR Mean age: 62 to 7/61.7 years Gender: male and female Baseline Hb: 10.0 g/dL, categorised as 10 g/dL to 12 g/dL
Interventions	Drug: epoetin alpha Dose: if body weight < 45 kg 10000 IU sc 2x/week, if body weight 45 kg to < 89 kg 10,000 IU sc three times a week, if body weight > 89 kg 10,000 IU sc four times per week Hb-target: 12 g/d to 14 g/dL Planned ESA duration: 12 weeks
Outcomes	Primary: transfusion-dependent anaemia Secondary: QoL, Hb response predictors, Hb, toxicity, survival, costs
Notes	fFull-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 37491)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Yes - randomisation Comment: method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality)	Low risk	Comment: mortality is an objective outcome

Ray-Coquard 2009 *(Continued)*

Mortality		
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Razzouk 2006

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 222, randomised ESA: 111, Control: 111 Dropouts: 0% Disease: solid tumours, HD, NHL, ALL tTeatment: chemotherapy Mean age: 12.4/10.8 years Gender:male and female Baseline Hb: 9.7 g/dL
Interventions	Drug: epoetin alpha Dose: 600 IU/kg iv weekly Hb target: 13 g/dL to 15 g/dL (age >12 years), 13 g/dL to 14 g/dL (age<12 years) duration: 16 weeks
Outcomes	Primary: QoL Secondary: Hb, transfusion
Notes	Full-text publication, additional unpublished data were obtained for an Individual Patient Data meta-analysis study (Bohlius 2009). Study ID number: 80515

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ".....randomly assigned to treatment groups in a 1:1 ratio...."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned in the literature
Blinding of participants and personnel (performance bias)	Low risk	Quote: "...double-blind...."

Razzouk 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Not found

Rose 1994

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 221, ESA = 142, control = 79 Dropouts: 0% Disease: CLL (stage III, IV) Treatment: chemotherapy and radiotherapy, without platinum Mean age: not reported Gender: not reported Baseline Hb: 9.2 g/dL
Interventions	Drug: epoetin alpha Dose: 150 U/kg three times per week sc Hb target: Hct 38% to 40% Duration: 12 weeks
Outcomes	Primary: Hct, haematological response Secondary: transfusion, safety, QoL
Notes	Abstract publication, additional unpublished data were obtained for the this Cochrane Review and an individual patient data meta-analysis study (Bohlius 2009, study number = 98358)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes - computer-generated

Rose 1994 *(Continued)*

Allocation concealment (selection bias)	Low risk	Yes - computer-generated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	Nno description
Other bias	Unclear risk	No description

Rosenzweig 2004

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 27, randomised: ESA = 14, control = 13 Dropouts: 0% Disease: metastatic breast cancer Treatment: less than 50% of participants received chemotherapy, some received hormones, categorised as other Mean age: 55.9/53.9 years Gender: female Baseline Hb: not reported, eligibility criterion Hb < 12 g/dL, categorised as Hb 10 g/d to 12 g/dL
Interventions	Drug: epoetin alpha Dose: 40,000 IU qw sc Hb target: NR Duration: 12 weeks
Outcomes	Primary: fatigue, QoL
Notes	Full-text publication, Study ID number = 76065
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Rosenzweig 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "subjects were randomized to group using sequential, opaque, sealed envelopes with the order unknown to the investigators."
Allocation concealment (selection bias)	Low risk	Quote:"...subjects were randomized to group using sequential, opaque, sealed envelopes with the order unknown to the investigators."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "....open label....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Quote:"The trial was halted early at the request of the DSMB when 4 (28.5%) subjects developed thrombotic events in the erythropoietin arm."

Smith 2003

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 86, randomised: ESA = 64, control = 22 Dropouts: 0% Disease: genitourinary, breast, gastrointestinal, lymphoma: myeloma, CLL, NHL Treatment: none Mean age: 66.7/68 years Gender: female Baseline Hb: 9.995 g/dL; <10 g/dL for two groups and 10 g/dL to 12 g/dL for the other two, categorised as <10 g/dL
Interventions	Drug: darbepoetin alpha Dose: see below Hb target: 1 g/d to 14 g/dL (women), 13 g/dL to 15 g/dL (men) Duration: 12 weeks
Outcomes	Primary: hematopoietic response Secondary: time to response, Hb response, Hb change, transfusions, serum darbepoetin concentration in a subset of patients

Smith 2003 *(Continued)*

Notes	Ful- text publication, Study ID number = 76561

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "....randomised in a 3: 1 ratio....." Comment: Nethod of randomiSation not described
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomised .....for the first 12 weeks (blinded treatment phase)....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: blinded treatment phase
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote:"'Baseline demographic and clinical characteristics of patients were generally well balanced between the cohorts including the placebo cohort."

Smith 2008

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 989, randomised: ESA = 517, control = 472 Dropouts: 0% Disease: lung, hematological malignancies, breast, gastrointestinal, genitourinary, other cancer (stage III-IV) Treatment: none Mean age: 64.3 / 64 years Gender: male Baseline Hb: 9.5 g/dL
Interventions	Drug: darbepoetin alpha Dose: 6.75 µg/kg sc Q4W Hb-target: 12 g/dL to 13 g/dL

Smith 2008 *(Continued)*

	Duration: 16 weeks
Outcomes	Primary: transfusion Secondary: Hb, QoL, safety
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 81215)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: ".....randomly allocated 1:1.....'" Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ".....Double-Blind....."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Not found

Steensma 2011

Study characteristics

Methods	Pprospective, multicentre, randomised trial, ESA + placebo controlled not blinded.
Participants	N =490 parenteral Iron =164 oral Iron = 163 oral placebo = 163 Dropouts: 0% Disease: chemotherapy-associated anaemia Treatment: patients with haemoglobin (Hb) less than 11 g/dL who were undergoing chemotherapy for no myeloid malignancies Mean age: 64/63/63 years

Steensma 2011 *(Continued)*

	Gender: female Baseline Hb:
Interventions	Drug:darbepoetin alfa (Aranesp; Amgen,Thousand Oaks, CA), ferric gluconate ferrous sulphate Dose: darbepoetin alfa 500 ug reached greater than 11.0 g/dL, thereafter darbepoetin 300 ug, ferrous sulphate 325 mg, ferric gluconate 187.5 mg Duration: darbepoetin alfa once every 3 weeks, ferric gluconate every 3 weeks ferrous sulphate oral daily, or oral placebo for 16 weeks.
Outcomes	No difference in the erythropoietic response rate of IV iron-treated patients achieved an erythropoietic response compared with patients who received oral iron or oral placebo No differences in the proportion of patients requiring red cell transfusions, changes in quality of life, or the dose of darbepoetin administered Patients with CAA, addition of IV ferric gluconate to darbepoetin failed to provide additional benefit compared with oral iron or oral placebo
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly assigned on a 1:1:1 basis...."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not mentioned
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: Aal the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Quote: "....study met an early stopping rule because of an excess of serious AEs in the IV iron arm."

Strauss 2008

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 74, randomised: ESA = 34, control = 40 Dropouts: 0% Disease: cervical cancer (stage IIB-IVA) Treatment: radio- and platinum-containing chemotherapy Mean age: 48.8/49.2 years Gender: not reported Baseline Hb: 11.5 g/dL
Interventions	Drug: epoetin beta Dose: 150 IU/kg sc three times a week Hb-target: 14 g/dL to 15 g/dL Duration: 12 weeks
Outcomes	Primary: tumour control failures Secondary: progression-free survival, overall response rate, relapses/metastases, overall survival, Hb change, QoL, safety
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 70404)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "…..centrally randomized……."
Allocation concealment (selection bias)	Low risk	Quote: "...centrally randomized.."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "……study was conducted as an open……,adaptive study."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections

Strauss 2008 *(Continued)*

Other bias	Unclear risk	Not found

Sweeney 1998

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 48, randomised: ESA = 24, control = 24 Dropouts: 0% Disease: breast, lung, prostate and cervix cancer Treatment: chemotherapy for 5 patients, radiotherapy for probably all of the patients Mean age: 62.7/62.3 years Gender: male and female Baseline Hb: ESA arm 12.07, control: 10.72 g/dL, categorised as 10 g/dL to 12 g/dL
Interventions	Drug: epoetin alfa Dose: 200 IU/kg/day Hb target: 14 g/dL for women and 15 g/dL for men Duration: 7 weeks
Outcomes	Hb, total white blood cell count and platelets, QoL
Notes	Full -ext publication, excluded for IPD-review, StudyID number = 77932

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote:".....randomized between r-HuEPO and control by creating random numbers separately by disease site and treatment centre in bins of 10 by a computer."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized between r-HuEPO and control by creating random numbers separately by disease site and treatment centre in bins of 10 by a computer."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there is no mention anything regarding blinding in the literature
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias)	Unclear risk	Comment: insufficient information to clarify any judgement

Sweeney 1998 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote: "....the two arms are well balanced without significant differences in baseline characteristics."

Ten Bokkel 1998

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 120, randomised: ESA = 87, control = 33 Dropouts: 0% Disease: ovarian carcinoma (stage II-IV) Treatment: platinum-based chemotherapy Mean age: 59.9/58.8 years Gender: female Baseline Hb: 11.6 g/dL
Interventions	Drug: epoetin beta Dose: a: 150 IU/kg sc three times a week, b: 300 IU/kg sc three times a week Hb-target: 14 g/dL to 15 g/dL Duration = during chemotherapy, 24 weeks
Outcomes	Primary: transfusion Secondary: Hb, reticulocytes, Hct, safety, tumour response, adverse events
Notes	Full-text publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 47852)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Yes - central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Nno description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome

Ten Bokkel 1998 *(Continued)*

Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Thatcher 1999

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 130, randomised: ESA = 86, control = 44 Dropouts: 0% Disease: SCLC Treatment: platinum-based chemotherapy Mean age: 58.8/60 years Gender: male and female Baseline Hb: 13.4 g/dL
Interventions	Drug: epoetin alpha Dose: ESA a: 150 IU/kg sc three times per week; ESAb: 300 IU/kg sc TIW three times per week Hb-target: 13 g/d to 15 g/dL Duration: 26 weeks
Outcomes	Change in Hb values, transfusion requirement, QoL, adverse events
Notes	Full-text publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001) and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 65529)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "....randomized...." Comment: method of randomisation is not described in the literature
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment is not described in the literature
Blinding of participants and personnel (performance bias)	High risk	Quote: "...open-label..."

Thatcher 1999 *(Continued)*

All outcomes		
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment:iInsufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote:"'...no statistically significant between-group differences."

Thépot 2016

Study characteristics	
Methods	Rrandomised controlled trial, not placebo-controlled
Participants	N = 98 (49 ine each group) Dropouts: 0% Disease: MDS or CMML Treatment: chemotherapy Mean age: 73.3/71.6 years Gender: male and female Baseline Hb: unclear
Interventions	Drug: AZA + epoetin-ß Dose: 60,000 U/w Hb-target: unclear Duration: unclear, quote: "median follow-up of 47.3 months"
Outcomes	Primary: RBC-TI after 6 cycles Secondary: minor and major response according to IWG 2000, response according to IWG 2006 after 4 and 6 cycles, response duration, overall survival, IPSS progression-free survival, toxicity
Notes	full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement

Thépot 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned". Method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned in the literature
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the literature
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to clarify any judgement
Selective reporting (reporting bias)	Unclear risk	Toxicity is not reported in the results.
Other bias	Unclear risk	No description

Thomas 2002

Study characteristics	
Methods	Rndomised controlled trial, not placebo-controlled
Participants	N = 130, randomised: ESA = 65, control = 65 Dropouts: 0% Disease: breast, gastrointestinal, gynaecological, other cancer Treatment: chemotherapy Mean age: not reported Gender: not reported Baseline Hb: 10.6 g/dL
Interventions	Drug: epoetin alpha Dose: if body weight > 45 kg 10,000 IU sc three times per week, if body weight < 45 kg 5000 IU sc three times per week Hb-target: 12 g/d to 14 g/dL Duration: 12 weeks
Outcomes	Hb, QoL, transfusions
Notes	Abstract publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 84090)

Thomas 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Thomas 2008

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 109 (from IPD), full-text: accrued: 114, 5 found subsequently not eligible randomised: ESA = 57, control = 52; planned were 460, vs IPD, vs 2006 Dropouts: 0% Disease: cervical cancer (stage IIB - IV A, M0) Treatment: platinum-based chemotherapy plus radiotherapy Mean age: 50/46 years Gender: not reported Baseline Hb: 10.7 g/dL
Interventions	Drug: epoetin alpha Dose: 40,000 IU sc weekly Hb-target: 13 g/dL to 14 g/dL Duration: 8 weeks maximum, categorised as 6 to 9 weeks
Outcomes	Primary: progression-free survival

Thomas 2008 *(Continued)*

	Secondary: OS, local control, distant recurrences, thromboembolic events
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 21481)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...patients were randomly assigned...." Comment: method of randomisation is not described in the literature
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment is not described in the literature
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there is no mention anything regarding blinding in the literature
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Quote: The study closed prematurely at the request of the sponsor, after less than 25% of the planned accrual due to potential concerns for TE with R-HUEPO and the subsequent withdrawal of study drug and study support by the sponsor.

Throuvalas 2000

Study characteristics

Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 55, randomised: ESA = 28, control = 27 Dropouts: 0% Disease: cervix and bladder carcinoma Treatment: platinum-based radiochemotherapy Mean age: not reported Gender: not reported

Throuvalas 2000 *(Continued)*

	Baseline Hb: 11.3 g/dL
Interventions	Drug: epoetin (?) Dose: 10,000 U five times per /week sc Hb target: NR Duration: 6 weeks
Outcomes	Change in Hb values, transfusion requirement, tumour response
Notes	Abstract publication, additional unpublished data were obtained for the first Cochrane Review (1985-2001), Study ID number = 83700

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes - random number generator...central allocation
Allocation concealment (selection bias)	Low risk	Yes - central allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Tjulandin 2010

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 223, randomised: epo theta = 76, Epo beta = 73, control = 74 Dropouts: 0% Disease: ovarian cancer, gastric cancer, breast cancer, lung cancer. other solid cancers Treatment: platinum-based chemotherapy

Tjulandin 2010 *(Continued)*

	Mean age: 53.7/57.3 years Gender: male and female Baseline Hb: 9.5 g/dL
Interventions	Drug a): epoetin theta, dose: 20,000 IU weekly Drug b): epoetin beta, dose: 150 IU/kg sc TIW Hb-target: 13 g/dL Duration: 12 weeks
Outcomes	Primary: haematological response Secondary: partial Hb response, RBCTs, number of bloods units transfused, safety, QoL
Notes	Full-text publication, Study ID number = 19632

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...randomised using a computer-generated allocation schedule in a 1:1:1 ratio....."
Allocation concealment (selection bias)	Low risk	Quote: "...randomised using a computer-generated allocation schedule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "....double-blind phase III study...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote: "The demographic and baseline characteristics of the 3 treatment groups were comparable."

Tjulandin 2011

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 186, randomised: ESA = 95, control = 91

Tjulandin 2011 *(Continued)*

	Dropouts: 0% Disease: haematological, breast and gastric cancer treatment: chemotherapy without platinum Mean age: 55.8/56.9 years Gender: male and female Baseline Hb: 9.2 g/dL
Interventions	Drug: epoetin theta Dose: 20,000 IU weekly Hb-target: 13 g/dL Duration: 12 weeks
Outcomes	Primary: haematological response Secondary: partial Hb response, RBCTs, number of bloods units transfused, safety, QoL
Notes	Full-text publication, Study ID number = 18036

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "…..randomised using a computer-generated allocation schedule in a 1:1 ratio….."
Allocation concealment (selection bias)	Low risk	Quote: "'…..randomised using a computer-generated allocation schedule.."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "….double blind treatment…."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote: "The demographic and baseline characteristics were comparable across the 2 treatment groups."

Toma 2013

Study characteristics

Toma 2013 *(Continued)*

Methods	Randomised controlled trial, open-label, no placebo control
Participants	N = 132 randomised Dropouts: 2.27% Disease: low-risk MDS Treatment: unclear Mean age: 73.5/73 years Gender: male and female Mean base Hb: unclear
Interventions	Drug: epoietin beta Dose: 60,000 U/w Hb-target: unclear Duration: unclear
Outcomes	Erythroid response; identification of biomarkers
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Yes - randomised Comment: method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	High - open label
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description

Toma 2013 *(Continued)*

Other bias	Unclear risk	No description

Tsuboi 2009

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 122, randomised: ESA = 63, control = 59 Dropouts: 4.10% Disease: lung cancer, malignant lymphoma (HL and NHL) Treatment: chemotherapy, both platinum- and non-platinum-containing, no numbers given Mean age: 62.1/61.8 years Gender: male + female Baseline Hb: 10.2 g/dL
Interventions	Drug: epoetin beta Dose: 36,000 IU sc weekly Hb target: >= 14 g/dL Duration: 8 weeks
Outcomes	Primary: Hb change Secondary: haematological response, transfusions, Hb,QoL, (survival, care: retrospective)
Notes	Full-text publication, abstract Watanabe 2006 was excluded for the IPD-Review, Study ID number = 92759

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was conducted by central registration system and a dynamic balancing method..."
Allocation concealment (selection bias)	Low risk	Quote"'Randomization was conducted by central registration system and a dynamic balancing method..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...Double-Blind...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias)	Unclear risk	Comment: Insufficient information to clarify any judgement

Tsuboi 2009 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Comment: Aal the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Comment: no information was found that could possibly raise other sources of bias

Untch 2011

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 733, randomised: ESA = 356, control = 377 Dropouts: 0.55% Disease: breast cancer (M0) Treatment: non platinum-containing chemotherapy Mean age: not reported Gender: female Baseline Hb: 13.6 g/dL
Interventions	Drug: darbepoetin alpha Dose: 4.5 ìg/kg sc Q2W Hb-target: 12.5 g/d to 13 g/dL Duration: during chemotherapy, approximately > 20 weeks
Outcomes	Primary: relapse-free survival time, OS Secondary: tumour control, safety and tolerability, transfusion, Hb level, QoL
Notes	Two full-text publications, in addition unpublished data were obtained for the individual patient data meta-analysis study (Bohlius 2009, study ID number = 66960)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised Comment: method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	unclear - description is unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	no description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is objective outcome

Untch 2011 *(Continued)*

Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Vansteenkiste 2002

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 320, randomised: ESA = 159, control = 161 Dropouts: 0% Disease: SCLC (limited and extensive), and NSCLC (stage I-IV) Treatment: platinum-based chemotherapy Mean age: 47.6/48 years Gender: male Baseline Hb: 10.1 g/dL
Interventions	Drug: darbepoetin alpha Dose: 2.25 mg/kg sc weekly Hb-target: 13 g/dL to 14 g/dL (women), 13 g/dL to 15 g/dL (men) Duration: 12 weeks
Outcomes	Primary: transfusion Secondary: Hb response, Hb, transfusion timing and quantity, QoL
Notes	Full-text publication, additional unpublished data were obtained for and an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 49684)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized...." Comment: Method of randomisation is not described in the literature
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment is not described in the literature
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: there is no mention about blinding in the literature

Vansteenkiste 2002 *(Continued)*

All outcomes		
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Not found

Welch 1995

Study characteristics	
Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 30, randomised: ESA = 15, control = 15 Dropouts: 0% Disease: ovarian carcinoma tTeatment: platinum-containing chemotherapy Mean age: not reported Gender: female Mean/median baseline Hb: 12.9 g/dL
Interventions	Drug: epoetin alpha Dose: 300 U/kg three times per week sc Hb - target: 12 g/dL to 15 g/dL Duration: 24 weeks
Outcomes	Cchange in Hb values, transfusion requirement, adverse events
Notes	Full-text publication, Study ID number = 97952

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised Comment: method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	No description

Welch 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Wilkinson 2006

Study characteristics	
Methods	Rndomised controlled trial, not placebo-controlled
Participants	N = 182, randomised: ESA = 121; control = 61 Dropouts: 0% Disease: ovarian cancer (stage I-IV) Treatment: chemotherapy Mean age: 59.1/60.3 years Gender: female Baseline Hb: 10.7 g/dL
Interventions	Drug: epoetin alpha Dose: if body weight > 45 kg 10,000 IU sc three times per week, if < 45 kg 5000 IU sc three times per week Hb-target: 12-14 g/dL Duration: maximum. 28 weeks
Outcomes	Primary: Hb response Secondary: QoL, transfusion, tumour response
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al Study ID number = 75688)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Wilkinson 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "...randomised 2: 1..."; Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: no mention of allocation concealment in the literature
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "....open-label..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Low risk	Quote: "Baseline demographic and clinical characteristics were generally comparable between the two treatment groups."

Winquist 2009

Study characteristics	
Methods	Randomised controlled trial, placebo-controlled
Participants	N = 56, randomised ESA: 26, control = 30 Disease: prostate cancer Dropouts: 0% Treatment: unclear Mean age: 71 years Gender: male Baseline Hb: 10.4 g/dL
Interventions	Drug: epoetin alpha Dose: 40,000 IU sc 3 times per week Hb target: 14.0 g/dL Duration: 16 weeks
Outcomes	Primary: QoL Secondary: Hb level, RBCTs, adverse events, survival
Notes	Letter publication, Study ID number 13321

Winquist 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "....randomly selected via central telephone by the Ontario Clinical Oncology Group...."
Allocation concealment (selection bias)	Low risk	Quote: "....randomly selected via central telephone ..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"'...double blind..."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment:insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Not found

Witzig 2005

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 344, randomised: ESA = 174, control = 170 Dropouts: 0% Disease: lung, breast, other cancer (active incurable advanced stage) Treatment: chemotherapy, platinum & non platinum Mean age: 63.6/63.7 years Gender: male and female Hb category: 9.5 g/dL
Interventions	Drug: epoetin alpha Dose: 40,000 IU sc weekly Hb-target: 13 g/dL to 15 g/dL Planned ESA duration: 16 weeks
Outcomes	Primary: transfusions Secondary: Hb change, Hb over time, predictors for response, incidence of nephrotoxicity,

Witzig 2005 *(Continued)*

	OS, tumour response, QoL
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 36512)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes - computer-generated central randomisation
Allocation concealment (selection bias)	Low risk	Yes - central randomisation; coded packs of identical appearance
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Comment: not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Selective reporting (reporting bias)	Unclear risk	No description
Other bias	Unclear risk	No description

Wright 2007

Study characteristics

Methods	Randomised controlled trial, placebo-controlled
Participants	N = 70, randomised: ESA = 33, control = 37 Dropouts: 0% Disease: NSCLC (advanced stage IIIA, B and IV, recurrent disease) Treatment: no anticancer therapy Mean age: 70/68 years Gender: male Baseline Hb: 10.3 g/dL
Interventions	Drug: epoetin alpha Dose: 40,000 IU sc weekly

Wright 2007 *(Continued)*

	Hb-target: 12 g/dL to 14 g/dL Duration = 12 weeks
Outcomes	Primary: QoL Secondary: Hb, Hct, transfusion, safety
Notes	Full-text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius 2009, Study ID number = 53572)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "....Computer-generated randomization....."
Allocation concealment (selection bias)	Low risk	Quote: "....Computer-generated randomization....."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "....double-blind...."
Blinding of outcome assessment (mortality) Mortality	Low risk	Comment: mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Low risk	Comment: double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to clarify any judgement
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes are discussed in both the results and discussion sections
Other bias	Unclear risk	Quote: "In the autumn of 2003, as other trials evaluating ERAs were being suspended or terminated because of unexpected rates of thrombotic events, Ortho Biotech requested a review of the accumulated data by the independent DSMC of the trial. This was an unplanned analysis."

Zhao 2018

Study characteristics

Methods	Randomised controlled trial, not placebo-controlled
Participants	N = 80 Dropouts: not reported Disease: gastrointestinal malignant tumour

Zhao 2018 *(Continued)*

	Treatment: chemotherapy Mean age: 64.5/63.6 years Gender: male Baseline Hb: unclear
Interventions	Drug: recombinant human erythropoietin and iron preparations Dose: unclear Hb-target: unclear Duration: unclear
Outcomes	Changes of haemoglobin, red blood cells, KPS score and adverse reactions
Notes	abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were divided into two groups by random number table according to their conditions
Allocation concealment (selection bias)	Unclear risk	Random number table
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the literature
Blinding of outcome assessment (mortality) Mortality	Low risk	Mortality is an objective outcome
Blinding of outcome assessment (all other outcomes) All other outcomes	Unclear risk	Not mentioned in the literature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of randomised and analysed patients is the same.
Selective reporting (reporting bias)	Low risk	Outcomes described in literature
Other bias	Unclear risk	No description

AUC: area under the curve ;**CLL:** chronic lymphatic leukaemia; **CRP:** C-reactive protein; **EPO:** erythropoietin; **ESA:** erythropoiesis-stimulating agents;**G-CSF:** Granulocyte-colony stimulating factor;**ESR:** erythrocyte sedimentation rate; **Hb:** haemoglobin;**Hct:** haematocrit;**IPD:** individual patient data; **ITT:** intention-to-treat; **IU:** international unit;**IV:** intravenous;**MM:** multiple myeloma: **NHL:** non Hodgkin lymphoma; **NSCLC:** non-small cell lung cancer; **OS:** overall survival; **QoL:** quality of life;**RBC:** red blood cell; **RBCTs:** red blood cell transfusions;**rHuEPO:** recombinant human erythropoietin; **sc:** subcutaneous;**SCLC:** small cell lung cancer

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

Study	Reason for exclusion
Antonadou 2001	Wrong intervention (iron unclear)
Bamias 2003	Wrong intervention (iron unclear)
Boccia 2019	Wrong comparator (two different IV iron preparations)
Cabanillas 2012	Wrong intervention (iron unclear)
Carabantes 1999	Wrong intervention (iron unclear)
EPO-GER-20 IPD	Wrong intervention (iron unclear)
Fenaux 2017	Wrong intervention (iron unclear)
Gebbia 2003	Wrong intervention (iron unclear)
Hedenus 2002	Wrong intervention (iron unclear)
Heidenreich 2015	Wrong intervention (iron unclear)
Katakami 2008	Wrong intervention (iron unclear)
Kunikane 2001	Wrong intervention (iron unclear)
Leyland-Jones 2015	Wrong intervention (iron unclear)
List 2016	Wrong intervention (iron unclear)
Mafodda 2017	Wrong study design (not randomised)
Mountzios 2016	Wrong comparator (prophylactic versus Hb-based erythropoiesis-stimulating agent administration)
OBE/EPO-INT-03 IPD	Wrong intervention (iron unclear)
P-174 J&J 2004	Wrong intervention (iron unclear)
Platzbecker 2017	Wrong intervention (iron unclear)
Rosen 2003	Wrong intervention (iron unclear)
Savonije 2005	Wrong intervention (iron unclear)
Silvestris 1995	Wrong intervention (iron unclear)
Suzuki 2008	Wrong intervention (iron unclear)
Tesch 2019	Wrong comparator (iron versus physician's choice (no treatment, oral iron, ESA,or both))
Thompson 2000	Wrong intervention (iron unclear)
Vansteenkiste 2009	Wrong study design (two different ESA doses)

Study	Reason for exclusion
Wurnig 1996	Wrong intervention (iron unclear)

Iron unclear: it is not known whether the patient received iron or not;**IV:** intravenous.

Characteristics of studies awaiting classification *[ordered by study ID]*

Anthony 2011

Methods	Principal investigator: not reported Start of study: not reported End of study: not reported
Participants	Target sample size: n = 375 patients enrolled Disease: cancer (acute leukaemia or myeloproliferative syndrome excluded)
Interventions	Intervention 1: ESA + IV iron Intervention 2: ESA + no iron
Outcomes	
Notes	

CTRI/2011/12/002273

Methods	Principal investigator: Dr V Satya Suresh Attilli: sureshattili@yahoo.com Dr Ajay Mehta: ajayonco@hotmail.com Dr Rajnish Nagarkar: drrajnagarkar@yahoo.co.in Dr Shailesh Bondarde: shaileshbondarde@yahoo.com Start of study: 01.03.2012 End of study: not mentioned, but estimated duration of trial: 4 months
Participants	Target sample size n =16 Disease: non-haematological malignancies
Interventions	Intervention 1: Iron isomaltoside 1000 (Monofer®) 500 mg IV bolus injections Intervention 2: Iron isomaltoside 1000 (Monofer®) 1000 mg IV infusions
Outcomes	
Notes	

EUCTR2004-002176-42-IT

Methods	Principal investigator: not mentioned Start of study: not mentioned, but date of competent authority decision: 30.11.2004 End of study: not mentioned
Participants	Target sample size n = 420 Disease: non myeloid tumours
Interventions	Intervention 1: NESPO* 1 SIR. 0,3mL 150 MCG + darbepoetin alfa Intervention 2: FERLIXIT*OS IV 5 F 5 mL62.5 MG (ferric sodium gluconate complex) Intervention 3: NESPO* 1 SIR. 0,6 mL 300 MCG + darbepoetin alfa
Outcomes	
Notes	Trial completed

EUCTR2005-005658-37-DK

Methods	Principal investigator: not mentioned Start of study: 07.07.2006 End of study: initial estimate of the duration of the trial: 3 years
Participants	Target sample size n =140 Disease: hormone refractory prostate cancer with progression of skeletal metastases
Interventions	Intervention 1: Aranesp® darbepoetin alfa Intervention 2: standard treatment for anaemia
Outcomes	
Notes	Prematurely terminated

EUCTR2006-000137-35-LT

Methods	Principal investigator: not mentioned start of study: 10.04.2006 End of study: not mentioned
Participants	Target sample size n = 60 Disease: metastatic breast cancer
Interventions	Intervention 1: capecitabine/docetaxel + beta epoetin Intervention 2: capecitabine/docetaxel

EUCTR2006-000137-35-LT *(Continued)*

Outcomes	
Notes	Prematurely ended

EUCTR2006-005965-20-SE

Methods	Principal investigator: not mentioned Start of study: 16.02.2007 End of study: 19.04.2007
Participants	Target sample size n = 210 disease: solid tumours or lymphoproliferative malignancies
Interventions	Intervention 1: NeoRecormon 30,000 IU Intervention 2: Venofer Intervention 3: NeoRecormon 10,000 IU Intervention 4: NeoRecormon 5000 IU
Outcomes	
Notes	Prematurely ended

EUCTR2007-005777-57-GR

Methods	Principal investigator: not mentioned start of study: 01.02.2008 End of study: not mentioned, but initial estimate of duration of trial: 10 months
Participants	Target sample size n = 110 Disease: haematological malignancies
Interventions	Intervention 1: EPO + TDI of CosmoFer® Intervention 2: EPO + oral Iron
Outcomes	
Notes	Prematurely ended

EUCTR2008-001721-34-BE

Methods	Principal investigator: not mentioned Start of study: 11.02.2009

EUCTR2008-001721-34-BE *(Continued)*

	End of study: not mentioned, but initial estimate of duration of trial: 2 years
Participants	Target sample size n = 225 Disease: anaemia in paediatric participants with solid tumours
Interventions	Intervention 1: darbepoetin alfa 100 ug Intervention 2: darbepoetin alfa 300 ug Intervention 3: darbepoetin alfa 500 ug
Outcomes	
Notes	Trial was not started due to being cancelled

EUCTR2008-002723-85-IT

Methods	Principal investigator: not mentioned Start of study: 07.04.2009 End of study: initial estimate of duration of the trial: 5 years and 4 months Date of global end of trial: 18.12.2009
Participants	Target sample size n = 450 Disease: IPSS low- or intermediate- 1 risk Myelodysplastic Syndromes
Interventions	Intervention 1:epoetin alfa Intervention 2: placebo
Outcomes	
Notes	Prematurely ended

EUCTR2009-015766-56-GR

Methods	Principal investigator: not mentioned Start of study: date of competent authority decision: 23.03.2010 End of study: initial estimate of duration of trial: 1 year 1 month 1 day Date of global end of trial: 01.06.2011
Participants	Target sample size n = 40 Disease: multiple myeloma
Interventions	Intervention 1: IV iron Intervention 2: no treatment

EUCTR2009-015766-56-GR *(Continued)*

Outcomes	
Notes	Prematurely ended

EUCTR2009-015767-14-SE

Methods	Principal investigator: not mentioned Start of study: date of competent authority decision: 23.04.2010 End of study: initial estimate of duration of trial: 1 year and 3 months Date of global end of trial: 09.11.2012
Participants	Target sample size n = 40 Disease: lymphoid malignancies
Interventions	Intervention 1: IV iron Intervention 2: no treatment
Outcomes	
Notes	Prematurely ended

EUCTR2011-001664-22-AT

Methods	Principal investigator: not mentioned Start of trial: date of competent authority decision: 22.12.2011 End of trial: initial estimate of duration of trial: 2 years Date of global end of trial: 31.12.2014
Participants	Target sample size n = 75 disease: breast cancer
Interventions	Intervention 1: iron Intervention 2: Aranesp® (darbepoetin alfa)
Outcomes	
Notes	Prematurely ended

ISRCTN01957333

Methods	Principal investigator: Dr. Tarinee Manchana Start of study: 31.08.2008

ISRCTN01957333 *(Continued)*

	End of study: 31.07.2009
Participants	Target sample size n = 44 Disease: gynaecological cancer
Interventions	Intervention 1: IV iron sucrose Intervention 2: oral iron (ferrous sulphate)
Outcomes	
Notes	

ISRCTN61345286

Methods	Principal investigator: Prof. Giuseppe Giaccone: g.giaccone@vumc.nl Start of study: 01.02.2001 End of study:
Participants	N = 34 Disease: solid malignancies
Interventions	Intervention 1: EPO Intervention 2: iron (III)-hydroxide-sucrose Intervention 3: ferrofumarate
Outcomes	
Notes	Trial completed

JPRN-JapicCTI-050013

Methods	
Participants	
Interventions	
Outcomes	
Notes	Trial completed

JPRN-JapicCTI-080582

Methods	

JPRN-JapicCTI-080582 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Trial completed

NCT03776032

Methods	Principal investigator: not mentioned Start of study: 14.09.1999 End of study: 27.02.2002
Participants	N = 320 Disease: lung cancer
Interventions	Intervention 1: darbepoetin alfa Intervention 2: placebo
Outcomes	
Notes	Trial completed

NTR250

Methods	
Participants	
Interventions	
Outcomes	
Notes	Trial completed

EPO: erythropoietin; **ESA:** erythropoiesis-stimulating agents;; **IPSS:** International prostate symptom score; **IU:** international unit;**IV:** intravenous.

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

ACTRN12620001105932p

Study name	
Methods	
Participants	N = 290

ACTRN12620001105932p *(Continued)*

	Disease: breast cancer
Interventions	Group 1: IV iron Group 2: standard of care
Outcomes	
Starting date	Start of study: 30.06.2021 (first participant enrolment) End of study: not mentioned
Contact information	Nick Murray, corinna.beckmore@bctrials.org.au
Notes	

Chen 2016

Study name	
Methods	
Participants	N = 603 Disease: malignant tumour
Interventions	Group 1: EPO 10,000 IU + IV iron 200 mg Group 2: EPO 10,000 IU + IV iron 100 mg Group 3: EPO 20,000 IU + no iron
Outcomes	
Starting date	Start of study: December 2016 End of study: November 2019
Contact information	Lin Chen 896571345@qq.com Yong Gao drgaoyong@163.com
Notes	

ChiCTR-IPR-16009059

Study name	
Methods	
Participants	N = 120 Disease: gynaecological cancer
Interventions	Group 1: EPO + IV iron

ChiCTR-IPR-16009059 *(Continued)*

	Group 2: EPO + oral iron
	Group 3: IV iron
	Group 4: oral iron
Outcomes	
Starting date	Start of study: 01.09.2016
	End of study: not mentioned
Contact information	Shen Huimin Huimin_shen@126.com
Notes	

ChiCTR-IPR-16009508

Study name	
Methods	
Participants	N = 120
	Disease: gynaecological cancer
Interventions	Group 1: EPO + IV iron
	Group 2: EPO + oral iron
	Group 3: IV iron
	Group 4: oral iron
	Group 5: (control group) IV iron
	Group 6: (control group) oral iron
Outcomes	
Starting date	Start of study: 01.11.2016
	End of study: 31.12.2017
Contact information	Shen Huimin Huimin_shen@126.com
Notes	

CTRI/2019/05/019378

Study name	
Methods	
Participants	N = 60

CTRI/2019/05/019378 *(Continued)*

	Disease: malignant neoplasm of unspecified ovary
Interventions	Group 1: IV iron + no EPO Group 2: oral iron + no EPO
Outcomes	
Starting date	Start of study: 17.06.2019 End of study: not mentioned
Contact information	Anupama R, anupamashyam@gmail.com
Notes	Not yet recruiting

EUCTR2016-002021-11-PL

Study name	
Methods	
Participants	N = 222 Disease: cancer
Interventions	Group 1: IV iron Group 2: IV placebo
Outcomes	
Starting date	Start of study: 13.07.2016 End of study: 21.12.2017
Contact information	Not mentioned
Notes	Trial completed

EUCTR2018-001669-17-GB

Study name	
Methods	
Participants	N = 40 Disease: cancer
Interventions	Group 1: IV iron Group 2: placebo IV

EUCTR2018-001669-17-GB *(Continued)*

Outcomes	
Starting date	Start of study: 28.08.2018 End of study: (initial estimate of the duration of trial) 2 years
Contact information	not mentioned
Notes	

ISRCTN13370767

Study name	
Methods	
Participants	N =40 Disease: cancer
Interventions	Group 1: IV iron Group 2: IV placebo
Outcomes	
Starting date	Start of study: 01.03.2018 End of study: 01.12.2020
Contact information	Edward Dickson Edward.dickson@nhs.net
Notes	Trial completed

KCT0004311

Study name	
Methods	
Participants	N = 341 Disease: cancer
Interventions	Group 1: IV iron Group 2: EPO + IV or oral iron
Outcomes	
Starting date	start of study: 28.10.2019 end of study: not mentioned

KCT0004311 *(Continued)*

Contact information	JunHo Jang
Notes	

NCT02731378

Study name	
Methods	
Participants	N = 603 Disease: malignant tumour
Interventions	Group 1: EPO + IV iron 200 mg Group 2: EPO + IV iron 100 mg Group 3: doubling EPO dose + no iron
Outcomes	
Starting date	Start of study: December 2016 End of study: November 2019
Contact information	Yong Gao
Notes	

NCT03683810

Study name	
Methods	
Participants	(Estimated enrolment) n = 50 Disease: cancer
Interventions	Group 1: EPO + iron Group 2: EPO + no iron
Outcomes	
Starting date	start of study: 14.01.2019 end of study: June 2022
Contact information	Andreas Charalambous, andreas.charalambous@cut.ac.cy Maria Christofi, m.christofi@cut.ac.cy

NCT03683810 *(Continued)*

Notes	status: recruiting

Zur Hausen 2016

Study name	
Methods	
Participants	N = 64 Disease: metastatic colorectal cancer
Interventions	Group 1: ferric carboxymaltose Group 2: Ferro sanol duodenal 100 mg
Outcomes	
Starting date	Start of study: March 2015 End of study: August 2020
Contact information	Not mentioned
Notes	Data from clinicaltrials.gov

EPO: erythropoietin; **IV:** intravenous

ADDITIONAL TABLES

Table 1. Results of network meta-analysis for outcome on-study mortality

Subnet 1							
Heterogeneity / inconsistency: Q = 36.41, df = 48, P = 0.89; I^2 = 0%, Tau^2 = 0							
ESA + IV iron	.	0.34 [0.01, 8.15]	.	.	.	0.11 [0.01, 2.04]	.
0.49 [0.02, 12.19]	**No ESA + oral iron**	0.70 [0.41, 1.18]	.	.	0.50 [0.05, 5.34]	.	.
0.34 [0.01, 8.15]	0.70 [0.41, 1.18]	**ESA + oral iron**	.	.	.	.	.
0.13 [0.01, 2.34]	0.27 [0.00, 20.17]	0.38 [0.01, 27.99]	**Placebo**	.	.	0.87 [0.79, 0.97]	.
0.13 [0.01, 2.29]	0.26 [0.00, 19.73]	0.37 [0.01, 27.38]	0.98 [0.78, 1.21]	**No treatment**	.	0.90 [0.74, 1.09]	0.34 [0.08, 1.41]
0.17 [0.00, 8.94]	0.35 [0.03, 3.95]	0.50 [0.05, 5.34]	1.30 [0.01, 174.72]	1.34 [0.01, 179.66]	**Placebo + oral iron**	.	.
0.11 [0.01, 2.04]	0.23 [0.00, 17.61]	0.34 [0.00, 24.44]	0.87 [0.79, 0.97]	0.90 [0.74, 1.09]	0.67 [0.01, 90.01]	**ESA + no iron**	.
0.04 [0.00, 1.09]	0.09 [0.00, 8.41]	0.13 [0.00, 11.68]	0.33 [0.08, 1.40]	0.34 [0.08, 1.41]	0.25 [0.00, 41.84]	0.38 [0.09, 1.60]	**No ESA + IV iron**
Subnet 2							
Heterogeneity / inconsistency: Q = 0.24, df = 1, P = 0.62; I^2 = 0%, Tau^2 = 0							
Placebo + iron, unclear application			0.78 [0.51, 1.21]			.	
0.78 [0.51, 1.21]			**ESA + iron, unclear application**			0.42 [0.12, 1.53]	
0.33 [0.08, 1.28]			0.42 [0.12, 1.53]			**No ESA + iron, unclear application**	

Upper triangle: direct estimates; lower triangle: network estimates. Only subnets with >1 designs. Comparisons should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Effect estimates are presented as risk ratios (RR) with corresponding 95% confidence interval. For the network estimates in the lower triangle an RR below 1.0 favours the column-defining treatment and for the direct estimates in the upper triangle an RR below 1.0 favours the row-defining treatment (less presence of deaths). To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Treatments are ordered by P-Score (ascending).
Subnet 1: No. of studies: 55. No. of treatments: 8. No. of pairwise comparisons: 55. No. of designs: 7
Subnet 2: No. of studies: 3. No. of treatments: 3. No. of pairwise comparisons: 3. No. of designs: 2

Table 2. Results of network meta-analysis for outcome haemoglobin response

Subnet 1						
Heterogeneity / inconsistency: Q_{total} = 57.45, df = 28, P < 0.01 / Q_{within} = 51.30, df = 25, P < 0.01 / $Q_{between}$ = 6.14, df = 3, P = 0.10; I^2 = 51.3%, Tau^2 = 0.0321						
ESA + IV iron	1.04 [0.71, 1.52]	1.14 [0.91, 1.43]	1.32 [1.11, 1.57]	.	.	.
1.08 [0.76, 1.53]	**ESA + placebo**	1.03 [0.70, 1.51]	.	.	.	.
1.15 [0.92, 1.43]	1.07 [0.75, 1.51]	**ESA + oral iron**	0.97 [0.67, 1.41]	.	3.45 [1.50, 7.90]	.
1.29 [1.09, 1.54]	1.20 [0.82, 1.76]	1.13 [0.87, 1.46]	**ESA + no iron**	3.06 [2.58, 3.63]	.	5.19 [4.02, 6.71]
3.95 [3.10, 5.04]	3.67 [2.42, 5.58]	3.45 [2.53, 4.70]	3.06 [2.58, 3.63]	**Placebo**	.	.
3.96 [1.68, 9.33]	3.67 [1.49, 9.04]	3.45 [1.50, 7.90]	3.06 [1.28, 7.30]	1.00 [0.41, 2.43]	**No ESA + oral iron**	.
6.71 [4.93, 9.14]	6.23 [3.93, 9.87]	5.85 [4.06, 8.42]	5.19 [4.02, 6.71]	1.70 [1.25, 2.31]	1.70 [0.69, 4.20]	**No treatment**

Upper triangle: direct estimates; lower triangle: network estimates. Only subnets with >1 designs. Comparisons should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Effect estimates are presented as risk ratios (RR) with corresponding 95% confidence interval. For the network estimates in the lower triangle an RR above 1.0 favours the column-defining treatment and for the direct estimates in the upper triangle an RR above 1.0 favours the row-defining treatment (more presence of haemoglobin responses). To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Treatments are ordered by P-Score (ascending).
Subnet 1: No. of studies: 31. No. of treatments: 7. No. of pairwise comparisons: 37. No. of designs: 7

Table 3. Comparison of direct and in direct evidence (in closed loops) for outcome Hb response

Comparison	**No. of studies**	**Network estimate**	**Direct estimate**	**Indirect estimate**	**Test for disagreement**
ESA + IV iron vs. ESA + no iron	6	1.29 [1.09, 1.54]	1.32 [1.11, 1.57]	0.53 [0.17, 1.67]	0.1234
ESA + IV iron vs. ESA + oral iron	4	1.15 [0.92, 1.43]	1.14 [0.91, 1.43]	1.25 [0.47, 3.32]	0.8565
ESA + IV iron vs. ESA + placebo	1	1.08 [0.76, 1.53]	1.04 [0.71, 1.52]	1.29 [0.54, 3.06]	0.6559
ESA + no iron vs. ESA + oral iron	2	0.89 [0.69, 1.15]	1.03 [0.71, 1.50]	0.77 [0.54, 1.11]	0.2792
ESA + oral iron vs. ESA + placebo	1	0.94 [0.66, 1.33]	0.97 [0.66, 1.43]	0.79 [0.34, 1.84]	0.6559

Estimates are reported as risk ratios with corresponding 95% confidence interval. Result of test for disagreement between direct and indirect evidence reported as p-value. Only comparisons for which both direct and indirect evidence exists are shown.

Table 4. Results of network meta-analysis for outcome red blood cell transfusions

Subnet 1							
Heterogeneity/Inconsistency: Q_{total} = 162.04, df = 65, P < 0.01 / Q_{within} = 159.35, df = 61, P < 0.01 / $Q_{between}$ = 2.68, df = 4, P = 0.61; I^2 = 59.9%, Tau^2 = 0.0447							
ESA + oral iron	0.81 [0.48, 1.38]	0.95 [0.48, 1.91]	0.41 [0.19, 0.91]	.	.	0.45 [0.34, 0.60]	.
0.90 [0.56, 1.43]	**ESA + IV iron**	0.90 [0.45, 1.82]	0.74 [0.53, 1.03]	.	.	.	.
0.88 [0.46, 1.68]	0.98 [0.51, 1.88]	**ESA + placebo**	.	.	.	.	.
0.67 [0.41, 1.09]	0.75 [0.54, 1.03]	0.76 [0.38, 1.52]	**ESA + no iron**	.	0.65 [0.59, 0.72]	.	0.59 [0.51, 0.69]
0.54 [0.32, 0.90]	0.60 [0.34, 1.06]	0.61 [0.28, 1.32]	0.80 [0.47, 1.37]	**No ESA + IV iron**	1.07 [0.48, 2.38]	0.68 [0.39, 1.18]	0.89 [0.23, 3.35]
0.44 [0.27, 0.72]	0.49 [0.35, 0.68]	0.50 [0.25, 1.00]	0.65 [0.59, 0.73]	0.82 [0.48, 1.39]	**Placebo**	.	.
0.43 [0.33, 0.57]	0.48 [0.29, 0.80]	0.49 [0.25, 0.97]	0.64 [0.38, 1.07]	0.80 [0.50, 1.29]	0.98 [0.58, 1.65]	**No ESA + oral iron**	.
0.40 [0.24, 0.66]	0.44 [0.31, 0.63]	0.45 [0.22, 0.91]	0.59 [0.51, 0.69]	0.74 [0.43, 1.28]	0.90 [0.75, 1.09]	0.92 [0.54, 1.57]	**No treatment**
Subnet 2							
Heterogeneity/Inconsistency: Q=5.00, df=4, p=0.29; I^2=19.9%, Tau^2=0.0168							
ESA + iron, unclearapplication			0.74 [0.54, 1.00]	0.46 [0.33, 0.64]			
0.74 [0.54, 1.00]			**Placebo + iron, unclear application**	.			
0.46 [0.33, 0.64]			0.63 [0.40, 0.98]	**No ESA + iron, unclear application**			

Upper triangle: direct estimates; lower triangle: network estimates. Only subnets with >1 designs. Comparisons should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Effect estimates are presented as risk ratios (RR) with corresponding 95% confidence interval. For the network estimates in the lower triangle an RR below 1.0 favours the column-defining treatment and for the direct estimates in the upper triangle an RR below 1.0 favours

the row-defining treatment (less presence of red blood cell transfusions). To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Treatments are ordered by P-Score (ascending).
Subnet 1: No. of studies: 69. No. of treatments: 8. No. of pairwise comparisons: 75. No. of designs: 9
Subnet 2: No. of studies: 6. No. of treatments: 3. No. of pairwise comparisons: 6. No. of designs: 2

Table 5. Comparison of direct and in direct evidence (in closed loops) for outcome red blood cell transfusions

Comparison	No. of studies	Network estimate	Direct estimate	Indirect estimate	Test for disagreement
ESA + IV iron vs. ESA + no iron	6	0.75 [0.54, 1.03]	0.74 [0.53, 1.03]	0.83 [0.27, 2.61]	0.8487
ESA + IV iron vs. ESA + oral iron	3	1.12 [0.70, 1.78]	1.23 [0.72, 2.09]	0.80 [0.30, 2.13]	0.4522
ESA + IV iron vs. ESA + placebo	1	0.98 [0.51, 1.88]	0.90 [0.45, 1.82]	1.58 [0.30, 8.46]	0.5448
ESA + no iron vs. ESA + oral iron	2	1.49 [0.92, 2.41]	2.43 [1.10, 5.37]	1.12 [0.61, 2.05]	0.1270
ESA + no iron vs. No treatment	19	0.59 [0.51, 0.69]	0.59 [0.51, 0.69]	0.74 [0.17, 3.14]	0.7669
ESA + no iron vs. Placebo	33	0.65 [0.59, 0.73]	0.65 [0.59, 0.72	1.07 [0.37, 3.11]	0.3697
ESA + oral iron vs. ESA + placebo	1	0.88 [0.46, 1.68]	0.95 [0.48, 1.91]	0.54 [0.10, 2.99]	0.5448
ESA + oral iron vs. No ESA + oral iron	6	0.43 [0.33, 0.57]	0.45 [0.34, 0.60]	0.24 [0.08, 0.69]	0.2592
No ESA + IV iron vs. No ESA + oral iron	2	0.80 [0.50, 1.29]	0.68 [0.39, 1.18]	1.27 [0.50, 3.24]	0.2592
No ESA + IV iron vs. No treatment	1	0.74 [0.43, 1.28]	0.89 [0.23, 3.35]	0.71 [0.39, 1.30]	0.7669
No ESA + IV iron vs. Placebo	1	0.82 [0.48, 1.39]	1.07 [0.48, 2.38]	0.65 [0.32, 1.34]	0.3697

Estimates are reported as risk ratios with corresponding 95% confidence interval. Result of test for disagreement between direct and indirect evidence reported as p-value. Only comparisons for which both direct and indirect evidence exists are shown.

Table 6. Results of network meta-analysis for outcome number of red blood cell transfusions

Subnet 1		
Heterogeneity / inconsistency: Q = 39.86, df = 17, P < 0.01; I^2 = 57.4%, Tau^2 = 0.2548		
ESA + no iron	-0.67 [-1.31, -0.03]	-0.90 [-1.29, -0.51]

Table 6. Results of network meta-analysis for outcome number of red blood cell transfusions *(Continued)*

-0.67 [-1.31, -0.03]	**No treatment**	.
-0.90 [-1.29, -0.51]	-0.23 [-0.97, 0.52]	**Placebo**
Subnet 2		
Heterogeneity / inconsistency: Not applicable (subnet consists of only two pairwise comparisons)		
ESA + oral iron	.	-0.80 [-1.15, -0.45]
-0.30 [-0.90, 0.30]	**No ESA + IV iron**	-0.50 [-0.99, -0.01]
-0.80 [-1.15, -0.45]	-0.50 [-0.99, -0.01]	**No ESA + oral iron**

Upper triangle: direct estimates; lower triangle: network estimates. Only subnets with >1 designs. Comparisons should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Effect estimates are presented as standardised mean differences (SMD) with corresponding 95% confidence interval. For the network estimates in the lower triangle an SMD below 0.0 favours the column-defining treatment and for the direct estimates in the upper triangle an SMD below 0.0 favours the row-defining treatment (smaller number of red blood cell transfusions). To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Treatments are ordered by P-Score (ascending).
Subnet 1: No. of studies: 19. No. of treatments: 3. No. of pairwise comparisons: 19. No. of designs: 2
Subnet 2: No. of studies: 2. No. of treatments: 3. No. of pairwise comparisons: 2. No. of designs: 2

Table 7. Results of network meta-analysis for outcome overall mortality

Subnet 1								
Heterogeneity / inconsistency: Q_{total} = 61.55, df = 65, P = 0.60 / Q_{within} = 59.02, df = 61, P = 0.55 / $Q_{between}$ = 2.53, df = 4, P = 0.64; I^2 = 0%, Tau^2 = 0								
ESA + placebo	.	.	.	0.50 [0.13, 1.97]	.	0.38 [0.10, 1.40]	.	.
0.61 [0.16, 2.34]	**No treatment**	0.97 [0.91, 1.03]	.	.	0.34 [0.08, 1.41]	.	.	.
0.59 [0.15, 2.27]	0.97 [0.91, 1.03]	**ESA + no iron**	0.99 [0.96, 1.02]	1.94 [0.18, 20.81]	.	0.76 [0.45, 1.29]	.	.
0.58 [0.15, 2.24]	0.96 [0.90, 1.03]	0.99 [0.96, 1.02]	**Placebo**	.	.	.	.	.
0.44 [0.12, 1.62]	0.72 [0.31, 1.66]	0.74 [0.32, 1.71]	0.75 [0.32, 1.73]	**ESA + oral iron**	.	0.74 [0.30, 1.83]	0.91 [0.84, 0.98]	0.50 [0.05, 5.34]
0.40 [0.11, 1.55]	0.67 [0.28, 1.58]	0.69 [0.29, 1.63]	0.69 [0.29, 1.64]	0.93 [0.66, 1.31]	**No ESA + IV iron**	.	0.94 [0.67, 1.33]	.
0.42 [0.12, 1.50]	0.69 [0.41, 1.15]	0.71 [0.43, 1.18]	0.72 [0.43, 1.19]	0.96 [0.44, 2.09]	1.03 [0.46, 2.34]	**ESA + IV iron**	.	.
0.40 [0.11, 1.47]	0.65 [0.28, 1.51]	0.67 [0.29, 1.56]	0.68 [0.29, 1.57]	0.91 [0.84, 0.98]	0.98 [0.70, 1.37]	0.95 [0.43, 2.07]	**No ESA + oral iron**	.
0.22 [0.01, 3.27]	0.36 [0.03, 4.43]	0.37 [0.03, 4.57]	0.37 [0.03, 4.62]	0.50 [0.05, 5.34]	0.54 [0.05, 5.91]	0.52 [0.04, 6.33]	0.55 [0.05, 5.90]	**Placebo + oral iron**
Subnet 2								
Heterogeneity / inconsistency: Q = 1.27, df = 3, P = 0.74; I^2 = 0%, Tau^2 = 0								
ESA + iron, unclear application			1.00 [0.87, 1.15]		1.25 [0.94, 1.66]			
1.00 [0.87, 1.15]			**Placebo + iron, unclear application**		.			
1.25 [0.94, 1.66]			1.24 [0.90, 1.71]		**No ESA + iron, unclear application**			

Upper triangle: direct estimates; lower triangle: network estimates. Only subnets with >1 designs. Comparisons should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Effect estimates are presented as risk ratios (RR) with corresponding 95% confidence interval. For the network estimates in the lower triangle an RR below 1.0 favours the column-defining treatment and for the direct estimates in the upper triangle an RR below 1.0 favours the row-defining treatment (less presence of deaths). To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Treatments are ordered by P-Score (ascending).
Subnet 1: No. of studies: 71. No. of treatments: 9. No. of pairwise comparisons: 75. No. of designs: 10
Subnet 2: No. of studies: 5. No. of treatments: 3. No. of pairwise comparisons: 5. No. of designs: 2

Table 8. Comparison of direct and indirect evidence (in closed loops) for outcome overall mortality

Comparison	No. of studies	Network estimate	Direct estimate	Indirect estimate	Test for disagreement
ESA + IV iron vs. ESA + no iron	4	1.41 [0.85, 2.34]	1.32 [0.78, 2.24]	3.02 [0.51, 17.69]	0.3785
ESA + IV iron vs. ESA + oral iron	3	1.05 [0.48, 2.28]	1.35 [0.55, 3.32]	0.48 [0.10, 2.31]	0.2655
ESA + IV iron vs. ESA + placebo	1	2.40 [0.67, 8.59]	2.65 [0.72, 9.81]	0.34 [0.00, 107.93]	0.4942
ESA + no iron vs. ESA + oral iron	1	0.74 [0.32, 1.71]	1.94 [0.18, 20.81]	0.65 [0.26, 1.58]	0.3969
ESA + no iron vs. No treatment	21	1.03 [0.97, 1.10]	1.03 [0.97, 1.10]	2.98 [0.50, 17.88]	0.2452
ESA + oral iron vs. ESA + placebo	1	2.29 [0.62, 8.51]	2.00 [0.51, 7.86]	10.64 [0.11, 1050.39]	0.4942
ESA + oral iron vs. No ESA + oral iron	8	0.91 [0.84, 0.98]	0.91 [0.84, 0.98]	0.31 [0.05, 1.88]	0.2452
No ESA + IV iron vs. No ESA + oral iron	1	0.98 [0.70, 1.37]	0.94 [0.67, 1.33]	2.72 [0.47, 15.81]	0.2452
No ESA + IV iron vs. No treatment	1	1.50 [0.71, 3.56]	2.95 [0.71, 12.34]	1.02 [0.35, 3.01]	0.2452

Estimates are reported as risk ratios with corresponding 95% confidence interval. Result of test for disagreement between direct and indirect evidence reported as p-value. Only comparisons for which both direct and indirect evidence exists are shown.

Table 9. Results of network meta-analysis for outcome thromboembolic events

Subnet 1			
Heterogeneity / inconsistency: Q = 31.54, df = 47, P = 0.96; I^2 = 0%, Tau^2 = 0			
No treatment	.	.	0.55 [0.41, 0.74]
0.74 [0.53, 1.04]	**Placebo**	.	0.74 [0.63, 0.86]
0.55 [0.29, 1.02]	0.74 [0.42, 1.30]	**ESA + IV iron**	1.00 [0.58, 1.73]
0.55 [0.41, 0.74]	0.74 [0.63, 0.86]	1.00 [0.58, 1.73]	**ESA + no iron**
Subnet 2			

Table 9. Results of network meta-analysis for outcome thromboembolic events *(Continued)*

Heterogeneity / inconsistency: Not applicable (subnet consists of only 2 studies)		
No ESA + iron, unclear application	.	0.68 [0.36, 1.28]
1.01 [0.31, 3.31]	**Placebo + iron, unclear application**	0.68 [0.25, 1.86]
0.68 [0.36, 1.28]	0.68 [0.25, 1.86]	**ESA + iron, unclear application**

Upper triangle: direct estimates; lower triangle: network estimates. Only subnets with >1 designs. Comparisons should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Effect estimates are presented as risk ratios (RR) with corresponding 95% confidence interval. For the network estimates in the lower triangle an RR below 1.0 favours the column-defining treatment and for the direct estimates in the upper triangle an RR below 1.0 favours the row-defining treatment (less presence of thromboembolic events). To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Treatments are ordered by P-Score (ascending).
Subnet 1: No. of studies: 50. No. of treatments: 4. No. of pairwise comparisons: 50. No. of designs: 3
Subnet 2: No. of studies: 2. No. of treatments: 3. No. of pairwise comparisons: 2. No. of designs: 2

Table 10. Results of network meta-analysis for outcome thrombocytopenia or haemorrhage

Subnet 1		
Heterogeneity / inconsistency: Q = 7.84, df = 11, P = 0.73, I^2 = 0%, Tau^2 = 0		
Placebo	.	0.84 [0.72, 0.99]
0.84 [0.55, 1.29]	**No treatment**	1.00 [0.67, 1.49]
0.84 [0.72, 0.99]	1.00 [0.67, 1.49]	**ESA + no iron**
Subnet 2		
Heterogeneity / inconsistency: Not applicable (subnetwork consists of only 2 studies)		
ESA + iron, unclear application	1.00 [0.40, 2.49]	0.69 [0.27, 1.76]
1.00 [0.40, 2.49]	**No ESA + iron, unclear application**	.
0.69 [0.27, 1.76]	0.69 [0.19, 2.57]	**Placebo + iron, unclear application**

Upper triangle: direct estimates; lower triangle: network estimates. Only subnets with >1 designs. Comparisons should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Effect estimates are presented as risk ratios (RR) with corresponding 95% confidence interval. For the network estimates in the lower triangle an RR below 1.0 favours the column-defining treatment and for the direct estimates in the upper triangle an RR below 1.0 favours the row-defining treatment (less presence of thrombocytopenia or haemorrhage). To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Treatments are ordered by P-Score (ascending).
Subnet 1: No. of studies: 13. No. of treatments: 3. No. of pairwise comparisons: 13. No. of designs: 2
Subnet 2: No. of studies: 2. No. of treatments: 3. No. of pairwise comparisons: 2. No. of designs: 2

Table 11. Results of network meta-analysis for outcome rash

Subnet 1		
Heterogeneity / inconsistency: Q = 9.88, df = 12, P = 0.63; I^2 = 0%, Tau^2 = 0		
No treatment	.	0.66 [0.28, 1.56]
0.80 [0.30, 2.13]	**Placebo**	0.83 [0.52, 1.32]
0.66 [0.28, 1.56]	0.83 [0.52, 1.32]	**ESA + no iron**

Upper triangle: direct estimates; lower triangle: network estimates. Only subnets with >1 designs. Comparisons should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Effect estimates are presented as risk ratios (RR) with corresponding 95% confidence interval. For the network estimates in the lower triangle an RR below 1.0 favours the column-defining treatment and for the direct estimates in the upper triangle an RR below 1.0 favours the row-defining treatment (less presence of rash. To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Treatments are ordered by P-Score (ascending).
Subnet 1: No. of studies: 14. No. of treatments: 3. No. of pairwise comparisons: 14. No. of designs: 2

Table 12. Results of network meta-analysis for outcome hypertension

Subnet 1		
Heterogeneity / inconsistency: Q = 17.54, df = 22, P = 0.73; I^2 = 0%, Tau^2 = 0		
No treatment	.	0.34 [0.14, 0.84]
0.35 [0.14, 0.89]	**Placebo**	0.96 [0.81, 1.15]
0.34 [0.14, 0.84]	0.96 [0.81, 1.15]	**ESA + no iron**

Upper triangle: direct estimates; lower triangle: network estimates. Only subnets with >1 designs. Comparisons should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Effect estimates are presented as risk ratios (RR) with corresponding 95% confidence interval. For the network estimates in the lower triangle an RR below 1.0 favours the column-defining treatment and for the direct estimates in the upper triangle an RR below 1.0 favours the row-defining treatment (less presence of hypertension). To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Treatments are ordered by P-Score (ascending).
Subnet 1: No. of studies: 24. No. of treatments: 3. No. of pairwise comparisons: 24 No. of designs: 2

APPENDICES

Appendix 1. CENTRAL search strategy

Cochrane Central Register of Controlled Trials (Central, 2021, Issue 06) in the Cochrane Library (searched 16 June 2021)

ID Search

#1 MeSH descriptor: [Hematinics] explode all trees

#2 MeSH descriptor: [Anemia] this term only

#3 (anaemi* or anemi*):ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Anemia, Iron-Deficiency] this term only

#6 MeSH descriptor: [Iron] explode all trees

#7 MeSH descriptor: [Iron Compounds] explode all trees

#8 iron*:ti,ab,kw

#9 (ferric or ferrous):ti,ab,kw

#10 (hemosider* or sideros* or transferrin*):ti,ab,kw

#11 #5 or #6 or #7 or #8 or #9 or #10

#12 MeSH descriptor: [Erythropoietin] explode all trees

#13 MeSH descriptor: [Erythropoiesis] explode all trees

#14 erythropoie*:ti,ab,kw

#15 (epo or epoetin or epoietin):ti,ab,kw

#16 (antianemia* or anti-anemia* or antianaemia* or anti-anaemia):ti,ab,kw

#17 (cera or micera* or hematide or hematinics or haematinics or eprex* or epogen* or rHuepo* or neorecormon* or nesp* or procrit* or recormon* or aranesp* or aranest* or darbepoetin* or darbepoietin* or darb or hexal or abseamed* or binocrit* or eporatio* or retacrit* or silapo* or r-HuEPO or HX575 or dynepo*):ti,ab,kw

#18 #12 or #13 or #14 or #15 or #16 or #17

#19 MeSH descriptor: [Neoplasms by Histologic Type] explode all trees

#20 MeSH descriptor: [Neoplasms by Site] explode all trees

#21 (neoplas* or tumor* or tumour* or krebs or cancer* or malignan* or carcino* or karzino* or sarcom* or leukaem* or leukem* or lymphom* or melano* or metastas* or mesothelio* or mesotelio* or gliom* or glioblastom* or osteo*sarcom* or blastom* or neuroblastom* or adenocarcinoma* or myeloma* or myelodysplas* or oncolog* or myelodysplas*):ti,ab,kw

#22 #19 or #20 or #21

#23 MeSH descriptor: [Antineoplastic Agents] explode all trees

#24 MeSH descriptor: [Remission Induction] explode all trees

#25 MeSH descriptor: [Antineoplastic Protocols] explode all trees

#26 ((consolidat* or induct* or maintenance or conditioning*) and (therap* or treat* or regimen* or patient*)):ti,ab,kw

#27 ((anticancer* or cancer*) NEAR/2 (therap* or treat*)):ti,ab,kw

#28 (remission* NEAR/2 therap*):ti,ab,kw

#29 (remission* NEAR/2 induction*):ti,ab,kw

#30 (chemotherap* or chemo-therap*):ti,ab,kw

#31 (antineoplast* or anti-neoplast*):ti,ab,kw

#32 ((cytosta* or cytotox*) NEAR/2 (therap* or treat* or regimen*)):ti,ab,kw

#33 #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32

#34 #4 and (#11 or #18) and (#22 or #33)

Appendix 2. MEDLINE search strategy

MEDLINE (Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to 16 June 2021 Search Strategy:

Searches

1 *ANEMIA/

2 (anaemi* or anemi*).tw,kf.

3 1 or 2

4 ANEMIA, IRON-DEFICIENCY/

5 exp IRON/

6 exp IRON COMPOUNDS/

7 iron*.tw,kf,nm.

8 (ferric or ferrous).tw,kf.

9 (hemosider* or sideros* or transferrin*).tw,kf.

10 or/4-9

11 exp ERYTHROPOIETIN/

12 ERYTHROPOIESIS/

13 erythropoie*.tw,kf.

14 (epo or epoetin or epoietin).tw,kf.

15 (antianemia* or anti-anemia* or antianaemia* or anti-anaemia).tw,kf.

16 (cera or micera* or hematide or hematinics or haematinics or eprex* or epogen* or rHuepo* or neorecormon* or nesp* or procrit* or recormon* or aranesp* or aranest* or darbepoetin* or darbepoietin* or darb or hexal or abseamed* or binocrit* or eporatio* or retacrit* or silapo* or r-HuEPO or HX575 or dynepo*).tw,kf.

17 or/11-16

18 exp NEOPLASMS BY HISTOLOGIC TYPE/

19 exp NEOPLASMS BY SITE/

20 neoplas*.tw,kf.

21 tumo?r*.tw,kf.

22 (krebs* or cancer*).tw,kf.

23 malignan*.tw,kf.

24 (carcino* or karzino*).tw,kf.

25 sarcom*.tw,kf.

26 leuk#?m*.tw,kf.

27 lymphom*.tw,kf.

28 melano*.tw,kf.

29 metastas*.tw,kf.

30 (mesothelio* or mesotelio*).tw,kf.

31 (gliom* or glioblastom*).tw,kf.

32 osteo?sarcom*.tw,kf,ot.

33 (blastom* or neuroblastom*).tw,kf.

34 adenocarcinoma*.tw,kf,ot.

35 myeloma*.tw,kf,ot.

36 myelodysplas*.tw,kf.

37 oncolog*.tw,kf.

38 myelodysplas*.tw,kf.

39 or/18-38

40 exp ANTINEOPLASTIC AGENTS/

41 REMISSION INDUCTION/

42 exp ANTINEOPLASTIC PROTOCOLS/

43 ((consolidat* or induct* or maintenance or conditioning*) and (therap* or treat* or regimen* or patient*)).tw,kf,ot.

44 ((anticancer* or cancer*) adj2 (therap* or treat*)).tw,kf,ot.

45 (remission* adj2 therap*).tw,kf,ot.

46 (remission* adj2 induction*).tw,kf,ot.

47 (chemotherap* or chemo-therap*).tw,kf,ot.

48 (Antineoplast* or anti-neoplast*).tw,kf,ot.

49 ((cytosta* or cytotox*) adj2 (therap* or treat* or regimen*)).tw,kf,ot.

50 dt.fs.

51 or/40-50

52 randomized controlled trial.pt.

53 controlled clinical trial.pt.

54 randomi?ed.ab.

55 placebo.ab.

56 drug therapy.fs.

57 randomly.ab.

58 trial.ab.

59 groups.ab.

60 or/52-59

61 exp ANIMALS/ not HUMANS/

62 60 not 61

63 CLINICAL TRIAL, PHASE III/

64 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.

65 (63 or 64) not 61

66 62 or 65

67 3 and (10 or 17) and (39 or 51) and 66

filter: *Cochrane Handbook 2019 RCT filter, sensitivity max version (*Lefebvre 2021*) (#52 - #62) and "Phase 3" filter (#63 - #65) (*Cooper 2019*)*

Appendix 3. Embase search strategy

Searches

1 *anemia/

2 (anaemi* or anemi*).ti,ab.

3 1 or 2

4 iron/ or iron deficiency anemia/ or (iron* or ferric*).ti,ab.

5 erythropoietin/

6 (epo or epoetin or epoietin or cera or micera* or hematide or hematinics or haematinics or eprex* or epogen* or rHuepo* or neorecormon* or nesp* or procrit* or recormon* or aranesp* or aranest* or darbepoetin* or darbepoietin* or darb or hexal or abseamed* or binocrit* or eporatio* or retacrit* or silapo* or r-HuEPO or HX575 or dynepo*).ti,ab.

7 (antianemia* or anti-anemia* or antianaemia* or anti-anaemia).ti,ab.

8 or/4-7

9 exp neoplasm/

10 exp neoplasms subdivided by anatomical site/

11 (neoplas* or tumor* or tumour* or cancer* or malignan* or carcino* or sarcom* or leuk#?m* or lymphom* or melamo* or metastas* or gliom* or glioblastom* or mesothelio* or osteosarcom* or osteosarcom* or adenocarcinoma* or myeloma* or myelodysplas* or oncolog*).ti,ab.

12 or/9-11

13 antineoplastic agent/

14 remission/

15 antineoplastic protocol/

16 ((consolidat* or induct* or maintenance or conditioning) adj7 (therap* or treat* or regimen* or patient*)).ti,ab.

17 ((anticancer* or cancer*) adj2 (therap* or treat*)).ti,ab.

18 (remission* adj2 (therap* or induction*)).ti,ab.

19 (chemotherap or chemo-therap* or antineoplast* or anti-neoplast*).ti,ab.

20 ((cytosta* or cytotox*) adj2 (therap* or treat* or regimen*)).ti,ab.

21 or/13-20

22 2 and 8 and (12 or 21)

23 Randomized controlled trial/

24 Controlled clinical study/

25 random*.ti,ab.

26 randomization/

27 intermethod comparison/

28 placebo.ti,ab.

29 (compare or compared or comparison).ti.

30 (open adj label).ti,ab.

31 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

32 double blind procedure/

33 parallel group$1.ti,ab.

34 (crossover or cross over).ti,ab.

35 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.

36 (controlled adj7 (study or design or trial)).ti,ab.

37 (volunteer or volunteers).ti,ab.

38 trial.ti.

39 or/23-38

40 phase 3 clinical trial/

41 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.

42 or/40-41

43 (animal experiment/ or Animal experiment/) not (human experiment/ or human/)

44 (39 or 42) not 43

45 3 and 8 and (12 or 21)

46 44 and 45

filter: *Cochrane Highly Sensitive Search Strategy for identifying controlled trials in Embase (2018 revision Ovid format) (#23 - #39) (*Glanville 2019*) and "Phase 3" filter (#40 - #42) (*Cooper 2019*)*

Appendix 4. ClinicalTrial.gov search strategy

Clinicaltrial.gov (https://www.clinicaltrials.gov/ct2/results/refine?show_xprt=Y)

expert search

(iron* OR ferric OR ferrous OR hemosider* OR sideros* OR transferrin* OR epo OR epoetin OR epoietin OR antianemia* OR "anti-anemia" OR antianaemia* OR "anti-anaemia" OR cera OR micera* OR hematide OR hematinics OR haematinics OR eprex* OR epogen* OR rHuepo* OR neorecormon* OR nesp* OR procrit* OR recormon* OR aranesp* OR aranest* OR darbepoetin* OR darbepoietin* OR darb OR hexal OR abseamed* OR binocrit* OR eporatio* OR retacrit* OR silapo* OR "r-HuEPO" OR HX575 OR dynepo*) AND (neoplas* OR tumor OR tumour OR cancer* OR malignan* OR carcino* OR sarcom* OR leukem* OR leukaem* OR lymphom* OR melano* OR metastas* OR mesothelio* OR mesotelio* OR gliom* OR glioblastom* OR osteosarcom* OR blastom* OR neuroblastom* OR adenocarcinoma* OR myeloma* OR myelodysplas* OR oncolog* OR myelodysplas* OR anticancer OR "anti-cancer" OR chemotherapy OR "chemo-therapy" OR antineoplast* OR "anti-neoplastic")

Appendix 5. WHO ICTRP search strategy

WHO ICTRP (https://trialsearch.who.int/AdvSearch.aspx)

Advanced search, recruitment status: ALL
In the intervention:
iron* OR ferric OR ferrous OR hemosider* OR sideros* OR transferrin* OR epo OR epoetin OR epoietin OR antianemia* OR "anti-anemia" OR antianaemia* OR "anti-anaemia" OR cera OR micera* OR hematide OR hematinics OR haematinics
In the condition:
neoplas* OR tumor OR tumour OR cancer* OR malignan* OR carcino* OR sarcom* OR leukem* OR leukaem* OR lymphom* OR melano* OR metastas* OR mesothelio* OR mesotelio* OR gliom* OR glioblastom* OR osteosarcom* OR blastom*

Advanced search, recruitment status: ALL
In the intervention:
iron* OR ferric OR ferrous OR hemosider* OR sideros* OR transferrin* OR epo OR epoetin OR epoietin OR antianemia* OR "anti-anemia" OR antianaemia* OR "anti-anaemia" OR cera OR micera* OR hematide OR hematinics OR haematinics
In the condition:
neuroblastom* OR adenocarcinoma* OR myeloma* OR myelodysplas* OR oncolog* OR myelodysplas* OR anticancer OR "anti-cancer" OR chemotherapy OR "chemo-therapy" OR antineoplast* OR "anti-neoplastic"

Advanced search, recruitment status: ALL
In the intervention:

eprex* OR epogen* OR rHuepo* OR neorecormon* OR nesp* OR procrit* OR recormon* OR aranesp* OR aranest* OR darbepoetin* OR darbepoietin* OR darb OR hexal OR abseamed* OR binocrit* OR eporatio* OR retacrit* OR silapo* OR "r-HuEPO" OR HX575 OR dynepo*
In the condition:
neoplas* OR tumor OR tumour OR cancer* OR malignan* OR carcino* OR sarcom* OR leukem* OR leukaem* OR lymphom* OR melano* OR metastas* OR mesothelio* OR mesotelio* OR gliom* OR glioblastom* OR osteosarcom* OR blastom*

Advanced search, recruitment status: ALL
In the intervention:
eprex* OR epogen* OR rHuepo* OR neorecormon* OR nesp* OR procrit* OR recormon* OR aranesp* OR aranest* OR darbepoetin* OR darbepoietin* OR darb OR hexal OR abseamed* OR binocrit* OR eporatio* OR retacrit* OR silapo* OR "r-HuEPO" OR HX575 OR dynepo*
In the condition:
neuroblastom* OR adenocarcinoma* OR myeloma* OR myelodysplas* OR oncolog* OR myelodysplas* OR anticancer OR "anti-cancer" OR chemotherapy OR "chemo-therapy" OR antineoplast* OR "anti-neoplastic"

Appendix 6. Study characteristics per pairwise comparison

Pairwise comparison: ESA + no iron versus no treatment

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Aapro 2008	463	2008	solid tumour	chemotherapy	epoetin	F	57.5	56.0	11.2	11.5
Attaollah Hirad-far 2018	60	2018	solid tumour	chemotherapy	epoetin	M+F	6.1	6.4	8.9	9.0
Boogaerts 2003	262	2003	mixed	chemotherapy	epoetin	M+F	62.0	62.0	9.0	9.2
Cazzola 1995	146	1995	haematological malignancy	chemotherapy	epoetin	M+F	68.0	67.0	9.5	9.3
Chang 2005	354	2005	solid tumour	chemotherapy	epoetin	F	50.4	50.1	11.2	-
Charu 2007	287	2007	mixed	no therapy	darbepoetin	F	71.7	67.2	10.1	10.3
Del Mastro 1997	62	1997	solid tumour	chemotherapy	epoetin	F	-	-	13.1	13.0
Goede 2016	62	2016	haematological malignancy	chemotherapy	darbepoetin	M	75.0	73.0	-	-
Machtay 2007	148	2007	solid tumour	radio/ radiochemother-apy	epoetin	M+F	64.0	61.0	12.0	12.1
Milroy 2011	424	2011	solid tumour	chemotherapy	epoetin	M+F	61.6	60.1	12.8[a]	12.6[a]
Oberhoff 1998	227	1998	solid tumour	chemotherapy	epoetin	M+F	53.0[a]	53.0[a]	10.3[a]	9.6[a]
Osterborg 1996	144	1996	haematological malignancy	chemotherapy	epoetin	M+F	65.0[a]	66.0[a]	-	-
Overgaard 2009	515	2009	solid tumour	radio/ radiochemother-apy	darbepoetin	M+F	59.0[a]	59.0[a]	13.2[a]	13.0[a]
Pronzato 2010	223	2010	solid tumour	chemotherapy	epoetin	F	53.3	54.3	10.6	10.8
Ray-Coquard 2009	218	2009	mixed	chemotherapy	epoetin	M+F	62.7	61.7	10.0	10.0

(Continued)

Rosenzweig 2004	27	2004	mixed	unclear/other	epoetin	F	55.9	53.9	-	-
Strauss 2008	74	2008	solid tumour	radio/ radiochemotherapy	epoetin	-	48.8	49.2	11.4[a]	11.6[a]
Thatcher 1999	130	1999	solid tumour	chemotherapy	epoetin	M+F	58.8[a]	60.0[a]	13.7	13.4
Thepot 2016	98	2016	haematological malignancy	chemotherapy	epoetin	M+F	73.3[a]	71.6[a]	-	-
Thomas 2002	130	2002	solid tumour	chemotherapy	epoetin	-	-	-	-	-
Thomas 2008	109	2008	solid tumour	radio/ radiochemotherapy	epoetin	-	50.0[a]	46.0[a]	-	-
Throuvalas 2000	55	2000	solid tumour	radio/ radiochemotherapy	epoetin	-	-	-	-	-
Toma 2013	132	2013	MDS	chemotherapy	epoetin	M+F	73.5[a]	73.0[a]	-	-
Welch 1995	30	1995	solid tumour	chemotherapy	epoetin	F	-	-	-	-
Wilkinson 2006	182	2006	solid tumour	chemotherapy	epoetin	F	59.1	60.3	10.8	10.7

[a] median was reported instead

ESA: erythropoiesis-stimulating agents; **F:** female; **M:** male; **Hb:** haemoglobin (g/dL); **MDS:** myelodysplastic syndrome

Pairwise comparison: ESA + no iron versus placebo

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Abels 1993	124	1993	mixed	No therapy	epoetin	M+F	61.2	62.5	-	-
Cascinu 1994	100	1994	solid tumour	chemotherapy	epoetin	M+F	58.0[a]	57.0[a]	86.3	87.3
Case 1993	157	1993	mixed	chemotherapy	epoetin	M+F	64.0	64.0	-	-
Dammacco 2001	145	2001	haematological malignancy	chemotherapy	epoetin	M+F	67.3	65.0	9.3	9.6
Engert 2010	1283	2010	haematological malignancy	chemotherapy	epoetin	M+F	34.0	34.0	-	-
EPO-INT-3 J&J 2004	201	2004	mixed	chemotherapy	epoetin	M+F	-	-	-	-
Fujisaka 2011	181	2011	solid tumour	chemotherapy	epoetin	M+F	67.0	63.5	9.4	9.3
Gascon 2019	2549	2017	solid tumour	chemotherapy	darbepoetin	M+F	62.0[a]	63.0[a]	10.2[a]	10.1[a]
Gordon 2008	220	2006	mixed	No therapy	darbepoetin	F	70.0	70.0	10.1	10.2
Goss 2005	104	2005	solid tumour	radio/ radiochemotherapy	epoetin	-	-	-	-	-
Grote 2005	224	2005	solid tumour	chemotherapy	epoetin	M+F	64.4	63.2	12.8	13
Hedenus 2003	349	2003	haematological malignancy	chemotherapy	darbepoetin	M+F	64.8	64.6	9.6	9.5
Henke 2003	351	2003	solid tumour	radio/ radiochemotherapy	epoetin	M+F	57.0	58.0	11.8	11.7
Henry 1995	132	1995	mixed	chemotherapy	epoetin	-	-	-	-	-

(Continued)

Hernandez 2009	391	2009	mixed	chemotherapy	darbepoetin	M+F	63.6	64.5	10.0	10.1
Italian 1998	85	1998	MDS	No therapy	epoetin	M+F	65.0	65.0	8.4	10.1
Kotasek 2002	161	2002	mixed	chemotherapy	darbepoetin	F	-	-	-	-
Kotasek 2003	259	2003	solid tumour	chemotherapy	darbepoetin	F	56.2	58.3	9.7	9.3
Kurz 1997	35	1997	solid tumour	chemotherapy	epoetin	-	52.7	54.4	9.9	9.9
Leyland-Jones 2005	939	2005	solid tumour	chemotherapy	epoetin	F	55.8	55.1	12.5	12.5
Littlewood 2001	375	2001	mixed	chemotherapy	epoetin	M+F	58.3	59.5	9.9	9.7
O'Shaughnessy 2005	100	2005	solid tumour	chemotherapy	epoetin	F	53.3	54.3	12.8	13.0
Osterborg 2002	343	2002	haematological malignancy	chemotherapy	epoetin	M+F	63.0[a]	64.0[a]	9.2	9.3
Pirker 2008	600	2008	solid tumour	chemotherapy	darbepoetin	M+F	60.6	61.3	12.0	11.9
Quirt 1996	56	1996	mixed	chemotherapy	epoetin	-	-	-	-	-
Razzouk 2006	222	2006	mixed	chemotherapy	epoetin	M+F	12.4	10.8	9.8	9.5
Rose 1994	221	1994	haematological malignancy	Unclear/Other	epoetin	-	-	-	-	-
Smith 2003	86	2003	mixed	No therapy	darbepoetin	F	66.7	68,0	9.8	10.0
Smith 2008	989	2008	mixed	No therapy	darbepoetin	M	64.3	64,0	9.5	9.5
Ten Bokkel 1998	120	1998	solid tumour	chemotherapy	epoetin	F	59.9	58.8	11.8	11.8
Tjulandin 2010	223	2010	solid tumour	chemotherapy	epoetin	M+F	53.7	57.3	9.6	9.5

(Continued)

Tjulandin 2011	186	2011	mixed	chemotherapy	epoetin	M+F	55.8	56.9	9.1	9.2
Tsuboi 2009	122	2009	mixed	chemotherapy	epoetin	M+F	62.1	61.8	10.4	10.0
Vansteenkiste 2002	320	2002	solid tumour	chemotherapy	darbepoetin	M	47.6	48.0	-	-
Winquist 2009	56	2009	solid tumour	Unclear/Other	epoetin	M	71.0[a]	71.0[a]	10.4[a]	10.4[a]
Wright 2007	70	2007	solid tumour	No therapy	epoetin	M	70.0[a]	68.0[a]	10.3	10.3

[a] median was reported instead

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **M:** male; **MDS:** myelodysplastic syndrome

Pairwise comparison: ESA + IV iron versus ESA + no iron versus ESA + oral iron

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean age N3	Mean base Hb N1	Mean base Hb N2	Mean base Hb N3
Auerbach 2004	157	2004	mixed	chemotherapy	epoetin	M+F	53.0	46.0	42.0	9.5	9.7	9.7
Henry 2007	187	2007	-	chemotherapy	epoetin	M+F	63.0	65.4	67.4	10.1	10.3	10.5

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **IV:** intravenous; **M:** male; **Hb:** haemoglobin (g/dL); **MDS:** myelodysplastic syndrome

Pairwise comparison: ESA + IV iron versus ESA + oral iron

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Maccio 2010	148	2010	solid tumour	chemotherapy	epoetin	M+F	67.3	68.8	9.7	9.8
Hajigholami 2021	89	2021	solid tumour	chemotherapy	epoetin	M+F	50.9	41.8	10.1	10.4

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **IV:** intravenous; **M:** male

Pairwise comparison: ESA + IV iron versus ESA + no iron

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Auerbach 2010	238	2010	solid tumour	unclear/other	epoetin	-	61.7	64.5	-	-
Bastit 2008	396	2008	mixed	chemotherapy	darbepoetin	M+F	61.7	60.3	-	-
Hedenus 2007	67	2007	haematological malignancy	no therapy	epoetin	M+F	74.0	77.0	10.3	10.3
Pedrazzoli 2008	149	2008	solid tumour	chemotherapy	darbepoetin	M+F	-	-	9.9	9.9

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **IV:** intravenous; **M:** male

Pairwise comparison: ESA + IV iron versus no ESA + IV iron

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Henke 1999	72	1999	solid tumour	radio/ radiochemotherapy	epoetin	M+F	-	-	12.3	10.9

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **IV:** intravenous; **M:** male

Pairwise comparison: ESA + IV iron versus ESA + placebo versus ESA + oral iron

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean age N3	Mean base Hb N1	Mean base Hb N2	Mean base Hb N3
Steensma 2011	490	2011	mixed	chemotherapy	darbepoetin	F	64.0	63.0	63.0	9.9	9.91	10.0

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **IV:** intravenous

Pairwise comparison: ESA + oral iron versus no treatment

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Sweeney 1998	48	1998	solid tumour	radio/ radiochemotherapy	epoetin	M+F	62.7	62.3	10.7	12.1

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **M:** male

Pairwise comparison: ESA + oral iron versus no ESA + oral iron

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Blohmer 2011	256	2011	solid tumour	radio/ radiochemotherapy	epoetin	F	41.0	42.0	-	-
Christodoulou 2009	337	2009	solid tumour	chemotherapy	epoetin	M+F	61.0	63.0	10.2	10.3
Debus 2006	385	2006	solid tumour	radio/ radiochemotherapy	epoetin	M+F	61.8	63.5	13.5	13.5
Debus 2014	385	2014	solid tumour	radio/ radiochemotherapy	epoetin	M+F	63.5	61.8	-	-
Dunphy 1999	30	1999	solid tumour	chemotherapy	epoetin	M+F	59.0	67.0	14.1	14.1
Hoskin 2009	300	2009	solid tumour	radio/ radiochemotherapy	epoetin	M+F	58.0	60.0	13.7	13.4
Iconomou 2003	112	2003	solid tumour	chemotherapy	epoetin	M+F	60.6	62.6	10.1	10.1
Moebus 2013	643	2013	solid tumour	chemotherapy	epoetin	F	52.0[a]	50.0[a]	12.8[a]	12.4[a]
Nitz 2014	1234	2014	solid tumour	chemotherapy	darbepoetin	-	-	-	-	-

[a] median was reported instead

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **M:** male

Pairwise comparison: ESA + oral iron versus placebo + oral iron

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Mystakidou 2005	100	2005	solid tumour	no therapy	epoetin	M+F	64.5[a]	63.0[a]	9.9	10.2

[a] median was reported instead

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **M:** male

Pairwise comparison: no ESA + IV iron versus no ESA + oral iron

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Ansari 2016	70	2016	solid tumour	chemotherapy	no ESA	M+F	56.9	58.5	10.4	9.6
Athibovonsuk 2013	64	2013	solid tumour	chemotherapy	no ESA	F	49.7	52.1	11.3	11.4
Birgegard 2015	350	2015	mixed	chemotherapy	no ESA	M+F	55.0	54.0	9.9	10.0
Noronha 2016	192	2016	>95% solid tumours	chemotherapy	no ESA	M+F	55.5[a]	50.0[a]	10.2[a]	10.1[a]

[a] median was reported instead

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **IV:** intravenous; **M:** male

Pairwise comparison: no ESA + IV iron versus no treatment

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Ng 2018	27	2018	solid tumour	chemotherapy	no ESA	M+F	69.0[a]	68.0[a]	9.7	11.5
Hedenus 2014	19	2014	haematological malignancy	chemotherapy	no ESA	M+F	69.5[a]	71.0[a]	9.5[a]	9.8[a]

[a] median was reported instead

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **IV:** intravenous; **M:** male

Pairwise comparison: no ESA + IV iron versus placebo

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Gilreath 2019	244	2019	mixed	chemotherapy	no ESA	-	-	-	-	-

ESA: erythropoiesis-stimulating agents;**Hb:** haemoglobin (g/dL); **IV:** intravenous

Pairwise comparison: ESA + iron, unclear application versus no ESA + iron, unclear application

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Aravantinos 2003	47	2003	solid tumour	chemotherapy	epoetin	-	-	-	-	-
Gupta 2009	115	2009	solid tumour	radio/ radiochemotherapy	epoetin	-	48.2	48.3	10.7	10.5
Huddart 2002	95	2002	solid tumour	chemotherapy	epoetin	-	-	-	-	-
Untch 2011_1	733	2011	solid tumour	chemotherapy	darbepoetin	F	-	-	-	-
Zhao 2018	80	2018	solid tumour	chemotherapy	epoetin	M	64.5	63.6	9.2	9.1

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **M:** male

Pairwise comparison: ESA + iron, unclear application versus placebo + iron, unclear application

Study	N	Year	Cancer type	Therapy	Type of ESA	Sex	Mean age N1	Mean age N2	Mean base Hb N1	Mean base Hb N2
Krzakowski 2008	313	2008	mixed	chemotherapy	epoetin	M+F	-	-	9.4	9.1
Witzig 2005	344	2005	solid tumour	chemotherapy	epoetin	M+F	63.6	63.7	9.5	9.4

ESA: erythropoiesis-stimulating agents; **F:** female; **Hb:** haemoglobin (g/dL); **M:** male

HISTORY

Protocol first published: Issue 4, 2017

CONTRIBUTIONS OF AUTHORS

Anne Adams: review development, screening, data extraction, risk of bias assessment, grading, statistical evaluation, interpretation of results, writing of the review

Benjamin Scheckel: review development, screening, data extraction, writing of the review

Anissa Habsaoui: review development, risk of bias assessment, writing of the review

Madhuri Haque: review development, risk of bias assessment, data extraction

Kathrin Kuhr: statistical evaluation

Ina Monsef: search strategy development

Julia Bohlius: methodological expertise

Nicole Skoetz: review development, methodological expertise, screening, data extraction, risk of bias assessment, grading, interpretation of results

DECLARATIONS OF INTEREST

Anne Adams: none known; she is a statistical editor with Cochrane Haematology, but was not involved in the editorial process for this review.

Benjamin Scheckel: none known.

Anissa Habsaoui: none known.

Madhuri Haque: none known.

Kathrin Kuhr: none known.

Ina Monsef: none known.

Julia Bohlius: none known; she is an editor with Cochrane Haematology, but was not involved in the editorial process for this review.

Nicole Skoetz: none known; she is an editor with Cochrane Haematology, but was not involved in the editorial process for this review.

SOURCES OF SUPPORT

Internal sources

- University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Germany

  Provision of the offices, including technical equipment
- Institute of Medical Statistics and Computational Biology, Germany

  Support with statistical expertise

External sources

- Federal Ministry of Education and Research, Germany

  Funding number 01KG1405

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of interventions

Since the indication and application form of iron often in the included studies remained unclear we had to add treatment comparisons to the intended network (compare bullet list in methods section and results).

To minimise the uncertainty in the network, we decided to exclude the treatment *iron unclear* because it is not known whether the patient has received iron or not.

Additionally, we decided to combine the treatments *no iron* and *iron if necessary*. According to the study protocols, both patient populations did not receive any iron at the start of the study. Therefore we consider both groups similar. However, in both populations (also in the "no iron" population), participants may have received iron if the attending physician deemed iron necessary. As the attending physician's decision could be different in different situations, participants may or may not have received iron (no clear criteria in studies indicated when iron was considered “necessary”).

Types of outcome measures

As the outcome overall survival was rarely reported in studies, we could not analyse this pre-planned time-to-event outcome. Instead, most studies reported numbers of people being dead (binary outcome, overall mortality). As survival/mortality outcomes are of utmost importance for participants, we analysed the binary outcome overall mortality, integrating also results form studies which reported overall survival.

We also decided to add the outcome number of patients with red blood cell transfusions, as this outcome is highly relevant for patients (more visits in specialised care centres for blood transfusion).

Missing outcome data

We did not contact study authors, because data were already available based on the IPD meta-analysis (Bohlius 2009).

Data synthesis

Since the focus of this review is on the network meta-analyses, and direct estimates are also reported in the league tables, we refrained from reporting forest plots of pairwise comparisons.

Subgroup analyses

We did not analyse subgroups for different routes of iron administration (IV, oral) since these were included as different treatment options in our network meta-analysis for each outcome.

Additionally, we did not conduct subgroup analyses for type of iron and duration of follow-up because these were less reported.

Furthermore, most of the studies included participants with solid or mixed tumours, so no subgroup analyses were performed for cancer type.

NOTES

Some passages in the protocol and review, especially in the methods part, are from the standard template of Cochrane Haematology.