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The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer treatment-induced anaemia (including review of technology appraisal no. 142): a systematic review and economic model

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Louise Crathorne,[1]* Nicola Huxley,[1] Marcela Haasova,[1] Tristan Snowsill,[1] Tracey Jones-Hughes,[1] Martin Hoyle,[1] Simon Briscoe,[1] Helen Coelho,[1] Linda Long,[1] Antonieta Medina-Lara,[2] Ruben Mujica-Mota,[1] Mark Napier[3] and Chris Hyde[1]

[1]Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter, UK
[2]University of Exeter Medical School, Exeter, UK
[3]Royal Devon and Exeter Hospital, Exeter, UK

*Corresponding author

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Abstract

The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer treatment-induced anaemia (including review of technology appraisal no. 142): a systematic review and economic model

Louise Crathorne,[1]* Nicola Huxley,[1] Marcela Haasova,[1] Tristan Snowsill,[1] Tracey Jones-Hughes,[1] Martin Hoyle,[1] Simon Briscoe,[1] Helen Coelho,[1] Linda Long,[1] Antonieta Medina-Lara,[2] Ruben Mujica-Mota,[1] Mark Napier[3] and Chris Hyde[1]

[1]Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter, UK
[2]University of Exeter Medical School, Exeter, UK
[3]Royal Devon and Exeter Hospital, Exeter, UK

*Corresponding author L.Crathorne@exeter.ac.uk

Background: Anaemia is a common side effect of cancer treatments and can lead to a reduction in quality of life. Erythropoiesis-stimulating agents (ESAs) are licensed for use in conjunction with red blood cell transfusions to improve cancer treatment-induced anaemia (CIA).

Objective: To investigate the effectiveness and cost-effectiveness of ESAs in anaemia associated with cancer treatment (specifically chemotherapy).

Data sources: The following databases were searched from 2004 to 2013: The Cochrane Library, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Web of Science, Cumulative Index to Nursing and Allied Health Literature, British Nursing Index, Health Management Information Consortium, Current Controlled Trials and ClinicalTrials.gov. The US Food and Drug Administration and European Medicines Agency websites were also searched. Bibliographies of included papers were scrutinised for further potentially includable studies.

Review methods: The clinical effectiveness review followed principles published by the NHS Centre for Reviews and Dissemination. Randomised controlled trials (RCTs), or systematic reviews of RCTs, of ESAs (epoetin or darbepoetin) for treating people with CIA were eligible for inclusion in the review. Comparators were best supportive care, placebo or other ESAs. Anaemia- and malignancy-related outcomes, health-related quality of life (HRQoL) and adverse events (AEs) were evaluated. When appropriate, data were pooled using meta-analysis. An empirical health economic model was developed comparing ESA treatment with no ESA treatment. The model comprised two components: one evaluating short-term costs and quality-adjusted life-years (QALYs) (while patients are anaemic) and one evaluating long-term QALYs. Costs and benefits were discounted at 3.5% per annum. Probabilistic and univariate deterministic sensitivity analyses were performed.

Results: Of 1457 titles and abstracts screened, 23 studies assessing ESAs within their licensed indication (based on start dose administered) were included in the review. None of the RCTs were completely aligned with current European Union licenses. The results suggest a clinical benefit from ESAs for anaemia-related outcomes and an improvement in HRQoL scores. The impact of ESAs on AEs and survival remains highly uncertain, although point estimates are lower, confidence intervals are wide and not statistically significant. Base-case incremental cost-effectiveness ratios (ICERs) for ESA treatment compared with no ESA treatment ranged from £19,429 to £35,018 per QALY gained, but sensitivity and scenario analyses demonstrate considerable uncertainty in these ICERs, including the possibility of overall health disbenefit. All ICERs were sensitive to survival and cost.

Limitations: The relative effectiveness of ESAs was not addressed; all ESAs were assumed to have equivalent efficacy. No studies were completely aligned with their European labelling beyond the starting dose evaluated. There is questionable generalisability given that the included trials were published > 20 years ago and there have been many changes to chemotherapy as well as to the quality of supportive treatment. Trial quality was moderate or poor and there was considerable unexplained heterogeneity for a number of outcomes, particularly survival, and evidence of publication bias. Adjustments were not made to account for multiple testing.

Conclusions: ESAs could be cost-effective when used closer to licence, but there is considerable uncertainty, mainly because of unknown impacts on overall survival.

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List of abbreviations

AE	adverse event
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CENTRAL	Cochrane Central Register of Controlled Trials
cHR	combined hazard ratio
CI	confidence interval
CIA	cancer treatment-induced anaemia
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CKD	chronic kidney disease
CrI	credible interval
DARE	Database of Abstracts of Reviews of Effects
df	degrees of freedom
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
EQ-5D	European Quality of Life-5 Dimensions
ESA	erythropoiesis-stimulating agent
FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
FACT-An	Functional Assessment of Cancer Therapy – Anaemia
FACT-An-An	Functional Assessment of Cancer Therapy – Anaemia Anaemia subscale
FACT-F	Functional Assessment of Cancer Therapy – Fatigue
FACT-G	Functional Assessment of Cancer Therapy – General
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hb	haemoglobin
HMIC	Health Management Information Consortium
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
INHB	incremental net health benefit
IPD	individual patient data
ITT	intention to treat
LASA	Linear Analogue Scale Assessment
MeSH	medical subject heading
MTA	multiple technology appraisal
NA	not applicable
NHP	Nottingham Health Profile
NHSBT	NHS Blood and Transplant
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
OR	odds ratio
OS	overall survival

PDI	Psychological Distress Inventory
PenTAG	Peninsula Technology Assessment Group
PFS	progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RBC	red blood cell
RBCT	red blood cell transfusion
RCT	randomised controlled trial
rHuEPO	recombinant human erythropoietin
RR	risk ratio
SD	standard deviation
SE	standard error
SF-36	Short Form questionnaire-36 items
SF-6D	Short Form questionnaire-6 Dimensions
SPC	Summary of Product Characteristics
TA	technology appraisal
VAS	visual analogue scale
WHO	World Health Organization
WMD	weighted mean difference

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence data removed and replaced by the statement 'commercial-in-confidence information removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Anaemia is a common side effect of cancer treatments and can lead to a reduction in quality of life. Erythropoiesis-stimulating agents (ESAs) are licensed for use in conjunction with red blood cell transfusions to improve cancer treatment-induced anaemia. To assess the effectiveness and cost-effectiveness of ESAs for the treatment of anaemia in cancer patients, a systematic review of clinical effectiveness and an economic evaluation were conducted. Twenty-three ESA studies with starting doses according to European labelling regulations were included in the review. Data suggest that there is clinical benefit from ESAs for anaemia-related outcomes and an improvement in health-related quality-of-life scores. The impact of ESAs on adverse events and survival remains highly uncertain. Base-case incremental cost-effectiveness ratios (ICERs) for ESA treatment compared with no ESA treatment ranged from £19,429 to £35,018 per quality-adjusted life-year gained, but sensitivity and scenario analyses demonstrate considerable uncertainty in these ICERs, including the possibility of overall health disadvantages. All ICERs were sensitive to survival and cost. ESAs could be cost-effective when used closer to licence, but there is considerable uncertainty, mainly because of unknown impacts on survival.

Scientific summary

Background

Anaemia is defined as a deficiency in red blood cells (RBCs). It is the most frequent haematological manifestation in patients with cancer: > 50% of all cancer patients will be anaemic regardless of the treatment received and approximately 20% of all patients undergoing chemotherapy will require a red blood cell transfusion (RBCT). There are a number of potential causal factors, which can be patient, disease or treatment related.

Anaemia is associated with many symptoms. These include dizziness, shortness of breath on exertion, palpitations, headache and depression. All affect health-related quality of life (HRQoL). Severe fatigue is probably the most commonly reported symptom and can lead to an inability to perform everyday tasks. However, fatigue in people with cancer can also have other causes, such as the disease itself, chemotherapy, radiotherapy, anxiety or depression.

Many people are anaemic when cancer is diagnosed, before any cancer treatment starts. The degree of anaemia caused by treatments such as chemotherapy often fluctuates depending on the nature of the treatment and the number of courses administered, but is typically at its worst 2–4 weeks after chemotherapy is given. Once cancer treatments are stopped, a period of 'normalisation' is likely, during which the haemoglobin (Hb) may return to pretreatment levels.

Options available for the management of cancer treatment-induced anaemia (CIA) include adjustments to the cancer treatment regimen, iron supplementation and RBCT. The majority of people who become anaemic do not receive any treatment for their anaemia, but those who become moderately or severely anaemic are usually given RBCTs. Complications related to RBCT include procedural problems, iron overload, viral and bacterial infections and immune complications. However, a small proportion of people are unable to receive RBCT (Jehovah's Witnesses and people with multiple antibodies to RBCs, as they have required regular RBCTs in the past).

Treatment landscape, 10 years on

Erythropoietin is a glycoprotein hormone that is produced mainly in the kidney and is responsible for regulating RBC production. Erythropoietin for clinical use is produced by recombinant DNA technology. Erythropoiesis-stimulating agents (ESAs) are used as an addition to, rather than as a replacement for, existing approaches to the management of anaemia induced by cancer treatment. RBCTs, in particular, may still be needed in people treated with ESAs.

Based on the previous assessment [Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al.* A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007;**11**(13)], National Institute for Health and Care Excellence (NICE) guidance [technology appraisal (TA)142] (NICE. *Epoetin Alfa, Epoetin Beta and Darbepoetin Alfa for Cancer Treatment-Induced Anaemia*. NICE technology appraisal guidance TA142. London: NICE; 2008) recommended the use of ESAs in combination with intravenous iron for the treatment of CIA in women with ovarian cancer receiving platinum-based chemotherapy with symptomatic anaemia (Hb ≤ 8 g/dl). The recommendation made in TA142 did not prohibit the use of other management strategies for the treatment of CIA, for example blood transfusion (NICE, 2008). In addition, guidance set out in TA142 recommended ESAs in combination with intravenous

iron for people with profound CIA who cannot be given blood transfusions (NICE, 2008). The ESA with the lowest acquisition cost should be used (NICE, 2008).

Although evidence at the time documented a clear improvement in haematological response and a reduction in the need for RBCTs associated with the use of ESAs, there was considerable uncertainty surrounding safety (in particular the frequency of thromboembolic events) and the impact on survival, giving rise to ongoing debate about the effectiveness and safety of ESAs in this area. Ten years on from the previous appraisal (2004), licences have been amended to reflect these concerns.

Initially, all ESAs were recommended for use at Hb levels of ≤ 11 g/dl, with target Hb levels not exceeding 13 g/dl. A safety review by the Pharmacovigilance Working Party at the request of the Committee for Medicinal Products for Human Use in 2008 resulted in changes to the Summary of Product Characteristics for all ESAs at the European Medicines Agency's (EMA) request. These changes came into effect in 2008 – after the previous guidance was issued – and included a decrease in the Hb value for treatment initiation to ≤ 10 g/dl; amendment of the Hb target values to 10–12 g/dl; and amendment of Hb levels for stopping treatment to > 13 g/dl. In addition, the EMA added the following criteria to the label: in patients not treated with chemotherapy, there is no indication for the use of ESAs and there might be an increased risk of death when ESAs are administered to a target of 12–14 g/dl; in people treated with curative intent, ESAs should be used with caution.

Current evidence

Previous guidance (TA142) was based on evidence presented by Wilson and colleagues (2007) as part of the Health Technology Assessment (HTA) process. This review had a wider focus than the present HTA in that it considered the use of ESAs with regard to their effectiveness in treating cancer-related anaemia, irrespective of whether it was caused by cancer treatment.

Scoping searches identified two relevant recent Cochrane reviews (Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, *et al.* Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2012;**12**:CD003407; 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 Syst Rev* 2009;**3**:CD007303). As in the study by Wilson and colleagues (2007), the focus of these reviews was the use of ESAs with regard to their effectiveness in treating cancer-related anaemia, irrespective of whether it was caused by cancer treatment.

Current evidence suggests that ESAs reduce the need for RBCT but increase the risk of thromboembolic events and deaths. There is suggestive evidence that ESAs may improve quality of life. Whether and how ESAs affect tumour control remains uncertain.

Objective

The following question was addressed by this report: 'What is the effectiveness and cost-effectiveness of ESAs in anaemia associated with cancer treatment (specifically chemotherapy)?'

The review was based on a predefined scope issued by NICE and was conducted in accordance with a predefined protocol. Given the publication of the 2012 Cochrane review (Tonia and colleagues 2012) and the fact that no studies were completely aligned with current UK authorisation, studies were considered eligible for inclusion in accordance with UK marketing authorisations if they used a licensed starting dose, irrespective of how they dealt with other criteria stipulated by the licence.

The ESAs considered were epoetin alfa (Eprex®, Janssen-Cilag Ltd and Binocrit®, Sandoz Ltd); epoetin beta (NeoRecormon®, Roche Products Ltd); epoetin theta (Eporatio®, Teva Pharmaceuticals Ltd); epoetin zeta (Retacrit®, Hospira UK Ltd) and darbepoetin alfa (Aranesp®, Amgen Inc.). All interventions were considered only according to their UK marketing authorisation. The key assumption maintained throughout this report is that all ESAs are equally effective.

Methods

Clinical effectiveness

The search strategy is based on the strategy used in the previous HTA review on this topic (Wilson and colleagues 2007). The databases searched included The Cochrane Library, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), British Nursing Index, Health Management Information Consortium, Current Controlled Trials and ClinicalTrials.gov. The US Food and Drug Administration and EMA websites were also searched. As this is an update of a previous review, databases were searched from 2004 to 2013. Search filters were applied to retrieve randomised controlled trials (RCTs) and quality-of-life studies. Bibliographies of included papers were scrutinised for further potentially includable studies. The reference lists of the industry submissions were also scrutinised for additional studies. Because of resource limitations, the search was restricted to English-language papers only. All references were managed using EndNote X5 (Thomson Reuters, CA, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) software.

Titles and abstracts returned by the search strategy were examined independently by four researchers and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained and examined independently for inclusion or exclusion and disagreements were again resolved by discussion. Included studies from the previous HTA review (Wilson and colleagues 2007) were also screened for inclusion by two researchers. Eligibility criteria were as follows:

- population: people with CIA
- intervention: ESAs (epoetin alfa, beta, theta and zeta and darbepoetin alfa) with starting doses according to European labelling
- comparator: best supportive care, defined as adjusting cancer treatment, RBCT and iron supplementation
- outcomes: Hb increase, RBCT requirement, overall survival (OS), adverse events (AEs) (thromboembolic events, hypertension, pruritus and seizures) and HRQoL
- study design: RCTs.

Data were extracted by one reviewer and checked by another. Disagreements were resolved by discussion.

The results of individual trials were pooled using meta-analysis when possible and justified. A random-effects model was assumed for all meta-analyses. When data were not reported in the published papers they were extracted from the 2012 Cochrane review (Tonia and colleagues 2012). This was justified on the basis that the Cochrane review authors had had access to additional unpublished materials when conducting their review. When meta-analysis was not possible narrative synthesis, supported by information collected in the data extraction tables, was used to summarise the evidence base.

Subgroup analyses were conducted: mean Hb level at baseline (< 10 g/dl, < 11 g/dl, < 12 g/dl, < 14.5 g/dl, not reported); Hb inclusion criteria (≤ 11 g/dl and > 11 g/dl); malignancy type (solid, haematological, mixed, not reported); ovarian cancer; chemotherapy type (platinum, non-platinum, chemotherapy plus radiotherapy, mixed chemotherapy, not reported); ESA type (short lasting, long lasting); iron supplementation (given, not given, given differently in treatment arm, not reported); duration of ESA medication (6–9 weeks, 12–16 weeks, 17–20 weeks, > 20 weeks); and study design [blinded (RCT), unblinded (randomised open label)]. In addition,

we also conducted post-hoc analyses considering inclusion Hb level closer to licence (≤ 11 g/dl and > 11 g/dl) and target Hb level closer to licence (≤ 13 g/dl and > 13 g/dl).

Cost-effectiveness review of past economic evaluations

The previous NICE appraisal (TA142) by Wilson and colleagues (2007) included a systematic review of published evidence of the cost-effectiveness of ESAs for CIA. Several databases (including MEDLINE and EMBASE) were searched, resulting in 491 records being identified. After screening by title and abstract, 44 full-text articles were retrieved for assessment. Five studies were eligible for inclusion and were critically appraised and summarised. Of these five studies, three were cost–utility analyses [i.e. studies reporting costs and quality-adjusted life-years (QALYs)].

We undertook to update the systematic review to identify any evidence regarding the cost–utility of ESAs, particularly with relevance to the NHS. ESA administration was considered within licence for inclusion in this review, based on dose frequency but not dose quantity (i.e. once weekly for any ESA, three times a week for epoetin alfa and epoetin zeta, once every 3 weeks for darbepoetin alfa and three to seven times weekly for epoetin beta). Fixed and weight-based dosages were allowed.

Searches were conducted in several databases (including MEDLINE and EMBASE), with the results limited to studies published since 2004 when possible, resulting in 1163 records being identified. Following removal of duplicate records, 843 titles and abstracts were screened independently by two reviewers. Fifty-four full-text articles were assessed for eligibility and 29 were judged to be eligible. Five studies were excluded as they were multiple publications, meaning that 24 studies were included.

Peninsula Technology Assessment Group cost–utility model

Model structure

In the Peninsula Technology Assessment Group (PenTAG) assessment, the model took the form of a simple, empirical model, informed directly by the systematic review of clinical effectiveness. The model compared patients receiving ESA therapy with patients not receiving ESA therapy and was split into two temporal sections, one to evaluate the short-term costs and QALYs (while patients are anaemic) and one to evaluate long-term QALYs.

Short-term costs were accrued in the form of ESA drug acquisition and administration, RBCT costs and costs of adverse events. Cancer costs were assumed to be equal for all patients. No difference in survival time in the short term was modelled between arms. Long-term costs were not modelled because of the uncertainty of such costs given the varied patient population and to avoid an arbitrary value disadvantaging a strategy with a survival benefit.

Short-term QALYs are accrued as the utility associated with empirical observation of Hb over time. Here, Hb levels over time were taken directly from clinical trials and this approach attempted to bolt on an economic evaluation to the RCTs of ESAs. The short-term QALY gain included time receiving ESA therapy and a time post-ESA therapy called normalisation, when patients return to their 'normal' Hb level (in the base case this is set to 12 g/dl).

Long-term QALYs are accrued because of potential differences in OS between the two arms. These are calculated by estimating OS in each arm and applying a long-term utility common to both arms; that is, it is assumed that long-term QALY differences come about only through a difference in survival as a result of ESA therapy, not through any enduring impact on HRQoL.

An exponential distribution was assumed for OS of patients not receiving ESA therapy in the base case, as this is consistent with results from a number of trials. A hazard ratio (HR) was applied to OS for lifetime for patients receiving ESA therapy. Alternative modelling assumptions were explored through scenario analyses.

Model parameters

On recommendation from NICE and in keeping with the clinical effectiveness review, equal effectiveness was assumed for ESAs. However, some parameters specific to each ESA, such as drug doses and costs, were varied between ESAs.

To ensure consistency between costs and benefits, all parameters were estimated on an intention-to-treat basis. For example, we used the mean weekly dosage of ESAs averaged over all patients at baseline for the full intended treatment duration. This average includes some patients who withdraw from ESA treatment during the trial.

Clinical effectiveness

Most parameters were estimated from outcomes reported by randomised trials included in the systematic review of clinical effectiveness. No evidence from RCTs was found for normalisation of Hb levels following chemotherapy cessation and so this part of the model had to be parameterised on the basis of clinical expert opinion.

Utilities

For the analysis, the model required two sources of utility values: (1) utility as a function of Hb levels during ESA treatment and during normalisation to reflect the impact of ESAs on HRQoL and (2) a constant utility value after normalisation, equal in all treatment arms.

A review was conducted of studies for (1) and a single study was chosen, from which the PenTAG base case was calculated (Harrow BS, Eaton CB, Roberts MB, Assaf AR, Luo X, Chen Z. Health utilities associated with hemoglobin levels and blood loss in postmenopausal women: the Women's Health Initiative. *Value Health* 2011;**14**:555–63) and scaled to the European Quality of Life-5 Dimensions (EQ-5D), giving a 0.028 increase in utility per unit increase for Hb. The long-term utility (2) was calculated using an estimate for cancer utility from Tengs and Wallace (Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care* 2000;**38**:583–637) and applying the age-related utility calculated from Ara and Brazier (Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**:509–18). This gave a utility of 0.76.

We did not explicitly model disutility from adverse events because of a lack of data.

Costs

In this analysis we modelled the following costs: blood test costs, ESA prices, RBCT costs (unit cost of blood and cost of transfusion appointment) and costs of adverse events. We did not model long-term costs in the base case given the uncertainty attached to these values as a result of the wide patient population. We assumed that the cost of intravenous iron supplementation could be ignored, as it will be very similar for all arms. Costs were adjusted to 2014/15 prices when appropriate.

Base-case ESA costs were taken from the *British National Formulary* (Joint Formulary Committee. *British National Formulary*. 66th ed. London: BMJ Group and Pharmaceutical Press; 2013). Wholesale acquisition costs for ESAs were also obtained and used in a scenario analysis. ESAs were assumed to be administered once weekly in the base case, by a mixture of general practitioners, district hospital staff nurses and self-administration. ESAs were also assumed to incur costs for four additional blood tests compared with the no ESA arm, in line with the possibility that additional blood tests would continue post chemotherapy for those patients on ESAs.

The adverse events that we accounted for in this cost-effectiveness analysis were identified through the clinical effectiveness review. In particular, we accounted for the cost of thromboembolic events, hypertension and thrombocytopenia. The unit costs of managing thromboembolic events (particularly pulmonary embolism and deep-vein thrombosis), hypertension and thrombocytopenia were identified

through NHS reference costs 2012–13 [Department of Health. *Reference Costs 2012–13*. London: Department of Health; 2013. URL: www.gov.uk/government/uploads/system/uploads/attachment_data/file/260403/nhs_reference_costs_2012–13.pdf (accessed16 June 2015)].

Unit costs for the supply of RBCs were taken directly from NHS Blood and Transplant 2012/13 costs (£122 per unit) [see www.nhsbt.nhs.uk/annualreview/blood-supply/ (accessed July 2015)] and unit costs of a transfusion appointment were calculated using figures reported in Varney and Guest (Varney SJ, Guest JF. The annual cost of blood transfusions in the UK. *Transfus Med* 2003;**13**:205–18).

Other model characteristics

A lifetime time horizon was used in the model. The perspective adopted was that of the NHS and Personal Social Services. Costs and benefits were discounted at 3.5% per annum.

The age and weight of patients in the model were estimated from the age and weight reported in clinical studies included in the systematic review of clinical effectiveness evidence.

Results

Clinical effectiveness

Number and quality of effectiveness studies

A total of 2376 titles/abstracts were identified through database searching from 2004 to 2013. Of 1515 titles and abstracts screened (including 1404 titles/abstracts identified via the PenTAG searches), 23 RCTs (reported in 34 publications) were found that matched the inclusion criteria for this review. All of the included studies had been included in the recent Cochrane review (Tonia and colleagues 2012). The PenTAG review included one full paper (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. *J Natl Cancer Inst* 2013;**105**:1018–26) which reported a study for which only an earlier abstract [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). *J Clin Oncol* 2007;**25**:S569] was included in the Cochrane review (Tonia and colleagues 2012). Thirteen studies compared ESAs plus supportive care for anaemia (including transfusions) with placebo plus supportive care for anaemia (including transfusions) alone and 10 studies compared ESAs plus supportive care for anaemia (including transfusions) with supportive care for anaemia (including transfusions) alone. Of note, none of the included studies evaluated ESAs entirely within the remit of their marketing authorisations; in particular, start and target Hb levels and stopping rules were all generally higher than specified in the licence.

Taken as a whole, the quality of the trials was moderate to poor. For most of the trials it was difficult to make a general assessment of study quality because of reporting omissions. Most notably, all trials lacked clarity in the reporting of allocation methods (the procedure for randomisation and/or allocation concealment).

Assessment of effectiveness

Overall, the analysis of haematological response (defined as an improvement in Hb of 2 g/dl or a 6% increase in haematocrit level) included 10 studies with 2228 participants. Meta-analysis showed a statistically significant difference in Hb response in favour of treatment [risk ratio (RR) 3.29, 95% confidence interval (CI) 2.84 to 3.81]. In total, 63% (759/1213) of participants who received ESAs achieved a haematological response, compared with 18% (182/1015) of participants who did not. Subgroup analyses were inconclusive. Treatment with ESAs reduced the number of patients receiving RBCTs by an estimated 37%. These estimates are consistent with previously reported estimates.

The results of previous reviews with respect to survival have varied and there is much debate surrounding the impact of ESAs on survival. Survival data were available from 21 trials including 5054 participants. The HR for survival was 0.97 (95% CI 0.83 to 1.13); the forest plot suggested that there was a tendency for smaller studies to favour ESA treatment. Although this estimate differed from those reported by Wilson and colleagues (2007) and Tonia and colleagues (2012) (1.05, 95% CI 1.00 to 1.11, and 1.03, 95% CI 0.83 to 1.13, respectively), there was considerable uncertainty around this estimate and statistically significant heterogeneity was identified ($I^2 = 42.4\%$; $\chi^2 = 29.5$, degrees of freedom = 17; $p = 0.03$). In addition, subgroup analyses did not identify groups at lower or higher risk.

On-study mortality was defined as death occurring up to 30 days after the active study period. Data, extracted from the Cochrane review (Tonia and colleagues 2012), were available from 21 studies including 5085 participants. Analyses suggested that treatment with ESAs in patients with CIA did not have a statistically significant effect on mortality (HR 0.86, 95% CI 0.67 to 1.11). In total, 11% (174/1586) of participants who received ESAs had died within 30 days of the active study period, compared with 12% (164/1381) of patients in the control groups.

All AEs were relatively rare compared with the other outcomes considered in this report. The AE with the highest rate was thrombocytopenia/haemorrhage [6% (55/877) in the ESA treatment groups and 6% (54/838) in the control groups]. The summary estimate for thrombocytopenia/haemorrhage in the PenTAG review was RR 0.93 (95% CI 0.65 to 1.34), compared with RR 1.21 (95% CI 1.04 to 1.42) in the Cochrane review (Tonia and colleagues 2012). However, although the point estimate is lower compared with previous results, the data are insufficient to rule out detrimental effects. Overall, the data suggest that treatment with ESAs in patients with CIA increases the risk for thromboembolic events (RR 1.46, 95% CI 1.08 to 1.99), increases the number of hypertension events (RR 1.80, 95% CI 1.14 to 2.85), increases the number of cases of pruritus (RR 2.04, 95% CI 1.11 to 3.75) (skin rash, irritation and pruritus were combined in the analyses) and results in a non-significant increase in the number of seizures (RR of 1.19, 95% CI 0.33 to 4.38), consistent with previous estimates.

Subgroup analyses

Two of the subgroups evaluated corresponded with the current NICE recommendations: women with ovarian cancer receiving platinum-based chemotherapy and people unable to receive a blood transfusion.

One trial (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. *Med Oncol* 1998;**15**:174–82) evaluated the use of ESAs in women with ovarian cancer. The data confirm the results from previous analyses with respect to anaemia-related outcomes; that is, improvements in haematological response and a reduction in RBCT requirement, but an increased risk for thromboembolic events in the ESA treatment group. OS was not measured. No trials were identified that evaluated people unable to receive RBCTs. However, it is reasonable to assume that ESAs are likely to be effective in improving the Hb level in this subpopulation.

In addition, subgroup analyses considering any type of cancer and platinum-based chemotherapy, platinum-based chemotherapy in head and neck malignancies and iron supplementation were conducted.

Other factors for consideration

As previously stated, studies were eligible for inclusion in the systematic review if they used a licensed starting dose, irrespective of how they dealt with other criteria stipulated by the licence. In addition to dose, we also assessed the impact of inclusion Hb level (≤ 11 g/dl vs. > 11 g/dl) and target Hb level (≤ 13 g/dl vs. > 13 g/dl) in post-hoc subgroup analyses.

A trend associated with the administration of ESAs according to licence recommendations was noticed. It appeared that effectiveness in terms of some outcomes was improved when ESAs were evaluated closer to their licensed indications, for example dose and inclusion Hb level (≤ 11 g/dl) and dose, inclusion Hb level (≤ 11 g/dl) and target Hb level (≤ 13 g/dl). Findings for anaemia-related outcomes showed improvements consistent with previous analyses. The effectiveness with regard to malignancy-related outcomes did appear to be affected by the licence application, and estimated effects of ESAs administered in accordance with licence recommendations were notably lower than those reported in previous analyses. Importantly, although the results for thromboembolic events from the PenTAG review agree with those in the Cochrane review (Tonia and colleagues 2012), suggesting an increase in thromboembolic events in patients in the ESA groups compared with the control groups, the closer the studies were to the licence recommendations the smaller the point estimates were (suggesting less detrimental effects of ESA).

However, all subgroup analyses must be interpreted with caution. The number of studies per subgroup is small and the CIs remain wide. The analyses may not have statistical power to detect the effects of the licence application on the effectiveness of outcomes, if such effects exist. Furthermore, we have not sought to address multiple testing issues that arise when considering subgroups, and so the statistical significance of the results may appear overstated.

Health-related quality of life

Thirteen trials measuring HRQoL were reported in 23 publications. Of these publications, 11 primary studies were included in the review by Wilson and colleagues (2007). Three new primary studies were identified in the update searches.

Taken as a whole, the quality of the trials was moderate to poor. For most of the trials it was difficult to make a general assessment about study quality because of reporting omissions. Baseline characteristics were unbalanced in two trials. Patients and physicians were blinded for the majority of trials, which is considered to have a significant impact on HRQoL assessed by self-reporting. Significant patient numbers were lost to follow-up for HRQoL outcomes in at least six trials.

Given the variability of reporting in the published papers, data for the Functional Assessment of Cancer Therapy – Fatigue (FACT-F) subscale, consisting of 13 specific items (score 0–52), were extracted from the Cochrane review by Tonia and colleagues (2012) for use in the PenTAG analyses. FACT-F scores were available from seven studies, with one new primary study identified. Overall, the conclusions from the PenTAG review were in agreement with those of the Cochrane review (Tonia and colleagues 2012), in that there was a statistically significant difference between patients treated with ESAs and control subjects when combining HRQoL parameters. However, the pooled mean difference between the treatment arm and the control arm was < 3 units, which is not considered clinically significant for FACT-F. Univariate subgroup analyses conducted for FACT-F outcomes according to chemotherapy type, malignancy type, intervention (epoetin or darbepoetin) and study duration also showed similarly statistically significant differences between the treatment arm and the control arm.

Meta-analysis was performed on Functional Assessment of Cancer Therapy – General and Functional Assessment of Cancer Therapy – Anaemia (seven items) data; however, only three studies were suitable for inclusion for each scale and their results displayed high levels of heterogeneity. The result of no statistical difference between the intervention arm and the control arm must therefore be treated with caution.

Overall, conclusions from the PenTAG review are in agreement with those from the Cochrane review (Tonia and colleagues 2012) and the previous HTA review (Wilson and colleagues 2007). We have attempted to include populations closer to the licence for ESAs to understand the effects on HRQoL at these doses. Furthermore, as the previous HTA (Wilson and colleagues 2007) was able to use only a vote-counting method to estimate the positive direction of effect, the results from the PenTAG review have been quantified and pooled to enable a more direct comparison between treatments.

Cost-effectiveness

Published economic evaluations

Of the 24 included studies, 12 were abstracts only. Two related to the previous NICE appraisal, three were new cost–utility studies (Fagnoni P, Limat S, Chaigneau L, Guardiola E, Briaud S, Schmitt B, *et al.* Clinical and economic impact of epoetin in adjuvant-chemotherapy for breast cancer. *Support Care Cancer* 2006;**14**:1030–7; Borg S, Glenngard AH, Österborg A, Persson U. The cost-effectiveness of treatment with erythropoietin compared to red blood cell transfusions for patients with chemotherapy induced anaemia: a Markov model. *Acta Oncol* 2008;**47**:1009–17; Tonelli and colleagues 2009) and two were or included new systematic reviews (Duh MS, Weiner JR, White LA, Lefebvre P, Greenberg PE. Management of anaemia: a critical and systematic review of the cost effectiveness of erythropoiesis-stimulating agents. *Pharmacoeconomics* 2008;**26**:99–120; Tonelli and colleagues 2009).

Data extraction was conducted for all 24 included studies, but attention was focused on the new cost–utility studies and new systematic reviews. New cost–utility studies were critically appraised using quality assessment tools [either the Evers checklist (Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5) or the Philips checklist (Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics* 2006;**24**:355–71), as appropriate]. Narrative synthesis was conducted.

All of the studies (pooling those included from the previous review and the new studies) finding favourable cost-effectiveness for ESAs were funded or conducted by industry. Many of these assumed that ESA therapy would lead to a survival benefit for patients, although this is not supported by recent systematic reviews and meta-analyses.

A key assumption in almost all analyses was that raising Hb levels would improve HRQoL, although in no case was this assumption based on published RCT evidence using a preference-based quality-of-life measure.

A number of studies assumed a period following the end of chemotherapy treatment during which Hb levels would gradually return to normal (termed normalisation) and participants in the ESA arm would continue to accrue incremental benefits in quality of life over participants in the no ESA arm; to our knowledge, no evidence for or against normalisation has been presented in the published literature.

In the absence of survival benefit the expected health gain from ESA therapy is small (up to 0.035 QALYs) and is subject to uncertainty.

Studies did not incorporate current list prices or wholesale acquisition costs, which could significantly reduce the drug acquisition component of the cost of ESA therapy and improve cost-effectiveness.

There is a need for an up-to-date analysis of the cost-effectiveness of ESAs in the NHS to reflect reduced drug acquisition costs, changes to licences and market entry of additional comparators. This analysis will need to explore the significant amount of uncertainty that still remains.

Appraisal of industry submissions

Six manufacturer submissions were potentially available for this multiple technology appraisal. However, no manufacturers submitted an economic evaluation.

Peninsula Technology Assessment Group model

Base case

We found that the deterministic base case had incremental cost-effectiveness ratios (ICERs) for ESA treatment compared with no ESA treatment from £19,429 to £35,018 per QALY gained. Given that this covers a wide range of values and the entirety of the £20,000–30,000 per QALY range that is often used as a cost-effectiveness threshold by NICE, it was considered appropriate to emphasise the results of the probabilistic sensitivity analysis (PSA).

Sensitivity analyses

The expected mean results from the PSA gave ICERs that were lower than those in the deterministic base case (£14,724–£27,226 per QALY gained). On average, 0.092 (95% CI of –0.264 to 0.447) QALYs were gained for ESA treatment compared with no ESA treatment. The incremental costs for the most cost-effective ESA [Binocrit (epoetin alfa)] were £1349 (95% CI £710 to £1987). The ICER for Binocrit had a 95% credible interval (CrI) that was dominated by no ESA use (fewer QALYs and higher costs) at its upper end, with a lower value of £2350 per QALY gained (rounded to the nearest £50). In 36% of simulations there was an OS loss, with 31.4% of simulations having an overall QALY loss. Given that this was the most cost-effective ESA treatment, it is unsurprising that the rest of the ESAs were also dominated at their upper CrI limit. These results suggest that ESAs may be cost-effective at a threshold of £20,000 per QALY, but this could also be a result of chance variation and there is a significant chance of QALY loss in patients receiving ESA therapy.

Scenario analyses

Scenario analyses were conducted to investigate what was driving the wide range of values in the ICER CrIs. The three considered most important were:

1. setting the OS HR to exactly 1, so that survival is the same for both patients on ESA therapy and patients not on ESA therapy
2. setting ESA costs to wholesale acquisition costs in an attempt to establish the real costs to the NHS
3. both setting the OS HR to exactly 1 and the ESA costs to wholesale acquisition costs.

In the first of these scenarios, in which survival is assumed to be equal for the two treatment arms, we found that the QALY gain was greatly reduced (0.014) (as well as the 95% CI 0.001 to 0.027), suggesting that much of the variability in the base-case QALYs comes from the QALYs accrued during long-term survival. The reduction in QALYs also increases the ICERs, with the most cost-effective ESA achieving an ICER of £96,754 per QALY gained (95% CrI £36,500 to > £300,000 per QALY gained) in the PSA. None of the CrIs for the ICERs fell below £30,000 per QALY gained, suggesting that in this scenario ESAs are unlikely to be cost-effective.

In the second scenario, in which wholesale acquisition costs were implemented, (commercial-in-confidence information has been removed) [for the least costly ESA: Retacrit (epoetin zeta)] per QALY gained. However, in this scenario the 95% CrI went from ESA dominating at one end (with more QALYs and lower costs than no ESA use) to ESA being dominated by the no ESA arm at the other end.

In the third scenario, in which survival is assumed to be equal for both treatment arms and wholesale acquisition costs are used (commercial-in-confidence information has been removed).

We also conducted scenario analyses on a subgroup of studies in which the initial Hb level for participants was ≤ 11 g/dl, as well as investigating the assumptions around OS. Univariate sensitivity analyses were also conducted. The uncertainties identified in the analyses of this subgroup of studies were less significant than those identified for the analyses of all studies (presented in the previous paragraphs).

Discussion

Strengths and limitations: clinical effectiveness and quality-of-life reviews

The overview of clinical effectiveness systematic reviews was conducted by an independent, experienced research team using the latest evidence and working to a prespecified protocol (PROSPERO CRD42013005812). This technology assessment builds on existing secondary research and economic evaluations. However, there are some important sources of uncertainty that impact on the conclusions:

- *Relative effectiveness*. We did not address the relative effectiveness of different ESAs. Lack of head-to-head RCT evidence would have been an important limitation if we had tried to do this.
- *Dose*. The protocol stated that ESAs should be evaluated in accordance with their UK marketing authorisations. However, given that no studies were completely aligned with the current UK marketing authorisation, we identified studies that were closest to the current UK marketing authorisation, focusing initially on the starting dose. It is important to note that beyond the start dose there were still significant differences from the current licence recommendations in the included studies. Also, we did not prespecify the criteria used to define 'closest to the current UK marketing authorisation', but we did explore alternative, stricter definitions.
- *Generalisability*. There may be other challenges to the applicability of the included trials, which were carried out up to 20 years ago. Chemotherapy has changed during this period, as has the quality of supportive treatment.
- *Study quality*. The included trials were of variable quality, but all were flawed to some degree. Most notably, all trials lacked clarity about randomisation and allocation concealment. The general problem of poor reporting of trials on this topic was greatly assisted by the recent Cochrane review (Tonia and colleagues 2012). The authors had gathered further information from investigators and manufacturers and this information was used in the meta-analysis for the current review.
- *Heterogeneity*. There is considerable unexplained statistical heterogeneity for a number of outcomes, particularly survival.
- *Publication bias*. There was some evidence in both the previous review (Wilson and colleagues 2007) and the Cochrane review (Tonia and colleagues 2012) that the results from small negative trials may not be available for inclusion in systematic reviews, suggesting the possibility of publication bias. For some outcomes in this review, for example HRQoL, this could not be further investigated because of the small number of included studies; for others, such as survival, there was continuing support for the possibility of publication bias. Industry-sponsored trials predominated.
- *Precision*. Although there is an apparent wealth of RCTs, only a minority of these were included because of the desire to address effectiveness as close as possible to current UK marketing authorisations. In consequence, the 95% CIs were often wide and included values indicating no difference in effect. In addition, it is not clear whether the total numbers of patients in the trials included were sufficient to establish the true presence or absence of an effect, either because events are uncommon, for example adverse events, or because the effect size that would be deemed to be clinically important is small, as would be the case with survival.
- *Multiple testing*. Although we were aware of the possibility of spuriously positive tests arising for statistical significance because of the multiple subgroup analyses carried out, we did not formally make adjustments for this.

The limitations identified impact on the key outcomes as follows:

- Haematological response and numbers transfused appear to be robust estimates, with no marked heterogeneity or subgroup effects.
- Hb change does show important heterogeneity, which may possibly indicate subgroup effects; however, analyses in this respect were inconclusive.
- HRQoL is affected by the variability of instruments used and study quality.
- Adverse events are mainly affected by the quality of information available, the variability in the definition of individual adverse events used and the width of the CIs.

- Survival is also subject to all of the limitations outlined above. Marked heterogeneity was identified for which no explanation could be provided. OS was defined as the longest follow-up available. This meant that there was a mix of studies with short- and long-term follow-up (i.e. OS effect estimates may be from different time points).

Strengths and limitations: systematic review of cost-effectiveness studies

The systematic review of cost-effectiveness evidence was conducted by an independent research team using the latest evidence and to a prespecified protocol. Two new systematic reviews were identified, neither of which identified studies that would have been eligible for this review.

Limitations were identified as follows:

- The searches were limited to English-language studies because of resource limitations.
- Only systematic reviews and cost–utility studies were fully critically appraised and considered in the narrative synthesis.
- Records from database searches published pre 2004 were excluded, although it was not possible to assess whether these had been screened for eligibility in the systematic review presented by Wilson and colleagues (2007). Studies using darbepoetin alfa once every 2 weeks were excluded as being out of licence, although these could have usefully contributed to the review.

Limitations: Peninsula Technology Assessment Group model

The main limitations of the updated model and its outputs are as follows:

- Despite being highly influential in terms of the model results, the marginally beneficial OS HR identified in the clinical effectiveness section has no strong biological rationale. Although many post-hoc suggestions have been advanced to try to explain both the increases and decreases in survival observed in individual ESA RCTs, most of these results can be explained by chance alone.
- The OS HR is applied on the assumption that proportional hazards apply for a lifetime after ESA therapy, although to our knowledge the proportional hazards assumption has not been tested. Most included studies had a limited follow-up period and so the long-term impact on survival is not well known. Limiting the effect of ESA therapy on survival to 3 years results in a significant worsening of the cost-effectiveness of ESAs.
- The mapping of Hb level to utility is a surrogate outcome with the problems that this entails. Furthermore, the utility identified for the base case was not ideal: it had to be additionally mapped to the EQ-5D and the patient population was cancer patients without ESA use only. The main weakness of the study design was that it was observational. This means that the estimated relationship between utility and Hb level may be biased because of unmeasured confounding variables and it is likely that this would bias the results in favour of the ESA arm compared with the control arm.
- Furthermore, evidence is lacking for the process of normalisation, this was entirely informed by clinical expert opinion.
- We also assumed constant cancer costs between the ESA arm and the no ESA arm; however, this may not be the case.
- The model assumes that there is no long-term cost difference between arms, but it does assume a long-term survival benefit for the ESA arm. As previous models indicated, this long-term aspect of the model is an area that has not been assessed in great detail before. As such, this is an area of which there needs to be better understanding.
- As the model is primarily driven by data from the clinical effectiveness review, the input parameters may not be in line with current practice. This also means that limitations of the clinical effectiveness review carry over to the cost-effectiveness results. Furthermore, the inherent uncertainty in the estimates from the clinical effectiveness meta-analysis and the associated limitations are a main source of uncertainty that occurs within the model. This also means that the effectiveness of the ESAs is assumed to be equal, as this follows from the clinical effectiveness review.

Conclusions

The previous HTA review (Wilson and colleagues 2007) concluded that:

> *Epo is effective in improving haematological response and reducing RBCT requirements. It also appears to improve HRQoL. Its impact on side-effects and survival remains highly uncertain. If there is no impact on survival, it seems highly unlikely that ESAs would be considered a cost-effective use of healthcare resources.*
>
> *p. iv*

Additional clinical effectiveness evidence identified in this updated systematic review continues to suggest that there is clinical benefit to be had from ESAs with respect to anaemia-related outcomes; that is, improvements in haematological response and a reduction in RBCT requirements. Data also suggest an improvement in HRQoL and this is better quantified than in the previous HTA review. The impact on side effects and survival, however, remains highly uncertain. Although the point estimates for both survival and thromboembolic events are lower than previously reported estimates, the 95% CIs are wide.

The conclusions concerning cost-effectiveness are also no clearer. Base-case ICERs for ESA treatment compared with no ESA treatment ranged from £19,429 to £35,018 per QALY gained, but sensitivity and scenario analyses demonstrate that there is considerable uncertainty in these results. In line with the previous HTA review, survival was an influential parameter. If the survival benefit reported in the clinical effectiveness review (0.97, 95% CI 0.83 to 1.13) is used, ESAs appear to be cost-effective on average, but this is highly uncertain and QALY loss cannot be ruled out (31.4% of simulations in the base case estimated a QALY loss from ESA therapy). However, if exactly equal survival is assumed regardless of ESA therapy, ESAs are predicted not to be cost-effective unless wholesale acquisition costs are used, in which case ESAs are predicted to be cost-effective on average, although approximately one in five simulations give an ICER of > £30,000 per QALY and approximately one in three simulations give an ICER of > £20,000 per QALY.

In summary, ESAs could be cost-effective, but there is considerable uncertainty in the results, mainly because of unknown impacts on OS.

Implications for service provision

- *Ongoing safety concerns*. When seeking clinical experts to advise us in this assessment we found that most relevant clinicians (i.e. oncologists, haematologists and gynaecologists) did not use ESA therapy in their clinical practice. This was generally because of concerns about safety and effectiveness (OS), as well as restrictions from previous NICE guidance (TA142).
- *Current usage*. It is difficult to assess how frequently ESA therapy is used within the indication of CIA because prescription records do not routinely link medication with indication and ESA therapy is widely used in individuals with chronic kidney disease (CKD). Some indirect evidence of the use of ESA therapy for CIA is available from the use of cost centres against which ESAs are recorded. Data analysed are suggestive of significant variability in current usage, consistent with the fact that many clinicians do not use ESAs because of safety concerns and current NICE guidance (TA142), although data quality is low and interpretation challenging.
- *Acquisition costs*. The costs at which hospitals acquire ESAs may be significantly lower than the list prices for these drugs. These prices are the subject of confidential negotiations and are commercially sensitive. At present, acquisition prices will largely be driven by demand for ESAs for individuals with CKD. Current prices could be amended if there are developments in the management of CKD or if demand for ESAs increases for patients with CIA (as might be expected following positive NICE guidance).

Suggested research priorities

- If ESAs are thought to have major potential for improving cancer care, large RCTs meeting current methods and reporting standards with adequate follow-up are needed to evaluate ESAs as administered in line with current marketing authorisations (including licence criteria for Hb levels).
- There should be improved estimates of the impact on tumour response and mortality; if these estimates are neutral or slightly beneficial it is plausible that ESAs could be cost-effective.
- There should be assessment of the frequency of the key potential adverse events related to ESA administration.
- More data are needed to assess the impact on HRQoL. These should include the effect on EQ-5D.
- More evidence is needed to assess the impact of Hb normalisation on utility.
- In addition to new trials, it may be valuable to revisit the Cochrane individual patient data meta-analysis and select studies that better fit 'licensed recommendations' with respect to Hb criteria and doses administered.
- It may also be helpful to explore reasons why an improvement in anaemia may lead to better outcomes; that is, whether ESAs allow better compliance with chemotherapy.

Study registration

This study is registered as PROSPERO CRD42013005812.

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Chapter 1 Background

Aim of the review

The aim of this assessment was to review and update research evidence as necessary to inform National Institute for Health and Care Excellence (NICE) guidance to the NHS in England and Wales on the clinical effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (ESAs) for the treatment of cancer treatment-induced anaemia (CIA) (see *Current service provision*).

The previous guidance [technology appraisal (TA)142[1]] was primarily based on evidence presented to NICE in the assessment report by Wilson and colleagues.[2] We have incorporated relevant evidence presented in the previous report and report new evidence gathered since 2004.

Description of the health problem

Anaemia is defined as 'a reduction of the haemoglobin (Hb) concentration, red blood cell (RBC) count, or packed cell volume below normal levels' (p. v244).[3] A commonly used classification of anaemia according to Hb level is shown in *Table 1*.[3]

It is the most frequent haematological manifestation in patients with cancer; > 50% of all cancer patients will be anaemic, regardless of the treatment received, and approximately 20% of all patients undergoing chemotherapy will require a red blood cell transfusion (RBCT).[4]

The cause of anaemia is usually multifactorial and may be patient, disease or treatment related.[4] The haematological features in anaemic patients depend on the different types of malignant disease, stage and duration of the disease, the regimen and intensity of tumour therapy and possible intercurrent infections or surgical interventions. Tumour-associated factors, such as tumour bleeding, haemolysis and deficiency in folic acid and vitamin B_{12}, can be acute or chronic. In the advanced stages of haematological malignancy, bone marrow involvement often leads to progressive anaemia. In addition, interaction between tumour cell populations and the immune system can lead to the release of cytokines, especially interferon-gamma, interleukin-1 and tumour necrosis factor. This disrupts endogenous erythropoietin synthesis in the kidney and suppresses differentiation of erythroid precursor cells in the bone marrow. As a result, patients with tumour anaemia may have relatively low levels of erythropoietin for the grade of anaemia observed. Moreover, activation of macrophages can lead to a shorter erythrocyte half-life and a decrease in iron utilisation.

TABLE 1 Classification of anaemia

Severity	WHO, Hb level (g/dl)	NCI, Hb level (g/dl)
Grade 0 (WNL)	≥ 11	WNL
Grade 1 (mild)	9.5–10.9	> 10 WNL
Grade 2 (moderate)	8.0–9.4	8–10
Grade 3 (serious/adverse)	6.5–7.9	6.5–7.9
Grade 4 (life-threatening)	< 6.5	< 6.5

NCI, National Cancer Institute; WHO, World Health Organization; WNL, within normal limits.
Source: Wilson and colleagues.

Chemotherapy may cause both transient and sustained anaemia.[4] Mechanisms of drug-induced anaemia in patients with cancer include stem cell death, blockage or delay of haematopoietic factors, oxidant damage to mature haematopoietic cells, long-term myelodysplasia and immune-mediated haematopoietic cell destruction.[4] Patients treated with platinum-based regimens develop anaemia most often and frequently need transfusions.[4] As a consequence, dose-intensified regimens or shortened treatment intervals, as well as multimodal therapies, are associated with a higher degree of anaemia.[4] Anaemia can also compromise the effect of treatment because low tissue oxygenation is associated with a reduced sensitivity of tumours to radiation and some forms of chemotherapy, contributing to the progression of cancer and reduction in survival.[4]

Among those patients with solid tumours, the incidence of anaemia is highest in patients with lung cancer (71%) or gynaecological cancer (65%); these patients have the highest frequency of anaemia and the highest rate of transfusion requirements.[4,5] The frequency of RBCT requirements in these patients varies from 47% to 100% depending on the cumulative dose of platinum chemotherapy received and other risk factors, for example age, disease stage and pretreatment Hb level. In haematological cancers, anaemia is an almost invariable feature of the disease.[4] In addition, some of the newer chemotherapeutic agents, such as taxanes or vinorelbine, are strongly myelosuppressive and frequently cause anaemia.[6]

The clinical manifestation and severity of anaemia can vary considerably among individual patients.[4] Mild-to-moderate anaemia can typically cause such symptoms as headache, palpitations, tachycardia and shortness of breath.[4] Chronic anaemia can result in severe organ damage affecting the cardiovascular system, immune system, lungs, kidneys and the central nervous system.[4] In addition to physical symptoms, the subjective impact of cancer-related anaemia on quality of life, mental health and social activities may be substantial.[4] A common anaemia-related problem is fatigue, which impairs the patient's ability to perform normal daily activities.[4]

Relationship between cancer treatment-induced anaemia and survival

Although the evidence is uncertain, some researchers hypothesise that anaemia in cancer patients is associated with a worse prognosis. According to Bohlius and colleagues,[7] one explanation may be that, as a result of a low Hb level, the tumour cells become hypoxic and are subsequently less sensitive to cytotoxic drugs, in particular oxygen-dependent chemotherapies.[8–10] Evidence for this, as reported in the study by Tonia and colleagues,[11] exists in studies in which tumour control and overall survival (OS) are improved in solid tumour patients with better tumour oxygenation.[10,12] There is also the practical implication that severe anaemia may require a dose reduction or delay of chemotherapy, subsequently leading to a poorer outcome. It is therefore plausible that efforts taken to reduce anaemia may improve tumour response and OS.[7] That said, it should be noted that Hb levels elevated to > 14 g/dl in women and > 15 g/dl in men are undesirable and may lead to increased viscosity, impaired tumour oxygenation and thromboembolic events.[13]

As an intervention used to increase Hb, and by association improve prognosis, some studies actually report a detrimental effect of ESAs on survival and tumour progression.[14–20] This effect is postulated to be caused by the presence of erythropoietin receptors on various cancers,[21–25] whereby the endogenously produced or exogenously administered erythropoietin promotes the proliferation and survival of erythropoietin receptor-expressing cancer cells.[7] However, controversy about the functionality of these receptors remains[26–30] and several studies show no effect on tumour progression for patients receiving ESAs.[17,31–33]

It should be noted that the majority of the studies examined in the systematic reviews by Bohlius and colleagues[7] and Tonia and colleagues[11] used a wide range of administration frequencies and dosages of ESAs (generally exceeding the licence), which may result in an increase in adverse events (AEs) and mortality. This knowledge, along with the generally poor reporting and data omission on factors such as tumour stage and method of assessment, led to the conclusion by Tonia and colleagues[11] that no clear evidence was found to either exclude or prove a tumour-promoting effect of ESAs.

Current management

Red blood cell transfusions

Anaemia in cancer patients can be treated with RBCTs, with 15% of people with solid tumours treated with RBCTs.[34]

Different cut-off values are used for transfusions, depending on clinical symptoms and patient characteristics, with a Hb level of < 9 g/dl commonly used.[34] After administration of 1 unit of RBCs, the Hb level rises by 1 g/dl, with the lifespan of transfused RBCs being 100–110 days. Complications related to RBCT are procedural problems, iron overload, viral and bacterial infections and immune injury.[34]

Erythropoietin-stimulating agents

Erythropoietin is an acidic glycoprotein hormone. Approximately 90% of the hormone is synthesised in the kidney and 10% is synthesised in the liver. Erythropoietin is responsible for regulating RBC production. Erythropoietin for clinical use is produced by recombinant DNA technology.[1]

Exogenously administered erythropoietin is used to shorten the period of symptomatic anaemia in patients receiving cytotoxic chemotherapy. It is used in addition to, rather than as a complete replacement for, the existing treatments. Blood transfusion, in particular, may still be needed.[1]

Marketing authorisations: haemoglobin levels

Initially, all ESAs were recommended for use at Hb levels of ≤ 11 g/dl, with target Hb levels not exceeding 13 g/dl. However, because of data showing a consistent, unexplained, excess mortality in cancer patients with anaemia treated with ESAs, a safety review of all available data on ESA treatment of patients with CIA was conducted in 2008 by the Pharmacovigilance Working Party at the request of the Committee for Medicinal Products for Human Use. As a result of this safety review, the European Medicines Agency (EMA) requested that the Summary of Product Characteristics (SPCs) for all ESAs be changed to highlight that ESAs should be used only if anaemia is associated with symptoms; to establish a uniform target Hb range for all ESAs; to mention the observed negative benefit risk balance in patients treated with high target Hb concentrations; and to include the relevant results of the trials triggering the safety review. SPCs for all ESAs were therefore revised in 2008 to decrease the Hb value for treatment initiation to ≤ 10 g/dl and to amend Hb treatment target values to 10–12 g/dl and Hb levels for stopping treatment to > 13 g/dl.

The EMA labels the use of ESAs as follows:

- in patients treated with chemotherapy and with a Hb level of ≤ 10 g/dl, treatment with ESAs might be considered to increase Hb (to within the target range of 10–12 g/dl) or to prevent further decline in Hb
- in patients not treated with chemotherapy, there is no indication for the use of ESAs and there might be an increased risk of death when ESAs are administered to a target Hb level of 12–14 g/dl
- in patients with curative intent, ESAs should be used with caution.

These changes to the licence (*Table 2*) were introduced subsequent to the previous NICE appraisal.

TABLE 2 Changes to marketing authorisations

Pre 2008	2008 onwards
• A Hb level of ≤ 11 g/dl, administered to a target Hb level of < 13 g/dl	• In patients treated with chemotherapy and with a Hb level of ≤ 10 g/dl, treatment with ESAs might be considered to increase Hb (to within target range of 10–12 g/dl) or prevent further decline in Hb • In patients not treated with chemotherapy, there is no indication for the use of ESAs and there might be an increased risk of death when ESAs are administered to a target Hb level of 12–14 g/dl • In patients with curative intent, ESAs should be used with caution

Details of current licence recommendations are summarised in *Table 3*.

Current service provision

National Institute for Health and Care Excellence guidance (TA142)[1] currently recommends ESAs in combination with intravenous iron as an option for:

- the management of CIA in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a Hb level of ≤ 8 g/dl. The use of ESAs does not preclude the use of existing approaches to the management of anaemia, including blood transfusion when necessary
- people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

When indicated, the ESA used should be the one with the lowest acquisition cost.

TABLE 3 Treatment recommendations according to licence

Product characteristics	Epoetin alfa, epoetin zeta	Epoetin beta	Epoetin theta	Darbepoetin alfa
Manufacturer (product)	Janssen-Cilag Ltd (Eprex®),[35] Sandoz Ltd (Binocrit®),[36] Hospira UK Ltd (Retacrit®)[37]	Roche Products Ltd (NeoRecormon®)[38]	Teva Pharmaceuticals Ltd (Eporatio®)[39]	Amgen Inc. (Aranesp®)[40]
Marketing authorisation	Treatment of anaemia and reduction of RBCT requirements in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, who are at risk of transfusion as assessed by their general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy)		Treatment of symptomatic anaemia in adults with non-myeloid malignancies receiving chemotherapy	
Starting Hb level	≤ 10 g/dl	≤ 10 g/dl	≤ 10 g/dl	≤ 10 g/dl
Target Hb level	10–12 g/dl	10–12 g/dl	10–12 g/dl	10–12 g/dl
Initial treatment	150 IU/kg SC TIW (or 450 IU/kg SC QW)	150 IU/kg SC TIW (or 450 IU/kg SC QW)	20,000 IU/QW	2.25 µg/kg SC QW [or 500 µg (6.75 µg/kg) SC Q3W]
Dose increase	4 weeks Hb increase < 1 g/dl and reticulocyte increase ≥ 40,000 cells/µl dose is doubled to 300 IU/kg TIW or 900 IU/kg QW	300 IU/kg SC TIW	4 weeks Hb increase < 1 g/dl dose is doubled to 40,000 IU/QW; if Hb increase insufficient at 8 weeks increase to 60,000 IU/QW	Not specified
Dose reduction	If Hb increases by ≥ 2 g/dl: 25–50%; if Hb > 12 g/dl: 25–50%		If Hb > 12 g/dl or increase is > 2 g/dl in 4 weeks: 25–50%	If Hb increases by ≥ 2 g/dl: 25–50%; if Hb ≥ 12 g/dl: 25–50%
Dose withholding	If Hb > 13 g/dl, until 12 g/dl reinitiate at 25% lower dose		If Hb > 13 g/dl, until 12 g/dl reinitiate at 25% lower dose	If Hb > 13 g/dl, until 12 g/dl reinitiate at 25% lower dose

IU, international unit; QW, once weekly; Q3W, once every 3 weeks; SC, subcutaneous; TIW, three times a week.

Description of the technologies under assessment

Several short- and long-acting ESAs are available, including epoetin alfa, epoetin beta and darbepoetin beta. Since the last appraisal (2004) [the Health Technology Assessment (HTA) monograph relating to this was published in 2007[2]], an additional two ESAs have become available: epoetin theta and epoetin zeta. All are administered by subcutaneous injection. This technology assessment report will consider six pharmaceutical interventions: epoetin alfa (Eprex®, Janssen-Cilag Ltd; Binocrit®, Sandoz Ltd), epoetin beta (NeoRecormon®, Roche Products Ltd), epoetin theta (Eporatio®, Teva Pharmaceuticals Ltd), epoetin zeta (Retacrit®, Hospira UK Ltd) and darbepoetin alfa (Aranesp®, Amgen Inc.).[1] Two of the six ESAs, Binocrit and Retacrit, are biosimilars of epoetin alfa. A 'biosimilar' medicine is similar to a biological medicine (the 'reference medicine') that is already authorised in the European Union and contains a similar active substance to the reference medicine. The reference medicine for both Binocrit and Retacrit is Eprex/Erypo®, which contains epoetin alfa. Unlike generic medicines, biosimilars are similar but not identical to the original biological medicine.[41,42] Treatment recommendations according to licence are summarised for each pharmaceutical intervention in *Table 3*.

This NICE appraisal focuses on the treatment of CIA. As such, the appraisal does not cover all aspects of the licensed indications, such as the prevention of anaemia or the treatment of symptomatic anaemia as a result of chronic renal failure.

Clinical guidelines

European Organisation for Research and Treatment of Cancer

In Europe, treatment guidelines for CIA have been formulated by the European Organisation for Research and Treatment of Cancer (EORTC), who most recently updated its recommendations on the use of ESAs in September 2007.[41] In 2010, joint treatment guidelines were issued by American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH).[42]

The EORTC guidelines recommend that patients whose Hb level is < 9 g/dl should be assessed for the need for RBCT in addition to ESAs.[41] The joint ASCO/ASH guidelines suggest that RBCT is also an option for patients with CIA and a Hb level of < 10 g/dl, depending on the severity of the anaemia or clinical circumstances, and may also be warranted by clinical conditions in patients with a Hb level of ≥ 10 g/dl but < 12 g/dl.[42]

Recommendations for ESA therapy for CIA are broadly similar between the EORTC guidelines and the joint ASCO/ASH guidelines, with small differences in the threshold for initiation of ESA therapy and variation in the wording related to Hb levels.[41,42]

The EORTC guidelines[41] emphasise that reducing the need for RBCT is a major goal of therapy in anaemic cancer patients and highlight that ESAs can achieve a sustained increase in Hb levels, unlike intermittent transfusions. The guidelines also state that there is no evidence that oral iron supplements increase the response to erythropoietic proteins, although there is evidence of a better response to erythropoietic proteins with intravenous iron.

British Columbia Cancer Agency

The British Columbia Cancer Agency (BCCA) guidelines recommend treatment with ESAs for the treatment of CIA when the Hb level is 10 g/dl and there is a minimum of 2 months of planned chemotherapy.[43]

The guidelines also state that the benefits of treatment must be weighed against the possible risks for individual patients: ESAs may increase the risk of death, serious cardiovascular events, thromboembolic events and stroke and they may shorten survival and/or increase the risk of tumour progression or recurrence, as shown in clinical trials in patients with breast, head and neck, lymphoid, cervical non-small-cell lung cancers and patients with active malignancies who are not treated with either chemotherapy or radiotherapy.[43]

Existing evidence

Existing systematic reviews of effectiveness

There have been a number of well-conducted systematic reviews evaluating the effects of ESAs for treating CIA in cancer patients. We identified 11 systematic reviews (reported in 14 publications) that fulfilled the definition of a systematic review prespecified in the protocol; a summary of the eligible systematic reviews and a quality assessment [compared with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[44]] is provided in *Appendix 1*.

Cochrane review

The Cochrane review by Tonia and colleagues[11] was the most recent and authoritative review. The Cochrane review's conclusions were that ESAs reduce the need for RBCTs but increase the risk for thromboembolic events and deaths. ESAs may improve quality of life but the effect of ESAs on tumour control is uncertain. The review concluded that 'Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumour growth (p. 2).[11]

This was an update of a Cochrane review first published in 2004.[7] Searches were conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE and other databases. Searches were carried out for the periods January 1985 to December 2001 for the first review, January 2002 to April 2005 for the first update and up to November 2011 for the most recent update. The authors of the review also contacted experts in the field and pharmaceutical companies [for access to individual patient data (IPD)]. Inclusion, quality assessment and data abstraction were undertaken in duplicate by several reviewers. Eligibility criteria are detailed and compared with those in the Peninsula Technology Assessment Group (PenTAG) review in *Table 4*. The Cochrane review differed from the PenTAG review in respect of the population (cancer-related anaemia vs. chemotherapy-induced anaemia) and the intervention [all ESAs irrespective of licence vs. ESAs within licence (defined based on start dose)].

TABLE 4 Differences between the systematic reviews of Tonia and colleagues[11] and PenTAG

Criteria	Tonia and colleagues[11]	Current systematic review
Population	Patients diagnosed with malignant disease (using clinical and histological/cytological criteria) and at risk of transfusion as assessed by their general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy). Excluded trials in which > 80% of participants were diagnosed with an acute leukaemia	Patients had to be receiving chemotherapy for solid tumours, malignant lymphoma, multiple myeloma or non-myeloid malignancies and at risk of transfusion as assessed by their general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy)
Intervention	ESAs to prevent or reduce anaemia, given singly or concomitantly with chemotherapy, radiotherapy or combination therapy	ESAs[a] to prevent or reduce anaemia, given concomitantly with chemotherapy
	Dose: included studies or study arms with low doses	Dose: licensed dose defined by start dose even if it did not align with other criteria specified by the licence
Comparator	Placebo or 'no treatment' was not required for inclusion but was considered in evaluating study quality	Placebo, standard care, no treatment/usual care
Outcomes	HaemR,[b] Hb change, RBCT, RBC units, OS, mortality, tumour response (CR), AEs, HRQoL	HaemR,[b] Hb change, RBCT, RBC units, OS, tumour response (CR), AEs, HRQoL
Study design	RCTs	RCTs, SRs of RCTs[c]

CR, complete response; haemR, haematological response; HRQoL, health-related quality of life; RCT, randomised controlled trial; SR, systematic review.
a Specifically epoetin alfa, beta, theta and zeta and darbepoetin alfa.
b Defined as an increase in Hb level of ≥ 2 g/dl or an increase in haematocrit of ≥ 6% percentage points.
c Used for scrutinisation of bibliographies and comparison of results.

A total of 91 studies with 20,102 participants were included in the Cochrane review by Tonia and colleagues.[11] The results from the Cochrane review are summarised in *Table 5* and compared with the results of the PenTAG HTA review throughout *Chapter 3*.

Cochrane review: meta-analysis based on individual patient data

Another Cochrane review[7] examined the effect of ESAs and identified factors that modify the effects of ESAs on OS, progression-free survival (PFS) and thromboembolic and cardiovascular events, as well as the need for transfusions and other important safety and efficacy outcomes in cancer patients. It concluded that 'ESA treatment in cancer patients increased on study mortality and worsened OS. For patients undergoing chemotherapy the increase was less pronounced, but an adverse effect could not be excluded' (p. 2).

The review was conducted in 2009. Searches were conducted in The Cochrane Library, MEDLINE, EMBASE and conference proceedings for eligible trials and manufacturers of ESAs were contacted to identify additional trials. The review included randomised controlled trials (RCTs) comparing ESAs plus RBCT (as necessary) with RBCT (as necessary) alone to prevent or treat anaemia in adult or paediatric cancer patients with or without concurrent antineoplastic therapy. Inclusion, quality assessment and data abstraction were undertaken in duplicate by several reviewers. A meta-analysis of RCTs was conducted and patient-level data were obtained and analysed by independent statisticians.

TABLE 5 Results: Cochrane review[11]

Outcomes measured	Results
Anaemia-related outcomes	
Hb change[a]	WMD 1.57, 95% CI 1.51 to 1.62; $\chi^2_{(het)} = 564.37$, df = 74; $p < 0.001$
	75 trials, $n = 11{,}609$
HaemR[b]	RR 3.39, 95% CI 3.10 to 3.71; $\chi^2_{(het)} = 95.56$, df = 45; $p < 0.001$
	46 trials, $n = 6413$
RBCT	RR 0.65, 95% CI 0.62 to 0.68; $\chi^2_{(het)} = 217.08$, df = 87; $p < 0.001$
	88 trials, $n = 16{,}093$
Units transfused	WMD –0.98, 95% CI –1.17 to –0.78; $\chi^2_{(het)} = 34.52$, df = 24; $p = 0.080$
	25 trials, $n = 4715$
Malignancy-related outcomes	
Tumour response	RR 1.02, 95% CI 0.98 to 1.06; $\chi^2_{(het)} = 16.10$, df = 18; $p = 0.59$
	19 trials, $n = 5012$
OS	HR 1.05, 95% CI 1.00 to 1.11; $\chi^2_{(het)} = 95.40$, df = 75; $p = 0.060$
	80 trials, $n = 19{,}003$
Mortality	HR 1.17, 95% CI 1.06 to 1.29; $\chi^2_{(het)} = 59.49$, df = 63; $p = 0.600$
	64 trials, $n = 14{,}179$
Safety-related outcomes	
Thromboembolic events	RR 1.52, 95% CI 1.34 to 1.74; $\chi^2_{(het)} = 34.99$, df = 55; $p = 0.980$
	60 trials, $n = 15{,}498$
Hypertension	RR 1.30, 95% CI 1.08 to 1.56; $\chi^2_{(het)} = 26.87$, df = 34; $p = 0.800$
	35 trials, $n = 7006$

continued

TABLE 5 Results: Cochrane review[11] (*continued*)

Outcomes measured	Results
Thrombocytopenia/haemorrhage	RR 1.21, 95% CI 1.04 to 1.42; $\chi^2_{(het)} = 14.50$, df = 20; $p = 0.800$ 21 trials, $n = 4220$
Seizures	RR 0.77, 95% CI 0.42 to 1.41; $\chi^2_{(het)} = 6.19$, df = 6; $p = 0.400$ 7 trials, $n = 2790$
Pruritus	RR 1.49, 95% CI 0.99 to 2.24; $\chi^2_{(het)} = 13.18$, df = 15; $p = 0.590$ 16 trials, $n = 4346$
HRQoL-related outcomes	
FACT-F 13 items (score 0–52)	MD 2.08, 95% CI 1.43 to 2.72; $\chi^2_{(het)} = 36.48$, df = 17; $p = 0.004$ 18 trials, $n = 4965$
Any subgroup effect	Yes: imputed vs. non-imputed data, baseline Hb level, type of anticancer therapy, duration of ESA treatment and ITT analysis

CI, confidence interval; df, degrees of freedom; FACT-F, Functional Assessment of Cancer Therapy – Fatigue; haemR, haematological response; het, heterogeneity; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intention to treat; RR, risk ratio; WMD, weighted mean difference.
a Fixed effects (Mantel-Haenzel): change from baseline to end of study.
b Fixed effects (Mantel-Haenzel): haematological response was defined as the proportion of participants with an increase in Hb level of ≥ 2 g/dl or as an increase in haematocrit of ≥ 6 percentage points.

A total of 13,933 cancer patients from 53 trials were analysed; 1530 patients died on study and 4993 died overall. ESAs increased on-study mortality [combined hazard ratio (cHR) 1.17; 95% confidence interval (CI) 1.06 to 1.30] and worsened OS (cHR 1.06; 95% CI 1.00 to 1.12), with little heterogeneity between trials ($I^2 = 0\%$, $p = 0.87$, and $I^2 = 7.1\%$, $p = 0.33$ respectively). Thirty-eight trials enrolled 10,441 patients receiving chemotherapy (*Table 6*). The cHR for on-study mortality was 1.10 (95% CI 0.98 to 1.24) and that for OS was 1.04 (95% CI 0.97 to 1.11). There was little evidence of a difference between trials of patients receiving different cancer treatments (*p*-value for interaction = 0.42).

Previous Health Technology Assessment review

The previous HTA review (Wilson and colleagues[2]) informed NICE guidance (TA142[1]). It assessed the effectiveness and cost-effectiveness of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. The review concluded that ESAs are effective in improving the haematological response and reducing RBCT requirements, but that the effect on health-related quality of life (HRQoL) is uncertain and the incidence of side effects and the effect on survival are highly uncertain. If there is no effect on survival it seems highly unlikely that ESAs would be considered a cost-effective use of health-care resources.

TABLE 6 Results: Cochrane review[7]

Outcomes measured	Results
Malignancy-related outcomes	
OS	cHR 1.04, 95% CI 0.97 to 1.11 38 trials, $n = 10,441$
On-study mortality	cHR 1.10, 95% CI 0.98 to 1.24 38 trials, $n = 10,441$

Using the Cochrane review[45] published in 2004 as the start point, Wilson and colleagues[2] conducted a systematic review of RCTs comparing ESAs with standard care. MEDLINE, EMBASE, The Cochrane Library and other databases were searched from 2000 (1996 in the case of darbepoetin alfa) to September 2004. Inclusion, quality assessment and data abstraction were undertaken in duplicate. Eligibility criteria are detailed and compared with those of the PenTAG review in *Table 7*. When possible, meta-analysis was employed. The economic assessment consisted of a systematic review of past economic evaluations, an assessment of economic models submitted by the manufacturers of the three ESAs and development of a new individual sampling model (see *Chapter 4*, *Wilson and colleagues: summary*).

A total of 46 RCTs were included in the review, 27 of which had been included in the Cochrane review.[7] All 46 studies compared ESA plus supportive care for anaemia (including transfusions) with supportive care for anaemia (including transfusions alone). Outcomes assessed were anaemia-related outcomes (haematological response, Hb change, RBCT requirements), malignancy-related outcomes (tumour response and OS), HRQoL and AEs.

Results from the previous HTA review[2] (*Table 8*) are compared with the results of the PenTAG review throughout *Chapter 3*.

TABLE 7 Differences between the systematic reviews of Wilson and colleagues[2] and PenTAG

Eligibility criteria	Wilson and colleagues[2]	Current systematic review
Population	Patients diagnosed with malignant disease (using clinical and histological/cytological criteria) and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy)	Patients had to be receiving chemotherapy for solid tumours, malignant lymphoma, multiple myeloma or non-myeloid malignancies and be at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy)
Intervention	ESAs to prevent or reduce anaemia, given singly or concomitantly with chemotherapy, radiotherapy or combination therapy	ESAs[a] to prevent or reduce anaemia, given concomitantly with chemotherapy
	Dose: included studies or study arms with low doses	Dose: licensed dose, defined by start dose, even if studies did not align with other criteria specified by the licence
Comparator	Placebo or 'no treatment' was not required for inclusion but was considered in evaluating study quality	Placebo, standard care, no treatment/usual care
Outcomes	HaemR,[b] Hb change, RBCT, RBC units, OS, mortality, tumour response (CR), AEs, HRQoL	HaemR,[b] Hb change, RBCT, RBC units, OS, tumour response (CR), AEs, HRQoL
Study design	RCTs	RCTs, SRs of RCTs[c]

CR, complete response; haemR, haematological response; SR, systematic review.
a Specifically epoetin alfa, epoetin beta and darbepoetin alfa.
b Defined as an increase in Hb level of ≥ 2 g/dl or an increase in haematocrit of ≥ 6 percentage points.
c Used for scrutinisation of bibliographies and comparison of results.

TABLE 8 Results: Wilson and colleagues[2]

Outcomes measured	Results
Anaemia-related outcomes	
Hb change[a]	WMD 1.63, 95% CI 1.46 to 1.80; $\chi^2_{(het)} = 23.74$, df = 19; $p = 0.21$ 10 trials, $n = 1620$
HaemR[b]	RR 3.40, 95% CI 3.01 to 3.83; $\chi^2_{(het)} = 23.60$, df = 32; $p = 0.86$ 21 trials, $n = 3740$
RBCT	RR 0.63, 95% CI 0.58 to 0.67; $\chi^2_{(het)} = 94.75$, df = 48; $p = 0.001$ 35 trials, $n = 5564$
Units transfused	WMD –1.05, 95% CI –1.32 to –0.78; $\chi^2_{(het)} = 8.96$, df = 16; $p = 0.91$ 14 trials, $n = 2353$
Malignancy-related outcomes	
Tumour response	RR 1.31, 95% CI 1.08 to 1.60; $\chi^2_{(het)} =$ NR; df = NR; $p =$ NR 9 trials, $n = 1260$
OS	HR 1.03, 95% CI 0.92 to 1.16; $\chi^2_{(het)} = 37.74$, df = 27; $p = 0.08$ 28 trials, $n = 5308$
Mortality	NR
Safety-related outcomes	***No safety-related meta-analysis***
HRQoL-related outcomes	***No HRQoL meta-analyses***

df, degrees of freedom; haemR, haematological response; het, heterogeneity; HR, hazard ratio; NR, not reported; RR, risk ratio; WMD, weighted mean difference.
a Fixed effects (Mantel-Haenzel): change from baseline to end of study.
b Fixed effects (Mantel-Haenzel): haematological response was defined as the proportion of participants with an increase in Hb level of ≥ 2 g/dl or as an increase in haematocrit of ≥ 6 percentage points.

Key points

- Anaemia is defined as a deficiency in RBCs. It is the most frequent haematological manifestation in patients with cancer; > 50% of all cancer patients will be anaemic, regardless of the treatment received, and approximately 20% of all patients undergoing chemotherapy will require a RBCT. The cause is multifactorial: patient, disease or treatment related.
- Anaemia is associated with many symptoms, all of which affect quality of life. These symptoms include dizziness, shortness of breath on exertion, palpitations, headache and depression. Severe fatigue is probably the most commonly reported symptom and can lead to an inability to perform everyday tasks. However, fatigue in people with cancer can also have other causes, for example the disease itself, chemotherapy, radiotherapy, anxiety or depression.
- Many people are anaemic when cancer is diagnosed, before any cancer treatment starts. The degree of anaemia caused by treatments such as chemotherapy often fluctuates depending on the nature of the treatment and the number of courses administered, but is typically at its worst 2–4 weeks after chemotherapy is given. Once cancer treatments are stopped, a period of 'normalisation' is likely, during which the Hb may return to pretreatment levels.

- Options available for the management of CIA include adjustments to the cancer treatment regimen, iron supplementation and blood transfusion. The majority of people who become anaemic do not receive any treatment for their anaemia, but those who become moderately or severely anaemic are usually given blood transfusions. Complications related to RBCT include procedural problems, iron overload, viral and bacterial infections and immune injury.
- Current evidence suggests that ESAs reduce the need for RBCT but increase the risk of thromboembolic events and death. There is suggestive evidence that ESAs may improve quality of life. Whether and how ESAs affect tumour control remains uncertain.
- Based on the previous assessment,[2] NICE guidance (TA142)[1] recommended the use of ESAs in combination with intravenous iron for the treatment of CIA in women with ovarian cancer receiving platinum-based chemotherapy with symptomatic anaemia (Hb $\leq$ 8 g/dl). The recommendation made in TA142 did not prohibit the use of other management strategies for the treatment of CIA, for example blood transfusion.[1] In addition, guidance set out in TA142 recommended ESAs in combination with intravenous iron for people with profound CIA who cannot be given blood transfusions.[1] The ESA with the lowest acquisition cost should be used.[1]

Chapter 2 Definition of the decision problem

Decision problem

The purpose of this assessment was to review and update as necessary guidance to the NHS in England and Wales on the clinical effectiveness and cost-effectiveness of ESAs [epoetin alfa (Eprex and Binocrit), epoetin beta (NeoRecormon), epoetin theta (Eporatio), epoetin zeta (Retacrit) and darbepoetin alfa (Aranesp)] within their licensed indications for the treatment of CIA.

The project was undertaken based on a published scope[46] and in accordance with a predefined protocol. There were no major departures from this protocol. The protocol stated that interventions would be evaluated in line with their UK marketing authorisations. However, as none of the included studies was completely aligned with the current licence we applied a definition of 'within licence', which was not predefined. Given the recent publication of the 2012 Cochrane review,[11] which considered all ESAs, irrespective of their licence, 'within licence' was defined as a licensed starting dose, irrespective of how other licence criteria were dealt with.

Population

The population was people receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma and people with non-myeloid malignancies at risk of transfusion as assessed by their general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy).

Haematological malignancy specifically refers to non-myeloid malignancy (chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma).

Interventions

The interventions considered were ESAs: epoetin alfa (Eprex and Binocrit), epoetin beta (NeoRecormon), epoetin theta (Eporatio), epoetin zeta (Retacrit) and darbepoietin alfa (Aranesp).

All interventions were considered according to their UK marketing authorisation with respect to the starting dose administered (see *Table 3*).

Comparators

The following comparators were considered:

- best supportive care (including adjustment to the cancer treatment regimen, RBCT and iron supplementation)
- one of the other interventions under consideration, provided it was used in line with its marketing authorisation.

Outcomes

Evidence in relation to the following kinds of outcomes were considered:

- haematological response to treatment: defined as a transfusion-free increase in Hb of ≥ 2 g/dl or a haematocrit increase of 6 percentage points
- need for blood transfusion after treatment: number of patients transfused and number of units transfused per patient
- tumour response: time to cancer progression
- OS
- AEs of treatment: hypertension, rash/irritation, pruritus, mortality, thromboembolic events, seizure, haemorrhage/thrombocytopenia, fatigue, pure red cell aplasia (a note was made of other AEs described within the trial reports)
- HRQoL: validated quality-of-life measures, for example the Functional Assessment of Cancer Therapy – General (FACT-G), Functional Assessment of Cancer Therapy – Fatigue (FACT-F) and Functional Assessment of Cancer Therapy – Anaemia (FACT-An), the European Quality of Life-5 Dimensions (EQ-5D) and the Short Form questionnaire-36 items (SF-36).

Research question

This assessment addressed the following research question: 'What is the effectiveness and cost-effectiveness of ESAs (epoetin alfa, beta, theta and zeta and darbepoetin alfa) for treating CIA (including review of TA142)?'

Chapter 3 Assessment of clinical effectiveness

The review commissioned by NICE was to update the previous guidance (TA142[1]) based on the HTA review conducted by Wilson and colleagues.[2] The differences between the remit of the previous review and that of the current review are discussed in *Chapter 1* (see *Previous Health Technology Assessment review*). The project was undertaken in accordance with a predefined protocol. There were no major departures from this protocol. The protocol stated that interventions would be evaluated in line with their UK marketing authorisations. However, as none of the included studies was completely aligned with the current licence we applied a definition of 'within licence', which was not predefined. Given the recent publication of the 2012 Cochrane review,[11] which considered all ESAs irrespective of their licence, 'within licence' was defined as a licensed starting dose irrespective of how other licence criteria were dealt with.

A scoping search was undertaken to identify existing reviews and other background material. Among this literature two recent Cochrane reviews were identified that assessed the effectiveness of ESAs.[7,47]

The aim was to systematically review the effectiveness of ESAs with regard to treating cancer treatment-related anaemia, their effects on patients regarding their underlying malignancy and survival and their effectiveness in improving quality of life and reducing the impact of AEs. Given the recent publication of the Cochrane review,[11] the focus for this review was to identify and consider trials in which ESAs have been used in a manner consistent with or closest to their respective marketing authorisations (see *Eligibility criteria*, *Dose*).

Methods

Identification of studies

The search strategy was based on the strategy used in the previous multiple technology appraisal (MTA) on this topic by Wilson and colleagues.[2] It combined free-text and medical subject heading (MeSH) terms for epoetin (generic and brand names), cancer and anaemia (see *Appendix 1*). Search filters were applied to retrieve RCTs, cost-effectiveness studies and quality-of-life studies. The search terms and structure of the search were mainly the same as in the study by Wilson and colleagues,[2] with additional search terms for epoetin theta, epoetin zeta and corresponding drug brand names. The search filters for RCTs, cost-effectiveness studies and quality-of-life studies were different from those used in Wilson and colleagues.[2] The filters were developed by an information specialist to ensure an appropriate balance of sensitivity and specificity. Changes to the previous MTA search strategy, including the filters, were made in MEDLINE and translated as appropriate for other databases. The MEDLINE randomised controlled trial (RCT) search strategy was checked by a clinical expert for inaccuracies and omissions relating to drug and cancer terms.

The databases were searched from the search end date of the previous MTA on this topic[2] (search end date 2004). Although epoetin alfa (Binocrit), epoetin theta and epoetin zeta were not covered in the previous report, we believe that relevant interventional research is highly unlikely to have been published on these drugs before this date given that the drugs were launched in 2007 (Binocrit and epoetin zeta) and 2009 (epoetin theta). All searches were also limited to English-language papers, although some foreign-language papers would have been identified by virtue of being included in other systematic reviews.

The following databases were searched: MEDLINE (Ovid), MEDLINE In-Process & Other Non-Indexed Citations (Ovid), EMBASE (Ovid), The Cochrane Library including CENTRAL, the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the HTA database, the NHS Economic Evaluation Database (NHS EED) and the Office for Health Economics Health Economic

Evaluations Database (HEED), Web of Science (Thomson Reuters), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO*host*), the British Nursing Index (ProQuest) and Health Management Information Consortium (HMIC) (Ovid). The US Food and Drug Administration (FDA) and EMA websites were also searched.

In addition, the following websites were searched for background information (all accessed 26 June 2015):

- medical societies:
  - British Society for Haematology: www.b-s-h.org.uk/
  - Association of Cancer Physicians: www.cancerphysicians.org.uk/
  - ASH: www.hematology.org/
  - ASCO: www.asco.org/
  - Canadian Oncology Societies: www.cos.ca/
  - Haematology Society of Australia and New Zealand: www.hsanz.org.au/
  - Clinical Oncology Society of Australia: www.cosa.org.au/
  - New Zealand Society for Oncology: www.nzsoncology.org.nz/
- UK charities:
  - Cancer Research UK: www.cancerresearchuk.org/home/
  - Macmillan: www.macmillan.org.uk/
  - Marie Curie: www.mariecurie.org.uk/
- non-UK charities:
  - American Cancer Society: www.cancer.org/
  - Canadian Cancer Society: www.cancer.ca/
  - Cancer Council Australia: www.cancer.org.au/
  - Cancer Society of New Zealand: www.cancernz.org.nz/
  - World Cancer Research Fund: www.wcrf-uk.org/.

The database search results were exported to, and deduplicated using, EndNote X5 (Thomson Reuters, CA, USA). Deduplication was also performed using manual checking. The search strategies and the numbers of references retrieved for each database are detailed in *Appendix 1*. After the reviewers completed the screening process, the bibliographies of included papers were scrutinised for further potentially includable studies.

A supplementary search was carried out in MEDLINE (Ovid) to search for utilities as a function of Hb levels and for information on Hb levels after chemotherapy ends. A systematic search was not required for this part of the review and so the search strategy was limited to MEDLINE. These searches are detailed in *Appendix 1*.

Wilson and colleagues[2]

Studies included in the previous HTA review[2] were screened against the inclusion criteria for the PenTAG review for includable studies.

Reference lists

Reference lists of included guidelines, systematic reviews and clinical trials were scrutinised for additional information.

Ongoing trials

A search for ongoing trials was also undertaken. Terms for the intervention ('epoetin' OR 'darbepoetin') and condition of interest (cancer* OR carcinoma* OR leukemia OR malignan* OR neoplasm* OR tumo?r OR myelo* OR lymphoma* OR oncolog* OR chemotherapy*) were used to search the trial registers ClinicalTrials.gov and Current Controlled Trials (International Standard Randomised Controlled Trial Number) for ongoing trials. Trials that did not relate to cancer-induced or chemotherapy-related anaemia were removed by hand sorting. Finally, duplicates, identified through their study identification numbers when possible, were removed. Searches were carried out on 28 August 2013.

Eligibility criteria

Study design

Only RCTs were included. Non-RCTs and quasi-randomised trials (such as when allocation is based on date of birth or day of month) were excluded.

Population

People receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma and at risk of transfusion as assessed by their general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy) and people with non-myeloid malignancies who are receiving chemotherapy were relevant to the scope of this review. There were no age restrictions; however, it is recognised that the licences for all of the interventions of interest do not cover the use of ESAs in children for this indication. Studies in which ESAs were given in the context of myeloablative chemotherapy ahead of bone marrow or peripheral blood stem cell transplantation or for short-term preoperative treatment to correct anaemia or to support collection of autologous blood before cancer surgery were excluded.

Interventions

Studies evaluating the use of ESAs were included if ESAs were given to treat CIA. The ESAs of interest for this appraisal were epoetin alfa (Eprex and Binocrit), epoetin beta (NeoRecormen), epoetin theta (Eporatio), epoetin zeta (Retacrit) or darbepoetin alfa (Aranesp).

Concomitant anaemia therapy, such as iron or granulocyte colony-stimulating factor (G-CSF) supplementation, was permitted, as was RBCT. However, G-CSF had to be administered to patients in both the treatment and the control arms.

Dose

For the main analysis for this systematic review, studies were considered eligible for inclusion if they evaluated a licensed (weight-based) starting dose, irrespective of how they dealt with other criteria stipulated by the licence (see *Table 3*).

With respect to European labelling, inclusion Hb levels ≤ 11 g/dl and > 11 g/dl and target Hb levels ≤ 13 g/dl and > 13 g/dl were considered in subgroup analyses; start dose plus an inclusion Hb level ≤ 11 g/dl and start dose plus an inclusion Hb level ≤ 11 g/dl plus a target Hb level ≤ 13 g/dl were also considered in post-hoc analyses.

Comparator

The main comparators of interest were placebo and best supportive care (including adjustment to the cancer treatment regimen, blood transfusion and iron supplementation). In addition, the comparator could be one of the other ESAs under consideration, provided that it was administered in line with the relevant marketing authorisation.

Outcomes

Outcomes sought from the studies fell into four categories: anaemia-related outcomes, malignancy-related outcomes, AE data and patient-specific outcomes such as quality-of-life outcomes and patient preferences:

- Anaemia-related outcomes: haematological response to treatment (defined as a transfusion-free increase in Hb of ≥ 2 g/dl or a haematocrit increase of 6%), mean Hb change and RBCT requirements [including number of patients transfused, number of units transfused per patient and number of units transfused per average patient (i.e. including participants not requiring transfusion)].
- Tumour response.
- OS.
- On-study mortality.
- AEs: hypertension, rash/irritation, pruritus, mortality, thromboembolic events, seizure, haemorrhage/thrombocytopenia, fatigue and pure red cell aplasia. A note was made of other AEs described within the trial.
- HRQoL: data on validated HRQoL measures was sought – anticipated HRQoL measures included Functional Assessment of Cancer Therapy (FACT) (including FACT-G, FACT-F and FACT-An) [see www.facit.org/FACITOrg/Questionnaires (accessed July 2015)]. A note was made of any other HRQoL measure reported.

Selection of studies

Studies retrieved from the update searches were selected for inclusion according to the inclusion/exclusion criteria specified in *Eligibility criteria*. First, titles and abstracts returned by the search strategy were screened for inclusion independently by four researchers. Disagreements were resolved by discussion, with the involvement of a fifth reviewer. Full texts of identified studies were obtained and screened in the same way. Abstract-only studies were included on the provision that sufficient methodological details were reported to allow critical appraisal of study quality.

In addition, studies included in the review conducted by Wilson and colleagues[2] were screened for inclusion against the eligibility criteria for this review (see *Chapter 1*, *Previous Health Technology Assessment review*).

On completion of the first round of screening, eligible studies were then rescreened. For this stage, studies were eligible for inclusion in the review only if the ESA treatments evaluated were administered in accordance with their European marketing authorisations with respect to the starting dose, irrespective of how the study dealt with other criteria stipulated by the licence (see *Table 3*).

Data extraction and management

Included full papers were split between four reviewers for the purposes of data extraction using a standardised data extraction form. Data extraction was checked independently by another reviewer and discrepancies were resolved by discussion, with the involvement of an additional review team member if necessary. Information extracted and tabulated included details of the study's design and methodology, baseline characteristics of participants and results for the outcomes of interest (see *Appendix 2*).

If several publications were identified for one study, the data from the most recent publication were evaluated and these data were amended with information from other publications.

For studies comparing more than one experimental arm with one control arm, we assigned a separate reference for each study arm, using the author and publication year of the main publication and adding the suffixes a and b, etc. For example, the study by Tjulandin and colleagues[48] compared two different experimental study arms with one control group. Because of this referencing system a study may appear more than twice in the list of included studies.

When there was incomplete information on key data, we referred to the 2012 Cochrane review.[11] For the Cochrane review the authors evaluated documents presented at the Oncologic Drugs Advisory Committee (ODAC) hearing at the US FDA held in May 2004, May 2007 and May 2008. These documents were reported to include briefing documents plus additional PowerPoint presentations prepared by medical review authors of the FDA, as well as documents and additional PowerPoint presentations prepared by the companies Roche, Johnson & Johnson and Amgen Inc.

Critical appraisal

The protocol stated that the Cochrane risk of bias tool would be used for quality appraisal; however, for consistency, assessments of study quality were performed using the same criteria as in the previous review.[2] The criteria used to critically appraise the included studies are summarised in *Table 9*. The results were tabulated and the relevant aspects described on the data extraction forms. Methodological notes were made for each included study on the data extraction forms, including the reviewer's observations on sample size, power calculations, participant attrition, methods of data analysis and conflicts of interest. In addition, GRADE (Grading of Recommendations Assessment, Development and Evaluation) analysis was carried out; the results are presented in *Appendix 3*.

Methods of data analysis/synthesis

When data permitted, the results of individual studies were pooled using the methods described below.

Because of heterogeneity, a random-effects model was assumed for all meta-analyses. For binary data, risk ratio (RR) was used as a measure of treatment effect and the DerSimonian–Laird method was used for pooling. For continuous data, standardised mean differences were calculated if the outcome was measured on the same scale in all trials. For HRQoL, only identical scales and subscales were combined in a given meta-analysis. For time-to-event data, that is, OS, data were extracted from the Cochrane review.[11] In the Cochrane review,[11] hazard ratios (HRs) were based on IPD; when IPD were not available, HRs were calculated from published reports including secondary analyses, using methods reported in Parmar and colleagues,[49] or binary mortality data.[11] Similarly, data from the Cochrane review[11] were used for mean Hb change, transfusion requirement, mean units of blood transfused, complete tumour response, HRQoL and AEs if this information was not available in the published trial reports.

One study[48] had two intervention arms that were separately compared with the control arm. To take account of the fact that some study-specific estimates would use the same control arm, the information was divided across the number of comparisons from the study. When pooling RRs, the number of events

TABLE 9 Quality assessment

Domain	Description
Treatment allocation	1. Was allocation truly random? (Yes: random numbers, coin toss, shuffle, etc.; no: patient ID number, date of birth, alternate; unclear: if the method not stated)
	2. Was treatment allocation concealed? (Yes: central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware; inadequate: allocation was alternate or based on information known to the triallist; unclear: insufficient information given)
Similarity of groups	3. Were the patients' characteristics at baseline similar in all groups?
Implementation of masking	4. Was the treatment allocation masked from the participants? (either stated explicitly or an identical placebo used)
	5. Was the treatment allocation masked from clinicians?
Completeness of trial	6. Were the numbers of withdrawals, dropouts and those lost to follow-up in each group stated?
	7. Did the analysis include an ITT analysis or were < 10% of the study arm excluded?

ITT, intention to treat.

and the total sample size in the control arm were divided equally across the comparisons and, when pooling mean differences, the total sample size in the control arm was adjusted and divided equally across the comparisons. However, if only one experimental arm was eligible for the analysis,[50–53] all participants assigned to the control arm were included.

The following prespecified subgroup analyses were conducted, if appropriate:

- Hb level at study entry (< 10 g/dl vs. < 11 g/dl vs. < 12 g/dl vs. < 14.5 g/dl vs. not reported)
- Hb inclusion criteria (≤ 11 g/dl vs. < 11 g/dl)
- target Hb (≤ 12 g/dl and > 12 g/dl)
- solid tumours compared with haematological malignancies (solid vs. haematological vs. mixed vs. not reported)
- ovarian cancer compared with other cancers
- type of chemotherapy treatment (platinum chemotherapy vs. non-platinum chemotherapy vs. chemotherapy plus radiotherapy vs. mixed chemotherapy vs. not reported)
- short-lasting ESAs compared with long-lasting ESAs (erythopoietins vs. darbepoetin)
- iron supplementation (iron supplementation given vs. no iron supplementation vs. iron handled differently in study arm vs. not reported)
- duration of ESA medication (6–9 weeks vs. 12–16 weeks vs. 17–20 weeks vs. > 20 weeks)
- study design (placebo vs. standard care).

In addition, based on subgroup analyses, meta-regression models were conducted including random effects and a subgroup as a covariate to assess the effects of subgroups on the outcomes. These analyses were conducted if there was a sufficient number of studies in each subgroup. The DerSimonian–Laird method was used to estimate between-study variance in meta-regression. All covariates showing a significant effect ($p < 0.05$) in a univariate analysis were further considered in a model selection. However, these analyses should be interpreted with caution as they can be exploratory only and should be considered as hypothesis-generating rather than hypothesis-testing analyses.[54,55]

We stated in the protocol that we would consider the use of iron supplementation plus ESAs; people with any type of cancer receiving platinum-based chemotherapy; people with head and neck malignancies; women with ovarian cancer; women with ovarian cancer receiving platinum-based chemotherapy; and people unable to receive blood transfusions.

All analyses were performed using Stata version 12 (StataCorp LP, College Station, TX, USA).

Sensitivity analysis

To allow comparison with the Cochrane review[11] and with the previous HTA review,[2] fixed-effects meta-analyses for the main analysis were also conducted.

Assessment of bias

Identified research evidence was interpreted according to the assessment of methodological strengths and weaknesses and the possibility of potential biases. Publication bias for the main outcomes was assessed using funnel plots. The Egger test[56] was used for continuous outcomes [mean difference, standard error (SE)] and the Harbord test[57] was used for binary outcomes [odds ratio (OR), log SE]. However, it should be noted that these tests typically have low power to detect funnel plot asymmetry and so the possibility of publication bias existing in the meta-analysis cannot be excluded even if there is no statistically significant evidence of publication bias. In addition, meta-regression models including random effects and using publication year as a covariate to assess the effect of publication year on the considered outcome were conducted.

Graphical representation of summary trial information

We present a summary of information relating to each trial at the end of each comparison section using Graphical Overview for Evidence Reviews (Gofer) software (developed by Dr Will Stahl-Timmins at the University of Exeter Medical School in association with PenTAG and the European Centre for Environment and Human Health). These figures graphically represent the study design, study quality and results in a format that allows quick comparison between trials.

Note

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Results

Studies identified

We screened the titles and abstracts of 1404 unique references identified by the PenTAG searches and additional sources and retrieved 292 papers for detailed consideration. Of these, 244 were excluded, five because they were unobtainable and 239 for other reasons (a list of these papers with reasons for their exclusion can be found in *Appendix 4*). Forty-eight studies met the prespecified criteria set out in the protocol and were considered eligible for inclusion. In assessing titles and abstracts, agreement between the two reviewers was good ($\kappa = 0.693$, 95% CI 0.648 to 0.738). At the full-text stage, agreement was substantial ($\kappa = 0.792$, 95% CI 0.705 to 0.879). At both stages, initial disagreements were easily resolved by consensus.

Twenty-nine studies from the previous HTA review[2] were also considered eligible for inclusion in the update review. We also searched the citations of all of the includable studies and systematic reviews (including the 2012 Cochrane review;[11] see *Appendix 5*). This process revealed an additional five primary studies.[58–62]

In restricting eligibility to ESA treatments evaluated in accordance with their European marketing authorisation with respect to starting dose, 47 studies were excluded (a list of these studies together with the study characteristics can be found in *Appendix 6*). In total, 23 primary studies[17,48,50–53,62–78] reported in 34 publications[17,48,50–53,58–60,62–86] were judged to meet the inclusion criterion for the review (*Table 10*); study characteristics are summarised in *Appendix 7*. Primary studies are linked to multiple secondary publications, as shown in *Appendix 8*.

Update searches were conducted on 2 December 2013 using the same methodology as described earlier. In total, 68 records were screened by two reviewers (LC and MH) and eight records were selected for full-text retrieval. No studies were judged eligible on full-text appraisal. A list of these papers with reasons for their exclusion can be found in *Appendix 4*.

The process of identifying studies is illustrated in detail in *Figure 1*.

TABLE 10 Study characteristics

Author, year	*n*	Agent	Control	Malignancy	Treatment	Outcomes	Multiple publications identified
Included studies from Wilson and colleagues[2] meeting the inclusion criteria for the PenTAG review							
Abels 1993[63]	413[a]	Epoetin alfa	Placebo	Haematological[b]	Chemotherapy: mixed	HaemR, Hb, HCT, RBCT, HRQoL,[c] AE[c]	Abels 1996,[59] Case 1993,[86] Henry 1994,[85] Henry 1995[58]
Aravantinos 2003[64]	47	Epoetin alfa	Standard	Solid	Chemotherapy: platinum based	Hb, HCT, RBCT	NA
[d]Boogaerts 2003[65]	262	Epoetin beta	Standard	Solid and haematological[b]	Chemotherapy: NR	HaemR, Hb, RBCT, HRQoL	NA
Dammacco 2001[66]	145	Epoetin alfa	Placebo	Haematological[b]	Chemotherapy: mixed[e]	HaemR, Hb, RBCT, HRQoL, AEs	NA
Del Mastro 1997[67]	62	rHuEPO[f]	Standard	Solid (breast)	Chemotherapy: non-platinum based	Hb, RBCT, HRQoL, AEs	NA
Dunphy 1999[68]	30	rHuEPO[f]	Standard	Solid (head and neck, lung)	Chemotherapy: mixed	Hb, RBCT	NA
Hedenus 2002[53]	33[g]	Darbepoetin alfa	Placebo	Haematological[b]	Chemotherapy: NR	HaemR, Hb, RBCT, AEs	NA
Hedenus 2003[17]	349	Darbepoetin alfa	Placebo	Haematological[b]	Chemotherapy: NR	HaemR, Hb, RBCT, AEs, HRQoL	Littlewood 2006[83]
Kotasek 2003[50]	249	Darbepoetin alfa	Placebo	Solid	Chemotherapy: NR	HaemR, Hb, RBCT, HRQoL	NA
Kurz 1997[69]	35	Epoetin alfa	Placebo	Solid (cervix, ovary, uterus)	Chemotherapy: mixed	HaemR, Hb, RBCT, HRQoL, AEs	NA
Littlewood 2001[70]	375	Epoetin alfa	Placebo	Mixed	Chemotherapy: non-platinum based	HaemR, Hb, RBCT, HRQoL, AEs	Aapro 2004,[82] Bajetta 2004,[81] Patrick 2003[60]
Österborg 2002[71]	349	Epoetin beta	Placebo	Haematological[b]	Chemotherapy: non-platinum based	HaemR, Hb, RBCT, HRQoL, AEs	Österborg 2005[79]
Silvestris 1995[72]	54	Epoetin alfa	Standard	Haematological[b]	Chemotherapy: NR	HaemR, Hb, AEs	NA
ten Bokkel Huinink 1998[51]	122	Epoetin beta	Standard	Solid (ovary)	Chemotherapy: platinum based	Hb, RBCT, AEs	NA
Thatcher 1999[52]	130	Epoetin alfa	Standard	Solid (SCLC)	Chemotherapy: mixed	Hb, RBCT, HRQoL, AEs	NA
Vansteenkiste 2002[73]	314	Darbepoetin alfa	Placebo	Solid (lung)	Chemotherapy: platinum based	HaemR, Hb, RBCT, HRQoL, AE, disease progression, survival	Vansteenkiste 2004[84]

Author, year	*n*	Agent	Control	Malignancy	Treatment	Outcomes	Multiple publications identified
PenTAG review update 2004 to July 2007							
Grote 2005[74]	224	Epoetin alfa	Placebo	Solid (SCLC)	Chemotherapy: mixed	Hb, RBCT, TR, survival, AEs	NA
Moebus 2013[62]	643	Epoetin alfa	Standard	Solid (breast)	Chemotherapy: non-platinum based	Hb, RBCT, HRQoL,[f] survival, AEs	NA
Ray-Coquard 2009[75]	218	Epoetin alfa	Standard	Mixed	Chemotherapy: NR	RBCT, OS, HRQoL, AEs	NA
Österborg 2005[79]	349	Epoetin beta	Placebo	Haematological[b]	Chemotherapy: non-platinum based	HaemR, Hb, RBCT, HRQoL, AEs	Österborg 2002[71]
Strauss 2008[76]	74	Epoetin beta	Standard	Solid (cervix)	Chemotherapy + radiotherapy	Hb, RBCT, TR, survival, AEs	NA
Tjulandin 2010[48]	223	Epoetin theta, epoetin beta	Placebo	Solid	Chemotherapy: platinum based	HaemR, RBCT, HRQoL,[h] AEs	NA
Tjulandin 2011[77]	186	Epoetin theta	Placebo	Mixed	Chemotherapy: non-platinum based	HaemR, RBCT, HRQoL, AEs	NA
[i]Untch 2011[78]	733	Darbepoetin alfa	Standard	Solid (breast)	Chemotherapy: non-platinum based	Hb, pathological response, disease progression, survival, AEs	Untch 2011[80i]

HaemR, haematological response; HCT, haematocrit; NA, not applicable; NR, not reported; refs, references; rHuEPO, recombinant human erythropoietin; SCLC, small-cell lung cancer; TR, tumour response.

a Study population included patients not receiving chemotherapy ($n = 124$), who were beyond the scope for the current review.
b Specifically, haematological non-myeloid malignancies (chronic lymphocytic leukaemia, non Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma within these studies).
c Outcomes reported for all participants (i.e. includes patients not receiving chemotherapy).
d Coiffier and colleagues[87] was included in the review by Wilson and colleagues.[2] For this review we identified and included the full paper.[65]
e Majority of participants reported to be on non-platinum chemotherapy.
f Assumed to be epoetin alfa or epoetin beta based on date of study and dose administered.
g Dose–response study: other doses of darbepoetin alfa included.
h HRQoL data not reported in published paper.
i The Untch and colleagues[78,80] trial was a Latin square design and is reported in two publications.

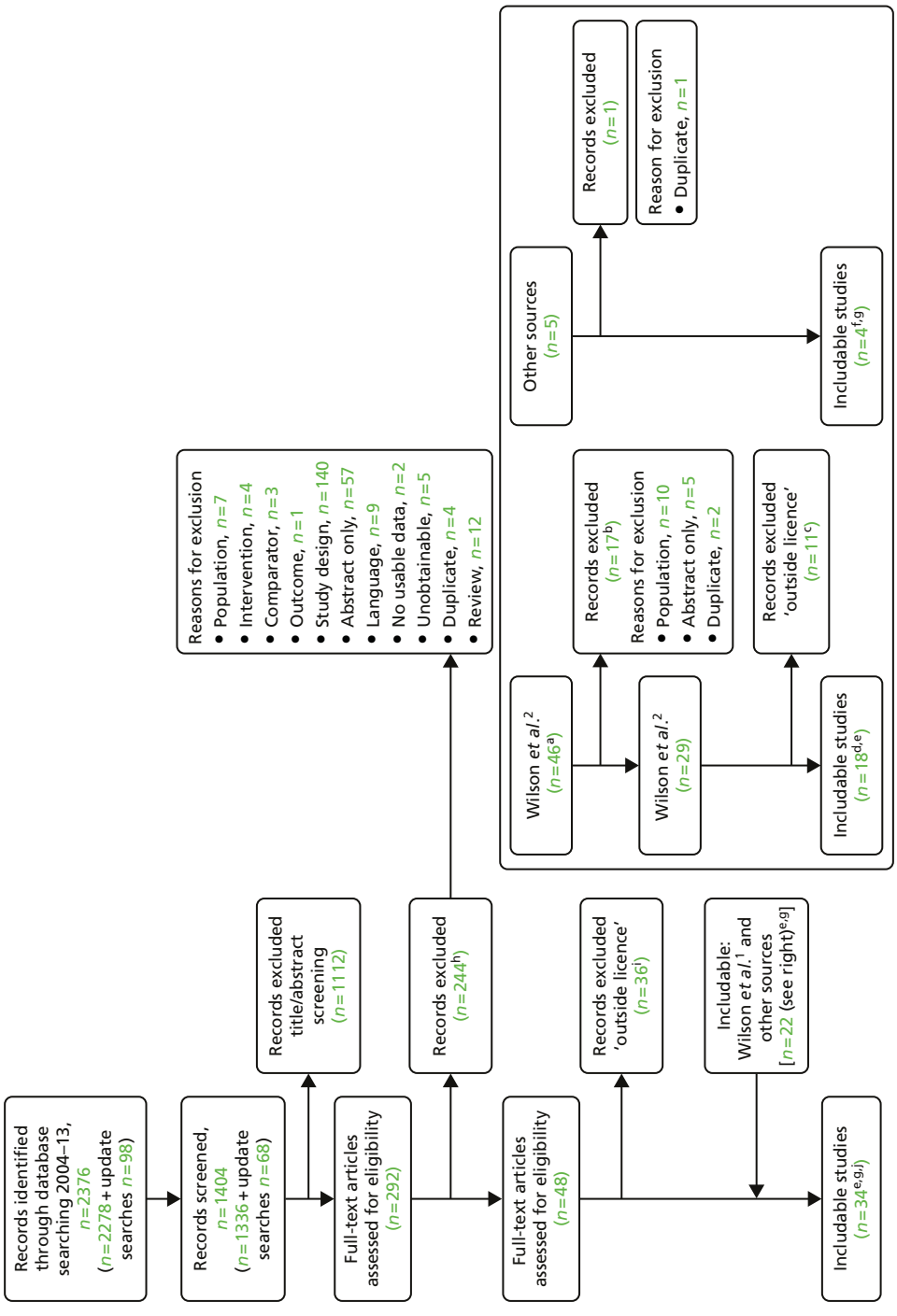

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart: clinical effectiveness review. a, Number of included studies in the previous HTA review.[2] b, Excluded studies listed in *Appendix 4* (see *Wilson and colleagues*[2] *excluded studies*). c, Baseline characteristics for studies excluded on dose ('outside of licence', $n = 11$) are reported in *Appendix 6*. Note that, for four included trials[50–53] that evaluated different ESA doses, only the within-license doses were included in the PenTAG review. As a result, the number of studies in the subsection of the table 'Wilson and colleagues[2]' is 15. d, Coiffier and colleagues[87] was included in the review by Wilson and colleagues.[2] The full paper[65] for this abstract was identified by citation chasing and included in the PenTAG review. e, Wilson and colleagues:[2] 16 primary trials[17,50–53,63–73] reported in 18 publications.[17,50–53,58,63–73,86] f, Other sources: 11 systematic reviews[2,7,11,41,88–94] reported in 12 publications.[2,7,11,41,88–95] g, Other sources: four studies[59,60,62,85] were identified as eligible for inclusion. h, Excluded studies listed in *Appendix 4* (see *Clinical effectiveness review: excluded studies*). i, Baseline characteristics for studies excluded on dose ('outside of licence', $n = 36$) are reported in *Appendix 6*. j, PenTAG searches 2004–13: seven primary trials[48,74–78,80] reported in 12 publications.[48,74–84]

Study characteristics

No head-to-head trials were identified in either the 2007 review[2] or the update searches. One three-arm trial compared epoetin beta and epoetin theta with placebo;[48] however, comparison was made only between each intervention and placebo. The majority of trials (> 50%) compared an ESA plus standard care with placebo plus standard care. Of these, four trials were identified in the update searches.[48,74,77,79] Of note, the Österborg and colleagues trial[79] evaluated long-term survival for epoetin beta plus standard care compared with placebo plus standard care from the earlier 2002 RCT.[71] The remaining trials compared an ESA plus standard care with standard care alone. Of these, four trials (reported in five publications) were identified in the update searches.[62,75,76,78,80]

Interventions and comparators

The following interventions were evaluated in the included studies: epoetin alfa, beta and theta and darbepoetin alfa (*Table 11*). In two of the included studies it was uncertain which ESA was evaluated [reported as recombinant human erythropoietin (rHuEPO)],[67,68] although it was assumed to be either epoetin alfa or epoetin beta based on the study dates and the doses evaluated. Of note, no studies of epoetin zeta met the eligibility criteria for this review (study design).

The ESA administration and dosing strategies varied considerably in the literature in terms of starting dose (fixed or weight based), trigger Hb level (the point below which ESAs should be administered, ≤ 10.0 g/dl), target Hb level (the point above which ESAs should be stopped or titrated, 10–12 g/dl), dose escalation (used if people do not achieve a haematological response within a specified time period), stopping rules for non-responders and duration of use following each chemotherapy session. These aspects will have an impact on clinical effectiveness. The majority (82%) of studies were initiated before the 2008 update of the SPCs and no studies were completely aligned with the UK marketing authorisation for these drugs in respect of these criteria (see *Appendix 9*).

This review focused only on those studies evaluating ESA treatment in accordance with UK marketing authorisations with respect to the starting dose (see *Dose*), irrespective of other aspects of the licence (e.g. starting or target Hb levels or stopping rules). For darbepoetin alfa, two studies[50,53] were dose ranging studies and therefore evaluated doses under and over the current licence recommendations, and two studies[51,52] included a second intervention group evaluating epoetin alfa at a start dose of 300 IU/kg.

TABLE 11 Interventions included in the trials

Intervention	Number of studies[a]	vs. placebo + SC	vs. SC alone	Total population,[b] *n*	Treated with ESA, *n* (%)
Epoetin alfa[c]	10[c]	5	5[c]	2284	1135 (56)
Epoetin beta[c]	4[c,d]	1[d]	3[c]	768	382 (50)
Epoetin theta	2[d]	2[d]	0	409	171 (42)
Epoetin zeta	0	–	–	–	–
Darbepoetin alfa	5	4	1	1678	727[e] (43)
rHuEPO[f]	2	–	2	92	46 (50)
Total	23[d]	12[d]	11		

SC, standard care.
a Only accounts for primary study.
b Number randomised.
c Two studies included a second intervention group evaluating epoetin alfa at a start dose of 300 IU/kg ($n = 86$).[51,52]
d One study[48] was a three-arm study evaluating epoetin theta and epoetin beta vs. placebo.
e Two included studies[50] were dose-ranging studies. Only one of the ESA treatment arms was eligible for inclusion in the review (17 of 198 participants treated with ESAs)[50] and 22 of 55 participants treated with ESAs.[51,52]
f Uncertain which erythropoietin was evaluated, although it was assumed to be either epoetin alfa or epoetin beta, based on the study dates and doses administered.

Only the licensed start doses from these studies were included in the PenTAG review. In addition, one study[78,80] evaluated darbepoetin alfa at a dose of 4.5 µg/kg once every 2 weeks. This was considered to be within licence, as the equivalent dose per week (2.25 µg/kg) is a licensed dose.

Of note, none of the included studies evaluated ESAs entirely within the remit of their marketing authorisations, in particular with respect to trigger and target Hb levels and stopping rules, all of which were generally higher than specified in the licence. *Appendix 9* provides a summary of the administration of ESAs within the included studies in relation to their respective licences. Two additional definitions of 'within licence' were considered in post-hoc analyses: (1) licensed start dose plus inclusion Hb level ≤ 11 g/dl and (2) licensed start dose plus inclusion Hb level ≤ 11 g/dl plus target Hb level ≤ 13 g/dl.

The majority of the trials gave ESA therapy over the course of the chemotherapy, with many continuing with ESA therapy for 4 weeks after chemotherapy, which is permissible within the licensed indications. The average time on erythropoietin treatment was 12 weeks, with trial duration clustering around 12–28 weeks. One study reported follow-up data.[79]

Concomitant treatments

There were several possible concomitant treatments – G-CSF, iron supplementation and RBCT, with some protocols giving recommendations for when transfusions should be given (referred to in this review as transfusion triggers) (see *Appendix 7*). Two studies were identified in which G-CSF was given. In one study[67] G-CSF was given at a dose of 5 µg/kg from day 4 until day 11 during the first five chemotherapy cycles, to allow accelerated chemotherapy. The second study[75] stated that G-CSF could be used in primary or secondary prophylaxis as recommended by ASCO and French Federation of Cancer Centre guidelines. However, it was unclear whether G-CSF was administered to any of the study participants during the study period.

In the majority of studies ($n = 14$[17,48,64,65,67–72,75–80]) iron supplementation was given. Reporting of details in this respect varied. A fixed daily dose of oral iron (either 200 mg or 325 mg) for all patients was most common, although in a few studies administration of oral iron supplementation was dependent on transferrin saturation levels (i.e. ≤ 20% or < 10%); in one study[70] daily oral iron supplementation was recommended, but if (during the study) transferrin saturation fell to ≤ 20% intravenous iron was recommended. In two studies that enrolled patients with a baseline transferrin saturation level of < 25%[71,79] and < 20%,[76] participants were given intravenous iron supplementation at a dose of 100 mg per week before the start of study treatment. In cases in which patients were contraindicated or the drug was not available, oral iron supplementation was administered. In one study[69] intravenous iron supplementation was administered following each dose of chemotherapy, beginning with the next cycle. One trial was identified in which concomitant iron supplementation was given only to patients receiving an erythropoietin.[78,80] Several studies reported that iron supplementation was allowed during the study without specifying details or that iron supplementation was given at the investigators' discretion. Nine studies did not report concomitant treatment and in two studies[52,73] iron supplementation during the study period was not permitted.

Population characteristics

Population characteristics of the included trials are summarised in *Tables 12* and *13*; characteristics are described in more detail in *Appendix 7*.

TABLE 12 Malignancies included in the trials

Malignancy	Mixed types	Specific malignancies
Solid tumours	Tjulandin 2010;[48] Aravantinos 2003;[64] Kotasek 2003;[50] Dunphy 1999;[68] Kurz 1997[69]	Moebus 2013[62] (breast); Untch 2011[78,80] (breast); Strauss 2008[76] (cervix); Grote 2005[74] (SCLC); Vansteenkiste 2002[73] (lung); Thatcher 1999[52] (SCLC); ten Bokkel Huinink 1998[51] (ovary); Del Mastro 1997[67] (breast)
Haematological[a]	Hedenus 2003;[17] Österborg 2002,[71] [b]Österborg 2005;[79] Hedenus 2002;[53] Dammacco 2001[66]	Silvestris 1995[72] (MM)
Mixed solid and haematological[a]	Tjulandin 2011;[77] Ray-Coquard 2009;[75] Boogaerts 2003;[65] Littlewood 2001;[70] [c]Abels 1993[63]	

MM, multiple myeloma; SCLC, small-cell lung cancer.
a Specifically, haematological non-myeloid malignancies (chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma within these studies).
b Follow-up of the study by Österborg and colleagues[71] study.
c Population includes patients receiving platinum-based and non-platinum-based chemotherapy and patients receiving no treatment.

TABLE 13 Malignancy treatments included in the trials

Malignancy	Trials
Chemotherapy: platinum based	Tjulandin 2010;[48] Vansteenkiste 2002;[73] Aravantinos 2003;[64] [a]ten Bokkel Huinink 1998;[51] Abels 1993[63]
Chemotherapy: non-platinum based	Moebus 2013;[62] Tjulandin 2011;[77] Untch 2011;[78,80] Österborg 2002,[71] [b]2005;[79] Littlewood 2001;[70] [a]Del Mastro 1997;[67] Abels 1993[63]
Chemotherapy: type unknown	Ray-Coquard 2009;[75] Boogaerts 2003;[65] Hedenus 2003;[17] Kotasek 2003;[50] Hedenus 2002;[53] Silvestris 1995[72]
Mixed chemotherapy	Grote 2005;[74] Dammacco 2001;[66] Dunphy 1999;[68] Thatcher 1999;[52] Kurz 1997[69]
Chemotherapy + radiotherapy	Strauss 2008[76]

a Population includes patients receiving platinum-based and non-platinum-based chemotherapy and patients receiving no treatment, but data are reported separately for each group.
b Follow-up of the study by Österborg and colleagues[71] study.

The age range of trial participants was 18–92 years. In the majority of included studies there was an equal distribution of men and women, with the obvious exception of trials whose populations had gynaecological and breast malignancies (within the breast malignancies group one patient was male[70]). However, in one study[68] (head, neck and lung tumours) gender was not distributed equally between the two treatment groups; in the treatment arm 92% of participants were men, compared with an equal distribution of men and women in the control arm (50% each).

The studies included a variety of malignancies (see *Table 12*). Five trials included patients with a mix of solid tumours.[48,50,64,68,69] One of the retrospective analyses identified[81] was a subgroup analysis of a breast cancer cohort enrolled in the study conducted by Littlewood and colleagues;[70] however, the overall study was not powered to discriminate treatment differences within subgroups. Eight of the included studies concentrated on specific solid tumour types (breast $n = 3$;[62,67,78,80] ovary $n = 1$;[51] cervix $n = 1$;[76] lung $n = 3$[52,73,74]). Four studies included a mix of haematological malignancies (specifically haematological non-myeloid malignancies: chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma);[17,53,66,71,79] of these, one study was reported in two papers,[71,79] with the later paper[79]

reporting long-term survival data from the earlier study.[71] One study focused on multiple myeloma.[72] Five studies included participants with a mix of solid and haematological malignancies.[63,65,70,75,77]

Malignancy treatments consisted of chemotherapy (platinum based and non-platinum based) and chemotherapy plus radiotherapy. In four studies participants received platinum-based chemotherapy,[48,51,64,73] in six studies participants were on non-platinum-based chemotherapy,[62,67,70,71,77–80] in one study participants received platinum-based and non-platinum-based chemotherapy,[63] in six studies participants were receiving chemotherapy but the type was unknown[17,50,53,65,72,75] and in five studies participants were on mixed chemotherapy treatment.[52,66,68,69,74] Of the group of trials in which participants received mixed chemotherapy, two[52,69] reported that the majority of participants received platinum-based chemotherapy (proportion not reported) and in one[66] of the studies the majority of participants received non-platinum-based chemotherapy (proportion not reported). One trial involved participants on chemotherapy plus radiotherapy.[75]

The majority of included studies specified the required baseline degree of anaemia in the eligibility criteria, with three studies not specifying this. The highest cut-off was a Hb level of $\leq$ 14.5 g/dl[74] and the lowest was a Hb level of $\leq$ 8 g/dl.[72] Despite this, the mean/median Hb level at baseline ranged from 9.2 g/dl to 14.1 g/dl in the intervention group and from 9.1 g/dl to 14.1 g/dl in the control group.

Quality of the included studies

It was originally intended to use the Cochrane risk of bias tool to assess study quality; however, all trials were assessed using the same quality assessment tool as in the previous HTA review.[2] Quality assessment criteria are presented in *Table 9* and the study quality appraisal is presented in *Table 14*. However, there is some variation in the method of quality assessment between the previous review and the current review. In the current appraisal, only information published in the primary studies was considered when conducting the quality appraisal, whereas the previous HTA review also used quality assessment information published in the 2004 Cochrane review.[45] Cochrane review authors contacted the trial investigators to request missing data, including information on study conduct. In addition, we have access to new information from papers published after the inclusion date for the previous review. Only primary studies were appraised, with secondary analyses of previously published data not assessed. Similarly, if a trial was reported in multiple publications, only one quality assessment of the trial was conducted. In total, 23 trials were assessed,[17,48,50–53,62,63–78] including eight trials not included in the previous HTA review.[2] In addition, GRADE analysis was carried out, with the results presented in *Appendix 3*.

Overall assessment

The 23 included RCTs were of variable quality but all are flawed, some because of reporting issues but others more substantially. For most of the trials it was difficult to make a general assessment about study quality because of reporting omissions. In fact, 10[51,52,62,64,66,67,70,71,73,78–80] of the 23 trials either did not report, or lacked clarity on, at least three of the seven items constituting the quality appraisal tool used (see *Table 9*). Most notably, all trials lacked clarity in the reporting of allocation methods (the procedure for randomisation and/or allocation concealment). Three of the studies were of generally high quality,[48,69,77] with each of these satisfactorily addressing five of the seven items of the quality appraisal tool used. However, even the reports of these three studies omitted important information relating to study quality. The study by Dunphy and colleagues[68] has the poorest quality profile, followed by that by Boogaerts and colleagues,[65] Ray-Coquard and colleagues[75] and Silvestris and colleagues.[72] Further details of the quality of the included studies according to individual items on the quality appraisal tool used are provided in the following sections.

Treatment allocation

Random allocation

The method of random allocation was clearly stated and sufficient in nine trials,[17,48,53,62,67,69,72,74,77] whereas 14 trials[50–52,63–66,68,70,71,73,75,76,78–80] did not specify the method used.

TABLE 14 Study quality

Author, year	Random allocation	Concealment of allocation	Baseline similarity	Patients blinded	Physicians blinded	Losses	ITT or < 10% dropout
Abels 1993[63]	Unclear[a]	NR	Unclear[b]	Yes	Yes	Partially	Yes
Aravantinos 2003[64]	Unclear[a]	NR	Unclear[b]	No	No	NR	Yes
Boogaerts 2003[65]	Unclear[a]	NR	No: previous chemotherapy, FACT-F	No	No	Partially	Yes
Dammacco 2001[66]	Unclear[a]	Unclear[c]	Unclear[b]	Yes	Yes	Yes	Yes, primary end point and HRQoL only
Del Mastro 1997[67]	Yes	NR	Unclear[b]	No	NR	Partially	Yes, apart from HRQoL (87% and 84% of participants were analysed in the treatment and control groups, respectively)
Dunphy 1999[68]	Unclear[a]	NR	No: gender	No	No	Yes	No
Grote 2005[74]	Yes	NR	Unclear[b]	Yes	Yes	Partially[d]	Yes
Hedenus 2002[53]	Yes	Unclear[c]	No: gender, platelet and neutrophil counts	Yes	Yes	Partially	Yes[e]
Hedenus 2003[17]	Yes	NR	Unclear	Yes	Yes	Partially[d]	Yes[e]
Kotasek 2003[50]	Unclear[a]	NR	Yes[f]	Yes	Yes	Partially[d]	Yes[e]
Kurz 1997[69]	Yes	Unclear[c]	Yes	Yes	Yes	NR	Yes, results report response for all participants; assumed ITT
Littlewood 2001[70]	Unclear[a]	NR	Unclear[b]	Yes	Yes	Yes	Yes, apart from HRQoL (80% and 73% of participants were analysed in the treatment and control groups, respectively)
Moebus 2013[62]	Yes	Unclear[c]	Unclear[b]	NR	NR	Yes	Yes
Österborg 2002[71]	Unclear[a]	NR	Unclear[b]	Yes	Yes	Partially[d]	Yes
Ray-Coquard 2009[75]	Unclear[a]	Unclear[c]	No: HRQoL[b]	No	No	Partially	Yes, apart from HRQoL (54% and 57% of participants were analysed in the treatment and control groups, respectively)

continued

TABLE 14 Study quality (*continued*)

Author, year	Random allocation	Concealment of allocation	Baseline similarity	Patients blinded	Physicians blinded	Losses	ITT or < 10% dropout
Silvestris 1995[72]	Yes	NR	NR	No	No	Yes	No
Strauss 2008[76]	Unclear[a]	Unclear[c]	Yes	No	No	Yes	Yes
ten Bokkel Huinink 1998[51]	Unclear[a]	NR	Unclear[b]	No	No	Partially	Yes, but two participants were excluded from ITT analyses
Thatcher 1999[52]	Unclear[a]	NR	Unclear[b]	No	NR	Yes	Yes, apart from HRQoL (75% and 61% of participants were analysed in the treatment and control groups, respectively)
Tjulandin 2011[77]	Yes	NR	Unclear[b]	Yes	Yes	Yes	Yes, apart from HRQoL (89.5–97.9% and 85.7–96.7% of participants were analysed in the treatment and control groups, respectively)
Tjulandin 2010[48]	Yes	Unclear[g]	Unclear[b]	Yes	Yes	Yes	Yes
Untch 2011[78]	Unclear[a]	NR	NR[h]	No	No	Partially[d]	Yes
Vansteenkiste 2002[73]	Unclear[a]	Unclear[c]	Unclear[b]	Yes	Yes	Partially	Yes,[e] apart from HRQoL (81% of participants were analysed in both the treatment group and the control group)

ITT, intention to treat; NR not reported.

a Randomisation details are not reported.

b *p*-values for baseline comparisons are not reported, although authors report 'similarity between groups'.

c Randomisation was performed using a centralised system but no details on allocation concealment were reported.

d Losses reported for the treatment period only; data for the follow-up period are not reported.

e < 10% dropout but ITT analysis was defined as all randomised participants who received at least one dose of the study drug.

f Baseline values were similar in the placebo and the 6.75 µg/kg darbepoetin alfa subgroup (subject of this review). In the 12.0 mg/kg group a higher proportion of patients had breast cancer and the mean baseline Hb concentration was higher.

g Authors stated that 'only the person administering study medication was unblinded'. This may imply that the person allocating treatment was unaware of the next allocation, but there is nothing explicitly stated and so concealment of allocation remains unclear.

h Authors stated that 'baseline characteristics were similar in the treatment arms'. It is assumed that this refers to the chemotherapy arms and thus a baseline comparison is not reported for the epoetin vs. no epoetin arms.

Concealment of allocation

The method of concealment of allocation was not clearly reported in any of the included trials. Fourteen trials[17,50–52,63–65,67,68,70–72,74,78–80] did not report any information on allocation concealment, whereas eight trials[48,53,62,66,69,73,75,76] provided some information. A centralised system for randomisation was reported in seven trials[53,62,66,69,73,75,76] and authors of one trial[48] stated that only the person administering study medication was unblinded. It is therefore possible that the allocation sequence was concealed in these eight trials. However, as no specific details on allocation concealment were reported, this remains unclear.

Similarity of groups

Only three trials[50,69,76] fully reported baseline characteristics, including *p*-values for baseline group comparisons. Authors of 14 trials[17,48,51,52,62–64,66,67,70,71,73,74,77,79] stated that there was 'similarity between groups'; however, no statistical information was reported to support this. Another four studies[53,65,68,75] reported some baseline differences for one or more outcomes, whereas no baseline characteristics were reported for two trials;[72,78,80] one[78,80] of these two trials used a Latin square design and baseline characteristics are reported for groups randomised by chemotherapy but not for the erythropoietin randomisation.

Implementation of masking

Treatment allocation masked from participants

Participants were blinded to treatment allocation in 12 trials.[17,48,50,53,63,66,69–71,73,74,77,79] Ten trials[51,52,64,65,67,68,72,75,76,78,80] did not blind participants from treatment allocation and one trial[62] did not report any information about blinding participants to treatment allocation.

Treatment allocation masked from clinicians

The 12 trials[17,48,50,53,63,66,69,70,71,73,74,77,79] that blinded participants to treatment allocation also masked treatment allocation from clinicians. Eight trials[51,64,65,68,72,75,76,78,80] did not blind clinicians to treatment allocation and three trials[52,62,67] did not report any information about blinding of clinicians to treatment allocation; these three trials compared erythropoietin groups with standard care.

Completeness of the trial

Reporting of losses to follow-up, withdrawals and dropouts

Losses to follow-up, withdrawals and dropouts were fully reported in nine trials[48,52,62,66,68,70,72,76,77] and partially reported in 12 trials.[17,50,51,53,63,65,67,71,79,73–75,78,80] Among the 12 trials in which this information was partially reported, five trials[17,50,71,74,78–80] reported withdrawals and dropouts until the end of the trials but did not provide any data on the follow-up period. Two trials[64,69] did not report any information on losses to follow-up, withdrawals and dropouts.

Intention-to-treat analysis or < 10% of participants lost

Intention-to-treat (ITT) analysis or < 10% of participants lost was reported in 14 studies[17,48,50,51,53,62,63–65,69,71,74,76,78–80] for all measured outcomes. ITT analysis or < 10% of participants lost was reported in seven studies[52,66,67,70,73,75,77] for the primary outcome and most of the secondary outcomes. Only two trials[68,72] did not use ITT analysis or reported ≥ 10% of participants lost.

Manufacturers' reviews of clinical effectiveness

Two submissions were presented summarising evidence on the effectiveness of darbepoetin alfa (Aranesp)[96] and epoetin alfa (Binocrit).[97]

One was a systematic review submitted by Amgen Inc. summarising evidence of the effectiveness of darbepoetin alfa (Aranesp) and the other was an evidence summary submitted by Sandoz Ltd, summarising trials from its clinical development programme and post-approval trials (biosimilar epoetin alfa; Binocrit). Although neither are part of the PenTAG systematic review, they are presented here for convenience and because the results are compared.

Epoetin alfa (Binocrit)

Sandoz Ltd submitted an evidence summary that contained a number of publications that were excluded from the PenTAG review because they did not meet the inclusion criteria. A list of these publications with reasons for their exclusion can be found in *Appendix 10*.

The evidence summary consisted of:

- Details of the clinical development programme for Binocrit:
  - Three Phase I studies: multiple intravenous doses of Binocrit compared with epoetin alfa 100 IU/kg three times a week;[98] multiple subcutaneous doses of Binocrit compared with epoetin alfa 100 IU/kg three times a week;[99] and multiple subcutaneous doses of Binocrit compared with epoetin beta 100 IU/kg three times a week.[100] All studies were of 4 weeks' duration.
  - Pivotal data: two Phase III studies.[101,102] Both of the Phase III studies were identified in the PenTAG review; one was excluded on population (chronic renal failure)[102] and the other was excluded on comparator (epoetin alfa assessed by class).[101]
- Post-approval data: four retrospective studies were identified, of which three were abstracts (one observational study,[103] one single-centre audit[104] and one retrospective, matched-cohort analysis[105]) and one was a fully published retrospective study.[106] These were not included in the PenTAG review as they were non-randomised studies.

Results from the identified studies were reported narratively. One Phase III trial[101] evaluated the efficacy and safety of Binocrit in the treatment of CIA in cancer patients ($n = 114$; $n = 94$ ITT population). The comparator was epoetin alfa (Erypo/Eprex) and the primary end point was haematological response (absolute increase in Hb of ≥ 2 g/dl between the screening/baseline period and the evaluation period in the absence of RBCT during the preceding 4 weeks). Haematological response (as defined) was reported in 62% ($n = 37/60$) (95% CI 48.2% to 78.9%) of participants treated with Binocrit and RBCT requirement was 32% ($n = 19/60$) compared with 38% ($n = 13/34$) in the epoetin alfa (Erypo/Eprex) group. The study reported comparable efficacy and a similar safety profile to that expected for the therapeutic area.

Results from non-RCT and observational studies were presented to support the application with regard to the effectiveness of ESAs in terms of the haematological response (Hb change, RBCT requirement). The reported results are consistent with existing evidence in respect of these outcomes.

Evidence was also presented to support the following additional aspects:

- pharmacoeconomic rationale for the use of biosimilars
- adjusting the current recommendation regarding the trigger Hb level (≤ 8 g/dl) to align with UK marketing authorisation, product SPCs and clinical guidelines (≤ 10 g/dl)
- advantages of using Binocrit over alternative ESAs, for example syringes have an innovative safety needle protector, extended shelf-life of 24 months.

Darbepoetin alfa (Aranesp)

Amgen Inc. presented a meta-analysis of pivotal trials as part of its submission. Searches for the systematic review were based on the previous HTA appraisal[2] and included RCT evidence published since 2004 evaluating the efficacy and safety of ESAs for the treatment of CIA in cancer patients, specifically darbepoetin alfa. Studies that used a licensed starting dose (500 µg, 6.75 µg/kg once every 3 weeks or 2.25 µg/kg once a week) were considered eligible for inclusion.

A total of nine studies were identified that evaluated darbepoetin alfa compared with best supportive care (placebo, no treatment, usual care) for the treatment of CIA in cancer patients. Four were included in the PenTAG review.[17,50,53,73] Five studies were abstracts[107–111] and as such were not included in the PenTAG systematic review as there was not enough information to quality appraise the abstracts; they are described in *Appendix 10*.

The pooled summary estimates presented for the effect of darbepoetin alfa on CIA in cancer patients are provided in *Table 15*.

The pooled summary estimates presented for the effect of ESAs (specifically darbepoetin alfa for this analysis) were largely consistent with the summary estimates in the PenTAG systematic review, particularly with respect to improvements in haematological response and reduction in RBCT requirements. No significant difference was observed for the outcome of Hb change. Estimates for the malignancy-related outcomes – tumour response and survival – suggested a benefit of treatment compared with the control; however, the results were not statistically significant and there was evidence of heterogeneity in the case of OS. In addition, data were insufficient in this respect to rule out detrimental effects; however, this uncertainty is consistent with previously reported estimates. Estimates for thromboembolic events (RR 2.15, 95% CI 1.41 to 3.28) were worse than estimates in the PenTAG review.

TABLE 15 Summary of the results of the meta-analyses in the Amgen Inc. submission

Outcome	Results from meta-analyses
Anaemia-related outcomes	
Hb change[a,b]	WMD 1.06, 95% CI 0.86 to 1.26, $p < 0.00001$; $\chi^2_{(het)} = 10.79$, df = 2; $p = 0.005$; $I^2 = 81\%$ 3 trials, $n = 1645$
HaemR[b,c]	RR 3.67, 95% CI 2.73 to 4.94, $p < 0.00001$; $\chi^2_{(het)} = 1.77$, df = 3; $p = 0.62$; $I^2 = 0\%$ 4 trials, $n = 528$
RBCT[b]	RR 0.56, 95% CI 0.49 to 0.64, $p < 0.00001$; $\chi^2_{(het)} = 4.43$, df = 6; $p = 0.62$; $I^2 = 0\%$ 7 trials, $n = 1744$
Units transfused[b]	WMD –1.25, 95% CI –1.84 to –0.66; $p < 0.00001$; heterogeneity NA 1 trial, $n = 298$
Malignancy-related outcomes	
Tumour response[b]	RR 0.99, 95% CI 0.89 to 1.09; $p = 0.84$; heterogeneity NA 1 trial, $n = 599$
OS[b]	HR 0.88, 95% CI 0.72 to 1.06; $p = 0.18$; $\chi^2_{(het)} = 4.74$, df = 3; $p = 0.19$; $I^2 = 37\%$ 4 trials, $n =$ NR
HRQoL	
FACT-F	3 trials: results indicated darbepoetin alfa and PBO have a similar effect on HRQoL; 1 study reported a non-significant difference in favour of darbepoetin alfa vs. PBO
FACT-An	1 trial: results indicated darbepoetin alfa and PBO have a similar effect on HRQoL (no significant difference between studies); 1 study reported a non-significant difference in favour of darbepoetin alfa vs. PBO
FACT-G	1 trial: results indicated darbepoetin alfa and PBO have a similar effect on HRQoL (no significant difference between studies)

continued

TABLE 15 Summary of the results of the meta-analyses in the Amgen Inc. submission (*continued*)

Outcome	Results from meta-analyses
Safety-related outcomes	
No. of AEs[b,d]	RR 1.03, 95% CI 0.94 to 1.12; $p = 0.51$; $\chi^2_{(het)} = 0.02$, df = 1; $p = 0.90$; $I^2 = 0\%$ 1 trial, $n = 665$
No. of SAEs[b,e]	RR 1.13, 95% CI 0.99 to 1.29; $p = 0.08$; $\chi^2_{(het)} = 0.03$, df = 1; $p = 0.86$; $I^2 = 0\%$ 2 trials, $n = 1798$
Thromboembolic events[b,f]	RR 2.15, 95% CI 1.41 to 3.28; $p = 0.0004$; $\chi^2_{(het)} = 0.88$, df = 2; $p = 0.64$; $I^2 = 0\%$ 3 trials, $n = 2112$

df, degrees of freedom; haemR, haematological response; het, heterogeneity; NA, not applicable; NSD, no significant difference; PBO, placebo; SAE, serious adverse event; WMD, weighted mean difference.
a Change from baseline to end of study.
b Fixed effects (Mantel–Haenszel).
c Haematological response was defined as the proportion of participants with an increase in Hb level of ≥ 2 g/dl or as an increase in haematocrit of ≥ 6 percentage points with a mean/median baseline Hb level of ≤ 12 g/dl at study entry.
d Incidence of any AE.
e Defined as fatal, life-threatening, requiring inpatient hospitalisation or prolongation of existing hospitalisation, resulting in persistent or significant disability/incapacity, a congenital anomaly/birth defect or 'another significant medical hazard' that does not meet any of the other criteria.
f Includes deep-vein thrombosis, pulmonary embolism, myocardial infarction and stroke.

Ongoing studies

Searches of ClinicalTrials.gov and Current Controlled Trials yielded a total of 218 trials. Of these, 95 trials were considered to be relevant to this review; however, in all cases it was not possible to ascertain whether ESAs were evaluated in accordance with their licensed indications. Seven studies were identified as ongoing ($n = 2$) or recruiting ($n = 5$). In six trials the current status was recorded as 'unknown'. Ten trials had terminated and, of these, three had results available. Finally, 72 studies had been completed. An overview of these trials is provided in *Appendix 11*.

Effectiveness

Anaemia-related outcomes

Anaemia-related outcomes included mean Hb change [measured as a change in Hb level (g/dl) from baseline until the end of the treatment period], haematological response (defined as the proportion of participants with an increase in Hb level of ≥ 2 g/dl or as an increase in haematocrit of ≥ 6 percentage points, unrelated to transfusion) and RBCT requirements [number of participants transfused and number of units transfused per average patient (i.e. including participants not requiring transfusion)].

Haemoglobin change

The mean Hb change was measured as a change in Hb level (g/dl) from baseline until the end of the treatment period. In total, 20 trials[17,48,50,51,53,62–72,74,76–79] measured Hb change, of which 16[17,48,50,51,53,63–67,69,70,74,77–79] were included in the meta-analysis. Two studies[62,76] [the study by Moebus and colleagues[62] was included as an abstract[33] in the Cochrane review by Tonia and colleagues[11]) reported only the median change in Hb (g/dl) without any measure of variance and in two studies,[68,72] no point estimates were reported and the results were presented graphically. These four studies were excluded from the analyses.

Overall, the analysis included 16 trials with 3170 participants.[17,48,50,51,53,63–67,69,70,74,77–79] Four trials were newly identified in the update searches.[48,74,77,78] As some trials with multiple experimental arms were split into subsets,[48,63] the number of trials displayed is 18.

The random-effects meta-analysis demonstrated a statistically significant difference in Hb change in favour of treatment [weighted mean difference (WMD) 1.59 g/dl, 95% CI 1.33 to 1.84 g/dl; *Figure 2*]. Although all individual studies indicated a beneficial effect of ESAs with regard to Hb change and varied only in magnitude, there was statistically significant heterogeneity between the trials [$I^2 = 75.9\%$, $p < 0.001$; $\chi^2 = 70.52$, degrees of freedom (df) = 17; $p < 0.01$]. To assess whether publication bias was likely, a funnel plot was constructed (see *Appendix 12*). The funnel plot analysis did not show statistically significant asymmetry ($p = 0.133$). In addition, a meta-regression using publication year as a covariate (to assess the effect of publication year on Hb change) showed that the effects of ESA on Hb change were independent of any effect of publication year ($p = 0.180$); the meta-regression plot is presented in *Appendix 12*. The fixed-effects meta-analysis undertaken as a sensitivity analysis also showed a statistically significant difference in Hb change in favour of treatment (WMD 1.49 g/dl, 95% CI 1.37 to 1.60 g/dl; $I^2 = 75.9\%$; $p < 0.001$); the forest plot of this analysis is provided in *Appendix 12*.

To identify sources of heterogeneity, subgroup analyses were conducted (*Table 16*). In addition, meta-regression models that included random effect and subgroup as covariates (to assess the effects of subgroups on Hb change) were performed; the *F*-statistics from these analyses are reported in *Table 16*. All covariates showing a significant effect ($p < 0.05$) in a univariate analysis were considered further in model selection.

Univariate analyses identified significant differences for one of the subgroups, ESA therapy [short-acting (erythropoietin) vs. long-acting (darbepoetin)] ($p = 0.023$; *Figure 3*). For subgroup analysis by erythropoietin treatment type, the short-acting ESA treatment (WMD 1.74 g/dl, 95% CI 1.49 to 2.00 g/dl; $I^2 = 62.7\%$; $p = 0.001$) appeared to have a greater benefit than the long-acting ESA treatment (WMD 1.06 g/dl, 95% CI 0.61 to 1.52 g/dl; $I^2 = 71.4\%$; $p = 0.015$). The results were also investigated visually. One small study[69] ($n = 35$) appeared to differ from most of the other included trials; this study reported the highest mean difference between the ESA group and the control group. Excluding this study from the meta-analysis did not change the overall conclusions (data not reported). We therefore included all 18 trials in the analysis of Hb change.

Summary Overall, there is a statistically significant effect of ESAs on Hb change. Compared with the control group, patients receiving ESAs achieve a weighted mean Hb increase of 1.59 g/dl from baseline to the end of treatment (95% CI 1.33 to 1.84 g/dl). We identified statistically significant heterogeneity between the trials ($I^2 = 75.9\%$; $p < 0.001$); however, all individual studies indicated a beneficial effect of ESAs with regard to Hb change. Subgroup analyses suggested that short-acting (erythropoietin) ESA treatment may offer greater benefits than long-acting (darbepoetin) ESA treatment. However, as the number of studies in the subgroup analysis was very small, this analysis may not have statistical power to detect the effects of short- or long-acting ESAs on Hb change, if such effects exist. Overall, the data confirm the results from previous analyses: compared with control groups, patients receiving ESAs improved their Hb levels.

Haematological response

This binary outcome was defined as the proportion of participants with an increase in Hb level of ≥ 2 g/dl or as an increase in haematocrit of ≥ 6 percentage points, unrelated to transfusion. Eight trials defined haematological response as the proportion of participants with an increase in Hb level of ≥ 2 g/dl,[17,48,50,65,66,70,77,79] one study defined haematological response as an increase in haematocrit of ≥ 6 percentage points[63] and one trial reported haematological response using both definitions;[53] for consistency, haematological response as defined by an increase in Hb level was used in the analyses. Two studies[69,73] described haematological response as an increase in Hb level of ≥ 2 g/dl or as a Hb level > 12 g/dl and were therefore excluded from the analyses.

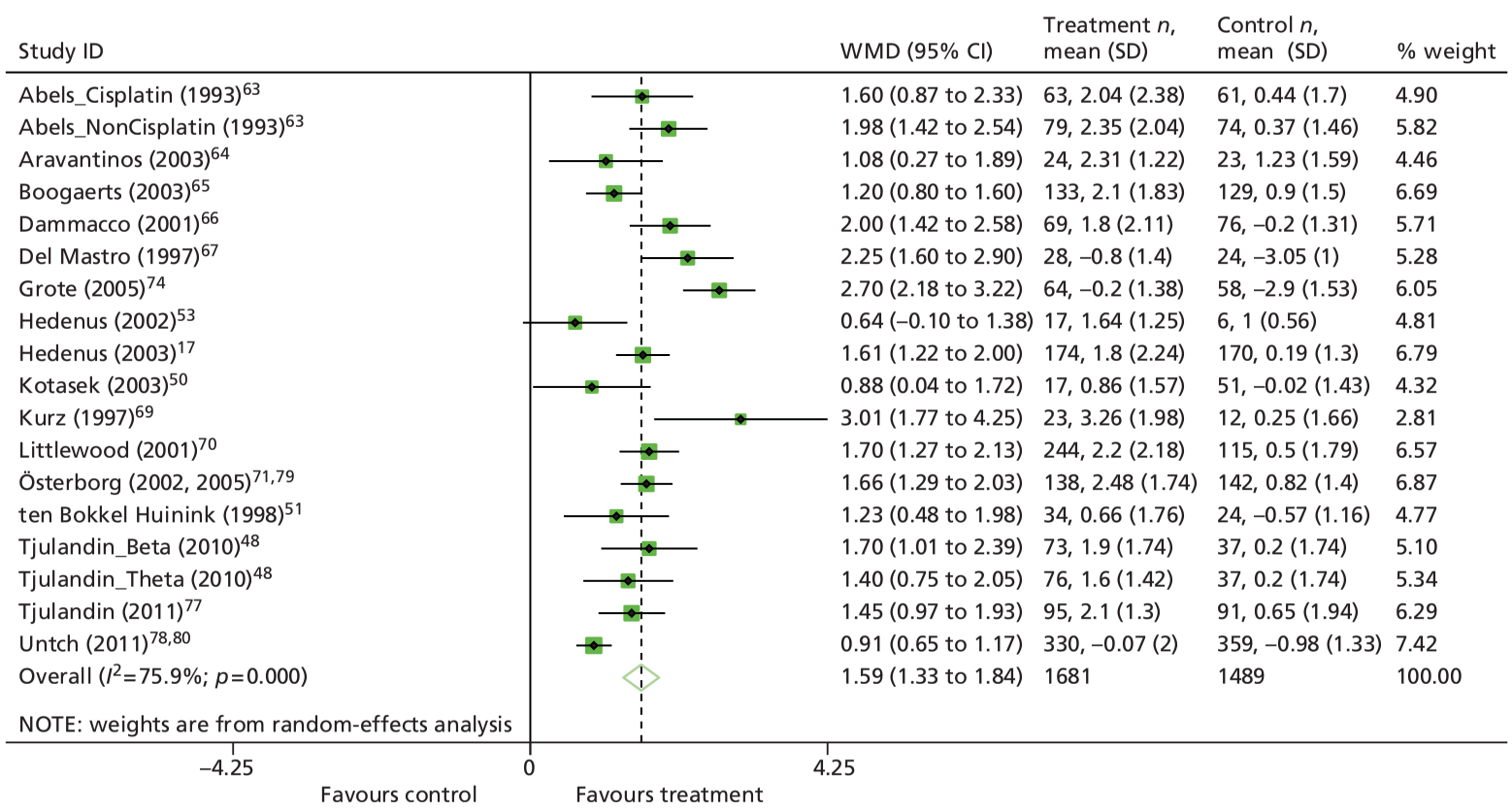

FIGURE 2 Forest plot: Hb change overall (g/dl). Random-effects meta-analysis (DerSimonian–Laird). SD, standard deviation.

TABLE 16 Subgroup analysis: Hb change (g/dl)

Subgroup	Number of trials	WMD	95% CI	I^2	Tau^2
Overall	18	1.59	1.33 to 1.84	75.9%; $p < 0.01$	0.22
Inclusion Hb level (g/dl)					
≤ 11.0	13	1.52	1.30 to 1.75	48.1%; $p = 0.03$	0.08
> 11.0	5	1.75	1.03 to 2.47	91.4%; $p < 0.01$	0.60
F (between : within)				$F_{1,16} = 0.47$; $p = 0.50$	
Baseline Hb level (g/dl)					
≤ 10.0	13	1.51	1.29 to 1.72	43.6%; $p = 0.05$	0.06
≤ 11.0	1	1.98	1.42 to 2.54	NA	0
≤ 12.0	1	1.23	0.48 to 1.98	NA	0
≤ 14.5	3	1.94	0.68 to 3.19	95.5%; $p < 0.01$	1.17
F (between : within)				$F_{3,14} = 0.60$; $p = 0.63$	
Target Hb level (g/dl)					
≤ 13.0	4	1.29	0.90 to 1.67	61.9%; $p = 0.05$	0.10
> 13.0	11	1.59	1.27 to 1.91	74.0%; $p < 0.01$	0.21
NR	3	2.03	1.42 to 2.65	46.0%; $p = 0.16$	0.14
F (between : within)				$F_{2,15} = 1.33$; $p = 0.29$	
Malignancy type					
Solid tumours	9	1.65	1.11 to 2.18	85.2%; $p < 0.01$	0.53
Haematological tumours	6	1.63	1.33 to 1.93	49.2%; $p = 0.08$	0.07
Mixed	3	1.44	1.15 to 1.74	28.1%; $p = 0.25$	0.02
F (between : within)				$F_{2,15} = 0.12$; $p = 0.89$	
Ovarian cancer					
Ovarian cancer	1	1.23	0.48 to 1.98	NA	0
Other cancers	17	1.60	1.34 to 1.87	77.2%; $p < 0.01$	0.23
F (between : within)				$F_{1,16} = 0.34$; $p = 0.57$	
Chemotherapy treatment[a]					
Platinum containing	5	1.42	1.10 to 1.75	0%; $p = 0.77$	0
Non-platinum containing	6	1.62	1.20 to 2.03	82.4%; $p < 0.01$	0.21
F (between : within)				$F_{1,9} = 0.40$; $p = 0.54$	
Iron supplementation					
Iron in both arms	10	1.60	1.38 to 1.82	40.7%; $p = 0.09$	0.05
Iron in an intervention arm	1	0.91	0.65 to 1.17	NA	0
NR	7	1.62	1.07 to 2.16	79.2%; $p < 0.01$	0.42
F (between : within)				$F_{2,15} = 1.07$; $p = 0.37$	

continued

TABLE 16 Subgroup analysis: Hb change (g/dl) (*continued*)

Subgroup	Number of trials	WMD	95% CI	I^2	Tau²
Study design					
RCT	13	1.70	1.43 to 1.97	64.9%; $p < 0.01$	0.15
ROL	5	1.30	0.86 to 1.73	72.0%; $p < 0.01$	0.16
F (between : within)				$F_{1,16} = 1.97$; $p = 0.18$	
Study duration (weeks)					
12–16	12	1.65	1.40 to 1.89	50.4%; $p = 0.02$	0.09
17–20	2	1.92	0.34 to 3.51	90.8%; $p < 0.01$	1.19
> 20	4	1.24	0.86 to 1.62	69.6%; $p = 0.02$	0.10
F (between : within)				$F_{2,15} = 1.67$; $p = 0.22$	
ESA					
Erythropoietin	14	1.74	1.49 to 2.00	62.7%; $p < 0.01$	0.14
Darbepoetin	4	1.07	0.61 to 1.52	71.4%; $p = 0.02$	0.14
F (between : within)				$F_{1,16} = 6.32$; $p = 0.02$	

NA, not applicable; NR, not reported; ROL, randomised open-label (standard care) study.
a Subgroup analyses by platinum-based compared with non-platinum-based chemotherapy; other studies excluded for the following reasons: chemotherapy type not reported or trial population in which participants received either platinum-based or non-platinum-based chemotherapy.

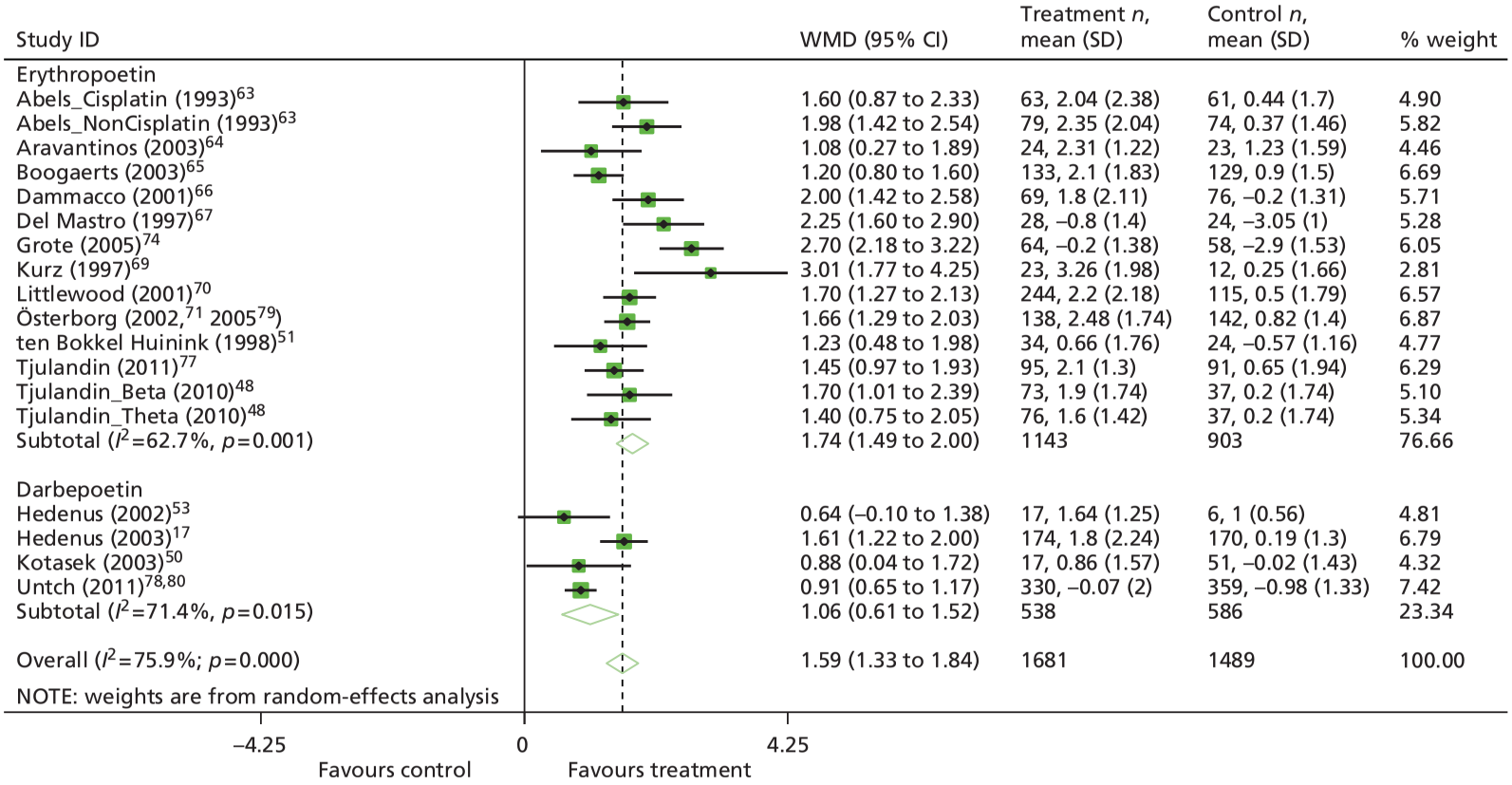

FIGURE 3 Forest plot: Hb change by treatment drug (g/dl). Note: random-effects meta-analysis (DerSimonian–Laird). SD, standard deviation.

Although both the previous HTA review[2] and the study by Tonia and colleagues[11] used the same definition of haematological response, only the study by Tonia and colleagues[11] excluded both the trial by Kurz and colleagues[69] and the trial by Vansteenkiste and colleagues[73] from the analyses. The previous HTA review[2] argued that most of the data in the trial by Vansteenkiste and colleagues[73] would have been derived from an increase in Hb of 2 g/dl (considering baseline Hb values) and included it in the analyses. Vansteenkiste and colleagues[73] reported mean baseline Hb levels of 10.28 g/dl [standard deviation (SD) 1.08 g/dl] and 9.93 g/dl (SD 1.01 g/dl) in the treatment and control groups respectively. Kurz and colleagues[69] reported mean baseline Hb levels of 9.88 g/dl (SD 0.89 g/dl) and 9.85 g/dl (SD 0.60 g/dl) in the treatment and control groups respectively. For consistency with the previous HTA review,[2] sensitivity analyses including the trials by Vansteenkiste and colleagues[73] and Kurz and colleagues[69] were performed.

Overall, the analysis of haematological response included 10 trials with 2228 participants.[17,48,50,53,63,65,66,70,77,79] Two trials were newly identified in the update searches.[48,77] As some trials with multiple experimental arms were split into subsets,[48,63] the number of trials displayed is 12.

Haematological response was observed in 759 out of 1213 participants in the ESA-treated groups, compared with 182 out of 1015 participants in the control groups. The random-effects meta-analysis showed a statistically significant difference in haematological response in favour of treatment (RR 3.29, 95% CI 2.84 to 3.81; *Figure 4*). Heterogeneity between the trials was not significant ($I^2 = 6.4\%$, $p = 0.383$; $\chi^2 = 11.75$, df = 11, $p = 0.383$), with all individual studies indicating a beneficial effect of ESAs with regard to haematological response. To test whether publication bias was present in the meta-analysis, funnel plot asymmetry was investigated (see *Appendix 12*). The funnel plot analysis did not suggest statistically significant asymmetry ($p = 0.275$). A meta-regression using publication year as a covariate to assess the effect of publication year on haematological response suggested that earlier published studies tended to report higher effects than later published studies ($p = 0.044$). The earlier studies also tended to be smaller trials (see the meta-regression plot in *Appendix 12*).

The fixed-effects meta-analysis undertaken as a sensitivity analysis also showed a statistically significant difference in haematological response in favour of treatment (RR 3.41, 95% CI 2.96 to 3.92; $I^2 = 6.4\%$; $p = 0.383$); the forest plot of the analysis is provided in *Appendix 12*. Including the trials by Kurz and colleagues[69] and Vansteenkiste and colleagues[73] in the meta-analysis did not affect the overall conclusions (RR 3.21, 95% CI 2.81 to 3.68; $I^2 = 8.2\%$, $p = 0.363$; the forest plot of the analysis is provided in *Appendix 12*). Similarly to the Hb change outcome, the trial by Kurz and colleagues[69] ($n = 35$) appeared to differ from most of the other included trials. This study reported the highest RR for haematological response, with wide CIs (RR 14.63, 95% CI 0.94 to 226.68).

Prespecified subgroup analysis was performed (*Table 17*). None of the studies with available haematological response data included ovarian cancer patients. Therefore, the planned ovarian cancer subgroup analysis was not completed. In addition, meta-regression models including random effect and subgroups as covariates to assess the effects of a subgroup on haematological response were performed; the *F*-statistics from these analyses are reported in *Table 17*. All covariates showing a significant effect ($p < 0.05$) in a univariate analysis were further considered in a model selection.

One study[70] provided separate results for the subgroups malignancy type (solid and haematological malignancy) and baseline Hb level [≤ 10.5 g/dl and > 10.5 g/dl (but ≤ 12 g/dl)]. In addition to results from the ITT population, results for these subgroups were also used in the PenTAG meta-analyses: using baseline Hb levels the effect estimate was RR 3.29 (95% CI 2.81 to 3.85, $I^2 = 13.4\%$; $p = 0.310$; see *Appendix 12*) and using malignancy type the effect estimate was RR 3.28 (95% CI 2.84 to 3.78, $I^2 = 13.4\%$; $p = 0.403$; see *Appendix 12*). In addition, the trial by Vansteenkiste and colleagues[73] also reported subgroup results for participants with baseline Hb levels < 10.0 g/dl and for participants with baseline Hb levels ≥ 10.0 g/dl (but ≤ 11 g/dl) (reported in Vansteenkiste and colleagues[84]). Including the trials by Kurz and colleagues[69] and Vansteenkiste and colleagues[73] in the meta-analyses with subgroup results had no impact on the overall conclusions.

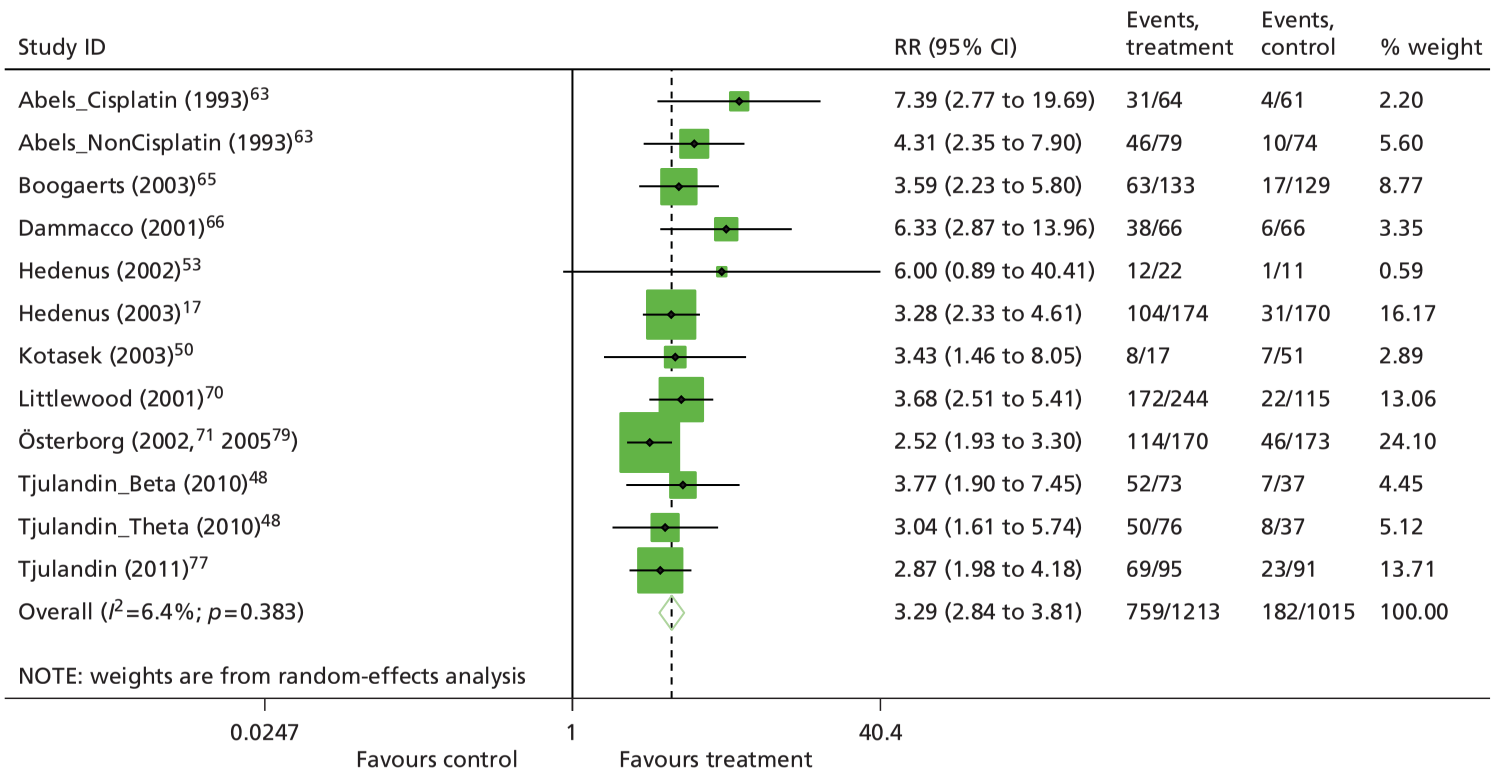

FIGURE 4 Forest plot: haematological response overall. Note: random-effects meta-analysis (DerSimonian–Laird). Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

TABLE 17 Subgroup analysis: haematological response

Subgroup	No. of trials	RR	CI	I^2	Tau^2
Analyses using all main trials					
Overall	12	3.29	2.84 to 3.81	6.4%; $p = 0.383$	< 0.01[a]
Chemotherapy treatment[b]					
Platinum containing	3	3.93	2.50 to 6.17	11.9%; $p = 0.32$	0.02
Non-platinum containing	4	3.05	2.43 to 3.82	29.9%; $p = 0.23$	0.02
F (between : within)				$F_{1,5} = 1.24$; $p = 0.32$	
Iron supplementation					
Iron in both arms	7	3.05	2.63 to 3.54	0%; $p = 0.67$	0
NR	5	4.94	3.38 to 7.20	0%; $p = 0.72$	0
F (between : within)				$F_{1,10} = 11.94$; $p < 0.01$	
Study design					
RCT	11	3.31	2.81 to 3.90	13.8%; $p = 0.32$	0.01
ROL	1	3.59	2.23 to 5.80	NA	0
F (between : within)				$F_{1,10} = 0.12$; $p = 0.73$	
Study duration (weeks)					
12–16	10	3.29	2.73 to 3.97	18.6%; $p = 0.27$	0.02
> 20	2	3.65	2.71 to 4.92	0%; $p = 0.94$	0
F (between : within)				$F_{1,10} = 0.23$; $p = 0.64$	
ESA					
Erythropoietin	9	3.41	2.80 to 4.16	29.7%; $p = 0.18$	0.03
Darbepoetin	3	3.35	2.45 to 4.58	0%; $p = 0.83$	0
F (between : within)				$F_{1,10} = 0$; $p = 0.96$	
Analyses using results for Hb inclusion subgroups[70]					
Overall	13	3.29	2.81 to 3.85	13.4%; $p = 0.31$	0.01
Inclusion Hb level (g/dl)					
≤ 11.0	12	3.20	2.78 to 3.68	2.0%; $p = 0.43$	< 0.01
> 11.0	1	25.52	1.66 to 392.30	NA	0
F (between : within)				$F_{1,11} = 104.53$; $p < 0.01$	
Baseline Hb level (g/dl)					
≤ 10.0	11	3.15	2.72 to 3.63	1.9%; $p = 0.42$	< 0.01
≤ 11.0	1	4.31	2.35 to 7.90	NA	0
≤ 12.0	1	25.52	1.66 to 392.30	NA	0
F (between : within)				$F_{2,10} = 49.43$; $p < 0.01$	
Target Hb level (g/dl)					
≤ 13.0	3	3.06	2.28 to 4.09	0%; $p = 0.79$	0
> 13.0	8	3.25	2.63 to 4.01	24.5%; $p = 0.23$	0.02
NR	2	5.00	2.99 to 8.37	0%; $p = 0.35$	0
F (between : within)				$F_{2,10} = 0.31$; $p = 0.74$	

TABLE 17 Subgroup analysis: haematological response (*continued*)

Subgroup	No. of trials	RR	CI	I^2	Tau²
Analyses using results for malignancy subgroups[70]					
Overall	13	3.28	2.84 to 3.79	4.3%; $p = 0.40$	< 0.01[c]
Malignancy type					
Solid tumours	4	3.70	2.63 to 5.18	0%; $p = 0.844$	0
Haematological tumours	7	3.55	2.70 to 4.67	43%; $p = 0.10$	0.05
Mixed	2	3.13	2.33 to 4.20	0%; $p = 0.47$	0
F (between : within)				$F_{2,10} = 0.89$; $p = 0.44$	

NA, not applicable; NR, not reported; ROL, randomised open-label (standard care) study.
a Tau² = 0.0044.
b Subgroup analyses by platinum-based compared with non-platinum-based chemotherapy; other studies excluded for the following reasons: chemotherapy type not reported or trial population in which participants received either platinum-based or non-platinum-based chemotherapy.
c Tau² = 0.0031.

Univariate analyses identified significant differences between trials reporting use of iron supplementation and trials not reporting use of iron supplementation ($p = 0.006$; *Figure 5*). Trials that did not report whether they used iron supplementation appeared to offer greater benefits (RR 4.94, 95% CI 3.38 to 7.20, $I^2 = 0\%$; $p = 0.752$) than trials using iron supplementation (RR 3.05, 95% CI 2.63 to 3.54, $I^2 = 0\%$; $p = 0.669$). The meta-regression model with iron subgroups is presented in *Appendix 12*. However, including the trials by Kurz and colleagues[69] and Vansteenkiste and colleagues[73] in the meta-regression model with iron supplementation as a covariate provided different results; the difference between trials using iron supplementation and trials not reporting iron supplementation was no longer significant ($p = 0.735$). As noted earlier, the trial by Kurz and colleagues[69] appeared to differ from the other included studies. A sensitivity analysis including the trial by Vansteenkiste and colleagues[73] but excluding that by Kurz and colleagues[69] again suggested that trials not reporting iron supplementation offer greater benefits ($p = 0.037$). The studies not reporting whether they used iron supplementation tended to be smaller (see *Figure 5*). Univariate analyses using the Hb subgroup results identified significant differences based on baseline and inclusion Hb levels (see *Table 17*). However, these results seemed to be driven mainly by the study by Littlewood and colleagues[70] [Hb subgroup < 12 g/dl; RR 25.52, 95% CI 1.66 to 392.3; I^2 = not applicable (NA); *Figure 6*] for both the baseline and the inclusion Hb levels. Because of collinearity we did not combine the baseline and inclusion Hb level subgroups in the same model. A model using the Hb baseline subgroup as a covariate suggests that participants with a higher baseline Hb level (< 12 g/dl; only one study was included in this subgroup) favoured treatment significantly more (RR 25.52, 95% CI 1.66 to 392.3, I^2 = NA) than participants with Hb baseline values of < 11 g/dl (RR 3.76, 95% CI 2.62 to 5.39, $I^2 = 0\%$; $p = 0.583$) and participants with Hb baseline values of < 10 g/dl (RR 3.10, 95% CI 2.64 to 3.64, $I^2 = 19.7\%$; $p = 0.244$; see *Figure 6*). The meta-regression with baseline Hb subgroup as a covariate is presented in *Appendix 12*. Including the trials by Kurz and colleagues[69] and Vansteenkiste and colleagues[73] in the meta-analyses with Hb subgroup results had no impact on the conclusions. However, it should be highlighted that only one trial ($n = 56$) contributed to the subgroup with Hb baseline levels of < 12 g/dl.

Because of the small number of studies in the meta-analysis, these meta-regressions and subgroup analyses have to be interpreted with caution (see *Methods of data analysis/synthesis*). The *Cochrane Handbook for Systematic Reviews of Interventions*[54] recommends at least 10 studies per subgroup. In addition, sensitivity analyses (e.g. including data from the trials by Kurz and colleagues[69] and Vansteenkiste and colleagues[73]) suggest that there are differences in the impact of covariates.

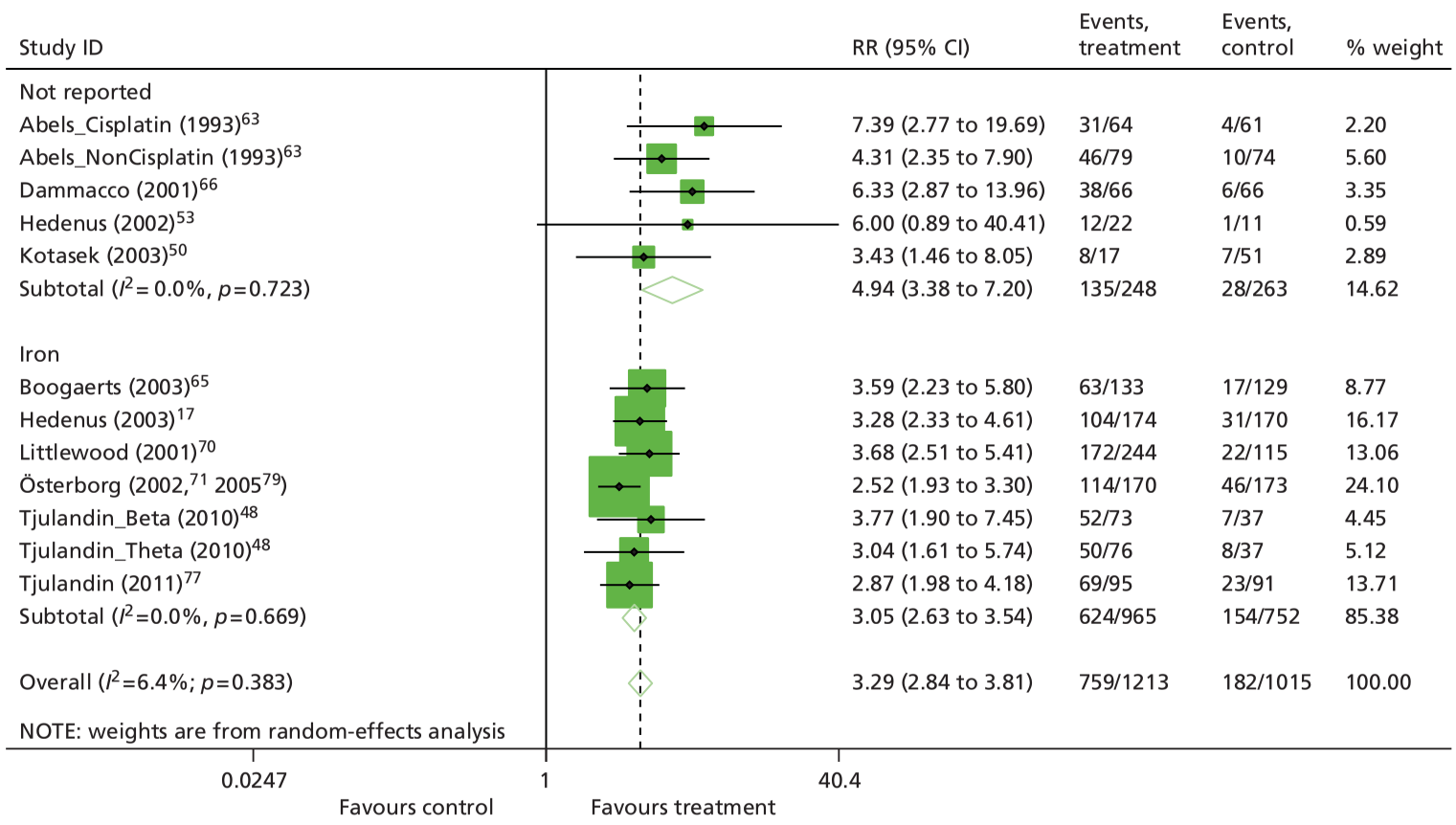

FIGURE 5 Forest plot: haematological response by iron supplementation. Note: random-effects meta-analysis (DerSimonian–Laird). Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

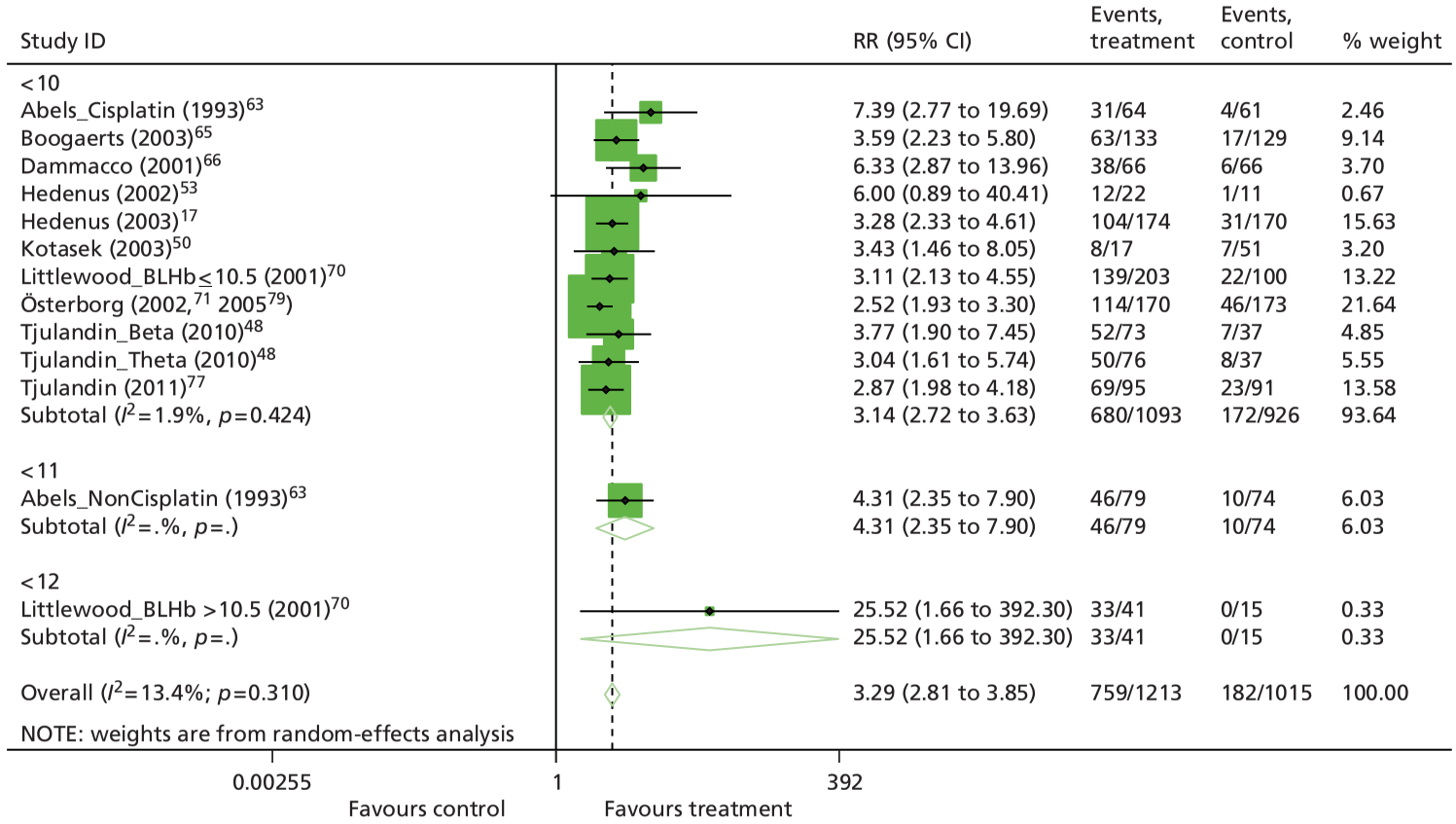

FIGURE 6 Forest plot: haematological response using Hb subgroups by Hb baseline level. Note: random-effects meta-analysis (DerSimonian–Laird). Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

Summary Analyses suggest that ESA treatment in CIA is effective in producing a haematological response as defined by an increase in Hb level of ≥ 2 g/dl or an increase in haematocrit of ≥ 6 percentage points. In total, 63% ($n = 759/1213$) of participants who received ESA treatment had a haematological response compared with 18% ($n = 182/1015$) of control patients. The heterogeneity between the trials was non-significant ($I^2 = 6.4\%$; $p = 0.383$), with all individual studies indicating a beneficial effect of ESAs with regard to Hb response. The results of the subgroup analyses were non-conclusive, suggesting that the analyses may not have the statistical power to detect effects of subgroups on haematological response if such effects exist. Overall, the results support previous analyses.

Red blood cell transfusion requirement

This binary outcome was defined as the proportion of participants requiring a RBCT. Overall, the analysis of RBCT requirement included 22 trials[17,48,50–53,62,63–70,73–79] with 4779 participants. Seven trials were newly identified in the update searches.[48,62,74–80] As some trials with multiple experimental arms were split into subsets,[48,63] the number of studies displayed is 24.

A RBCT was required by 554 of 2480 participants treated with ESAs compared with 835 of 2299 participants receiving placebo/no treatment. The random-effects meta-analysis showed a statistically significant difference in RBCT requirement in favour of the treatment group (RR 0.63, 95% CI 0.57 to 0.69; *Figure 7*). The heterogeneity between the trials was not significant ($I^2 = 10.5\%$, $p = 0.315$; $\chi^2 = 25.71$, df = 23, $p = 0.315$). All but one individual study[78,80] indicated a beneficial effect of ESAs with regard to RBCT requirement. To test whether publication bias was present in the sample included in the meta-analysis, funnel plot asymmetry was investigated (see *Appendix 12*). The funnel plot analysis did not show statistically significant asymmetry ($p = 0.234$). A meta-regression using publication year as a covariate to assess the effect of publication year on RBCT requirement was not statistically significant ($p = 0.208$; see meta-regression plots in *Appendix 12*).

The fixed-effects meta-analysis undertaken as a sensitivity analysis showed a statistically significant difference in RBCT requirement in favour of treatment (RR 0.62, 95% CI 0.51 to 0.67); the forest plot of this analysis is provided in *Appendix 12*).

Prespecified subgroup analyses were performed (*Table 18*). In addition, meta-regression models including random effect and subgroups as a covariate to assess the effects of a subgroup on RBCT requirement were performed. The *F* statistics from these analyses are reported in *Table 18*. All covariates showing a significant effect ($p < 0.05$) in a univariate analysis were considered further in model selection.

One study[70] reported results for the subgroups malignancy type (solid and haematological malignancy) and baseline Hb level [≤ 10.5 g/dl and > 10.5 g/dl (but ≤ 12 g/dl)]. Vansteenkiste and colleagues[73] also reported subgroup results for participants with baseline Hb levels < 10.0 g/dl and ≥ 10.0 g/dl (but ≤ 11 g/dl) (reported in Vansteenkiste and colleagues[84]). In addition to results from the ITT population, results for these subgroups were included in the PenTAG meta-analyses: using the Hb subgroups the effect estimate was RR 0.61 (95% CI 0.55 to 0.68, $I^2 = 22.4\%$; $p = 0.015$) and using the malignancy subgroups the effect estimate was RR 0.62 (95% CI 0.56, 0.68, $I^2 = 15.8\%$; $p = 0.239$; see *Appendix 12*).

Univariate analyses did not identify any significant differences based on the predefined subgroups (see *Table 18*).

Summary The RR for receiving a RBCT was statistically significantly reduced by 37% in the study groups receiving ESAs (RR 0.63, 95% CI 0.57 to 0.69). Heterogeneity between the studies was non-significant ($I^2 = 10.5\%$; $p = 0.315$). Overall, the data confirm the results from previous analyses that ESAs reduce the RR for receiving a RBCT in patients with CIA.

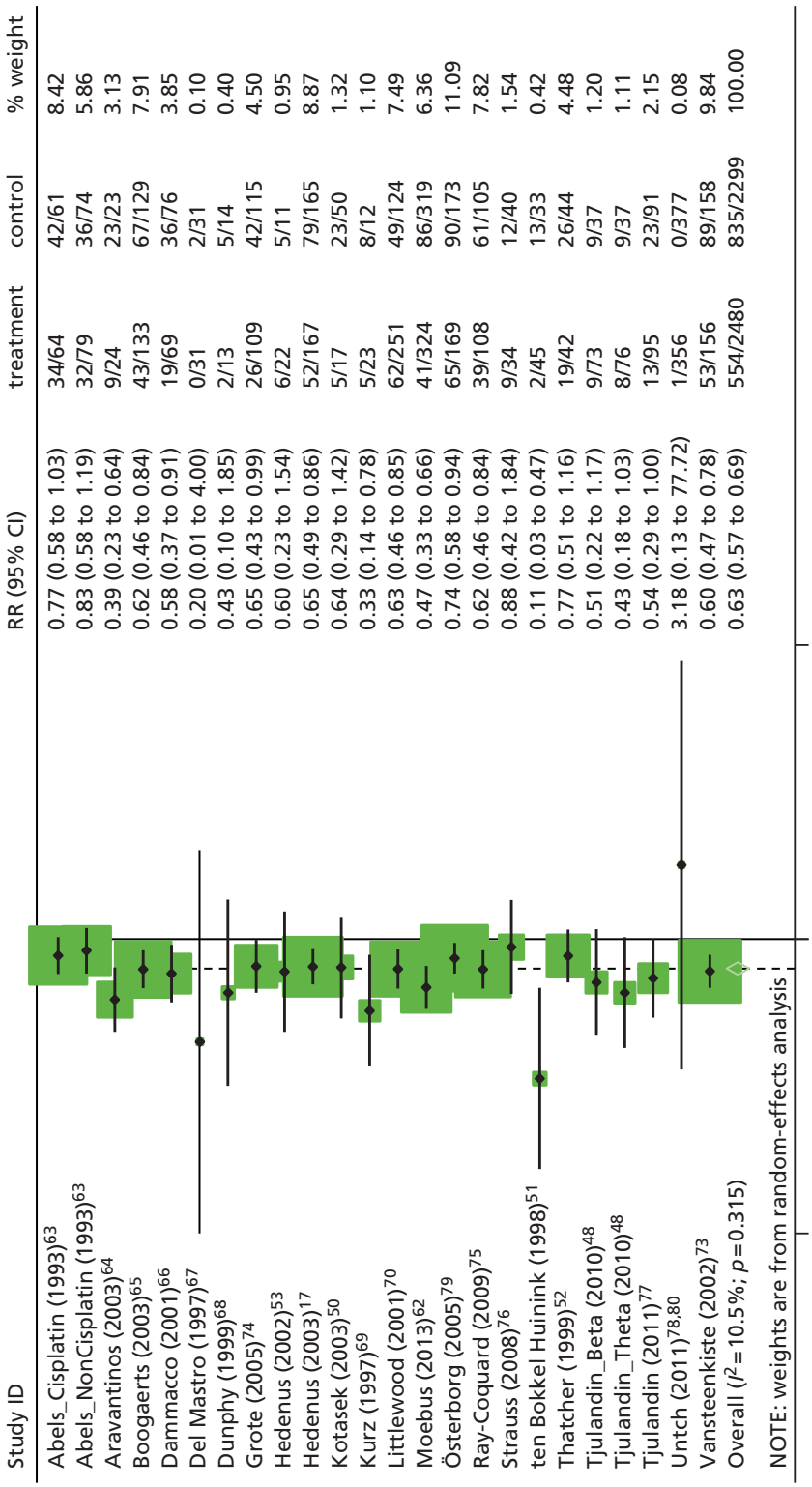

FIGURE 7 Forest plot: RBCT. Notes: random-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] report data for epoetin theta and epoetin beta and Abels and colleagues[63] report data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

TABLE 18 Red blood cell transfusion: subgroup analyses

Subgroup	Number of trials	RR	CI	I^2	Tau^2
Analyses using all main trials					
Overall	24	0.63	0.57 to 0.69	10.5%; $p = 0.32$	0.01
Chemotherapy treatment[a]					
Platinum containing	6	0.52	0.37 to 0.72	60.0%; $p = 0.03$	0.08
Non-platinum containing	7	0.65	0.53 to 0.79	31.1%; $p = 0.19$	0.02
F (between : within)				$F_{1,11} = 0.21$; $p = 0.66$	
Iron supplementation					
Iron in both arms	14	0.61	0.54 to 0.68	0%; $p = 0.460$	0
Iron in an intervention arm	1	3.18	0.13 to 77.7	NA	0
Iron not used	1	0.77	0.50 to 1.16	NA	0
NR	8	0.66	0.55 to 0.80	29.4%; $p = 0.193$	0.02
F (between : within)				$F_{3,20} = 1.08$; $p = 0.38$	
Study design					
RCT	14	0.66	0.60 to 0.73	0%; $p = 0.78$	0
ROL	10	0.56	0.45 to 0.71	37.7%; $p = 0.11$	0.04
F (between : within)				$F_{1,22} = 0.61$; $p = 0.44$	
Study duration (weeks)					
6–9	2	0.76	0.40 to 1.47	0%; $p = 0.39$	0
12–16	14	0.66	0.60 to 0.74	0%; $p = 0.73$	0
17–20	3	0.50	0.38 to 0.66	26.5%; $p = 0.26$	0.02
> 20	5	0.62	0.45 to 0.85	48.0%; $p = 0.10$	0.05
F (between : within)				$F_{3,20} = 0.57$; $p = 0.64$	
ESA					
Erythropoietin	19	0.62	0.55 to 0.70	27.1%; $p = 0.13$	0.02
Darbepoetin	5	0.63	0.52 to 0.75	0%; $p = 0.89$	0
F (between : within)				$F_{1,22} = 0.03$; $p = 0.86$	
Analysed using results for baseline Hb subgroups[70,73]					
Overall	26	0.61	0.55 to 0.68	22.4%; $p = 0.15$	0.02
Inclusion Hb level (g/dl)					
≤ 11.0	16	0.64	0.57 to 0.71	7.3%; $p = 0.37$	< 0.01
> 11.0	10	0.56	0.44 to 0.72	39.1%; $p = 0.10$	0.05
F (between : within)				$F_{1,24} = 0.72$; $p = 0.40$	
Baseline Hb level (g/dl)					
≤ 10.0	15	0.64	0.58 to 0.71	0%; $p = 0.69$	0
≤ 11.0	2	0.60	0.31 to 1.18	81.4%; $p = 0.02$	0.19
≤ 12.0	3	0.38	0.14 to 1.00	74.1%; $p = 0.02$	0.52
≤ 14.5	5	0.69	0.52 to 0.92	0%; $p = 0.69$	0
NR	1	0.47	0.34 to 0.66	NA	NA
F (between : within)				$F_{1,24} = 0.28$; $p = 0.60$	

TABLE 18 Red blood cell transfusion: subgroup analyses (*continued*)

Subgroup	Number of trials	RR	CI	I^2	Tau^2
Target Hb level (g/dl)					
≤ 13.0	4	0.52	0.34 to 0.80	48.4; $p = 0.14$	0.04
> 13.0	19	0.60	0.53 to 0.67	0%; $p = 0.70$	0
NR	3	0.71	0.51 to 1.00	22.4%; $p = 0.15$	0.02
F (between : within)				$F_{2,23} = 0.82$; $p = 0.45$	
Analysed using results for malignancy subgroups[70]					
Overall	25	0.62	0.56 to 0.68	15.8%; $p = 0.24$	0.01
Malignancy type					
Solid tumours	15	0.56	0.48 to 0.66	17.2%; $p = 0.26$	0.01
Haematological tumours	7	0.68	0.59 to 0.79	15.3%; $p = 0.31$	0.02
Mixed	3	0.61	0.50 to 0.75	0%; $p = 0.92$	0
F (between : within)				$F_{2,22} = 0.70$; $p = 0.51$	

NR, not reported; ROL, randomised open-label (standard care) study.
a Subgroup analyses by platinum-based compared with non-platinum-based chemotherapy; other studies excluded for the following reasons: chemotherapy type not reported or trial population in which participants received either platinum-based or non-platinum-based chemotherapy.

Number of red blood cell units transfused

Overall, 10 trials[51,52,63,65,66,69,73,74,77,79] evaluating a total of 1920 participants were included in the analysis of RBC units transfused. As one study[63] was split into subsets, the number of trials displayed is 11. Two trials were newly identified;[74,77] neither was included in the Cochrane review[11] for the analysis of this outcome. All except one study[77] reported the mean number of units transfused per average participant (i.e. regardless of whether participants had received a RBCT). For Tjulandin and colleagues[77] this was calculated from the data presented in the published paper.

The overall mean difference between groups showed a statistically significant benefit for participants receiving ESAs (WMD –0.87, 95% CI –1.28 to –0.46; *Figure 8*); the ESA group received fewer units of blood per participant than the control group. The heterogeneity between the studies was significant ($I^2 = 59.3\%$; $p = 0.006$). All but one study indicated a reduced need for RBCs in participants receiving ESAs compared with control subjects. A funnel plot analysis did not suggest statistically significant asymmetry ($p = 0.137$; see *Appendix 12*).

One study[73] provided separate results for participants with baseline Hb levels of < 10.0 g/dl, and ≥ 10.0 g/dl (but ≤ 11.0 g/dl). Meta-analysis including these subgroup results was conducted (WMD –0.87, 95% CI –1.24 to –0.50; see *Appendix 12*). The fixed-effects meta-analysis undertaken as a sensitivity analysis showed a statistically significant difference for number of RBC units transfused in favour of treatment (WMD –0.64, 95% CI –0.79 to –0.48); the forest plot of this analysis is provided in *Appendix 12*.

To identify sources of heterogeneity, subgroup analyses were conducted (*Table 19*). In addition, meta-regression models including random effect and a subgroup as a covariate to assess the effects of subgroups on Hb change were performed; the *F*-statistics from these analyses are reported in *Table 19*. All covariates showing a significant effect ($p < 0.05$) in a univariate analysis were considered further in a model selection.

Univariate analyses identify any significant differences based on the predefined subgroups.

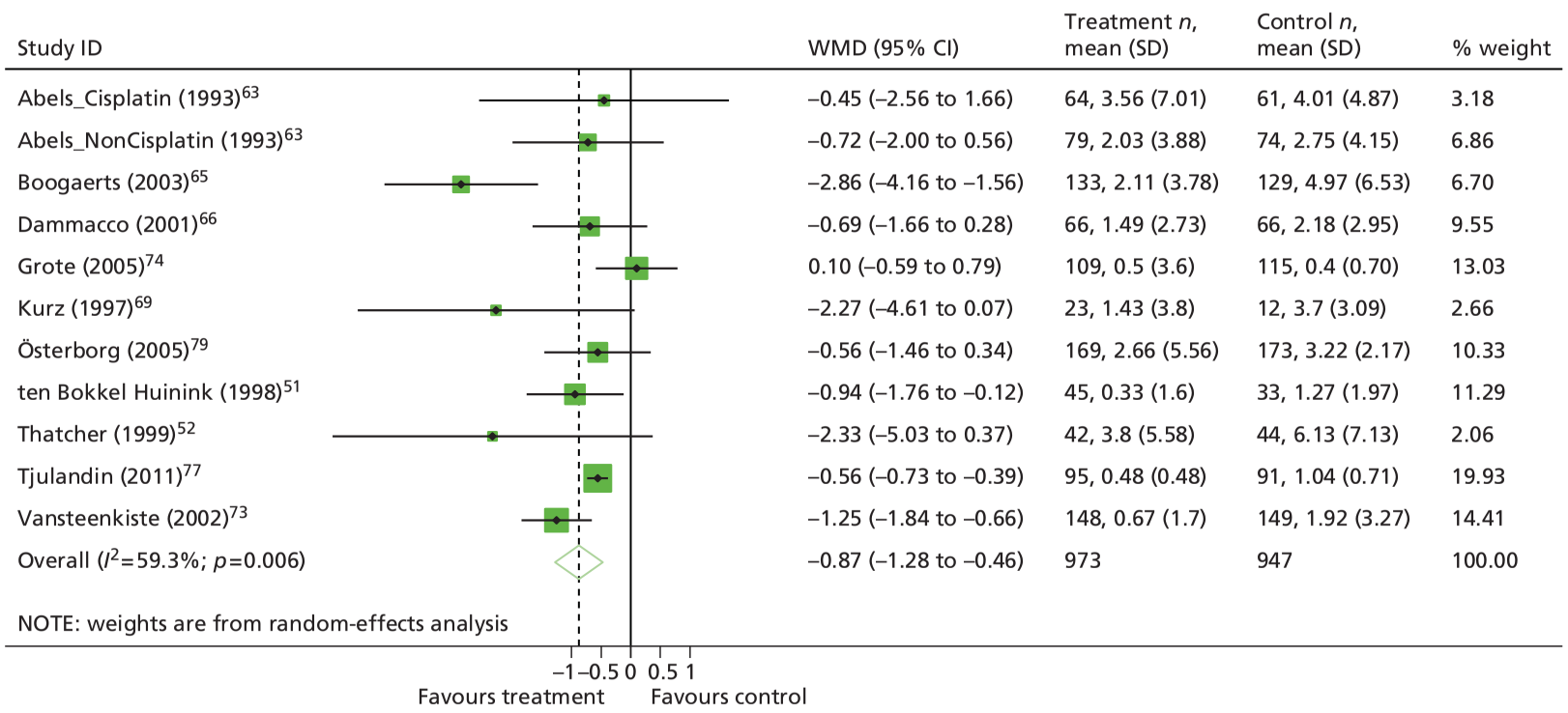

FIGURE 8 Forest plot: mean number of RBC units transfused. Notes: random-effects meta-analysis (DerSimonian–Laird); trial with multiple experimental arms split into subsets in the analysis: Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy; mean units transfused per average participant (i.e. regardless of whether participants had received a RBCT).

TABLE 19 Red blood cell units: subgroup analyses

Subgroup	No. of trials	WMD	95% CI	I^2	Tau^2
Overall	11	–0.87	–1.28 to –0.46	59.3%; $p = 0.02$	0.21
Chemotherapy treatment[a]					
Platinum containing	3	–1.11	–1.58 to –0.64	0%; $p = 0.69$	0
Non-platinum containing	3	–0.56	–0.73 to –0.39	0%; $p = 0.97$	0
F (between : within)				$F_{1,4} = 4.63$; $p = 0.10$	
Iron supplementation					
Iron in both arms	4	–1.30	–2.31 to –0.29	78.3%; $p < 0.01$	0.73
Iron not used	1	–2.30	–5.03 to –0.37	NA	0
NR	6	–0.70	–1.19 to –0.20	43.7%; $p = 0.11$	0.16
F (between : within)				$F_{2,8} = 0.09$; $p = 0.44$	
Study design					
RCT	8	–0.63	–0.97 to –0.30	35.4%; $p = 0.15$	0.07
ROL	3	–1.91	–3.37 to –0.44	68.6%; $p = 0.04$	1.10
F (between : within)				$F_{1,9} = 4.25$; $p = 0.07$	
Study duration (weeks)					
12–16	7	–0.70	–0.96 to –0.44	11.7%; $p = 0.34$	0.02
17–20	1	0.10	–0.59 to 0.79	NA	0
> 20	3	–1.91	–3.37 to –0.44	68.6%; $p = 0.04$	1.08
F (between : within)				$F_{2,8} = 3.72$; $p = 0.07$	
ESA					
Erythropoietin	10	–0.89	–1.43 to –0.35	53.8%; $p = 0.02$	0.36
Darbepoetin	1	–1.25	–1.84 to –0.66	NA	0
F (between : within)				$F_{1,9} = 0.27$; $p = 0.61$	
Malignancy type					
Solid tumours	5	–0.95	–1.73 to –0.17	65.7%; $p = 0.02$	0.44
Haematological tumours	4	–0.63	–1.19 to –0.06	0%; $p = 0.99$	0
Mixed	2	–1.62	–3.86 to –0.63	91.6%; $p < 0.01$	2.42
F (between : within)				$F_{2,88} = 0.50$; $p = 0.62$	
Ovarian cancer					
Ovarian cancer	1	–0.94	–1.76 to –0.12	NA	0
Other cancers	10	–0.88	–1.34 to –0.42	62.5%; $p < 0.01$	0.25
F (between : within)				$F_{1,9} = 0.00$; $p = 0.98$	
Analysed using results for baseline Hb subgroups[73]					
Overall	12	–0.87	–1.24 to –0.50	55.6%; $p = 0.01$	0.17
Inclusion Hb level (g/dl)					
≤ 11.0	9	–0.99	–1.41 to –0.56	56.2%; $p = 0.02$	0.18
> 11.0	3	–0.63	–1.67 to 0.41	64.7%; $p = 0.06$	0.49
F (between : within)				$F_{1,10} = 0.76$; $p = 0.41$	

continued

TABLE 19 Red blood cell units: subgroup analyses (*continued*)

Subgroup	No. of trials	WMD	95% CI	I^2	Tau²
Baseline Hb level (g/dl)					
≤ 10.0	7	–1.13	–1.76 to –0.49	65.3%; $p = 0.01$	0.39
≤ 11.0	2	–0.88	–1.35 to –0.40	0%; $p = 0.80$	0
≤ 12.0	1	–0.94	–1.76 to –0.12	NA	0
≤ 14.5	2	–0.75	–3.02 to –1.52	65.8%; $p = 0.09$	1.94
F (between : within)				$F_{3,8} = 0.36$; $p = 0.79$	
Target Hb level (g/dl)					
≤ 13.0	1	–0.56	–0.74 to –0.39	NA	0
> 13.0	8	–1.01	–1.57 to –0.45	65.7%; $p < 0.01$	0.39
NR	3	–0.94	–1.93 to –0.05	0%; $p = 0.46$	0
F (between : within)				$F_{2,9} = 0.20$; $p = 0.82$	

NR, not reported; ROL, randomised open-label (standard care) study.
a Subgroup analyses by platinum-based compared with non-platinum-based chemotherapy; other studies excluded for the following reasons: chemotherapy type not reported or trial population in which participants received either platinum-based or non-platinum-based chemotherapy.

Summary Overall, there is a statistically significant effect of ESAs on the number of RBC units transfused. The WMD in RBC units was –0.87 (95% CI –1.28 to –0.46), suggesting that fewer units per participant were used in the treatment arm than in the control arm. We identified statistically significant heterogeneity between the trials ($I^2 = 59.3\%$; $p = 0.006$); however, all but one of the individual studies indicated a beneficial effect of ESAs with regard to RBC units transfused. Overall, the data confirm the results from previous analyses that there is only a slight difference in the number of RBC units transfused between the intervention group and the control group.

Anaemia-related outcomes: overall summary

All studies included in the analyses of anaemia-related outcomes were of moderate or poor quality. The general problem of reporting of trials on this topic was greatly assisted by the recent Cochrane review,[11] as the authors had gathered further details from investigators and manufacturers, which were used in the meta-analysis for this review.

In total, 20 studies measured Hb change, of which 16 were included in the meta-analysis. All of the studies indicated a beneficial effect of ESAs with regard to Hb change, which varied only in magnitude. The overall WMD for Hb level increase was 1.59 g/dl. Hb change was not restricted to patients who were transfusion free; therefore, the results may have been confounded by transfusion in some of the patients.

Haematological response was defined as the proportion of participants with an increase in Hb level of ≥ 2 g/dl or an increase in haematocrit of ≥ 6 percentage points, unrelated to transfusion. In total, 10 trials reported this outcome and all were included in the meta-analysis. The analysis showed that participants treated with ESAs were three times more likely to experience a ≥ 2 g/dl increase in Hb than participants in the control group, with 63% ($n = 759/1213$) of participants who received ESAs having a haematological response compared with 18% ($n = 182/1015$) of control patients. Estimates of haematological response were considered robust, with no marked heterogeneity or subgroup effects.

The number of patients receiving RBCTs was the third outcome assessed to investigate the effects of ESAs on CIA. In total, 22 trials reported this outcome and all were included in the meta-analysis. Data were reported for the trial period; the RR of receiving a RBCT was 0.63 in favour of ESAs, equating to 22% of participants in the ESA treatment groups receiving RBCT compared with 33% in the control groups.

The number of transfusions per patient was also investigated. Only 10 trials reported this outcome and many of these data were obtained by the Cochrane review authors through further questions to the trial authors. There was little difference between the ESA group and the control group with regard to the amount of blood transfused. Estimates of numbers transfused were considered robust, with no marked heterogeneity or subgroup effects.

Effectiveness estimates were consistent with previously reported estimates for anaemia-related outcomes (*Table 20*). A graphical summary of the study characteristics, quality appraisal and results for these outcomes is presented in *Figure 9*.

Tumour response

We identified seven trials[51,66,70,74,76,78,79] that measured a complete tumour response. Overall, the analysis included seven trials with 1909 participants. Three trials were newly identified in the update searches.[74,76,78]

A complete tumour response was reported in 177 out of 1003 participants in the ESA-treated groups and 142 out of 906 participants in the control groups. The random-effects meta-analysis showed a RR of 1.10 (95% CI 0.86 to 1.41; *Figure 10*), which was not statistically significant. There was non-significant heterogeneity between the trials ($I^2 = 37.5\%$, $p = 0.143$; $\chi^2 = 9.59$, df = 6, $p = 0.143$); however, the direction of effects of the individual studies varied (see *Figure 10*). Because there were only seven primary studies included in the meta-analysis, the funnel plot analysis to assess whether publication bias was likely

TABLE 20 Anaemia-related outcomes results comparison: Wilson and colleagues[2] vs. Tonia and colleagues[11] vs. PenTAG

Outcome	[a]Wilson and colleagues[2]	[a]Tonia and colleagues[11]	PenTAG[a]	PenTAG[b]
Hb change (g/dl)[c,d]	WMD 1.63, 95% CI 1.46 to 1.80; $\chi^2_{(het)} = 23.74$, df = 19; $p = 0.21$	WMD 1.57, 95% CI 1.51 to 1.62; $\chi^2_{(het)} = 564.37$, df = 74; $p < 0.001$	WMD 1.49, 95% CI 1.37 to 1.60; $\chi^2_{(het)} = 70.52$, df = 17; $p < 0.001$	WMD 1.59, 95% CI 1.33 to 1.84; $\chi^2_{(het)} = 70.52$, df = 17; $p < 0.001$
	10 trials, $n = 1620$	75 trials, $n = 11{,}609$	18 trials, $n = 3170$	18 trials, $n = 3170$
HaemR[d,e]	RR 3.40, 95% CI 3.01 to 3.83; $\chi^2_{(het)} = 23.60$, df = 32; $p = 0.86$	RR 3.39, 95% CI 3.10 to 3.71; $\chi^2_{(het)} = 95.56$, df = 45; $p < 0.001$	RR 3.41, 95% CI 2.96 to 3.92; $\chi^2_{(het)} = 11.75$, df = 11; $p = 0.383$	RR 3.29, 95% CI 2.84 to 3.81; $\chi^2_{(het)} = 11.75$, df = 11; $p = 0.383$
	21 trials, $n = 3740$	46 trials, $n = 6413$	12 trials, $n = 2228$	12 trials, $n = 2228$
RBCT[d]	RR 0.63, 95% CI 0.58 to 0.67; $\chi^2_{(het)} = 94.75$, df = 48; $p = 0.001$	RR 0.65, 95% CI 0.62 to 0.68; $\chi^2_{(het)} = 217.08$, df = 87; $p < 0.001$	RR 0.62, 95% CI 0.58 to 0.67; $\chi^2_{(het)} = 25.71$, df = 23; $p = 0.315$	RR 0.63, 95% CI 0.57 to 0.69; $\chi^2_{(het)} = 25.71$, df = 23; $p = 0.315$
	35 trials, $n = 5564$	88 trials, $n = 16{,}093$	24 trials, $n = 4799$	24 trials, $n = 4799$
Units transfused[d]	WMD –1.05, 95% CI –1.32 to –0.78; $\chi^2_{(het)} = 8.96$, df = 16; $p = 0.91$	WMD –0.98, 95% CI –1.17 to –0.78; $\chi^2_{(het)} = 34.52$, df = 24; $p = 0.080$	WMD –0.64, 95% CI –0.79 to –0.48; $\chi^2_{(het)} = 24.55$, df = 10; $p = 0.006$	WMD –0.87, 95% CI –1.28 to –0.46; $\chi^2_{(het)} = 24.55$, df = 10; $p = 0.006$
	14 trials, $n = 2353$	25 trials, $n = 4715$	11 trials, $n = 1920$	11 trials, $n = 1920$

HaemR, haematological response; het, heterogeneity.
p-values reported for heterogeneity.
a Fixed effects (Mantel–Haenzel).
b Random effects (DerSimonian–Laird).
c Change from baseline to end of study.
d The number of trials accounts for multiple experimental arms for some studies.
e Haematological response was defined as the proportion of participants with an increase in Hb level of ≥ 2 g/dl or as an increase in haematocrit of ≥ 6 percentage points.

(a)

Trial		Chemo	Malignancy	Note	Design	Duration (weeks)	Outcomes				QA			
						0 10 20 30	Hb change	HaemR	RBCT	Units	Random	Baseline	Blinding	Losses
Abels	1993[63]	Plat Non-plat No chemo	Haem	$n=413$		Epo Alfa $n=206$ Placebo $n=190$ Missing $n=17$					■	□	■	■
	SG	Plat		$n=132$	1	Epo Alfa $n=64$ Placebo $n=61$ Missing $n=7$	●	●	○	○	■	□	■	■
	SG	Non-plat		$n=157$		Epo Alfa $n=79$ Placebo $n=74$ Missing $n=4$	●	●	○	○	■	□	■	■
Aravanitos	2003[64]	Plat	Solid	$n=47$		Epo Alfa $n=24$ Control $n=23$	●		●		□	□	□	■
Boogaerts	2003[65]	?	?	$n=262$		Epo Beta $n=133$ Control $n=129$	●	●	●	●	□	□	□	■
Dammaco	2001[66]	Mixed	Haem	$n=145$	2	Epo Alfa $n=69$ Placebo $n=76$	●	●	●	○	□	□	■	■
Del Mastro	1997[67]	Non-plat	Solid	$n=62$	3	rHuEPO $n=31$ Control $n=31$	●		○		■	□	□	■

Quality appraisal key
Random:
concealment of allocation (above)
random allocation (below)
Baseline:
baseline characteristics
Blinding:
blinding of clinicians (above)
blinding of patients (below)
Losses:
ITT or <10% (above)
losses (below)

■ Positive quality check
□ Partial quality check
□ Negative quality check
☒ Not reported

Outcomes key
● Favours treatment
◪ Favours control
○ Non-significant outcomes

FIGURE 9 Anaemia-related outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–8 and 10–12. 1: Hb change: epo alfa $n=63$; 2: HaemR and units: epo alfa $n=66$ and placebo $n=66$; 3: Hb change: rHuEPO $n=28$ and control $n=24$; 4: Hb change: epo alfa $n=64$ and control $n=58$; 5: Hb change: darbe alfa $n=17$ and placebo $n=6$; 6: RBCT: darbe alfa $n=167$ and placebo $n=165$; 7: HaemR = increase in Hb of ≥ 2 g/dl and/or Hb level >12 g/dl; 8: RBCT: epo alfa $n=251$ and placebo $n=124$; 9: Latin square design; 10: Hb change: epo beta $n=138$ and placebo $n=142$; 11: Hb change: licensed epo alfa $n=34$ and control $n=24$; 12: Hb change: darbe alfa $n=330$ and placebo $n=359$. ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; haemR, haematological response; non-plat, non-platinum; plat, platinum; QA, quality appraisal; units, units transfused. (*continued*)

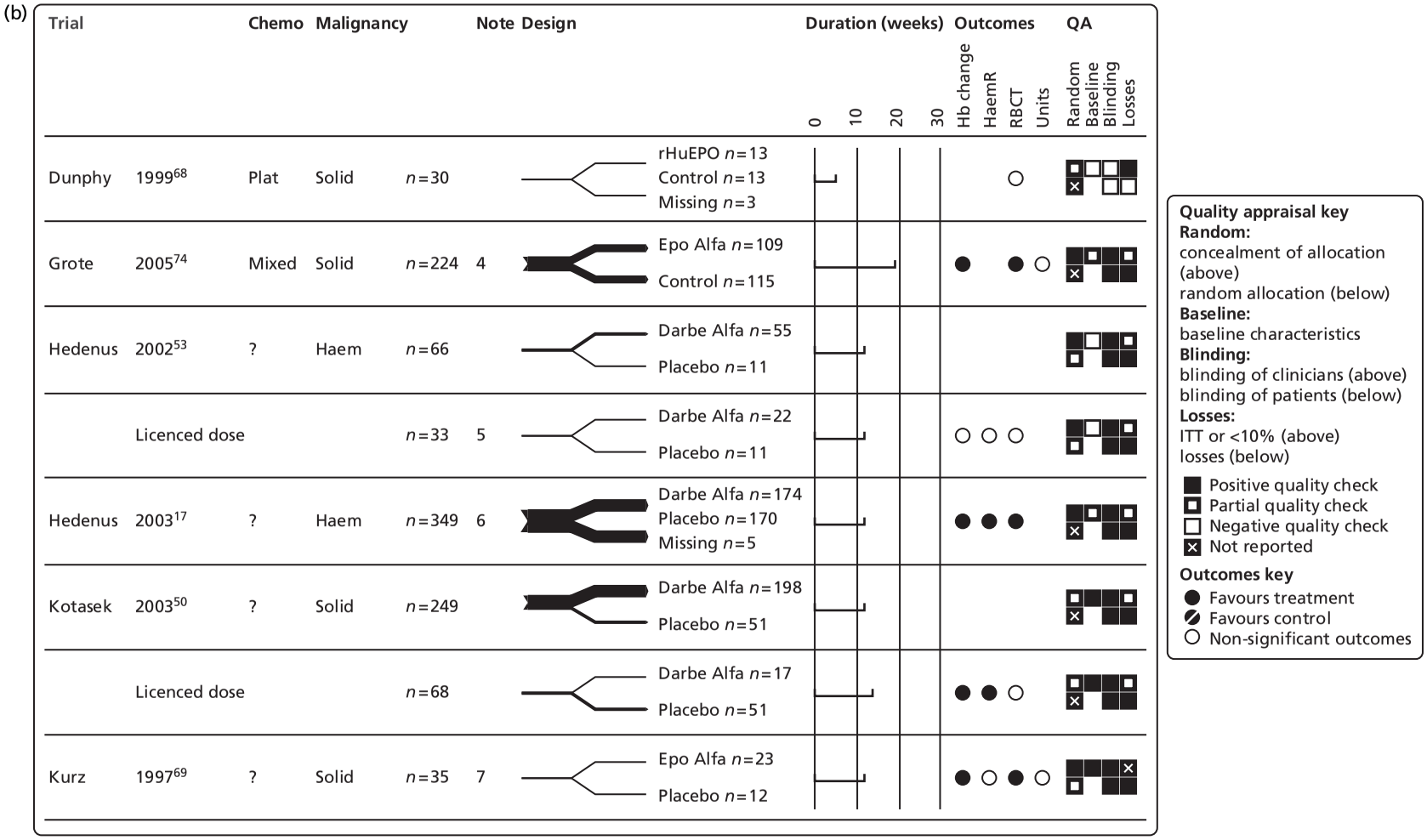

FIGURE 9 Anaemia-related outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–8 and 10–12. 1: Hb change: epo alfa $n = 63$; 2: HaemR and units: epo alfa $n = 66$ and placebo $n = 66$; 3: Hb change: rHuEPO $n = 28$ and control $n = 24$; 4: Hb change: epo alfa $n = 64$ and control $n = 58$; 5: Hb change: darbe alfa $n = 17$ and placebo $n = 6$; 6: RBCT: darbe alfa $n = 167$ and placebo $n = 165$; 7: HaemR = increase in Hb of ≥ 2 g/dl and/or Hb level > 12 g/dl; 8: RBCT: epo alfa $n = 251$ and placebo $n = 124$; 9: Latin square design; 10: Hb change: epo beta $n = 138$ and placebo $n = 142$; 11: Hb change: licensed epo alfa $n = 34$ and control $n = 24$; 12: Hb change: darbe alfa $n = 330$ and placebo $n = 359$. ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; haemR, haematological response; non-plat, non-platinum; plat, platinum; QA, quality appraisal; units, units transfused. (*continued*)

(c)

Trial		Chemo	Malignancy	Note	Design	Duration (weeks) 0 10 20 30	Outcomes Hb change	HaemR	RBCT	Units	QA Random	Baseline	Blinding	Losses
Littlewood	2001[70]	Non-plat	Solid and Haem	*n*=375	8	Epo Alfa *n*=224 Placebo *n*=115 Missing *n*=16	●	●	●		■	■	■	■
	SG		Solid	*n*=202		Epo Alfa *n*=131 Placebo *n*=61 Missing *n*=10		●	○		■	■	■	■
	SG		Haem	*n*=173		Epo Alfa *n*=113 Placebo *n*=54 Missing *n*=6		●	●		■	■	■	■
Moebus	2013[62]	Non-plat	Solid	*n*=643	9	Epo Alfa *n*=320 Control *n*=305 Missing *n*=18			●		■	■	■	■
Österborg	2005[79]	Non-plat	Haem	*n*=349	10	Epo Beta=169 Placebo *n*=173 Missing *n*=7	●	●	●	○	■	■	■	■
Ray-Coquard	2009[75]	?	Solid and Haem	*n*=218		Epo Beta=110 Control *n*=108 Missing *n*=5			●		■	□	□	■
Silvestris	1995[72]	?	Haem	*n*=54		Epo Beta=30 Control *n*=24 Missing *n*=5					■	■	□	■
Strauss	2005[76]	+Radio	Solid	*n*=74		Epo Beta *n*=34 Control *n*=40			○		■	■	□	■

Quality appraisal key
Random:
concealment of allocation (above)
random allocation (below)
Baseline:
baseline characteristics
Blinding:
blinding of clinicians (above)
blinding of patients (below)
Losses:
ITT or <10% (above)
losses (below)

■ Positive quality check
■ Partial quality check
□ Negative quality check
■ Not reported

Outcomes key
● Favours treatment
◪ Favours control
○ Non-significant outcomes

FIGURE 9 Anaemia-related outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–8 and 10–12. 1: Hb change: epo alfa $n=63$; 2: HaemR and units: epo alfa $n=66$ and placebo $n=66$; 3: Hb change: rHuEPO $n=28$ and control $n=24$; 4: Hb change: epo alfa $n=64$ and control $n=58$; 5: Hb change: darbe alfa $n=17$ and placebo $n=6$; 6: RBCT: darbe alfa $n=167$ and placebo $n=165$; 7: HaemR = increase in Hb of ≥ 2 g/dl and/or Hb level >12 g/dl; 8: RBCT: epo alfa $n=251$ and placebo $n=124$; 9: Latin square design; 10: Hb change: epo beta $n=138$ and placebo $n=142$; 11: Hb change: licensed epo alfa $n=34$ and control $n=24$; 12: Hb change: darbe alfa $n=330$ and placebo $n=359$. ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; haemR, haematological response; non-plat, non-platinum; plat, platinum; QA, quality appraisal; units, units transfused. (*continued*)

(d)

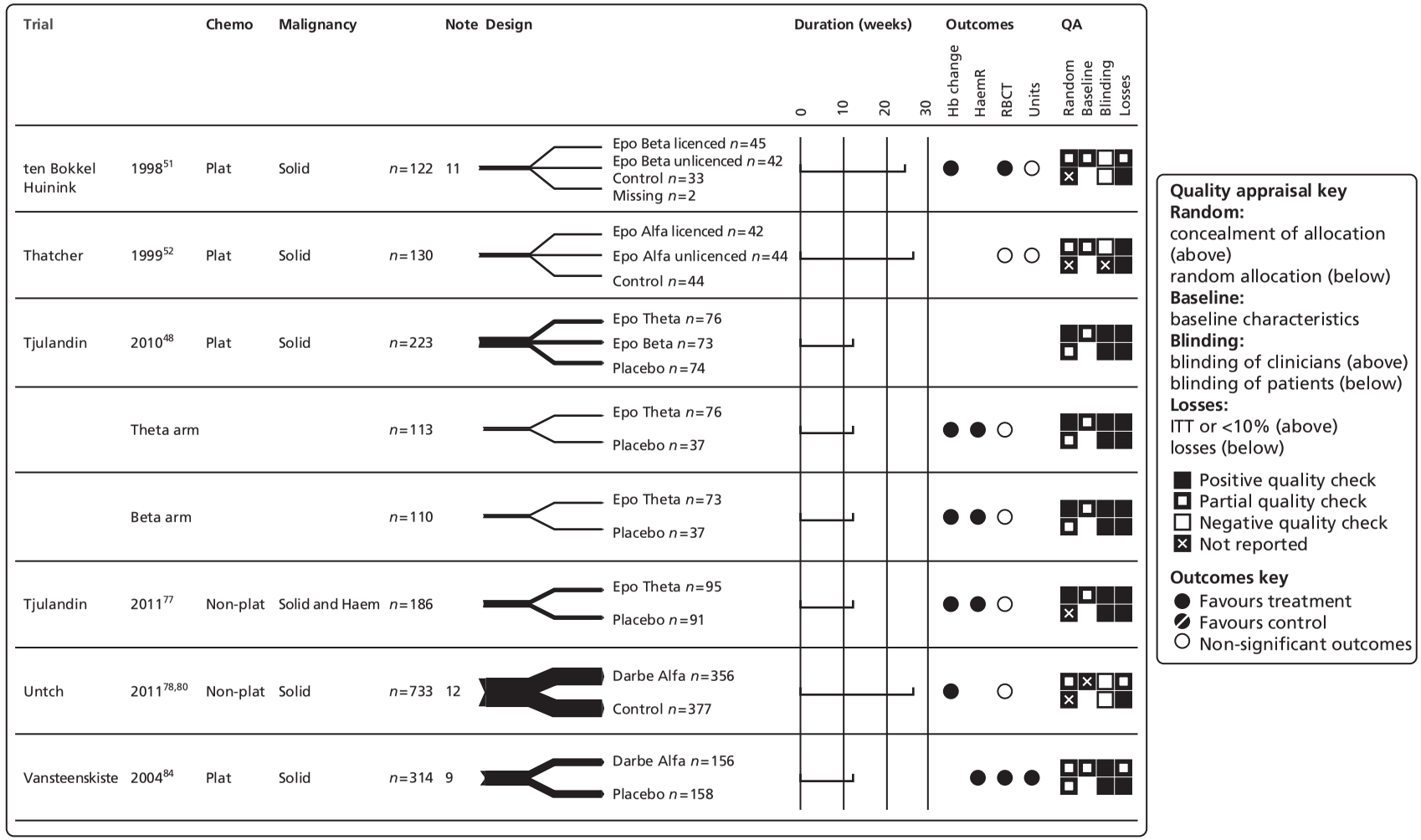

FIGURE 9 Anaemia-related outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–8 and 10–12. 1: Hb change: epo alfa $n = 63$; 2: HaemR and units: epo alfa $n = 66$ and placebo $n = 66$; 3: Hb change: rHuEPO $n = 28$ and control $n = 24$; 4: Hb change: epo alfa $n = 64$ and control $n = 58$; 5: Hb change: darbe alfa $n = 17$ and placebo $n = 6$; 6: RBCT: darbe alfa $n = 167$ and placebo $n = 165$; 7: HaemR = increase in Hb of ≥ 2 g/dl and/or Hb level > 12 g/dl; 8: RBCT: epo alfa $n = 251$ and placebo $n = 124$; 9: Latin square design; 10: Hb change: epo beta $n = 138$ and placebo $n = 142$; 11: Hb change: licensed epo alfa $n = 34$ and control $n = 24$; 12: Hb change: darbe alfa $n = 330$ and placebo $n = 359$. ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; haemR, haematological response; non-plat, non-platinum; plat, platinum; QA, quality appraisal; units, units transfused.

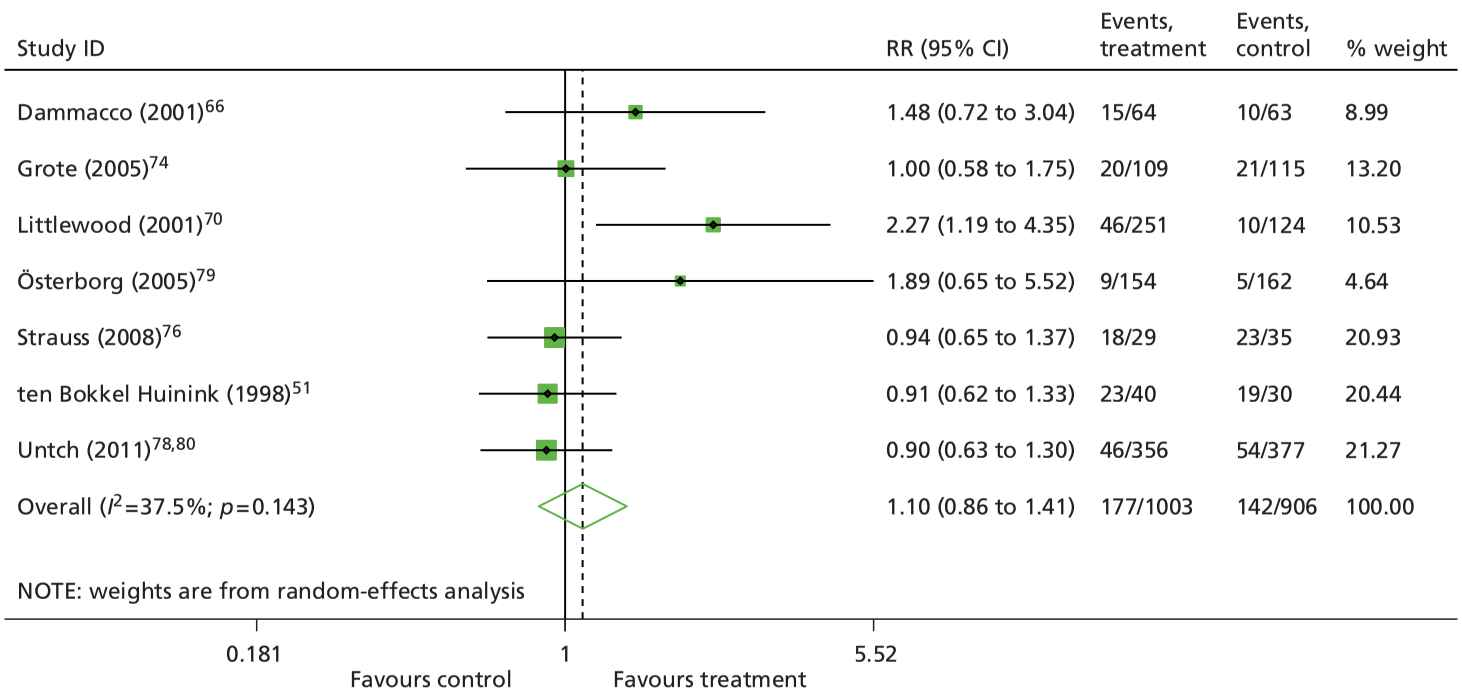

FIGURE 10 Forest plot: tumour response (complete response). Note: random-effects meta-analysis (DerSimonian–Laird). Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

was not conducted.[54] The fixed-effects meta-analysis undertaken as a sensitivity analysis showed similar non-significant results (RR 1.20, 95% CI 0.85 to 1, 71, $I^2 = 37.5\%$; $p = 0.143$); the forest plot of the analysis is included in *Appendix 12*.

The previous HTA review,[2] using a fixed-effects model, suggested that ESAs have detrimental effects with regard to tumour response (RR 1.31, 95% CI 1.08 to 1.60). However, the Cochrane review[11] did not find any differences between the control group and the treatment group with regard to tumour response (RR 1.02, 95% CI 0.98 to 1.06). It must be emphasised that the current analysis included only studies complying with the licenced ESA dose, whereas the HTA review and the Cochrane review did not apply any restrictions regarding the ESA posology. The HTA meta-analyses included nine trials with 1260 participants and the Cochrane review included 19 trials with 5012 participants.

Prespecified subgroup analyses and meta-regression models with subgroups as covariates were not conducted because only seven trials were included in the meta-analysis.

In addition, Tonia and colleagues[11] used additional quality criteria to assess the quality of trials reporting data on tumour control. The study population had to be homogeneous (i.e. all participants had to have the same tumour type/stage), all participants had to receive a predefined, identical anticancer therapy and the study had to be designed to assess tumour outcomes prospectively and/or tumour outcomes were defined as the primary or secondary study outcome. Trials were also considered if they were stratified by treatment and/or by tumour type (tumour stage). Only two studies[76,78,80] included in the current review met the additional criteria of Tonia and colleagues.[11]

Summary

Seven trials reported tumour response, all of which were included in the meta-analysis. All were of moderate or poor quality. The general problem of reporting of trials on this topic was greatly assisted by the recent Cochrane review,[11] as the authors had gathered further details from investigators and manufacturers, which were used in the meta-analysis for this review. Analyses suggest that treatment with ESAs in patients with cancer-induced anaemia did not have a significant effect on complete tumour response (RR 1.10, 95% CI 0.86 to 1.41). In total, 18% ($n = 177/1003$) of participants who received ESAs had a complete tumour response compared with 16% ($n = 142/906$) of patients in the control groups. There was non-significant heterogeneity between the trials ($I^2 = 37.5\%$; $p = 0.143$); however, the direction of the effects of ESAs with regard to tumour response varied across the individual trials. The data from the seven trials suggest that there is no difference between patients treated with ESAs and patients in the control groups with regard to tumour response; however, the data are insufficient to exclude detrimental effects. It should also be noted that this is a difficult area of assessment, especially in a heterogeneous mix of tumour types, and the results should be treated with caution. Data are presented alongside the results from previous analyses in *Table 21*. (See *Figure 13* for a graphical summary of the study characteristics, quality appraisal and results for this outcome.)

TABLE 21 Tumour response results comparison: Wilson and colleagues[2] vs. Tonia and colleagues[11] vs. PenTAG

Outcome	[a]Wilson and colleagues[2]	[a]Tonia and colleagues[11]	PenTAG[a]	PenTAG[b]
Tumour response[c]	RR 1.31, 95% CI 1.08 to 1.60; $\chi^2_{(het)}$ = NR, df = NR; p = NR	RR 1.02, 95% CI 0.98 to 1.06; $\chi^2_{(het)} = 16.10$, df = 18; $p = 0.59$	RR 1.20, 95% CI 0.85 to 1.71; $\chi^2_{(het)} = 9.59$, df = 6; $p = 0.14$	RR 1.10, 95% CI 0.86 to 1.41; $\chi^2_{(het)} = 9.59$, df = 6; $p = 0.14$
	10 trials, $n = 1260$	19 trials, $n = 5012$	7 trials, $n = 1909$	7 trials, $n = 1909$

het, heterogeneity; NR, not reported.
p-values reported for heterogeneity.
a Fixed effects (Mantel–Haenzel).
b Random effects (DerSimonian–Laird).
c The number of trials accounts for multiple experimental aims for some studies.

Overall survival

For OS, data were extracted from the Cochrane review.[11] In the Cochrane review the reported HRs were based on IPD. When IPD were not available, the authors extracted HRs from published reports, including secondary analyses, using methods reported in Parmar and colleagues[49] or from binary mortality data. OS was calculated from the longest follow-up available and varied between studies.

Overall survival data were available from 21 trials[17,48,50–53,62,63,65–70,73–79] including 5054 participants. Seven studies[48,62,74–78] were newly identified. Two studies[48,63] were split into subsets, two studies[53,69] reported zero events and three studies[50–52] reported events/effect size for a combined treatment arm (studies evaluated different ESA doses) and as such included unlicensed doses; as a result, the number of studies included in the meta-analysis is 18.

The OS estimate is provided in *Figure 11* (HR 0.97, 95% CI 0.83 to 1.13). The heterogeneity between trials was significant, with an I^2 of 42.4% ($p = 0.030$; $\chi^2 = 29.5$, df = 17, $p = 0.030$); the forest plot suggested that there was a tendency for smaller studies to favour treatment. Funnel plot analysis identified one outlier[68] and also suggested that smaller studies had a tendency to favour treatment; a funnel plot without the outlier is presented in *Appendix 12*. The Harbord test was not performed because raw data were not available.

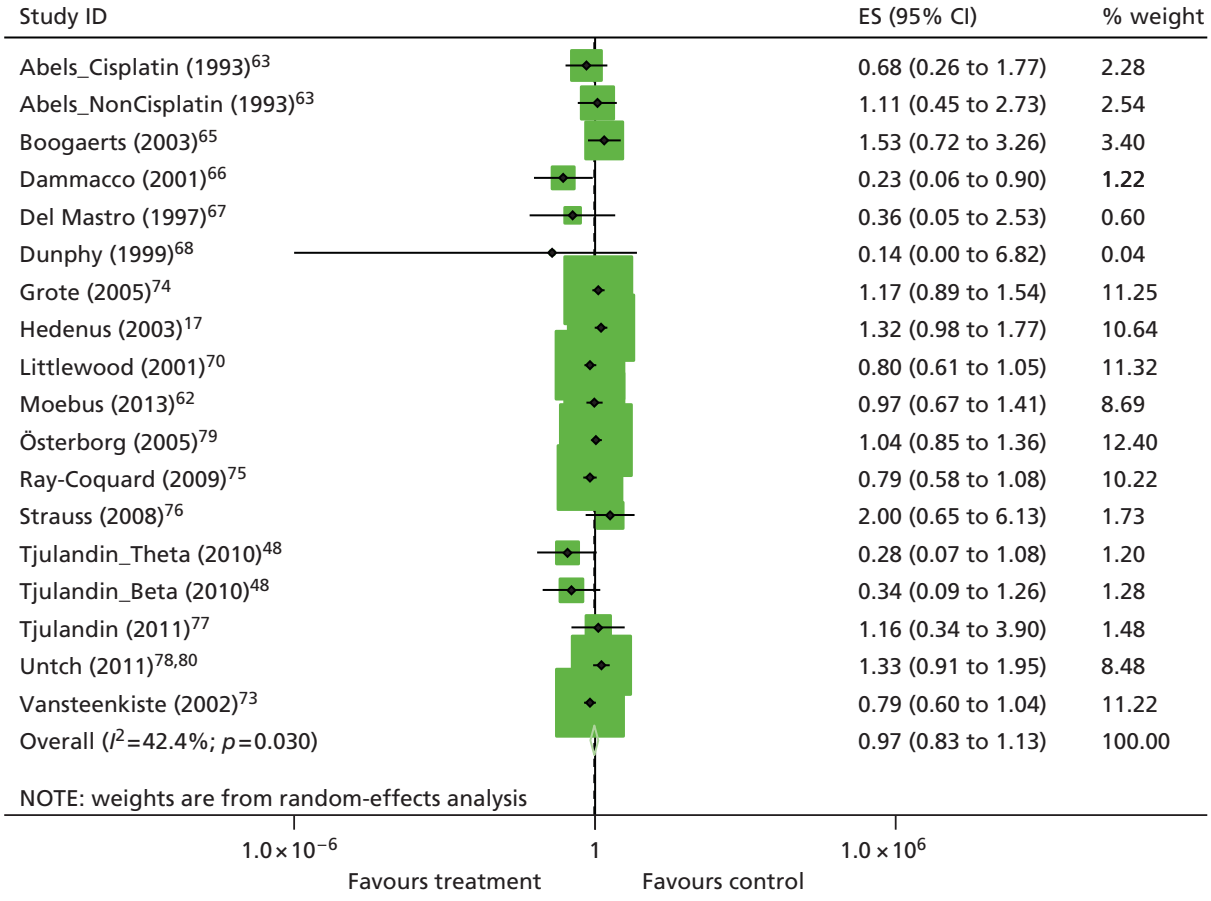

FIGURE 11 Forest plot: OS. Notes: random-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy; effect sizes reported are HRs; IPD data as reported in Tonia and colleagues[11] (Cochrane review) for Abels and colleagues,[63] Boogaerts and colleagues,[65] Dammacco and colleagues,[66] Grote and colleagues,[74] Hedenus and colleagues,[17] Littlewood and colleagues,[70] Österborg and colleagues,[71] Ray-Coquard and colleagues,[75] Strauss and colleagues[76] and Vansteenkiste and colleagues.[73] HRs reported for other trials calculated using other accepted methods. ES, effect size.

A meta-regression using publication year as a covariate (to assess the effect of publication year on OS) showed that the effects of ESAs on OS were independent of any effect of publication year ($p = 0.579$; the meta-regression plot is presented in *Appendix 12*).

To identify sources of heterogeneity we performed subgroup analyses (*Table 22*). In addition, meta-regression models that included random effect and subgroups as covariates (to assess the effects of a subgroup on OS) were performed. The *F* statistics from these analyses are reported in *Table 22*. All covariates showing a significant effect ($p < 0.05$) in a univariate analysis were considered further in model selection.

TABLE 22 Overall survival: subgroup analyses

Subgroup	No. of trials	HR	95% CI	I^2	Tau^2
Overall	18	0.97	0.83 to 1.13	42.4%; $p = 0.03$	0.04
Inclusion Hb level (g/dl)					
≤ 11.0	10	0.91	0.70 to 1.20	51.7%; $p = 0.03$	0.07
> 11.0	8	0.99	0.81 to 1.20	35.5%; $p = 0.15$	0.02
F (between : within)				$F_{1,16} = 0.09$; $p = 0.77$	
Baseline Hb level (g/dl)					
≤ 10.0	11	0.88	0.71 to 1.08	53.0%; $p = 0.02$	0.05
≤ 11.0	1	1.11	0.45 to 2.73	NA	NA
≤ 12.0	1	2.00	0.65 to 1.13	NA	NA
≤ 14.5	4	1.20	0.96 to 1.50	0%; $p = 0.56$	0
NR	1	0.97	0.67 to 1.41	NA	NA
F (between : within)				$F_{4,13} = 0.78$; $p = 0.56$	
Target Hb level (g/dl)					
≤ 13.0	4	0.73	0.32 to 1.64	61.8%; $p = 0.05$	0.41
> 13.0	12	0.97	0.82 to 1.14	46.6%; $p = 0.04$	0.03
NR	2	0.88	0.46 to 1.70	0%; $p = 0.47$	0
F (between : within)				$F_{2,15} = 0.03$; $p = 0.97$	
Malignancy type					
Solid tumours	9	0.96	0.74 to 1.25	46.3%; $p = 0.06$	0.06
Haematological tumours	5	1.01	0.73 to 1.40	48.5%; $p = 0.10$	0.05
Mixed	4	0.84	0.69 to 1.02	0%; $p = 0.40$	0
F (between : within)				$F_{2,15} = 0.40$; $p = 0.68$	
Chemotherapy treatment[a]					
Platinum containing	4	0.67	0.46 to 0.98	14.5%; $p = 0.32$	0.03
Non-platinum containing	7	0.99	0.86 to 1.14	0%; $p = 0.42$	0
F (between : within)				$F_{1,9} = 3.48$; $p = 0.10$	

continued

TABLE 22 Overall survival: subgroup analyses (*continued*)

Subgroup	No. of trials	HR	96% CI	I^2	Tau²
Iron supplementation					
No iron	12	0.96	0.79 to 1.17	38.9%; $p = 0.08$	0.03
Iron in an intervention arm	1	1.33	0.91 to 1.95	NA	0
NR	5	0.87	0.61 to 1.23	54.0%; $p = 0.07$	0.07
F (between : within)				$F_{2,15} = 0.72$; $p = 0.50$	
Study design					
RCT	11	0.92	0.75 to 1.13	52.4%; $p = 0.02$	0.05
ROL	7	1.05	0.81 to 1.36	28.1%; $p = 0.21$	0.03
F (between : within)				$F_{1,16} = 0.50$; $p = 0.49$	
Study duration (weeks)					
6–9	2	1.90	0.63 to 5.76	0%; $p = 0.51$	0
12–16	11	0.86	0.68 to 1.08	48.8%; $p = 0.03$	0.05
17–20	2	1.10	0.88 to 1.37	0%; $p = 0.43$	0
> 20	3	1.10	0.72 to 1.67	66.4%; $p = 0.05$	0.09
F (between : within)				$F_{3,14} = 0.87$; $p = 0.48$	
ESA					
Erythropoietin	15	0.92	0.77 to 1.10	31.2%; $p = 0.12$	0.03
Darbepoetin	3	1.10	0.77 to 1.58	74.6%; $p = 0.03$	0.08
F (between : within)				$F_{1,16} = 0.92$; $p = 0.35$	

NR, not reported; ROL, randomised open-label (standard care) study.
a Subgroup analyses by platinum-based compared with non-platinum-based chemotherapy; other studies excluded for the following reasons: chemotherapy type not reported or trial population in which participants received either platinum-based or non-platinum-based chemotherapy.

Univariate analyses did not identify any significant differences based on the predefined subgroups (see *Table 22*). The fixed-effects meta-analysis undertaken as a sensitivity analysis showed similar results (HR 0.98, 95% CI 0.89 to 1.08); the forest plot of this analysis is included in *Appendix 12*. Both fixed- and random-effects estimates suggested that there was no difference in OS between the control arm and the treatment arm. Interestingly, the fixed-effects estimate reported in the recent Cochrane review[11] favoured the control arm, suggesting that higher mortality occurred in patients treated with ESAs (HR 1.05, 95% CI 1.00 to 1.11). The previous HTA review[2] did not find a significant difference between the control arm and the treatment arm with regard to survival (HR 1.03, 95% CI 0.92 to 1.16). It must be emphasised that the current analysis included only studies complying with the licenced ESA dose, whereas the Cochrane review did not apply any restrictions regarding the ESA posology. The Cochrane review included 76 studies in the OS meta-analysis; however, subgroup analyses comparing studies using licensed and unlicensed ESA doses were not conducted.

Summary

In total, 21 trials reported OS. All were of moderate or poor quality. The general problem of reporting of trials on this topic was greatly assisted by the recent Cochrane review,[11] as the authors had gathered further details from investigators and manufacturers, which were used in the meta-analysis for this review. Eighteen trials were included in the meta-analysis. Analyses suggest that treatment with ESAs in patients with CIA did not have a significant effect on OS. In total, 35% ($n = 818/2317$) of participants who received ESAs died and 35% ($n = 744/2137$) of patients in the control groups died. The risk of death was 0.97 (HR 0.97, 95% CI 0.83 to 1.13). However, there was significant heterogeneity between the trials ($I^2 = 42.4\%$; $p = 0.030$), for which no explanation could be provided. In addition, OS was calculated from the longest follow-up available (no minimum was required) and, as such, this variation between the studies (short-term and long-term studies) should be considered when interpreting the results. Overall, data suggest that, if the licensed ESA dose is followed, there are no detrimental effects of ESAs on OS; however, these results are subject to the limitations acknowledged and should be interpreted with caution. Effectiveness estimates are presented alongside previously reported estimates for OS in *Table 23*. (See *Figure 13* for a graphical summary of the study characteristics, quality appraisal and results for this outcome.)

On-study mortality

For on-study mortality, data were extracted from the Cochrane review.[11] In the Cochrane review, reported HRs were based on IPD. When IPD were not available, the authors extracted HRs from published reports, including secondary analyses, using the methods reported in Parmar and colleagues.[49] On-study mortality was defined as deaths occurring up to 30 days after the active study period.

Mortality data were available from 21 trials[17,48,50–53,62,63,65–70,73–79] including 5085 participants. Seven studies[48,62,74–78] were newly identified. Two studies[48,63] were split into subsets, six studies[62,67,69,76,78,79] reported zero events and four studies[50–53] reported events/effect size for combined treatment arms (studies evaluated different ESA doses) and as such included unlicensed doses. As a result, the number of trials included in the meta-analysis is 14 (including 2967 participants). One study reported mortality events in the control arm, whereas there were no deaths recorded in the treatment arm (HR 0.14, 95% CI 0.00 to 6.82).[68]

The results from the on-study mortality meta-analysis are provided in *Figure 12* (HR 0.86, 95% CI 0.67 to 1.11). Heterogeneity between trials was not significant ($I^2 = 16.4\%$, $p = 0.274$; $\chi^2 = 15.55$, df = 13, $p = 0.274$); however, the forest plot may suggest a tendency for smaller studies to favour treatment (see *Figure 12*). Similarly to the OS data, funnel plot analysis (see *Appendix 12*) identified one outlier[68] and was also suggestive of a tendency for smaller studies to favour treatment; a funnel plot without the outlier is presented in *Appendix 12*. The Harbord test was not performed because raw data were not available.

TABLE 23 Overall survival results comparison: Wilson and colleagues[2] vs. Tonia and colleagues[11] vs. PenTAG

Outcome	[a]Wilson and colleagues[2]	[a]Tonia and colleagues[11]	PenTAG[a]	PenTAG[b]
OS[c]	HR 1.03, 95% CI 0.92 to 1.16; $\chi^2_{(het)} = 37.74$, df = 27; $p = 0.08$	HR 1.05, 95% CI 1.00 to 1.11; $\chi^2_{(het)} = 95.40$, df = 75; $p = 0.060$	HR 0.98, 95% CI 0.89 to 1.08; $\chi^2_{(het)} = 29.50$, df = 17; $p = 0.03$	HR 0.97, 95% CI 0.83 to 1.13; $\chi^2_{(het)} = 29.50$, df = 17; $p = 0.03$
	28 trials, $n = 5308$	80 trials, $n = 19,003$	18 trials, $n = 4454$	18 trials, $n = 4454$

het, heterogeneity.
p-values reported for heterogeneity.
a Fixed effects (Mantel–Haenzel).
b Random effects (DerSimonian–Laird).
c The number of trials accounts for multiple experimental arms for some studies.

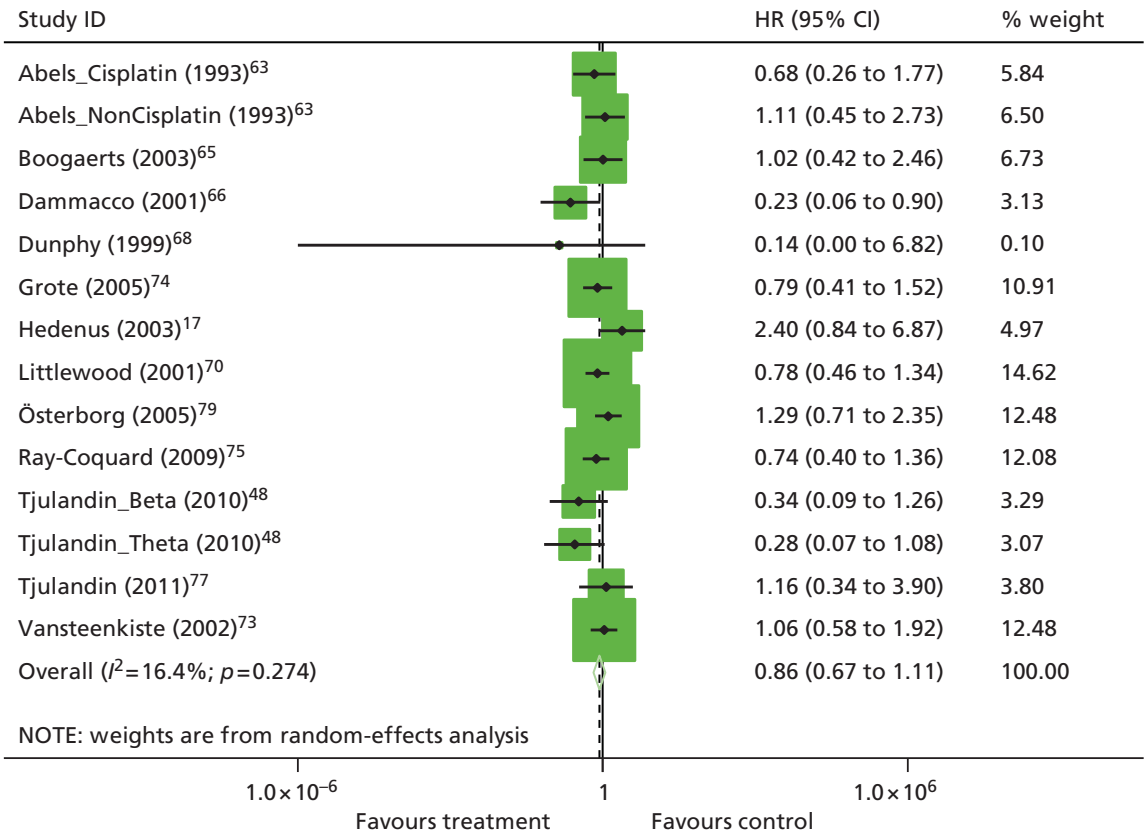

FIGURE 12 Forest plot: on-study mortality. Notes: random-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy; IPD data as reported in Tonia and colleagues[11] (Cochrane review) for Abels and colleagues,[63] Boogaerts and colleagues,[65] Dammacco and colleagues,[66] Grote and colleagues,[74] Hedenus and colleagues,[17] Littlewood and colleagues,[70] Österborg and colleagues,[71] Ray-Coquard and colleagues,[75] Strauss and colleagues[76] and Vansteenkiste and colleagues.[73] HRs reported for other trials calculated using other accepted methods.

A meta-regression using publication year as a covariate (to assess the effect of publication year on on-study mortality) suggested that the effects of ESAs on mortality were independent of when the trial results were published ($p = 0.465$; the meta-regression plot is presented in *Appendix 12*).

The fixed-effects meta-analysis undertaken as a sensitivity analysis showed similar results (HR 0.87, 95% CI 0.70 to 1.09); the forest plot of this analysis is provided in *Appendix 12*. Both fixed- and random-effects estimates suggested no difference in on-study mortality between the control arm and the treatment arm. Interestingly, the fixed-effects estimate reported in the recent Cochrane review[11] favoured the control arm, suggesting that higher mortality occurred in patients treated with ESAs (HR 1.17, 95% CI 1.03 to 1.29). Again, it must be emphasised that the current analysis included only studies complying with the licensed ESA dose, whereas the Cochrane review did not apply any restrictions regarding the ESA posology. The Cochrane review included 64 studies in the on-study mortality meta-analysis, but subgroup analyses comparing studies using licensed and unlicensed ESA doses were not conducted.

Predefined subgroup analyses were performed (*Table 24*). None of the studies with available Hb response data included ovarian cancer patients. Therefore, the planned ovarian cancer subgroup analysis was not completed. In addition, to assess the effects of subgroups on mortality, meta-regression models were performed that included random effect and subgroups as covariates; the *F* statistics from these analyses are reported in *Table 24*. All covariates showing a significant effect ($p < 0.05$) in a univariate analysis were considered further in model selection.

Univariate analyses did not identify any significant differences based on the predefined subgroups.

TABLE 24 Mortality: subgroup analyses

Subgroup	No. of trials	HR	95% CI	I^2	Tau^2
Overall	14	0.86	0.67 to 1.11	16.4%; $p = 0.27$	0.04
Inclusion Hb level (g/dl)					
≤ 11.0	10	0.89	0.61 to 1.30	37.7%; $p = 0.11$	0.13
> 11.0	4	0.77	0.55 to 1.08	0%; $p = 0.98$	0
F (between : within)				$F_{1,12} = 0.74$; $p = 0.41$	
Baseline Hb level (g/dl)					
≤ 10.0	11	0.84	0.62 to 1.15	33.2%; $p = 0.13$	0.09
≤ 11.0	1	1.11	0.45 to 2.73	NA	0
≤ 14.5	2	0.78	0.41 to 1.50	0%; $p = 0.67$	0
F (between : within)				$F_{2,11} = 0.14$; $p = 0.87$	
Target Hb level (g/dl)					
≤ 13.0	3	0.50	0.20 to 1.22	29.7%; $p = 0.24$	0.19
> 13.0	9	0.92	0.70 to 1.22	20.0%; $p = 0.27$	0.04
NR	2	0.88	0.46 to 1.70	0%; $p = 0.47$	0
F (between : within)				$F_{2,11} = 0.89$; $p = 0.44$	
Malignancy type					
Solid tumours	5	0.71	0.44 to 1.15	17.6%; $p = 0.30$	0.06
Haematological tumours	5	0.98	0.54 to 1.79	52.7%; $p = 0.08$	0.24
Mixed	4	0.83	0.58 to 1.17	0%; $p = 0.88$	0
F (between : within)				$F_{2,11} = 0.61$; $p = 0.56$	
Chemotherapy treatment[a]					
Platinum containing	4	0.64	0.34 to 1.18	36.0%; $p = 0.20$	0.14
Non-platinum containing	4	1.01	0.71 to 1.43	0%; $p = 0.65$	0
F (between : within)				$F_{1,6} = 1.36$; $p = 0.29$	
Iron supplementation					
Iron in both arms	9	0.89	0.63 to 1.26	25.6%; $p = 0.22$	0.07
NR	5	0.82	0.55 to 1.21	14.5%; $p = 0.32$	0.03
F (between : within)				$F_{1,12} = 0.09$; $p = 0.77$	
Study design					
Blinded (RCT)	11	0.86	0.63 to 1.17	33.0%; $p = 0.14$	0.09
Unblinded (ROL)	3	0.82	0.49 to 1.35	0.0%; $p = 0.77$	0
F (between : within)				$F_{1,12} = 0.07$; $p = 0.80$	

continued

TABLE 24 Mortality: subgroup analyses (*continued*)

Subgroup	No. of trials	HR	95% CI	I^2	Tau²
Study duration (weeks)					
6–9	1	0.14	0 to 365.61	NA	0
12–16	10	0.85	0.59 to 1.23	39.6%; $p = 0.09$	0.13
17–20	1	0.79	0.41 to 1.52	NA	0
> 20	2	0.84	0.53 to 1.32	0.0%; $p = 0.61$	0
F (between : within)				$F_{3.10} = 0.070$; $p = 0.97$	
ESA					
Erythropoietin	12	0.80	0.63 to 1.02	1.0%; $p = 0.43$	< 0.01
Darbepoetin	2	1.42	0.66 to 3.05	43.0%; $p = 0.19$	0.14
F (between : within)				$F_{1.12} = 2.51$; $p = 0.14$	

NR, not reported; ROL, randomised open-label (standard care) study.
a Subgroup analyses by platinum-based compared with non-platinum-based chemotherapy; other studies excluded for the following reasons: chemotherapy type not reported or trial population in which participants received either platinum-based or non-platinum-based chemotherapy.

Summary

On-study mortality was assessed in 12 trials of moderate or poor quality. Analyses suggested that treatment with ESAs in patients with CIA did not have a significant effect on on-study mortality. In total, 11% ($n = 174/1586$) of participants who received ESAs had died within 30 days of the active study period compared with 12% ($n = 164/1381$) of patients in the control groups. The risk of death was 0.86 (HR 0.86, 95% CI 0.67 to 1.1). There was no significant heterogeneity between the trials ($I^2 = 16.4\%$, $p = 0.274$). Overall, data suggested that, if the licensed ESA dosage is followed, there are no detrimental effects of ESAs on on-study mortality. However, these results should be interpreted with caution. Effectiveness estimates are compared with previously reported estimates in *Table 25* and a graphical summary of the study characteristics, quality appraisal and results for this outcome is presented in *Figure 13*.

TABLE 25 On-study mortality results comparison: Wilson and colleagues[2] vs. Tonia and colleagues[11] vs. PenTAG

Outcome	[a]Wilson and colleagues[2]	[a]Tonia and colleagues[11]	PenTAG[a]	PenTAG[b]
Mortality[c]	NR	HR 1.17, 95% CI 1.03 to 1.29; $\chi^2_{(het)} = 59.49$, df = 63; $p = 0.600$	HR 0.87, 95% CI 0.70 to 1.09; $\chi^2_{(het)} = 15.55$, df = 13; $p = 0.274$	HR 0.86, 95% CI 0.67 to 1.11; $\chi^2_{(het)} = 15.55$, df = 13; $p = 0.274$
		72 trials,[c] $n = 15{,}935$	14 trials, $n = 2967$	14 trials, $n = 2967$

het, heterogeneity; NR, not reported.
p-values reported for heterogeneity.
a Fixed effects (Mantel–Haenzel).
b Random effects (DerSimonian–Laird).
c The number of trials accounts for multiple experimental arms for some studies.

(a)

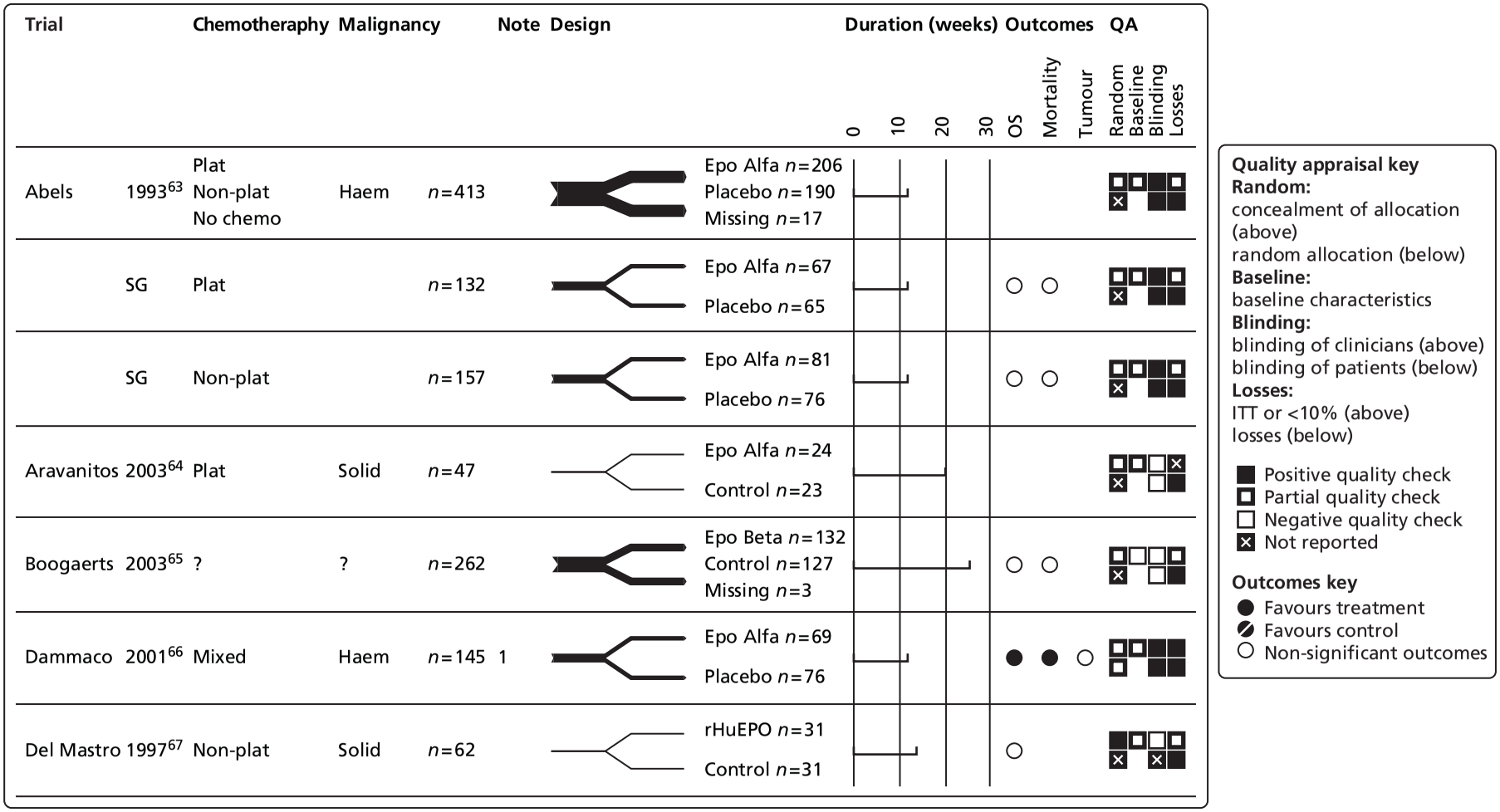

FIGURE 13 Tumour response, OS and mortality outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–4. 1: tumour response reported for epo alfa $n = 64$ and placebo $n = 63$; 2: tumour response reported for epo beta $n = 154$ and placebo $n = 162$; 3: OS reported for darbe alfa $n = 345$ and control $n = 369$ and mortality reported for darbe alfa $n = 353$ and control $n = 376$; 4: OS and mortality reported for all randomised participants ($n = 320$), whereas other outcomes were reported using all randomised participants receiving at least one dose of study treatment ($n = 314$). ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; non-plat, non-platinum; plat, platinum; QA, quality appraisal. (*continued*)

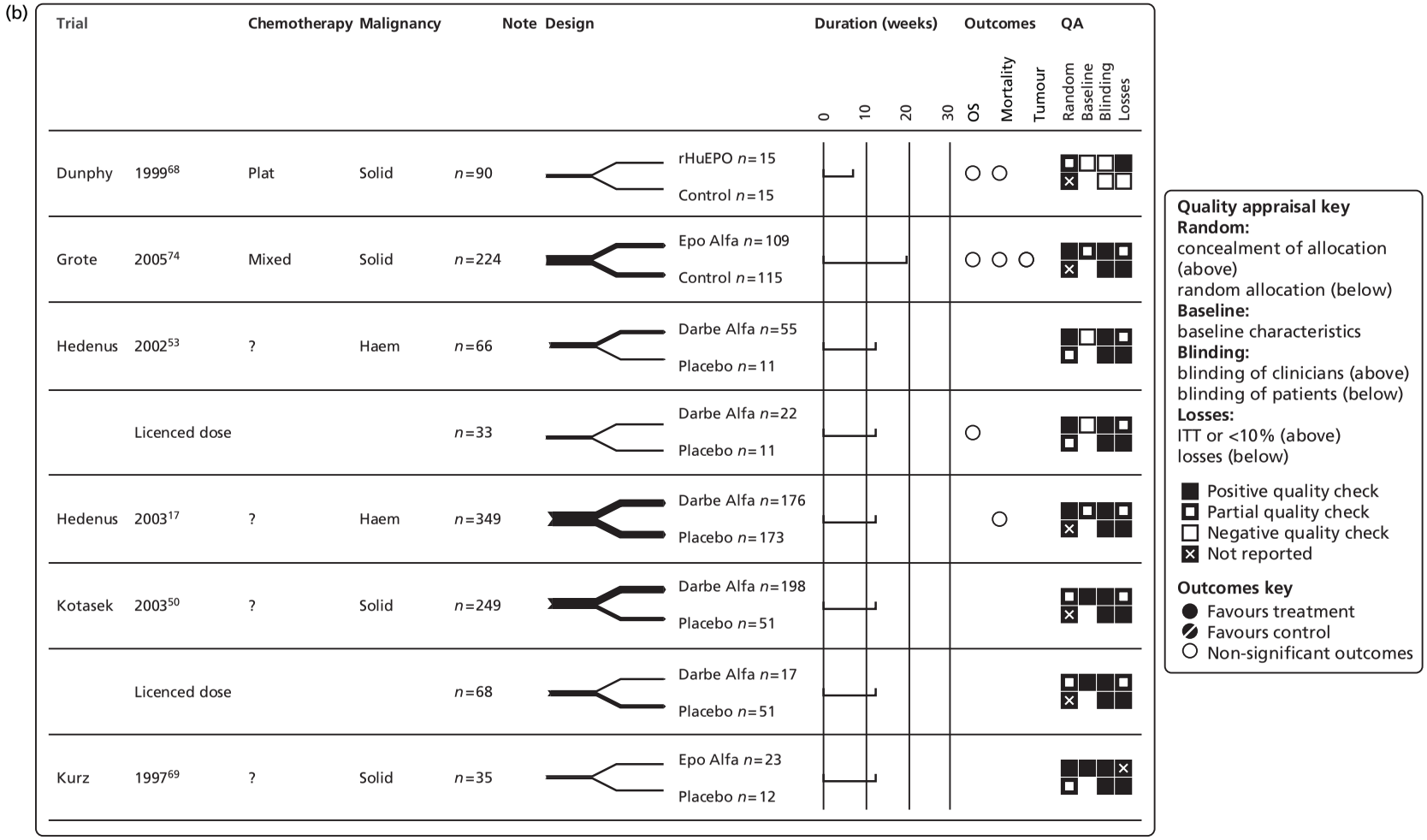

FIGURE 13 Tumour response, OS and mortality outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–4. 1: tumour response reported for epo alfa $n = 64$ and placebo $n = 63$; 2: tumour response reported for epo beta $n = 154$ and placebo $n = 162$; 3: OS reported for darbe alfa $n = 345$ and control $n = 369$ and mortality reported for darbe alfa $n = 353$ and control $n = 376$; 4: OS and mortality reported for all randomised participants ($n = 320$), whereas other outcomes were reported using all randomised participants receiving at least one dose of study treatment ($n = 314$). ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; non-plat, non-platinum; plat, platinum; QA, quality appraisal. (*continued*)

(c)

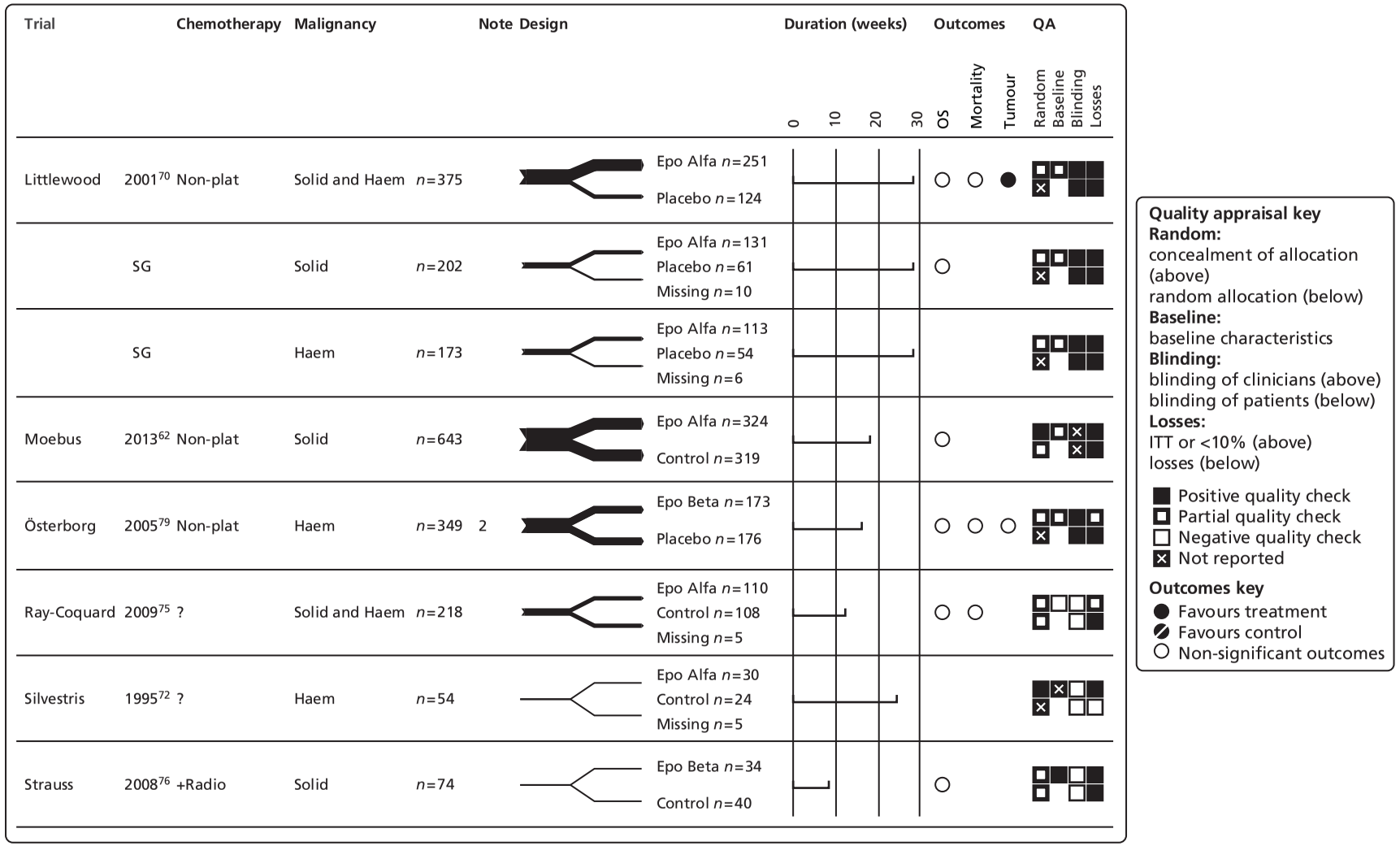

FIGURE 13 Tumour response, OS and mortality outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–4. 1: tumour response reported for epo alfa $n = 64$ and placebo $n = 63$; 2: tumour response reported for epo beta $n = 154$ and placebo $n = 162$; 3: OS reported for darbe alfa $n = 345$ and control $n = 369$ and mortality reported for darbe alfa $n = 353$ and control $n = 376$; 4: OS and mortality reported for all randomised participants ($n = 320$), whereas other outcomes were reported using all randomised participants receiving at least one dose of study treatment ($n = 314$). ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; non-plat, non-platinum; plat, platinum; QA, quality appraisal. (*continued*)

(d)

Trial		Chemotherapy	Malignancy		Note	Design	Duration (weeks)	Outcomes			QA			
							0 10 20 30	OS	Mortality	Tumour	Random	Baseline	Blinding	Losses
ten Bokkel Huinink	1998[51]	Plat	Solid	*n*=122		Epo Beta licenced *n*=45 Epo Beta unlicenced *n*=40 Control *n*=30 Missing *n*=7				○	■ ■ ✕	✕	□ □	■ ■
Thatcher	1999[52]	Plat	Solid	*n*=130		Epo Alfa licenced *n*=42 Epo Alfa unlicenced *n*=44 Control *n*=44					■ ■ ✕	✕	□ ✕	■ ■
Tjulandin	2010[48]	Plat	Solid	*n*=223		Epo Theta *n*=76 Epo Beta *n*=73 Placebo *n*=74					■ ■ □		■ ■	■ ■
	Theta arm			*n*=113		Epo Theta *n*=76 Placebo *n*=37		○	○		■ ■ □		■ ■	■ ■
	Beta arm			*n*=110		Epo Beta *n*=73 Placebo *n*=37		○	○		■ ■ □		■ ■	■ ■
Tjulandin	2011[77]	Non-plat	Solid and Haem	*n*=186		Epo Theta *n*=95 Placebo *n*=91		○	○		■ ■ ✕		■ ■	■ ■
Untch	2011[78,80]	Non-plat	Solid	*n*=733	3	Darbe Alfa *n*=345 Control *n*=369		○			■ ✕ ✕	✕	□ □	■ ■
Vansteenskiste	2004[84]	Plat	Solid	*n*=320	4	Darbe Alfa *n*=159 Placebo *n*=161		○	○		■ ■ □		■ ■	■ ■

Quality appraisal key
Random:
concealment of allocation (above)
random allocation (below)
Baseline:
baseline characteristics
Blinding:
blinding of clinicians (above)
blinding of patients (below)
Losses:
ITT or <10% (above)
losses (below)

■ Positive quality check
□ Partial quality check
□ Negative quality check
✕ Not reported

Outcomes key
● Favours treatment
◐ Favours control
○ Non-significant outcomes

FIGURE 13 Tumour response, OS and mortality outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–4. 1: tumour response reported for epo alfa *n* = 64 and placebo *n* = 63; 2: tumour response reported for epo beta *n* = 154 and placebo *n* = 162; 3: OS reported for darbe alfa *n* = 345 and control *n* = 369 and mortality reported for darbe alfa *n* = 353 and control *n* = 376; 4: OS and mortality reported for all randomised participants (*n* = 320), whereas other outcomes were reported using all randomised participants receiving at least one dose of study treatment (*n* = 314). ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; non-plat, non-platinum; plat, platinum; QA, quality appraisal.

Safety

Adverse events of relevance to this review included thromboembolic events, hypertension, thrombocytopenia/haemorrhage, seizures, pruritus and red cell aplasia.

All studies reporting AEs were of moderate or poor quality. There was considerable variability in the reporting of AEs among the included studies, for example some reported AEs that occurred in > 5% of patients, some reported AEs that occurred in > 10% of patients and some reported the overall number of events. In addition, there was some variability in the definitions of AEs used in the studies. Given the greater access to data in the Cochrane review,[11] these data were used to conduct meta-analyses for the following AEs: thromboembolic events, thrombocytopenia and haemorrhage, hypertension, seizures and pruritus (defined as pruritus, rash and irritation).

No studies were identified that reported red cell aplasia. In addition, this safety outcome was not analysed in the Cochrane review.

Thromboembolic events

We identified 14 trials[17,51,52,62,63,66,70,73–79] that measured thromboembolic events, including 4013 participants. Of these, 2029 participants were treated with ESAs. As one multiarm study[63] was split into subsets, the number of studies displayed is 15. Five included studies were newly identified in the update searches.[62,75–78] If thromboembolic events were not reported, data from the Cochrane review by Tonia and colleagues[11] were used in the PenTAG analyses. One study[52] did not report any thromboembolic events in the treatment or placebo arms and was excluded from the meta-analysis.

Data from Moebus and colleagues[62] were used in the PenTAG meta-analyses (whereas the analysis in Tonia and colleagues[11] used data from Moebus and colleagues[33]). The Moebus and colleagues[62] trial showed an increased risk for patients treated with ESAs compared with control participants (RR 2.26, 95% CI 1.09 to 4.70), whereas there was no difference between the treatment arm and the control arm in the study by Moebus and colleagues.[33]

Thromboembolic events were reported in 103 out of 2029 participants treated with ESAs, compared with 66 out of 1984 participants in the control group. The random-effects meta-analysis showed a RR of 1.46 (95% CI 1.07 to 1.99), favouring the control group (*Figure 14*). There was no heterogeneity between the trials ($I^2 = 0\%$, $p = 0.733$; $\chi^2 = 9.52$, df = 13, $p = 0.733$), with 11 studies indicating detrimental effects of ESA treatment and three studies indicating beneficial effects of ESA treatment with regard to thromboembolic events. To test whether publication bias was present in the sample included in the meta-analysis, a funnel plot was constructed (see *Appendix 12*). The funnel plot analysis did not show statistically significant asymmetry ($p = 0.627$). In addition, a meta-regression using publication year as a covariate to assess the effect of publication year on thromboembolic events suggested that the effects of ESAs on thromboembolic events were independent of when the trial results were published ($p = 0.871$); the meta-regression plot is presented in *Appendix 12*.

The fixed-effects meta-analysis undertaken as a sensitivity analysis showed similar results, favouring the control participants over those receiving ESAs (RR 1.52, 95% CI 1.13 to 2.05, $I^2 = 0\%$; $p = 0.733$); the forest plot of the analysis is included in *Appendix 12*.

Prespecified subgroup analyses were conducted (*Table 26*). In addition, meta-regression models including random effect and a subgroup as a covariate to assess the effects of subgroups on thomboembolic events were performed; the *F* statistics from these analyses are reported in *Table 26*. All covariates showing a significant effect ($p < 0.05$) in a univariate analysis were considered further in a model selection.

Univariate analyses did not identify any significant differences based on the predefined subgroups (see *Table 26*).

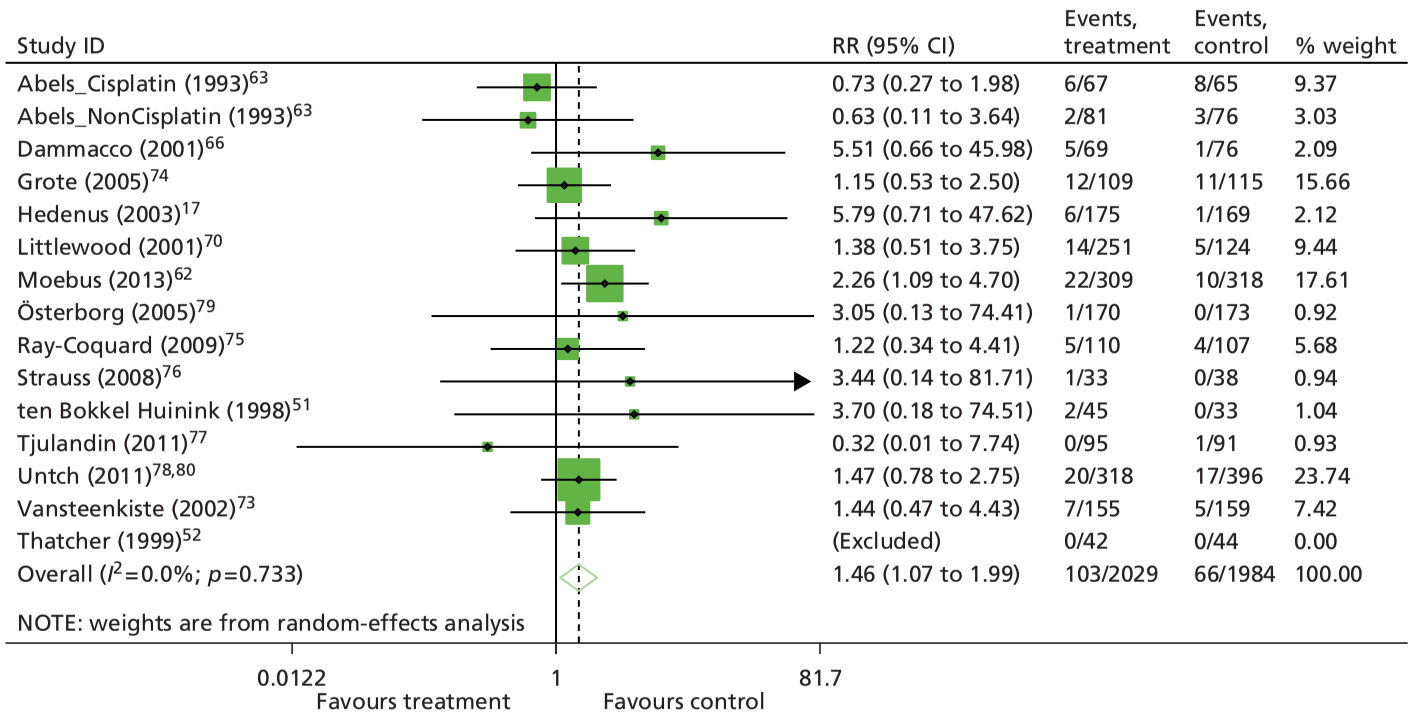

FIGURE 14 Forest plot: thromboembolic events (overall). Notes: random-effects meta-analysis (DerSimonian–Laird); trial with multiple experimental arms split into subsets in the analysis: Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

TABLE 26 Thromboembolic events: subgroup analyses

Subgroup	Number of trials	RR	95% CI	I^2	Tau^2
Overall	14	1.46	1.08 to 1.99	0%; $p = 0.73$	0
Inclusion Hb level (g/dl)					
≤ 11.0	7	1.29	0.66 to 2.54	12.2%; $p = 0.34$	0.10
> 11.0	7	1.55	1.08 to 2.21	0%; $p = 0.88$	0
F (between : within)				$F_{1,12} = 0.35$; $p = 0.57$	
Baseline Hb level (g/dl)					
≤ 10.0	8	1.34	0.82 to 2.21	0%; $p = 0.52$	0
≤ 11.0	1	0.63	0.11 to 3.64	NA	0
≤ 12.0	2	3.58	0.40 to 31.59	0%; $p = 0.97$	0
≤ 14.5	2	1.33	0.82 to 2.17	0%; $p = 0.64$	0
NR	1	2.26	1.09 to 4.70	NA	0
F (between : within)				$F_{4,9} = 0.53$; $p = 0.72$	
Target Hb level (g/dl)					
≤ 13.0	2	1.38	0.75 to 2.57	0%; $p = 0.36$	0
> 13.0	10	1.73	1.72 to 2.54	0%; $p = 0.82$	0
NR	2	0.70	0.29 to 1.68	0%; $p = 0.88$	0
F (between : within)				$F_{2,11} = 1.75$; $p = 0.22$	
Malignancy type					
Solid tumours	6	1.59	1.09 to 2.32	0%; $p = 0.82$	0
Haematological tumours	5	1.57	0.57 to 4.34	35.1%; $p = 0.19$	0.46
Mixed	3	1.21	0.57 to 2.61	0%; $p = 0.69$	0
F (between : within)				$F_{2,11} = 1.09$; $p = 0.37$	
Ovarian cancer					
Ovarian cancer	1	3.97	0.18 to 74.51	NA	0
Other cancers	13	1.45	1.06 to 1.97	0%; $p = 0.69$	0
F (between : within)				$F_{1,12} = 0.61$; $p = 0.45$	
Chemotherapy treatment[a]					
Platinum containing	3	1.06	0.51 to 2.20	0%; $p = 0.47$	0
Non-platinum containing	6	1.57	1.04 to 2.37	0%; $p = 0.66$	0
F (between : within)				$F_{1,7} = 0.54$; $p = 0.49$	
Iron supplementation					
Iron in both arms	7	1.86	1.13 to 3.07	0%; $p = 0.73$	0
Iron in an intervention arm	1	1.47	0.78 to 2.75	NA	0
NR	6	1.15	0.70 to 1.89	0%; $p = 0.53$	0
F (between : within)				$F_{2,11} = 0.21$; $p = 0.82$	

continued

TABLE 26 Thromboembolic events: subgroup analyses (*continued*)

Subgroup	Number of trials	RR	95% CI	I^2	Tau²
Study design					
RCT	9	1.24	0.81 to 1.90	0%; $p = 0.55$	0
ROL	5	1.74	1.12 to 2.69	0%; $p = 0.83$	0
F (between : within)				$F_{1,12} = 0.01$; $p = 0.94$	
Study duration (weeks)					
6–9	1	3.44	0.15 to 81.71	NA	0
12–16	8	1.24	0.72 to 2.13	0%; $p = 0.45$	0
17–20	2	1.64	0.84 to 3.18	35.7%; $p = 0.21$	0.08
> 20	3	1.48	0.88 to 2.51	0%; $p = 0.83$	0
F (between : within)				$F_{3,10} = 0.17$; $p = 0.91$	
ESA					
Erythropoietin	11	1.40	0.96 to 2.04	0%; $p = 0.65$	0
Darbepoetin	3	1.60	0.94 to 2.71	0%; $p = 0.46$	0
F (between : within)				$F_{1,12} = 037$; $p = 0.56$	

NR, not reported; ROL, randomised open-label (standard care) study.
a Subgroup analyses by platinum-based compared with non-platinum-based chemotherapy; other studies excluded for the following reasons: chemotherapy type not reported or trial population in which participants received either platinum-based or non-platinum-based chemotherapy.

Summary Analyses suggest that treatment with ESAs in patients with CIA increases the risk for thromboembolic events (RR 1.46, 95% CI 1.08 to 1.99). In total, 5% ($n = 103/2029$) of participants who received ESAs reported thromboembolic events compared with 3% ($n = 66/1984$) of patients in the control groups. There was no heterogeneity between the trials ($I^2 = 0\%$; $p = 0.733$). Overall, the data confirm results from previous trials that there is an increased risk of thromboembolic events in patients treated with ESAs compared with control participants.

Hypertension

We identified 10 trials[48,51,52,63,66,70,72,73,77,79] that measured hypertension, including 2086 participants. Of these, 1152 participants were treated with ESAs. As two multiarm studies[48,63] were split into subsets, the number of studies displayed is 12. Two included studies[48,77] were newly identified in the update searches. If hypertension was not reported, we used data from the Cochrane review by Tonia and colleagues[11] in the PenTAG analyses.

Hypertension was reported in 62 out of 1152 participants (5%) treated with ESAs compared with 27 out of 934 participants (3%) in the control groups. The random-effects meta-analysis showed a risk ratio of 1.80 (95% CI 1.14 to 2.85; *Figure 15*), favouring the control. There was no statistical heterogeneity between the trials ($I^2 = 0\%$; $\chi^2 = 7.10$, df = 11; $p = 0.791$); however, the direction of the effects of ESAs with regard to hypertension varied across the individual trials (see *Figure 15*). To test whether publication bias was present in the sample included in the meta-analysis, a funnel plot was constructed (see *Appendix 12*). The funnel plot analysis did not show statistically significant asymmetry ($p = 0.689$). In addition, a meta-regression using publication year as a covariate to assess the effect of publication year on hypertension suggests that the effects of ESAs on hypertension were independent of when the trial results were published ($p = 0.735$); the meta-regression plot is presented in *Appendix 12*.

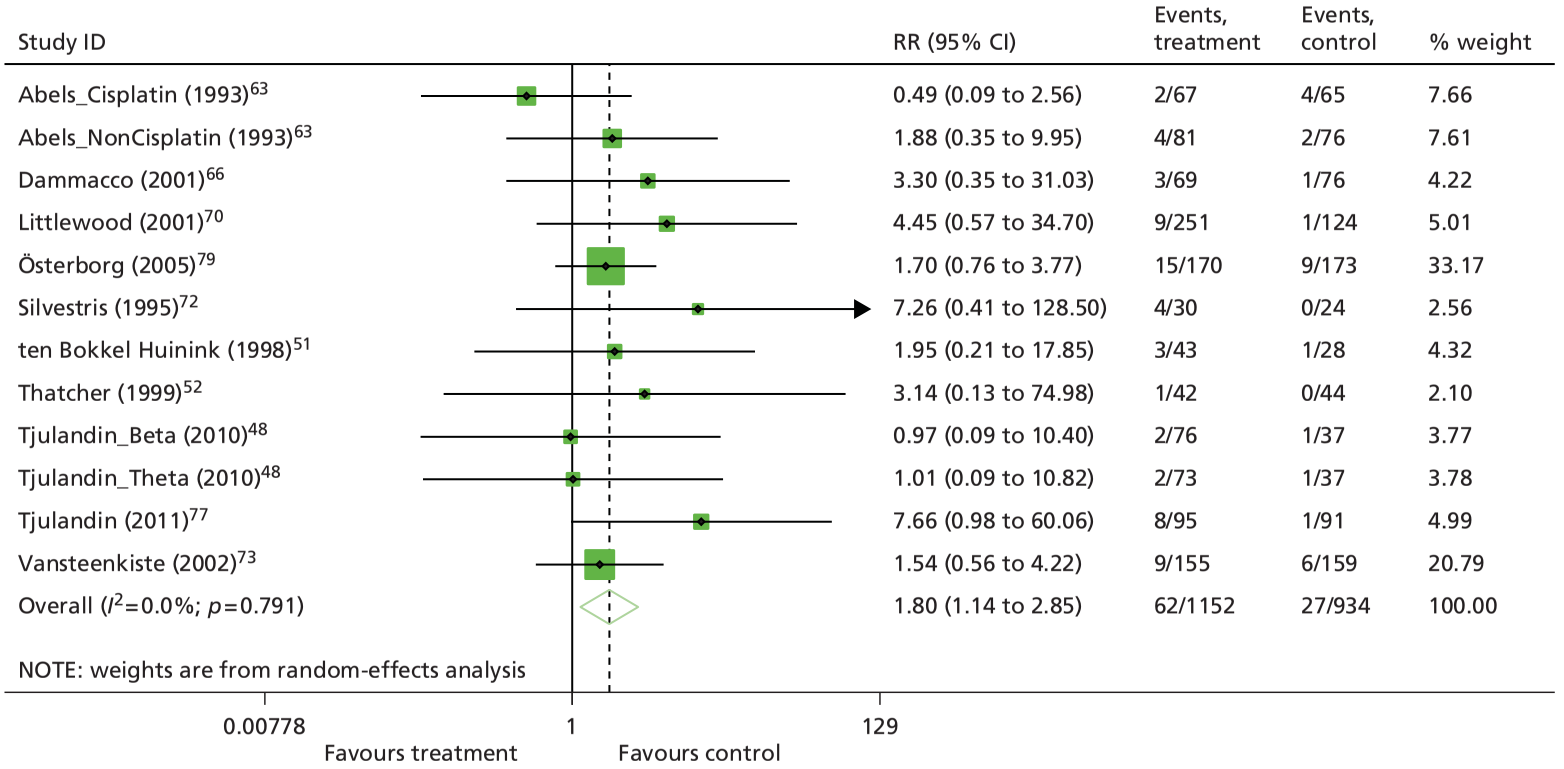

FIGURE 15 Forest plot: hypertension (overall). Notes: random-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

The fixed-effects meta-analysis undertaken as a sensitivity analysis showed similar results (RR 1.97, 95% CI 1.27 to 3.07, $I^2 = 0\%$; $p = 0.791$); the forest plot of the analysis is included in *Appendix 12*.

Prespecified subgroup analyses were conducted (*Table 27*). In addition, meta-regression models including random effect and a subgroup as a covariate to assess the effects of subgroups on hypertension were performed; the *F* statistics from these analyses are reported in *Table 27*. All covariates showing a significant effect ($p < 0.05$) in a univariate analysis were considered further in a model selection.

Univariate analyses did not identify any significant differences based on the predefined subgroups (see *Table 27*).

TABLE 27 Hypertension: subgroup analyses

Subgroup	No. of trials	RR	95% CI	I^2	Tau^2
Overall	12	1.80	1.14 to 2.85	0%; $p = 0.79$	0
Inclusion Hb level (g/dl)					
≤ 11.0	9	1.68	1.03 to 2.74	0%; $p = 0.64$	0
> 11.0	3	3.06	0.78 to 11.91	0%; $p = 0.86$	0
F (between : within)				$F_{1,10} = 0.07$; $p = 0.79$	
Baseline Hb level (g/dl)					
≤ 10.0	9	1.76	1.07 to 2.89	0%; $p = 0.54$	0
≤ 11.0	1	1.88	0.35 to 9.95	NA	0
≤ 12.0	1	1.95	0.21 to 17.85	NA	0
≤ 14.5	1	3.14	0.13 to 74.98	NA	0
F (between : within)				$F_{3,8} = 0.10$; $p = 0.96$	
Target Hb level (g/dl)					
≤ 13.0	3	2.19	0.53 to 9.12	16.8%; $p = 0.30$	0.27
> 13.0	6	1.89	1.09 to 3.28	0%; $p = 0.94$	0
NR	3	1.39	0.35 to 5.53	32.9%; $p = 0.23$	0.49
F (between : within)				$F_{2,9} = 0.07$; $p = 0.93$	
Malignancy type					
Solid tumours	5	1.51	0.69 to 3.28	0%; $p = 0.97$	0
Haematological tumours	5	1.63	0.88 to 3.02	0%; $p = 0.48$	0
Mixed	2	5.83	1.36 to 24.98	0%; $p = 0.71$	0
F (between : within)				$F_{2,9} = 4.07$; $p = 0.06$	
Ovarian cancer					
Ovarian cancer	1	1.95	0.21 to 17.85	NA	0
Other cancers	11	1.79	1.12 to 2.87	0%; $p = 0.72$	0
F (between : within)				$F_{1,10} = 0.14$; $p = 0.71$	
Chemotherapy treatment					
Platinum containing	5	1.17	0.57 to 2.41	0%; $p = 0.81$	0
Non-platinum containing	4	2.20	1.15 to 4.19	0%; $p = 0.49$	0
F (between : within)				$F_{1,7} = 3.89$; $p = 0.09$	

TABLE 27 Hypertension: subgroup analyses (*continued*)

Subgroup	No. of trials	RR	95% CI	I^2	Tau^2
Iron supplementation					
Iron in both arms	6	2.13	1.13 to 3.99	0%; $p = 0.55$	0
No iron supplementation	1	3.14	0.13 to 74.98	NA	0
NR	5	1.44	0.72 to 2.86	0%; $p = 0.552$	0
F (between : within)				$F_{2,9} = 0.96$; $p = 0.42$	
Study design					
RCT	9	1.70	1.05 to 2.76	0%; $p = 0.65$	0
ROL	3	3.17	0.68 to 14.72	0%; $p = 0.77$	0
F (between : within)				$F_{1,10} = 0.84$; $p = 0.38$	
Study duration (weeks)					
12–16	8	1.61	0.98 to 2.64	0%; $p = 0.66$	0
> 20	4	3.58	1.05 to 12.24	0%; $p = 0.90$	0
F (between : within)				$F_{1,10} = 1.69$; $p = 0.22$	
ESA					
Erythropoietin	11	1.88	1.12 to 3.15	0%; $p = 0.73$	0
Darbepoetin	1	1.54	0.56 to 4.22	NA	0
F (between : within)				$F_{1,10} = 0.38$; $p = 0.55$	

NR, not reported; ROL, randomised open-label (standard care) study.

Summary Analyses suggest that treatment with ESAs in people with CIA increases the number of hypertension events (RR 1.80, 95% CI 1.14 to 2.85). In total, 5% ($n = 62/1152$) of participants who received ESAs reported hypertension compared with 3% ($n = 27/934$) of participants in the control groups. There was no heterogeneity between the trials ($I^2 = 0\%$; $p = 0.791$). Overall, the data confirm the results from previous analyses that there is an increased risk of hypertension in patients receiving ESAs compared with control participants.

Thrombocytopenia/haemorrhage

Data for thrombocytopenia (decrease of platelets in the blood)/haemorrhage were available from seven trials.[52,65–67,70,76,78] Overall, the analysis included all seven studies with 1715 participants. If thrombocytopenia/haemorrhage were not reported, data were obtained from the Cochrane review by Tonia and colleagues.[11]

Thrombocytopenia/haemorrhage was reported in 55 out of 877 participants treated with ESAs, compared with 54 out of 838 participants in the control groups. The random-effects meta-analysis showed a RR of 0.93 (95% CI 0.65 to 1.34; *Figure 16*), which was not statistically significant. There was no statistical heterogeneity between the trials ($I^2 = 0\%$; $\chi^2 = 3.02$, df = 6, $p = 0.807$); however, the direction of the effects of ESAs with regard to hypertension varied across the individual trials. Because there were only seven primary studies included in the meta-analysis, the funnel plot analysis to test whether publication bias was present was not conducted.[54]

The fixed-effects meta-analysis undertaken as a sensitivity analysis showed similar non-significant results (RR 0.91, 95% CI 0.63 to 1.30; see *Appendix 12*).

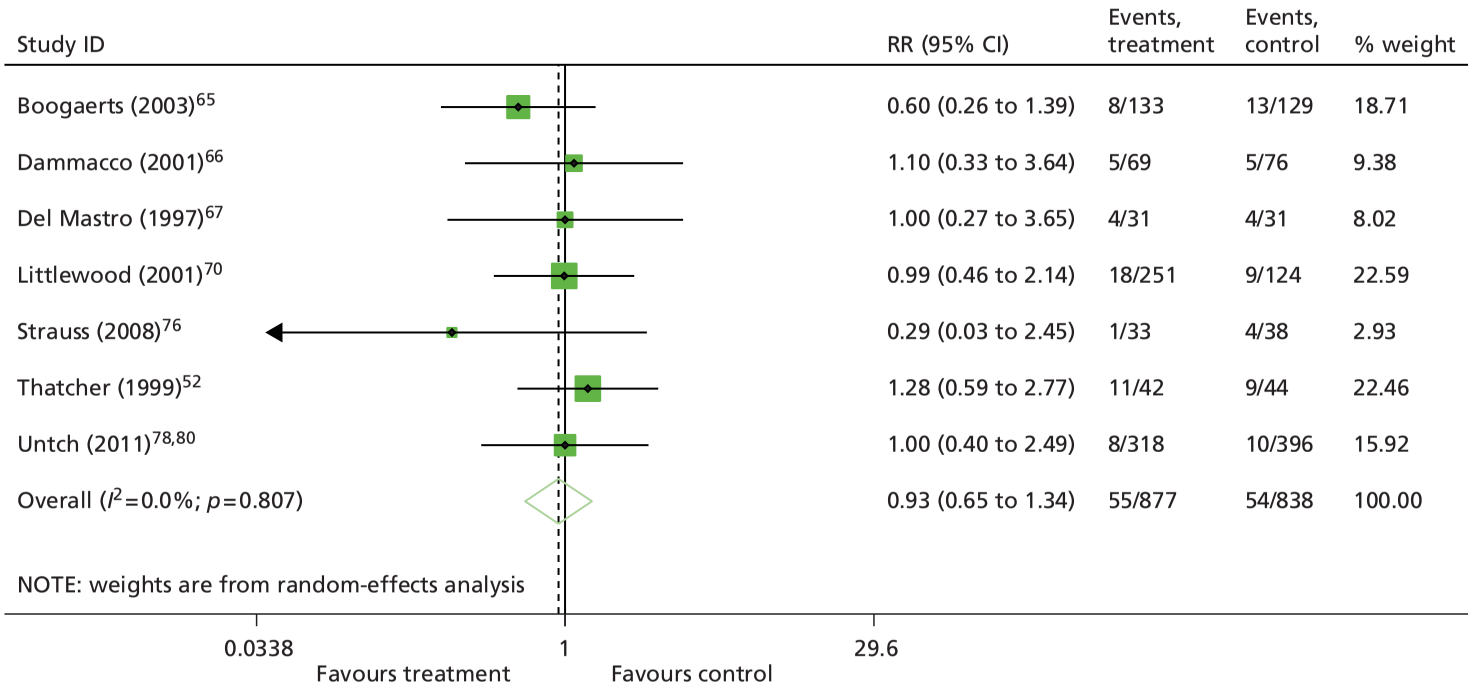

FIGURE 16 Forest plot: thrombocytopenia/haemorrhage (overall). Note: random-effects meta-analysis (DerSimonian–Laird). Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

Prespecified subgroup analyses and meta-regression models with subgroups as covariates were not conducted because only seven trials were included in the meta-analysis.

Summary Analyses suggest that treatment with ESAs in people with CIA did not have an effect on thrombocytopenia/haemorrhage (RR 0.93, 95% CI 0.65 to 1.34). In total, 6% ($n = 55/877$) of participants who received ESAs and 6% ($n = 54/838$) of participants in the control groups reported thrombocytopenia/haemorrhage. There was no heterogeneity between the trials ($I^2 = 0\%$; $p = 0.807$). Overall, the data seem to be different from previous analyses in suggesting that ESAs do not have a detrimental effect on thrombocytopenia/haemorrhage.

Seizures

Data on seizures were available from one trial[63] including 289 participants. As this trial was split into subsets, the number of studies displayed in the forest plot is two. If seizures were not reported, we used data from the Cochrane review by Tonia and colleagues[11] in the PenTAG analyses.

Overall, five seizure events were reported in the ESA-treated group ($n = 148$) and four in the control group ($n = 141$), resulting in a RR of 1.19 (RR 1.19; 95% CI 0.33 to 4.38; *Figure 17*). There was no heterogeneity between the trials ($I^2 = 0\%$, $p = 0.742$; $\chi^2 = 0.11$, df = 5, $p = 0.742$), although the two included trials indicated effects in opposite directions. Because only two primary studies were included in the meta-analysis, the funnel plot analysis to test whether publication bias was present was not conducted.[54] The fixed-effects meta-analysis undertaken as a sensitivity analysis showed similar non-significant results (RR 1.19, 95% CI 0.33 to 4.35, $I^2 = 0\%$; $p = 0.742$; see *Appendix 12*).

Prespecified subgroup analyses and meta-regression models with subgroups as covariates were not conducted because only two trials were included in the meta-analysis.

Summary Analyses suggest that treatment with ESAs in patients with CIA did not have a significant effect on seizures (RR 1.19, 95% CI 0.33 to 4.38). In total, 3% (5/148) of participants who received ESAs had a seizure; similarly, 3% (4/141) of participants in the control groups had a seizure. There was no heterogeneity between the trials ($I^2 = 0\%$; $p = 0.742$). Although data from one study suggests that ESAs do not have a detrimental effect on seizures, there was no significant difference between groups. The possibility of detrimental effects of ESAs on the number of seizures, however, cannot be excluded. Overall, the data confirm the results from previous analyses.

Pruritus (pruritus, rash and irritation)

We identified seven trials[52,63,67,69,76,77,79] that measured pruritus (pruritus, rash and irritation were considered[11]) including 904 participants. Of these, 450 participants were treated with ESAs. Two included studies were newly identified in the update searches.[76,77] If pruritus events were not reported, we used data from the Cochrane review by Tonia and colleagues[11] in the PenTAG analyses. One study[69] did not report any pruritus events in the treatment and placebo arms and was excluded from the meta-analysis.

The random-effects meta-analysis showed a risk ratio of 2.04 (95% CI 1.11 to 3.75; *Figure 18*), favouring the control. There was no heterogeneity between the trials ($I^2 = 0\%$, $p = 0.872$; $\chi^2 = 1.83$, df = 5, $p = 0.872$), with all of the individual studies indicating a detrimental effect of treatment with ESAs with regard to the number of pruritus events. Because only six primary studies were included in the meta-analysis, the funnel plot analysis to test whether publication bias was present was not conducted.[54] The fixed-effects meta-analysis undertaken as a sensitivity analysis showed similar results (RR 2.16, 95% CI 1.18 to 3.92, $I^2 = 0\%$; $p = 0.872$); the forest plot of the analysis is included in *Appendix 12*.

The prespecified subgroup analyses and meta-regression models with subgroups as covariates were not conducted because only six trials were included in the meta-analysis.

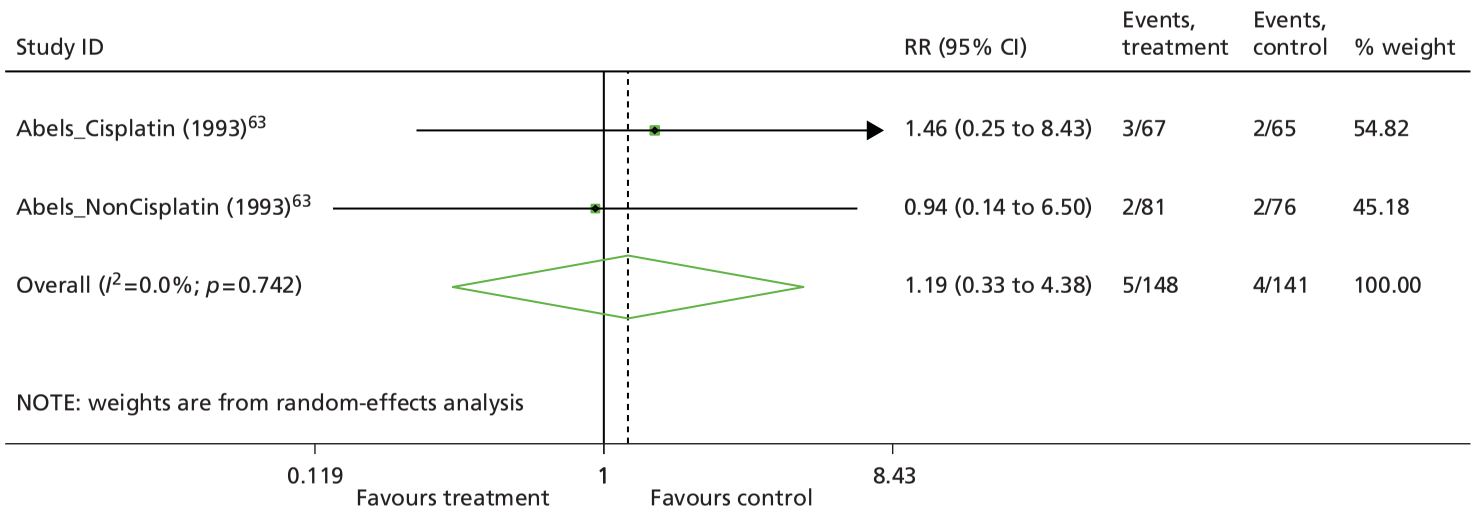

FIGURE 17 Forest plot: seizures (overall). Notes: random-effects meta-analysis (DerSimonian–Laird); trial with multiple experimental arms split into subsets in the analysis: Abels and colleagues[63] reported data for participants on platinum-based and non-platinum-based chemotherapy. Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

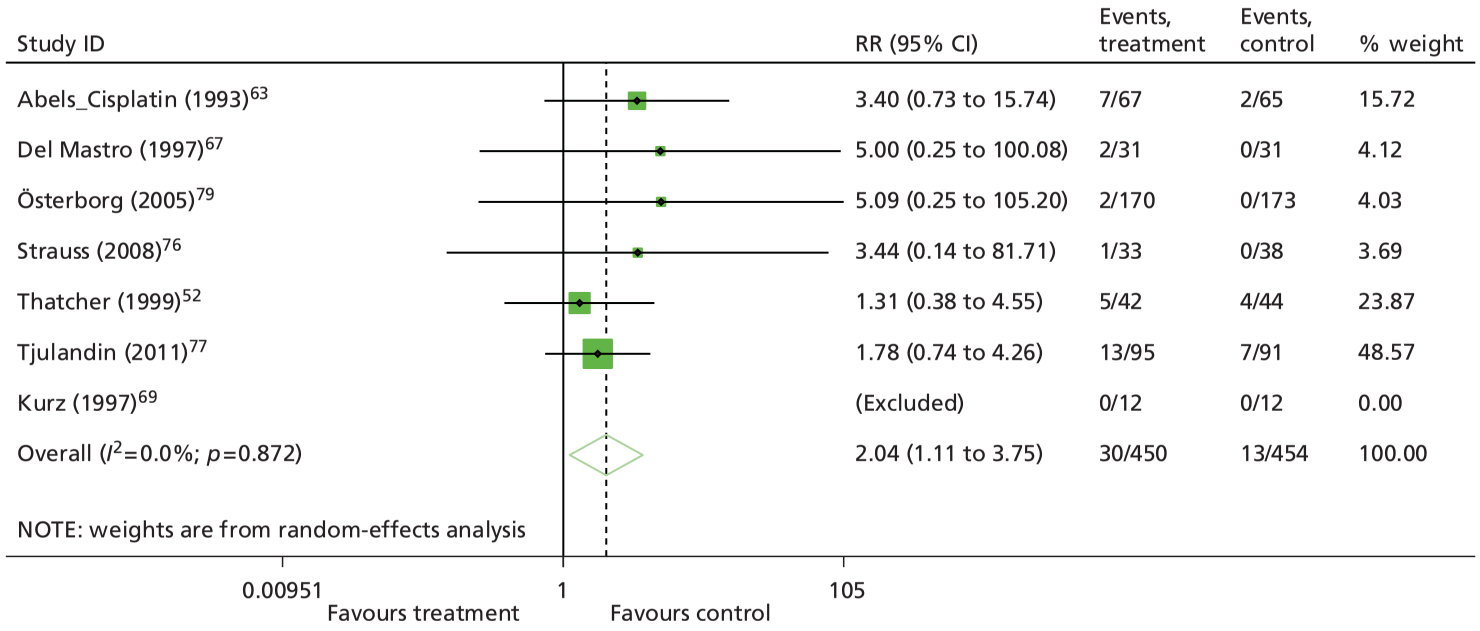

FIGURE 18 Forest plot: pruritus (overall). Note: random-effects meta-analysis (DerSimonian–Laird). Events, treatment = number of events/number of participants in the treatment group; events, control = number of events/number of participants in the control group.

Summary Analyses suggest that treatment with ESAs in people with CIA increases the number of cases of pruritus (RR 2.04, 95% CI 1.11 to 3.75). In total, 7% (30/450) of participants who received ESAs reported pruritus compared with 3% (13/454) of participants in the control groups. There was no heterogeneity between the trials ($I^2 = 0\%$; $p = 0.872$), with all of the individual studies indicating a detrimental effect of treatment with ESAs with regard to pruritus. Overall, the data seem to be different compared with those from previous analyses. The data suggest that ESAs increase the number of cases of pruritus in patients with chemotherapy-induced anaemia. The definition of pruritus encompassed pruritus, rash and irritation (as defined in the Cochrane review[11]) and the marked variation in event rates may be a result of the definition of pruritus used. These results should be interpreted with caution.

Safety-related outcomes: summary

All studies were of moderate or poor quality. In addition, there was considerable variability in the reporting of AEs among the included studies. Given the greater access to data in the Cochrane review[11] than in the primary papers, relevant data from the Cochrane review[11] were used to conduct meta-analyses for the AEs of interest. Overall, the data suggested that there is an increased risk of thromboembolic events and hypertension after treatment with ESAs, consistent with previous estimates (*Table 28*). Data for seizures are also consistent with previous meta-analyses, showing no effects of ESAs on seizures (see *Table 28*). Of note is that all AEs are relatively rare compared with other outcomes considered in this report (e.g. RBCT, Hb change and mortality).

TABLE 28 Safety-related outcomes results comparison: Wilson and colleagues[2] vs. Tonia and colleagues[11] vs. PenTAG

Outcome	[a]Wilson and colleagues[2]	[a]Tonia and colleagues[11]	PenTAG[a]	PenTAG[b]
Thromboembolic events[c,d]	NR	RR 1.52, 95% CI 1.34 to 1.74; $\chi^2_{(het)} = 34.99$, df = 55; $p = 0.980$	RR 1.52, 95% CI 1.13 to 2.05; $\chi^2_{(het)} = 9.52$, df = 14; $p = 0.872$	RR 1.46, 95% CI 1.07 to 1.99; $\chi^2_{(het)} = 9.52$, df = 14; $p = 0.872$
		60 trials, $n = 15{,}498$	15 trials, $n = 4013$	15 trials, $n = 4013$
Hypertension[d]	NR	RR 1.30, 95% CI 1.08 to 1.56; $\chi^2_{(het)} = 26.87$, df = 34; $p = 0.800$	RR 1.97, 95% CI 1.27 to 3.07; $\chi^2_{(het)} = 7.10$, df = 11; $p = 0.791$	RR 1.80, 95% CI 1.14 to 2.85; $\chi^2_{(het)} = 7.10$, df = 11; $p = 0.791$
		35 trials, $n = 7006$	12 trials, $n = 2086$	12 trials, $n = 2086$
Thromobocytopenia/ haemorrhage	NR	RR 1.21, 95% CI 1.04 to 1.42; $\chi^2_{(het)} = 14.50$, df = 20; $p = 0.800$	RR 0.91, 95% CI 0.63 to 1.30; $\chi^2_{(het)} = 3.02$, df = 11; $p = 0.807$	RR 0.93, 95% CI 0.65 to1.34; $\chi^2_{(het)} = 3.02$, df = 11; $p = 0.807$
		21 trials, $n = 4220$	7 trials, $n = 1715$	7 trials, $n = 1715$
Seizure[d]	NR	RR 0.77, 95% CI 0.42 to 1.41; $\chi^2_{(het)} = 6.19$, df = 6; $p = 0.400$	RR 1.19, 95% CI 0.33 to 4.35; $\chi^2_{(het)} = 0.11$, df = 1; $p = 0.742$	RR 1.19, 95% CI 0.33 to 4.38; $\chi^2_{(het)} = 0.11$, df = 1; $p = 0.742$
		7 trials, $n = 2790$	2 trials, $n = 289$	2 trials, $n = 289$
Pruritus[c]	NR	RR 1.49, 95% CI 0.99 to 2.24; $\chi^2_{(het)} = 13.18$, df = 15; $p = 0.590$	RR 2.16, 95% CI 1.18 to 3.92; $\chi^2_{(het)} = 1.83$, df = 5; $p = 0.872$	RR 2.04, 95% CI 1.11 to 3.75; $\chi^2_{(het)} = 1.83$, df = 5; $p = 0.872$
		16 trials, $n = 4346$	7 trials, $n = 904$	7 trials, $n = 904$

het, heterogeneity; NR, not reported.
a Fixed effects (Mantel–Haenszel).
b Random effects (DerSimonian–Laird).
c One study was excluded as no events were reported in the treatment and placebo arms.
d The number of trials accounts for multiple experimental arms for some studies.

The PenTAG analyses suggest that there is an increased risk of pruritus, with a significant difference found between patients treated with ESAs and participants in the control arms (RR 2.04, 95% CI 1.11 to 3.75). In comparison, the Cochrane review[11] did not find a significant difference between patients treated with ESAs and participants in the control arms (RR 1.49, 95% CI 0.99 to 2.24). It must be highlighted that both the current review and the Cochrane review[11] combined events of skin rash, irritation and pruritus in the meta-analyses. However, the rates of skin rash, irritation and pruritus may differ and the way that this outcome has been defined may be the cause of the marked variation in event rates.

Also, the summary estimate for risk of thrombocytopenia/haemorrhage associated with ESA treatment found in the PenTAG review was a RR of 0.93 (95% CI 0.65 to 1.34), suggesting that treatment with ESAs in patients with CIA did not have an effect on thrombocytopenia/haemorrhage. However, the Cochrane review[11] found a RR of 1.21 (95% CI 1.04 to 1.42), suggesting detrimental effects of ESAs with regard to thrombocytopenia/haemorrhage.

It must be emphasised that the current analyses included only studies complying with the licenced ESA dose, whereas the Cochrane review did not apply any restrictions regarding the ESA posology. However, these results should be interpreted with caution (see *Chapter 6*, *Strengths and limitations of the systematic review of studies of effectiveness for more details*).

A graphical summary of the study characteristics, quality appraisal and results for the safety outcomes is presented in *Figure 19*.

Subgroup analyses

The results of the subgroup analyses by iron supplementation and platinum-based chemotherapy are reported throughout this chapter (see *Effectiveness*).

Use of iron supplementation varied among the studies, for example oral iron supplementation given as needed (dosage and trigger level differed between studies) or as standard and/or intravenous iron supplementation (see *Concomitant treatments*). In addition, limited details in the publications hindered the interpretation of this outcome. Subgroup analyses did not identify any significant differences between groups.

Five studies[48,51,63,64,73] evaluated the use of ESAs in people with any type of cancer receiving platinum-based chemotherapy. The point estimates for this subgroup are reported in *Table 29*.

Results from this subgroup analysis are consistent with the findings from the overall analysis for the anaemia-related outcomes, that is, an improved haematological response and a reduction in RBCT requirements, and are different from the results reported in the Cochrane review.[11] Similarly to the overall analysis, the results for the malignancy-related outcomes (OS and on-study mortality) suggest fewer detrimental effects for people with chemotherapy-induced anaemia treated with ESAs. These effects are also reflected in the decrease in the number of people experiencing thromboembolic events. However, these results should be interpreted with caution. The number of studies per subgroup is small, some of the changes are not statistically significant and the CIs remain wide. It is also important to remember that multiple testing issues arise when subgroups are tested and that CIs presented here have not been adjusted for multiple testing.

(a)

Trial		Chemo	Malignancy	Note	Design	Duration (weeks) 0 10 20 30	Outcomes: Thrombotic	Hypertension	Thrombo/haemor	Seizure	Rash	QA: Random	Baseline	Blinding	Losses
Abels	1993[63]	Plat Non-plat No chemo	Haem	*n*=413		Epo Alfa *n*=206 Placebo *n*=190 Missing *n*=17						■	■	■	■ ✕
	SG	Plat		*n*=132		Epo Alfa *n*=67 Placebo *n*=65	○	○		○	○	■	■	■	■ ✕
	SG	Non-plat		*n*=157		Epo Alfa *n*=81 Placebo *n*=76	○	○		○		■	■	■	■ ✕
Aravanitos	2003[64]	Plat	Solid	*n*=47		Epo Alfa *n*=24 Control *n*=23						■	■	□	✕ ✕
Boogaerts	2003[65]	?	?	*n*=262		Epo Beta *n*=133 Control *n*=129			○			■	□	□	■ ✕
Dammaco	2001[66]	Mixed	Haem	*n*=145		Epo Alfa *n*=69 Placebo *n*=76	○	○	○			■	■	■	■ □
Del Mastro	1997[67]	Non-plat	Solid	*n*=62		rHuEPO *n*=31 Control *n*=31			○		○	■	■	□	■ ✕

Quality appraisal key
Random:
concealment of allocation (above)
random allocation (below)
Baseline:
baseline characteristics
Blinding:
blinding of clinicians (above)
blinding of patients (below)
Losses:
ITT or <10% (above)
losses (below)

■ Positive quality check
□ Partial quality check
□ Negative quality check
✕ Not reported

Outcomes key
● Favours treatment
◪ Favours control
○ Non-significant outcomes

FIGURE 19 Safety-related outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–4. 1: hypertension reported for epo beta *n* = 43 and control *n* = 28; 2: participants who received at least one dose of study treatment even if they did not meet the eligibility criteria were included in the safety population; 3: one participant randomised to the darbe alfa arm did not receive the study treatment and was included in the placebo arm for the safety evaluation. ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; non-plat, non-platinum; plat, platinum; QA, quality appraisal; thrombo/haemor, thrombosis/haemorrhage. (*continued*)

(b)

Trial		Chemo	Malignancy		Note	Design	Duration (weeks)	Outcomes	QA
							0 10 20 30	Thrombotic Hypertension Thrombo/haemor Seizure Rash	Random Baseline Blinding Losses
Dunphy	1999[68]	Plat	Solid	*n*=30		rHuEPO *n*=13 Control *n*=14 Missing *n*=3			
Grote	2005[74]	Mixed	Solid	*n*=224		Epo Alfa *n*=109 Placebo *n*=115		○	
Hedenus	2002[53]	?	Haem	*n*=66		Darbe Alfa *n*=55 Placebo *n*=11			
Licenced dose				*n*=33		Darbe Alfa *n*=22 Placebo *n*=11			
Hedenus	2003[17]	?	Haem	*n*=349		Darbe Alfa *n*=175 Placebo *n*=169 Missing *n*=5		○	
Kotasek	2003[50]	?	Solid	*n*=249		Darbe Alfa *n*=198 Placebo *n*=51			
Licenced dose				*n*=68		Darbe Alfa *n*=17 Placebo *n*=51			
Kurz	1997[69]	?	Solid	*n*=35		Epo Alfa *n*=23 Placebo *n*=12		○	

Quality appraisal key
Random:
concealment of allocation (above)
random allocation (below)
Baseline:
baseline characteristics
Blinding:
blinding of clinicians (above)
blinding of patients (below)
Losses:
ITT or <10% (above)
losses (below)

■ Positive quality check
■ Partial quality check
□ Negative quality check
⊠ Not reported

Outcomes key
● Favours treatment
⊘ Favours control
○ Non-significant outcomes

FIGURE 19 Safety-related outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–4. 1: hypertension reported for epo beta *n*=43 and control *n*=28; 2: participants who received at least one dose of study treatment even if they did not meet the eligibility criteria were included in the safety population; 3: one participant randomised to the darbe alfa arm did not receive the study treatment and was included in the placebo arm for the safety evaluation. ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; non-plat, non-platinum; plat, platinum; QA, quality appraisal; thrombo/haemor, thrombosis/haemorrhage. *(continued)*

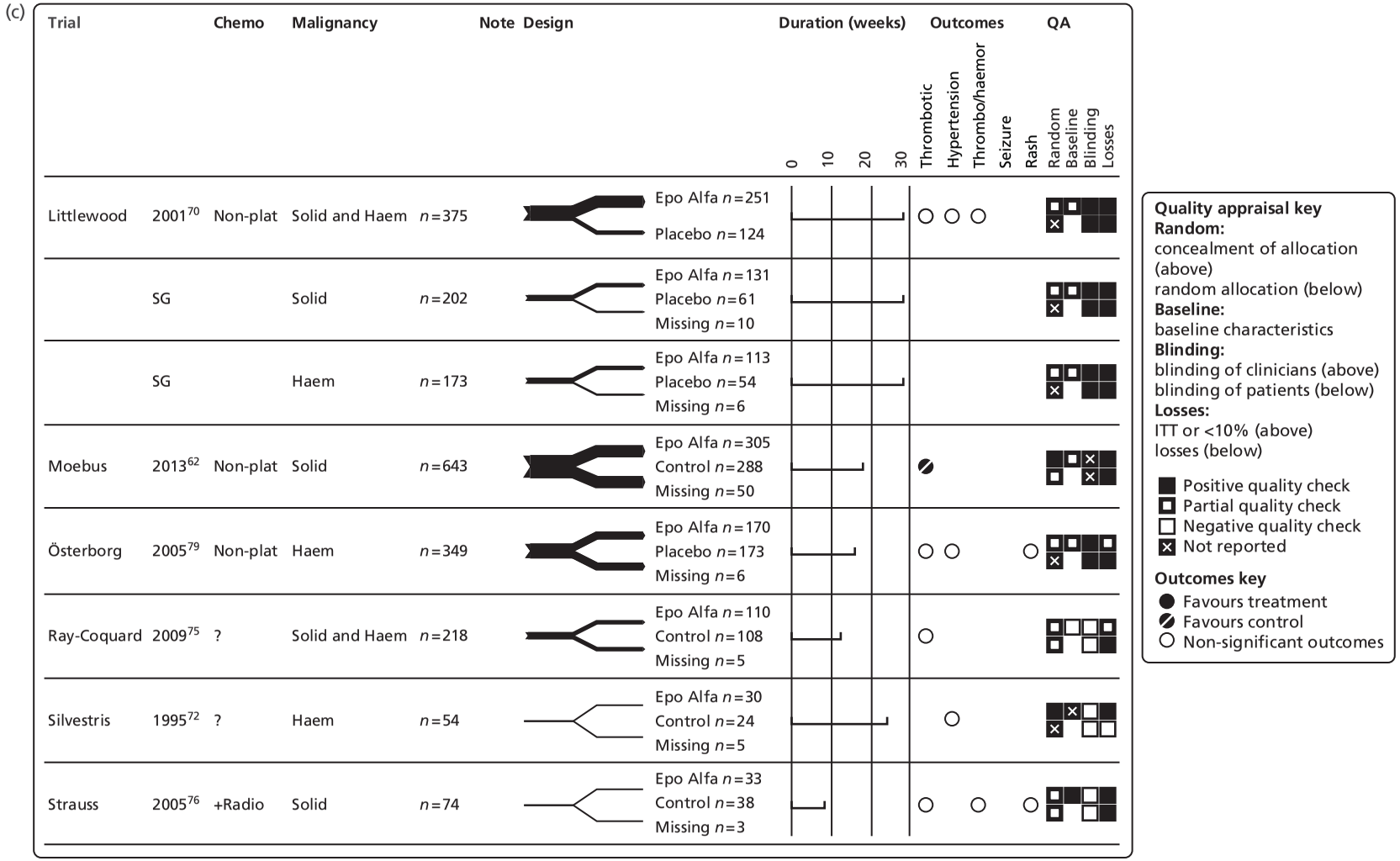

FIGURE 19 Safety-related outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–4. 1: hypertension reported for epo beta $n = 43$ and control $n = 28$; 2: participants who received at least one dose of study treatment even if they did not meet the eligibility criteria were included in the safety population; 3: one participant randomised to the darbe alfa arm did not receive the study treatment and was included in the placebo arm for the safety evaluation. ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; non-plat, non-platinum; plat, platinum; QA, quality appraisal; thrombo/haemor, thrombosis/haemorrhage. (*continued*)

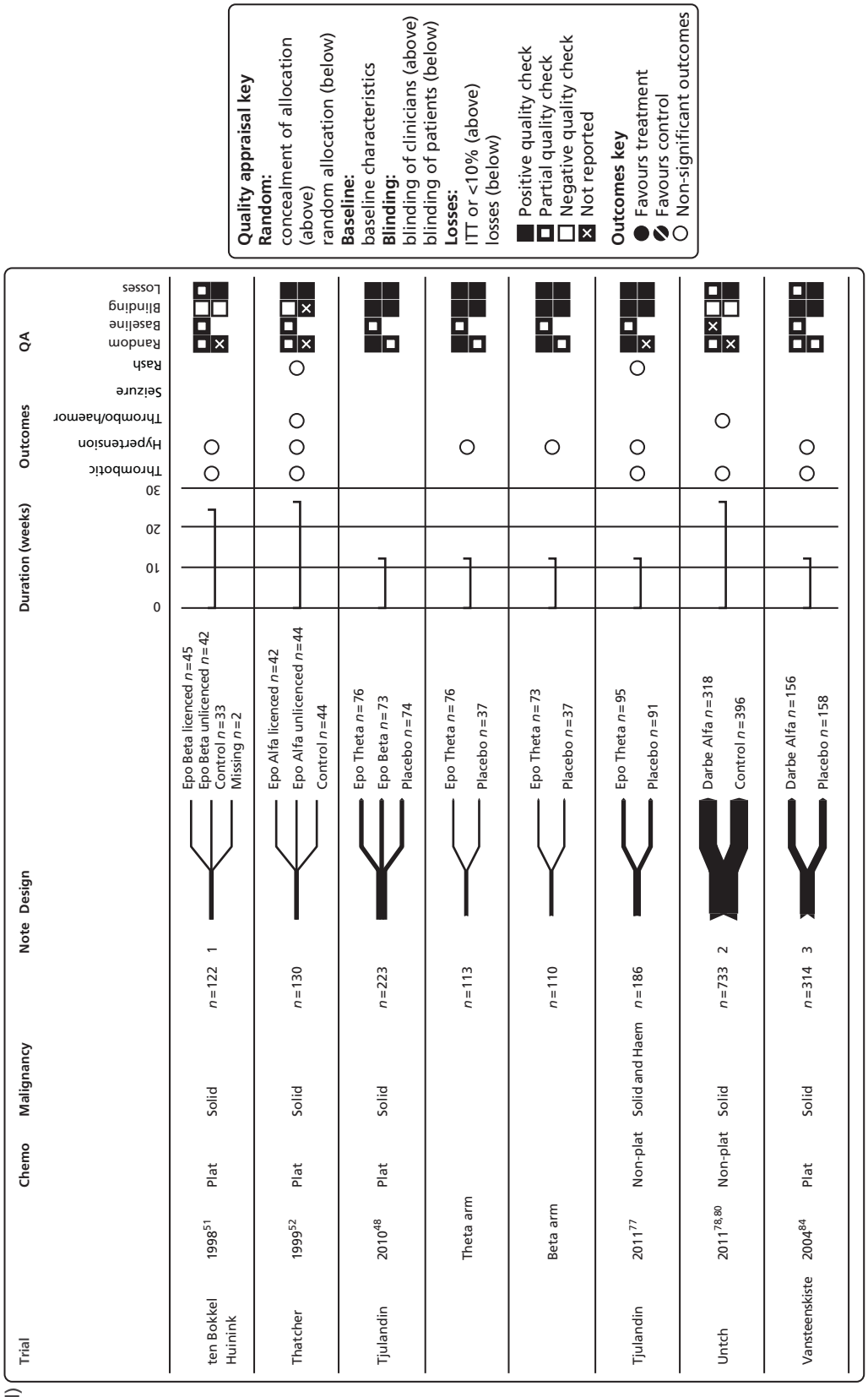

FIGURE 19 Safety-related outcomes: graphical summary. Notes: for some of the included trials, data for some anaemia-related outcomes were not available for all participants; where different, the numbers included are reported in notes 1–4. 1: hypertension reported for epo beta $n = 43$ and control $n = 28$; 2: participants who received at least one dose of study treatment even if they did not meet the eligibility criteria were included in the safety population; 3: one participant randomised to the darbe alfa arm did not receive the study treatment and was included in the placebo arm for the safety evaluation. ?, unknown; chemo, chemotherapy; darbe, darbepoetin; epo, epoetin; haem, haematological; non-plat, non-platinum; plat, platinum; QA, quality appraisal; thrombo/haemor, thrombosis/haemorrhage.

TABLE 29 People with any type of cancer receiving platinum-based chemotherapy: outcomes summary

Outcome measure	Results
Anaemia-related outcomes	
Hb change (g/dl)	WMD 1.42, 95% CI 1.10 to 1.75; $I^2 = 0\%$, $p = 0.774$ Trials: 5[a]
HaemR	RR 3.93, 95% CI 2.50 to 6.17; $I^2 = 11.9\%$, $p = 0.321$ Trials: 3[a]
RBCT	RR 0.52, 95% CI 0.37 to 0.72; $I^2 = 60.0\%$, $p = 0.029$ Trials: 6[a]
RBC units	WMD –1.11, 95% CI –1.58 to –0.64; $I^2 = 0\%$, $p = 0.685$ Trials: 3
Malignancy-related outcomes	
Tumour response	RR 0.91, 95% CI 0.62 to 1.33; $I^2 = NA$ Trials: 1
OS	HR 0.67, 95% CI 0.46 to 0.98; $I^2 = 14.5\%$, $p = 0.319$ Trials: 4[a]
On-study mortality	HR 0.63, 95% CI 0.34 to 1.18; $I^2 = 36.0\%$, $p = 0.196$ Trials: 4[a]
Safety-related outcomes	
Thromboembolic events	RR 1.06, 95% CI 0.51 to 2.20; $I^2 = 0\%$, $p = 0.473$ Trials: 3
Hypertension	RR 1.17, 95% CI 0.57 to 2.41; $I^2 = 0\%$, $p = 0.808$ Trials: 5[a]
Seizures	RR 1.46, 95% CI 0.25 to 8.43; $I^2 = NA$ Trials: 1
Pruritus	RR 3.40, 95% CI 0.73 to 15.74; $I^2 = NA$ Trials: 1

HaemR, haematological response.
a The number of trials accounts for multiple experimental arms for some studies.

We also investigated women with ovarian cancer and women with ovarian cancer receiving platinum-based chemotherapy. Only one study evaluated participants with ovarian cancer;[51] all participants ($n = 122$) received platinum-based chemotherapy. The outcomes measured were Hb change, RBCT, RBC units transfused, tumour response and safety. The point estimates for these outcomes are reported in *Table 30*. Other studies may have included some ovarian cancer patients; however, the results are reported for whole study populations and not by malignancy type.

No studies were identified that evaluated people with head and neck malignancies receiving platinum-based chemotherapy. Similarly, no trials were identified that evaluated people unable to receive RBCTs (e.g. Jehovah's Witnesses and people who have multiple antibodies to RBCs because they have required regular transfusions in the past). Clinical advice suggests that it is reasonable to assume that ESAs are likely to improve Hb levels in this subpopulation. It is also considered reasonable to believe that, if people can be supported through the period of life-threatening anaemia, they will recover; if ESAs are not allowed they run the risk of death.

Definition of 'within licence'

For this HTA review, studies were considered eligible for inclusion if they evaluated starting doses of ESAs according to European labelling, irrespective of how they dealt with Hb levels (see *Chapter 1*, *Marketing authorisations: haemoglobin levels*).

TABLE 30 Women with ovarian cancer and women with ovarian cancer receiving platinum-based chemotherapy: outcomes summary

Outcome measure	Results
Anaemia-related outcomes	
HaemR	NR
Hb change (g/dl)	WMD 1.23, 95% CI 0.48 to 1.98; $I^2 = NA$ Trials: 1
RBCT	RR 0.11, 95% CI 0.03 to 0.47; $I^2 = NA$ Trials: 1
RBC units	WMD –0.94, 95% CI –1.76 to –0.12; $I^2 = NA$ Trials: 1
Malignancy-related outcomes	
Tumour response	RR 0.91, 95% CI 0.62 to 1.33; $I^2 = NA$ Trials: 1
OS	NR
On-study mortality	NR
Safety-related outcomes	
Thromboembolic events	RR 3.70, 95% CI 0.18 to 74.51; $I^2 = NA$ Trials: 1
Hypertension	RR 0.11, 95% CI 0.03 to 0.47; $I^2 = NA$ Trials: 1

HaemR, haematological response; NR, not reported.

With respect to European labelling, additional measures of dose efficiency [inclusion Hb level (≤ 11 g/dl and > 11 g/dl) and target Hb level (≤ 13 g/dl and > 13 g/dl)] were also considered in post-hoc analyses. Studies contributing to these subgroups are listed in *Table 31*. In addition, we also considered measures relating to the administration of ESAs in conjunction with study quality, specifically blinding (double-blind RCTs).

Results from these subgroup analyses are summarised in *Table 32*.

Post-hoc analyses offer some limited evidence to suggest that compliance with European labelling results in better outcomes: there are no detrimental effects of ESAs on either on-study or overall mortality in patients with chemotherapy-induced anaemia. These effects are consistent with an improved tumour response and a decrease in the number of thromboembolic events. However, these analyses must be interpreted with caution. The number of studies per subgroup is small, some of the effect sizes are not statistically significant and the CIs remain wide. In addition, the analyses may not have the statistical power to detect the effects of adherence to European labelling on outcomes, if such effects exist. It should also be noted that this is a difficult area of assessment, especially in a heterogeneous mix of tumour types. Furthermore, we have not sought to address multiple testing issues that arise when considering subgroups, and so inference is not straightforward.

Health-related quality of life

Health-related quality of life has become a key clinical outcome. Anaemia is often associated with cancer, either because of the disease itself or because of the subsequent treatment. Therefore, the patient may experience exhaustion, fatigue, weakness, impaired concentration, respiratory distress and chest pain, which will, in turn, significantly impact on HRQoL.[70] As ESAs may relieve CIA by increasing Hb levels, HRQoL is a particular outcome of interest for the interventions under review.

TABLE 31 Trials contributing to subgroup analysis with regard to 'closer to' licence recommendations (by start dose, inclusion Hb level and target Hb level)

Subgroup by 'closer to' licence recommendations	Trials	References
Starting dose criteria met	23	[a]Abels 1993;[63] Aravantinos 2003;[64] Boogaerts 2003;[65] Dammacco 2001;[66] Del Mastro 1997;[67] Dunphy 1999;[68] Grote 2005;[74] Hedenus 2002;[53] Hedenus 2003;[17] Kotasek 2003;[50] Kurz 1997;[69] Littlewood 2001;[70] Moebus 2013;[62] [b]Österborg 2002;[71] [b]Österborg 2005;[79] Ray-Coquard 2009;[75] Silvestris 1995;[72] Straus 2008;[76] ten Bokkel Huinink 1998;[51] [a]Thatcher 1999;[52] Tjulandin 2010;[48] [c]Tjulandin 2011;[77] [b]Untch 2011;[78,80] Vansteenkiste 2002[73]
Starting dose criteria met and inclusion Hb ≤ 11 g/dl	14	[a]Abels 1993;[63] Aravantinos 2003;[64] Boogaerts 2003;[65] Dammacco 2001;[66] Hedenus 2002;[53] Hedenus 2003;[17] Kotasek 2003;[50] Kurz 1997;[69] Littlewood 2001[70] (≤ 10 g/dl[c]); [b]Österborg 2002;[71] [b]Österborg 2005;[79] Silvestris 1995;[72] [a]Tjulandin 2010;[48] Tjulandin 2011;[77] Vansteenkiste 2002[73] (Hb < 10 g/dl and ≥ 10 and ≤ 11 g/dl[d])
Starting dose criteria met, inclusion Hb ≤ 11 g/dl and target Hb ≤ 13 g/dl	2	[a]Tjulandin 2010;[48] Tjulandin 2011[77]

a Trials with multiple experimental arms, split into two subsets: Tjulandin and colleagues[48] – epoetin theta and epoetin beta; Abels and colleagues[63] – platinum-based and non-platinum-based chemotherapy.
b Trial was reported in two publications.
c Only results from the Hb subgroup ≤ 10 g/dl of the trial population contributed to this analysis.
d Only results from the Hb subgroups < 10 g/dl and ≥ 10 and ≤ 11 g/dl of the subgroup population contributed to this analysis.

TABLE 32 Effectiveness according to per-licence recommendations: subgroup analyses using Hb subgroup results from Littlewood and colleagues[70] and Vansteenkiste and colleagues[73]

	Start dose, double-blind RCT			Licence start dose, double-blind RCT			Licence start dose, inclusion Hb ≤ 11 g/dl			Licence start dose, inclusion Hb ≤ 11 g/dl			Licence start dose, inclusion Hb ≤ 11 g/dl and target Hb ≤ 13 g/dl		
Outcome	Number of studies	ES (95% CI)	I^2, *p*-value	Number of studies	ES (95% CI)	I^2, *p*-value	Number of studies	ES (95% CI)	I^2, *p*-value	Number of studies	ES (95% CI)	I^2, *p*-value	Number of studies	ES (95% CI)	I^2, *p*-value
Hb change (g/dl)[a,b]	18	WMD 1.59 (1.33 to 1.84)	75.9%, $p<0.01$	13	WMD 1.70 (1.43 to 1.97)	64.9%, $p<0.01$	13	WMD 1.52 (1.30 to 1.75)	48.1%, $p=0.03$	11	WMD 1.59 (1.35 to 1.84)	46.4%, $p=0.05$	3	WMD 1.50 (1.16 to 1.83)	0%, $p=0.80$
HaemR[a,b,c]	13	RR 3.29 (2.81 to 3.85)	13.4%, $p=0.31$	12	RR 3.30 (2.77 to 3.93)	19.5%, $p=0.25$	12	RR 3.20 (2.78 to 3.68)	2.0%, $p=0.43$	11	RR 3.20 (2.74 to 3.75)	8.9%, $p=0.36$	3	RR 3.06 (2.28 to 4.09)	0%, $p=0.79$
RBCT[a,b,d]	26	RR 0.61 (0.55 to 0.68)	22.4%, $p=0.15$	16	RR 0.64 (0.58 to 0.72)	6.4%, $p=0.38$	16	RR 0.64 (0.57 to 0.71)	7.3%, $p=0.37$	14	RR 0.66 (0.59 to 0.74)	0%, $p=0.52$	3	RR 0.50 (0.33 to 0.77)	0%, $p=0.92$
RBC units[a,e]	12	WMD –0.87 (–1.24 to –0.50)	55.6%, $p=0.01$	9	WMD –0.9 (–0.93 to –0.36)	28.0%, $p=0.20$	9	WMD –0.99 (–1.41 to –0.56)	56.2%, $p=0.01$	8	WMD –0.63 (–0.79 to –0.47)	0.6%, $p=0.43$	1	WMD –0.56 (–0.74 to –0.39)	NA
Tumour response	7	RR 1.10 (0.86 to 1.41)	37.5%, $p=0.14$	4	RR 1.50 (1.01 to 2.23)	21.5%, $p=0.28$	2	RR 1.60 (0.88 to 2.90)	0%, $p=0.70$	2	RR 1.60 (0.88 to 2.90)	0%, $p=0.70$	0	NA	NA
OS[a,b]	18	HR 0.97 (0.83 to 1.13)	42.4%, $p=0.03$	11	HR 0.92 (0.75 to 1.13)	52.4%, $p=0.02$	10	HR 0.91 (0.70 to 1.20)	51.7%, $p=0.03$	9	HR 0.87 (0.65 to 1.15)	53.7%, $p=0.03$	3	HR 0.50 (0.20 to 1.23)	29.7%, $p=0.24$
On study mortality[a,b]	14	HR 0.86 (0.67 to 1.11)	16.4%, $p=0.27$	11	HR 0.86 (0.63 to 1.17)	33.0%, $p=0.14$	10	HR 0.89 (0.61 to 1.30)	37.7%, $p=0.11$	9	HR 0.86 (0.56 to 1.32)	44.5%, $p=0.07$	3	HR 0.50 (0.20 to 1.23)	29.7%, $p=0.24$
Thromboembolic events[a]	14	RR 1.46 (1.07 to 1.99)	0%, $p=0.73$	9	RR 1.24 (0.81 to 1. 90)	0%, $p=0.55$	7	RR 1.29 (0.66 to 2.54)	12.2%, $p=0.34$	7	RR 1.29 (0.66 to 2.54)	12.2%, $p=0.34$	1	RR 0.32 (0.01 to 7.74)	NA
Hypertension[a,b]	12	RR 1.80 (1.14 to 2.85)	0%, $p=0.79$	9	RR 1.70 (1.05 to 2.76)	0%, $p=0.65$	9	RR 1.68 (1.03 to 2.74)	0%, $p=0.64$	8	RR 1.61 (0.98 to 2.64)	0%, $p=0.66$	3	RR 2.19 (0.53 to 9.12)	16.8%, $p=0.30$
Thrombocytopenia/ haemorrhage	7	RR 0.93 (0.65 to 1.34)	0%, $p=0.81$	5	RR 0.89 (0.57 to 1.39)	0%, $p=0.58$	2	RR 0.73 (0.37 to 1.46)	0%, $p=0.41$	1	RR 1.10 (0.33 to 3.64)	NA	0	NA	NA
Seizures[a]	2	RR 1.19 (0.33 to 4.38)	0%, $p=0.74$	2	RR 1.19 (0.33 to 4.38)	0%, $p=0.74$	2	RR 1.19 (0.33 to 4.38)	0%, $p=0.74$	2	RR 1.19 (0.33 to 4.38)	0%, $p=0.74$	0	NA	NA
Pruritus	6	RR 2.04 (1.11 to 3.75)	0%, $p=0.87$	3	RR 2.20 (1.05 to 4.58)	0%, $p=0.66$	3	RR 2.20 (1.05 to 4.58)	0%, $p=0.66$	3	RR 2.20 (1.05 to 4.58)	0%, $p=0.66$	1	RR 1.78 (0.74 to 4.26)	NA

ES, effect size; HaemR, haematological response; units, units transfused per participant.
a Abels and colleagues[63] reported data for participants on platinum-based and non-platinum-based chemotherapy, which were combined.
b Tjulandin and colleagues[48] reported data for epoetin beta and epoetin theta, which were combined.
c Using Hb subgroups from Littlewood and colleagues.[70]
d Using Hb subgroups from Littlewood and colleagues[70] and Vansteenkiste and colleagues.[73]
e Using Hb subgroups from Vansteenkiste and colleagues.[73]

Methods

A search specifically targeted at HRQoL was conducted (see *Identification of studies*). Titles and abstracts identified in the quality of life searches were screened according to the eligibility criteria presented earlier (see *Eligibility criteria*); however, these titles and abstracts were screened specifically for HRQoL outcomes.

Results from included studies were tabulated and narratively reported. In addition, meta-analyses were used to provide an overview with an estimate of overall effect.

Results

In total, 13 trials[17,50,52,63,65–67,69–71,73,75,77] (reported in 23 publications[17,50,52,58–60,63,65–67,69–71,73,75,77,79,81–86]) were identified (full details relating to the selection of studies and a PRISMA flow diagram are provided in *Appendix 13*).

Study characteristics

Study characteristics are reported in *Table 10*. A summary of the HRQoL measures included in the studies is provided in *Table 33*.

A range of questionnaires was used to measure HRQoL and subsequent changes in response to treatment. The scales are summarised in *Appendix 13*; however, this review focuses on the FACT tool, as it is has been widely used in ESA trials and is considered to have good responsiveness to change and good convergent and discriminant validity.[11] Furthermore, the FACT tool is the only tool in this review for which there are sufficient studies to enable meta-analysis.

The FACT tool, which asks patients to focus on HRQoL issues over the previous 7 days, is part of a collection of HRQoL questionnaires (*Figure 20*), beginning with a generic questionnaire called the FACT-G. There are now over 50 different scales and symptom indexes, some of which have been modified over time. The FACT scales used in this review are listed in *Table 33*. Copies of these questionnaires and details of scoring and interpretation are available at: http://www.facit.org/FACITOrg/Questionnaires (accessed September 2015). It should be noted that since 1997 the scale has been known as FACIT.

TABLE 33 Health-related quality-of-life instruments included in the studies

HRQoL measure	Studies
FACT-G	Österborg 2002;[71] Littlewood 2001;[70] Aapro 2004;[82] Bajetta 2004;[81] Patrick 2003;[60] Tjulandin 2011[77]
FACT-An	Österborg 2002;[71] Tjulandin 2011[77]
FACT-F	Österborg 2002;[71] Littlewood 2001;[70] Boogaerts 2003;[65] Hedenus 2003;[17] Vansteenkiste 2002;[73] Aapro 2004;[82] Bajetta 2004;[81] Kotasek 2003;[50] Littlewood 2006;[83] Patrick 2003;[60] Tjulandin 2011[77]
FACT-An-An	Aapro 2004;[82] Boogaerts 2003;[65] Littlewood 2001;[70] Österborg 2002[71]
SF-36	Boogaerts 2003;[65] Patrick 2003[60]
CLAS/LASA	Dammacco 2001;[66] Littlewood 2001;[70] Aapro 2004;[82] Bajetta 2004;[81] Patrick 2003[60]
PDI	Del Mastro 1997[67]
EORTC QLQ-C30	Ray-Coquard 2009[75]
BSI	Littlewood 2006[83]
NHP	Dammacco 2001[66]
VAS	Abels 1993;[63] Boogaerts 2003;[65] Kurz 1997;[69] Thatcher 1999[52]

BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analog Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT-An-An, FACT – Anaemia Anaemia subscale; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; PDI, Psychological Distress Inventory; VAS, visual analogue scale.

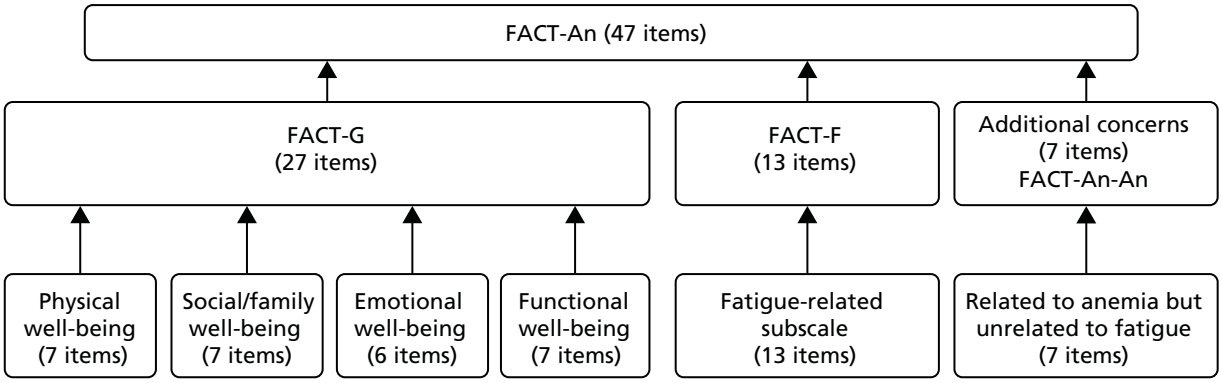

FIGURE 20 Overview of the FACT scales used in this review. Fact-An-An, FACT-Anaemia Anaemia subscale.

Using both anchor-based and distribution-based methods to analyse FACT-F, FACT-G and FACT-An, data from three samples of patients ($n = 50$, $n = 131$ and $n = 2402$) determined the minimal clinically important difference to be FACT-F = 3.0, FACT-G = 4.0 and FACT-An = 7.0.[112]

Trials identified in the previous Health Technology Assessment review

Of the 11 trials identified in the previous HTA review,[2] nine indicated that there was a statistically significant difference in HRQoL between patients treated with ESAs and control participants (*Figure 21*). Of the two studies that did not show ESAs to be effective compared with placebo, one used an unvalidated assessment tool (Health State Utility Scale)[69] and the other used the Psychological Distress Inventory (PDI).[67]

Thatcher and colleagues[52] reported that only the overall HRQoL level revealed a statistically significant improvement favouring epoetin alfa ($p < 0.05$). Evaluation of World Health Organization (WHO) performance scores revealed similar findings, with no significant between- or within-group differences.[52]

Trials identified, 2004 to current

Three trials were identified following the previous HTA review.[2] Of these, one was a follow-up study[79] of a study identified previously.[71] Österborg and colleagues[79] report a statistically significant increase in favour of epoetin beta; however, the variability between patients was considerable. Ray-Coquard and colleagues[75] stated that there were no statistically detectable differences during the study period, although none of these data were reported. Tjulandin and colleagues[77] also found no significant differences between the epoetin theta group and the placebo group.

Post-hoc studies identified, 2004 to current

Five studies[60,81–84] reported trends that favour ESA. However, Bajetta and colleagues[81] and Littlewood and colleagues[83] did not analyse this statistically.

Additional results to the primary study[73] provided by Vansteenkiste and colleagues[84] indicated a significant difference ($p = 0.0147$) in HRQoL between the darbepoetin alfa group and the placebo group for those with a baseline Hb level of < 10 g/dl. In contrast, no difference was apparent between groups for those with a baseline Hb of ≥ 10 g/dl.

(a)

Study		Chemotherapy	Malignancy	Notes	Design	Quality				Outcomes										
						Random	Baseline similarity	Blinding	Losses	VAS	SF-36	FACT-An	FACT-F	FACT-G	FACT-An-An	CLAS/LASA	PDI	EORTC-QLQ-C30	BSI	NHP	D&A
Aapro	2004[82]	Non-plat	Solid and haem		*n*=375	Epo Alfa *n*=251 Placebo *n*=124 Missing *n*=85–93							●	●	●	●					
Abels	1993[63]	Non-plat	Solid and haem	1	*n*=413	Epo Alfa *n*=213 Placebo *n*=200 Missing *n*=111–187				●											
Bajetta	2004[81]	Non-plat	Solid and haem		*n*=114	Epo Alfa *n*=78 Placebo *n*=36 Missing *n*=8–24							○	○		○					
Boogaerts	2003[65]	?	Solid and haem		*n*=262	Epo Beta *n*=133 Control *n*=129 Missing *n*=39–49				●	●		●		○						
Dammaco	2001[66]	Mixed	Haem		*n*=145	Epo Alfa *n*=69 Placebo *n*=76 Missing *n*=7										○				○	

Quality appraisal key
Random:
concealment of allocation (above)
random allocation (below)
Baseline:
baseline characteristics
Blinding:
blinding of clinicians (above)
blinding of patients (below)
Losses:
ITT or <10% (above)
losses (below)

■ Positive quality check
▣ Partial quality check
□ Negative quality check
☒ Not reported

Outcomes key
● Favours treatment
◪ Favours control
○ Non-significant outcomes

FIGURE 21 Health-related quality of life: graphical summary. Notes: 1: Study population included patients not receiving chemotherapy; 2: 87% and 84% of participants were analysed in the treatment and control groups, respectively; 3: 80% and 73% of participants were analysed in the treatment and control groups, respectively; 4: 54% and 57% of participants were analysed in the treatment and control groups, respectively; 5: 75% and 61% of participants were analysed in the treatment and control groups, respectively; 6: 90–98% and 86–97% of participants were analysed in the treatment and control groups, respectively; 7: 81% of participants were analysed in the treatment and control groups. ?, unknown; BSC, best supportive care; BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analog Scale; D&A, depression and anxiety subscale of the BSI; darbe, darbepoetin; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; epo, epoetin; FACT-An-An, FACT–Anaemia Anaemia subscale; haem, haematological; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; non-plat, non-platinum; PDI, Psychological Distress Inventory; plat, platinum; VAS, visual analogue scale. (*continued*)

(b)

Study		Chemotherapy	Malignancy	Notes	Design		Quality	Outcomes
							Random Baseline similarity Blinding Losses	VAS SF-36 FACT-An FACT-F FACT-G FACT-An-An CLAS/LASA PDI EORTC-QLQ-C30 BSI NHP
Dammacco	2001[66]	Mixed	Haem		$n=145$	Epo Alfa $n=69$ Placebo $n=76$ Missing $n=7$		○
Del Mastro	1997[67]	Non-plat	Solid	2	$n=62$	Epo Alfa $n=31$ BSC $n=31$ Missing $n=7$		⊘
Hedenus	2004[17]	?	Haem		$n=344$	Darbe Alfa $n=174$ Placebo $n=170$ Missing $n=55$		●
Kotasek	2003[50]	?	Solid		$n=68$	Darber Alfa $n=17$ Placebo $n=51$		●
Kurz	1997[69]	Mixed	Solid and haem		$n=35$	Epo Alfa $n=23$ Placebo $n=12$		⊘

Quality appraisal key
Random:
concealment of allocation (above)
random allocation (below)
Baseline:
baseline characteristics
Blinding:
blinding of clinicians (above)
blinding of patients (below)
Losses:
ITT or <10% (above)
losses (below)

■ Positive quality check
◪ Partial quality check
□ Negative quality check
☒ Not reported

Outcomes key
● Favours treatment
⊘ Favours control
○ Non-significant outcomes

FIGURE 21 Health-related quality of life: graphical summary. Notes: 1: Study population included patients not receiving chemotherapy; 2: 87% and 84% of participants were analysed in the treatment and control groups, respectively; 3: 80% and 73% of participants were analysed in the treatment and control groups, respectively; 4: 54% and 57% of participants were analysed in the treatment and control groups, respectively; 5: 75% and 61% of participants were analysed in the treatment and control groups, respectively; 6: 90–98% and 86–97% of participants were analysed in the treatment and control groups, respectively; 7: 81% of participants were analysed in the treatment and control groups. ?, unknown; BSC, best supportive care; BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analog Scale; D&A, depression and anxiety subscale of the BSI; darbe, darbepoetin; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; epo, epoetin; FACT-An-An, FACT–Anaemia Anaemia subscale; haem, haematological; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; non-plat, non-platinum; PDI, Psychological Distress Inventory; plat, platinum; VAS, visual analogue scale. (*continued*)

(c)

Study		Chemotherapy	Malignancy	Notes	Design	Quality	Outcomes
Littlewood	2001[70]	Non-plat	Solid and haem	3	*n* = 375	Epo Alfa *n* = 251 Placebo *n* = 124 Missing *n* = 85	FACT-F, FACT-G, FACT-An-An, CLAS/LASA
Littlewood	2006[83]	?	Haem		*n* = 344	Darbe Alfa *n* = 174 Placebo *n* = 170 Missing *n* = 41	FACT-F, D&A
Österborg	2002[71] 2005[79]	Non-plat	Haem		*n* = 343	Epo Beta *n* = 170 Placebo *n* = 173 Missing *n* = 68	FACT-An, FACT-F, FACT-G, FACT-An-An
Patrick	2003[60]	Non-plat	Solid and haem		*n* = 375	Epo Alfa *n* = 251 Placebo *n* = 124	SF-36, FACT-F, FACT-G, CLAS/LASA
Ray-Coquard	2009[75]	?	Solid and haem	4	*n* = 218	Epo Alfa *n* = 110 Control *n* = 108 Missing *n* = 96	EORTC-QLQ-C30

Quality: Random; Baseline similarity; Blinding; Losses

Outcomes: VAS; SF-36; FACT-An; FACT-F; FACT-G; FACT-An-An; CLAS/LASA; PDI; EORTC-QLQ-C30; BSI; NHP; D&A

Quality appraisal key
Random:
concealment of allocation (above)
random allocation (below)
Baseline:
baseline characteristics
Blinding:
blinding of clinicians (above)
blinding of patients (below)
Losses:
ITT or <10% (above)
losses (below)

- Positive quality check
- Partial quality check
- Negative quality check
- Not reported

Outcomes key
- Favours treatment
- Favours control
- Non-significant outcomes

FIGURE 21 Health-related quality of life: graphical summary. Notes: 1: Study population included patients not receiving chemotherapy; 2: 87% and 84% of participants were analysed in the treatment and control groups, respectively; 3: 80% and 73% of participants were analysed in the treatment and control groups, respectively; 4: 54% and 57% of participants were analysed in the treatment and control groups, respectively; 5: 75% and 61% of participants were analysed in the treatment and control groups, respectively; 6: 90–98% and 86–97% of participants were analysed in the treatment and control groups, respectively; 7: 81% of participants were analysed in the treatment and control groups. ?, unknown; BSC, best supportive care; BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analog Scale; D&A, depression and anxiety subscale of the BSI; darbe, darbepoetin; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; epo, epoetin; FACT-An-An, FACT–Anaemia Anaemia subscale; haem, haematological; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; non-plat, non-platinum; PDI, Psychological Distress Inventory; plat, platinum; VAS, visual analogue scale. (*continued*)

(d)

Study	Chemotherapy	Malignancy	Notes	Design	Quality	Outcomes
					Random Baseline similarity Blinding Losses Vas SF-36 FACT-An FACT-F FACT-G FACT-An-An CLAS/LASA PDI EORTC-QLQ-C30 BSI NHP D&A	
Thatcher 1999[52]	Plat	Solid	5	*n*=130		⊘
				Epo Alfa *n*=42 Control *n*=44 Missing *n*=26		
Tjulandin 2011[77]	Non-plat	Solid and haem	6	*n*=186		○ ○ ○
				Epo Theta *n*=95 Placebo *n*=91 Missing *n*=18		
Vansteenskiste 2002[73]	Plat	Solid	7	*n*=314		○
				Darbe Alfa *n*=156 Placebo *n*=158 Missing *n*=59		
Vansteenskiste 2004[84]	Plat	Solid		*n*=314		⊘
				Darbe Alfa *n*=156 Placebo *n*=158 Missing *n*=59		

Quality appraisal key
Random:
concealment of allocation (above)
random allocation (below)
Baseline:
baseline characteristics
Blinding:
blinding of clinicians (above)
blinding of patients (below)
Losses:
ITT or <10% (above)
losses (below)

■■ Positive quality check
■□ Partial quality check
□□ Negative quality check
⊠ Not reported

Outcomes key
● Favours treatment
⊘ Favours control
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FIGURE 21 Health-related quality of life: graphical summary. Notes: 1: Study population included patients not receiving chemotherapy; 2: 87% and 84% of participants were analysed in the treatment and control groups, respectively; 3: 80% and 73% of participants were analysed in the treatment and control groups, respectively; 4: 54% and 57% of participants were analysed in the treatment and control groups, respectively; 5: 75% and 61% of participants were analysed in the treatment and control groups, respectively; 6: 90–98% and 86–97% of participants were analysed in the treatment and control groups, respectively; 7: 81% of participants were analysed in the treatment and control groups. ?, unknown; BSC, best supportive care; BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analog Scale; D&A, depression and anxiety subscale of the BSI; darbe, darbepoetin; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; epo, epoetin; FACT-An-An, FACT–Anaemia Anaemia subscale; haem, haematological; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; non-plat, non-platinum; PDI, Psychological Distress Inventory; plat, platinum; VAS, visual analogue scale.

Meta-analysis: Functional Assessment of Cancer Therapy – Fatigue (13 items) score (random effects)

Given the variability of reporting in the published papers, FACT-F data were extracted from the Cochrane review by Tonia and Colleagues[11] for use in the PenTAG analyses. Functional Assessment of Cancer Therapy – Fatigue scores were available from seven studies[17,50,65,70,71,73,77,79] including 1794 participants. One new primary study was identified.[77]

The WMD was 2.54 (95% CI 1.42 to 3.65; *Figure 22*). There was low heterogeneity between the trials ($I^2 = 14.9\%$; $p = 0.32$) (*Table 34*). Because only seven primary studies were included in the meta-analysis, the funnel plot analysis to test whether publication bias was present was not conducted in accordance with published giudelines.[54] The fixed-effects meta-analysis undertaken as a sensitivity analysis showed similar significant results (see *Appendix 13*, *Figure 108*). All of the studies were similar in terms of quality; however, the trial reported by Boogaerts and colleagues[65] did not employ blinding for participants. Removing this study from the meta-analysis had a minimal impact on the results (WMD 2.21, 95% CI 1.131 to 3.280; see *Appendix 13*, *Figure 113*), but did improve heterogeneity ($I^2 = 0\%$, $p = 0.51$).

Meta-analysis was performed on FACT-G and FACT-An Anaemia subscale (FACT-An-An) data; however, only three studies[70,71,77,79] were suitable for inclusion for each scale with high levels of heterogeneity [see *Table 34* and *Appendix 13*, *Figures 114* and *115* (FACT-G), and *Figures 116* and *117* (FACT-An)]. The results of no statistical difference between the intervention and the control must therefore be treated with caution.

Univariate subgroup analyses were conducted for FACT-F outcomes according to chemotherapy type, malignancy type, intervention (epoetin or darbepoetin) and study duration and showed significant results; however, the number of studies included was small (see *Table 34* and *Appendix 13*, *Figures 109–112*).

Health-related quality-of-life outcomes: overall summary

Effectiveness estimates are presented alongside previously reported estimates for HRQoL (see *Table 34*). A graphical summary of the study characteristics, quality appraisal and results for these outcomes is presented in *Figures 21* (HRQoL) and *23* (FACT-F).

Overall, the conclusions of the PenTAG review are in agreement with those of the Cochrane review[11] in that there is a statistically significant difference between patients treated with ESAs and control participants when combining HRQoL parameters; however, this is probably not clinically important (minimal clinically important difference = 3.0[112]). As with previous reviews, however, it should be noted that there are several methodological concerns that may result in bias, for example the substantial quantity of missing data, expecting patients to complete repeated questionnaires leading to a shift in patient response and the various modes of administration of the questionnaires.

FIGURE 22 Health-related quality of life: FACT-F (13 items) – overall. Note: random-effects meta-analysis (DerSimonian–Laird). BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analogue Scale; D&A, depression and anxiety subscale of the BSI; darbe, darbepoetin; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; epo, epoetin; FACT-An-An, FACT-An Anaemia subscale; haem, haematological; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; non-plat, non-platinum; plat, platinum; VAS, visual analogue scale.

TABLE 34 Health-related quality of life: results comparison for the FACT tool – Wilson and colleagues[2] vs. Tonia and colleagues[11] vs. PenTAG

FACT scale	[a]Wilson and colleagues[2]	[a]Tonia and colleagues[11]	PenTAG[a]	PenTAG[b]
FACT-F (13 items; score 0–52)[c]	NR	WMD 2.08, 95% CI 1.43 to 2.72; $\chi^2_{(het)} = 36.48$, df = 17; $p = 0.004$	WMD 2.49, 95% CI 1.48 to 3.51; $\chi^2_{(het)} = 7.05$, df = 6; $p = 0.000$	WMD 2.54, 95% CI 1.42 to 3.65; $\chi^2_{(het)} = 7.05$, df = 6; $p = 0.000$
		18 trials, $n = 4965$	7 trials, $n = 1794$	7 trials, $n = 1794$
Any subgroup effect	NR	Yes: imputed vs. non-imputed data, baseline Hb level, type of anticancer therapy, duration of ESA treatment and ITT analysis	–	Possible: malignancy, intervention and duration
[c]FACT-F (13 items; score 0–52) without Boogaerts 2003[65]	–	–	–	WMD 2.21, 95% CI 1.13 to 3.28; $\chi^2_{(het)} = 4.31$, df = 5; $p = 0.000$
				6 trials, $n = 1581$
FACT-G (27 items; score 0–108)[c]	NR	NR	WMD 3.16,[e] 95% CI 1.11 to 5.21; $\chi^2_{(het)} = 6.82$, df = 2; $p = 0.003$	WMD 2.98,[e] 95% CI –0.83 to 6.78; $\chi^2_{(het)} = 6.82$, df = 2; $p = 0.13$
			3 trials, $n = 686$	3 trials, $n = 686$
FACT-An-An (seven items; score 0–28)[c,d]	NR	NR[d]	WMD 1.05,[f] 95% CI 0.93 to 1.12; $\chi^2_{(het)} = 80.66$, df = 2; $p = 0.00$	WMD 2.60,[f] 95% CI –0.52 to 5.72; $\chi^2_{(het)} = 80.66$, df = 2; $p = 0.00$
			3 trials, $n = 686$	3 trials, $n = 686$

het, heterogeneity; MD, minimal difference; NR, not reported.
p-values reported for heterogeneity.
a Fixed effects (Mantel–Haenszel).
b Random effects (DerSimonian–Laird).
c Change from baseline to end of study.
d The FACT-An scale (47 items) was used only by Tjulandin and colleagues[77] and Österborg and colleagues,[79] so no meta-analysis was performed on this scale. Three studies analysed the FACT-An-An subscale (seven items). Of note, Tonia and colleagues[11] refer to a FACT-An 20-item scale, which is made up of the FACT-F 13-item scale plus the FACT-An-An seven-item scale.
e SD for Littlewood and colleagues[70] imputed from Tjulandin and colleagues[77] and Österborg and colleagues.[79]
f SD for Littlewood and colleagues[70] imputed from Österborg and colleagues.[79]

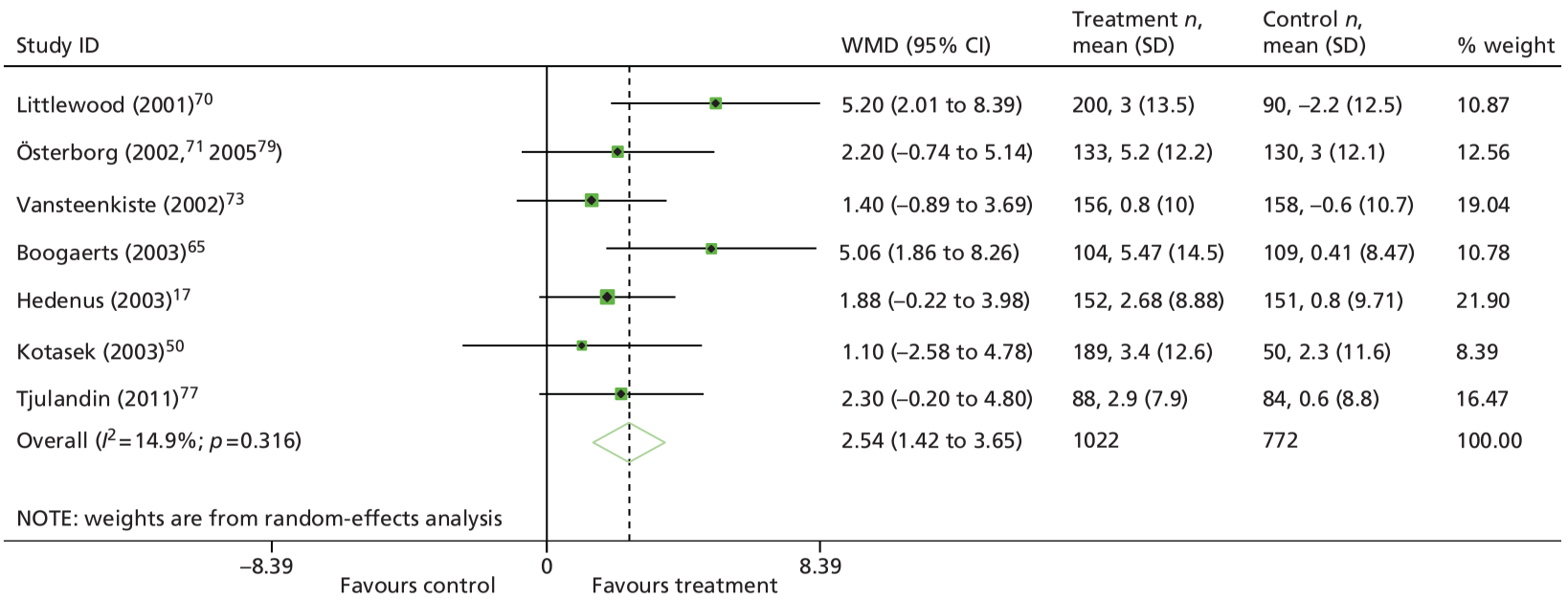


FIGURE 23 Forest plot: HRQoL overall. Note: random effects meta-analysis (DerSimonian–Laird).

Key points

- From a total of 1517 titles and abstracts screened, 11 systematic reviews (reported in 12 publications) and 23 RCTs (reported in 34 publications) were found that matched the inclusion criteria and were considered 'within licence' based on the start dose administered.
- Of note, none of the included studies evaluated ESAs entirely within the remit of their marketing authorisations. In particular, starting and target Hb levels and stopping rules were all generally higher than specified in the licences. This could be because the majority of studies (82%) were initiated before the changes to the licences in 2008.
- Overall, the included trials were of moderate or poor quality. All were flawed because of reporting issues but some were more flawed than others. Most notably, all trials lacked clarity in the reporting of allocation methods (the procedure for randomisation and/or allocation concealment). For most of the studies it was difficult to make a general assessment about quality because of reporting omissions.
- Pooled estimates for anaemia-related outcomes were consistent with previous estimates in terms of both haematological response and requirement for RBCT and were in favour of ESA treatment. The estimates for haematological response and numbers transfused seem to be robust, with no marked heterogeneity or subgroup effects. However, the analyses for Hb change did include important heterogeneity, which may possibly indicate subgroup effects; analyses in this respect were inconclusive.
- The HR for OS was 0.97 (95% CI 0.83 to 1.13) although the forest plot suggested that there was a tendency for smaller studies to favour treatment. However, this estimate is subject to uncertainty and no definitive conclusions can be drawn.
- The HR for on-study mortality (deaths occurring up to 30 days after the active study period) was 0.86 (95% CI 0.67 to 1.11).

Adverse events

- Overall, pooled data suggest that treatment with ESAs is associated with an increased risk for thromboembolic events, hypertension, seizure and rash, consistent with previous estimates. The risk for thrombocytopenia/haemorrhage associated with ESA treatment remains unclear and there were too few data to rule out detrimental effects.
- Adverse events are mainly affected by the quality of information available, the variability in the definition of AEs used and the width of the CIs.

Health-related quality of life

- There is a statistically significant difference in HRQoL between patients treated with ESAs and control participants when combining HRQoL parameters, which is, however, probably not clinically important (minimal clinically important difference = 3.0[112]).
- Meta-analysis was performed for the FACT-G and FACT-An-An subscales; however, only three studies were suitable for inclusion for each scale with high levels of heterogeneity. The result of no statistical difference between the intervention and the control must therefore be treated with caution.
- Publication bias was noted in the Cochrane review,[11] suggesting over-reporting of studies that showed beneficial effects of ESAs. It was not possible to examine publication bias using funnel plots because there were fewer than 10 included studies; therefore, it was not possible to confirm or refute the claims made in the Cochrane review.
- Health-related quality of life is affected by the variability of instruments used and the moderate or poor study quality, for example patients and physicians were not blinded in the majority of trials, which is considered to have a significant impact on HRQoL assessed by self-reporting. Significant numbers were lost to follow-up for HRQoL outcomes in at least six trials.

Subgroup and exploratory analyses

- Only one study evaluated the use of ESAs in women with ovarian cancer. All participants in this study received platinum-based chemotherapy.
- Subgroup analyses of platinum-based chemotherapy in people with any type of cancer showed a trend towards a slight benefit associated with ESA treatment in terms of on-study mortality or OS in patients with chemotherapy-induced anaemia. However, these results should be treated with caution because of the small number of studies included in the analysis.
- No studies were identified that considered the use of ESAs among people unable to receive RBCTs. However, it is reasonable to assume that ESAs are likely to work in improving Hb in this subpopulation. It is also reasonable to believe that, if patients can be supported through the period of life-threatening anaemia, their Hb level will recover; if ESAs are not allowed, they run the risk of death.
- Post-hoc analyses (starting dose plus inclusion Hb level $\leq$ 11.0 g/dl and starting dose plus inclusion Hb level $\leq$ 11.0 g/dl plus target Hb level $\leq$ 13.0 g/dl) offer some limited evidence to suggest that compliance to European labelling results in better outcomes, although results should be interpreted with caution (when considering the subgroup of trials. Data suggest that, if the licensed recommendations for ESA administration are followed, there are no detrimental effects of ESAs on on-study mortality or overall mortality in patients with chemotherapy treatment-induced anaemia. Although these effects are consistent with improved tumour response and a decrease in the number of thromboembolic events, these results should be interpreted with caution, as the point estimates are not statistically significant and the CIs around the estimates remain wide. Furthermore, we have not sought to address multiple testing issues that arise when considering subgroups and so inference is not straightforward.

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

The cost-effectiveness of ESAs within their licensed indications for the treatment of chemotherapy-induced anaemia compared with each other and with best supportive care was assessed in a systematic review of the literature.

This systematic review of cost-effectiveness evidence was an update of a systematic review reported by Wilson and colleagues,[2] which informed previous NICE guidance TA142.[1] The methods and results of the previous systematic review are summarised in the following section and the methods and results for this update review are described in *Update review*.

Economic evaluations submitted by manufacturers would have been included in the systematic review but no such evaluations were submitted.

Wilson and colleagues:[2] summary

A systematic review of cost-effectiveness evidence was reported by Wilson and colleagues,[2] which informed previous NICE guidance TA142.[1]

Objective

The objective of this systematic review was 'to identify and appraise past economic evaluations of erythropoietin in the treatment of anaemia associated with cancer treatment' (p. 83).[2]

Methods

Searches were conducted in a range of databases, as detailed in *Table 35*. Industry submissions were also evaluated and searched for additional references.

Separate search strategies were developed for costs, economic models and quality-of-life studies, which are detailed in Appendix 3 of Wilson and colleagues.[2]

The inclusion criteria were such that included studies were 'all economic evaluations (cost–benefit, cost–utility, cost-effectiveness and cost–consequence analyses) of erythropoietin for anaemia associated with cancer treatment from 1995 to July 2004' (p. 83).[2] Screening was performed by one reviewer.

TABLE 35 Databases searched in the systematic review by Wilson and colleagues[2]

Database	Interface	Date range
MEDLINE	Ovid	1966 to July Week 4 2004
EMBASE	Ovid	1980 to Week 30 2004
DARE	–	2004 Issue 3
NHS EED	–	2004 Issue 3
OHE HEED	–	July 2004

OHE HEED, Office for Health Economics Health Economic Evaluations Database.

Included studies were critically appraised using the checklist suggested by Drummond and colleagues.[113] Single points were assigned to all but one criterion on the Drummond checklist when met; these were summed to give an overall quality score for a study.

Data were abstracted from the studies using a framework used by the West Midlands group in previous technology appraisals. Data abstraction was performed by one reviewer and checked by another.

Qualitative analysis was performed by one reviewer based on manually identified patterns in tabulated data. Conclusions were scrutinised by two other reviewers.

Results

The electronic database searches retrieved 491 citations. No additional citations were identified from industry submissions. Full texts were retrieved for 44 citations (the remainder being excluded as irrelevant on the basis of title and/or abstract). Five studies[114–118] were included following full-text screening (the remainder generally being excluded for not considering both costs and benefits). *Figure 24* provides the study flow diagram for the systematic review.

Three cost–utility studies[114–116] included in the systematic review reported by Wilson and colleagues[2] are also included in the update review and are hence not reported here.

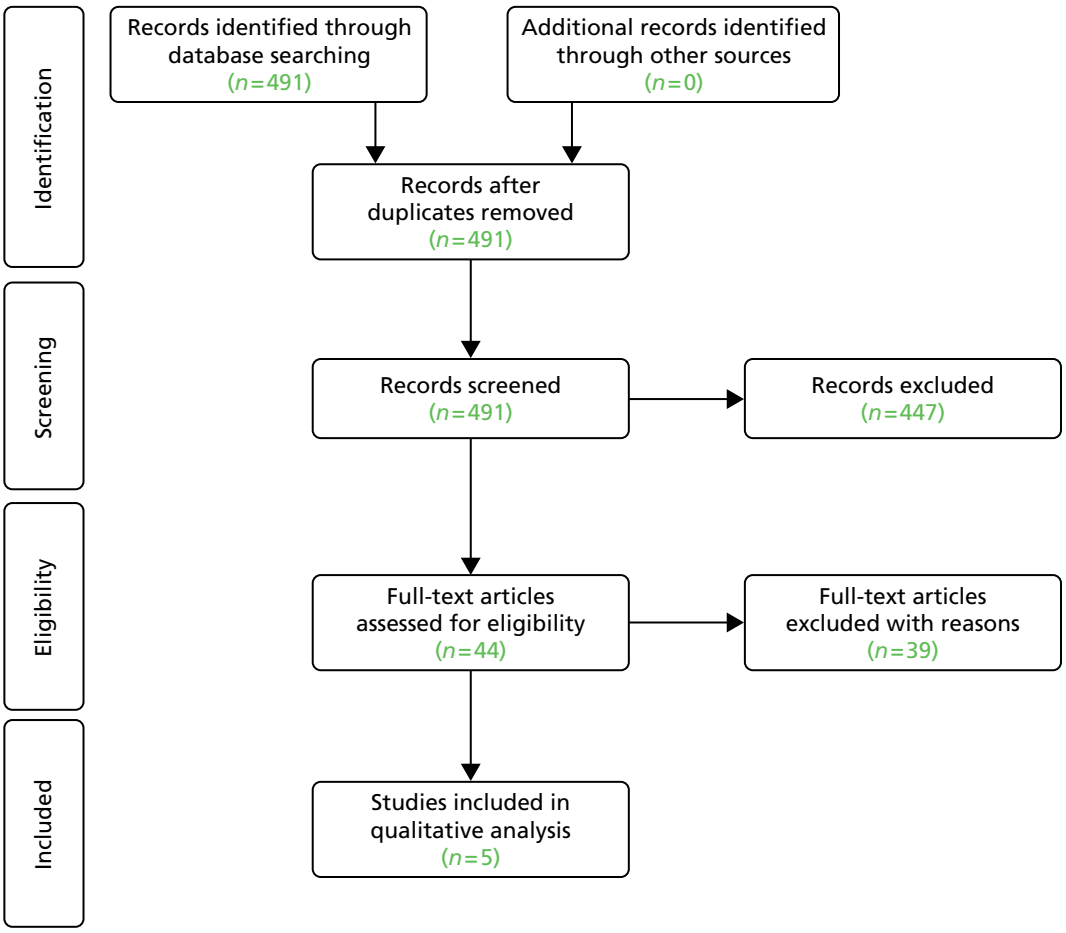


FIGURE 24 Study flow diagram for the systematic review of cost-effectiveness evidence reported by Wilson and colleagues.[2] Adapted from the PRISMA flow diagram.

Of the other two included studies, Ortega and colleagues[117] used a willingness-to-pay experiment to determine the societal benefit of epoetin alfa in monetary terms and compare this to the predicted incremental costs of epoetin alfa. The benefit described was avoidance of transfusion and was separately valued by cancer patients and the general population. The benefit of reversing anaemia was not valued. The incremental costs outweighed the benefits in monetary terms and the conclusion was therefore that epoetin alfa was less cost-effective than standard care with RBCT. Sheffield and colleagues[118] used a decision tree to model the costs and consequences of epoetin alfa use and concluded that epoetin alfa would be dominated by standard care with RBCT; that is, it would be more expensive and produce worse outcomes. Wilson and colleagues[2] highlighted several assumptions made that seemed implausible.

Update review

Objective

The objective of the update review was specified in the appraisal protocol (see www.crd.york.ac.uk/PROSPEROFILES/5812_PROTOCOL_20130824.pdf): this systematic review aims to update the systematic review of cost-effectiveness studies that was conducted in 2004 as part of the review of evidence to inform NICE's earlier guidance on these drugs (TA142).[1]

The review aimed to summarise the main results of past studies and identify any key economic costs and trade-offs relevant to the decision problem. It also aimed to indicate the strengths and weaknesses of different modelling approaches in this treatment area.

Therefore, data were extracted and studies quality assessed only for those economic evaluations or costing studies published since 2004 that are of relevance to the current decision problem.

Methods

Searches

Search strategies were designed by an information specialist (SB) and were based on the searches for clinical effectiveness evidence with additional terms to limit the results to economic evaluations (see *Appendix 1*). *Table 36* provides a summary of the databases searched. When possible, searches were limited to publications since 2004.

TABLE 36 Databases searched in the update review[a]

Database	Interface	Date range
MEDLINE	Ovid	1946 to May Week 3 2013
MEDLINE In-Process & Other Non-Indexed Citations	Ovid	To 28 May 2013
EMBASE	Ovid	1980 to Week 21 2013
NHS EED	The Cochrane Library	April 2013, Issue 2 of 4
Web of Science	Thomson Reuters	Searched 29 May 2013
CINAHL	EBSCO*host*	Searched 29 May 2013
OHE HEED	The Cochrane Library	Searched 29 May 2013

OHE HEED, Office for Health Economics Health Economic Evaluations Database.
a A date filter term was used to specify publication date from 2004 (except for OHE HEED).

In addition, supplementary searches not limited to cost-effectiveness were conducted in the following databases on 24–30 May 2013 (see *Appendix 1*):

- CDSR (via The Cochrane Library): April 2013, Issue 4 of 12
- DARE and HTA database (via The Cochrane Library): April 2013, Issue 4 of 12
- HMIC (via Ovid): 1979 to March 2013.

Screening

Inclusion and exclusion criteria were the same as for the clinical effectiveness systematic review (see *Chapter 3*, *Eligibility criteria*), with the following exceptions (as specified in the appraisal protocol):

- non-randomised studies were included (e.g. decision model-based analyses or analyses of patient-level cost and effectiveness data alongside observational studies)
- full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost–consequence analyses were included (economic evaluations that reported only average cost-effectiveness ratios were included only if the incremental ratios could be easily calculated from the published data)
- stand-alone cost analyses based in the UK NHS were also sought and appraised.

For the purpose of this review, 'administered in accordance with licensed indications' was taken to mean the frequency of administration but not the dose quantity. Licences allowed for all ESAs to be administered weekly, for darbepoetin alfa to be administered every 3 weeks, for epoetin alfa and epoetin zeta to be administered three times a week and for epoetin beta to be administered three to seven times a week. Fixed dosages and weight-based dosages were allowed; this is a different application of the licence from that in the systematic review of clinical effectiveness evidence (see *Changes from the protocol*).

Titles and abstracts were screened for relevance by two reviewers (NH and TS), with disagreements resolved by discussion. Full texts were retrieved for references judged to be relevant and these were screened for eligibility by the same reviewers, with disagreements resolved by discussion.

The bibliographies of review articles not judged to be eligible for inclusion were examined by one reviewer (TS) to identify other potentially relevant references. These references were retrieved and checked for eligibility in the same way as full texts from the database searches.

Data extraction

Study characteristics and results were abstracted by one reviewer (TS) using a template adapted from the systematic review by Wilson and colleagues.[2] In addition, parameters that could be used in the construction of an independent economic model were identified and noted.

Selection of studies for detailed appraisal and reporting

Data extraction was conducted for all included studies but, for reasons of expediency, not all studies that were eligible according to the inclusion and exclusion criteria were selected for detailed appraisal and reporting. Instead, only systematic reviews ($n = 2$) and cost–utility studies ($n = 3$) were selected for detailed appraisal and reporting. Data extraction for these studies was checked by a second reviewer (HC).

Quality appraisal

Selected studies (all new systematic reviews and cost–utility studies) were quality assessed by one reviewer (TS) using the checklist developed by Evers and colleagues.[119] In line with the instructions accompanying the final checklist, when there was insufficient information available in the article to assess the quality of an item, the item was marked 'no'. In contrast to the previous review there was no attempt to assign scores to studies on the basis of the quality appraisal checklist.

When studies were based on decision models they were further quality assessed using the checklist developed by Philips and colleagues.[120]

Analysis

The results of the included studies were qualitatively analysed on the basis of visual inspection of the tabulated extracted data. Draft conclusions were drawn by one reviewer (TS) and scrutinised by all authors from PenTAG.

Changes from the protocol

For the purpose of the cost-effectiveness review, 'administered in accordance with licensed indications' was taken to mean the frequency of administration but not the dose quantity or calculation (i.e. fixed and weight-based doses were accepted). Had the same criteria been used as for the systematic review of clinical effectiveness evidence then several cost–utility analyses would have been excluded:

- Cremieux and colleagues,[115] Fagnoni and colleagues[121] and Tonelli and colleagues[88] would have been excluded for using fixed doses
- the Roche and Ortho Biotec submissions would have been excluded as the doses were not reported in Wilson and colleagues[2]
- the de novo analysis in Wilson and colleagues[2] would have been excluded as doses were not reported.

Given the importance of the above studies to the conclusions of this review, it appears reasonable to have not included dose quantity or calculation method in the assessment of study eligibility for the cost-effectiveness review.

At the full-text screening stage only one study was excluded for using an unlicensed dosing schedule; the study by Glaspy and colleagues,[122] which was published only as an abstract, used darbepoetin alfa once every two weeks.

Data extraction was conducted for all included studies, but only a subset of studies (systematic reviews and cost–utility studies) was selected for detailed appraisal and reporting. This change was to ensure that efforts were focused on the studies that were most relevant to the appraisal given the significant number of non-quality-adjusted life-year (QALY) outcomes of limited utility to decision-makers attempting to maximise the total health benefit across health-care spending. This resulted in the exclusion of 12 studies in abstract form only (characteristics and results of these studies are provided in *Appendix 14*) and six studies in full paper form (for characteristics and results of these studies see the following section).[9,123–127] Also, the monograph by Wilson and colleagues[2] and TA142[1] were not considered as part of the update review.

Results

Figure 25 shows the study flow diagram for this update review. The electronic database searches for cost-effectiveness evidence identified 1131 records and the supplementary searches identified 32 records. After deduplication 843 records remained, all of which were screened by title and abstract. Of these, 47 were identified for full-text screening and 43 full texts were retrieved and assessed for eligibility. The bibliographies of six reviews[128–133] (which were excluded as they were not deemed to be systematic) were examined by one reviewer (TS) and a further seven records were identified for full-text screening, of which six were retrieved. A total of five records could not be retrieved.

One study by Roungrong and colleagues,[134] a cost–utility analysis of epoetin alfa for cancer patients with anaemia in Thailand, could not be obtained. The Centre for Reviews and Dissemination produced a critical appraisal of the study for NHS EED,[135] which revealed that the study was generally well conducted except for the limited reporting of clinical data sources and that it concluded that epoetin alfa would not be a cost-effective alternative to standard care with RBCT.

Three studies published in 1997/1998 also could not be obtained, one of which was by Sheffield and colleagues[118] and was included in the previous systematic review by Wilson and colleagues.[2] Of the other two studies, one appears to be a conference abstract of a cost–utility study[136] and the other appears to be a full paper but is likely to be a review rather than a primary study.[137]

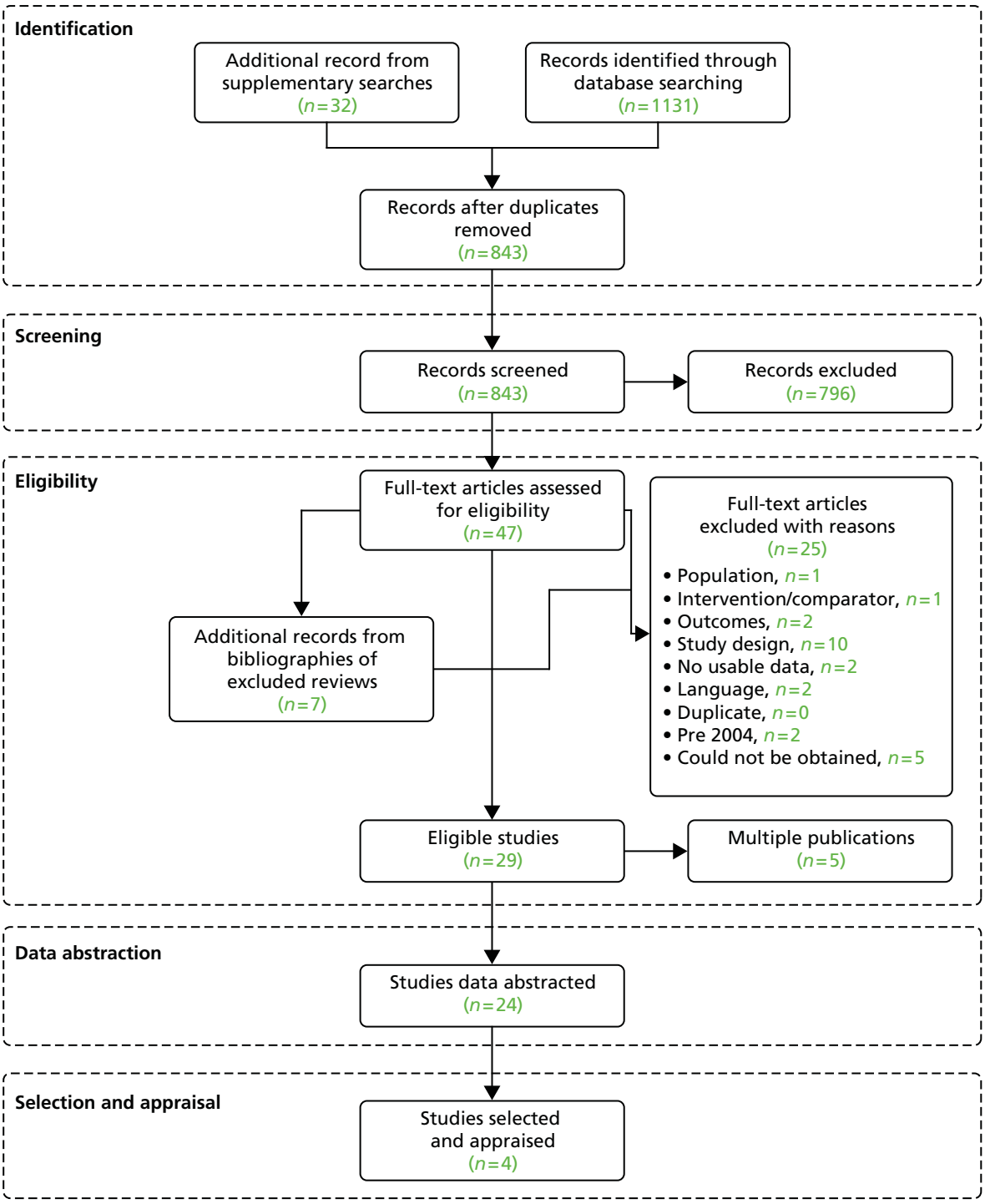


FIGURE 25 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of update review.

Finally, one conference abstract by Malonne and colleagues[138] could not be obtained, although the title suggests that this study may have evaluated only costs.

Of the full texts assessed for eligibility, 29[1,2,123,127,139–158] were deemed to meet the eligibility criteria. The reasons for exclusion after full-text screening are detailed in *Appendix 15*. Five texts[123,139–142] were deemed to be multiple publications, including four abstracts and a peer-reviewed journal paper by Klarenbach and colleagues[142] deemed to be a multiple publication of the Canadian Agency for Drugs and Technologies in Health technology assessment report by Tonelli and colleagues[88] (see *Appendix 16*), leaving 24 primary studies[2,1,124–127,143–158] from which data were abstracted. Twelve primary publications were conference abstracts,[143–154] three were or included systematic reviews[2,88,155] and two were related to the previous NICE appraisal.[1,2] The results of Wilson and colleagues,[2] which informed TA142,[1] are discussed in *Chapter 1* (see *Existing systematic reviews of effectiveness*) and, although not appraised as a part of this update review, the results are considered as conclusions are drawn.

Summary tables of study characteristics, key parameters and findings for the abstracts are provided in *Appendix 14*. (See *Tables 44–46* for summary tables of the study characteristics, key parameters and findings for the full papers.)

Of the eligible studies, four[88,121,155,156] were selected for detailed appraisal. These consisted of one stand-alone systematic review by Duh and colleagues[155] and three new cost–utility studies,[88,121,156] of which one also contained a systematic review.[88]

Summaries of the identified systematic reviews

Duh and colleagues[155] Duh and colleagues[155] conducted a systematic review of the medical literature to identify cost and cost-effectiveness studies of epoetin alfa, epoetin beta and darbepoetin alfa. MEDLINE and 'all other PubMed databases' were searched from January 2000 to April 2007 for English-language references with human subjects and combinations of the following sets of terms:

- intervention terms: epoetin, darbepoetin, Procrit®, Aranesp, Epogen®, erythropoietin, erythropoietic agent
- outcome terms: cost, effectiveness, pharmacoeconomic.

It is notable that the authors did not include studies comparing ESAs with standard care not including ESA therapy.

The authors identified 67 studies in the field of oncology, in addition to 39 in the field of chronic kidney disease (CKD) and 46 in other areas. We report only the aspects of the report relating to oncology. Ten of the 67 studies were selected for review and a further nine studies were identified through conferences (meetings of ASCO, ASH, European Society for Medical Oncology and European Hematology Association in the period 2003–6) or bibliographies to give a total of 19 studies reviewed.

The authors appear to have conducted some limited critical appraisal, although no specific critical appraisal tool appears to have been used. A narrative synthesis was conducted using textual descriptions and tabulation.

All 19 studies identified compared epoetin alfa with darbepoetin alfa, with three studies additionally including epoetin beta as a comparator. No evaluations included standard care without ESA therapy as a comparator.

Various outcome measures were used and in five studies no effectiveness measures were reported. No cost–utility studies (i.e. studies with QALYs as the outcome measure) were identified.

Cost ratios are presented for all but one study and suggest that epoetin alfa is cheaper than darbepoetin alfa in most cases, although the authors acknowledge that many studies do not include costs other than drug acquisition costs.

Cost-effectiveness results were not always presented when effectiveness outcomes were listed as being included; only measures of drug costs were given for nine of the fourteen studies with listed effectiveness outcomes, and in all five studies in which cost-effectiveness results were presented epoetin alfa has a lower average cost-effectiveness ratio than darbepoetin alfa.

The authors made a number of arguments that seemed to be designed to undermine the results from existing cost–utility studies that produced incremental cost-effectiveness ratios (ICERs) above cost–utility thresholds, notably:

- The studies are outdated and corresponding changes in pricing and practice patterns, as well as emerging clinical effectiveness evidence, should be considered.
- ESAs approach acceptable cost–utility thresholds only when a survival benefit is assumed. As a survival benefit is not a 'main outcome' of ESA therapy and such benefits are uncertain, cost–utility results 'may be best used to augment evidence from studies that measure costs and effectiveness separately' (pp. 115–16).[155]

The authors also suggested that cumulative changes in Hb levels are more relevant for payers than overall responses at a particular point in time, suggesting that failing to use cumulative measures will underestimate the value of epoetin alfa, which it is claimed achieves a response more rapidly than darbepoetin alfa (the authors cited an earlier publication sharing two authors with the systematic review, including the primary author).

The authors acknowledged that financial support was provided by Ortho Biotec (manufacturers of epoetin alfa), who provided editorial review and approval of the manuscript. There was inconsistent reporting of study results, which may have biased the apparent results in favour of epoetin alfa.

Tonelli and colleagues[88] Tonelli and colleagues[88] conducted a systematic review of the medical literature and health economic literature to identify economic evaluations of ESAs in adult patients with malignancy and anaemia. MEDLINE, EMBASE, EconLit and NHS EED were searched on 11–21 October 2007 using search strategies listed in an appendix.

Studies were included if they met the following criteria (reproduced verbatim as permitted):[88]

- *Evaluated the incremental impact of an ESA against a comparator group on relevant costs and health outcomes*
- *Included one of the following in the comparator group: placebo, no therapy with ESAs, different ESA or same ESA but varying hemoglobin target, dose or schedule*
- *Included (in a cost-minimization analysis) comparisons of different ESAs or comparisons of alternative route or schedule of administration of ESAs to achieve a similar hemoglobin target, only if based on RCT data for effectiveness*
- *Examined a cohort of adult patients with malignancy and anemia*

Included studies were quality appraised using a checklist adapted from the literature and relevant data (including industry funding) were extracted.

A qualitative synthesis of included studies was planned as a small number of studies was expected.

The combined searches produced 1134 citations, of which 58 were identified for full-text scrutiny. Forty-seven studies were excluded, leaving 11 primary studies included in the systematic review.

Five of the 11 studies were cost–utility analyses:

- the HTA review by Wilson and colleagues[2] was carried out for the previous NICE appraisal
- the study by Fagnoni and colleagues[121] was also identified in this update review
- the studies by Martin and colleagues,[116] Cremieux and colleagues[115] and Barosi and colleagues[114] were all included in the systematic review reported by Wilson and colleagues.[2]

Quality appraisal of these studies demonstrated that none met all of the quality criteria but all met most of the quality criteria.

A narrative review identified that only one study[116] reported an attractive incremental cost–utility ratio. Tonelli and colleagues[88] noted that this was an industry-sponsored study and that a subgroup of RCT patients with stage IV breast cancer who demonstrated a survival advantage with epoetin use (although this survival advantage did not reach statistical significance) was identified to inform the model; the favourable cost-effectiveness results did not remain when the whole population of the RCT was used instead.

The six non-cost–utility studies were:

- a discrete choice experiment by Ossa and colleagues[159] to ascertain the utility of anaemia-related health states and the willingness to pay for epoetin alfa
- a model-based cost-effectiveness analysis by Borget and colleagues[157] of darbepoetin alfa compared with standard care without ESA use in patients with lung cancer, with an effectiveness measure related to the final Hb level achieved
- a cost–consequences analysis by Reed and colleagues,[160] based on an open-label RCT of epoetin alfa once weekly and darbepoetin alfa every 2 weeks in patients with solid malignancies
- a study by Casadevall and colleagues[161] of epoetin and recombinant human granulocyte colony-stimulating factor and supportive care in patients with myelodysplastic syndrome (this was excluded from this review because of concomitant treatment with G-CSF)
- the studies by Ortega and colleagues[117] and Sheffield and colleagues,[118] both identified in the systematic review reported by Wilson and colleagues.[2]

Tonelli and colleagues[88] noted in their discussion that ESA use leads to large incremental costs that do not tend to be significantly altered across a range of costs for RBCT. They noted that, when health outcomes were converted to a common metric (QALYs for cost–utility analyses, costs for cost–benefit analyses), most of the base-case analyses indicated that ESAs were not a cost-effective use of health resources.

Tonelli and colleagues[88] identified that the lack of preference-based utility scores from RCTs was a weakness and that, even with many opportunities for confounding and bias, which could favour ESA use, nevertheless, most studies produced unfavourable estimates of cost-effectiveness.

Characteristics of the new cost–utility studies

Fagnoni and colleagues[121] In this study the authors retrospectively identified 192 consecutive breast cancer patients receiving either of two standard adjuvant chemotherapy regimens between 1999 and 2004, of whom 91 were treated before the use of epoetin was allowed (1999–2001) and 101 could have received epoetin (2002–4). Patients were excluded if their disease progressed during the 22-week study period or if they failed to complete the chemotherapy course within the study period. A cost–utility analysis was conducted from a health-care perspective by modelling costs and quality of life for patients in the study according to individual patient records.

Per-patient costs were calculated by extracting resource use from individual patient computerised records and applying unit costs (see *Table 42*). All costs were in euros at 2004 prices. Exact doses administered were recorded and priced. An official tariff was used for the cost of blood transfusions per RBCT unit.

Blood transfusions were recorded separately but were also accounted for in hospitalisation costs. Thus, to avoid double counting, RBCT costs that had been collected for each patient were removed from this per diem cost.

Quality of life was modelled as a function of Hb level, according to the Linear Analogue Scale Assessment (LASA) methodology described by Crawford and colleagues.[162] Hb levels were measured at least every 3 weeks (i.e. at least once per chemotherapy cycle). The lowest Hb level measured was taken as the Hb level for each chemotherapy cycle.

Four sensitivity analyses were conducted. In the first, different methodologies were explored for modelling quality of life as a function of Hb level. In the second, unit costs were all scaled up or down by 30%. In the third, subgroups were identified by age or chemotherapy regimen. In the fourth, indirect costs relating to sick leave were included, reducing the population to those initially active and for whom French public health insurance data were available.

Borg and colleagues[156] In this study the authors constructed an economic model based on the model presented by Wilson and colleagues[2] to evaluate the cost–utility (measured in euros or Swedish kronor per QALY) of epoetin alfa compared with RBCT.

Two epoetin alfa strategies were included, in both of which RBCTs were given and epoetin alfa treatment was initiated if the Hb level fell below 10 g/dl. In the first epoetin alfa strategy, called EPO_{LOW}, patients received epoetin alfa until they reached a target Hb level of 12 g/dl (reflecting Swedish treatment guidelines at the time of writing). In the second epoetin alfa strategy, called EPO_{HIGH}, the target Hb level was 13 g/dl (reflecting earlier Swedish treatment guidelines). Patients responding to epoetin alfa were classed as responders and did not discontinue epoetin alfa until the target Hb was reached. Patients not responding were treated with epoetin alfa for two chemotherapy cycles (each 4 weeks) before being discontinued. No dose doubling was included in the base-case analysis.

Three RBCT strategies were included, with trigger Hb levels of 9, 10 and 11 g/dl for transfusion of 2 units of RBCs.

After chemotherapy cessation (six treatment cycles of 4 weeks each), Hb levels normalise to 13 g/dl at a rate of 1 g/dl per 4 weeks.

The effectiveness of epoetin alfa in achieving a Hb response was estimated by calibrating to a study in which doses were doubled if a response was not achieved within 4 weeks, with some adjustment (perhaps arbitrary) to remove the impact of dose doubling.

A health-care perspective was adopted and the following costs were included: drug acquisition, nurse-led hospital oncology clinic (one-off drug administration for epoetin alfa), acquisition of filtered RBCs and RBCT administration. Unit costs for drug acquisition were derived from Pharmaceutical Specialities in Sweden [Farmaceutiska Specialiteter i Sverige (FASS); it is not clear whether these are list prices or acquisition prices]; other unit costs were derived from the price list of the Swedish Southern Health Care Region for 2007.

Utilities were mapped from Hb levels using data from Wilson and colleagues.[2]

Tonelli and colleagues[88] In this study the authors constructed an economic model to examine the cost–utility of ESA use in adults matching those enrolled in trials of ESAs for the treatment of anaemia related to cancer.

The economic model consisted of two submodels, one representing the 15 weeks during which ESAs are administered in RCTs and another representing the following year, during which the impact of ESAs on long-term survival is assessed.

Inputs for the model were drawn from a systematic review of clinical effectiveness evidence conducted by the authors and included:

- quality-of-life improvement (calculated using a relationship between Hb levels and HRQoL)
- Hb level improvement from baseline to the end of the trial period
- reduction in RBC units transfused
- short-term mortality (within 15 weeks)
- long-term mortality (within 1 year).

Although an increase in all AEs was found in the systematic review of clinical effectiveness, this was not included in the base-case analysis because of the heterogeneous nature of these AEs and the lack of data regarding resource utilisation and the costs of these AEs.

A health-care perspective was adopted and costs were included for:

- ESA acquisition (epoetin alfa in the base case, darbepoetin alfa in a scenario analysis)
- RBCT (acquisition and administration).

In the base-case analysis, gains in Hb level for patients receiving ESA therapy over patients not receiving ESA therapy were assumed to be instantaneous (acting in favour of ESA cost-effectiveness) but the gains were not assumed to persist beyond the 15 weeks of the RCTs (i.e. instantaneous normalisation, acting against the cost-effectiveness of ESA therapy). In a scenario analysis the gains were assumed to persist for an additional 11 weeks.

Quality of the new cost–utility studies

The quality appraisal checklist developed by Evers and colleagues[119] was applied to the three new cost–utility studies (*Table 37*). None of the studies reported the use of discounting, although, given the short time horizons used, discounting would have been unlikely to materially affect the results. All three studies performed an incremental analysis and included some sensitivity or scenario analyses, but only that by Tonelli and colleagues[88] was judged to have included sensitivity analyses of all important variables. No study produced a probabilistic sensitivity analysis (PSA).

In addition, the quality appraisal checklist developed by Philips and colleagues[120] was applied to the two new model-based cost–utility studies (*Table 38*). The reviewer (TS) believes that the only item for which quality was not indicated that would materially affect the conclusions is that Borg and colleagues[156] did not subject many of the key parameters, the values of which were uncertain, to sensitivity analyses.

Key parameters of all cost–utility studies

Erythropoietin-stimulating agent dosage ESA dosing strategies vary significantly in the literature (*Table 39*) in terms of:

- start dose (fixed or weight based)
- trigger Hb level (i.e. the point below which ESAs should be administered)
- target Hb level (i.e. the point above which ESAs should be stopped or titrated)
- dose escalation (sometimes used if patients do not achieve a haematological response within a specified time period)
- ESA abandonment for persistent non-responders
- duration of continued ESA use following chemotherapy cessation.

TABLE 37 Quality appraisal of the new model-based cost–utility studies using the checklist developed by Evers and colleagues[119,163]

Item	Fagnoni and colleagues[113]	Borg and colleagues[145]	Tonelli and colleagues[114]
1. Is the study population clearly described?	Yes	Yes	Yes
2. Are competing alternatives clearly described?	Yes	Yes	Yes
3. Is a well-defined research question posed in an answerable form?	Yes	Yes	Yes
4. Is the economic study design appropriate to the stated objective?	Yes	Yes	Yes
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	No	Yes	No
6. Is the actual perspective chosen appropriate?[a]	Yes	Yes	Yes
7. Are all important and relevant costs for each alternative identified?	No	Yes	No
8. Are all costs measured appropriately in physical units?	Yes	Yes	Yes
9. Are costs valued appropriately?	No	Yes	Yes
10. Are all important and relevant outcomes for each alternative identified?	No	Yes	Yes
11. Are all outcomes measured appropriately?	Yes	Yes	Yes
12. Are outcomes valued appropriately?	Yes	Yes	Yes
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes	Yes
14. Are all future costs and outcomes discounted appropriately?	No	No	No
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	No	No	Yes
16. Do the conclusions follow from the data reported?	Yes	Yes	Yes
17. Does the study discuss the generalisability of the results to other settings and patient/client groups?	No	No	Yes
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	No	No
19. Are ethical and distributional issues discussed appropriately?	No	No	Yes

a For this decision problem, a health-care perspective was deemed to be appropriate.

TABLE 38 Quality appraisal of the new model-based cost–utility studies using the checklist developed by Philips and colleagues[120]

Item	Borg and colleagues[145]	Tonelli and colleagues[114]
Structure (S)		
S1: Statement of decision problem/objective	No	Yes
S2: Statement of scope/perspective	Yes	Yes
S3: Rationale for structure	No	No
S4: Structural assumptions	No	Yes
S5: Strategies/comparators	No	No
S6: Model type	Yes	Yes
S7: Time horizon	Yes[a]	No
S8: Disease states/pathways	Yes	Yes
S9: Cycle length	No	NA
Data (D)		
D1: Data identification	No	Yes
D2: Pre-model data analysis	(No)[b]	(Yes)[b]
D2a: Baseline data	Yes	Yes
D2b: Treatment effects	No	Yes
D2c: Quality of life weights (utilities)	Yes	Yes
D3: Data incorporation	Yes	No
D4: Assessment of uncertainty	(No)[b]	(No)[b]
D4a: Methodological	No	Yes
D4b: Structural	No	Yes
D4c: Heterogeneity	No	Yes
D4d: Parameter	No	No
Consistency (C)		
C1: Internal consistency	No	Yes
C2: External consistency	Yes	Yes

a Assuming no survival benefit from ESAs.
b Summary responses for the subresponses [i.e. '(Yes)' if all below are 'Yes' or '(No)' if any below are 'No'].
Source: reproduced from Philips and colleagues,[120] covered by the UK government's non-commercial license for public sector information. URL: www.nationalarchives.gov.uk/doc/non-commercial-government-licence/non-commercial-government-licence.htm.

TABLE 39 Dosage in primary cost–utility analyses

Study	Start dose	Trigger Hb level (g/dl)	Target Hb level (g/dl)	Dose escalation	ESA abandonment	Duration of continued use
Barosi 1998[114]	Epoetin alfa Q3W: 150 IU/kg	10.7	None	None	None	NR
Cremieux 1999[115]	Epoetin alfa Q3W: 10,000 IU	NR	None	None	None	None
Martin 2003[116]	Epoetin alfa Q3W: 150 IU/kg	10.5	None	Dose doubled after 4 weeks (no further details)	NR	4 weeks (expected)
Amgen Inc. model[2]	Darbepoetin alfa QW: 2.25 µg/kg	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
Ortho Biotec model[2]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
Roche model[2]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
Wilson 2007[2]	Not clear	13	13[b]	None	12 weeks	NR
Fagnoni 2006[121]	Epoetin alfa QW: 40,000 IU	11.5	NR	Dose doubled if no response after 6 weeks	12 weeks	NR
Borg 2008[156]	Epoetin alfa Q3W: 150 IU/kg	10	12	None	8 weeks	NR[c]
Tonelli 2009[88]	Epoetin alfa QW: 42,148 IU	None[d]	None	None	None	NR

NR, not reported; QW, once weekly; Q3W, once every 3 weeks.
a Not reported in Wilson and colleagues.[2]
b Half-dose was assumed if Hb = 12–13 g/dl.
c A possible interpretation is that use was continued until target Hb level reached.
d In the base case patients were assumed to start with a Hb level of 10.3 g/dl.

These aspects of dosing will potentially affect clinical effectiveness (see *Chapter 3*, *Dose*, and *Appendix 9*) and will almost certainly affect cost-effectiveness.

Start doses were generally well reported and were broadly consistent with licensed doses. Trigger Hb levels were not always reported and varied from 10 g/dl in Borg and colleagues[156] to 13 g/dl in Wilson and colleagues.[2] The target Hb level was reported in only two studies and was 13 g/dl in Wilson and colleagues[2] and 12 g/dl in Borg and colleagues.[156]

Dose escalation was included in the analyses by Martin and colleagues[116] and Fagnoni and colleagues;[121] in both cases the dose was doubled, after 4 and 6 weeks of inadequate response, respectively. Dose escalation may improve clinical effectiveness, but it adds costs, which may lead to an overall worsening of cost-effectiveness (indeed, Borg and colleagues[156] found that dose doubling was not cost-effective relative to non-escalated dosing).

Abandonment of ESA therapy was included in the analyses by Wilson and colleagues[2] at 12 weeks, Fagnoni and colleagues[121] at 12 weeks and Borg and colleagues[156] at 8 weeks. Abandoning ESA therapy for non-responders is likely to improve cost-effectiveness; as such, patients are unlikely to benefit from further therapy that would incur significant costs. Earlier abandonment may improve the cost-effectiveness of ESA therapy.

Continuation of ESA therapy following chemotherapy cessation was explicitly reported only in the study by Martin and colleagues,[116] in which patients were expected to receive ESA therapy for 4 weeks following chemotherapy cessation, although delays in chemotherapy treatment would reduce the duration of continued use. Continuation of ESA therapy is allowed for in ESA licenses up to 4 weeks, which could hasten the return to normal Hb levels for patients receiving ESAs and increase the QALY benefit estimated to arise in the normalisation period.

Impact of erythropoiesis-stimulating agent use on utility/health-related quality of life

The impact of ESA use on utility or HRQoL in all of the cost–utility studies is shown in *Table 40*.

All cost–utility studies except that by Martin and colleagues[116] included an improvement in utility or HRQoL as a result of ESA use. Several studies (those published most recently) estimated utility or HRQoL as a function of Hb level and therefore indirectly estimated the impact of ESA use on utility or HRQoL by estimating the impact of ESA use on Hb levels. Fagnoni and colleagues[121] estimated the impact of Hb level on quality of life as measured by LASA. Barosi and colleagues[114] and Cremieux and colleagues[115] both estimated the impact of ESA use on HRQoL directly.

TABLE 40 Methods for short-term QALY estimation in primary cost–utility analyses

Study	Utility/HRQoL estimation method	Utility profile over time
Barosi 1998[114]	Baseline HRQoL from Glaspy and colleagues[164] adjusted according to Abels[165] (visual analogue scale)	Instantaneous improvement (not explicitly stated)
Cremieux 1999[115]	HRQoL reported by randomised placebo-controlled trial patients (LASA method)[63]	Not clear
Martin 2003[116]	NA[a]	NA
Amgen Inc. model[2]	Hb level (six levels) mapped to utility using unpublished data from Amgen Inc. study (EQ-5D data from Phase III active controlled darbepoetin alfa trial; data collected weekly from around 100 patients over 16 weeks)[2]	Gradual improvement[2]
Ortho Biotec model[2]	Hb level (four levels) mapped to utility using unpublished data from Ortho Biotec study (TTO from community values of different levels of fatigue)[2]	NR[b]
Roche model[2]	Hb level (four levels) mapped to utility using unpublished data from Roche study (TTO study of general population)[2]	Hb levels from RCTs[c]
Wilson 2007[2]	Hb level (seven levels) mapped to utility using unpublished data provided by Ortho Biotec	Gradual improvement for responders
Fagnoni 2006[121]	Hb level (11 levels ever experienced by patients) mapped to HRQoL (LASA) following Crawford and colleagues[155]	Clinical study
Borg 2008[156]	Hb level (seven levels) mapped to utility following Wilson and colleagues[2]	Gradual improvement for responders
Tonelli 2009[88]	Hb increment linearly mapped to utility following Ossa and colleagues[159]	Instantaneous improvement

NR, not reported; TTO, time trade-off.
a ESA use is assumed to have no impact on quality of life; QALY benefits are obtained through improved survival for patients receiving ESAs.
b Not reported in Wilson and colleagues.[2]
c As reported by Wilson and colleagues.[2]

It was not always clear whether the impact of ESA use on utility/HRQoL was instantaneous. Wilson and colleagues[2] and Borg and colleagues[156] explicitly modelled the proportion of patients in different Hb levels over time. This approach results in a gradual improvement in utility for patients responding to ESA treatment. A gradual improvement in utility is also seen in the Amgen Inc. model in the previous NICE appraisal.[2] Tonelli and colleagues explicitly stated that the improvement in Hb levels, and hence utility, was assumed to be instantaneous (which acts in favour of ESA use in their analysis). Fagnoni and colleagues[121] mapped the Hb levels of patients in a retrospective observational study to HRQoL, hence the improvement in Hb levels was translated exactly into HRQoL improvement.

Normalisation Normalisation is the process of Hb recovering to normal levels following chemotherapy cessation. This was explicitly modelled in all three submissions in the previous NICE appraisal, as reported by Wilson and colleagues.[2] Wilson and colleagues[2] also included normalisation in their base-case analysis, although they assumed a slightly faster reversion to normal Hb levels. Borg and colleagues[156] followed the model design of Wilson and colleagues[2] and, as a result, used the same rate of recovery (*Table 41*).

Earlier studies did not include normalisation. Fagnoni and colleagues[121] produced a cost–utility analysis based on a retrospective observational study in which patients were followed up for up to 7 weeks following chemotherapy cessation. If normalisation did occur it would have been measured and included in the analysis, but there is no mention of normalisation in the text. Tonelli and colleagues[88] did not assume normalisation in their base-case analysis, but in a sensitivity analysis they extended the utility benefit of ESA use for 11 weeks after chemotherapy cessation. No explicit rate of normalisation or normal Hb level was defined.

In general, assuming a slower rate of normalisation or a higher 'normal' Hb level favours ESA use.

None of the studies explicitly stated whether or for how long ESA treatment was continued beyond chemotherapy cessation, which could impact on the rate of normalisation as well as increase costs.

Drug acquisition costs The drug acquisition costs for ESAs would be expected to have a significant impact on the cost-effectiveness of ESAs given that these costs tend to account for the majority of the total incremental costs. The quality of reporting with regard to drug acquisition costs was variable, notably with Wilson and colleagues[2] reporting cost per dose rather than unit costs for epoetin alfa and epoetin beta (*Table 42*). None of the studies appears to be an outlier with regard to drug acquisition costs, but it is notable that the current NHS list prices appear to be lower than the prices used in the UK studies and that pharmacies may reasonably be expected to obtain some discount on list prices.

TABLE 41 Normalisation in primary cost–utility analyses

Study	Time frame for normalisation	Rate of normalisation (g/dl/week) (slower rate favours ESA use)	Normal Hb level (g/dl) (higher level favours ESA use)	Duration of continued ESA use
Amgen Inc. model[2]	12 weeks	0.1	NR[a]	NR[a]
Ortho Biotec model[2]	Overall time frame 36 months	0.2	13	NR[a]
Roche model[2]	NR in Wilson and colleagues[2]	0.2	Solid tumours: 13; haematological tumours: 11.9	NR[a]
Wilson 2007[2]	NR	0.25	13	NR
Borg 2008[145]	32 weeks	0.25	13	NR

NR, not reported.
a Not reported in Wilson and colleagues.[2]

TABLE 42 Drug acquisition unit costs in primary cost–utility studies

Study	Price year, currency	Epoetin alfa (per 1000 IU)	Epoetin beta (per 1000 IU)	Darbepoetin alfa (per µg)
Barosi 1998[114]	NR, US dollars	≈10.00	–	–
Cremieux 1999[115]	1997, US dollars	9.50	–	–
Martin 2003[116]	2000, UK pounds	8.38	–	–
Amgen Inc. model[2]	NR[a]		–	1.68
Ortho Biotec model[2]	NR[a]	83.30 per dose (Q3W)	–	–
Roche model[2]	NR[a]		83.80 per dose (Q3W)	–
Wilson 2007[2]	NR, UK pounds	83.30 per dose (Q3W)	83.80 per dose (Q3W)	1.68
Fagnoni 2006[121]	2004, euros	8.90	–	–
Borg 2008[156]	2007, euros[b]	10.55	–	–
Tonelli 2009[88]	2008, Canadian dollars	14.40	–	2.88
NHS list price[166]	2013, UK pounds	Eprex: 5.53; Binocrit: 5.09	7.01	1.47

NR, not reported; Q3W, once every 3 weeks.
a Not reported in Wilson and colleagues.[2]
b Calculated from the cost in Swedish kronor per IU of epoetin alfa.

Results of all cost–utility studies

Table 43 compares the base-case results across the cost–utility studies identified in this review. More detailed reporting of the results is provided in the following sections.

Barosi and colleagues[114] The combination of improved quality of life and reduced risk from blood-borne diseases transmitted through RBCTs resulted in a gain of 0.023 QALYs (8.4 quality-adjusted life-days) at an additional cost of US$4362, resulting in an ICER of US$190,000 per QALY.

Various sensitivity analyses were considered, including varying the risk of blood-borne infections, extending survival for cancer patients to match the general population life expectancy, adjusting patient age and varying the quality of life improvement from ESA use, of which most did not result in ICERs of < US$100,000 per QALY. If the ESA acquisition cost was reduced by 50% the ICER fell to < US$100,000 per QALY. A scenario analysis was considered in which all patients receiving ESAs had no RBCTs and anaemia was improved in all patients; for this the ICER remained high at US$146,000 per QALY. Using the base-case drug acquisition cost, ESA use was cost-effective (ICER < US$100,000 per QALY) only if used in patients who would be heavily transfused and could avoid at least 4.5 RBC units.

Cremieux and colleagues[115] Patients in the epoetin alfa arm accrued total costs of US$7551, whereas those in the standard care arm accrued total costs of US$1416. These costs included indirect costs for patients who needed to attend hospital three times weekly for epoetin alfa administration and for patients requiring transfusion. Opportunity costs accounted for US$723 in the epoetin alfa arm and US$176 in the standard care arm. Reduced transfusion usage in the epoetin alfa arm resulted in cost savings of US$428, but these were more than offset by epoetin alfa costs of US$6563. Drug acquisition was the most expensive resource, accounting for US$4560 in the epoetin alfa arm.

Analysis of the data using cumulative Hb gains yielded a cumulative effectiveness measure of 21.0 for the epoetin arm and 3.2 for the standard care arm, giving an incremental effectiveness of 17.8 (units g/dl/week).

TABLE 43 Base-case results for all cost–utility studies

Study	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY)
Barosi 1998[114]	Epoetin alfa: US$4568; no ESA: US$206		+US$4362	+0.023	US$190,000
Cremieux 1999[115]	Epoetin alfa: US$7551; no ESA: US$1416	No base case	+US$6135	No base case	US$111,000–US$214,000
Martin 2003[116]	Epoetin alfa: £10,768; no ESA: £6515	Epoetin alfa: 1.0375; no ESA: 0.5570	+£4253	+0.4805	£8851
Amgen Inc. model[2] (short-term analysis)	Darbepoetin alfa: £3570; no ESA: £1156	Darbepoetin alfa: 0.0309; no ESA: 0.0146	+£2594	+0.0163	£159,000
Amgen Inc. model[2] (long-term analysis)	–	–	–	–	£23,600
Ortho Biotec model[2]	–	–	+£4021	–	£13,000
Roche model[2] (solid tumours)	–	–	+£3727	+0.132	£28,200
Roche model[2] (haematological tumours)	–	–	+£3510	+0.042	£83,700
Wilson 2007[2]	–	–	+£4450	+0.030	£150,000
Fagnoni 2006[121]	Epoetin alfa: €1649; no ESA: €34	–	+€1615	+0.0052	€311,000
Borg 2008[156]	Epoetin alfa: €3750; no ESA: €2881	Epoetin alfa: 0.5687; no ESA: 0.5334	+€870	+0.035	€24,700
Tonelli 2009[88] (short-term analysis)	–	–	+CA$8643	+0.03	CA$267,000
Tonelli 2009[88] (long-term analysis)	–	–	+CA$8643	–0.086	ESA use dominated by no ESA use

Quality of life was measured at baseline and at the end of the study using the LASA. Epoetin alfa patients gained 8.3 mm (the scale is 100 mm in length), whereas standard care patients lost 1.0 mm; therefore, the incremental effectiveness was 9.3 mm. Two methods were suggested for converting LASA measurements to 'utilities': the first assumed that a 9.3-mm gain would correspond to a 0.093 gain in utility; the second assumed that a 9.3-mm gain would correspond to a 0.184 gain in utility (based on the mean measurement of 50.6 mm). Neither of these methods actually produces a preference-based utility estimate. Using transfusion rates and cumulative doses from the RCT that provided the LASA measurements resulted in ICERs of $214,000 per QALY when the utility gain was assumed to be 0.093 and $111,000 per QALY when the utility gain was assumed to be 0.184.

Various sensitivity analyses were performed but in all the ICER was > $100,000 per QALY for epoetin alfa use.

Martin and colleagues[116] In the base-case analysis epoetin alfa use resulted in greater discounted mean costs (£10,768 vs. £6515; difference +£4253) and greater discounted mean QALYs (1.0375 vs. 0.5570; difference + 0.4805). The base-case ICER was £8851 per QALY.

The increased costs for epoetin alfa patients were a result of the epoetin alfa costs (£3995) and increased costs in the follow-up phase (because of greater time spent in the follow-up phase). Increased costs were partially compensated for by decreased costs in the active, supportive and terminal phases and a very small reduction in blood unit costs.

The difference in QALYs came about solely through improved survival; that is, there is no QALY gain from relieving the symptoms of anaemia. Patients receiving epoetin alfa accrued 0.5079 more QALYs in the follow-up phase, with very small reductions in QALYs in the active, supportive and terminal phases.

A joint sensitivity analysis was conducted by bootstrapping effectiveness and cost estimates from the RCT. This analysis demonstrated a 94% probability of cost-effectiveness at the £30,000-per-QALY threshold.

A number of scenario analyses were conducted in which the resulting ICER was < £30,000 per QALY. When all patients from the RCT (rather than only stage IV breast cancer patients) were used to estimate the effectiveness of epoetin alfa the ICER was £39,300 per QALY.

Fagnoni and colleagues[121] The authors state that 'The population studied in both groups had no difference in terms of clinical and therapeutic characteristics when one takes into account the evolution of the diagnostic diagrams and recommended treatment strategies between the two studied periods (1999–2001 and 2002–2004)' (p. 1032).[121] The initial Hb and haematocrit levels were very similar for both patient groups. The median number of Hb measurements per patient was the same ($n = 6$) for both groups.

In the possible use of treatment with epoetin alfa group, 46/101 (45.5%) participants actually received epoetin alfa. The mean Hb level at initiation of epoetin alfa treatment was 11.3 g/dl (range 9.4–12.5 g/dl). No RBCTs occurred in either group and a similar proportion of patients was hospitalised because of anaemia in both groups (2.0% in the possible use of treatment with epoetin alfa group vs. 2.2% in the no epoetin alfa group). On average, patients in the possible use of treatment with epoetin alfa group spent almost 6 weeks with a Hb level > 13.49 g/dl, whereas those in the no epoetin alfa group spent just over 3 weeks with a Hb level > 13.49 g/dl. Mapping Hb levels to quality of life resulted in an increase of 0.0052 QALYs after the introduction of epoetin alfa over the 22-week study period.

The average cost of epoetin alfa treatment was €1593 per patient. The average cost of hospitalisation was €56 per patient for the possible use of treatment with epoetin alfa group and €34 for the no epoetin alfa group, although this was not statistically significant. The base-case ICER was €311,000 per QALY.

None of the sensitivity analyses reduced the ICER for possible epoetin alfa treatment compared with no epoetin alfa treatment to < €160,000 per QALY. The different methodologies for estimating quality of life according to Hb level produced some differences in the QALY difference between the groups: using the relationship between Hb level and FACT-G resulted in the greatest QALY difference (0.0099 QALYs), whereas an alternative LASA methodology resulted in the smallest QALY difference (0.0046 QALYs). It should be noted that none of these HRQoL measures is preference based.

Borg and colleagues[156] The base-case comparison was between the epoetin alfa arm with a target Hb level of 12 g/dl and the RBCT arm with a trigger level of 10 g/dl (the same trigger level as in the epoetin alfa arm). Patients in the epoetin alfa arm were estimated to incur total costs of €3750, whereas those in the RBCT arm were expected to incur total costs of €2881 (difference +€870). The additional cost of epoetin alfa (€2054) was partially compensated for by savings in RBCT costs (€1185). Patients were expected to accrue 0.5687 QALYs in the epoetin alfa arm and 0.5334 QALYs in the RBCT arm (difference +0.0353 QALYs). The base-case ICER was €24,700 per QALY.

A scenario analysis was conducted in which the rate of normalisation was doubled from 1 g/dl per 4-week model cycle to 2 g/dl per cycle; the resulting ICER (epoetin alfa vs. RBCT) was €29,500 per QALY.

Another scenario analysis was conducted, in which patients not responding to epoetin alfa after 4 weeks had their dose doubled; the resulting ICER (epoetin alfa double dose vs. standard epoetin alfa dose) was €136,900 per QALY.

An epoetin alfa strategy with a higher target Hb level of 13 g/dl was more expensive than the base-case epoetin alfa strategy (+€609) but generated very little benefit (+0.0018 QALYs), resulting in an ICER of €336,500 per QALY.

Red blood cell transfusion strategies with trigger levels of 9 g/dl and 11 g/dl were also considered. An increased trigger level led to increased costs and QALYs. With a trigger level of 9 g/dl, RBCT cost €2360 and resulted in 0.4948 QALYs. With a trigger level of 11 g/dl, RBCT cost €3340 and resulted in 0.5605 QALYs. All strategies were on the cost-effectiveness frontier (i.e. no strategies were dominated or extendedly dominated); therefore, if RBCT with a trigger level of 11 g/dl was to be considered a valid comparator, the ICER for epoetin alfa would be €50,000 per QALY.

Tonelli and colleagues[88] In the base-case analysis epoetin alfa use resulted in increased costs (CA$8643) and increased benefits (0.03 QALYs) over 15 weeks, resulting in an ICER of CA$267,000 per QALY. Over a 1-year time frame costs were unchanged, but increased long-term mortality resulted in decreased benefits (–0.086 QALYs); epoetin alfa use was dominated by standard care as a result. Similar results were obtained with darbepoetin alfa.

Several univariate sensitivity analyses and scenario analyses were conducted. When the mortality parameters were varied within their 95% CIs, ESA use remained not cost-effective, even at a threshold of CA$100,000 per QALY. When alternative methods of estimating the relationship between Hb levels and utility were used, ESA use became less cost-effective. A number of other scenario analyses were conducted, the most favourable of which involved limiting the studies informing the model to those with a target Hb level of ≤ 12 g/dl and/or an initial Hb level of ≤ 10 g/dl, but even in these the ICERs remained above CA$70,000 per QALY.

Summary tables for the other full non-selected studies

The study characteristics, key parameters and results for the other full non-selected studies are summarised in *Tables 44–46* respectively.

Discussion

All cost–utility studies presenting favourable results were funded or produced by industry.

Martin and colleagues[116] produced an analysis demonstrating good cost-effectiveness in a subgroup of cancer patients on the basis of a substantial survival advantage in a RCT, but there are numerous problems with this analysis:

- the stage IV breast cancer subgroup was not identified a priori (nor indeed were any subgroups identified a priori) and was likely selected as the subgroup in which the observed survival benefit was greatest
- survival was not a primary outcome of the RCT and indeed the RCT was not powered to detect survival differences and survival was added as a supplementary outcome after the trial started;[81] this leaves open the possibility of reporting bias of survival results
- the RCT was neither powered nor stratified for subgroup analyses and there were baseline differences between the epoetin alfa and the placebo arms

The three industry submissions in the previous NICE appraisal[2] achieved ICERs of < £30,000 per QALY only by the inclusion of survival benefits that have not generally been reproduced in more recent meta-analyses. Analyses not including survival benefits seem to predict small incremental benefits of ESA therapy in the range of 0.0052–0.035 QALYs.

TABLE 44 Study characteristics of the full non-selected studies

Characteristic	Ben-Hamadi and colleagues[148]	Persson and colleagues[125]	Borget and colleagues[157]	Spaepen and colleagues[126]	Aapro and colleagues[158]	Pashos and colleagues[127]
Evaluation type	Cost-effectiveness analysis	Cost–consequences analysis	Cost-effectiveness analysis	Cost–consequences analysis	Cost-minimisation study	Cost–consequences analysis
Modelling used	Limited	Yes	Yes	Limited	Minimal	No
Nature of modelling	Integration of drug acquisition costs based on dose escalation rate	Calculation of drug costs	Markov model	Statistical matching of patients receiving different ESAs to estimate costs	Multiplication of dosing level by unit price	
Perspective	Payer	Health care[a]	Health care	Health care	Health care	Drug costs only
Country (setting)	USA (not explicitly stated)	Sweden	France (not explicitly stated)	Belgium (hospital)	Germany, France, UK, Italy, Spain	USA
Intervention/comparator	Epoetin alfa QW: 40,000 IU, escalated to 60,000 IU after 4 weeks if Hb increase < 1 g/dl; darbepoetin alfa QW: 2.25 µg/kg, escalated to 4.5 µg/kg if Hb increase < 1 g/dl and/or given RBCT	Epoetin alfa TIW: 150 IU/kg;[b] darbepoetin alfa QW: 2.25 µg/kg[b]	Darbepoetin alfa QW; standard care: RBCT if Hb < 8 g/dl or 8–10 g/dl and signs of poor tolerance of anaemia	Darbepoetin alfa; epoetin alfa; epoetin beta[c]	Originator epoetin alfa QW: 40,000 IU, 450 IU/kg; biosimilar epoetin alfa QW: 30,000 or 40,000 IU, 450 IU/kg; epoetin beta QW: 30,000 IU, 450 IU/kg; darbepoetin alfa QW: 150 µg, 2.25 µg/kg; darbepoetin alfa Q3W: 500 µg, 6.75 µg/kg	Epoetin alfa QW: 40,000 IU; darbepoetin alfa Q3W: 500 µg
Population	Patients with chemotherapy-induced anaemia	Patients with cancer therapy-related anaemia receiving epoetin alfa or darbepoetin alfa	Lung cancer patients	Adult cancer patients receiving ESA support at some point	Patients with chemotherapy-induced anaemia	Adult cancer patients receiving ESA therapy

continued

TABLE 44 Study characteristics of the full non-selected studies (*continued*)

Characteristic	Ben-Hamadi and colleagues[148]	Persson and colleagues[125]	Borget and colleagues[157]	Spaepen and colleagues[126]	Aapro and colleagues[158]	Pashos and colleagues[127]
Outcomes considered	Treatment success (proportion of patients not requiring RBCT)	Haematological response, AUC_{HB}, proportion of patients receiving RBCT, number of RBC units transfused	Proportion of patients receiving RBCT, number of RBC units transfused, mean Hb level	TA-free survival (composite of transfusion-free survival and anaemia-related readmission-free survival)	None (costs only)	Proportion of patients requiring packed RBCT, units of packed RBC transfused per patient, increase in Hb level from baseline
Time frame	16 weeks	16 weeks	36 weeks	For duration of records until loss of follow-up at end of calendar year	18 weeks	Duration of ESA treatment up to maximum of 16 weeks
Discounting	Not stated	Not stated	Not stated	Not stated	Not discounted	Not stated
Funding	Ortho Biotec (manufacturer of epoetin alfa)	Johnson & Johnson (manufacturer of epoetin alfa)	Not stated	Amgen Inc. (manufacturer of darbepoetin alfa)	Sandoz Biopharmaceuticals [manufacturer of biosimilar epoetin alfa (Binocrit)]	Ortho Biotec (manufacturer of epoetin alfa)

AUC_{HB}, area under the Hb change curve; Q3W, once every 3 weeks; QW, once weekly; TIW, three times weekly.
a Included costs of drug acquisition, hospitalisation and RBCT.
b Swedish treatment guidelines: dose doubled if inadequate response after 4 weeks; treatment discontinued if Hb > 14 g/dl.
c Reimbursed only if administered to patients with Hb < 11 g/dl and/or receiving platinum-based chemotherapy.

TABLE 45 Key parameters of the full non-selected studies

Parameter	Ben-Hamadi and colleagues[148]	Persson and colleagues[125]	Borget and colleagues[157]	Spaepen and colleagues[126]	Aapro and colleagues[158]	Pashos and colleagues[127]
Effectiveness (source): transfusion, response rate, survival, QALYs	Epoetin alfa: Witzig and colleagues;[167] darbepoetin alfa: Kotasek and colleagues[168]	Retrospective chart review performed at three Swedish hospitals	2-year retrospective study	Retrospective analysis of Belgian national patient database	Assumed equivalent	Dosing and Outcomes Study of Erythropoiesis-Stimulating Therapies (DOSE)
Effectiveness (data): transfusion, response rate	Treatment success (proportion of patients not requiring RBCT) Weeks 0–16: epoetin alfa 75%; darbepoetin alfa 63% Weeks 5–16: epoetin alfa 85%; darbepoetin alfa 73%	Results by day 112:[a] Haematological response (Hb increase ≥ 1 g/dl): epoetin alfa 100%; darbepoetin alfa 80% Haematological response (Hb increase ≥ 2 g/dl): epoetin alfa 86%; darbepoetin alfa 63% AUC_{HB} (Hb g/dl/day, mean $\pm$ SD): epoetin alfa 203.0 ± 122.9; darbepoetin alfa 157.0 ± 162.3 Patients receiving one or more RBCT: epoetin alfa 14/29; darbepoetin alfa 14/30 Mean units of RBC transfused: epoetin alfa 1.71; darbepoetin alfa 1.95	Proportion of patients receiving RBCT: darbepoetin alfa 19.1%; standard care 33.6% Mean number of RBC units transfused: darbepoetin alfa 2.11 ± 0.47; standard care 2.97 ± 1.47	TA-free survival (composite of transfusion-free survival and anaemia-related readmission-free survival) (95% CI): darbepoetin alfa 84.37% (79.22% to 88.35%); epoetin alfa 84.60% (80.72% to 87.75%); epoetin beta 84.94% (80.03% to 88.72%) Transfusion-free survival (95% CI): darbepoetin alfa 84.46% (79.29% to 88.43%); epoetin alfa 84.86% (81.00% to 87.99%); epoetin beta 85.51% (80.70% to 89.19%) Anaemia-related readmission-free survival (95% CI): darbepoetin alfa 89.16% (84.71% to 92.38%); epoetin alfa 88.66% (85.18% to 91.36%); epoetin beta 87.91% (83.31% to 91.29%)	NA	Proportion of patients requiring RBCT: epoetin alfa 13.9%; darbepoetin alfa 22.5% ($p = 0.026$) RBC units: epoetin alfa 0.4; darbepoetin alfa 0.7 ($p = 0.020$) Increase in Hb from baseline (g/dl) at week 12: epoetin alfa 0.6; darbepoetin alfa 0.1 ($p = 0.032$)

continued

TABLE 45 Key parameters of the full non-selected studies (*continued*)

Parameter	Ben-Hamadi and colleagues[148]	Persson and colleagues[125]	Borget and colleagues[157]	Spaepen and colleagues[126]	Aapro and colleagues[158]	Pashos and colleagues[127]
Effectiveness (data): survival, QALYs	NA	NA	NA	NA	NA	NA
HRQoL/utility (source)	NA	NA	NA	NA	NA	NA
HRQoL/utility (data)	NA	NA	NA	NA	NA	NA
Costs (source)	Medi-Span® Master Drug Data Base (MDDB), May 2005	Drug acquisition: list price in 2003 Swedish Pharmacopoeia; hospitalisation and RBCT: official list of regional administrative prices	Transfusion costs from national unit costs; darbepoetin alfa drug costs from drug purchase prices paid by the hospital	Belgian national databases	This study; list price (Germany, France, Italy, Spain); negotiated price (UK)	Wholesale acquisition costs
Cost year	2005	2003	Not stated	2003–5 (patient specific); 2006 across all patients in sensitivity analysis	2010	May 2009

AUC_{HB}, area under the Hb change curve.
a Results also presented at 28, 56 and 84 days.

TABLE 46 Results of the full non-selected studies

Parameter	Ben-Hamadi and colleagues[148]	Persson and colleagues[125]	Borget and colleagues[157]	Spaepen and colleagues[126]	Aapro and colleagues[158]	Pashos and colleagues[127]
Measure	Cost per 1% successful treatment	Cost	Cost per g/dl Hb	Cost per patient	Relative savings with use of biosimilar epoetin alfa[a]	Cumulative drug cost per patient
Cost year, currency	2005, US$	2003, SEK	Not stated, US$	2003–5, €	2010, €	2009, US$
Base case	Epoetin alfa dominates Average ICERs: Weeks 0–16: epoetin alfa US$121; darbepoetin alfa US$215 Weeks 5–16: epoetin alfa US$106; darbepoetin alfa US$186	Total treatment cost at day 112: epoetin alfa SEK 74,701; darbepoetin alfa SEK 85,285	Darbepoetin alfa: mean Hb 13.0 ± 0.5 g/dl; mean cost US$1732 ± 897 Standard care: mean Hb 11.9 ± 1.0 g/dl; mean cost US$996 ± US$643 ICER: US$669 per g/dl Hb	Overall costs: darbepoetin alfa €16,949 ± €1025; epoetin alfa €19,472 ± €901; epoetin beta €19,295 ± €1048	Fixed dosing using biosimilar epoetin alfa 40,000/30,000 IU per week: Originator epoetin alfa 13.8%/35.4%; epoetin beta 16.4%/37.3%; darbepoetin alfa QW 25.5%/44.2%; darbepoetin alfa Q3W 33.0%/49.7% Weight-based dosing using biosimilar epoetin alfa: Originator epoetin alfa 13.8%; epoetin beta 16.4%; darbepoetin alfa QW 44.2%; darbepoetin alfa Q3W 44.2%	Epoetin alfa US$4261; darbepoetin alfa US$8643

continued

TABLE 46 Results of the full non-selected studies (*continued*)

Parameter	Ben-Hamadi and colleagues[148]	Persson and colleagues[125]	Borget and colleagues[157]	Spaepen and colleagues[126]	Aapro and colleagues[158]	Pashos and colleagues[127]
Probabilistic results	NR	NR	NA	NA	NA	NA
Sensitivity analyses	Using average sale price + 6% (as used for reimbursement for Medicare Part B-covered drugs) Epoetin alfa dominates Average ICERs: Weeks 0–16: epoetin alfa US$97; darbepoetin alfa US$159 Weeks 5–16: epoetin alfa US$86; darbepoetin alfa US$137	Costs modelled for observed/fixed patient body weights and response rates	Reducing cost of transfusion or baseline prevalence of anaemia led to standard care having a lower average ICER	Applying 2006 prices does not alter the conclusion that darbepoetin alfa is significantly cheaper than epoetin alfa and epoetin beta	Results presented individually for five treatment scenarios; relative savings are unchanged	NA

NR, not reported; QW, once weekly; Q3W, once every 3 weeks; SEK, Swedish krone.

a Results presented are calculated from the cost for each treatment averaged (unweighted) across five treatment scenarios. Costs represent European G5 costs as calculated from weighted average of price, weighted by population of European G5 countries.

The only analysis not including a survival benefit and producing a favourable estimate of cost-effectiveness was that by Borg and colleagues,[156] which demonstrated a significantly lower incremental cost of ESAs than other analyses, including those funded or produced by industry. The average cumulative dose predicted by the model may be calculated by dividing the total cost of epoetin alfa (€2054) by the cost of epoetin alfa per 4-week cycle (€1329) to estimate an average 1.546 cycles, giving an average cumulative dose of approximately 195,000 IU (based on a 70-kg patient, as chosen by the authors), whereas data from the clinical study informing the model by Persson and colleagues[125] suggest a cumulative dose of 460,000 IU. Dose doubling was included in the clinical study, but this would not account for the discrepancy; indeed, the maximum mean dosage for those receiving epoetin alfa was 37,143 IU, compared with a start mean dosage of 31,786 IU. This suggests that the analysis by Borg and colleagues[156] assumes that patients discontinue epoetin alfa sooner than expected from the study from which clinical effectiveness estimates were drawn, leading to questions about the internal validity of the study.

None of the studies incorporated any impact of ESA therapy on chemotherapy management.

Conclusions

For ESA therapy to be cost-effective some or all of the following seem to be necessary:

- a significant survival advantage for patients receiving ESA therapy
- utility improvements as a result of improvements in Hb level
- a low cumulative dose of ESA
- a normalisation period in which the benefits of ESAs persist beyond chemotherapy cessation (and beyond ESA cessation).

A significant survival advantage has not been shown in general either by the recent Cochrane review[11] or by the systematic review in *Chapter 3*.

The primary claimed benefit of ESA therapy is improved HRQoL following correction of anaemia, but this has not been demonstrated on general HRQoL measures (such as the EQ-5D) in published and peer-reviewed RCTs. Significant predicted improvements in utility have resulted from the application of the results of Ossa and colleagues,[159] but this study has several methodological weaknesses (see *Chapter 5*, *Clinical effectiveness parameters*). Tonelli and colleagues[88] have noted that, as a result of using utility estimates derived from Ossa and colleagues,[159] a 0.15 difference in utility between the ESA and the non-ESA arms was predicted, on a par with the utility associated with a kidney transplant for a patient with end-stage kidney disease on dialysis, which they regarded as a potential overestimation.

Achieving a low cumulative dose of ESAs (without sacrificing significant clinical effectiveness) will likely result from identifying non-responders as early as possible and discontinuing ESA therapy in them; focusing ESA therapy on patients with moderate to severe anaemia, in whom it is likely to impact on quality of life and survival, rather than continuing ESA therapy to achieve Hb levels of > 12 g/dl; and employing dose escalation only if it is shown to be clinically effective. These strategies have largely been included in current licences and guidance notes, but there is not yet RCT evidence of clinical effectiveness when ESAs are used fully within licence.

Some amount of normalisation would logically be expected, but no clinical evidence for this has been presented in the economic analyses, even from observational studies. If normalisation is a significant contributor to the benefit of ESAs in analyses it should be subjected to extensive sensitivity analysis to reflect the significant amount of uncertainty.

Wilson and colleagues[2] concluded that AEs relating to ESA therapy or RBCT would be unlikely to impact on cost-effectiveness. The two new model-based cost–utility analyses[88,156] did not include AEs and provide no further insight into this. Fagnoni and colleagues[121] included anaemia-related hospitalisation costs, but it appears that these costs are valued according to average costs of hospitalisation rather than AE-specific hospitalisation costs. They do not demonstrate a significant difference in costs in this area.

The new cost–utility studies did not demonstrate a significant impact on cost-effectiveness of the cost of RBCT.

All studies appear to include greater drug acquisition costs than would be expected now in the NHS as the list price has come down. As drug acquisition costs are the largest component of the incremental costs in all analyses, any discounts would be expected to impact total incremental costs. However, disaggregated total costs as well as incremental costs would be needed to make an appropriate adjustment, and these have not been reported by Wilson and colleagues.[2] Furthermore, NHS hospitals could be expected to achieve discounts from the list price, further improving cost-effectiveness.

Following this update review there remains some uncertainty about the cost-effectiveness of ESAs given the recent reduction in drug acquisition costs and changes to licences designed to address safety concerns. If no survival benefit is assumed then a maximum QALY gain of 0.030–0.035 seems reasonable based on the results from Wilson and colleagues,[2] Borg and colleagues[156] and Tonelli and colleagues.[88] This could be an overestimate, as there is a lack of high-quality evidence that ESA therapy improves HRQoL on generic measures such as the EQ-5D.

There is a need for an up-to-date analysis of the cost-effectiveness of ESAs in the NHS to reflect reduced drug acquisition costs, changes to licences and market entry of additional comparators. This analysis will need to explore the significant amount of uncertainty that still remains.

Strengths and limitations

This review included a comprehensive search of the literature and inclusion and exclusion criteria were not unnecessarily restrictive, unlike those of the systematic review by Duh and colleagues,[155] which excluded standard care without ESAs as a comparator. The two systematic reviews by Duh and colleagues[155] and Tonelli and colleagues[88] did not identify cost–utility studies that were not identified in this review. The full text of one cost–utility study by Roungrong and colleagues[134] could not be obtained, but the Centre for Reviews and Dissemination[135] critical appraisal of this study suggests that it would not change the conclusions of the review.

The methods and results of the included cost–utility studies were described and critically appraised and conclusions were drawn by comparing the methods and results of all cost–utility studies.

Records from database searches published pre 2004 were excluded, although it was not possible to assess whether these had been screened for eligibility in the systematic review presented by Wilson and colleagues.[2]

The reviewers (TS and NH) excluded darbepoetin alfa given once every 2 weeks as an allowed intervention as biweekly administration is not allowed within the licence for darbepoetin alfa. This could be viewed as a limitation of the review, but at the full paper screening stage this resulted in the exclusion of only a single abstract not describing a cost–utility analysis.

No critical appraisal or narrative synthesis of non-cost–utility studies was performed, which could also be viewed as a limitation of this review. Cost–utility analyses are preferred for NICE appraisals, therefore this is not a significant limitation within the NICE appraisal context, but the value of this review to other audiences may have been limited, although cost–utility analyses are also preferred by many other decision-makers.

The analyses identified in this review are outdated in some ways because of changes in ESA costs and licences and the market entry of new ESAs, but this is a drawback of the published literature rather than the review methods.

Areas of uncertainty

It is not clear what incremental costs could be expected by the introduction of ESAs at current list prices or wholesale acquisition prices. The cost of drug administration is also uncertain and dependent on whether patients are assumed to self-administer drugs. The cost of RBCT in the NHS has not been recently evaluated by the studies identified, but there is evidence that cost-effectiveness may not be particularly sensitive to the cost of RBCT (although this is from studies in which drug acquisition costs dominate to a greater extent than would now be expected). Studies did not include the costs of blood tests or outpatient clinics and so it is not clear how these might impact on cost-effectiveness. Cumulative doses of ESAs, when given within licence, are also uncertain.

The benefits from ESAs are highly uncertain. If ESAs impact on survival then this will have a significant effect on cost-effectiveness, even though ESAs are not given to enhance survival. A systematic review and meta-analysis was conducted as a part of this appraisal and several others exist that do not rule out an impact on survival. If ESA therapy does not result in a meaningful improvement in quality of life then this will also have a significant impact on cost-effectiveness. There is an absence of high-quality evidence in this area. Benefits from normalisation are also highly uncertain and have a significant impact on cost-effectiveness.

Overall, the clinical effectiveness of ESAs measured in QALYs is highly uncertain, as are the costs of ESAs.

Update searches

Update searches were conducted on 2 December 2013 using the same methodology as described earlier. Fifty-one records were screened by two reviewers (TS and LC) and one record was selected for full-text retrieval. The study was judged to be eligible on full-text appraisal by TS and NH. The study was neither a cost–utility study nor a systematic review and its results do not alter the conclusions of this review (see *Appendix 17* for further details).

Economic evaluations submitted by the manufacturers

No economic evaluations were submitted by any of the manufacturers.

Key points

- Ten cost–utility analyses and two systematic reviews were identified by updating an existing review by Wilson and colleagues.[2]
- Five cost–utility analyses suggested that ESA therapy is cost-effective; these were all funded by industry[116,156] or conducted by industry (submissions by Amgen Inc., Roche and Ortho Biotec as reported by Wilson and colleagues[2]).
- The inclusion of survival benefits was common to four favourable analyses (Martin and colleagues[116] and the industry submissions as reported by Wilson and colleagues[2]), although no statistically significant survival benefit has been shown.
- The fifth favourable analysis[156] may suffer from problems of internal validity as it appears that the cumulative dose of epoetin alfa in the analysis was less than half that in the clinical study informing the effectiveness estimates; this would account for the lower than usual incremental drug acquisition costs.
- A key assumption in almost all of the analyses was that raising Hb levels would improve HRQoL, although in no case was this assumption based on published RCT evidence using a preference-based quality-of-life measure.
- A number of studies assumed a period following treatment during which Hb levels would gradually return to normal (termed 'normalisation'), during which patients in the ESA arm would continue to accrue incremental benefits in terms of quality of life over patients in the no ESA arm; no evidence for or against normalisation has been presented.
- In the absence of survival benefits the expected health gain from ESA therapy is small (up to 0.035 QALYs) and is subject to uncertainty.
- Studies did not incorporate current list prices or wholesale acquisition costs, which could significantly reduce the drug acquisition cost component of ESA therapy and improve cost-effectiveness.

Chapter 5 Independent economic assessment

Methods

Model structure

In the PenTAG assessment, the economic evaluation takes the form of a simple, empirical model, informed directly by the systematic review of clinical effectiveness. This differs from standard mechanistic modelling approaches (such as Markov or discrete event simulation models), which require specific states and processes to be modelled.

The model compares patients receiving ESA therapy with patients not receiving ESA therapy (referred to as the ESA arm and the control arm) and is split into two temporal sections, one to evaluate the short-term costs and QALYs (while patients are anaemic) and one to evaluate long-term QALYs.

Short-term costs are accrued in the form of ESA drug acquisition and administration costs, RBCT costs and costs of AEs. Although patients may incur significant costs through cancer treatment (e.g. chemotherapeutic agents), these costs are not modelled as they are assumed to be equal for the ESA arm and the control arm (the potential ramifications of this assumption are discussed in *Chapter 6*, *Chemotherapy costs*). Short-term QALYs are accrued as HRQoL is improved by ESA therapy correcting anaemia and associated symptoms (e.g. fatigue); no difference in time spent in the short-term phase is modelled between the arms.

Long-term QALYs are accrued because of potential differences in OS between the two arms; it is assumed that HRQoL is equal for both arms in this phase as patients no longer have CIA and HRQoL is driven by symptoms of cancer. Although patients may incur significant ongoing costs related to cancer treatment (e.g. costs of maintenance chemotherapy, subsequent chemotherapy cycles or relapse), because these are highly uncertain (because of the wide range of cancers that patients may have and the treatments for them) and because the inclusion of such costs could perversely worsen cost-effectiveness for the arm with greater OS, these costs are not modelled in the base case. The potential ramifications of this assumption are explored through a univariate sensitivity analysis in *Univariate sensitivity analysis*, *Long-term costs*, and are discussed in *Chapter 6* (see *Chemotherapy costs*).

Short-term costs and quality-adjusted life-years

Short-term costs in the model include ESA drug acquisition and administration costs, RBCT-related costs and costs relating to AEs. In all cases resource use and unit costs are estimated separately. Resource use for ESA drug acquisition and administration is estimated in *ESA withdrawal rate and mean weekly dose* and *Duration of ESA treatment*. Resource use for RBCT is estimated in *Number of red blood cell transfusions*. Resource use for AEs is estimated in *Adverse event costs*. Unit costs are estimated in *Costs*.

We have considered three possible model structures for the estimation of short-term QALYs (*Table 47*):

1. Using reported HRQoL outcomes directly from RCTs of ESAs – Hb levels are not modelled. Ideally, this would be the preferred model structure. However, this option is not available because:

    - Although many RCTs report outcomes measured by disease-specific health questionnaires, such as FACT-An, FACT-F and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), no RCTs report generic preference-based HRQoL measures such as the EQ-5D or Short Form questionnaire-6 Dimensions (SF-6D), which are required to estimate health utilities. Indeed, this limitation has been noted by Grant and colleagues.[89]

TABLE 47 Possible model structures for the short-term economic evaluation of ESAs

	Model structures		
Criteria assessed	Quality of life from trial	Mechanistic modelling of Hb over time	Empirical observation of Hb over time
Complexity	Simplest	Complex, more parameters required	Intermediate
Flexibility to depart from characteristics of the RCTs, e.g. patient age, initial Hb level, subsequent Hb level, ESA doses	Less flexibility	More flexibility, e.g. to mirror difference in clinical practice compared with RCTs, changes to licences	Less flexibility
Data availability	Preference-based HRQoL data not available from RCTs	Quality data for many parameters not available, e.g. impact on Hb of increase in ESA dose	Yes, taken from the PenTAG systematic review of RCTs
Ability to use outcomes from multiple RCTs (PenTAG systematic review of RCTs)	Yes	Not for some parameters, e.g. incremental change in Hb level. Also, some parameters are a function of the characteristics of RCTs, e.g. OS HR of ESAs	Yes, with exception of HRQoL outcomes
Accuracy of utilities during ESA treatment and normalisation	Accurate, but excluding Hb outcomes	Assumes HRQoL impact of ESAs captured through the Hb level. Quality of life as a result of AEs is captured independently	
Examples of previous economic evaluations	Barosi and colleagues;[114] Cremieux and colleagues[115]	Wilson and colleagues;[2] Borg and colleagues[156]	Tonelli and colleagues;[88] Fagnoni and colleagues[121]

- Very little information can be gained from mapping from the disease-specific health questionnaires to the EQ-5D (see *Estimation of the impact of erythropoiesis-stimulating agents on health utilities from mapping disease-specific questionnaires to the European Quality of Life-5 Dimensions*). Despite this, some previous cost-effectiveness analyses (e.g. Cremieux and colleagues[115]) have taken this approach, using quality of life based on visual analogue scales (VASs) or LASA methodology, which is not recommended as health state values elicited using these scales are not based on stated trade-offs between quantity and quality of life by surveyed individuals.[169]
- A variant of this method is seen in Fagnoni and colleagues,[121] in which Hb levels over time were taken directly from a clinical trial and then mapped to utility, although this was not according to generic HRQoL measures such as the EQ-5D.

2. Mechanistic modelling of the exact Hb level over time during ESA treatment. It is necessary to model many processes, including:

   - doses of ESAs at all times, which are driven by Hb levels, and Hb responses to ESAs
   - times when RBCTs are given and Hb responses to these
   - starting Hb levels.

   One of the motivations for modelling Hb levels over time is that these are widely reported in the ESA RCTs and it is possible to estimate health utilities as a function of Hb level.
   This option has the attraction of flexibility to depart from the characteristics of the RCTs. However, we have not chosen this option because (1) data for many of the required parameters are simply not available and (2) it is not possible to incorporate many of the outcomes from the systematic review of clinical effectiveness (see *Table 49*).
3. Empirical observation of Hb over time.
   Here, Hb levels over time are taken directly from clinical trials. This approach attempts to bolt on an economic evaluation to the RCTs of ESAs. This option has been chosen because (1) good estimates of all of the necessary parameters are available and (2) the method can use many of the outcomes from the systematic review of clinical effectiveness (see *Chapter 3*).

A summary model diagram is presented in *Figure 26*. This diagram demonstrates how Hb levels are modelled according to the baseline Hb level [see *Initial (baseline) haemoglobin level*], the expected change in Hb level for patients not receiving ESA therapy (see *Change in haemoglobin level for patients not receiving erythropoiesis-stimulating agent therapy*), the expected final difference in Hb level between arms (see *Table 49*) and the average difference in Hb levels between arms as a proportion of the final difference (see *Mean difference in haemoglobin levels between treatment arms as a proportion of the difference at the end of the trial*). The concept of normalisation, which takes place after cancer treatment has ended, is described fully in *Normalisation of haemoglobin levels following chemotherapy cessation*.

It is important to note that we model the average Hb profiles *across the patient population* rather than modelling individual patients' Hb profiles. As such, the Hb profile is considerably smoother than that expected for an individual patient.

Long-term quality-adjusted life-years

Long-term QALYs are calculated by estimating OS in each arm and applying a long-term utility that is common to both arms; that is, it is assumed that long-term QALY differences come about only through a difference in survival as a result of ESA therapy, not through any enduring impact on HRQoL. Long-term utility is estimated in *Peninsula Technology Assessment Group base-case utilities after erythropoiesis-stimulating agent discontinuation*.

The systematic review of clinical effectiveness provided estimates for the HR for survival between the ESA arm and the control arm, but to implement this in the model required an estimate of baseline survival for patients without ESA treatment. As ESAs can be administered to individuals with a range of cancers, a wide range of OS estimates appear in clinical studies.

Review of best practice

Here, we briefly outline key points from Latimer[170,171] on best practice, as they apply to this setting (note that this paper principally advises on best practice in the case of patient-level data from a single study rather than summary data from multiple studies):

> *1. Mean time-to-event should be estimated rather than medians.*
>
> *2. Parametric models should be used, rather than restricted means approaches, unless data is almost entirely complete.*
>
> *3. The analyst should demonstrate that a range of parametric models have been considered and compared, in order to make evident that the model choice has not been arbitrary. . . .*
>
> *4. The fit of alternative models should be assessed systematically. . . .*
>
> *5. [Proportional hazards] modelling should only be used if the proportional hazards assumption can be clearly justified. . . .*
>
> *6. Where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model. . . .*
>
> *7. The duration of treatment effect assumption is important when a PH approach is taken, and in the extrapolated portion of survival curves when individual parametric models are fitted to treatment arms. . . .*
>
> *8. The process of excluding data points should only be undertaken when it can be clearly demonstrated that certain points are erroneous outliers. . . .*
>
> *Reproduced with permission from Latimer[170,171]*

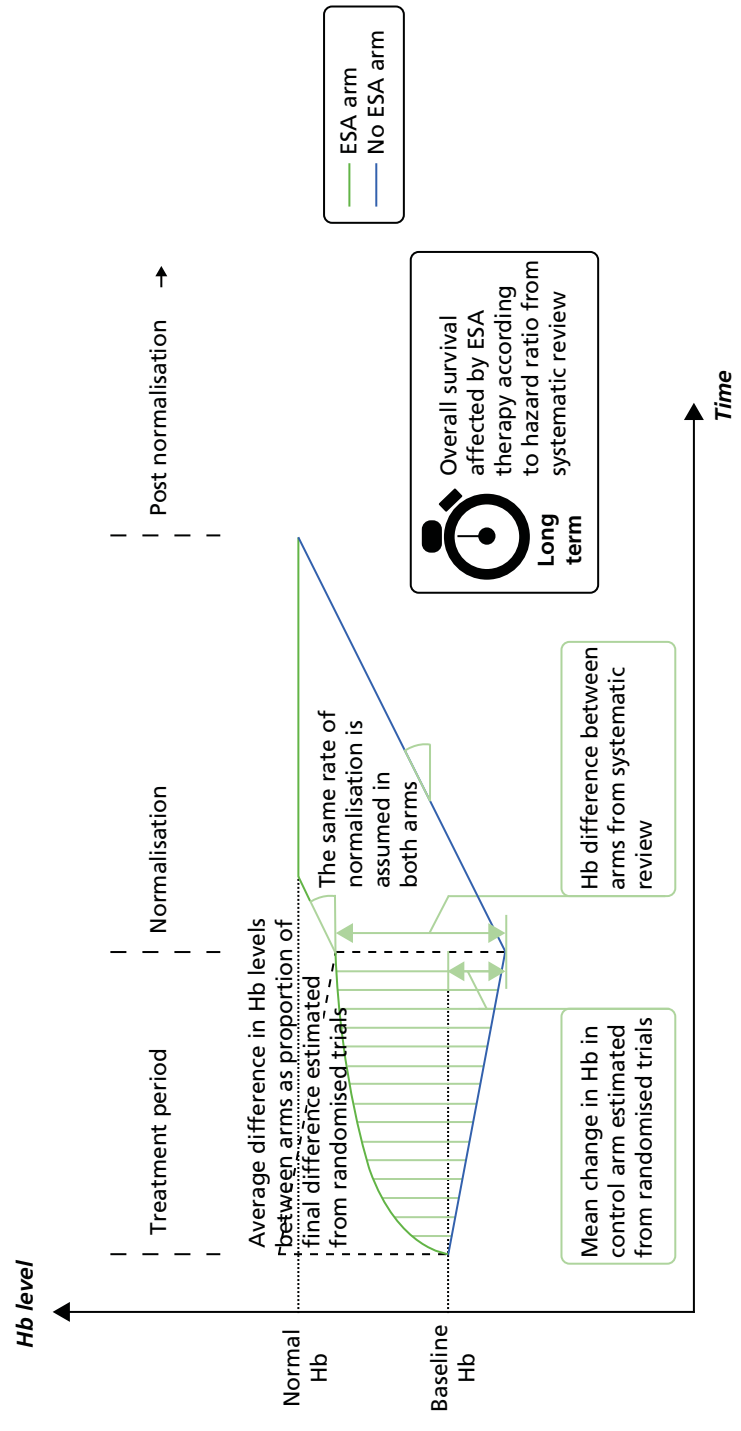


FIGURE 26 Diagram indicating model assumptions about Hb levels by model stage. Note: Hb levels mapped to utility to calculate short-term QALYs.

Modelling approach

We examined OS curves from all studies included in the systematic review of clinical effectiveness in which such survival curves were shown for patients receiving and not receiving ESA therapy.

For each survival curve we constructed the corresponding cumulative hazard curve to assess how the hazard function behaved over time. Plots of cumulative hazard over time can be useful in identifying candidate parametric survival functions; for example, if the cumulative hazard curve is a straight line then an exponential distribution may be appropriate and if the cumulative hazard function has a sigmoid shape this suggests the need for a survival function with a non-monotonic hazard.

When OS figures were provided as vector graphics (as was the case for Ray-Coquard and colleagues[75] and Moebus and colleagues[62]) the exact survival curve was extracted using Inkscape [freely available from www.inkscape.org/ (accessed 24 June 2015)] and transformed appropriately using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). When OS figures were provided as raster graphics the underlying image was extracted using Inkscape and then transformed using the GNU Image Manipulation Program [freely available from www.gimp.org/ (accessed 24 June 2015)] and MathMap [freely available from www.complang.tuwien.ac.at/schani/mathmap/ (accessed 24 June 2015)], as outlined in *Appendix 18*. This approach meant that no data points were excluded.

We additionally constructed the corresponding Weibull plot (a plot of log cumulative hazard vs. log time) using the same methodology. A straight line on a Weibull plot suggests that a Weibull distribution may be appropriate and parallel straight lines for different arms suggests that a proportional hazards Weibull model can be used.

Visual inspection of the cumulative hazard plots suggested that an exponential survival function would fit both arms in the studies by Vansteenkiste and colleagues[73] and Österborg and colleagues[79] (*Table 48*).

The plots for Littlewood and colleagues[70] suggest that neither a Weibull nor an exponential survival function would fit the arms well. It is also not clear whether a proportional hazards assumption would be valid, as the survival curves converge after significant censoring.

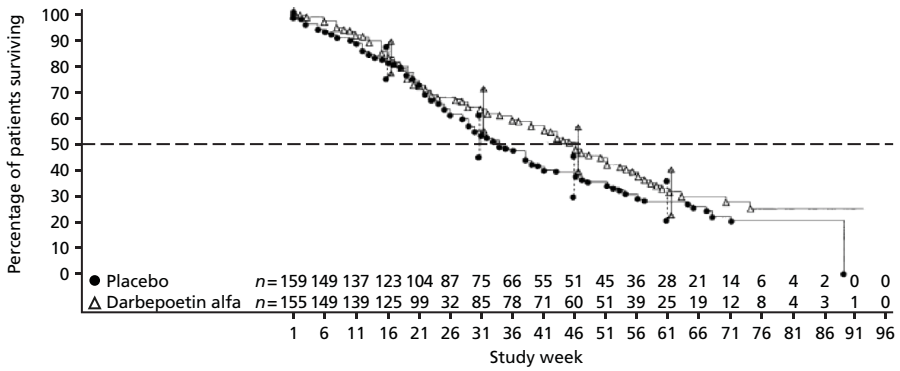
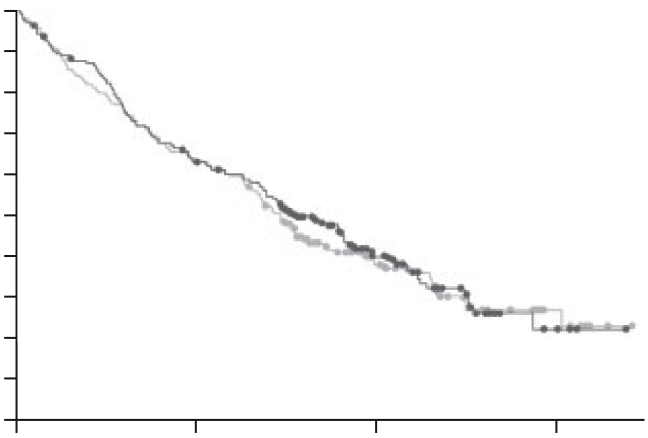
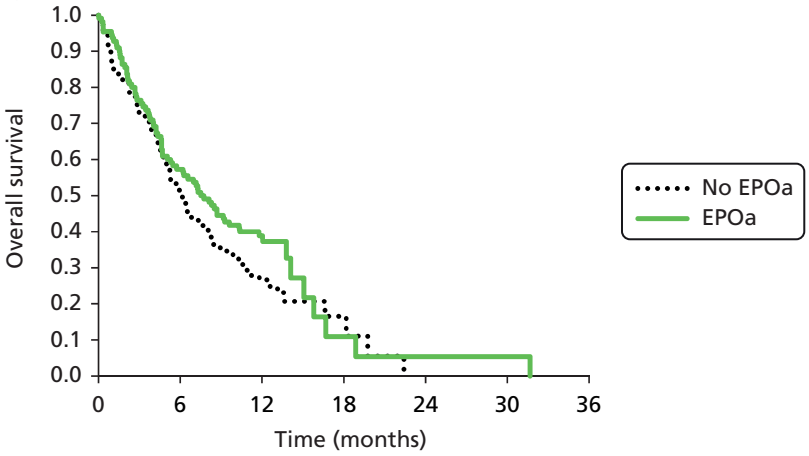
The plots for Grote and colleagues[74] suggest that an exponential survival function could be valid, as the cumulative hazard plot diverges from being linear only after significant censoring, although if the Kaplan–Meier curve beyond divergence is considered informative it could suggest a delayed treatment effect on OS.

The survival plot for Ray-Coquard and colleagues[75] suggests that OS data are mature in this study (as 0% Kaplan–Meier survival is reached), but in fact the vast majority of patients are censored after around 12 months' follow-up. Up to this time exponential survival does not seem unreasonable.

The plots for Untch and colleagues[80] suggest that exponential survival may not be appropriate (see *Table 48*). Examination of the Weibull plot suggests that a Weibull survival function may be appropriate. It might also be appropriate to use piecewise exponential survival with a very low hazard rate for the first year and then a higher hazard rate thereafter given that the rightmost upturn in the cumulative hazard plot occurs only after significant censoring. A proportional hazards assumption would not be unreasonable given the Weibull plot.

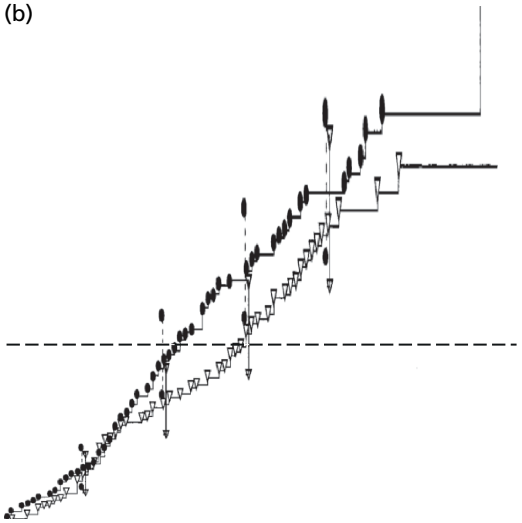
The plots for Moebus and colleagues[62] are noteworthy as they seem to suggest a non-monotonic hazard function, ruling out exponential, Weibull and Gompertz distributions for fitting (see *Table 48*). This study evaluated performance in breast cancer (stages II–IIIa) patients, who might be expected to have a reasonable prognosis, and hence a long tail (as would be associated with a log-logistic or log-normal distribution) might not be inappropriate as it could be for other cancers.

TABLE 48 Overall survival curves extracted from RCTs

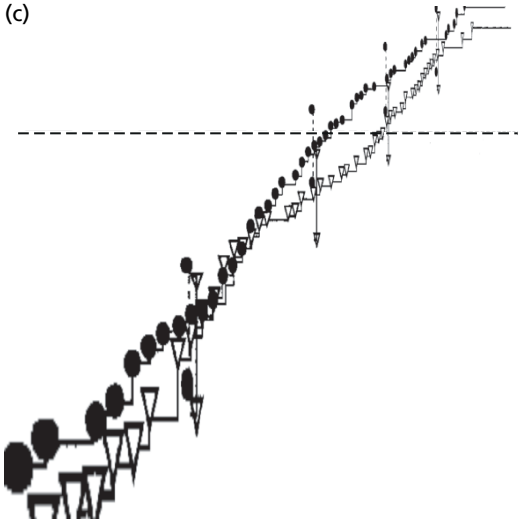
Study	Survival curve
Vansteenkiste 2002[73]	(a)  Reproduced from Vansteenkiste J, Pirker R, Massuti B, Barata F, Font A, Fiegl M, *et al.* Double-blind, placebo-controlled, randomised phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst* 2002;**94**:1211–1220[73] by permission of Oxford University Press (UK) © European Society for Medical Oncology (ESMO) All rights reserved (URL: http://jnci.oxfordjournals.org/content/94/16/1211.full.pdf+html)
Österborg 2005[79]	(d)  Reproduced from Österborg A, Brandberg Y, Hedenus M. (2005). Impact of epoetin-beta on survival of patients with lymphoproliferative malignancies: long-term follow up of a large randomized study. *Br J Haematol* 2005;**129**:206–9.[79] Copyright 2005 Österborg. This material is reproduced with permission of John Wiley & Sons, Inc.
Ray-Coquard 2009[75]	(g) 

Cumulative hazard curve	Weibull plot

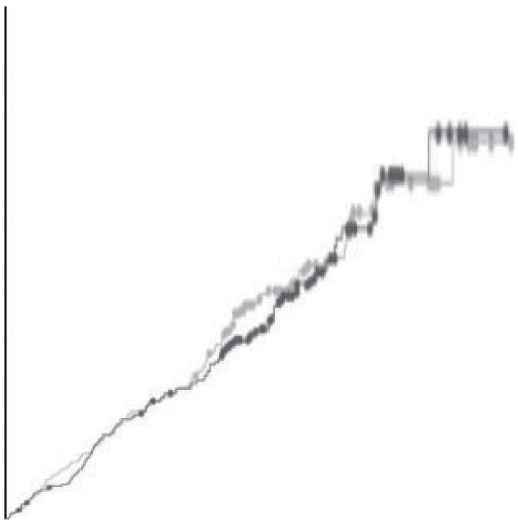
(b)



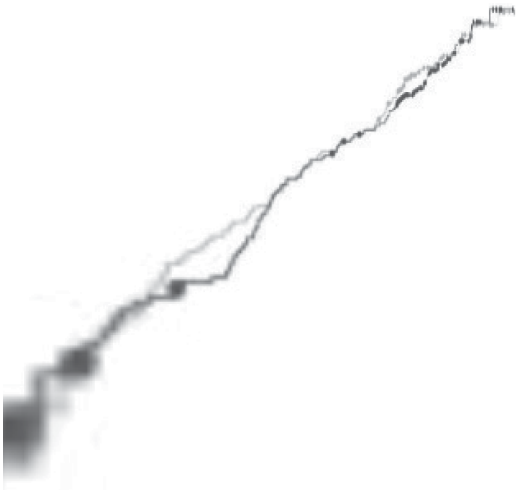
(c)



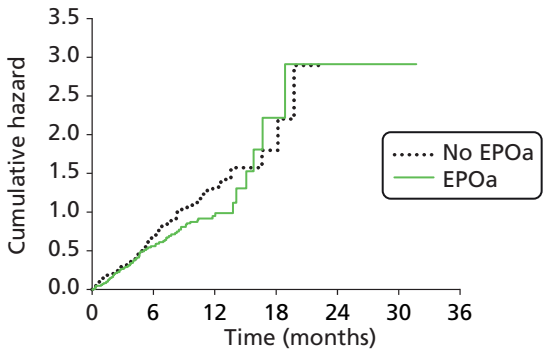
(e)



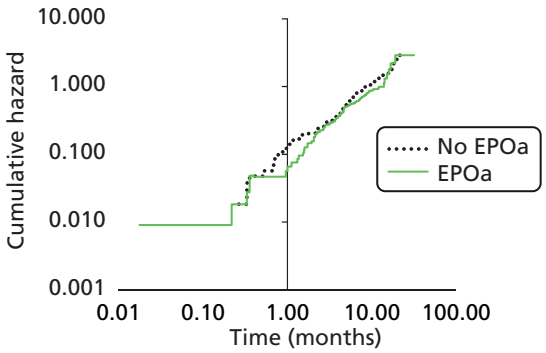
(f)



(h)

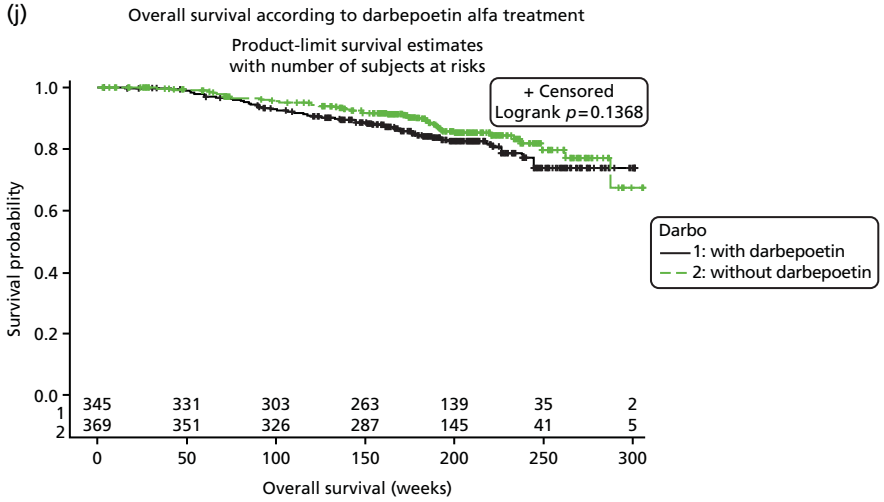
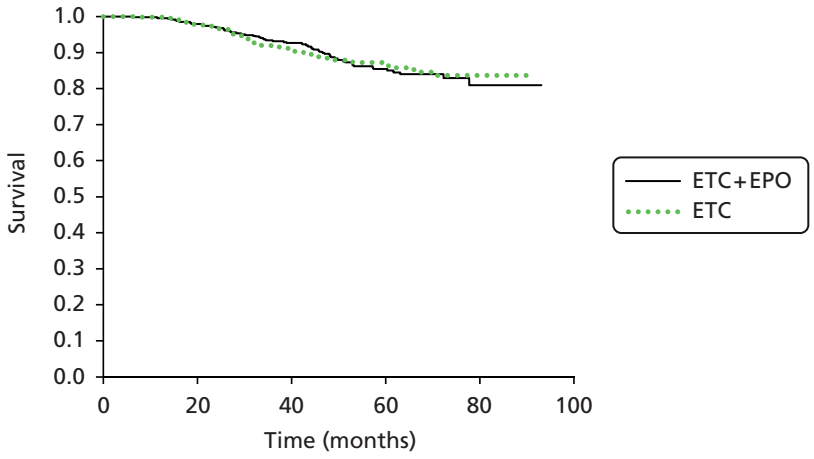


(i)



continued

TABLE 48 Overall survival curves extracted from RCTs (*continued*)

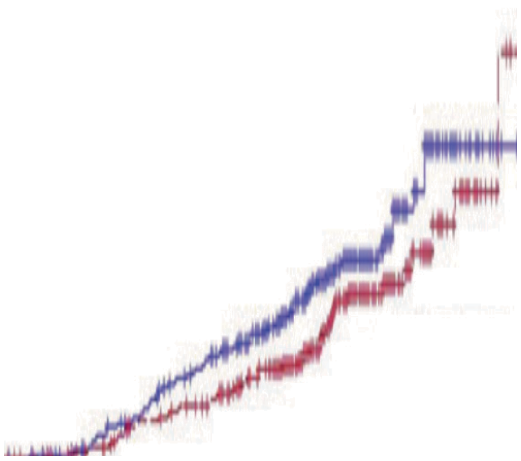
Study	Survival curve
Untch 2011[78,80]	(j)  Reproduced from Untch M, Minckwitz G, Konecny GE, Conrad U, Fett W, Kurzeder C, *et al.* PREPARE trial: a randomised phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer–outcome on prognosis. *Ann Oncol*: official journal of the European Society for Medical Oncology/ESMO. 2011;**22**:1999–2006[80] by permission of Oxford University Press (UK) © European Society for Medical Oncology (ESMO) All rights reserved (URL: http://annonc.oxfordjournals.org/content/22/9/1999.full.pdf+html)
Moebus 2013[62]	(m) 

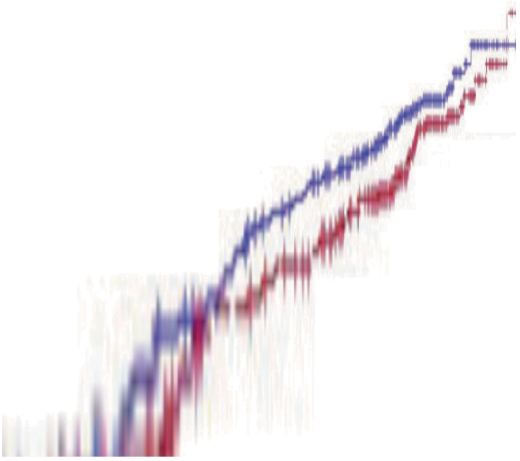
EPO, erythropoietin; ETC, epirubicin, paclitaxel and cyclophosphanide.

Note

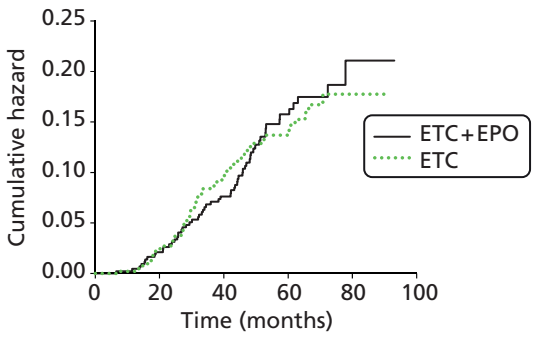
As copyright was not granted for the reproduction of plots for Littlewood and colleagues[70] and Grote and colleagues[74] these have not been included in this table.

Cumulative hazard curve	Weibull plot
(k)	(l)

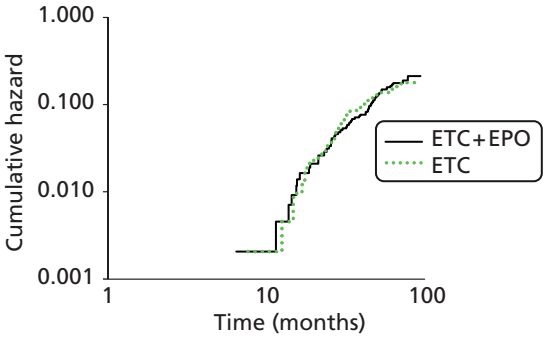




(n)



(o)



Given that some included studies supported the use of an exponential survival function and that the exponential survival function is frequently used in the modelling of cancer, we used an exponential survival function in the base case with proportional hazards.

To explore the significant structural uncertainty we also performed three scenario analyses:

1. The survival in the control arm was unchanged from the base case and survival for patients receiving ESA therapy was estimated using proportional hazards for the first 3 years followed by an equal hazard rate to that of the control arm (as though the effect of ESA therapy on mortality lasts for only 3 years). The length of follow-up is not reported for a number of studies contributing to the HR for OS, although it is likely for a number of studies that follow-up was extremely limited. Of the studies providing Kaplan–Meier curves, follow-up was > 3 years only for Untch and colleagues[80] (median follow-up 43.5 months) and Moebus and colleagues[62] (median follow-up 62 months).
2. A Weibull survival function was fitted to the control arm survival curve from Untch and colleagues[80] and a proportional hazards assumption was applied using the same HR as applied in the base case.
3. Two log-normal survival functions were fitted to the two arms in the study by Littlewood and colleagues[70] and were extrapolated to a mean life expectancy for 59-year-old members of the general population (weighted average of male and female life expectancy according to the gender balance in the study). Limiting the extrapolation to life expectancy was carried out to approximate the inclusion of background mortality, which was otherwise not modelled and would not have been adequately represented in the Kaplan–Meier curve (which covers only approximately 3 years of follow-up).

We were able to perform a PSA for the first two scenarios (although OS in the control arm was not varied probabilistically in the second scenario), but a PSA was not performed for the third scenario as we had no adequate information to incorporate uncertainty about OS in this instance.

Closed-form expressions for the expected discounted life-years in each arm were available for the exponential distribution and for the first scenario (assuming a rate of continuous discounting of r_c):

$$\text{mean discounted life-years in control arm (base case and first scenario; } \lambda = \text{mortality rate)} = 1/(\lambda + r_c) \quad (1)$$

$$\text{mean discounted life-years in ESA arm (base case; } \lambda = \text{mortality rate, } \beta = \text{HR)} = 1/(\lambda \times \beta + r_c) \quad (2)$$

$$\text{mean discounted life-years (first scenario; } \lambda = \text{mortality rate, } \beta = \text{HR)} = (1-\exp(-(\lambda \times \beta + r_c) \times 3.0))/(\lambda \times \beta + r_c) + \exp(-(\lambda + r_c) \times 3.0)/(\lambda + r_c). \quad (3)$$

Closed-form expressions for the expected discounted life-years were not available for the Weibull or log-normal distributions, so these were calculated numerically using trapezoidal integration with a step size of 0.1 years.

Overall survival describes how the OS models were parameterised.

Model parameters

On guidance from NICE, and so that a larger set of clinical study results could be used, clinical effectiveness parameters are not given for individual ESAs but for ESAs as a whole. In other words, in the PenTAG cost-effectiveness modelling there are assumed to be no differences in clinical effectiveness between the alternative ESAs. The only exceptions are for parameters unique to each of the ESAs, such as drug doses and costs.

Appendix 19 provides a summary table which includes all of the model parameters.

Clinical effectiveness parameters

As explained in the previous section, the PenTAG economic evaluation is intended to link directly to the clinical evidence from the RCTs of ESAs. In this section we outline the relevant parameters and their estimates taken from the RCTs.

To ensure consistency between costs and benefits, all parameters were estimated on the basis of ITT. For example, we used the mean weekly dosage of ESAs averaged over all patients at baseline for the full intended treatment duration. This average includes some patients who withdrew from ESA treatment during the trial. This ensures consistency with clinical outcomes, such as the mean difference between treatment arms in the change in Hb level from baseline and the mean difference in the number of units of RBCs transfused between the ESA arm and the control arm, as these quantities are also estimated from all randomised patients.

The ESA withdrawal rate and mean weekly dose are incorporated in the economic model but are often reported only indirectly in trials. The derivations of these parameters (see *Table 50*) are provided in *Erythropoietin-stimulating agent withdrawal rate and mean weekly dose*. Similarly, the mean difference in Hb levels between treatment arms over the entire ESA treatment period (as a proportion of the difference at the end of the trial) is another key parameter in the economic model, but one that is often reported only indirectly. The derivation of this parameter is provided in *Mean difference in haemoglobin levels between treatment arms as a proportion of the difference at the end of the trial*.

The mean weekly dose and frequency of administration can differ between ESAs because of differences in licensing. These differences are discussed in *Erythropoietin-stimulating agent withdrawal rate and mean weekly dose* and *Cost of administering erythropoiesis-stimulating agents,* respectively.

Some parameters were taken directly from random-effects meta-analyses in the PenTAG systematic review of clinical evidence (*Table 49*):

- OS HR
- difference in Hb change from baseline
- difference in number of RBC units transfused
- relative risk of AEs (thromboembolic events, hypertension and thrombocytopenia).

Other parameters were calculated from the inputs in those meta-analyses (see *Table 49*):

- Hb change from baseline in the control arm
- number of RBC units transfused in the control arm
- absolute risk of AEs in the control arm.

Further parameters were not extracted as part of the systematic review of clinical effectiveness evidence and needed to be additionally extracted for the economic analysis:

- OS in the control arm
- baseline Hb level
- mean weekly ESA dose (adjusted for dose escalation, interruption and withdrawal)
- mean difference between Hb change curves as a proportion of the final difference in Hb change from baseline
- duration of ESA treatment
- age
- weight.

TABLE 49 Clinical parameters used in the economic model taken directly from the PenTAG systematic review

Parameter	Pooled mean used in the PenTAG model base case (SE)	Pooled mean used in scenario analysis (SE)	Section
OS (HR)	0.967 (0.079)	0.914 (0.137)	See *Chapter 3*, *Overall survival*
Change in Hb from baseline to end of ESA treatment: difference between ESA and control arms	1.59 (0.130)	1.52 (0.115)	See *Chapter 3*, *Haemoglobin change*
Mean number of RBC units transfused in control arm	2.09	2.30	Calculated from reported outcomes of the RBC units meta-analysis (see *Chapter 3*, *Number of red blood cell units transfused*)
Mean difference in number of RBC units between the ESA and control arms	−0.87 (0.21)	−0.99 (0.22)	See *Chapter 3*, *Number of red blood cell units transfused*
Relative risk of AEs in ESA vs. control arm (reported on natural log scale)			
Thromboembolic events	ln(1.46) = 0.378 (0.158)	ln(1.29) = 0.255 (0.344)	See *Chapter 3*, *Thromboembolic events*
Hypertension	ln(1.8) = 0.588 (0.234)	ln(1.68) = 0.519 (0.250)	See *Chapter 3*, *Hypertension*
Thrombocytopenia	ln(0.93) = −0.073 (0.185)	ln(0.73) = −0.315 (0.350)	See *Chapter 3*, *Thrombocytopenia/ haemorrhage*
Probability of AEs in control arm (%)			
Thromboembolic events	3.3 (0.4)	3.7 (0.8)	Calculated from reported numbers of AEs (see *Chapter 3*, *Safety*)
Hypertension	2.9 (0.5)	1.8 (1.0)	
Thrombocytopenia	6.4 (0.8)	2.5 (0.8)	

Table 50 provides the estimates for some of these outcomes from clinical studies, which are then pooled as described in later sections. The methods used to incorporate the other parameters are discussed in later sections.

We found no evidence from RCTs of normalisation of Hb levels following chemotherapy cessation, therefore this part of the model had to be parameterised on the basis of clinical expert opinion (see *Normalisation of haemoglobin levels following chemotherapy cessation*).

In the base case we used all 24 studies included in the systematic review of clinical effectiveness evidence (see *Chapter 3*). There is some heterogeneity in this collection of studies, which may be the result of treatment intention differences; for example, in some studies the intention may be to correct anaemia, whereas in others the intention may be to prevent anaemia.

In an attempt to produce an analysis more consistent with the licensed use of ESAs (for anaemia correction) we performed a scenario analysis in which the subgroup of studies with an inclusion Hb level of ≤ 11.0 g/dl (or lower) was used. Although this subgroup still includes 13 studies, the precision of some effectiveness estimates was reduced (particularly as not all studies include all outcomes) and the subgroup may still include studies in which a higher target Hb level than recommended in the licence was chosen.

TABLE 50 Additional clinical effectiveness outcomes from RCTs

Study	Mean weekly ESA dose[a]	Hb			Mean OS
		Mean baseline Hb level (g/dl)	Mean increase in Hb level (g/dl) in control arm	Mean difference in Hb levels between treatment arms as a proportion of the difference at the end of the trial (%)[b]	
Wilson and colleagues:[2] included studies meeting inclusion criteria for the PenTAG review					
Abels 1993[63]	307 IU/kg[c]	NR	NR	NR	NR
Aravantinos 2003[64]	NR	EA 9.80, No tx 9.32	+1.23	23	NR
Boogaerts 2003[65]	463 IU/kg	EB 9.0, No tx 9.2	+0.9[d]	68[d]	NR
Dammacco 2001[66]	496 IU/kg	EA 9.3, PBO 9.6	0.0	56	NR
Del Mastro 1997[67]	429 IU/kg	EA 13.0, No tx 13.1	−3.05	73	NR
Dunphy 1999[68]	467 IU/kg	14.1	−2.8	77	NR
Hedenus 2002[53]	2.20 µg/kg	DA (2.25 µg/kg QW[e]) 9.4 (SD 1.3), PBO 9.5 (1.0)	+1.00	59	NR
Hedenus 2003[17]	NR	9.54	+0.19	NR	NR
Kotasek 2003[50]	2.025 µg/kg	DA 9.93,[f] PBO 9.87	−0.02	NR	NR
Kurz 1997[69]	NR	EA 9.88, No tx 9.85	+0.25	50	NR
Littlewood 2001[70]	NR	9.8	+0.5	110	12-month survival: EA 60%, PBO 49%; median survival (months): EA 17, PBO 11
Österborg 2002,[71] 2005[79]	NR	EB 9.2, PBO 9.3	NR	NR	EB 17.4 months,[d] PBO 18.0 months[d]
Silvestris 1995[72]	733 IU/kg	(From figure) Non-transfusion dependent: EA 7.6,[d] No tx 7.8;[d] transfusion dependent: EA 7.4,[d] No tx 7.8[d]	(From figure) Combining transfusion dependent and non-transfusion dependent: +0.22[d]	(Combining transfusion dependent and non-transfusion dependent) 84[d]	NR
ten Bokkel Huinink 1998[51]	302 IU/kg	EA (150 IU/kg TIW) 12.0,[d] No tx 11.8[d]	NR	NR	NR
Thatcher 1999[52]	335 IU/kg	EA 13.7,[d] PBO 13.4[d]	NR	92	NR
Vansteenkiste 2002[73]	161 µg[g]	10.11	NR	NR	DA 46 weeks,[d] PBO 36 weeks[d]

continued

TABLE 50 Additional clinical effectiveness outcomes from RCTs (*continued*)

Study	Mean weekly ESA dose[a]	Hb			Mean OS
		Mean baseline Hb level (g/dl)	Mean increase in Hb level (g/dl) in control arm	Mean difference in Hb levels between treatment arms as a proportion of the difference at the end of the trial (%)[b]	
PenTAG review update 2004 onwards					
Grote 2005[74]	Cannot be calculated as intended treatment duration not fixed	EA 12.8, PBO 13.0	−2.7	232[h]	EA 10.5 months,[d] PBO 10.4 months[d]
Moebus 2013[62]	414 IU/kg	EA 12.40,[d] No tx 12.80[d]	−2.20	77	5-year OS: EA 81%, No tx 83%
Ray-Coquard 2009[75]	NR	EA 10.0, No tx 10.0	NR	NR	EA 7.6 months,[d] No tx 6.0 months[d]
Strauss 2008[76]	26,338 IU	EB 11.4, No tx 11.6	−0.7	76	NR
Tjulandin 2010[48]	ET 23,594 IU, EB 31,251 IU	ESA 9.5, PBO 9.4	+0.2	ET 62, EB 60	NR
Tjulandin 2011[77]	ET 22,235 IU	ET 9.2, PBO 9.1	+0.65	50	NR
Untch 2011[78,80]	NR	DA 13.64, No tx 13.61	−0.98	NR	At median follow-up (43.5 months): DA 88.0%, No tx 91.8%

DA, darbepoetin alfa; EA, epoetin alfa; EB, epoetin beta; ET, epoetin theta; No tx, no treatment; NR, not reported; PBO, placebo; QW, once weekly; TIW, three times weekly.

a See *Erythropoietin-stimulating agent withdrawal rate and mean weekly dose* for a description of the estimation methods.

b See *Appendix 20* for calculation details.

c Reported in Henry and Abels.[85]

d Median.

e Median weekly dose.

f Includes patients randomised to unlicensed doses.

g Calculated from data reported in Vansteenkiste and colleagues.[84]

h The final Hb levels shown in *Figure 2* of Grote and colleagues[74] do not coincide with those described in the text – data have been extracted from the graph for the mean difference in Hb over time and from the text for the mean increase in Hb levels in the control arm.

Note

Study and baseline characteristics are reported in *Appendix 7* and dose administered (application of licence) within the studies is reported in *Appendix 9*.

If target Hb level is used to identify subgroups, the number of included studies falls significantly; only two studies have an inclusion Hb level ≤ 11.0 g/dl and a target Hb level ≤ 13.0 g/dl.[48,77] One additional study[80] had a target Hb level ≤ 13.0 g/dl (but not an inclusion Hb level ≤ 11.0 g/dl). We did not believe these subgroups to be adequate to inform the model because of a lack of precision and possible bias, as Untch and colleagues[78,80] did not meet a number of study quality standards.

Two notable clinical outcomes from the RCTs were not used in the economic model: the haematological response rate and the tumour response rate. The haematological response rate is defined as the proportion of patients achieving either an increase in Hb of at least 2 g/dl or a haematocrit increase of at least 6%. We did not use this outcome in the model for two reasons. First, we used more detailed information on the change in Hb level from the RCTs. Second, as far as we are aware, the impact of haematocrit levels on quality of life is unknown. Tumour response rate RCT data were not used in the PenTAG model because the tumour response rate is modelled indirectly by its impact on survival and we did not model the cancer disease pathway.

There is significant uncertainty surrounding a number of clinical effectiveness parameters and it is important that the impact of this uncertainty on the decision problem is demonstrated. We performed a PSA in which model parameters were varied according to probability distributions with expected values equal to the deterministic parameter values. Although it would be best practice for certain parameters to be correlated in the PSA, there were not enough data for such an approach and, as such, all parameters were drawn independently.

It would also be best practice to have the distributions of parameters in the PSA reflect the between-study variance after accounting for the within-study variance; however, the within-study variance was not reported or not extracted for outcomes not included in the systematic review of clinical effectiveness. As a result, for some parameters we used the sample SD of the extracted outcomes from studies as the SE in the model. This is preferable to using the sample SE as this would underestimate uncertainty (as it would not incorporate the within-study variance). The sample SD was also weighted using the same weights as the central estimate.

Number of red blood cell transfusions

The systematic review of clinical effectiveness evidence provides a summary estimate for the difference in number of RBC units transfused per patient between patients receiving and patients not receiving ESAs of −0.87 (95% CI −1.28 to −0.46). The CI corresponds to a SE of 0.21 units. This summary estimate is from a random-effects meta-analysis and we used the same weights to estimate the absolute mean number of RBC units transfused for patients not receiving ESA therapy (2.09 units). As the absolute mean number of RBC units transfused does not affect cost-effectiveness, this was not varied in the PSA.

In the scenario analysis with the subgroup of studies in which the inclusion Hb level was ≤ 11.0 g/dl the difference in number of RBC units transfused was −0.99 (95% CI −1.41 to −0.56) and the absolute mean number of RBC units transfused in the no ESA arm was 2.30 units.

Assuming that the average number of RBC units per transfusion is equal regardless of ESA use, we can calculate the average number of transfusions that occur for each transfused patient. In the base case we used an average number of units per transfusion of 2.7 units.[172] A normal distribution was used for this parameter in the PSA, with the SE equal to 20% of the mean.

Erythropoietin-stimulating agent withdrawal rate and mean weekly dose

Erythropoietin-stimulating agent dosages are adaptive, in many cases being increased when an inadequate initial response is obtained and decreased or interrupted if Hb levels rise too fast or too high. Furthermore, patients may withdraw from ESA therapy for a number of reasons. As most of the clinical effectiveness data informing the model was calculated on an ITT basis (the general exception being AE data), it is important that the amount of ESA drug use is commensurate.

The modelling approach adopted was to combine the withdrawal rate, dose escalation, dose reduction, etc., into a single parameter, the ITT mean weekly dose. This was estimated, when possible, from data published in the studies included in the systematic review of clinical effectiveness. No single method of estimation would work for all studies, so we briefly outline the most common methods employed:

- if the mean dose actually administered (denoted *D*) is reported, as well as the mean treatment duration (*T*) and intended treatment duration (*T**), the ITT mean weekly dose is calculated as $D \times T \div T^*$
- the mean treatment duration can also be estimated if it is not reported: if the number or proportion of patients remaining on ESA therapy is reported at various time points, these can be interpolated and then the area under the proportion–time curve is approximately equal to the mean treatment duration
- if the mean cumulative dose per patient is given, this can be divided by the intended treatment duration to calculate the ITT mean weekly dose.

Table 51 lists the clinical effectiveness studies with estimates of ITT mean weekly dose and the corresponding weights of those studies in the random-effects meta-analysis of Hb change. In the base case the weights were taken from the full set of RCTs. In a scenario analysis the weights were used from the subgroup in which the initial Hb level was ≤ 11 g/dl. An average weight of 66.6 kg was assumed to convert from weight-based to fixed doses and produce the estimates in *Table 52*. As no studies were found with epoetin zeta ITT mean weekly doses, we assumed the same mean weekly dose as for epoetin alfa because of the similarity of their licences.

TABLE 51 Mean weekly doses from clinical effectiveness studies

			Weight[a]	
Study	ESA	ITT mean weekly dose	Base case[b]	Scenario analysis[c]
Abels 1993[63]	Epoetin alfa	307 IU/kg[d]	10.72[e]	14.61[e]
Boogaerts 2003[65]	Epoetin beta	463 IU/kg	6.69	11.14
Dammacco 2001[66]	Epoetin alfa	496 IU/kg	5.71	8.11
Del Mastro 1997[67]	Epoetin alfa	429 IU/kg	5.28	NA
Dunphy 1999[68]	Epoetin alfa	467 IU/kg	NA	NA
Hedenus 2002[53]	Darbepoetin alfa	2.20 µg/kg	4.81	6.01
Kotasek 2003[50]	Darbepoetin alfa	2.025 µg/kg	4.32	5.07
Silvestris 1995[72]	Epoetin alfa	733 IU/kg	NA	NA
ten Bokkel Huinink 1998[51]	Epoetin alfa	302 IU/kg	4.77	NA
Thatcher 1999[52]	Epoetin alfa	335 IU/kg	NA	NA
Vansteenkiste 2002[73]	Darbepoetin alfa	161 µg[f]	NA	NA
Moebus 2013[62]	Epoetin alfa	414 IU/kg	NA	NA
Strauss 2008[76]	Epoetin beta	26,338 IU	NA	NA
Tjulandin 2010[48]	Epoetin theta	23,594 IU	5.34	7.18
	Epoetin beta	31,251 IU	5.10	6.64
Tjulandin 2011[77]	Epoetin theta	22,235 IU	6.29	9.78

a Weighting taken from random-effects meta-analysis of mean Hb change in the systematic review.
b Studies with a licensed start dose.
c Studies with a licensed start dose and an initial Hb level ≤ 11 g/dl.
d Reported in Henry and Abels.[85]
e Sum of weights for cisplatin and non-cisplatin chemotherapy.
f Reported in Vansteenkiste and colleagues.[84]

TABLE 52 Mean ESA doses in the model

ESA	Base case	Scenario analysis
Epoetin alfa (IU/week)	24,729	24,745
Epoetin beta (IU/week)	31,021	30,840
Epoetin theta (IU/week)	22,859	22,810
Epoetin zeta (IU/week)	24,729	24,745
Darbepoetin alfa (µg/week)	141.1	140.1

As there is significant uncertainty in the ITT mean weekly dose, we assumed a gamma distribution with means as shown in *Table 52* and SEs equal to 20% of the means.

Duration of erythropoiesis-stimulating agent treatment

As stated in *Clinical effectiveness parameters*, clinical effectiveness parameters were estimated on an ITT basis. As such, the duration of ESA treatment was taken to be 12 weeks in this analysis, as this is the estimate acquired from the majority (13/23) of the RCTs included in the PenTAG meta-analysis. Some RCTs included longer treatment durations, but 17 of 23 reported a treatment duration of $\leq$ 18 weeks and all but one study with unambiguous reporting reported a duration of $\leq$ 24 weeks. In a univariate sensitivity analysis we explored the impact of varying treatment duration up to 24 weeks, which is also the maximum duration included in the study by Wilson and colleagues.[2] It is noted that the duration of ESA treatment affects the short-term QALY gain, as a longer duration of treatment allows time for more QALYs to accrue.

Erythropoietin-stimulating agent drug administration was modelled per protocol rather than on an ITT basis (i.e. withdrawals were not incorporated). In the base case this does give a higher cost of administration for ESAs than we would otherwise expect; however, this increase in the cost of drug administration is small enough that it does not greatly influence the overall costs. This cost is further discussed in *Cost of administering erythropoiesis-stimulating agents*.

Initial (baseline) haemoglobin level

The initial Hb level of patients has an impact on the Hb level after chemotherapy has finished and therefore has an impact on how long it takes for Hb levels to return to normal. Initial Hb levels are well reported in the included RCTs. *Figure 27* shows the range of baseline Hb levels recorded. There is heterogeneity in the initial Hb levels, which is likely to be a result of the different inclusion criteria used.

In the base case we calculated a weighted average baseline Hb level with weights taken from the random-effects meta-analysis of mean Hb change. In a scenario analysis the weights from the subgroup with an inclusion Hb level of $\leq$ 11.0 g/dl were used.

The resulting baseline Hb levels are 10.38 g/dl (base case) and 9.40 g/dl (scenario analysis), as shown in *Table 53*. The SE in the base case was estimated from the weighted SD of the baseline Hb levels as 1.59 g/dl, with the effect that 95% of simulated values fall in the range 7.28–13.49 g/dl. The SE in the scenario analysis was calculated as 0.22 g/dl, with the effect that 95% of simulated values fall in the range 8.97–9.84 g/dl.

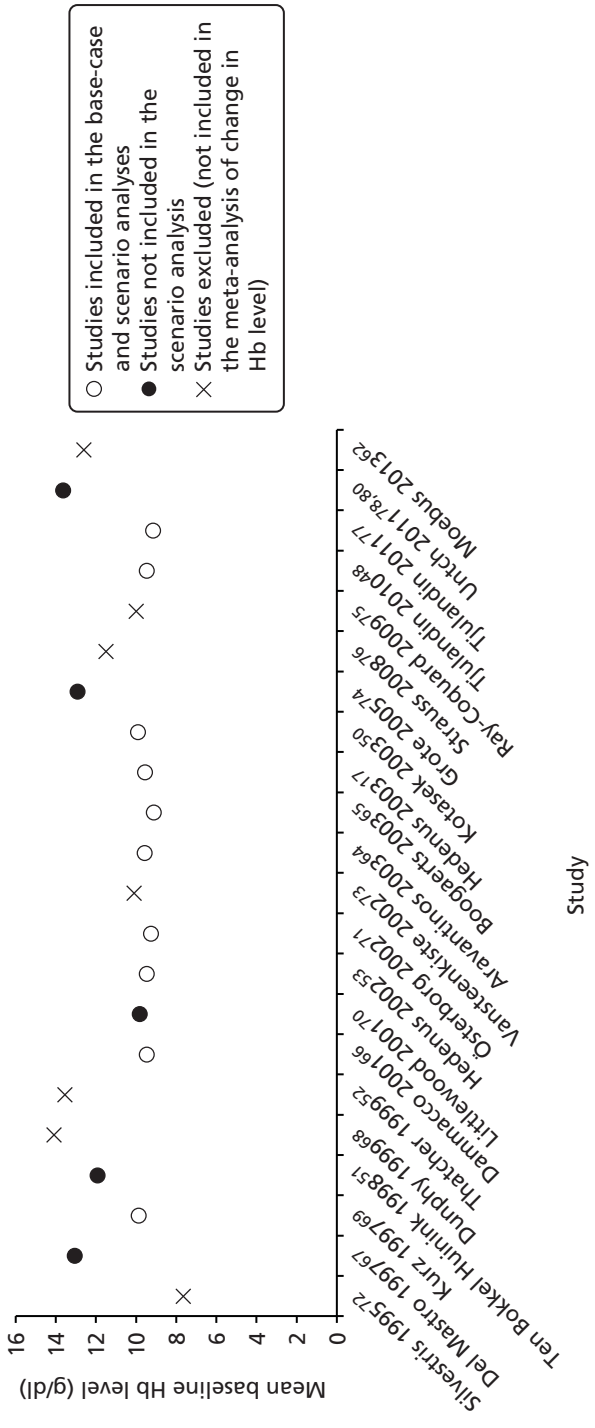


FIGURE 27 Initial Hb level by study.

TABLE 53 Calculation of baseline Hb level parameters

Study	Baseline Hb level (g/dl)	Weight[a]	
		Base case[b]	Scenario analysis[c]
Aravantinos 2003[64]	9.56	4.46	5.34
Boogaerts 2003[65]	9.1	6.69	11.14
Dammacco 2001[66]	9.45	5.71	8.11
Del Mastro 1997[67]	13.05	5.28	NA
Dunphy 1999[68]	14.1	NA	NA
Hedenus 2002[53]	9.45	4.81	6.01
Hedenus 2003[17]	9.54	6.79	11.51
Kotasek 2003[50]	9.90	4.32	5.07
Kurz 1997[69]	9.865	2.81	2.78
Littlewood 2001[70]	9.8	6.57	NA
Österborg 2002,[71] 2005[79]	9.25	6.87	11.82
Silvestris 1995[72]	7.65	NA	NA
ten Bokkel Huinink 1998[51]	11.9	4.77	NA
Thatcher 1999[52]	13.55	NA	NA
Vansteenkiste 2002[73]	10.11	NA	NA
Grote 2005[74]	12.9	6.05	NA
Moebus 2013[62]	12.60	NA	NA
Ray-Coquard 2009[75]	10.0	NA	NA
Strauss 2008[76]	11.5	NA	NA
Tjulandin 2010[48]	9.45	10.44[d]	13.82[d]
Tjulandin 2011[77]	9.15	6.29	9.78
Untch 2011[78,80]	13.625	7.42	NA
Summary estimate (base case)	10.38	89.28 (100%)	–
Summary estimate (scenario)	9.40	–	85.38 (100%)

a Weighting taken from the random-effects meta-analysis of mean Hb change in the systematic review.
b Studies with a licensed start dose.
c Studies with a licensed start dose and an initial Hb level $\leq$ 11 g/dl.
d Weights summed over the epoetin beta and epoetin theta arms.

Change in haemoglobin level for patients not receiving erythropoiesis-stimulating agent therapy

Haemoglobin levels are expected to vary over time for patients even if they do not receive ESA therapy. This has an important impact on how long Hb levels take to return to normal. It is expected that the Hb trajectories for patients in different studies will vary because of the differing effects of chemotherapy regimens and cancers on Hb levels.

Figure 28 shows the change in Hb level for patients not receiving ESAs in the different RCTs and *Table 54* shows how these data are combined to form the parameter values in the base-case analysis and the scenario analysis in the subgroup of studies with an inclusion Hb level of $\leq$ 11.0 g/dl.

The resulting change in Hb level for patients not receiving ESA therapy is –0.155 g/dl in the base case and 0.469 g/dl in the scenario analysis. The weighted sample SD was used to estimate the SE in the base case as 1.25 g/dl, meaning that 95% of the simulated values range from –2.60 to 2.29 g/dl. In the scenario analysis the SE was estimated as 0.41 g/dl, meaning that 95% of the simulated values range from –0.33 to 1.27 g/dl.

Mean difference in haemoglobin levels between treatment arms as a proportion of the difference at the end of the trial

The mean difference in Hb levels between treatment arms over the entire ESA treatment period, as a proportion of the difference at the end of the trial, is another key parameter for the economic model, but one that is often reported only indirectly.

We therefore calculated, for each week, the improvement in Hb level from baseline in each treatment arm and this quantity as a proportion of the improvement from baseline to the end of treatment. We then took an average to give the mean difference over the treatment period (see *Appendix 20* for details).

Figure 29 shows the values from included studies. While for most studies the parameter value is under 100%, for two studies the parameter value is over 100% because the final difference in Hb level is less than at earlier times in the trial (i.e. the Hb trajectories of the two arms converge over time). *Table 55* shows the derivation of the parameter values used in the model (on the basis of a weighted-average using weights from the random-effects meta-analysis of Hb level change).

The parameter value in the base case is 80.6% and the value in the scenario analysis is 55.5%. The weighted sample SD was used to estimate the SE, calculated as 55.0% in the base case and 12.0% in the scenario analysis. A gamma distribution was assumed such that in the base case 95% of simulated values fall in the range 10.9–218.6% and in the scenario analysis 95% of simulated values fall in the range 34.4–81.4%.

Normalisation of haemoglobin levels following chemotherapy cessation

It has been assumed in some previous economic evaluations of ESAs[2,156] that after chemotherapy cessation Hb levels will return to 'normal' (see *Chapter 4*). Although this is an intuitive assumption that is generally supported by clinical expert opinion, we have not found direct evidence of this process (termed normalisation) in the published literature. Given that approximately half of the QALY gain from ESA therapy could be accrued during normalisation,[2] the modelling of normalisation is likely to be very important in determining overall cost-effectiveness.

The PenTAG modelling approach matches that adopted in previous economic evaluations, namely that in the normalisation period Hb levels rise at a constant rate (the same rate for all patients regardless of treatment) until they reach a 'normal level'. Assuming a slower rate of normalisation results in improved incremental effectiveness of ESA therapy over standard care, as does assuming a higher normal Hb level.

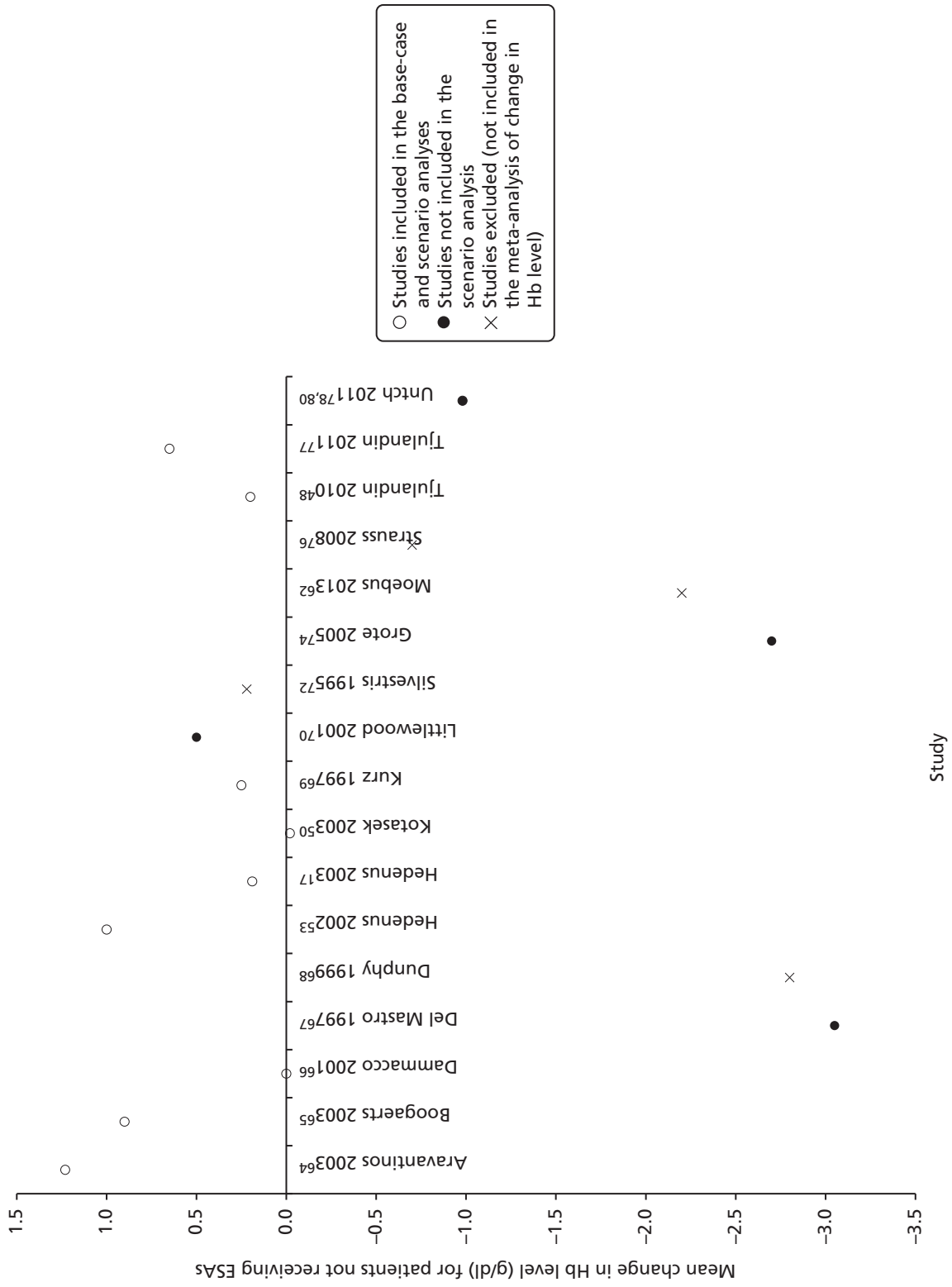


FIGURE 28 Change in Hb level for patients not receiving ESAs at the end of the study period.

TABLE 54 Change in Hb level for patients not receiving ESAs at the end of the study period

Study	Change in Hb level (g/dl)	Weight[a]	
		Base case[b]	Scenario analysis[c]
Aravantinos 2003[64]	1.23	4.46	5.34
Boogaerts 2003[65]	0.9	6.69	11.14
Dammacco 2001[66]	0.0	5.71	8.11
Del Mastro 1997[67]	–3.05	5.28	NA
Dunphy 1999[68]	–2.8	NA	NA
Hedenus 2002[53]	1.00	4.81	6.01
Hedenus 2003[17]	0.19	6.79	11.51
Kotasek 2003[50]	–0.02	4.32	5.07
Kurz 1997[69]	0.25	2.81	2.78
Littlewood 2001[70]	0.5	6.57	NA
Österborg 2002,[71] 2005[79]	NR	6.87	11.82
Silvestris 1995[72]	0.22	NA	NA
ten Bokkel Huinink 1998[51]	NR	4.77	NA
Thatcher 1999[52]	NR	NA	NA
Vansteenkiste 2002[73]	NR	NA	NA
Grote 2005[74]	–2.7	6.05	NA
Moebus 2013[62]	–2.20	NA	NA
Ray-Coquard 2009[75]	NR	NA	NA
Strauss 2008[76]	–0.7	NA	NA
Tjulandin 2010[48]	0.2	10.44[d]	13.82[d]
Tjulandin 2011[77]	0.65	6.29	9.78
Untch 2011[78,80]	–0.98	7.42	NA
Summary estimate (base case)	–0.155	77.64 (100%)	
Summary estimate (scenario analysis)	0.469		73.56 (100%)

NR, not reported.
a Weighting taken from the random-effects meta-analysis of mean Hb change in the systematic review.
b Studies with a licensed start dose.
c Studies with a licensed start dose and an initial Hb level $\leq$ 11 g/dl.
d Weights summed over the epoetin beta and epoetin theta arms.

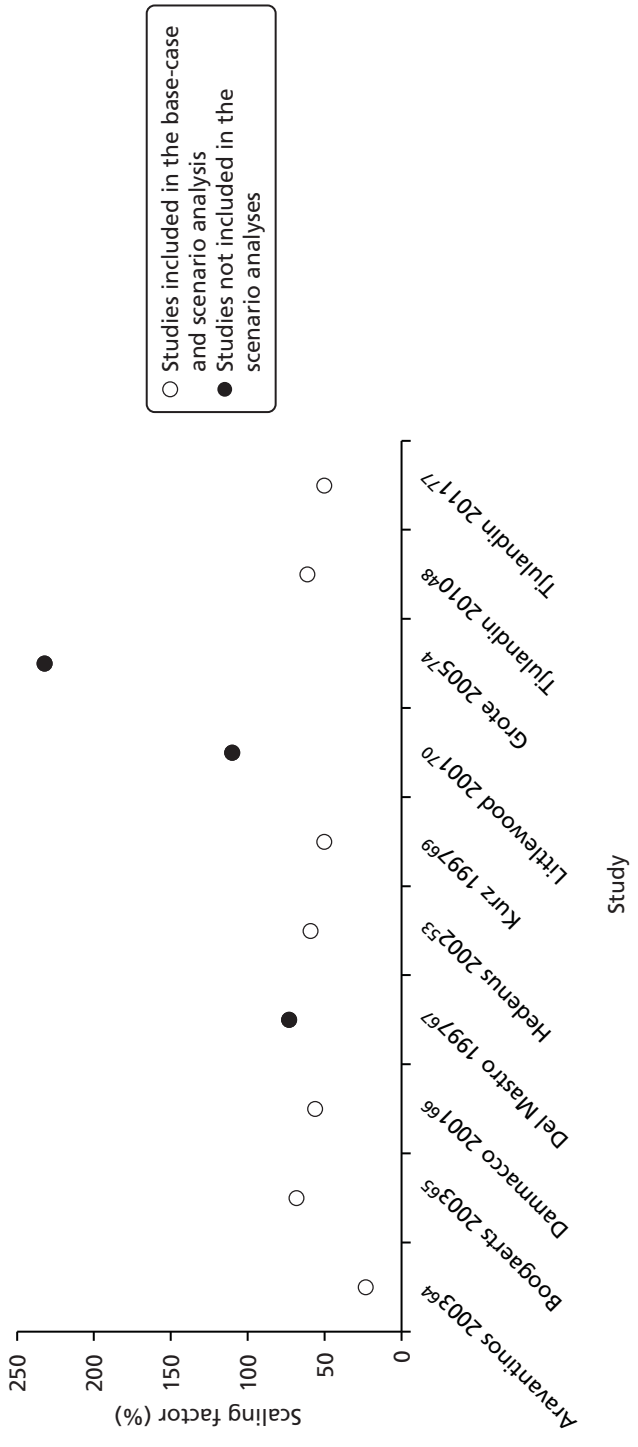


FIGURE 29 Mean difference in Hb levels between treatment arms as a proportion of the difference at the end of the trial.

TABLE 55 Mean difference in Hb levels between treatment arms as a proportion of the difference at the end of the trial

Study	Mean difference in Hb levels as proportion of the difference at the end of the trial (%)	Weight[a]	
		Base case[b]	Scenario analysis[c]
Aravantinos 2003[64]	23	4.46	5.34
Boogaerts 2003[65]	68	6.69	11.14
Dammacco 2001[66]	56	5.71	8.11
Del Mastro 1997[67]	73	5.28	NA
Dunphy 1999[68]	77	NA	NA
Hedenus 2002[53]	59	4.81	6.01
Hedenus 2003[17]	NR	6.79	11.51
Kotasek 2003[50]	NR	4.32	5.07
Kurz 1997[69]	50	2.81	2.78
Littlewood 2001[70]	110	6.57	NA
Österborg 2002,[71] 2005[79]	NR	6.87	11.82
Silvestris 1995[72]	84	NA	NA
ten Bokkel Huinink 1998[51]	NR	4.77	NA
Thatcher 1999[52]	92	NA	NA
Vansteenkiste 2002[73]	NR	NA	NA
Grote 2005[74]	232	6.05	NA
Moebus 2013[62]	77	NA	NA
Ray-Coquard 2009[75]	NR	NA	NA
Strauss 2008[76]	76	NA	NA
Tjulandin 2010[48]	ET 62, EB 60; midpoint 61	10.44[d]	13.82[d]
Tjulandin 2011[77]	50	6.29	9.78
Untch 2011[78,80]	NR	7.42	NA
Summary estimate (base case)	80.6	59.11 (100%)	
Summary estimate (scenario analysis)	55.5		56.98 (100%)

EB, epoetin beta; ET, epoetin theta; NR, not reported.
a Weighting taken from the random-effects meta-analysis of mean Hb change in the systematic review.
b Studies with a licensed start dose.
c Studies with a licensed start dose and an initial Hb level $\leq$ 11 g/dl.
d Weights summed over the epoetin beta and epoetin theta arms.

Table 56 provides normalisation parameters from previous economic evaluations and those suggested by clinical experts. A normal Hb level of 12 g/dl appears to be a good compromise with regard to the values suggested (this figure may be lower for haematological cancers, but this is not modelled). This was varied in the PSA with a distribution $N(\mu,\sigma^2)$, with $\mu = 12.0$ and $\sigma = 0.51$, with the result that 95% of simulated values lie in the range 11.0–13.0 g/dl. It is possible for patients receiving ESA therapy in the model to finish ESA therapy with a higher Hb level than the 'normal level', in which case their actual Hb level is assumed to be the normal level on the basis that clinicians would not seek to raise Hb levels above normal levels for a patient. We also assumed that the same utility gradient with respect to Hb level is observed (contrary to some studies that show a levelling off), on the basis that clinicians would raise Hb levels in such patients only to improve HRQoL and therefore utility. If it is actually the case that utility levels off, then this method will overestimate the short-term QALY gain when Hb levels of ≥ 12 g/dl are modelled.

Given that the base-case initial Hb level is 10.38 g/dl and the base-case change in Hb for patients not receiving ESAs is –0.15 g/dl, normalisation is expected to take the Hb level from 10.23 g/dl to 12.00 g/dl, a rise of 1.77 g/dl. One clinical expert suggested that normalisation could be complete within 6–8 weeks; this would suggest a rate of normalisation of 0.22–0.30 g/dl/week, which is consistent with other estimates.

A normalisation rate of 0.2 g/dl/week is broadly consistent with previous evaluations and clinical expert opinion and this was used as the PenTAG base-case value. In PSA this was varied according to $N(\mu,\sigma^2)$, with $\mu = 0.2$ and $\sigma = 0.051$, with the result that 95% of simulated values lie in the range 0.1–0.3 g/dl/week.

It was assumed on the basis of clinical opinion that normalisation will be complete within 3 month; this was incorporated in the model as a cap on the maximum time to normalisation, with the rate of normalisation effectively being increased when necessary to meet this cap.

TABLE 56 Normalisation parameters

Source	Rate of normalisation (g/dl/week)	Normal Hb level (g/dl)
Previous economic evaluations		
Amgen Inc. model[2]	0.1	≥ 12
Roche model[2]	0.2	13 (solid tumours), 11.9 (haematological tumours)
Ortho Biotec model[2]	0.2	13
Birmingham model[2]	0.25	13
Borg 2008[145]	0.25	13
Clinical expert opinion		
Expert 1 (KS)	Normalised within 3 months	
Expert 2 (CR)	0.125	11
Expert 3 (MN)	0.25	11
Expert 4 (NR)	Normalised within 6–8 weeks	12

Overall survival

To parameterise the base case (exponential survival function with proportional hazards) we calculated what rate parameter (λ) would be necessary to achieve either the reported median survival or the reported Kaplan–Meier survival at a specified point in time in the control arm for each included study. We then calculated a weighted geometric mean of the rates (using the weights from the random-effects meta-analysis of the OS HR) using the formula:

$$\bar{\lambda}_{GM} = \left(\prod_{i=1}^{n} \lambda_i^{w_i} \right)^{1 / \sum_{i=1}^{n} w_i} = \exp\left(\frac{\sum_{i=1}^{n} w_i \ln \lambda_i}{\sum_{i=1}^{n} w_i} \right), \quad (4)$$

where λ_i is the estimate of λ from a study and w_i is the weight given to that study. The weighted geometric mean was chosen, as the same mean OS is obtained whether the average of λ values or the average of OS is used.

Table 57 provides the calculation of the summary estimates in the base case (all studies included) and in the scenario analysis (including only studies with an inclusion Hb level of ≤ 11.0 g/dl).

The resulting values for λ correspond to a mean OS in the control arm of 2.670 years in the base case and 1.447 years in the scenario analysis. In the PSA the baseline OS was set to follow a gamma distribution, with a SE of 50% of the mean to capture the high level of uncertainty and the range of cancers from which patients receiving ESA therapy may suffer.

Overall survival for patients in the ESA arm was calculated by applying the HR provided in the clinical effectiveness review to the OS for patients not receiving ESA therapy. In the base case the hazard rate is 0.967, giving a mean undiscounted survival for patients on ESA therapy of 2.762 years. In the scenario analysis the hazard rate is 0.914, resulting in a mean undiscounted survival for patients on ESAs of 1.583 years. In the PSA the HR was distributed as log-normal to match the result of the random-effects meta-analysis (as the HR was

TABLE 57 Calculation of the OS parameter

Study	Reported OS	Calculated λ	Weight[a]	
			Base case[b]	Scenario analysis[c]
Littlewood 2001[70]	KM at 1 year: 49%	0.713	11.32	NA
Vansteenkiste 2002[73]	Median: 34 weeks	1.060	11.22	21.13
Grote 2005[74]	Median: 10.4 months	0.800	6.05	NA
Österborg 2005[79]	Median: 18.0 months	0.462	12.40	22.46
Ray-Coquard 2009[75]	Median: 6.0 months	1.386	10.22	NA
Untch 2011[78,80]	KM at 43.5 weeks: 91.8%	0.024	8.48	NA
Moebus 2013[62]	KM at 5 years: 83%	0.037	8.69	NA
Summary estimate (base case)		0.374	100%	
Summary estimate (scenario analysis)		0.691		100%

KM, Kaplan–Meier survival estimate.
a Weights taken from the random-effects meta-analysis of the OS HR.
b Studies with a licensed start dose.
c Studies with a licensed start dose and an inclusion Hb level ≤ 11.0 g/dl.

meta-analysed following log-transformation). Using a HR possibly derived from Cox proportional hazards and other non-parametric analyses to adjust a parametric survival function could result in a different result from that obtained after derivation of the HR by parametric fitting, but given the limited data we believe that this is the most appropriate approach. We allowed for the alternative survival distributions to examine whether our results were robust to the adopted base-case assumptions.

Analyses of structural uncertainty in modelling overall survival In the first scenario analysis exploring structural uncertainty in the modelling of OS, the HR for the first 3 years was set to be equal to the HR used in the base case and thereafter a HR of exactly 1 was used.

In the second scenario analysis exploring structural uncertainty in the modelling of OS (in which a Weibull curve was fitted to the control arm of Untch and colleagues[80] and a proportional hazards assumption was applied), the HR derived from the systematic review of clinical effectiveness evidence was used, as in the base case. The Weibull curve was fitted to the control arm of the survival plot by extracting several data points and then finding the fit that minimised the sum of squared errors using Solver in Microsoft Excel. The resulting parameters [using the proportional hazards parameterisation: $S(t) = \exp(-\lambda \times t^{\gamma})$; t in years] were $\lambda = 0.010987$ and $\gamma = 1.950282$. *Figure 30* shows the Weibull function overlaid on the original Kaplan–Meier curve, demonstrating a very good fit.

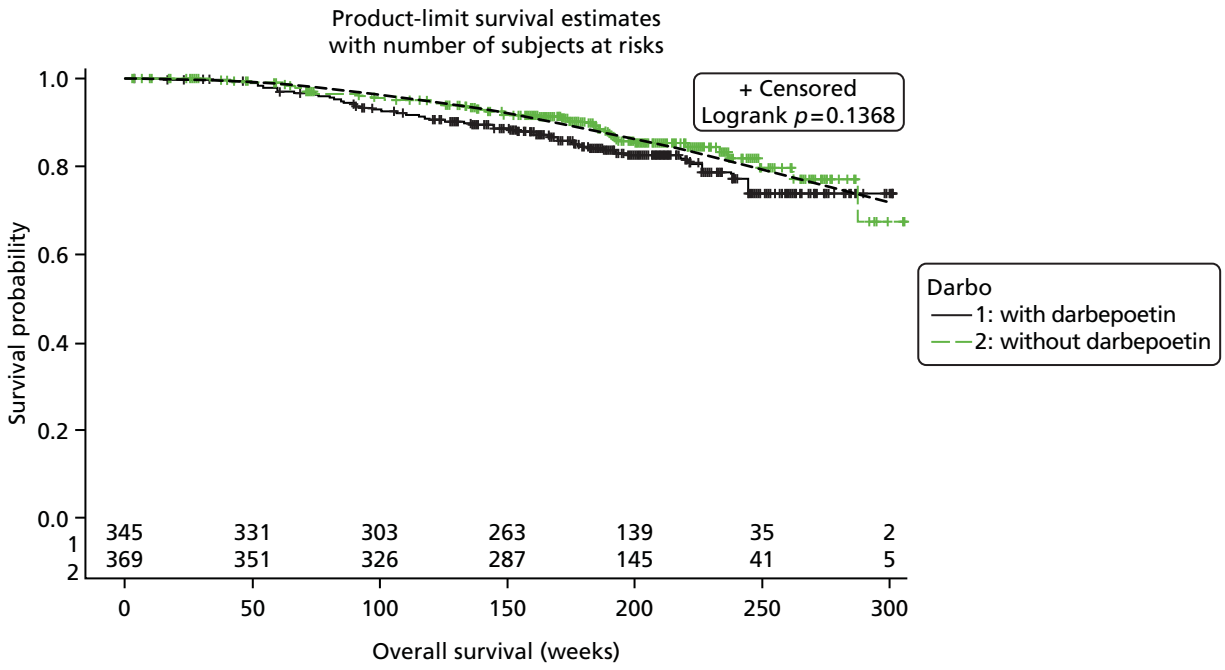


FIGURE 30 Weibull distribution fitted to the Kaplan–Meier survival curve from Untch and colleagues.[78,80] Black dashed line = Weibull curve fitted to the control arm. Reproduced from Untch M, Minckwitz G, Konecny GE *et al.* PREPARE trial: a randomised phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer – outcome on prognosis. *Ann Oncol*: official journal of the European Society for Medical Oncology/ESMO. 2011; 22, 1999–2006[80] by permission of Oxford University Press (UK) © European Society for Medical Oncology (ESMO) All rights reserved (URL: http://annonc.oxfordjournals.org/content/22/9/1999.full.pdf+html).

In the third scenario analysis exploring structural uncertainty all parameters were estimated by fitting to the survival curves in Littlewood and colleagues.[70] The HR from the systematic review of clinical effectiveness evidence cannot be applied in this case as a log-normal curve is used, which cannot be used in conjunction with a proportional hazards assumption. The resulting parameters (time measured in months) were $\mu = 2.501676$ in the control arm and 2.826619 in the ESA arm and $\sigma = 1.483129$ in the control arm and 1.348525 in the ESA arm. According to interim life tables for England and Wales (2010–12),[173] the additional life expectancy for an individual aged 59 years (the approximate mean age of patients in the study by Littlewood and colleagues[70]) is 23.2 years for men and 26.0 years for women. As 251 of 375 participants were female, we estimated an additional life expectancy of 25.1 years. Log-normal functions overlaid on the original Kaplan–Meier plots appear to demonstrate a reasonable fit. Under 2% of the population in both arms was modelled as still alive at 25.1 years, after which it was assumed that survival is zero.

Figures 31 and *32* show the various OS distributions employed for the control and ESA arms respectively.

Figures 33–37 show the OS distributions for both arms under each OS modelling assumption.

Utilities

As explained in *Model structure*, the PenTAG model requires two sources of utility values: (1) utility as a function of Hb levels during ESA treatment and during normalisation to reflect the impact of ESAs on HRQoL and (2) a constant utility value after normalisation, equal in all treatment arms.

The cost-effectiveness of ESAs is likely to be very sensitive to both of these, depending on how survival is accounted for in the model. In particular, cost-effectiveness is sensitive to the rate at which utilities change with respect to changes in Hb (i.e. the gradient of the utility/Hb graph) and this appears to be an area that has not been researched in depth for previous cost-effectiveness reviews. It is therefore necessary to research this carefully and in detail.

As explained in *Model structure*, utility is modelled as a function of Hb level during ESA treatment and during normalization to reflect the impact of ESAs on HRQoL. As such, we implicitly assume that ESAs do not impact on HRQoL in any other way. However, it is possible that ESAs affect some other aspect of health that is not captured by changes in Hb levels.

We used only RCTs to populate these parameters, as only RCTs can support valid causal inferences about the effects of a particular treatment on quality of life.[89] With RCTs, potentially confounding factors such as disease severity, which may affect both direct treatment outcomes and quality of life, should be distributed equally among the trial arms and in order not to bias estimates of the effect of treatment on quality of life.[89]

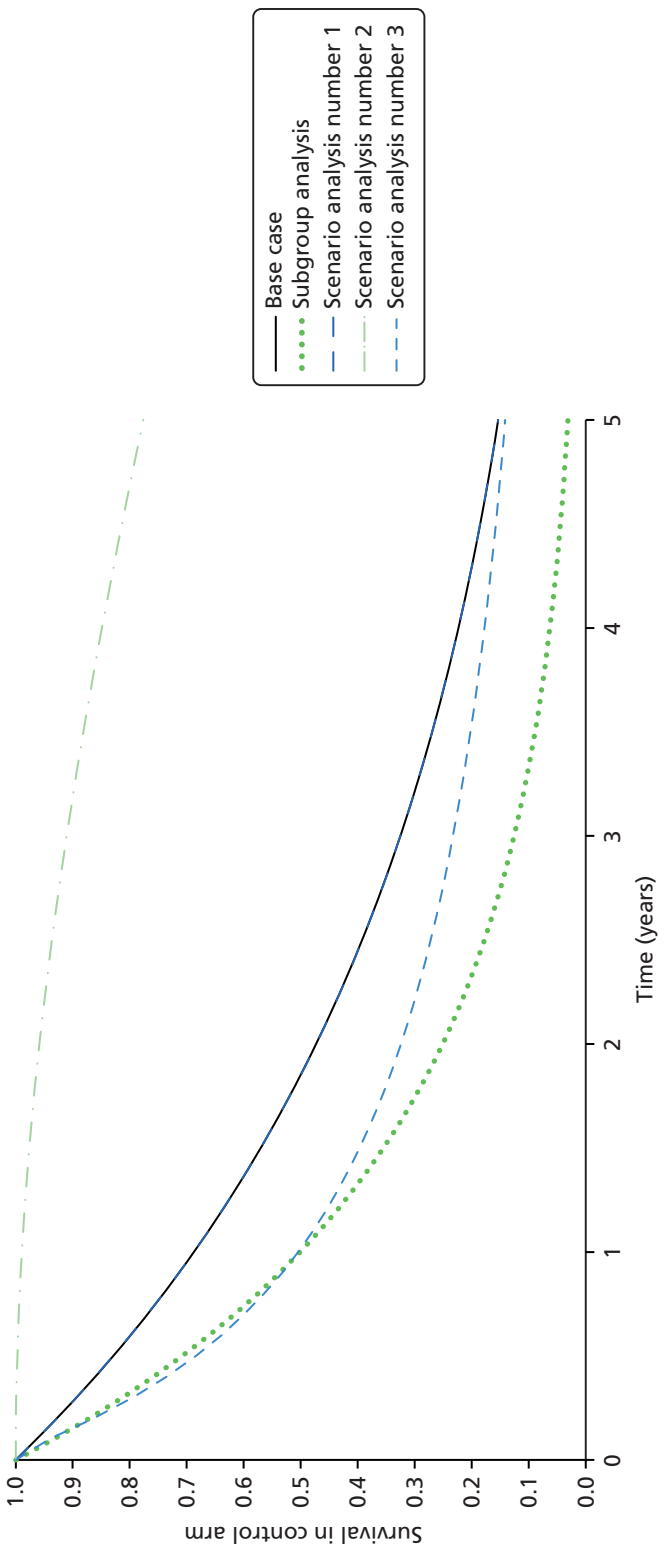


FIGURE 31 Overall survival distributions used for the control arm.

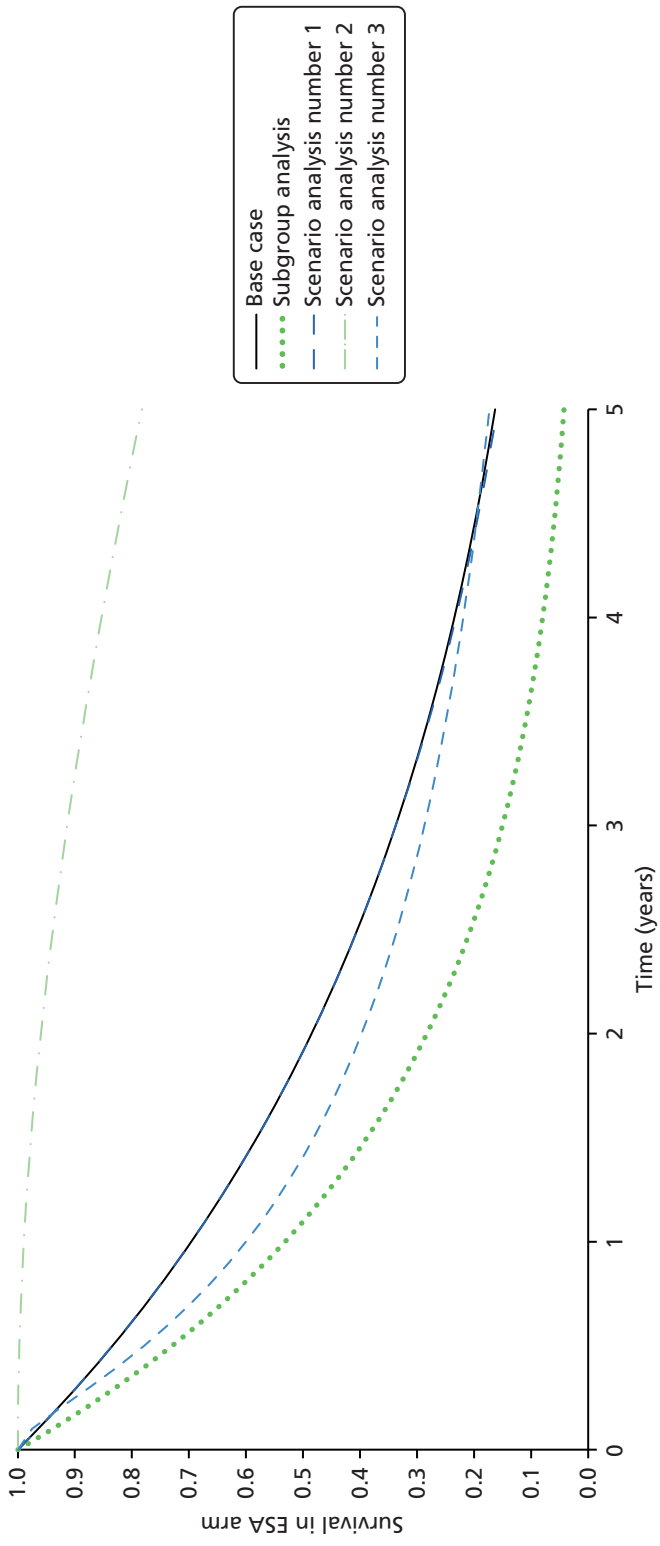


FIGURE 32 Overall survival distributions used for the ESA arm.

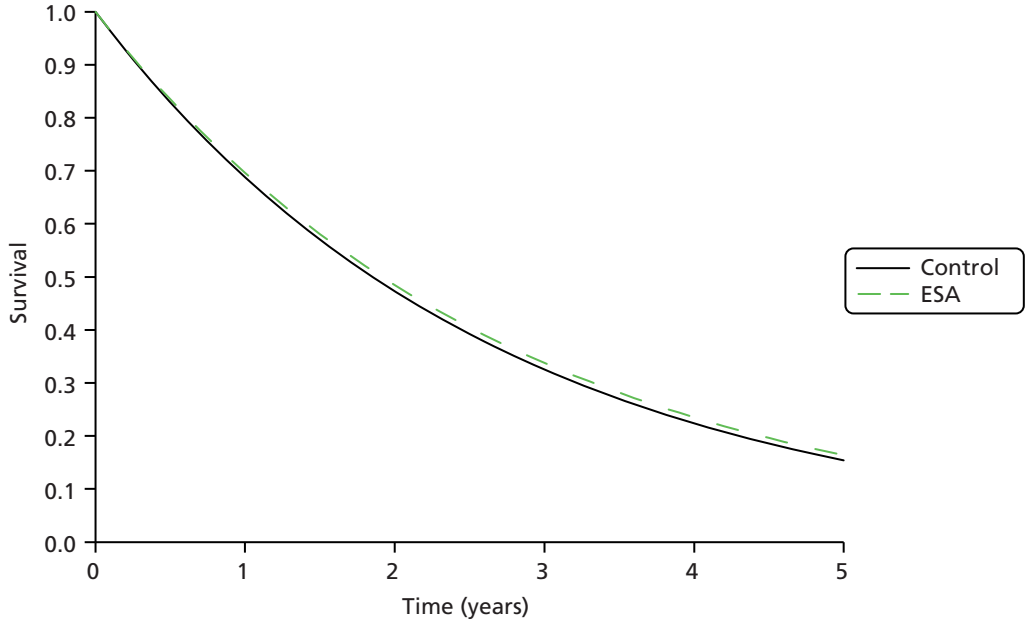


FIGURE 33 Overall survival distributions used in the deterministic base case.

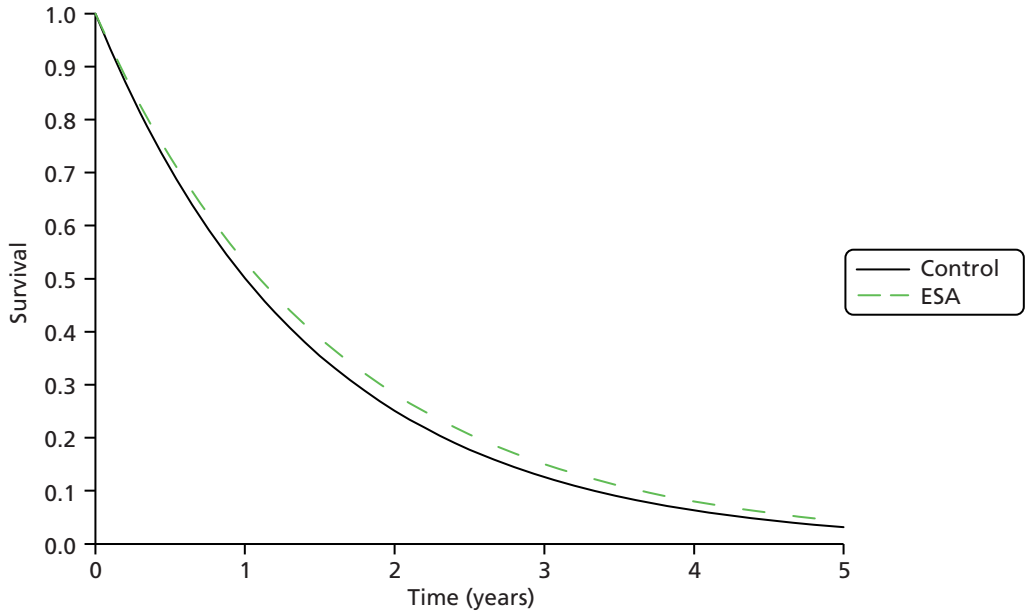


FIGURE 34 Overall survival distributions used in the subgroup analysis in which the inclusion Hb level is ≤ 11.0 g/dl.

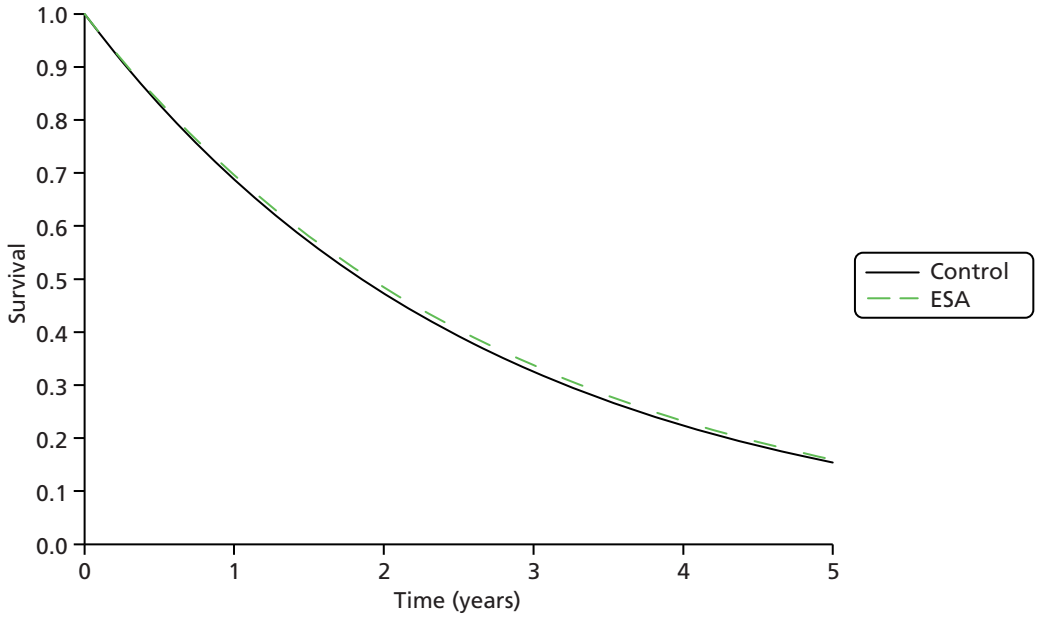


FIGURE 35 Overall survival distributions used in the first scenario analysis (as in the base case except that the HR applies only for the first 3 years).

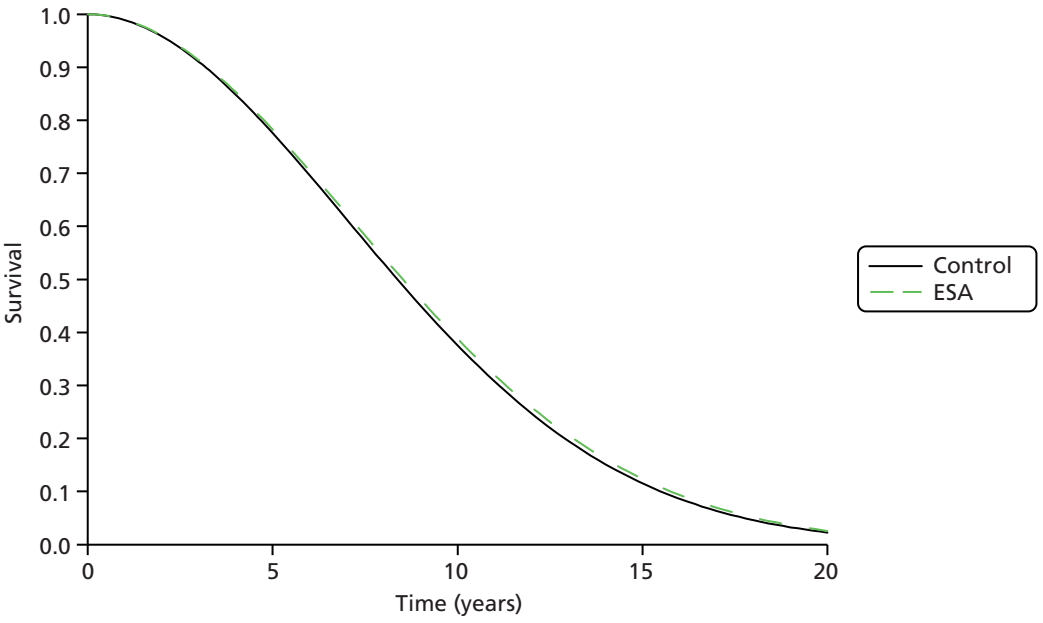


FIGURE 36 Overall survival distributions used in the second scenario analysis (Weibull distribution fitted to the control arm of Untch and colleagues[78,80]).

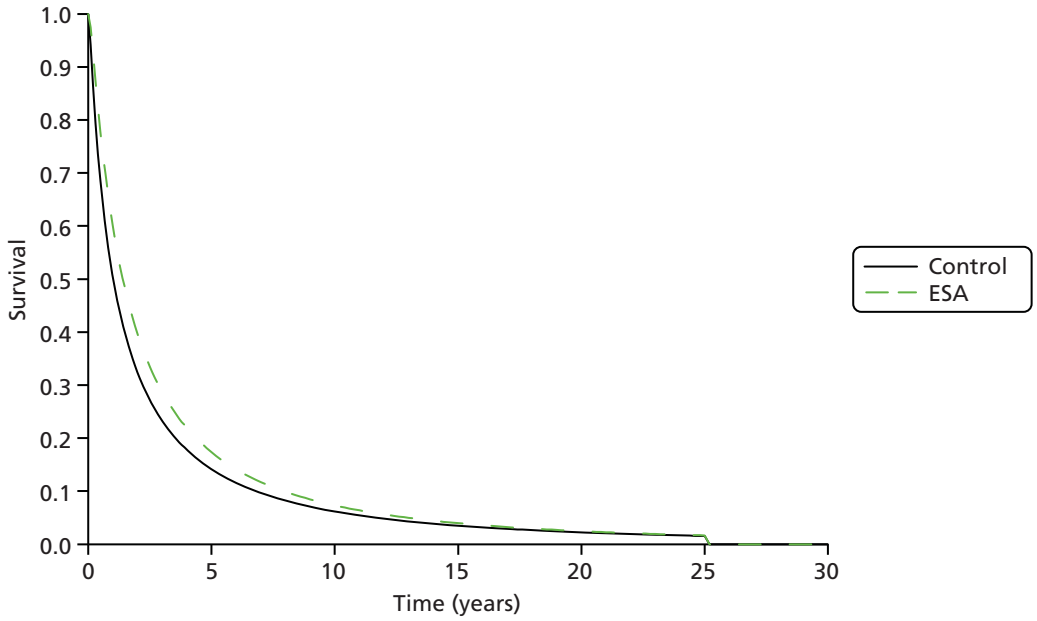


FIGURE 37 Overall survival distributions used in the third scenario analysis (log-normal distributions fitted to the survival curves in Littlewood and colleagues[70] and truncated at 25.1 years).

Utilities in cost-effectiveness models of erythropoiesis-stimulating agents

In *Model structure* we outlined approaches to estimating utilities in published economic evaluations of ESAs for cancer-related anaemia. Here, we elaborate on this (*Table 58*) to assess the usefulness of approaches to the incorporation of utilities in published economic evaluations.

All studies except that by Martin and colleagues[116] assume that ESAs affect HRQoL during ESA treatment. Most studies, including the previous HTA review,[2] estimate the impact of ESAs on HRQoL through the impact of ESAs on Hb levels.

Only two analyses modelled the impact of ESAs on HRQoL directly rather than through the impact on Hb levels. One of these[114] used the VAS and the other[115] used the LASA to estimate HRQoL. We believe that both instruments are seriously flawed in terms of assessing utilities as they do not allow trading off life expectancy with quality of life, as required by NICE.[169]

Of the seven studies that modelled the impact of ESAs on HRQoL through the impact of ESAs on Hb levels, we consider the approach of Fagnoni and colleagues[121] to be inappropriate because it also used the LASA.

Both the Ortho Biotec and Roche models[2] use utility data from Ossa and colleagues.[174] This is reported only in abstract form but is reported fully in Ossa and colleagues,[159] which we have identified and critiqued in *Studies reporting utilities as a function of haemoglobin levels*. The industry submissions differ in their partitioning of Hb levels into anaemia states.

The Amgen Inc. submission[2] relied on unpublished data and used utility values elicited from patients on both experimental and licensed doses of darbepoetin (patients who discontinued darbepoetin were not followed up).

The data underlying the estimates of utilities as a function of Hb levels from Borg and colleagues[156] also relied on unpublished data.

TABLE 58 Summary of the use of utilities in previous models of the cost-effectiveness of ESAs for cancer-related anaemia

	During ESA treatment			After ESA treatment	
Study	Method of utility estimation	Source data and method of utility estimation	Critique	Source data and method of utility estimation	Critique
Barosi 1998[114]	ESAs affect HRQoL directly	VAS from Abels[157]	VAS method not recommended by NICE[a]	Not modelled as short time horizon	
Cremieux 1999[115]	ESAs affect HRQoL directly	LASA from Abels[63]	LASA scale not recommended	Not modelled as short time horizon	
Martin 2003[116]	ESAs do not affect quality of life	NA	Justification not given	Utilities: 0.13–0.73 depending on stage of breast cancer. Estimated from 30 nurses using standard gamble	Poor methodology and restricted to breast cancer
Amgen Inc. model[2]	Utility distribution per Hb level	Unpublished study of EQ-5D according to Hb level during Amgen Inc. RCT of darbepoetin. Data collected weekly from approximately 100 patients over 16 weeks	Details unpublished, therefore unable to critique	0.66 (assumed same as baseline)	Justification not given
Ortho Biotec model[2]	Function of Hb level	Data from Ossa and colleagues[166] on community values of different levels of fatigue (using TTO method), sponsored by Ortho Biotec	Abstract only. Translation of anaemia states to Hb levels unreported	Not reported	
Roche model[2]	Function of Hb level	Utilities from Ossa and colleagues,[166] TTO and regression analysis	Abstract only. Authors include employee of Roche	0.81 (assumed same as baseline)	Justification not given; mix of utility measurements used to choose baseline (standard gamble, TTO and EQ-5D)
Wilson 2007[2]	Function of Hb level	Unpublished data from Ortho Biotec	Unpublished, therefore unable to critique	Not reported	
Fagnoni 2006[121]	Function of Hb level	LASA from Crawford and colleagues[155]	LASA not recommended as no value set	Not modelled as short time horizon	
Borg 2008[156]	Function of Hb level	Following model in Wilson and colleagues[2]	Based on unpublished utilities study, therefore unable to critique	Not modelled	
Tonelli 2009[88]	Function of Hb level	Ossa and colleagues[152]	See critique in *Studies reporting utilities as a function of Hb level*	Not reported	

TTO, time trade-off.

a Not recommended as it does not reflect patient or public relative valuations or preferences for health states.

Utilities after ESA treatment are reported in three cost-effectiveness studies, that by Martin and colleagues,[116] the Amgen Inc. model[2] and the Roche model.[2] We do not consider the corresponding utilities further because the values from Martin and colleagues[116] relate to breast cancer only, minimal detail is given for the value used in the Amgen Inc. model[2] and both the Amgen Inc. and Roche models[2] use the baseline utility to inform the utility after treatment. This means that the utility is not specific to post treatment and instead relies on the assumed baseline utility for this population. Some studies (e.g. Cremieux and colleagues[115] and Fagnoni and colleagues[121]) do not report utilities after ESA treatment because they consider only a short time horizon.

Principles for the identification of studies to inform the choice of utilities

In this section we follow the principles for the identification, review and synthesis of health state utility values from the literature, as recommended by the NICE Decision Support Unit in the UK.[175] There are no agreed reporting standards for studies of utilities, but the following information is key to understanding the nature, quantity and quality of evidence:[175]

- the population describing the health state (e.g. age, sex, disease severity)
- the approach used to describe the health state
- the utility value elicitation technique, for example time trade-off, standard gamble, visual analogue score
- sample size
- respondent selection and recruitment and inclusion and exclusion criteria
- survey response rates, numbers lost to follow-up (and reasons), methods of handling missing data.

Clearly, the relevance of the data to the decision model and to the agency to which the model will be submitted is important. In the current project, the NICE reference case[169] is used. Modification of utility values from the literature for use in economic models, and sensitivity analyses using less relevant utility values, should be considered.[175]

A systematic search for studies reporting utilities should be undertaken.[175] For the current project, the search method is given in *Appendix 1*. In addition, sources of utility values were obtained from published models on the cost-effectiveness of ESAs (see *Utilities in cost-effectiveness models of erythropoiesis-stimulating agents*).

Studies reporting utilities as a function of haemoglobin level

Our search for studies to inform utility values as a function of Hb levels yielded 235 publications. On inspection of titles and abstracts, four papers were deemed sufficiently relevant to read in full.[176–179]

Three papers reported studies that measured HRQoL as a function of Hb level.[176–178] Wisloff and colleagues[179] did not provide estimates of utilities as a function of Hb level. Instead, in a study of multiple myeloma patients, the authors concluded that Hb level has limited impact on HRQoL as measured by the cancer-specific questionnaire EORTC QLQ-C30. They stressed that Hb level may be correlated with tumour type, disease severity and response to treatment, which themselves may affect quality of life. The authors therefore concluded that it is essential to adjust for these variables to assess the impact of Hb level on HRQoL.

In addition, we critiqued two further studies, the first of which was that by Ossa and colleagues,[159] whose preliminary results[174] were used in the cost-effectiveness analysis of two of the TA142 industry submissions and therefore formed the basis of the utility values reported in the Wilson and colleagues[2] model. It was also used in the cost-effectiveness analysis of Tonelli and colleagues.[88] In addition, we critiqued the study by Crawford and colleagues,[162] used in the cost-effectiveness analysis of Fagnoni and colleagues.[121] The key characteristics and results of all five fully critiqued studies are provided in *Table 59*. We did not critique the industry submissions from Wilson and colleagues,[2] as the data underpinning the Roche and Ortho Biotec submissions are presented in Ossa and colleagues[159] and in the methods of the Amgen Inc. submission utility was not explicitly reported as a function of Hb.

TABLE 59 Summary of characteristics of studies measuring utility as a function of Hb levels

Characteristic	[a]Harrow and colleagues[176]	Tajima and colleagues[178]	Ossa and colleagues[159]	Lloyd and colleagues[177]	Crawford and colleagues[162]	Amgen Inc. submission
Health elicitation by patients?	Yes	Yes	No	First study: yes; second study: no	Yes	Yes
Preference elicitation instrument	SF-6D	EQ-5D	Health state vignettes reflecting chemotherapy-induced anaemia based on FACT-An and EQ-5D. Validated by three oncology specialists and six cancer-related anaemia patients	Health state vignettes reflecting cancer-related anaemia. Reviewed by clinicians and quality of life experts	LASA	EQ-5D
Preference valuation	General public used standard gamble	Japanese general publication used TTO	General public used TTO	First study: general public used standard gamble; second study: cancer patients used TTO	None	NR, presumably TTO
Study population size	13,433	537	110	First study: 85 members of the general public; second study: 26 cancer patients	Approx. 4000	NR
Study population	Women with cancer aged 50–79 years, mean age 63 years	CKD patients; 52% male, mean age 55 years, mean Hb 12.7 g/dl	100 members of the general population	First study: general population; second study: cancer patients receiving chemotherapy, some anaemia, mean age 60 years	Cancer patients undergoing chemotherapy, mean age 63 years	Patients on darbepoetin, some on experimental dosing
Country	USA	Japan	UK	UK	USA	NR
Year	1993–8	2008	2004	Not stated but assume 2000s	1990s	NR, pre 2004
Loss to follow-up?	NA as measurement at baseline	NA as measurement at baseline	NA	NA	Appears not to be large	Numbers NR but there was loss to follow-up
Study funding	Study funded by US government. Analysis funded by industry (Pfizer)	Funded by Japanese government	Industry (Roche)	Industry (Ortho Biotec)	Industry (Ortho Biotec)	Industry (Amgen Inc.)

Characteristic	[a]Harrow and colleagues[176]	Tajima and colleagues[178]	Ossa and colleagues[159]	Lloyd and colleagues[177]	Crawford and colleagues[162]	Amgen Inc. submission
Results: ΔUtility for ΔHb of 1 g/dl	0.009 over Hb 9–12 g/dl	0.016	0.109 over Hb 8.7–11.0 g/dl	First study: 0.032; second study: 0.062, over Hb 8.5–11.5 g/dl	0.029 over Hb 9–11 g/dl	0.030 over Hb 8.5–11.5 g/dl
Major strengths	Sample size very large; health elicited by patients, as required by NICE;[89] generic preference elicitation instrument SF-6D	EQ-5D is preferred by NICE;[169] public valued using TTO, as preferred by NICE;[169] sample size large; health elicited by patients, as required by NICE[169]	None	In second study, health elicited by patients with experience of CIA	Sample size very large; health elicited by patients, as required by NICE;[169] patients with CIA	Health elicited by patients, as required by NICE;[169] patients with CIA; EQ-5D is preferred by NICE[169]
Minor strengths	Preference valuation standard gamble appropriate (although TTO preferred by NICE[89]); government funded	Government funded	UK based; TTO preferred by NICE[169]	UK based		
Major weaknesses	Observational study, hence possibly unmeasured confounding variables;[b] however, many covariates were controlled for in the analysis	Patients with CKD, not cancer. Observational study, hence possibly unmeasured confounding variables; however, many covariates were controlled for in the analysis, e.g. albumin, creatinine, GFR, age, gender	Health status not elicited from patients, a requirement for the NICE reference case;[169] health state vignettes assessed by experts, whereas NICE prefers patient self-reports using classification systems of generic questionnaires;[169] small sample size of 110	Health state vignettes, whereas NICE prefers patient self-reports using generic questionnaires;[169] very small sample size of 26 cancer patients	LASA instrument utilities are not obtained by a choice-based method, which is required by NICE[169]	Observational study, hence possibly unmeasured confounding variables;[b] all utilities taken from patients on the same dose of ESA (utilities not taken when ESA use discontinued); poorly reported
Minor weaknesses	Women only; US, not UK based; NICE prefers use of the EQ-5D to the SF-6D;[169] patients not necessarily having chemotherapy	Utility values of health states derived elicited from Japanese, not UK, general public	Although health vignettes reported to reflect CIA, descriptions could equally apply to cancer-related anaemia; population under-represents ethnic minorities and over-represents wealthy people;[b] industry funded	Industry funded	US not UK based; industry funded	Industry funded

GFR, glomerular filtration rate; NR, not reported; TTO, time trade-off.
a Total of 136,472 people; results for 13,433 cancer patients reported here.
b Disadvantage acknowledged by study authors.

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In the study by Harrow and colleagues,[176] 13,433 women with cancer completed the SF-6D questionnaire at baseline. This represents a useful data set as the sample size was very large, health was appropriately elicited by patients and an appropriate preference elicitation instrument, the SF-6D, was used (see *Table 59*). However, the main weakness is that this was an observational study, which means that there could have been unmeasured covariates that contributed to the observed relationship between utility values and Hb levels. For example, patients with low Hb levels may have been more likely to have had more advanced cancer. This would tend to bias the apparent impact of Hb level on utilities, probably in the direction of a steeper gradient. However, the authors tried to minimise the risk of confounding by controlling for many covariates in their analysis. Utilities were found to increase only slightly from 9 to 14 g/dl of Hb and decrease thereafter (*Figures 38* and *39* and see *Table 59*).

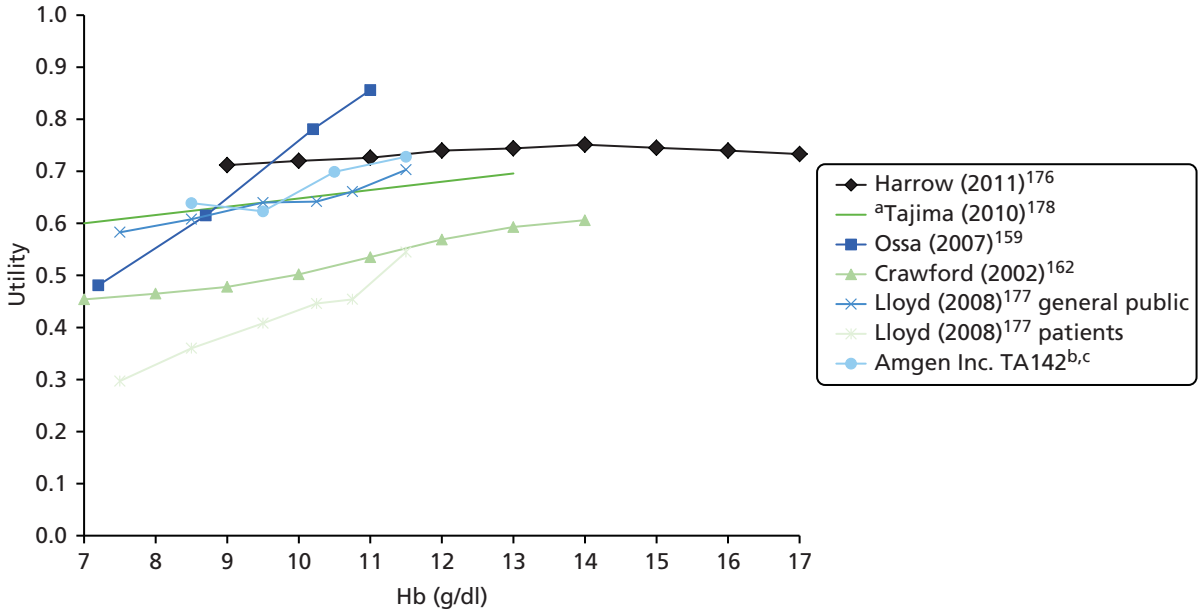

FIGURE 38 Utilities as a function of Hb level by study. a, Tajima and colleagues[178] report the relationship between change in Hb level and utility (slope of the line) but not absolute utility at each Hb level. We set the utility at Hb 7 g/dl to equal 0.6 so that the utility estimates fall within plausible Hb ranges, as reported by other studies. b, Utilities cannot be directly compared, as they are reported on different scales and elicited through different tools. c, Data presented as part of the HTA review for TA142 published as Wilson and colleagues.[2]

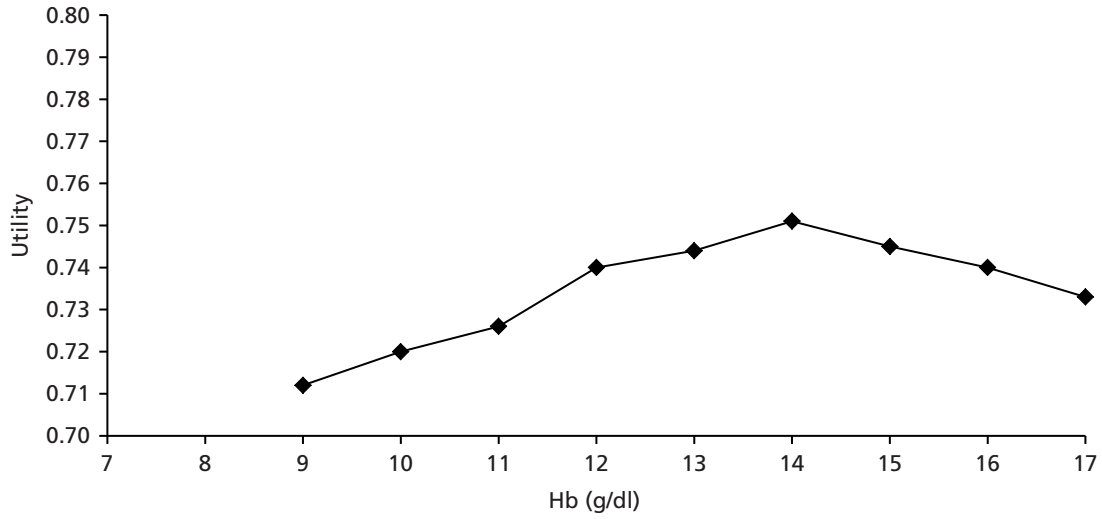

FIGURE 39 Utilities as a function of Hb level from Harrow and colleagues. Source: Harrow and colleagues.[176]

The study by Tajima and colleagues[178] was also an observational study, which, among other factors, investigated the impact of Hb level on utilities for patients with CKD in Japan. This is also a useful data set because, as preferred by NICE,[169] health was self-reported by patients using the EQ-5D classification system and the resulting health states were valued using utilities elicited from the general public using the time trade-off technique. However, the two main weaknesses are that (1) this was an observational study, which means that there could have been unmeasured covariates that contributed to the observed relationship between utility values and Hb levels and (2) patients had CKD, not cancer. Any bias resulting from (1) was minimised as several potentially confounding variables were included in the regression analysis. As for (2), it would be only a minor weakness if one could plausibly assume that the comorbidity of anaemia impacts HRQoL additively and in the same way in different patient groups. In this study utilities were found to increase only slightly, at a rate of 0.016 per unit change in Hb (see *Table 59*). It should also be noted that, as this study was conducted in Japan, the results may not entirely translate to a British population.

We believe that there are substantial weaknesses in the remaining three studies. There are many weaknesses in the study by Ossa and colleagues,[159] including the use of health state vignettes (see *Table 59*). Hence, we attach little importance to the finding that utility increases steeply from 7 to 11 g/dl of Hb (see *Figure 38*).

The study by Lloyd and colleagues[177] also has many important weaknesses, including the use of health state vignettes and the very small sample size. Hence, we attach little importance to the finding that utility increases steeply from 7.5 to 11.5 g/dl of Hb (see *Figure 38*).

In the study by Crawford and colleagues,[162] health was appropriately elicited from patients. However, the one important weakness of the study was that the health preference elicitation instrument used was the LASA, whose self-assessment consists of five questions on physical, emotional, spiritual, intellectual and overall well-being, rated on a scale from 0 to 10. As such, utilities are not obtained by a choice-based method, such as the time trade-off or standard gamble, which is required by NICE.[169] Hence, we attach little importance to the finding that utility increases moderately from 7 to 14 g/dl of Hb (see *Figure 38*).

As stated above, the cost-effectiveness of ESAs may be very sensitive to the rate at which utilities change with respect to changes in Hb (i.e. the gradient of the utility/Hb graph). Cost-effectiveness is likely to be insensitive to the absolute utilities during the period of treatment with ESAs because mortality is assumed to be zero during this period for both the ESA treatment arm and the best supportive care arm.

Estimation of the impact of erythropoiesis-stimulating agents on health utilities from mapping disease-specific questionnaires to the European Quality of Life-5 Dimensions

As mentioned in *Clinical effectiveness parameters*, very little information can be gained from mapping from the disease-specific health questionnaires to the EQ-5D. Of the RCTs included in the PenTAG systematic review of clinical effectiveness, one study[75] used the EORTC QLQ-C30 questionnaire and one study[77] used the FACT-G questionnaire. These have been mapped to the EQ-5D by Dakin.[180]

However, in the first case, it is not possible to perform such a mapping because the required EORTC QLQ-C30 information is not provided. In the second case, it is possible to make an approximate estimation of the impact of epoetin alfa on utilities. At the end of treatment we can estimate the difference in utilities between arms; in the case of Tjulandin and colleagues[77] this is $0.007 \times 6.1 = 0.04$, where 6.1 is the difference in FACT-G total score in Littlewood and colleagues[70] ($2.5 + 3.6$) and 0.007 is the coefficient from the utility mapping paper.[180] The authors of this paper found a better mapping function using the dimensions of the FACT-G questionnaire rather than the total score.

All of the other RCTs in the PenTAG systematic review that reported HRQoL use questionnaires for which we understand there is no mapping to the EQ-5D nor to the SF-6D.[180]

Peninsula Technology Assessment Group base-case utilities by haemoglobin level

As mentioned in the previous section, we consider the studies by Harrow and colleagues[176] and Tajima and colleagues[178] to be the most methodologically robust. The key differences between the two studies are:

- the study by Harrow and colleagues[176] has the advantage of relating to people with cancer, whereas the study by Tajima and colleagues[178] concerns people with CKD
- the study by Tajima and colleagues[178] has the advantage of using the EQ-5D valued using time trade-off, both preferred by NICE,[174] whereas Harrow and colleagues[176] used the SF-6D valued using the standard gamble.

Both studies find that the impact of Hb level on utilities is rather slight. In Harrow and colleagues,[176] over the range Hb 9–12 g/dl, utilities increase by 0.009 per unit increase in Hb. This scales to 0.028 per unit increase in Hb on the EQ-5D, using the results of Brazier and colleagues'[181] regression analysis. In Tajima and colleagues,[178] over a similar Hb range, utilities increase by 0.016 per unit increase in Hb.

These results are consistent with the findings of Wisloff and colleagues[179] and with our review of HRQoL that there is only weak evidence that ESAs improve HRQoL (see *Chapter 3*, *Health-related quality-of-life outcomes: overall summary*).

The results are also consistent with the estimated impact of epoetin alfa on utilities (see the previous section). At the end of treatment, the estimated difference in utilities between arms is 0.04. Given that we estimate a coefficient for Hb of 0.016 and that the difference in Hb between arms in the study by Littlewood and colleagues[70] was 1.7 g/dl, we would estimate a difference in utility of 0.022 for Littlewood and colleagues,[70] which is plausibly close.

For our base-case utilities we used the scaled utility value from Harrow and colleagues.[176] This was chosen over the EQ-5D results from Tajima and colleagues[178] mainly on the basis that Harrow and colleagues' population of people with cancer more closely matches our own. We therefore assumed that utilities increase by 0.028 per unit increase in Hb. This utility was then applied until the end of normalisation and adjusted for the mean difference in Hb levels between the ESA arm and the no ESA arm at the relevant time points to calculate the short-term QALY gain.

For the PSA we assumed a gamma distribution with a mean of 0.028 and a SE of 20% of the mean, reflecting Harrow and colleagues.[176] We also performed univariate sensitivity analyses using the estimate from Tajima and colleagues[178] (0.016), as well as the unscaled value from Harrow and collegues[176] (0.009) and the estimate used in the previous HTA review[2] (0.060).

As stated above, the main weakness of both studies is that they are observational. This means that the estimated relation between utility and Hb level may be biased because of unmeasured confounding variables. However, as suggested by Tonelli and colleagues,[88] any such bias is likely to lead to an overestimate of the rate of change of utility as a function of Hb. This is because (1) people with low Hb levels may be more likely to have more advanced cancer and hence lower reported utilities and (2) people who are told that their Hb level is low may underestimate their reported quality of life. This bias has the effect of biasing cost-effectiveness in favour of ESAs compared with no ESAs.

Peninsula Technology Assessment Group base-case utilities after erythropoiesis-stimulating agent discontinuation

The value of utilities after ESA discontinuation is difficult to generalise as the patient populations in source studies cover a wide range of cancers. The average age (59.1 years) taken from the RCTs is equivalent to a utility of 0.830, using the formula published by Ara and Brazier[182] (Equation 4) and assuming the probability of being male to be 46% based on ONS cancer registration statistics for 2011[183] for people aged 50–60 years.

$$\text{Formula for age related utility: } U = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2. \quad (5)$$

We can therefore surmise that the utility must be lower than this after ESA discontinuation. In the previous HTA review,[2] once people had returned to a Hb level of ≥ 13 g/dl, their utility was 0.810. In this assessment people normalise to a lower Hb value than in the previous HTA review[2] and, given the similarity of this value to that in people in the general population, we use a lower utility value for people in the long term. Tengs and Wallace[184] reported a utility for cancer of 0.83–0.92 (irrespective of age) using a time trade-off method. Applying this to the age-related utility gives a range of values from 0.68 to 0.76. Comparing this range to the values reported in *Utilities in cost-effectiveness models of erythropoiesis-stimulating agents*, as well as to those reported in previous PenTAG cancer HTA assessments,[185,186] we conclude that using the higher estimate of 0.76 is the most appropriate utility.

Again, this is a parameter that is highly uncertain (because of the lack of data), which could have a potentially large impact on the overall QALYs accrued in the analysis. As such, in the PSA we vary the utility multiplier 0.92 as a beta distribution with a SE of 20% of the mean (0.184). The resulting SE of the long-term utility is $0.830 \times 0.184 = 0.153$.

Utilities not included in the Peninsula Technology Assessment Group model

In the previous sections we have described two sources of utility values within the model. An additional source of disutility can come from the AEs associated with ESA use. These utilities are not modelled explicitly and instead the disbenefit associated with AEs is accounted for only by cost.

This decision was made for several reasons, the main reason being that AE data in the RCTs are extremely poorly defined. First, the AEs themselves are poorly defined and, for example, a thromboembolic event can refer to several events, including pulmonary embolism and deep-vein thrombosis. These specific AEs are often not specified within the RCTs or different RCTs will include different AEs within their definition. Second, the severity and length of impact of the AEs are not consistent across the RCTs and are undefined for the pooled results. These poor definitions make it difficult to assign either costs or QALYs to AEs, and make it especially difficult to define the disutility of an AE and translate this into a QALY; indeed, there were no data to define these results.

One area in which the long-term disbenefit of AEs is implicitly included is survival. As with short-term mortality, any mortality associated with AEs should be implicitly identified by the survival estimates encountered in the RCTs, as these are extracted from the same pool of studies.

We acknowledge the lack of utilities associated with AEs as a limitation of the model and discuss this in *Chapter 6* (see *Adverse events*).

Costs

In this analysis we model the following costs: blood test costs, cost of ESAs, RBCT costs (unit cost of blood and cost of the transfusion appointment) and costs of AEs. We do not model long-term costs in the base case given the uncertainty attached to these values as a result of the wide patient population. Additionally, any arbitrary cost added to long-term survival would disadvantage any arm with a survival benefit, which will be demonstrated in a sensitivity analysis.

Adjustments to 2014/15 prices

All costs and prices in the model were inflated to 2011/12 prices using the Hospital and Community Health Services (HCHS) Pay and Prices Index[187] and then further inflated by 3.65% per annum for 2 years to 2014/15 prices, where 3.65% is the average (geometric mean) inflation of the index between 2006/7 and 2011/12.

Erythropoietin-stimulating agent prices

Table 60 presents the 2013 drug prices for ESAs, which have been taken from the *British National Formulary*.[166] Separately we report the expected wholesale acquisition costs (see *Wholesale acquisition costs*), which we used to conduct a sensitivity analysis on plausible actual costs to the NHS.

The majority of ESA dosages are calculated based on weight, with the exception of epoetin theta. As such, there is no standard dose for each patient and *Table 60* demonstrates the various vial sizes for the ESAs that can make up a dose. Given the wide variety of vial sizes, we believe that drug wastage will be minimal and therefore did not account for this in our analysis.

Using the various vial sizes we calculated the costs per 1000 IU for epoetin alfa, beta, theta and zeta and per µg for darbepoetin. These depend on the vial size of the ESA for some of the ESAs, for example for a vial size no greater than 20,000 IU for Eprex the cost is £5.53 per 1000 IU, but if a larger vial size is used the cost is £6.64 per 1000 IU. In the base case we used the lowest cost per 1000 IU, for each of the ESAs, as this covered the largest range of vial sizes. These base-case costs are provided in *Table 61*.

The overall cost per dose for each ESA was then calculated using the number of units/µg per week.

The ESA unit costs were not varied in the PSA.

TABLE 60 Available vial sizes and costs of ESAs

	Epoetin alfa (£)		Epoetin beta (£)	Epoetin theta (£)	Epoetin zeta (£)		Darbepoetin alfa (£)
Units	Eprex	Binocrit	NeoRecormon	Eporatio	Retacrit	µg	Aranesp
500			3.51			10	14.68
1000	5.53	5.09		5.99	5.66	15	22.02
2000	11.06	10.18	14.03	11.98	11.31	20	29.36
3000	16.59	15.27	21.04	17.98	16.97	30	44.04
4000	22.12	20.36	28.06	23.97	22.63	40	58.73
5000	27.65	25.46	35.07	29.96	28.28	50	73.41
6000	33.19	30.55	42.08		33.94	60	88.09
8000	44.25	40.73			45.25	80	117.45
10,000	55.31	50.91	70.14	59.92	56.57	100	146.81
20,000	110.62		140.29	119.84	113.13	130	190.86
30,000	199.11		210.43	179.75	169.70	150	220.22
40,000	265.48				226.26	300	440.43
50,000			374.48			500	734.05

Source: *British National Formulary*.[166]

TABLE 61 Base-case ESA costs used in the PenTAG analysis

ESA		Per 1000 IU (£)	Per µg (£)
Epoetin alfa	Eprex	5.53	
	Binocrit	5.09	
Epoetin beta	NeoRecormon	7.01	
Epoetin theta	Eporatio	5.99	
Epoetin zeta	Retacrit	5.66	
Darbepoetin alfa	Aranesp		1.47

Source: Based on *British National Formulary*[166] prices.

Wholesale acquisition costs

Drug manufacturers are free to sell to hospitals below the list price and acquisition costs under these sales would usually be commercially confidential. Manufacturers will typically employ a price–volume methodology in which more substantial savings are available to purchasers if commitments are made regarding the minimum quantity to be purchased. Because of different purchasing decisions by hospitals (in part because of different patient population sizes), the same drug will be acquired at a range of prices. Ideally, in an economic evaluation one would wish to use the average acquisition cost for each drug in the base case, but such information is generally kept confidential.

In this appraisal the manufacturers consented at the NICE Consultee Information Meeting (7 August 2013) to pharmacists revealing the confidential prices to PenTAG. We received the latest tenderings to London hospitals (South East England Specialist Pharmacy Services, Commercial Medicines Unit, 27 September 2013, personal communication). These were understood to be from the most recent tendering process and therefore the most representative prices going forwards.

As shown in *Table 62*, all manufacturers were prepared to offer some level of discount from the list prices and some (not all) were prepared to offer a discount with minimal commitment to volume. It can also be seen that the London hospitals did not secure the cheapest prices for all ESAs.

TABLE 62 Erythropoietin-stimulating agent wholesale prices offered to London hospitals

ESA	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Epoetin alfa (Eprex)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Epoetin alfa (Binocrit)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Epoetin beta (NeoRecormon)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Epoetin zeta (Retacrit)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Darbepoetin alfa (Aranesp)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

Commercial-in-confidence information has been removed.

If PenTAG were to adopt the strike prices agreed by London hospitals this would represent a significant bias in favour of the ESAs for which significant discounts were obtained. London hospitals entered contracts committing to a volume of at least 8000 people, which would have been sufficient to command the best offer from any manufacturer had all volume been promised to a single manufacturer.

If all ESAs are deemed to be equally effective then all purchasers should exclusively purchase the ESA that minimises total costs (i.e. that with the lowest combined drug acquisition and administration costs). By concentrating full purchasing power it should be possible for all purchasers to get the best offer price from each manufacturer.

We therefore believe that the best offer to London hospitals is the best unbiased estimate of the wholesale acquisition cost of ESAs. PenTAG noted that epoetin theta is not included in the list of ESAs offered to the London hospitals and therefore no wholesale acquisition cost can be estimated for this ESA.

The best offer prices cannot be guaranteed to last beyond the contract agreed between the manufacturer and the purchaser – in the case of the London hospitals the contract was for 12 months with the option to extend by a further 24 months.

Cost of administering erythropoiesis-stimulating agents

There are multiple dosing options for most of the ESAs and we chose the base-case dosing schedule for each on the basis of both the evidence available in the RCTs and the advice of our clinical experts. This allowed us to be consistent with our other evidence as well as clinical practice, including incorporating information on missed doses. In the base case we assumed that dosing occurs once a week for all ESAs. In sensitivity analysis we investigated the different dosing schedules for each ESA, as shown in *Table 63*.

In the context of CKD, ESAs are typically self-administered by the patient when possible (advice from MN) and, in the case of the industry submissions presented in this review,[2] the majority of patients are expected to self-administer. However, consultations with our clinical experts (KS, MN, CR, NR) suggested a more varied view on ESA administration, with some indicating that, for the therapy under review (CIA), with a comparatively short period of treatment, it may be more likely for patients not to self-administer. As our experts covered a range of cancers and backgrounds, we decided that the most appropriate decision in the base case was to take an average of the opinions on how ESAs should be administered in practice. Therefore, of the ESAs administered each week, in the base case 16.25% are administered during patients' chemotherapy appointments, 43.13% are administered during a general practitioner appointment or by a district nurse and 40.63% are self-administered (*Table 64*). We did not allocate these values to specific patients, as patients are likely to encounter a combination of these practices during their time on ESAs (advice from CR). This also means that we did not explicitly account for instances such as the weeks when patients do not have a chemotherapy appointment, as this is factored into the average values. Given the uncertainty around these values, as part of our sensitivity analysis we examined the situation in which ESAs are administered to cancer patients in a similar manner to that for CKD patients. The costs of each type of administration and the overall average cost for ESA administration are presented in *Table 64*. In the PSA the probabilities were drawn from a Dirichlet distribution.

TABLE 63 Dosing schedules for ESAs based on licensed indications

ESA	Base-case dose	Sensitivity analyses
Epoetin alfa	Once weekly	3 times a week
Epoetin beta	Once weekly	3–7 times a week
Epoetin theta	Once weekly	3 times a week
Epoetin zeta	Once weekly	3 times a week
Darbepoetin alfa	Once weekly	Once every 3 weeks

TABLE 64 Erythropoietin-stimulating agent administration costs

ESA administration	Cost (£)	Source	% of ESAs[a]	Source
Appointment with district nurse	18.80	PSSRU[188]	21.56	Clinical experts NR, KS, MN, CR
Appointment with general practice nurse	10.74	PSSRU[188]	21.56	
Appointment with hospital staff nurse	11.01	PSSRU[188]	16.25	
Self-administered	0	Assumed	40.63	
Average cost per ESA administration	8.16			

PSSRU, Personal Social Services Research Unit.
% of ESAs may not sum to 100% because of rounding.

As stated in *Duration of erythropoiesis-stimulating agent treatment*, the duration of ESA treatment is calculated on an ITT basis and, as such, the cost of administration may be slightly exaggerated. However, as the average cost per ESA administration is £8.16, the cost does not have a significant impact on the results compared with the cost of ESA drug prices in the base case.

Additional blood tests for erythropoiesis-stimulating agents

Another additional cost for ESAs is incurred by an increase in the number of blood tests (advice from clinical experts KS and NR). Opinion appears to be divided on how much of an increase this would be. In the base case we assumed that blood tests would occur regularly for both patients who are on ESAs and those who are not while patients are undergoing chemotherapy treatment, but that additional blood tests would continue post chemotherapy for those patients on ESAs. In the base case we costed for four additional blood tests. We assumed that these were carried out by a general practice nurse at a cost of £42.98 per hour (£40 in 2012/13[188] inflated to 2014 prices) and that the appointment takes 15.5 minutes of nurse time, based on the average surgery consultation time,[189] resulting in a cost of £11.10. We also added the NHS reference cost for phlebotomy [Healthcare Resource Group (HRG) code DAPS08) of £3.91 (inflated from £3.64 in 2012/13).[190] The total cost of a blood test is then £15.01. As the cost of blood tests is relatively small compared with the other costs associated with CIA, we do not expect any increase or reduction in the number of blood tests to have a significant impact on the results. To represent uncertainty in these parameters all parameters were drawn from gamma distributions in the PSA, with SE equal to 20% of the mean.

Adverse event costs

The AEs that we accounted for in this cost-effectiveness analysis were identified through the clinical effectiveness review. In particular, we accounted for the costs of:

- thromboembolic events
- hypertension
- thrombocytopenia.

Resource use for patients not receiving ESA therapy was estimated from the systematic review of clinical effectiveness evidence by simple pooling of all studies to calculate how many patients did and did not experience at least one AE. A beta distribution was constructed for the PSA on the basis of these figures. Patients were assumed to experience, at most, one AE of each type. Resource use for patients receiving ESA therapy was calculated similarly but also applying the relative risk obtained from the systematic review of clinical effectiveness evidence (see *Chapter 3*).

The unit costs of managing thromboembolic events (particularly pulmonary embolism and deep-vein thrombosis), hypertension and thrombocytopenia were identified through NHS reference costs 2012–13[190] and updated to 2014/15 prices. These figures are presented in *Table 65* and are the weighted averages

dependent on HRG codes. No decision was made to specify HRG codes beyond the particular AE, to reflect the fact that the relative risks identified in the PenTAG clinical effectiveness systematic review refer to any AE, regardless of severity. These costs are significantly larger than those reported in TA142,[2] in which the cost of an AE was only £101, but attempts to identify how this figure arose were unsuccessful, beyond identifying it in the Ortho Biotec submission. The previous Roche submission in TA142 had previously attached a cost of monitoring for hypertension of £4 a week and the Amgen Inc. submission a cost of £185 for a deep-vein thrombosis, although sources of these costs were unclear. The NHS reference costs themselves report a wide range of costs for managing each of the AEs and, as such, these costs were altered in the PSA following a gamma distribution with SEs equal to 20% of the means.

Red blood cell acquisition costs

Unit costs for the supply of RBCs were taken directly from NHS Blood and Transplant (NHSBT) 2012/13 costs (£122 per unit)[191] and uprated to 2014/15 prices. This cost is significantly different from the cost of blood products in outpatient care reported in the NHS reference costs 2012–13[190] (average cost around £1300). However this cost is for all blood products, not just RBCs, and as such it has a skewed distribution: for HRG code XD05Z (Blood Products, Band 1) the average unit cost is £1269, but the upper quartile cost is £482. We did not use the NHS reference costs because of the imprecision around the term 'blood products'. Furthermore, the cost of RBCs from the NHSBT is similar to the unit cost reported in a publicly accessible letter detailing the outcomes of the National Commissioning Group for Blood meeting on 9 October 2007,[192] which detailed the cost of RBCs for 2008/9 as £139.72. A gamma distribution was used for the cost of a RBC unit with the SE equal to 20% of the mean.

Cost of a transfusion appointment

The closest cost reported in the NHS reference costs for an outpatient blood transfusion appointment is the outpatient cost for a blood and bone marrow transplant. As with the cost of blood products, this covers more than the specific figure needed for our analysis. Returning to the TA142 analysis[2] the cost value reported came from the study by Varney and Guest.[172] Attempts were made to find updated versions of the figure reported in this paper, with marginal success. Audits from the NHSBT indicate that the numbers of transfusions, as well as the percentages of associated complications, have decreased since the Varney and Guest[172] study was conducted, but the associated costs were not available for this analysis. As such, we used the same figure as reported in Varney and Guest[172] and uprated the cost to 2014/15 costs (*Table 66*). A gamma distribution was used for the unit cost of a RBC transfusion appointment, with the SE equal to 20% of the mean.

TABLE 65 Costs of AEs

AE	PenTAG base case (£)	HRG codes
Thromboembolic events	1243	DZ09D, DZ09E, DZ09F, DZ09G, DZ09H (pulmonary embolus), QZ20A, QZ20B, QZ20C, QZ20D, QZ20E (DVT)
Hypertension	826	EB04Z (hypertension)
Thrombocytopenia	744	SA12G, SA12H, SA12J, SA12K (thrombocytopenia)

DVT, deep-vein thrombosis.

TABLE 66 Unit costs of RBCT

Item	PenTAG base case (£)	Source
Unit cost of RBCs	127	NHSBT[191]
Cost of transfusion appointment	688	Varney and Guest[172]

Intravenous iron supplementation

National Institute for Health and Care Excellence guidance states that, in circumstances in which ESA therapy is recommended, it should be used in combination with intravenous iron as this is associated with a greater probability of a haematological response.[1]

Intravenous iron supplementation was not included in any of the cost–utility studies identified in the update systematic review of cost-effectiveness (see *Chapter 4*, *Update review*).

Iron supplementation is likely to be given to anaemic patients independently of whether they receive ESA therapy, therefore differences in resource use between patients receiving and patients not receiving ESA therapy are likely to be very small (e.g. if anaemia is corrected sooner then iron supplementation would be used for less time) and we have not sought studies from which to estimate such resource use differences.

The cost of intravenous iron has been assumed to be negligible in previous economic studies. To check that this is a reasonable assumption we briefly estimated the cost of the acquisition and administration of intravenous iron. Assuming that intravenous iron would be given in the form of iron dextran 100 mg once weekly (alongside ESA administration), the acquisition cost of CosmoFer® (Pharmacosmos) would be £7.97 per week (2-ml ampule of 50 mg/ml iron dextran).[166]

Resource use for drug administration is difficult to estimate, as patients may already be attending an outpatient clinic for chemotherapy and ESA therapy. We assumed that the incremental resource use for intravenous iron supplementation is minimal and of the same order of magnitude as the drug acquisition cost.

Given that resource use is likely to be very similar between patients receiving and patients not receiving ESA therapy (and that no clinical data would directly inform an estimate of the difference), and given that unit costs are also small in comparison to the cost of ESA acquisition and RBCT, we assumed that the cost of intravenous iron supplementation can be ignored as it will be very similar for all arms.

Other model characteristics

Time horizon, perspective and discounting

A lifetime time horizon was used in the model. The perspective adopted was that of the NHS and Personal Social Services. Costs and benefits were discounted at 3.5% per annum.

Patient characteristics

The age and weight of patients in the model were estimated from the age and weight reported in clinical studies included in the systematic review of clinical effectiveness evidence. A simple average was taken across the studies to estimate the mean, and the SD across studies was used to estimate the SE used in the PSA.

The mean age in the base case was estimated as 59.1 years (SE 5.3 years) and in the scenario analysis with an inclusion Hb level of $\leq$ 11.0 g/dl it was estimated as 60.8 years (SE 4.2 years).

The mean weight in the base case was estimated as 66.6 kg (SE 3.3 kg) and in the scenario analysis it was estimated as 66.1 kg (SE 3.6 kg).

The proportion of male patients was estimated as 46% based on cancer registration statistics in England in 2011 (individuals aged 50–59 years).[183]

Key points

- Our economic model consists of two components: short term and long term.
- In the short-term component:
  - The mean Hb levels across the population were estimated as a function of time for those receiving and not receiving ESA therapy. Hb levels were mapped to utilities to derive QALYs.
  - The difference in Hb levels between the ESA arm and the non-ESA arm at the end of treatment was taken from the systematic review of clinical effectiveness (see *Chapter 3*).
  - Anaemia correction was not assumed to be instantaneous in the ESA arm; instead, the average difference in Hb levels between the ESA arm and the non-ESA arm across the duration of treatment was set to a proportion of the final difference in Hb levels based on results from the randomised trials.
  - The short-term component includes a period during which Hb levels return to normal, a process called 'normalisation'. We found no published data on normalisation, so clinical expert advice and previous economic models were used to inform our modelling.
  - Dose adjustment, dose interruption and treatment withdrawal from ESA therapy were incorporated into an ITT mean weekly dose estimated from randomised trials to attempt to achieve consistency between drug acquisition costs and effectiveness outcomes.
  - The relationship between Hb levels and utilities was estimated from the published literature and assumed to be linear in the range of interest.
  - The drug acquisition costs for ESAs were taken from NHS list prices.
  - Some patients (41%) were assumed to self-administer ESAs, whereas the rest required an appointment with a nurse.
  - Thromboembolic events, hypertension and thrombocytopenia were included as AEs that incurred costs but which did not incur disutility.
  - The units of blood required in RBCTs for the ESA and no ESA arms were estimated from the clinical effectiveness review. Units per transfusion were estimated from the published literature and were assumed to be the same for all arms. Costs associated with transfusions were estimated from NHSBT and the published literature. The cost of a transfusion appointment was inflated from 2001 estimates, which were the most recent available.
- In the long-term component:
  - A constant rate of mortality was assumed with an expected survival duration of 2.67 years for those not receiving ESA therapy, calculated from studies identified in the systematic review of clinical effectiveness. The rate of mortality was adjusted for those receiving ESA therapy using the HR derived in the systematic review of clinical effectiveness (see *Chapter 3*).
  - A constant utility of 0.76 was assumed for the whole population to derive QALYs.

Results

We first present the base-case cost-effectiveness results, comparing six different ESA anaemia treatments with usual treatment not involving ESAs, for adult patients with CIA. The options for anaemia treatment are either RBCTs only or ESAs with RBCTs. Given the differing cost of ESAs, the results for patients on ESAs are examined across the different manufacturers.

Next, we present the cost-effectiveness results under a number of scenarios and the PSA results. These scenarios include:

- analysis in which survival is assumed to be equal in both the ESA arm and the no ESA arm
- the impact of wholesale acquisition costs for ESAs, when applied to both the base-case results and the scenario analysis, in which survival is assumed to be equal in both arms
- subgroup analysis based on studies in which the initial Hb level of patients was ≤ 11 g/dl
- analyses investigating the OS assumptions.

We also present a comparison of our base-case results with the results presented in TA142.[1]

We do not present results for either of the subgroups originally recommended for ESA therapy from TA142: ovarian cancer patients on platinum-based chemotherapy and patients unable to undergo a blood transfusion (on medical or religious grounds). This is because of the lack of suitable data on these two subgroups (see *Chapter 3*).

Base case

For our base case we present the summary results but emphasise the uncertainty in the model through scenario analyses and the PSA, as the deterministic results do not account for such uncertainty.

Cost-effectiveness results

The summary cost-effectiveness results are presented in *Table 67* and *Figure 40*. Costs, which all occur within the first year, and short-term QALY gains remain undiscounted, but QALYs gained in the long term are discounted.

TABLE 67 Summary base-case results

		Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	No ESA	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Total costs per strategy (£)	912	2414	2283	3384	2416	2451	3258
Total incremental costs vs. no ESA (£)	–	1502	1371	2472	1504	1539	2346
Total discounted QALYs gained vs. no ESA	–	0.0706	0.0706	0.0706	0.0706	0.0706	0.0706
ICER vs. no ESA (£/QALY)	–	21,279	19,429	35,018	21,309	21,804	33,233
ICER (£/QALY)	–	Dominated by Binocrit	19,429	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit
INHB vs. no ESA at WTP of £20,000/QALY	–	–0.005	0.002	–0.053	–0.005	–0.006	–0.047
INHB vs. no ESA at WTP of £30,000/QALY	–	0.021	0.025	–0.012	0.020	0.019	–0.008

INHB, incremental net health benefit; WTP, willingness to pay.

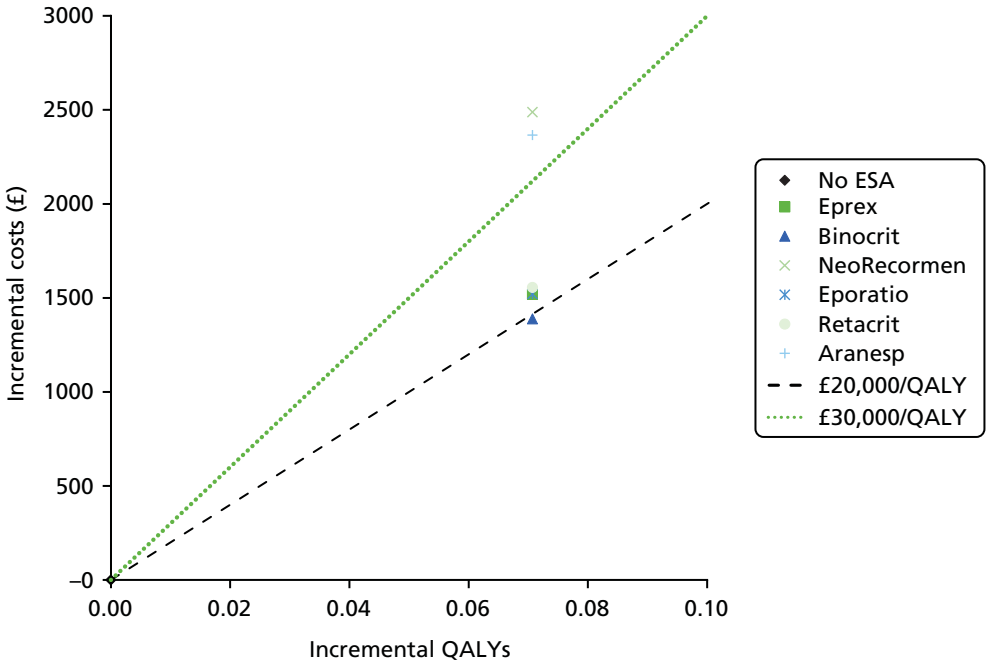

FIGURE 40 Incremental costs and QALYs per patient by anaemia treatment strategy.

As *Table 67* shows, the ICERs for the ESA strategies compared with no ESA use in the deterministic base-case analysis range from £19,429 to £35,018 per QALY gained. Five of these ICERs are all above the NICE-designated willingness-to-pay threshold of £20,000 per QALY and two (NeoRecormen and Aranesp) lie above the upper £30,000 per QALY willingness-to-pay threshold. One ESA (Binocrit) lies below the £20,000-per-QALY threshold but is very close to this threshold, with an ICER of £19,429 per QALY gained. These results are represented pictorially in *Figure 40*. As our ICERs cover a range from < £20,000 to > £30,000 per QALY and are highly sensitive to the parameter estimates, it is important that we demonstrate the impact of the uncertainty in these ICERs and quantify the probability that these ICERs represent the true results.

When the ICERs are translated into incremental net health benefit (INHB) compared with no ESA use, the INHB ranges from –0.053 to 0.002 QALYs at a willingness-to-pay of £20,000 per QALY and from –0.012 to 0.025 QALYs at a willingness-to-pay of £30,000 per QALY, depending on the ESA. This represents a slight net health benefit from the use of ESAs for most ESAs at the £30,000 per QALY willingness-to-pay threshold, but only a net health benefit for one ESA (Binocrit) at the £20,000-per-QALY threshold. Again, it is important to assess the likelihood of this very modest potential net benefit. Inevitably, given the assumed identical effectiveness, we also find that when the ESA strategies are compared with each other, they are dominated by the ESA with the lowest total ESA cost (in this case Binocrit). This is because the only model parameter that differs between each type of ESA is the cost of the drug itself. Therefore, ESAs with a higher cost are dominated by the ESA with the lowest cost when they are directly compared.

We now briefly describe the breakdown of costs and QALY results that give our overall results.

Costs

In the base case, costs are accrued only in the short term (within the first year) so that long-term costs unrelated to anaemia do not disadvantage a treatment with a survival benefit. The costs reported in the base case are therefore not discounted.

Table 68 shows that the total cost per patient in all arms is not particularly high, implying that small changes to these costs may have large impacts on the overall results. The largest cost for all ESA arms is the cost of the ESA itself (£1510–£2485). The largest cost for a patient not on ESA therapy is the cost of a RBCT (£799).

Adverse events have the one of the lowest total costs, in both the ESA arm and the no ESA arm. However, it is important to note that the data from the RCTs used to populate the values of the AE model parameters were available only as the probabilities of having at least one AE (hypertension, thrombocytopenia, thromboembolic events) and the model costs this as only one AE. Given the uncertainty around the AE data, we explored their impact on the results in sensitivity analyses (see *Univariate sensitivity analysis*, *Adverse event costs*).

As we have assumed the same dosing schedule for all ESAs in the base case (once weekly) and that all ESAs are likely to be administered in the same manner, the administration cost for each ESA is equal. Similarly, because of assumptions of equal effectiveness, the costs of AEs, RBCT and additional blood tests are the same for all ESAs.

Incremental results (see *Table 68* and *Figure 41*) demonstrate that, although there is an estimated cost saving of £332 for RBCTs avoided, this is outweighed by the additional costs accrued in each ESA arm.

TABLE 68 Summary of costs in the base case

		Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	No ESA	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Total cost per strategy (£)	912	2414	2283	3384	2416	2451	3258
ESA cost (£)	0	1641	1510	2611	1643	1678	2485
ESA administration cost (£)	0	98	98	98	98	98	98
AE cost (£)	113	148	148	148	148	148	148
RBCT cost (£)	799	467	467	467	467	467	467
Cost of additional blood tests (£)	0	60	60	60	60	60	60
Incremental results							
Incremental cost vs. no ESA (£)	–	1502	1371	2472	1504	1539	2346
ESA cost (£)	–	1641	1510	2611	1643	1678	2485
ESA administration cost (£)	–	98	98	98	98	98	98
AE cost (£)	–	35	35	35	35	35	35
RBCT cost (£)	–	–332	–332	–332	–332	–332	–332
Cost of additional blood tests (£)	–	60	60	60	60	60	60

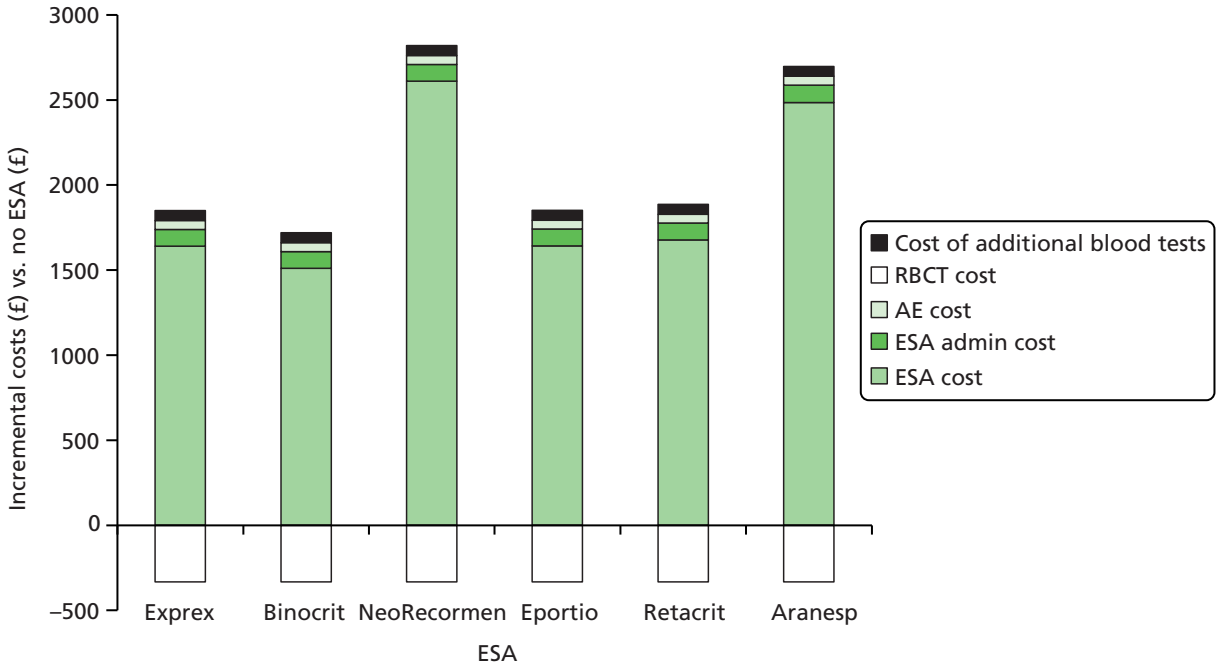

FIGURE 41 Incremental costs vs. no ESA use in the base case.

Quality-adjusted life-years and survival gain

As *Table 69* demonstrates, there is a life-year and QALY gain for patients on ESAs compared with no ESAs, both in the short term (QALY gain as a consequence of an increase in Hb level) and in the long term (a survival gain resulting in a QALY increase). We do not report QALYs for the no ESA arm, instead reporting all QALYs as incremental compared with no ESA treatment. This is because in the short term we do not allocate a specific utility value to each Hb level, instead assigning an increase in utility per Hb increase of 1 g/dl. We therefore do not calculate the short-term utility for the patients in the no ESA arm, instead calculating the difference in utility between arms using the Hb levels. QALYs gained (or lost) by the ESA arm compared with the no ESA arm are then calculated by applying this difference in utility across the appropriate time frame. For consistency, the long-term utility is applied to the difference in survival between the arms, giving the QALYs gained (or lost) by the ESA arm rather than specific QALYs for each arm.

As the results are based on new meta-analyses in PenTAG's clinical effectiveness review, these results are not conducted separately for each ESA product.

Figure 42 demonstrates where these QALYs are accrued. Over three-quarters of the QALY gain results from the modelled increased survival.

TABLE 69 Incremental life-years and QALYs, ESAs vs. no ESAs

Treatment arm	Incremental life-year and QALY gains (ESA vs. no ESA)
Undiscounted life-years gained vs. no ESAs	0.0911
Discounted life-years gained vs. no ESAs	0.0762
Total discounted QALYs gained vs. no ESAs	0.0706
Total short term	0.0124
Short term during cancer treatment	0.0083
Short term during normalisation	0.0042
Long term	0.0582

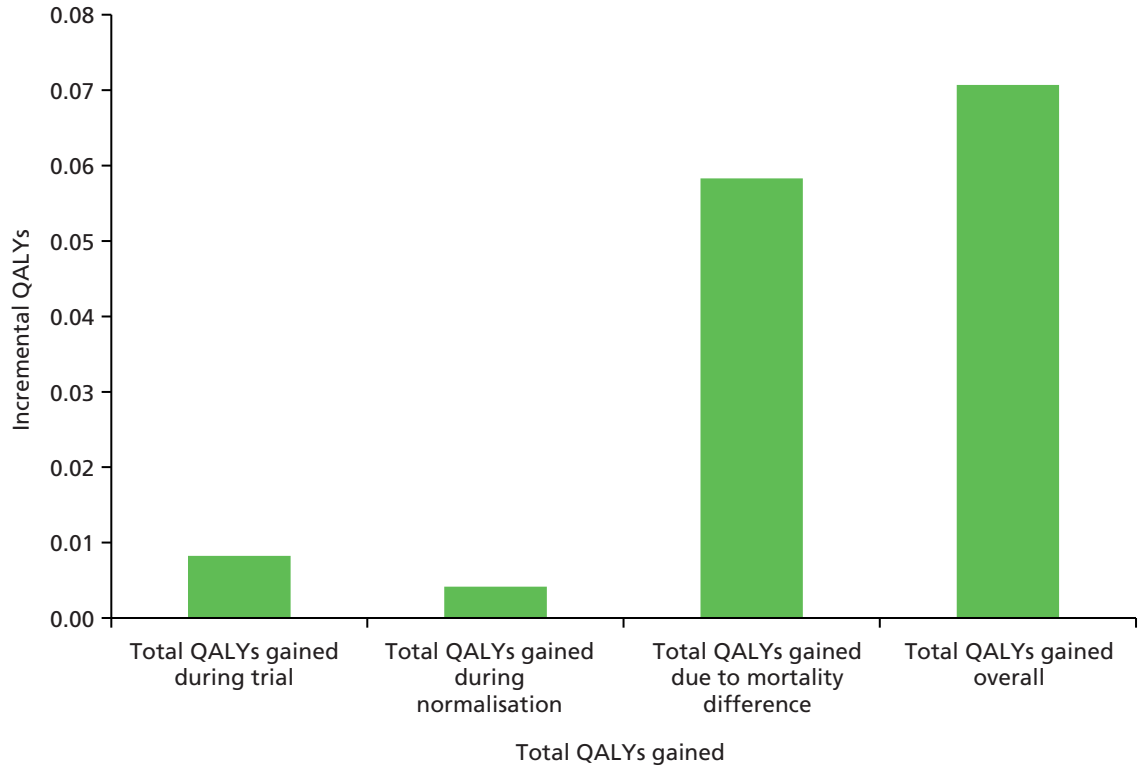

FIGURE 42 Incremental QALY gain vs. no ESAs.

Short-term QALYs are accrued during chemotherapy and in the post-chemotherapy period designated as normalisation. Again, all ESA types are treated as equal in this regard and, as with the costs, these values are not discounted because of the short time frame within which they occur. In our analysis we do not explicitly model any additional ESA use during the normalisation period (it is possible for patients to still be on ESA therapy for up to 4 weeks after chemotherapy); therefore this QALY gain could be greater. Our estimated short-term QALY gain, 0.0124, is lower than that in other comparable studies (e.g. Wilson and colleagues,[2] in which the short-term gain in the base case is 0.030) because of PenTAG's smaller utility gain associated with an increase in Hb level.

The long-term QALY gain for patients on ESAs compared with those not on ESAs is a direct result of the life-years gained, as the utility is assumed to be the same in both arms once patients' Hb levels have normalised. Given the time frame of this section of the model, the life-years gained and associated QALYs are discounted in the final results. The number of discounted life-years gained for patients on ESAs is 0.0762. This translates to a discounted QALY gain of 0.0582, which is significantly larger than the QALY gain from short-term Hb level improvement. This demonstrates the importance of the estimated survival effect of ESA usage. Although our base case includes a survival benefit associated with ESA use, this survival benefit is not demonstrated with statistical significance, as discussed in the PenTAG clinical effectiveness review, and is one parameter that is investigated thoroughly in sensitivity analysis in an attempt to quantify its effects on the results. It is this parameter in particular that drives the cost-effectiveness results and emphasises the importance of our PSA.

Probabilistic sensitivity analysis of the Peninsula Technology Assessment Group base case

Here, we present the results of the PSA for our base case. *Table 70* presents the average PSA results compared with the ICERs in the deterministic base case. On average, the ICERs are slightly reduced in the PSA compared with the deterministic base case. However, as we can see from the 95% CIs for the costs and QALYs, the true ICERs are likely to cover a wide range. Indeed, the credible intervals (CrIs) cover a range from £2500 per QALY to the point where they are dominated (with ESAs having higher costs and lower QALYs than the no ESA arm).

TABLE 70 Summary base-case probabilistic results

	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Deterministic ICER vs. no ESA (£/QALY)	21,279	19,429	35,018	21,309	21,804	33,233
Mean probabilistic ICER vs. no ESA (95% CrI) (£/QALY)	**16,135 (2529 to Dtd)**	**14,724 (2322 to Dtd)**	**27,226 (4067 to Dtd)**	**16,312 (2581 to Dtd)**	**16,484 (2439 to Dtd)**	**25,684 (3841 to Dtd)**
Incremental QALYs vs. no ESA (95% CI)	**0.092 (–0.264 to 0.447)**	**0.092 (–0.264 to 0.447)**	**0.092 (–0.264 to 0.447)**	**0.092 (–0.264 to 0.447)**	**0.092 (–0.264 to 0.447)**	**0.092 (–0.264 to 0.447)**
Incremental short-term QALYs vs. no ESA (95% CI)	0.014 (0.001 to 0.028)	0.014 (0.001 to 0.028)	0.014 (0.001 to 0.028)	0.014 (0.001 to 0.028)	0.014 (0.001 to 0.028)	0.014 (0.001 to 0.028)
Incremental long-term QALYs vs. no ESA (95% CI)	0.077 (–0.278 to 0.433)	0.077 (–0.278 to 0.433)	0.077 (–0.278 to 0.433)	0.077 (–0.278 to 0.433)	0.077 (–0.278 to 0.433)	0.077 (–0.278 to 0.433)
Incremental costs vs. no ESA (95% CI) (£)	**1478 (792 to 2164)**	**1349 (710 to 1987)**	**2494 (1401 to 3586)**	**1494 (826 to 2163)**	**1510 (720 to 2249)**	**2353 (1327 to 3379)**
Incremental ESA costs vs. no ESA (95% CI) (£)	1624 (986 to 2262)	1495 (908 to 2082)	2640 (1588 to 3693)	1641 (1005 to 2277)	1656 (953 to 2360)	2499 (1492 to 3507)
Incremental ESA administration costs vs. no ESA (95% CI) (£)	97 (4 to 191)	97 (4 to 191)	97 (4 to 191)	97 (4 to 191)	97 (4 to 191)	97 (4 to 191)
Incremental AE costs vs. no ESA (95% CI) (£)	37 (1 to 74)	37 (1 to 74)	37 (1 to 74)	37 (1 to 74)	37 (1 to 74)	37 (1 to 74)
Incremental RBCT costs vs. no ESA (95% CI) (£)	–341 (–556 to –125)	–341 (–556 to –125)	–341 (–556 to –125)	–341 (–556 to –125)	–341 (–556 to –125)	–341 (–556 to –125)
Cost of additional blood tests vs. no ESA (95% CI) (£)	60 (41 to 79)	60 (41 to 79)	60 (41 to 79)	60 (41 to 79)	60 (41 to 79)	60 (41 to 79)
INHB vs. no ESA at WTP of £20,000 per QALY (95% CI)	**0.018 (–0.339 to 0.375)**	**0.024 (–0.332 to 0.381)**	**–0.033 (–0.392 to –0.326)**	**0.017 (–0.338 to 0.372)**	**0.016 (–0.342 to 0.374)**	**–0.026 (–0.386 to –0.334)**

Dtd, dominated (more expensive and fewer QALYs than relevant comparator); WTP, willingness to pay.
Bold text indicates total rows (e.g. incremental QALYs vs. no ESA = incremental short-term QALYs + incremental long-term QALYs), and overall incremental probabilistic cost-effectiveness results (e.g. probabilistic ICER and INHB).

The average INHB for each ESA in the PSA is slightly higher than in the deterministic base case, especially when the ESA was close to the boundary of the £20,000 per QALY willingness-to-pay threshold in the deterministic base case. However, when the 95% CI for each INHB is examined, it is clear that there is quite a range that each INHB can lie on. The breakdown of costs and QALYs indicates where the majority of the uncertainty in the overall costs and QALYs comes from. Unsurprisingly, as they appeared to be the main drivers in the deterministic scenario, the ESA costs and the long-term QALY gain appear to have the largest impact on the uncertainty around the overall costs and QALYs.

To represent the uncertainty further, we plotted the simulation results for Binocrit (currently the cheapest of the different ESAs) in *Figure 43*.

The scatterplot demonstrates that all data points fall within the north-west and north-east quadrants so that none of the simulations resulted in a cost saving from ESA use. The four quadrants and their proportions of data points are summarised in *Table 71*. From examining the cost results of the model, in 100% of simulations the ESA arm had higher costs for ESA use and reduced costs for RBCTs and in 0.8% of simulations there was a reduction in the costs of AEs compared with the no ESA arm. This 0.8% occurs when the RR of thrombocytopenia is favourable for ESA use and the additional costs of thrombocytopenia in the control arm outweigh the costs in the ESA arm. However, as the simulations demonstrate, this reduction in cost for AEs does not produce an overall cost saving (the cost saving for the ESA arm in these occurrences is < £10).

A significant proportion (31.4%) of the data points also reflect an estimated loss of QALYs. This suggests the possibility that ESAs may actually result in a reduction in QALYs while still having an increased cost. There is always a QALY gain from ESA use in the short term, as the CI for the difference in Hb level at the end of the trial between the ESA arm and the no ESA arm never favours no ESA use, therefore this loss of QALYs is a direct result of the wide CI for the OS HR. The model shows that 36% of simulations have a QALY loss in the long term (as a result of the OS HR favouring no ESA therapy over ESA use) and in the majority of these simulations (≈87.2%) this is larger than the QALY gain in the short term, resulting in an overall QALY loss. This suggests that the OS HR is the primary driver of the QALY results for the simulations.

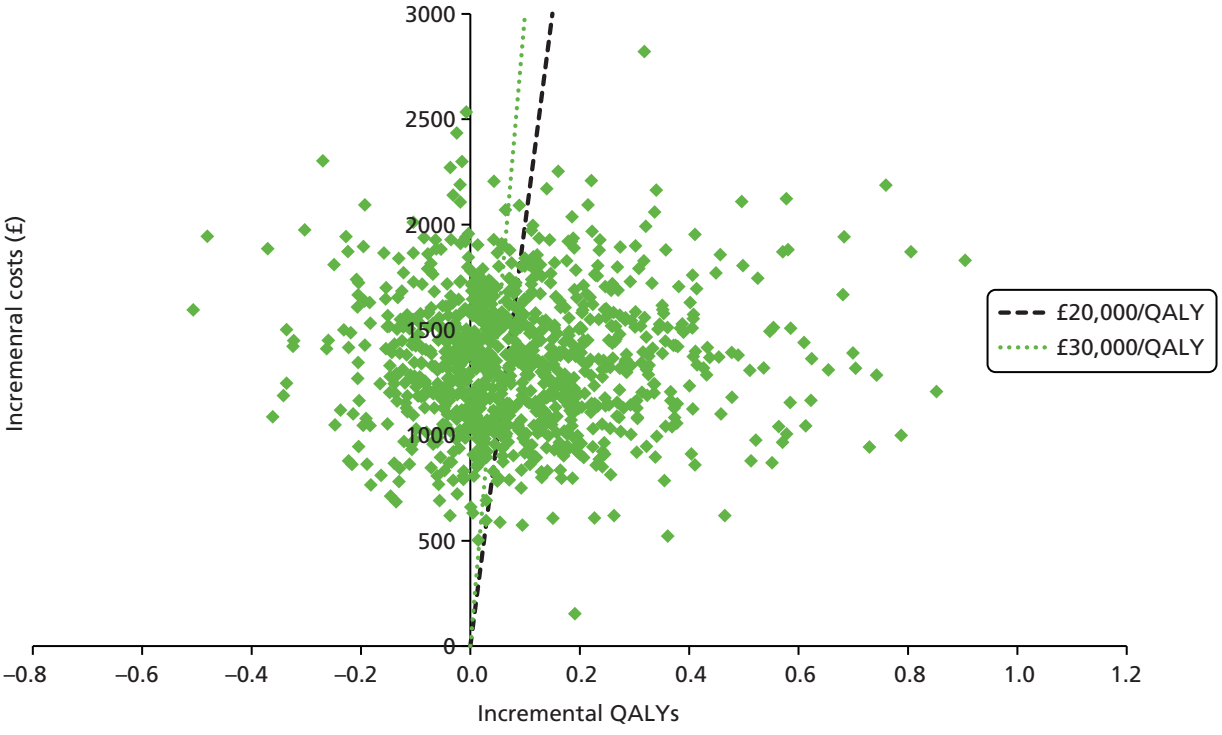

FIGURE 43 Probabilistic sensitivity analysis base-case incremental costs and QALYs: scatterplot.

TABLE 71 Percentage of PSA simulations by cost increase/saving and health loss/gain

Cost	Health loss	Health gain
Increase	31.4	68.6
Saving	0	0

Table 72 shows that, at a willingness-to-pay threshold of £20,000 per QALY, 50.9% of simulations fall above this threshold (of which 31.4% are dominated by the no ESA arm). The percentage of simulations that therefore put ESAs within the region of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY is 48.1%. Comparing this value to the 31.4% of simulations in which ESA use is dominated, we can conclude that the likelihood of ESAs being cost-effective is highly uncertain.

When we compare the cost-effectiveness acceptability curves (CEACs) of all of the ESA strategies (*Figure 44*), we see that below a willingness-to-pay threshold of £150,000 per QALY, no single ESA strategy is as probable to be cost-effective as the current practice arm, with the majority converging to a probability far below that of the no ESA arm. The probability of the no ESA arm being cost-effective reduces swiftly as the willingness-to-pay threshold lowers, to the extent that, by a willingness-to-pay threshold of £20,000 per QALY, it falls to < 50%. However, at this £20,000-per-QALY threshold we also see that the ESA arm most likely to be cost-effective still has a < 25% probability of being cost-effective. All other ESA arms have a probability of being cost-effective of < 20% for any willingness-to-pay threshold of < £150,000 per QALY.

The cost-effectiveness acceptability frontier (CEAF) (*Figure 45*) compares the expected net health benefits of strategies at various willingness-to-pay thresholds. Given the higher average costs and equal QALY gains of the other ESAs, Binocrit consistently has the highest net health benefit of the ESAs and therefore is the only ESA to appear on the CEAF. We see that, at a willingness to pay of £15,000 per QALY, Binocrit appears to be the most favourable option (i.e. it has the highest probability of producing the highest net health benefit).

Overall, the PSA results demonstrate that the uncertainty inherent in the parameter estimates, particularly those relating to long-term QALY gains, is highly influential on the results. There appears to be the potential for ESAs to be cost-effective at a £20,000-per-QALY threshold, depending on their cost, but this is to be viewed with caution given that there is also the possibility of ESAs producing a survival loss and uncertainty which ESAs would be cost-effective.

Scenario analysis 1: setting overall survival as equal across arms

As the long-term QALYs from any potential survival benefit are highly influential on the cost-effectiveness results and both the clinical and the statistical significance of any survival benefit may be disputed, we present a scenario in which the OS HR is set to exactly 1 (and not varied in the PSA). For the purposes of this scenario we present first the deterministic results, then a threshold analysis of the mean weekly cost to establish the cost at which ESAs become cost-effective and, finally, a PSA to investigate how removing the long-term survival benefit in the model affects the model results.

TABLE 72 Percentage of PSA simulations in which ESA therapy is not cost-effective

	ESA dominated vs. no ESA	ICERs > £20,000 per QALY vs. no ESA	Total in which ESA is not cost-effective (at £20,000 threshold)
Probability	31.4	19.5	50.9

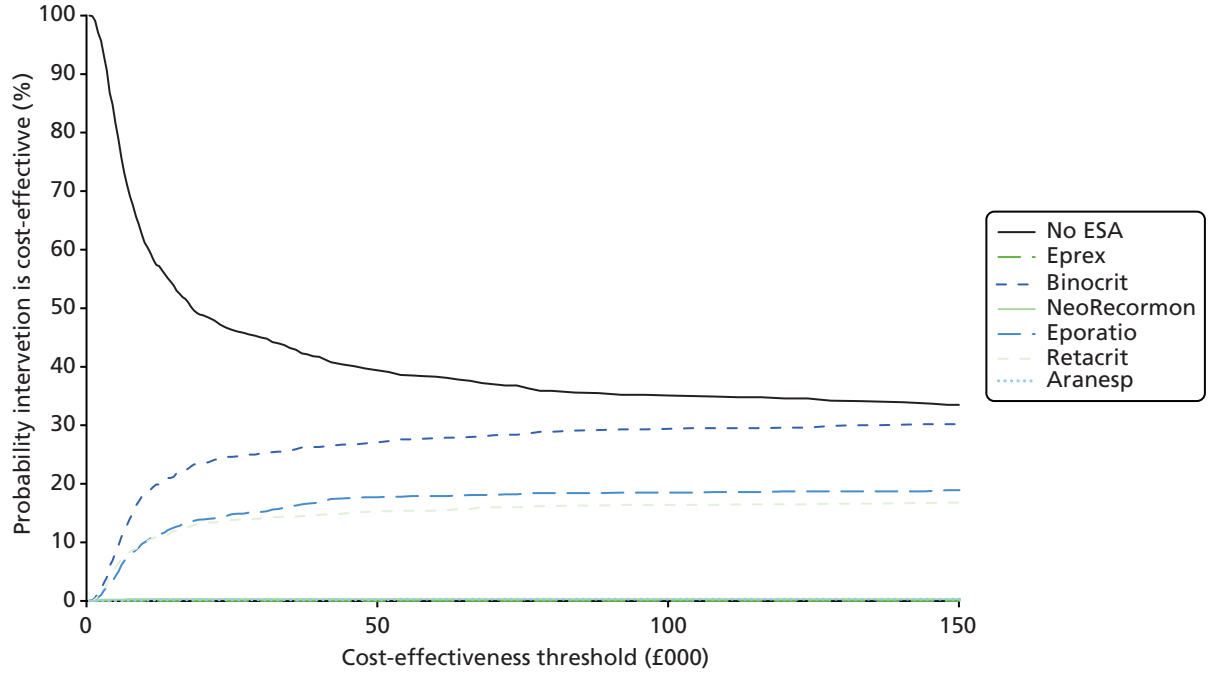

FIGURE 44 Cost-effectiveness acceptability curves from the base-case PSA.

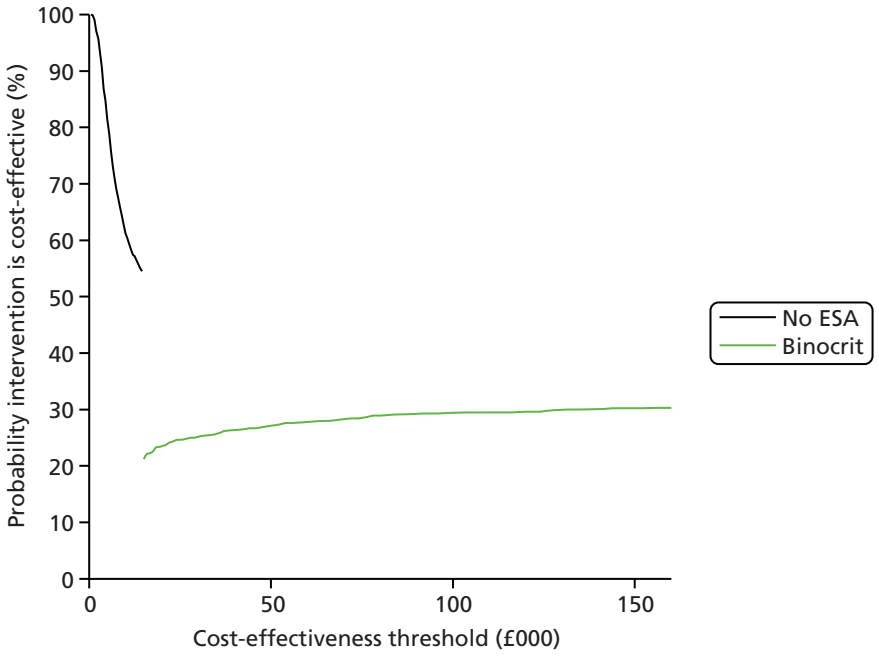

FIGURE 45 Cost-effectiveness acceptability frontier for the base-case PSA.

Deterministic analysis: scenario analysis 1

As this scenario is identical to the base case, but with the long-term aspect effectively removed, the costs and short-term QALYs in the deterministic analysis are the same as those in the base case except that the long-term incremental QALYs become equal to 0. This can be demonstrated by comparing *Table 73* with *Table 67*.

The overall QALY gain is now greatly reduced from 0.0706 in the base case to 0.0124, a reduction of 82%. As the costs have remained the same we see that the ICERs are greatly increased, such that all ESAs have an ICER > £110,000 per QALY compared with the no ESA arm. These ICERs lie well above the £30,000-per-QALY threshold depicted in *Figure 46*. This therefore suggests that, if no survival benefit is assumed, ESAs do not appear to be cost-effective compared with current practice.

Threshold analysis of erythropoiesis-stimulating agent costs: scenario analysis 1

As part of this scenario analysis, which assumes no impact on OS, we considered what cost of ESA therapy would reduce the ICERs to below the £20,000-per-QALY threshold. As the ESA dose cost depends on both the unit cost and the size of the dose, we performed a threshold analysis on the weekly ESA cost. In the base case we see that the dose cost per week ranges from £137 to £218. By testing a range of dose costs per week and fixing all other values, for the ICER to fall below £20,000 per QALY gained in this scenario, the weekly cost of ESA therapy must fall below £32 (*Table 74*). As any alteration in dose would likely affect the effectiveness of the ESAs, the only variation in the base-case analysis implied by this scenario is a reduction in the unit cost of between 75% and 85%.

TABLE 73 Summary cost-effectiveness results for scenario analysis 1

		Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	No ESA	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Total cost per strategy (£)	912	2414	2283	3384	2416	2451	3258
Total incremental cost vs. no ESA (£)	–	1502	1371	2472	1504	1539	2346
Total discounted QALYs gained vs. no ESA	–	0.0124	0.0124	0.0124	0.0124	0.0124	0.0124
ICER vs. no ESA (£/QALY)	–	120,995	110,477	199,118	121,166	123,983	188,968
ICER (£/QALY)	–	Dominated by Binocrit	£110,477	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit
INHB vs. no ESA at WTP of £20,000/QALY	–	–0.063	–0.056	–0.111	–0.063	–0.065	–0.105
INHB vs. no ESA at WTP of £30,000/QALY	–	–0.038	–0.033	–0.070	–0.038	–0.039	–0.066

WTP, willingness to pay.

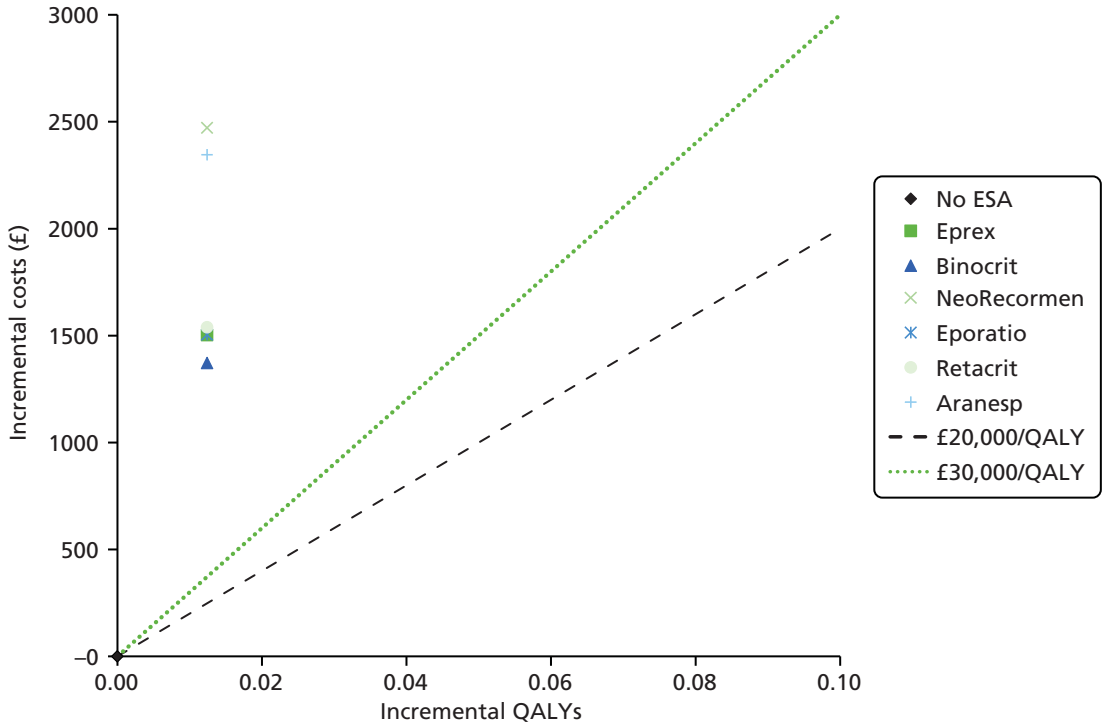

FIGURE 46 Incremental costs and QALYs for scenario analysis 1.

TABLE 74 Threshold analysis results for ESA cost per week

Dose cost per week (£)	Total ESA cost (£)	ICER (£/QALY)
30	360	17,799
31	372	18,765
32	384	19,732
33	396	20,699
34	408	21,666
35	420	22,632
Minimum base-case value: 137	2283	110,477

(Commercial-in-confidence information has been removed). An analysis of the wholesale acquisition costs is provided separately in *Scenario analysis 2: using wholesale acquisition costs*, but this analysis does indicate that, for a certain cost, ESAs may be cost-effective even without a modelled survival gain.

Probabilistic sensitivity analysis: scenario analysis 1

We also performed a PSA on this scenario to see how uncertain the results are once the uncertainty around survival is removed. As the results in *Table 75* show, the 95% CIs around the incremental QALYs and INHBs are much reduced compared with the base case, suggesting that a large component of the uncertainty has been removed by eliminating the uncertainty surrounding OS. This is also consistent with no ESA therapy being cost-effective at the highest cost-effectiveness threshold. The lower limit of the 95% CrI for the ICERs does not fall below £30,000 per QALY gained for any of the ICERs, suggesting that in this scenario ESAs are unlikely to be cost-effective.

TABLE 75 Summary PSA results for scenario analysis 1

	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
Treatment arm	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Deterministic ICER vs. no ESA (£/QALY)	120,995	110,477	199,118	121,166	123,983	188,968
Mean probabilistic ICER vs. no ESA (95% CrI) (£/QALY)	106,007 (40,506 to > 300,000)	96,754 (36,897 to > 300,000)	174,193 (71,732 to > 500,000)	104,706 (41,987 to > 300,000)	106,745 (40,827 to > 300,000)	166,848 (69,324 to > 500,000)
Incremental QALYs (95% CI)	0.014 (0.001 to 0.027)	0.014 (0.001 to 0.027)	0.014 (0.001 to 0.027)	0.014 (0.001 to 0.027)	0.014 (0.001 to 0.027)	0.014 (0.001 to 0.027)
Incremental cost (95% CI) (£)	1504 (777 to 2232)	1373 (695 to 2051)	2472 (1387 to 3556)	1486 (816 to 2156)	1515 (787 to 2242)	2368 (1311 to 3425)
INHB vs. no ESA at WTP of £20,000 per QALY (95% CI)	–0.061 (–0.100 to –0.022)	–0.054 (–0.091 to –0.018)	–0.109 (–0.165 to –0.054)	–0.060 (–0.096 to –0.024)	–0.062 (–0.100 to –0.023)	–0.104 (–0.159 to –0.050)

WTP, willingness to pay.

Note

The results are slightly different from those in the base case because of a different simulation being run.

Indeed, when we examine the scatterplot of the simulations (*Figure 47*), we see that the distribution of points along the horizontal axis is greatly reduced, both because there is no longer a QALY loss and because the QALY benefit is not spread across such a wide area. In fact, if we consider the scatterplot on the same axes as for the base-case result (*Figure 48*), we see a much narrower distribution of QALY estimates. Given the much smaller QALY difference estimates in this case and the same differences in costs compared with the base case, we find that 99.7% of the data points lie above the £20,000-per-QALY threshold.

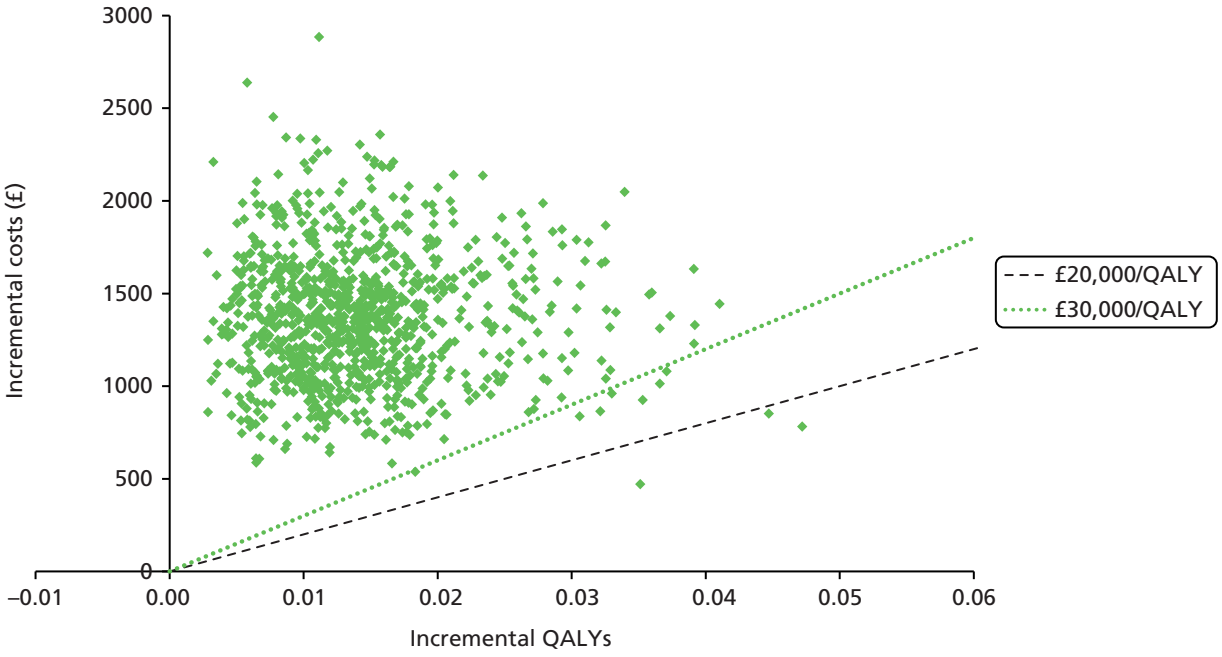

FIGURE 47 Incremental costs and QALYs by PSA simulation for scenario analysis 1.

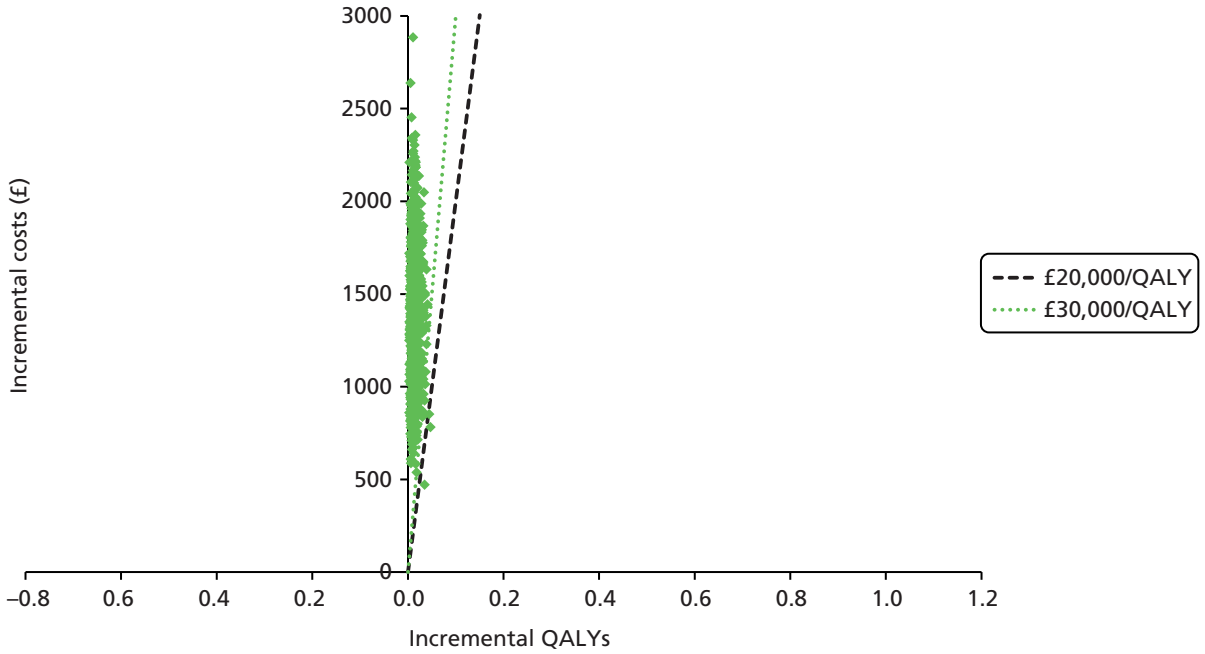

FIGURE 48 Incremental costs and QALYs by PSA simulation for scenario analysis 1 and scaled to the axes used in the base case.

The CEACs for this scenario (*Figure 49*) demonstrate a much more gradual decline in the probability of cost-effectiveness for the no ESA arm, with increase in the cost-effectiveness threshold, as well as an increase in the ESA arms, compared with the base case. The ESA arms also begin to converge at a higher probability than in the base case, although this is still well below 50%. The CEAF (*Figure 50*) also demonstrates a much higher willingness-to-pay threshold (£100,000 per QALY) at which one of the ESAs (Binocrit) may produce a higher net health benefit compared with the no ESA arm.

The results from this PSA suggest that, if ESA use is assumed to have exactly no impact on survival, the current practice of not using ESAs appears to be the most cost-effective option at a willingness-to-pay threshold of £30,000 per QALY.

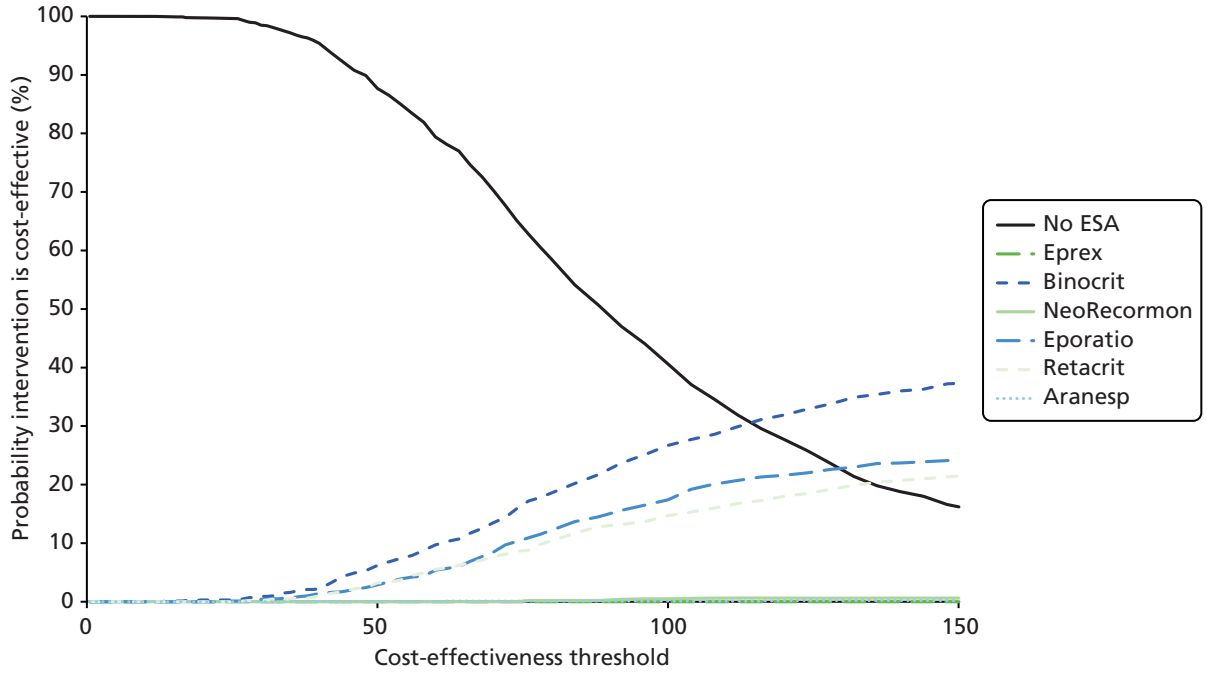

FIGURE 49 Cost-effectiveness acceptability curves for scenario analysis 1.

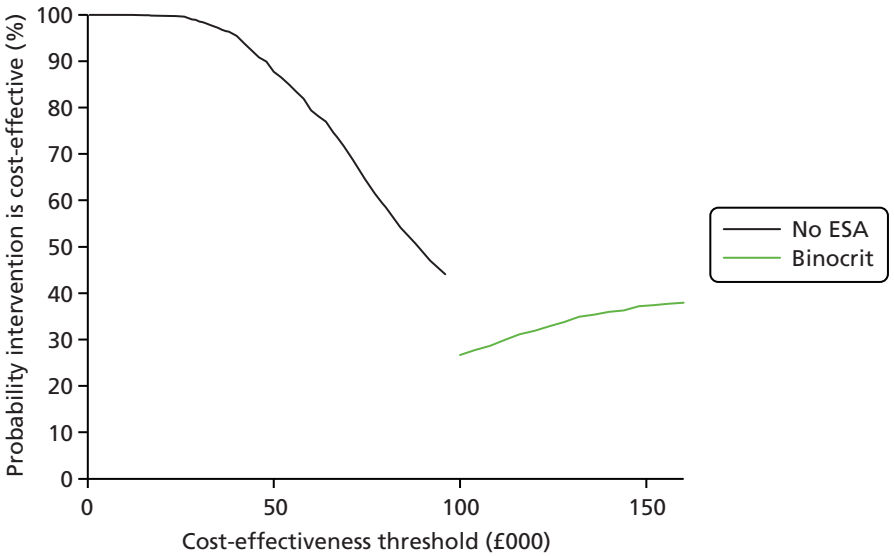

FIGURE 50 Cost-effectiveness acceptability frontier for scenario analysis 1.

Scenario analysis 2: using erythropoiesis-stimulating agent wholesale acquisition costs

Although we have partly investigated the impact of reducing the costs of the ESAs in scenario 1, we also consider it important to apply the actual costs that we have available into the model. To give a complete picture, we apply these costs both in the base case and in scenario 1, in which there is no survival benefit accounted for. This allows us to investigate the impact of these costs, regardless of the beliefs about survival.

As we did not receive any cost information for epoetin theta, epoetin theta is omitted from these results.

Scenario analysis 2a: application to the base-case results

As *Table 76* shows, all costs in this scenario are greatly reduced compared with the base case and the ICERs range from (Commercial-in-confidence information has been removed) per QALY gained, depending on the ESA, in the deterministic case. As with the base case, when the averages are taken from the PSA results, we see that the ICERs are further reduced, but in either case they are all far below the willingness-to-pay threshold of £20,000 per QALY gained. Although the ICERs indicate that the most cost-effective ESA is Retacrit (having the lowest cost), the INHB PSA results indicate that the 95% CIs for INHB overlap for all ESAs, suggesting that the cost-effectiveness of the ESAs is similar. (Commercial-in-confidence information has been removed).

If we examine the PSA results for the most cost-effective ESA in this scenario (*Figure 51*), we see that the majority of data points lie around the origin. A summary of where the data points lie is provided in *Table 77* and shows that in 26.4% of simulations ESA therapy was dominated by no ESA therapy (cost increase and QALY loss), but in 5% of cases ESA therapy dominated the no ESA arm (cost saving and QALY gain). ESAs dominate when the cost saving from a reduction in RBCT use outweighs the additional costs from ESA use. For a significant proportion of the simulations (37.1%) the cost of ESA therapy (dose and administration) is smaller than the cost saving from RBCT use, but the additional AE costs and blood test costs prevent the majority of these simulations from having an overall cost saving. Therefore, when the unit costs of the ESA are reduced, the other potential costs associated with ESA use become more important.

The CEACs for this scenario (*Figure 52*) show that, at a willingness-to-pay threshold of at least £3500 per QALY, Retacrit has the highest probability of being cost-effective. Furthermore, the probability of no ESA use being cost-effective is greatly reduced for all thresholds. The CEAF (*Figure 53*) demonstrates that Retacrit becomes the optimal strategy at a willingness-to-pay threshold of £2000 per QALY.

The results of this scenario suggest that the ESAs are more cost-effective than in the base case. However, the long-term QALYs are still highly uncertain and the reduction in costs makes the impact of their uncertainty more influential than in the base case. As such, the probability of ESAs being cost-effective is still uncertain.

Scenario analysis 2b: application to scenario analysis 1 results, no survival benefit

The summary results for the wholesale acquisition costs applied to scenario analysis 1, in which survival is assumed to be equal for both the ESA arm and the no ESA arm (Commercial-in-confidence information has been removed) (*Table 78*). As expected, the ICERs for both the deterministic and the average probabilistic results are larger than those found when the wholesale acquisition costs are applied to the base case. However, the majority of ESAs have ICERs that are <£20,000 per QALY and there is therefore an indication that, at the prices paid for the ESAs, they could be cost-effective, regardless of the survival benefit. However, the upper limit of the 95% CrIs is still > £30,000 per QALY for all ESAs. It is noted that there is still much crossover in the INHB 95% CIs, suggesting that it is difficult to choose between the ESAs.

TABLE 76 Summary cost-effectiveness results for scenario analysis 2a: wholesale acquisition costs applied in the base case – deterministic and probabilistic results

		Epoetin alfa		Epoetin beta	Epoetin zeta	Darbepoetin alfa
Treatment arm	**No ESA**	**Eprex**	**Binocrit**	**NeoRecormen**	**Retacrit**	**Aranesp**
Deterministic results						
Total cost per strategy (£)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Total incremental cost vs. no ESA (£)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Total discounted QALYs gained vs. no ESA	–	0.0706	0.0706	0.0706	0.0706	0.0706
ICER vs. no ESA (£/QALY)	–	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
ICER (£/QALY)	–	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Probabilistic results						
Total cost per strategy (£)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Total incremental cost vs. no ESA (95% CI) (£)		Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Total discounted QALYs gained vs. no ESA (95% CI)		0.083 (–0.251 to 0.418)	0.083 (–0.251 to 0.418)	0.083 (–0.251 to 0.418)	0.083 (–0.251 to 0.418)	0.083 (–0.251 to 0.418)
ICER vs. no ESA (£/QALY)		Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
INHB vs. no ESA at WTP of £20,000/QALY (95% CI)		Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

Dtd, dominated (more expensive and fewer QALYs than relevant comparator); Dts, dominates (less expensive and more QALYs than relevant comparator); WTP, willingness to pay.

FIGURE 51 Incremental costs and QALYs: PSA results for scenario analysis 2a. Commercial-in-confidence information has been removed.

TABLE 77 Percentage of the PSA simulations by cost increase/saving and health loss/gain for scenario analysis 2a applied to the base case

Cost	Health loss	Health gain
Increase	26.4	65.9
Saving	2.7	5.0

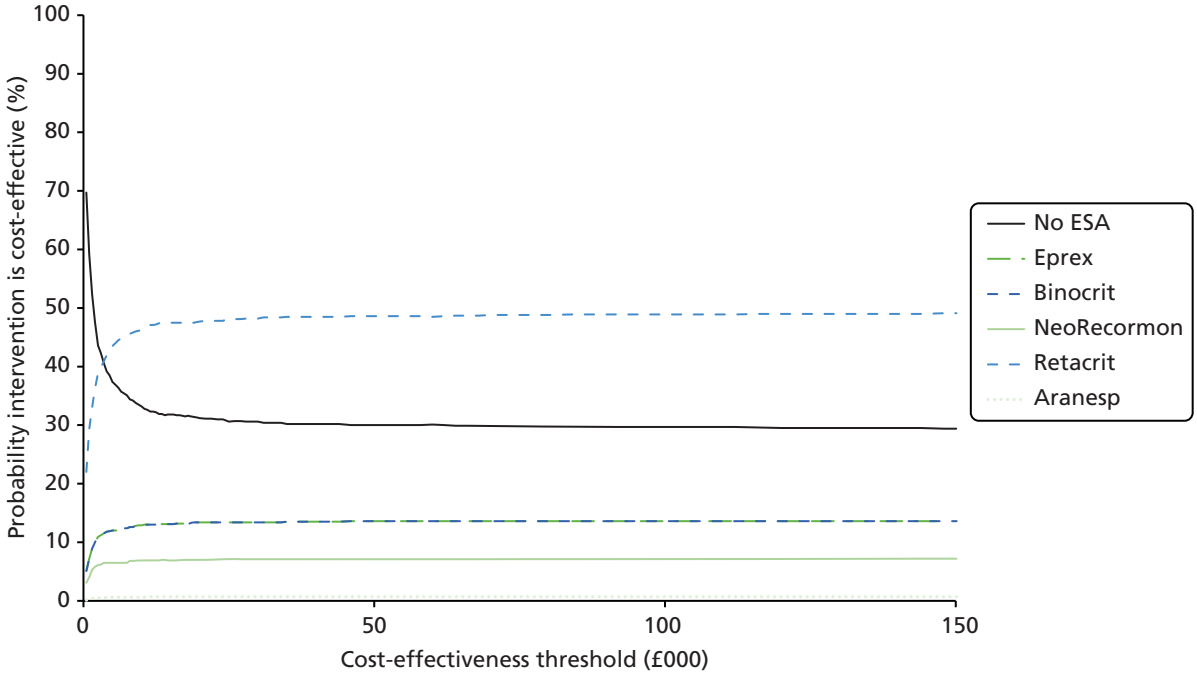

FIGURE 52 Cost-effectiveness acceptability curves: scenario analysis 2a.

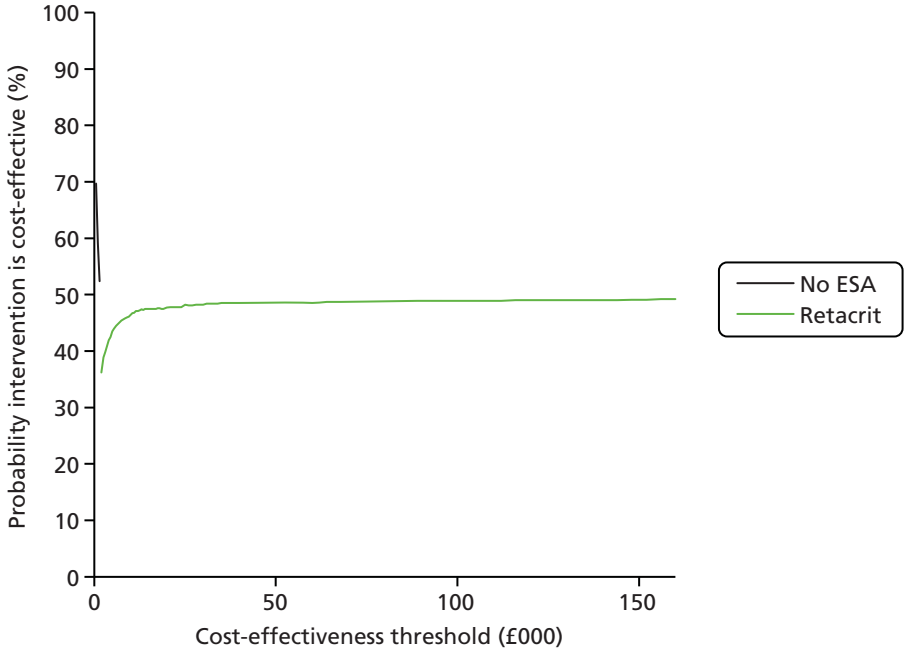

FIGURE 53 Cost-effectiveness acceptability frontier: scenario analysis 2a.

TABLE 78 Summary cost-effectiveness results for scenario analysis 2b: wholesale acquisition costs applied with no survival benefit – deterministic and probabilistic results. Commercial-in-confidence information has been removed

As with scenario analysis 1, when the survival component is removed from the model, the distribution of data points is greatly reduced (*Figure 54*). In this scenario, 8.2% of simulations are both cost saving and QALY increasing, but 34.4% still lie above the £20,000-per-QALY threshold. As before, for a significant proportion of the simulations (36.7%), the cost of ESA therapy (dose and administration) is smaller than the cost saving from a reduction in RBCT use, but the additional AE costs and blood test costs prevent the majority of these simulations from having an overall cost saving. This value is slightly different from that when wholesale acquisition costs are applied in the base case because of a different run of the simulations.

The CEACs for this scenario (*Figure 55*) appear to be quite different from those in the previous scenarios. At a willingness-to-pay threshold of £75,000 per QALY, all ESAs have a higher probability of being cost-effective than no ESA. Furthermore, the probability that Retacrit is cost-effective at a willingness-to-pay threshold of £20,000 per QALY is > 50%, higher than in the other scenarios.

The CEAF for this scenario indicates that Retacrit is the most optimal choice at a willingness-to-pay threshold of £9500 per QALY (*Figure 56*).

FIGURE 54 Incremental costs and QALYs: PSA results for scenario analysis 2b. Commercial-in-confidence information has been removed.

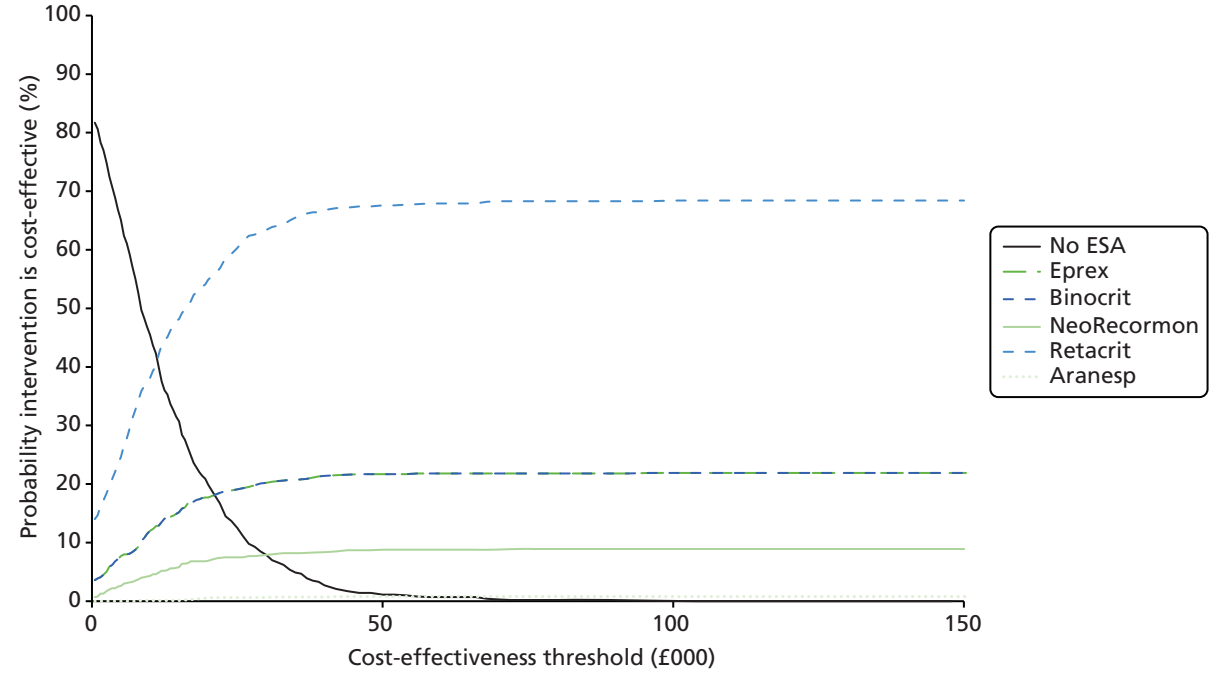

FIGURE 55 Cost-effectiveness acceptability curves: scenario analysis 2b.

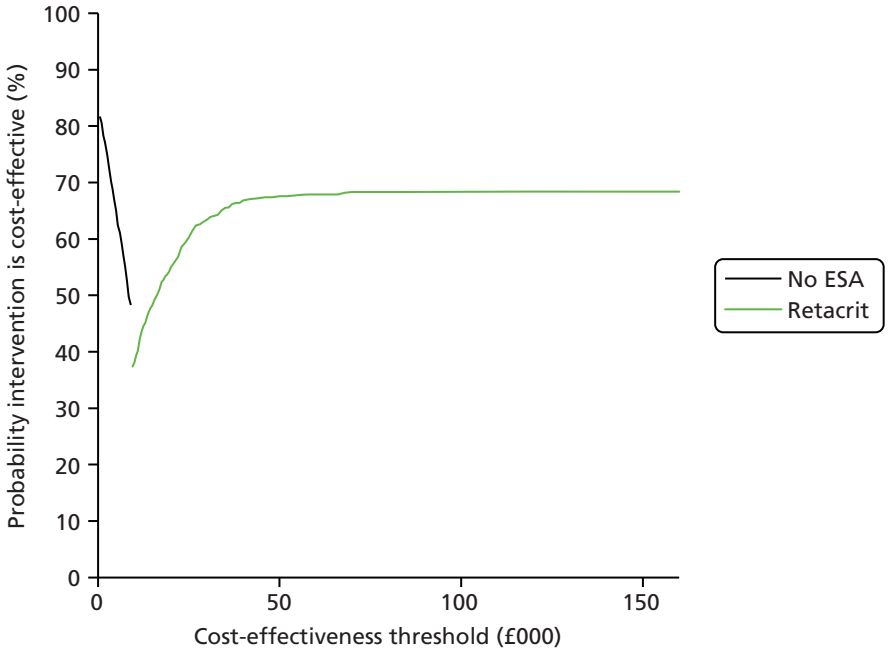

FIGURE 56 Cost-effectiveness acceptability frontier for scenario analysis 2b.

The overall results of this scenario demonstrate that, when the ESA prices are lowered to those that are available currently to the NHS, the cost-effectiveness of ESAs appears to be much improved, regardless of whether survival is accounted for in the model. If survival is assumed to be equal in both the ESA arm and the no ESA arm then ESA therapy being cost-effective seems plausible; however, it is equally plausible that it is not cost-effective. Even if survival is not assumed to be equal, there is still a significant proportion of the simulations in which a survival disbenefit occurs and, as such, there is the possibility of ESAs being dominated by current practice.

Scenario analysis 3: subgroup of randomised controlled trials based on the initial haemoglobin level

Deterministic analysis: scenario analysis 3

We next present a scenario analysis that uses only data from RCTs in which only patients with an inclusion Hb level of ≤11 g/dl are included. This subgroup was used in an attempt to get closer to the licensed indication while maintaining a large enough subgroup of studies to gain estimates for all parameters. Summary estimates are presented in *Table 79*. The input parameters for this scenario are provided in *Appendix 19* and described in *Methods*. One of the main changes in input parameters in this scenario analysis is a higher estimated gain in OS from the use of ESA therapy [HR reduced from 0.97 (95% CI 0.83 to 1.13) to 0.91 (95% CI 0.70 to 1.20)]

TABLE 79 Summary cost-effectiveness results for scenario analysis 3

		Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	No ESA	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Total cost per strategy (£)	956	2396	2266	3350	2394	2434	3222
Total incremental cost vs. no ESA (£)	–	1441	1310	2394	1438	1478	2267
Total discounted QALYs gained vs. no ESA	–	0.1040	0.1040	0.1040	0.1040	0.1040	0.1040
ICER vs. no ESA (£/QALY)	–	13,849	12,593	23,013	13,826	14,206	21,785
ICER (£/QALY)	–	Dominated by Binocrit	£12,593	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit
INHB vs. no ESA at WTP of £20,000/QALY	–	0.032	0.039	–0.016	0.032	0.030	–0.009
INHB vs. no ESA at WTP of £30,000/QALY	–	0.056	0.060	0.024	0.056	0.055	0.028

WTP, willingness to pay.

As *Table 79* shows, the ICERs for the ESA strategies compared with no ESA use in the deterministic base case range from £12,593 to £23,013 per QALY gained. Four of these ICERs are below the NICE-designated willingness-to-pay threshold of £20,000 per QALY and two (NeoRecormen and Aranesp) lie above this threshold but below the upper £30,000 per QALY willingness-to-pay threshold. These results are represented pictorially in *Figure 57*. As with our base case, the ICERs cover a range around the £20,000-per-QALY threshold, therefore we felt that it was important to demonstrate the impact of the uncertainty in these ICERs and quantify the probability that these ICERs represent the true results.

When these ICERs are translated into INHBs compared with no ESA use, the INHB ranges from –0.016 to 0.039 QALYs at a willingness-to-pay threshold of £20,000 per QALY and from 0.024 to 0.060 QALYs at a willingness-to-pay threshold of £30,000 per QALY, depending on the ESA. This represents a net health benefit from the use of ESAs for all ESAs at the £30,000 per QALY willingness-to-pay threshold and a net health benefit for most ESAs at the £20,000-per-QALY threshold.

When the ESA strategies are compared with each other, we find that, as in the base case, they are dominated by the ESA with the lowest total ESA cost (in this case Binocrit). This is mostly expected as the parameters in the base case that are altered for this scenario analysis are those relevant to effectiveness; however, there are also differences in the mean weekly dose of each ESA compared with the base case, which alters costs.

Figure 58 shows that the incremental costs in this scenario are similar to those in the PenTAG base case (see *Figure 40*). One difference from the base case is that the incremental QALYs gained during normalisation are similar to the incremental QALYs gained during treatment (*Figure 59*). This happens because of a lower starting Hb level and a longer normalisation period in this scenario compared with the base case. The total incremental QALYs gained in the short term, however, are broadly similar to those in the base case (0.011 as opposed to 0.012). The total QALYs gained as a result of the mortality difference are also higher than in the base case (0.093 as opposed to 0.058). This gives a much higher overall QALY gain of 0.104 (compared with 0.071 in the base case) and explains why the ICERs appear much reduced.

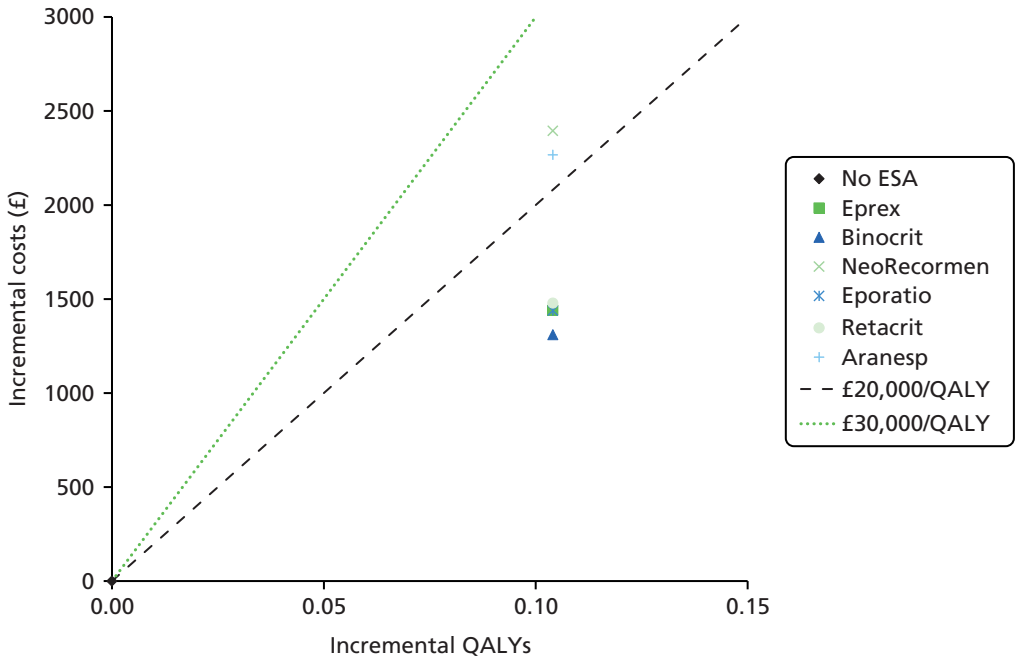

FIGURE 57 Incremental costs and QALYs for scenario analysis 3.

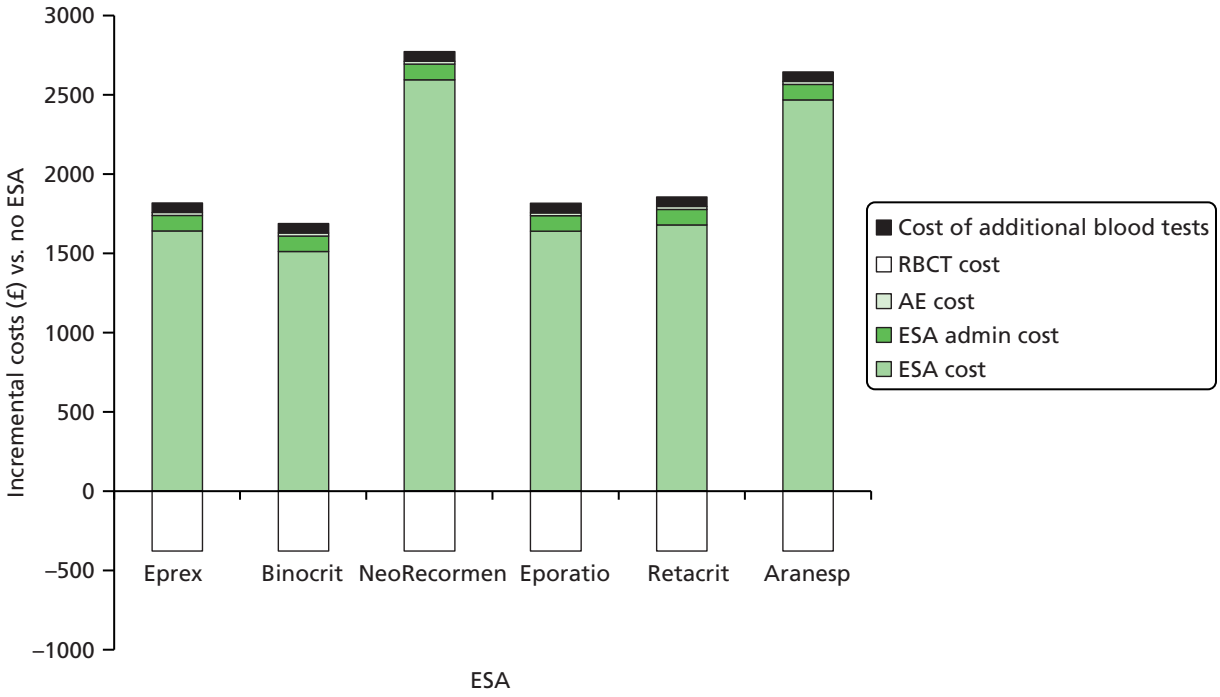

FIGURE 58 Incremental costs vs. no ESA for scenario analysis 3.

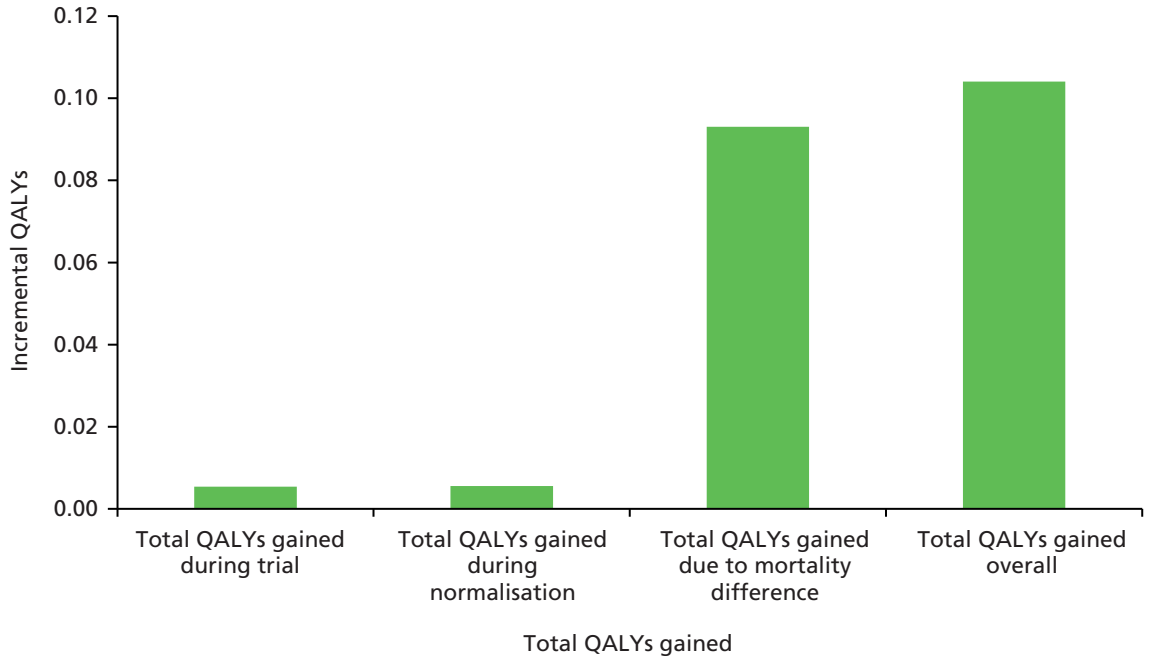

FIGURE 59 Incremental QALYs gained vs. no ESA in scenario analysis 3.

Probabilistic analysis: scenario analysis 3

We also conducted a PSA for this scenario to see what effect limiting the subgroup had on the uncertainty in the results. A summary of the average results is presented in *Table 80*; as in the base case, the average PSA ICERs are slightly less than the estimates from the deterministic results, but the upper limit of the CrIs is still dominated by no ESA use. *Figure 60* shows that, compared with the equivalent plot for the base case, there appears to be just as much, if not more, uncertainty in this subgroup of studies, particularly in terms of QALY gains.

As with the base case, we see that a significant proportion (23.1%) of data points incur an increase in cost with a loss in QALYs and another 19.4% have a health gain but are above the £20,000-per-QALY threshold. In total, 3.2% of simulations had an overall QALY gain but a survival disbenefit, with QALYs gained only in the short term. The percentage of simulations in which ESAs are within the region of being cost-effective at £20,000 per QALY is 57.5%, which is slightly larger than in the base case.

The CEACs for this PSA (*Figure 61*) suggest that Binocrit may have a higher probability of being cost-effective than no ESA use at a willingness-to-pay threshold of £42,000 per QALY, but that this probability is still fairly low (< 35%). All other ESA arms have a probability of being cost-effective of < 25% for any willingness-to-pay threshold < £150,000 per QALY.

The CEAF (*Figure 62*) suggests that, at a willingness-to-pay threshold of at least £10,500 per QALY, Binocrit appears to be the most favourable option.

TABLE 80 Summary cost-effectiveness results from the PSA of scenario analysis 3

	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Deterministic ICER vs. no ESA (£/QALY)	13,849	12,593	23,013	13,826	14,206	21,785
Mean probabilistic ICER vs. no ESA (95% CrI) (£/QALY)	11,403 (1916 to Dtd[a])	10,363 (1706 to Dtd[a])	19,157 (3473 to Dtd[a])	11,339 (1888 to Dtd[a])	11,573 (1929 to Dtd[a])	17,745 (3351 to Dtd[a])
Incremental QALYs (95% CI)	0.126 (–0.276 to 0.528)	0.126 (–0.276 to 0.528)	0.126 (–0.276 to 0.528)	0.126 (–0.276 to 0.528)	0.126 (–0.276 to 0.528)	0.126 (–0.276 to 0.528)
Incremental cost (95% CI) (£)	1436 (701 to 2171)	1305 (620 to 1991)	2413 (1305 to 3521)	1428 (729 to 2128)	1458 (722 to 2193)	2235 (1193 to 3277)
INHB vs. no ESA at WTP of £20,000 per QALY (95% CI)	0.054 (–0.350 to 0.458)	0.061 (–0.343 to 0.465)	0.005 (–0.399 to 0.409)	0.055 (–0.350 to 0.459)	0.053 (–0.352 to 0.458)	0.014 (–0.390 to 0.418)

Dtd, dominated (more expensive and fewer QALYs than relevant comparator); WTP, willingness to pay.
a Not applicable as ESA is dominated by no ESA in > 2.5% of simulations regardless of the cost-effectiveness threshold.

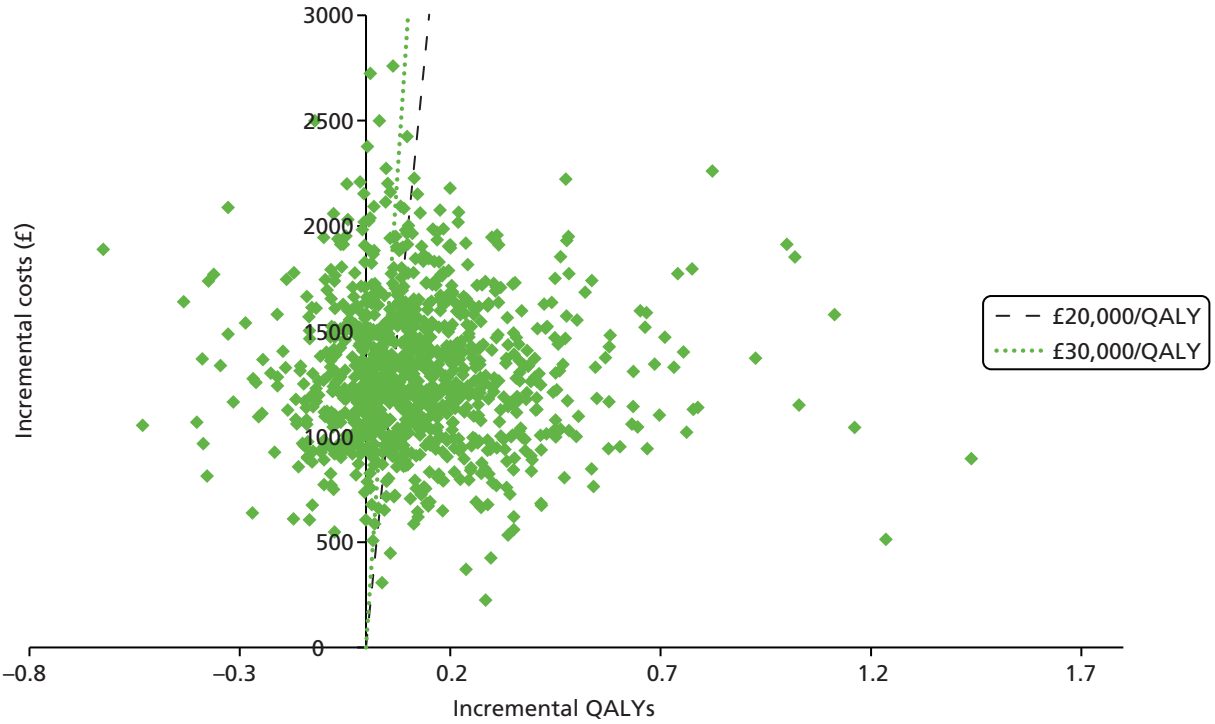

FIGURE 60 Incremental costs and QALYs of PSA simulations for scenario analysis 3.

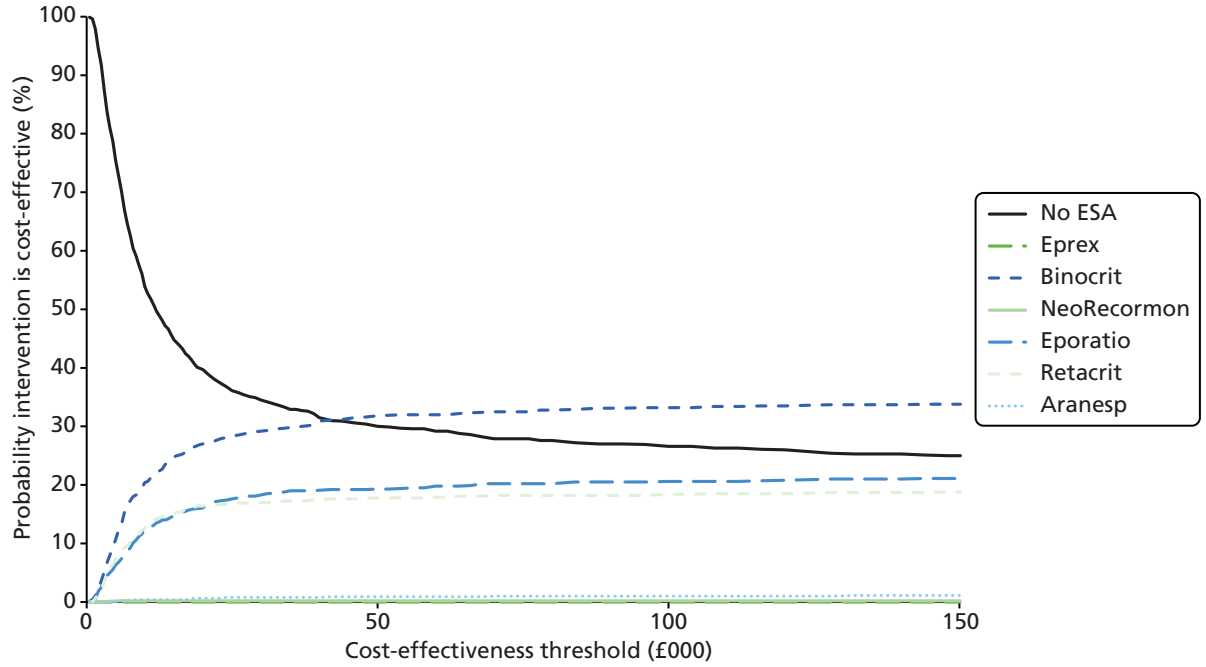

FIGURE 61 Cost-effectiveness acceptability curves for scenario analysis 3.

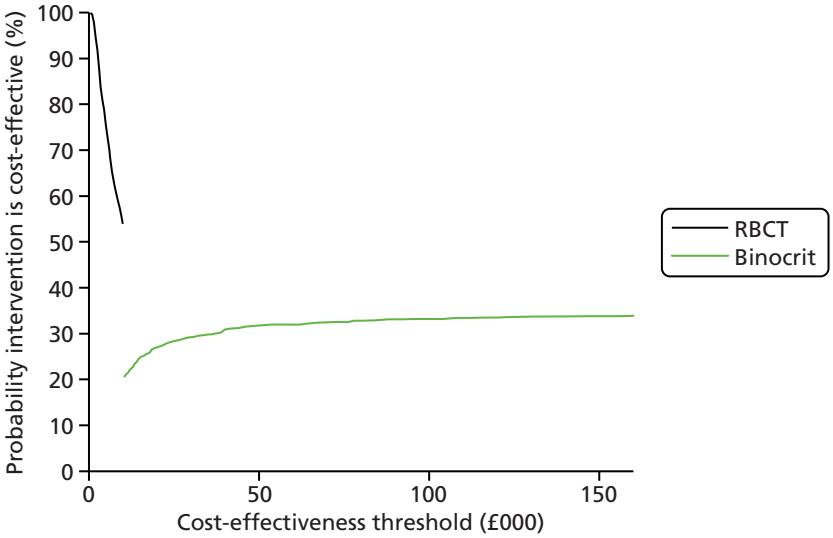

FIGURE 62 Cost-effectiveness acceptability frontier for scenario analysis 3.

This scenario suggests that ESAs may be more cost-effective when patients are limited to this subgroup. This could be interpreted as an indication that, when ESAs are used within their correct licensing, they appear to be more cost-effective. However, the PSA clearly shows that there is still a high level of uncertainty and this should be kept in mind when considering these results. In particular, in 23.1% of the simulations for Binocrit, ESA use is dominated, having fewer QALYs and higher costs than no ESA use.

Overall survival scenario analyses

As described in *Modelling approach*, we performed three scenario analyses exploring the structural assumptions with regard to OS.

Hazard ratio applying for only 3 years

Overall survival in the base case is estimated for both arms using an exponential distribution, with the OS in the control arm estimated by synthesising outcomes from included RCTs and the OS in the ESA arm estimated by applying a constant HR to the survival in the control arm, with the HR taken from the systematic review of clinical effectiveness evidence. As follow-up is limited for trials, we explored the impact of assuming that the HR applies for only the first 3 years, after which patients in both arms experience the same rate of mortality. Deterministic and probabilistic results are both available in this scenario.

Deterministic analysis

The short-term costs and QALYs remain unchanged for both arms. The long-term life-years and QALYs are unchanged in the control arm, but in the ESA arm they are slightly reduced:

- the mean incremental undiscounted life-years are estimated at 0.028, reduced from 0.091 in the base case
- the mean incremental discounted long-term QALYs are estimated at 0.0198, reduced from 0.0582 in the base case
- the mean incremental discounted total QALYs are estimated at 0.0322, reduced from 0.0706 in the base case.

These results suggest that 66% of the long-term QALY gain and 54% of the total QALY gain in the base case are accrued over 3 years after ESA treatment.

The reduction in QALY gain means that cost-effectiveness is worsened and now none of the ESAs are cost-effective at a willingness-to-pay threshold of £20,000 or £30,000 per QALY (*Table 81*). Binocrit remains the most cost-effective of the ESAs, but its ICER is estimated at £42,584 per QALY.

Probabilistic analysis

The PSA scatterplot for the incremental cost-effectiveness of Binocrit compared with no ESA is given in *Figure 63* (with the same axis scales as presented in the base case). The scatterplot shows that a considerable amount of uncertainty about the incremental QALYs has been eliminated by assuming a HR of 1 from 3 years onwards. Even so, approximately one in four simulations predicts an overall QALY loss for patients receiving ESA therapy because of an adverse impact on OS in the first 3 years (*Table 82* and *Figure 63*).

The summary probabilistic cost-effectiveness results are shown in *Table 83*; the ICERs are not changed significantly from the deterministic results, with the ICER for Binocrit remaining the lowest compared with no ESA therapy at £39,836 per QALY.

Cost-effectiveness acceptability curves and the CEAF are provided in *Figures 64* and *65*, respectively. The CEAF switches from no ESA to Binocrit at a willingness-to-pay threshold of ≥ £40,000 per QALY.

Weibull curve fitted to the overall survival in Untch and colleagues

In this scenario the HR from the systematic review of clinical effectiveness is maintained as in the base case, but the OS in the control arm is set to a Weibull distribution fitted to the OS in Untch and colleagues.[80] Deterministic and probabilistic results are given for this scenario analysis, although the OS in the control arm is not varied in the PSA.

TABLE 81 Summary deterministic cost-effectiveness results for the scenario analysis in which the OS HR applies for only 3 years

		Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	No ESA	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Total cost per strategy (£)	912	2414	2283	3384	2416	2451	3258
Total incremental cost vs. no ESA (£)	–	1502	1371	2472	1504	1539	2346
Total discounted QALYs gained vs. no ESA	–	0.0322	0.0322	0.0322	0.0322	0.0322	0.0322
ICER vs. no ESA (£/QALY)	–	46,638	42,584	76,751	46,704	47,790	72,839
ICER (£/QALY)	–	Dominated by Binocrit	42,584	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit
INHB vs. no ESA at WTP of £20,000/QALY	–	–0.043	–0.036	–0.091	–0.043	–0.045	–0.085
INHB vs. no ESA at WTP of £30,000/QALY	–	–0.018	–0.014	–0.050	–0.018	–0.019	–0.046

WTP, willingness to pay.

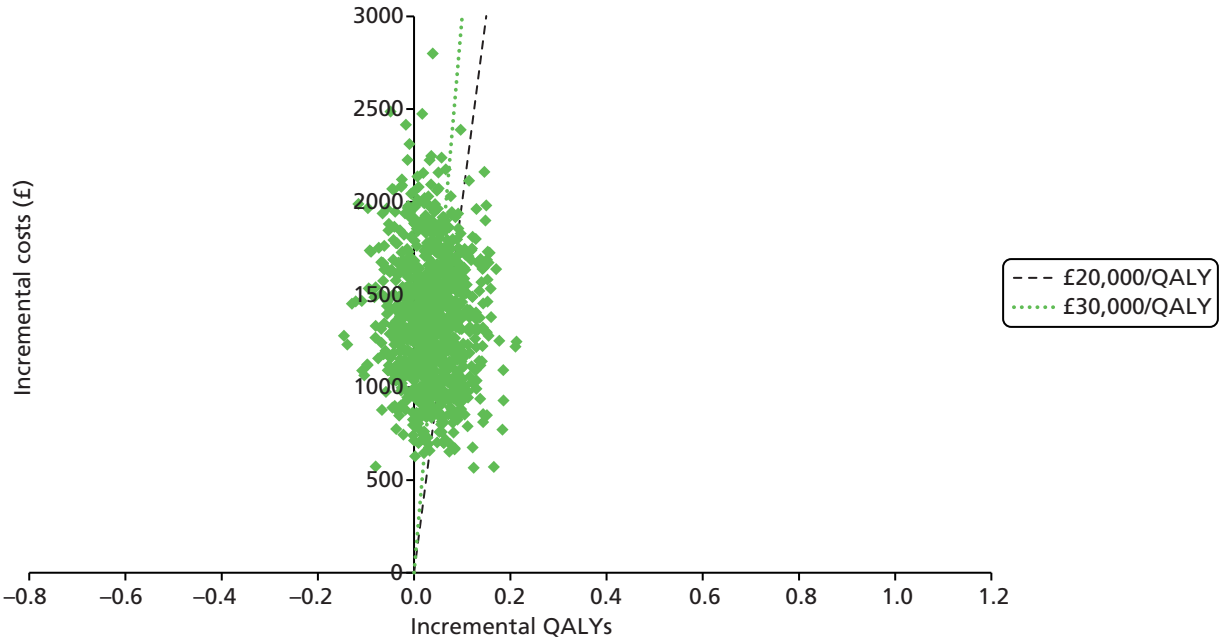

FIGURE 63 Incremental costs and QALYs: PSA results for the scenario analysis in which the OS HR applies for only 3 years.

TABLE 82 Percentage of PSA simulations by cost increase/saving and health loss/gain

Cost	Health loss	Health gain
Increase	24.9	75.1
Saving	0	0

TABLE 83 Summary probabilistic cost-effectiveness results for the scenario analysis in which the OS HR applies for only 3 years

		Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	No ESA	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Total cost per strategy (£)	941	2440	2308	3398	2436	2475	3293
Total incremental cost vs. no ESA (£)	–	1499	1367	2457	1495	1534	2352
Total discounted QALYs gained vs. no ESA	–	0.0343	0.0343	0.0343	0.0343	0.0343	0.0343
ICER vs. no ESA (95% CrI) (£/QALY)	–	43,667 (9371 to Dtd[a])	39,836 (8523 to Dtd[a])	£71,589 (15,002 to Dtd[a])	43,568 (9422 to Dtd[a])	44,689 (8795 to Dtd[a])	68,532 (14,287 to Dtd[a])
INHB vs. no ESA at WTP of £20,000/QALY	–	–0.041	–0.034	–0.089	–0.040	–0.042	–0.083
INHB vs. no ESA at WTP of £30,000/QALY	–	–0.016	–0.011	–0.048	–0.016	–0.017	–0.044

Dtd, dominated (more expensive and fewer QALYs than the relevant comparator); WTP, willingness to pay.
a Not applicable as ESA is dominated by no ESA in > 2.5% of simulations regardless of the cost-effectiveness threshold.

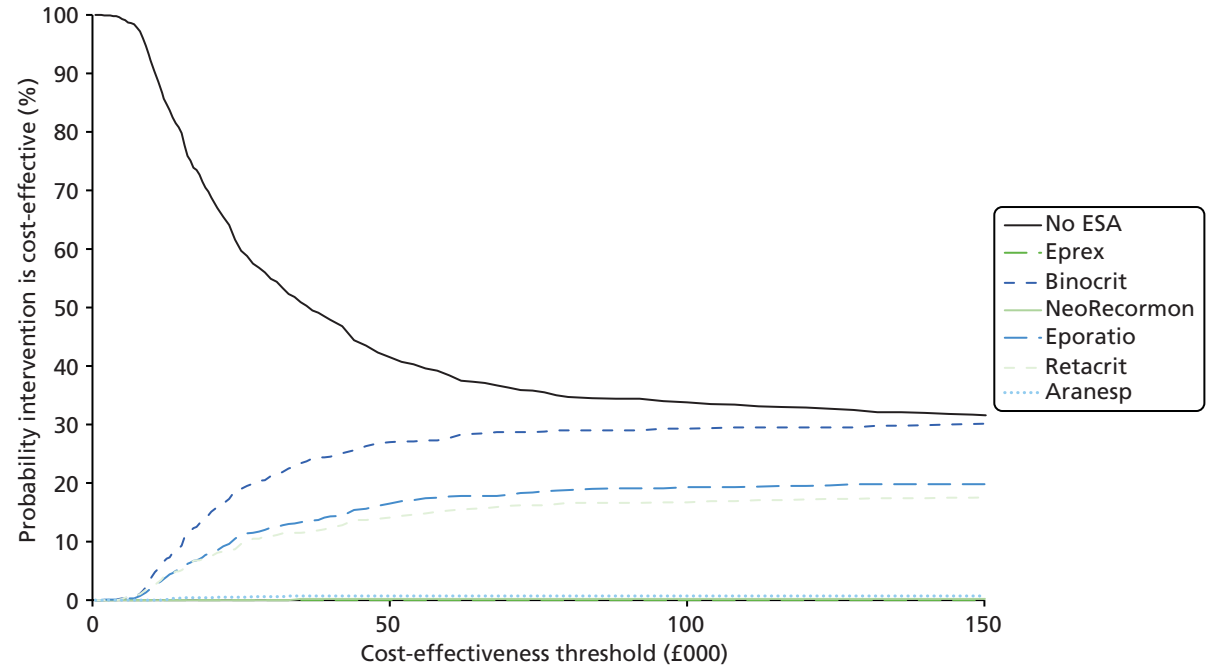

FIGURE 64 Cost-effectiveness acceptability curves for the scenario analysis in which the OS HR applies for only 3 years.

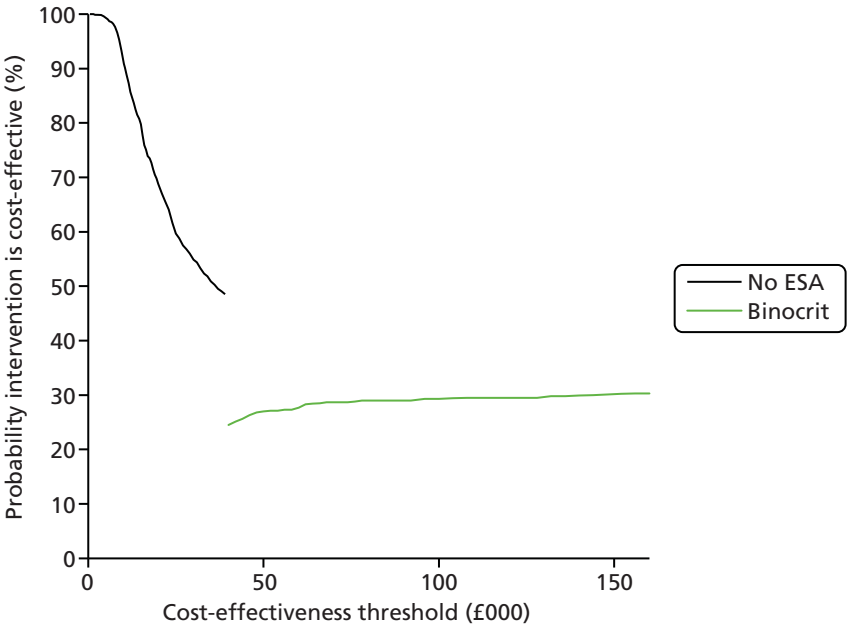

FIGURE 65 Cost-effectiveness acceptability frontier for the scenario analysis in which the OS HR applies for only 3 years.

Deterministic results

The short-term costs and QALYs remain unchanged for both arms. The long-term incremental life-years and QALYs are increased:

- the mean incremental undiscounted life-years are estimated at 0.156, increased from 0.091 in the base case
- the mean incremental discounted long-term QALYs are estimated at 0.0807, increased from 0.0582 in the base case
- the mean incremental discounted total QALYs are estimated at 0.0931, increased from 0.0706 in the base case.

The increase in QALY gain means that cost-effectiveness is improved and now four of the ESAs are cost-effective at a willingness-to-pay threshold of £20,000 per QALY (*Table 84*). Binocrit remains the most cost-effective of the ESAs, with an ICER estimated at £14,726 per QALY.

Probabilistic analysis

The PSA scatterplot for the incremental cost-effectiveness of Binocrit compared with no ESA is given in *Figure 66* (with the same axis scales as presented in the base case). The scatterplot shows that changing the baseline OS function does not have a significant impact on the considerable uncertainty regarding the incremental QALYs (*Table 85*).

The summary probabilistic cost-effectiveness results are shown in *Table 86*; the ICERs are not changed significantly from the deterministic results, with the ICER for Binocrit remaining the lowest compared with no ESA therapy, at £12,649 per QALY.

TABLE 84 Summary deterministic cost-effectiveness results for the scenario analysis in which the control arm OS is fitted to the OS in Untch and colleagues[78,80]

		Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	No ESA	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Total cost per strategy (£)	912	2414	2283	3384	2416	2451	3258
Total incremental cost vs. no ESA (£)	–	1502	1371	2472	1504	1539	2346
Total discounted QALYs gained vs. no ESA	–	0.0931	0.0931	0.0931	0.0931	0.0931	0.0931
ICER vs. no ESA (£/QALY)	–	16,128	14,726	26,541	16,150	16,526	25,188
ICER (£/QALY)	–	Dominated by Binocrit	14,726	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit
INHB vs. no ESA at WTP of £20,000/QALY	–	0.018	0.025	–0.030	0.018	0.016	–0.024
INHB vs. no ESA at WTP of £30,000/QALY	–	0.043	0.047	0.011	0.043	0.042	0.015

WTP, willingness to pay.

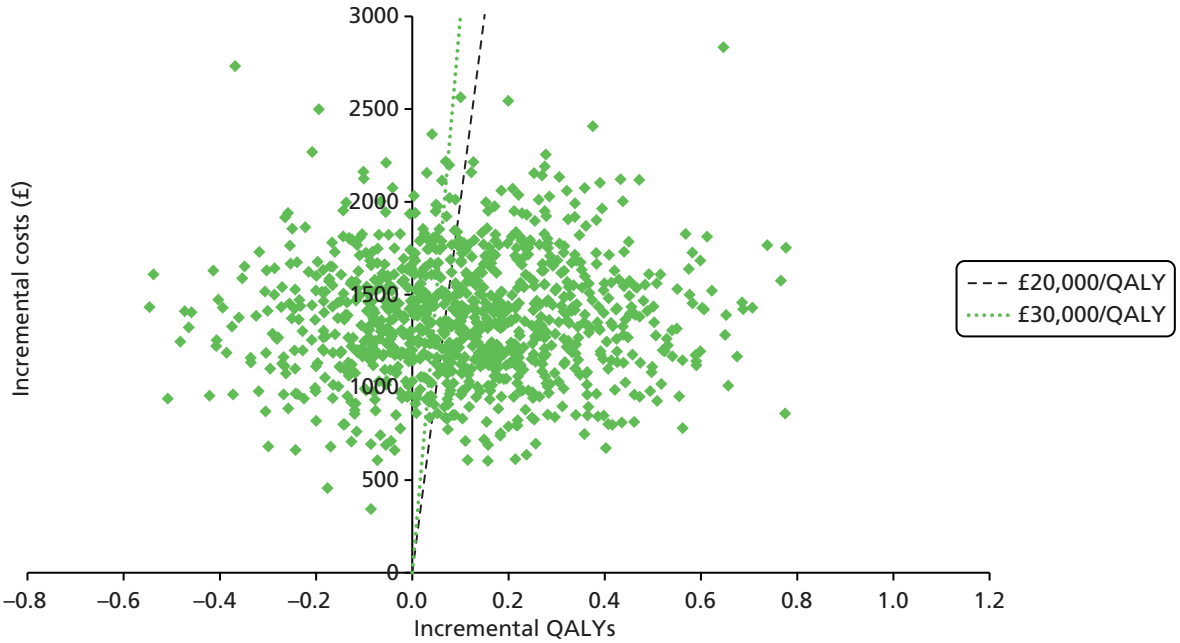

FIGURE 66 Incremental costs and QALYs: PSA results for the scenario analysis in which the control arm OS is fitted to the OS in Untch and colleagues.[78,80]

TABLE 85 Percentage of PSA simulations by cost increase/saving and health loss/gain

Cost	Health loss	Health gain
Increase	30.7	69.3
Saving	0	0

TABLE 86 Summary probabilistic cost-effectiveness results for the scenario analysis in which the control arm OS is fitted to the OS in Untch and colleagues[78,80]

		Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	No ESA	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Total cost per strategy (£)	932	2438	2307	3379	2428	2471	3279
Total incremental cost vs. no ESA (£)	–	1506	1375	2447	1496	1539	2347
Total discounted QALYs gained vs. no ESA	–	0.1087	0.1087	0.1087	0.1087	0.1087	0.1087
ICER vs. no ESA (95% CrI) (£/QALY)	–	13,857 (2297 to Dtd)	12,649 (2091 to Dtd)	22,516 (4004 to Dtd)	13,767 (2243 to Dtd)	14,160 (2319 to Dtd)	21,590 (3573 to Dtd)
INHB vs. no ESA at WTP of £20,000/QALY (95% CI)	–	0.033 (–0.400 to 0.467)	0.040 (–0.393 to 0.473)	–0.014 (–0.449 to 0.422)	0.034 (–0.402 to 0.470)	0.032 (–0.405 to 0.468)	–0.009 (–0.447 to 0.429)
INHB vs. no ESA at WTP of £30,000/QALY (95% CI)	–	0.058 (–0.374 to 0.491)	0.063 (–0.370 to 0.496)	0.027 (–0.407 to 0.461)	0.059 (–0.376 to 0.494)	0.057 (–0.378 to 0.492)	0.030 (–0.405 to 0.466)

Dtd, dominated; WTP, willingness to pay.

Cost-effectiveness acceptability curves and the CEAF are provided in *Figures 67* and *68*, respectively The CEAF switches from no ESA to Binocrit at a willingness-to-pay threshold of ≥ £13,000 per QALY. It is notable that the no ESA arm is cost-effective in more simulations than any of the ESAs at cost-effectiveness thresholds up to £150,000 per QALY.

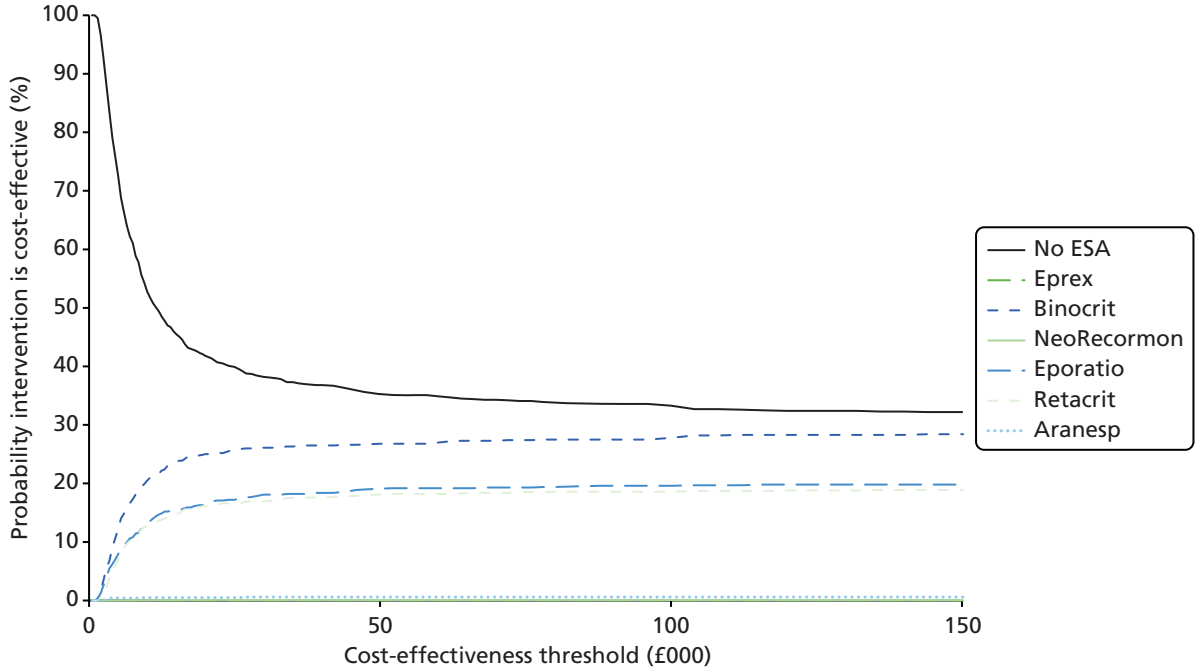

FIGURE 67 Cost-effectiveness acceptability curves for the scenario analysis in which the control arm OS is fitted to the OS in Untch and colleagues.[78,80]

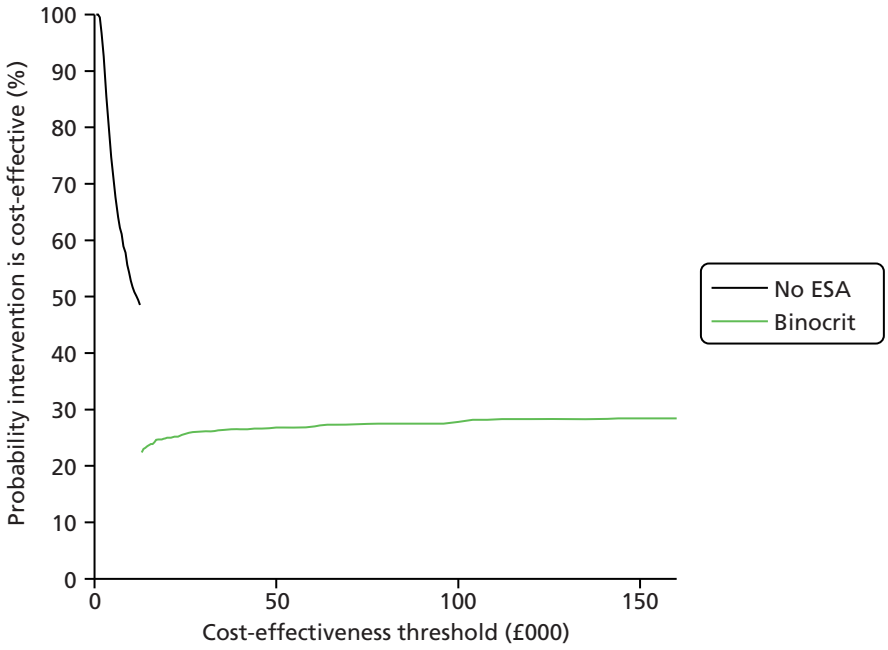

FIGURE 68 Cost-effectiveness acceptability frontier for the scenario analysis in which the control arm OS is fitted to the overall survival in Untch and colleagues.[78,80]

Log-normal curves fitted to Littlewood and colleagues[70]

Kaplan–Meier curves from Littlewood and colleagues[70] suggest that neither exponential nor Weibull curves would fit OS in the population accurately. A log-normal distribution was shown graphically to give a reasonable fit and so for this scenario analysis separate log-normal survival functions were fitted to the Kaplan–Meier curves for the two arms and extrapolated. The HR from the systematic review of clinical effectiveness cannot be applied, as the log-normal distribution allows only accelerated failure time modelling and not proportional hazards.

No probabilistic results are presented for this scenario as we did not attempt to quantify the uncertainty in the fitting of the log-normal distributions, but given that the improved survival in the ESA arm was not statistically significant ($p = 0.13$ by the log-rank test) it is likely that uncertainty would remain in the cost-effectiveness results, given how critical OS is to cost-effectiveness.

The short-term costs and QALYs remain unchanged for both arms. The long-term incremental life-years and QALYs are significantly increased:

- the mean incremental undiscounted life-years are estimated at 0.471, increased from 0.091 years in the base case
- the mean incremental discounted long-term QALYs are estimated at 0.3087, increased from 0.0582 in the base case
- the mean incremental discounted total QALYs are estimated at 0.3211, increased from 0.0706 in the base case.

The increase in QALY gain means that cost-effectiveness is improved and now all of the ESAs are cost-effective at a threshold of £20,000 per QALY (*Table 87*). Binocrit remains the most cost-effective of the ESAs, with an ICER estimated at £4271 per QALY.

TABLE 87 Summary deterministic cost-effectiveness results for the scenario analysis in which OS curves are fitted to Littlewood and colleagues[70]

		Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Treatment arm	No ESA	Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Total cost per strategy (£)	912	2414	2283	3384	2416	2451	3258
Total incremental cost vs. no ESA (£)	–	1502	1371	2472	1504	1539	2346
Total discounted QALYs gained vs. no ESA	–	0.3211	0.3211	0.3211	0.3211	0.3211	0.3211
ICER vs. no ESA (£/QALY)	–	4678	4271	7698	4684	4793	7306
ICER (£/QALY)	–	Dominated by Binocrit	4271	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit	Dominated by Binocrit
INHB vs. no ESA at WTP of £20,000/QALY	–	0.246	0.253	0.197	0.246	0.244	0.204
INHB vs. no ESA at WTP of £30,000/QALY	–	0.271	0.275	0.239	0.271	0.270	0.243

WTP, willingness to pay.

It is worth noting that the study by Littlewood and colleagues[70] is just one study out of a number of studies to which we could have fitted OS curves, including two[74,80] that suggested a survival disbenefit from ESA use (although not statistically significant) and two[62,79] that showed no clear effect on survival of ESA therapy. We are not presenting this scenario as an alternative base case but simply demonstrating the very significant impact that assumptions about OS have on cost-effectiveness.

Univariate sensitivity analysis

As the scenario analyses examine in depth the impact of ESA costs and OS, as well as the overall uncertainty in the model parameters, the univariate sensitivity analysis is used to investigate particular aspects identified or not covered by the PSA. A summary of these univariate sensitivity analyses is provided in *Table 88*.

Long-term costs

As discussed in *Methods*, long-term costs are not accounted for in the base case of the model, partly as the difference in costs between arms was problematic given the range of cancers included and partly because to set an equal annual cost in both arms would disadvantage any arm with a survival benefit. Therefore, this sensitivity analysis is not supposed to be an account of true costs, as it is not unexpected that patients with a survival benefit would have different cancer treatment costs and that these costs may even be reduced. Instead, the long-term annual costs are set to an arbitrary £20,000 (regardless of ESA use) to demonstrate how this value disadvantages the ESAs in the base case. Indeed in this analysis, the additional long-term costs increase the ICERs of all ESAs to > £30,000 per QALY gained.

Utility associated with an increase in haemoglobin level of 1 g/dl

A range of values for the utility associated with Hb level was investigated in the methods section. PenTAG's chosen base-case value was based on a cancer population and was transformed to the EQ-5D, as preferred by NICE. In the sensitivity analysis, the original SF-6D value (0.009), the EQ-5D value identified from CKD patients (0.016) and the original value from Wilson and colleagues[2] (0.060) were used as alternatives.

As the model is quite sensitive to changes in QALYs, by reducing the utility to 0.009 or 0.016 the ICERs of the ESAs increase, with the effect that they all lie above the £20,000-per-QALY threshold, with the most cost-effective ICERs calculated as £22,062 per QALY gained for a short-term utility of 0.009 (equal to a short-term gain of 0.004 QALYs) and £21,013 per QALY gained for a short-term utility of 0.016 (equal to a short-term gain of 0.007 QALYs). Increasing the utility to 0.06, as in the case of the TA142 model,[2] increased the short-term QALY gain to 0.027 QALYs and reduced the ICERs with the result that all ESAs have an ICER of > £30,000 per QALY compared with no ESA.

Erythropoietin-stimulating agent dosing schedule

The licensed doses for ESAs can be given on different schedules. In the base case this was set to once per week, as this was in line both with what licensing allows and with what occurred most frequently in the RCTs. However, previous assessments, including TA142, assumed that doses would be given three times a week.[2,106–108,145] As such, we explored the alternative dosing schedules for each of the ESAs, as applicable.

Darbepoetin alfa has the option of being given once every 3 weeks, reducing its total administration cost from £98 to £33. This had a fairly minor impact on the ICER for Aranesp, reducing it from £33,200 per QALY gained to £32,300 per QALY gained (rounded to the nearest hundred). As none of the other ESAs was affected, their ICERs remained the same as in the base case.

Epoetin alfa and epoetin zeta can be given three times a week, increasing their total administration cost to £294. In the scenario in which epoetin alfa is increased to a three times a week schedule and the other ESAs are held as in the base case, Binocrit no longer has an ICER below £20,000 per QALY gained and Eporatio becomes the least costly ESA. When epoetin zeta is assumed to have a three times a week schedule, the ICER for Retacrit increases from £21,800 to £24,600 per QALY gained (rounded to the nearest hundred).

TABLE 88 Summary results for the univariate sensitivity analysis

Parameter	Value in base case	Sensitivity analysis alternative values	ICERs vs. no ESA (£/QALY)					
			Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
Base case			21,279	19,429	35,018	21,309	21,804	33,233
Long-term costs	£0	£20,000/year	42,877	41,027	56,616	42,907	43,402	54,831
Utility associated with increase in Hb level of 1 g/dl	0.028	0.009	24,162	22,062	39,763	24,196	24,759	37,736
		0.016	23,013	21,013	37,872	23,046	23,582	35,942
		0.060	17,718	16,177	29,157	17,743	18,155	27,671
ESA dosing schedule	Once per week, all ESAs	DA Q3W	21,279	19,429	35,018	21,309	21,804	32,308
		EA TIW	24,053	22,204	35,018	21,309	21,804	33,233
		EB TIW	21,279	19,429	37,792	21,309	21,804	33,233
		EB 7 times/week	21,279	19,429	43,342	21,309	21,804	33,233
		EZ TIW	21,279	19,429	35,018	21,309	24,579	33,233
ESA administration	43.1%[a] and 16.3%[b] nurse, 40.6% self administered	25% nurse, 75% self administered	20,519	18,669	34,258	20,549	21,045	32,473
RBCT appointment cost	£688	£344	22,849	20,999	36,588	22,879	23,375	34,803
		£1376	18,138	16,288	31,877	18,168	18,663	30,092

Parameter	Value in base case	Sensitivity analysis alternative values	ICERs vs. no ESA (£/QALY)					
			Eprex	Binocrit	NeoRecormen	Eporatio	Retacrit	Aranesp
AE costs								
Thromboembolic event	£1243	£621	21,144	19,294	34,883	21,174	21,670	33,098
		£2486	21,548	19,698	35,287	21,578	22,074	33,502
Hypertension	£826	£413	21,143	19,294	34,882	21,173	21,669	33,097
		£1652	21,549	19,700	35,288	21,579	22,075	33,503
Thrombocytopenia	£744	£372	21,302	19,453	35,041	21,332	21,828	33,257
		£1488	21,231	19,381	34,970	21,261	21,757	33,185
Duration of ESA treatment	12 weeks	24 weeks	41,108	37,796	65,710	41,162	42,049	62,514
		Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

DA, darbepoetin alfa; EA, epoetin alfa; EB, epoetin beta; EZ, epoetin zeta; Q3W, once every 3 weeks; TIW, three times a week.
a General practice or district nurse.
b Nurse at chemotherapy appointment.

Epoetin beta can be given either once weekly or have the dose divided and administered three to seven times per week. This dosing schedule gives ICERs for NeoRecormen of between £37,792 and £43,342 per QALY gained, an increase of 8–24% from the base case ICER of £35,018 per QALY gained.

These results demonstrate that, even though ESA administration is a small component of the overall costs in the base case, it can have a larger impact on the results if the ESAs are to be administered more than once a week. This is particularly true if the ICERs lie close to the threshold: in the base case Binocrit is cost-effective at a threshold of £20,000 per QALY but, if ESAs are administered three times per week as opposed to once, Binocrit no longer appears to be cost-effective at this threshold.

Although this sensitivity analysis demonstrates the impact of changes to the administration costs, it is possible that, when the dosing schedule is altered in practice, how the dose is administered may also change. For example, it is possible that if a dose was required daily, patients could more frequently be expected to self-administer.

Erythropoietin-stimulating agent administration

As was discussed in *Methods*, who administers ESAs is not entirely agreed by clinicians. There may be many reasons for this, including factors such as patient ability/preferences and chemotherapy schedule. As such, our base case reflects an average view across the clinicians' opinions available.

In this analysis we examined the possibility that ESAs would be given on a schedule closer to that of CKD patients, being administered 25% of the time by a nurse and 75% of the time by self-administering. If this approach was adopted for cancer patients, the overall cost of ESA administration would be reduced to £44 and the ICERs for all ESAs would be reduced so that, in particular, Eprex and Eporatio would have ICERs of £20,500 per QALY gained (rounded to the nearest hundred), very close to the £20,000-per-QALY threshold.

Red blood cell transfusion appointment costs

The cost of the transfusion appointment was taken from a very old source[172] and uprated to 2014/15 prices. As such, the true cost may vary considerably. Therefore, this sensitivity analysis attempted to investigate the impact that altering the cost of a RBCT appointment has, by halving and then doubling the cost.

When the cost of a RBCT appointment is halved to £344, the ICERs for the ESAs compared with no ESA increase by around £1500 each, resulting in all lying above the willingness-to-pay threshold of £20,000 per QALY. This is a result of the reduced RBCT cost making the cost saving from ESA use smaller. Similarly, when the cost of the RBCT appointment is doubled to £1376, the cost saving between the ESA arm and the no ESA arm increases and the ICERs are reduced, so that four of the ESAs have ICERs below the £20,000-per-QALY threshold.

It therefore appears that the cost of a RBCT appointment can have an effect on the ICERs, particularly if they are close to the willingness-to-pay threshold in the base case.

Adverse event costs

Another cost parameter for which limited data were found in the base case was the cost of AEs and, as such, this sensitivity analysis investigates the impact of changing these costs. As with the RBCT costs, they were halved and doubled to demonstrate the impact rather than to demonstrate alternative values.

The results in *Table 88* show that altering individual AE costs has very little impact on the overall cost-effectiveness results, with ICERs altering by only a few hundred pounds in each case. As in the base case, the no ESA arm is more likely to suffer from thrombocytopenia; the ICERs alter differently for thrombocytopenia compared with the other AEs, with a reduction in the cost of thrombocytopenia causing an increase in the ICERs for the ESAs compared with no ESA use.

The reason that changing the costs of AE costs appears to have such a small impact is because the costs of AEs are very similar for patients in both arms. This is primarily driven by the lack of information on the number of each type of AE that occurs in each arm and their severity, as both are likely to affect the overall cost of the AEs. In the model the arms are assumed to have the same level of severity of AEs and the model costs for one instance of any individual AE rather than multiple instances. As such, further information is required to properly evaluate the effect of a change in AE costs on the overall results.

Duration of erythropoiesis-stimulating agent treatment

Another parameter that varied quite substantially in the RCTs was the duration of ESA therapy. As such, we assessed the impact of increasing the duration of therapy to 24 weeks, as described in *Methods*.

Doubling the duration of treatment increases both the short-term QALYs (from 0.0124 in the base case to 0.0207 when the duration is doubled) and the costs. This is because doubling the duration doubles both the QALYs gained on ESA treatment and the costs directly associated with ESA use. However, as treatment duration is a small component of the overall QALYs gained but a large component of the overall costs, the ICERs for the ESAs compared with no ESA use are greatly increased when the treatment duration increases. All of the ICERs are above the £30,000-per-QALY threshold, with the lowest ICER being £37,796 per QALY gained compared with no ESA use.

Of note, when the ESA costs are reduced to those of their wholesale acquisition costs, the ICERs all fall below the £20,000-per-QALY threshold.

Comparison with Wilson and colleagues[2]

As we are conducting an update of the HTA review by Wilson and colleagues,[2] we attempted to compare our results with those previously reported. *Table 89* demonstrates that there is a large difference between the most cost-effective ESA in the PenTAG base case and the most cost-effective ESA in the base case reported in TA142,[2] with ICERs of £19,429 and £150,342 per QALY, respectively.

To attempt to account for these differences, we adjusted the PenTAG model to incorporate parameters used in the TA142 report.[2] Parameters that we were able to identify and enter into the model included baseline and normalised Hb levels, utility associated with Hb level and long-term utility, mean survival, the OS HR, ESA weekly cost (dose and administration), transfusion costs and probabilities, AE costs and probabilities and ESA treatment duration. The values for these parameters are reported in *Appendix 19*. Preferably, we would have updated the TA142 model to match our parameters, but no model copy was available. We attempted to discover whether the differences in the results were caused primarily by model structure or by the updated parameters. To make the results of our adjusted model comparable, costs were kept as reported in the TA142 monograph.[2]

TABLE 89 Comparison of the base-case results between the PenTAG review and the HTA review of Wilson and colleagues[2]

	PenTAG base case (Binocrit)	TA142 base case[2]	PenTAG model, adapted to use TA142 base-case parameters
Short-term QALY gain vs. no ESA	0.012	0.030	0.059
Long-term QALY gain vs. no ESA	0.058	0.000	0.000
Incremental QALYs, ESA vs. no ESA	0.071	0.030	0.059
Incremental cost (£), ESA vs. no ESA	1371	4450	6448
ICER (£/QALY), ESA vs. no ESA	19,429	150,342	109,055

Note
The costs for the TA142 and adjusted PenTAG models are given at TA142 prices, but the PenTAG base case is reported for 2014/15 prices.

Unfortunately, as only limited outputs were reported in Wilson and colleagues,[2] the comparison of the models is also restricted. Certain parameters in the PenTAG model, particularly those crucial to short-term utility, could not be accounted for using the parameters given in the TA142 monograph.[2] One specific example of this is the mean difference in Hb levels between treatment arms as a proportion of the difference at the end of the trial, which, as a parameter in our model, identifies when the benefit to the Hb level from ESA use occurs. This was obviously not parameterised in the Wilson model, as the Hb level changes were modelled mechanistically. Also, the normalisation rate was only approximated to 0.2 g/dl in the TA142 model but had to be entered as exactly 0.2 g/dl in the PenTAG model.

Table 89 shows that, when the PenTAG model is adapted to use the parameters reported in TA142, the ICER increases to £110,680 per QALY gained, a value much closer to that in the original TA142 model results.

By comparing the adjusted PenTAG model and the TA142 base case, we see that the altered PenTAG model has both a larger QALY gain and a larger cost than those reported in TA142. We believe that this is mostly the result of not being able to substitute all of the parameters from TA142 into the PenTAG model or having to use parameters from the TA142 model in a different manner from which they were intended, based on underlying model assumptions.

One particular example of this is the use of the maximum duration of ESA treatment from TA142 of 24 weeks because an average value could not be calculated, which would result in both higher costs and higher QALYs in the PenTAG model than those reported in TA142. Furthermore, the weekly cost is taken as a maximum and does not reflect the dose reduction that could occur in the TA142 model. This occurs because the PenTAG model accounts for dose changes by setting the input parameter for mean dose to reflect the ITT basis, whereas the Wilson and colleagues[2] model approaches this mechanistically, adjusting the dose depending on the health state. Unfortunately, no information on the size of the initial dose was reported in the TA142 model, therefore we do not know what size dose the cost is equivalent to. Comparing our weekly ESA dose cost (£126–218) with the weekly ESA cost calculated using the TA142 values (£251) we can see that there is a slight increase in cost per week for ESAs in TA142, which is partly because of a change in the unit cost but primarily because of the difference in size of the dose.

As previously discussed, one parameter that greatly affects the QALY gains in the short term in the PenTAG model, but which was not available from the TA142 monograph, is the mean difference in Hb levels between treatment arms as a proportion of the difference at the end of the trial. The larger this value is, the larger the benefits of ESAs and the greater the QALY gain in the short term. In the PenTAG base case this value is set to 81%. By varying this parameter we can see how easily this alters the results (*Table 90*). We do not use this analysis to find the appropriate value for this parameter (as there are other factors affecting the QALY gain, some of which are also linked to cost results) but merely to show that this is one parameter in the PenTAG model that could not be altered based on the information given in the TA142 monograph but which is likely to be different and, as such, has an impact on the ICERs.

We also note that the measure for the utility gain in the short term for the TA142 model was elicited using the time trade-off method, whereas the values in the PenTAG model have been converted to the EQ-5D. The utility value from TA142 could not be converted to the EQ-5D, which also accounts for some of the differences in QALYs between the PenTAG adapted model and the TA142 model. This is discussed in more detail in *Utilities*.

We believe that these model differences account for the difference between the adjusted PenTAG model and the TA142 base case.

TABLE 90 Sensitivity analysis of the mean difference in Hb levels between treatment arms as a proportion of the difference at the end of the trial, when applied to the TA142 parameters

Value (%)	Total QALY gain	ICER (£/QALY)
Base case: 81	0.059	109,055
10	0.027	235,633
20	0.032	202,366
30	0.036	177,331
40	0.041	157,808
50	0.045	142,157
60	0.050	129,330
70	0.054	118,627
80	0.059	109,560
90	0.063	101,780
100	0.068	95,032

Notwithstanding the comparison difficulties just described, by comparing the adjusted PenTAG results with the PenTAG base case we can identify which updated parameters have had the most impact:

- The short-term QALY gain is reduced in the PenTAG base case as a result of our much reduced utility gain associated with increases in Hb level.
- The PenTAG base case also includes a long-term QALY gain from a modelled favourable impact on survival, which was not assumed in the TA142 modelling. The OS HR was 1 in the TA142 model but is 0.97 in the PenTAG base case, based on a pooled estimate from 18 studies identified as more closely reflecting current licensed usage (i.e. patients receiving chemotherapy and receiving the licensed start dose).
- The costs of receiving ESAs are also greatly reduced in the PenTAG base case as a result of a reduction in the costs of ESAs (in terms of both unit costs and dose reduction), a reduction in the number of administrations of ESAs and a reduced time frame over which ESAs are administered.

Key points

- The cost of ESA therapy is the largest cost component in any ESA arm and the cost of RBCT is the largest cost component for no ESA use.
- The costs of AEs, RBCTs and additional blood tests are equal across ESA arms.
- When ESAs are used there are cost savings in terms of a reduction in the number of RBCTs.
- ICERs for ESA treatment compared with no ESA treatment range from £19,429 to £35,018 per QALY gained in the deterministic case. The PSA gave ICERs that were lower than in the deterministic base case (£14,724–27,226 per QALY gained). On average, 0.092 (95% CI –0.264 to 0.447) QALYs were gained for ESA treatment compared with no ESA treatment. The incremental cost for the most cost-effective ESA (Binocrit; epoetin alfa) was £1349 (95% CI £710 to £1,987). The ICER for Binocrit had a 95% CrI that was dominated by no ESA use (fewer QALYs and higher costs) at its upper interval, with a lower value of £2332 per QALY gained. In total, 36% of simulations from the PSA had an OS loss, with 31.4% of simulations having an overall QALY loss.
- Three important scenario analyses considered were (1) setting the OS HR to exactly 1, so that survival is the same for both patients on ESA therapy and those not on ESA therapy; (2) setting ESA costs to wholesale acquisition costs in an attempt to establish the real costs to the NHS; and (3) setting the OS HR to exactly 1 and the ESA costs to wholesale acquisition costs.

- In the first of these scenarios, when survival is assumed to be equal for both treatment arms, the QALY gain is greatly reduced [as well as the 95% CI 0.014 (0.001 to 0.027)] compared with the base case. The most cost-effective ESA achieved an ICER of £96,754 per QALY gained (95% CrI £36,897 to > £300,000 per QALY gained) in the PSA.
- In the second scenario, when wholesale acquisition costs were used there was a reduction in the expected mean ICER from the PSA to (Commercial-in-confidence information has been removed) (for the least costly ESA – Retacrit) per QALY gained. However, in this scenario the 95% CrI went from ESA dominating, with more QALYs and lower costs than no ESA use, to being dominated by the no ESA arm.
- In the third scenario, when survival was assumed to be equal for both treatment arms and wholesale acquisition costs were used, the expected ICER from the PSA for Retacrit is (Commercial-in-confidence information has been removed).
- We also conducted scenario analyses on a subgroup of studies in which the initial inclusion Hb level for participants was ≤ 11 g/dl. This resulted in changes to many of the parameters; in particular the OS HR reduced to 0.91 in the deterministic results. The expected ICERs were reduced compared with the base case, but the level of uncertainty was maintained.
- Scenario analyses were conducted on the OS modelling assumptions. Although all affected the ICERs, the most significant result showed that, when the impact of any survival benefit is included for only 3 years, ESAs appear to become much less cost-effective, with all ICERs > £30,000 per QALY.
- Univariate sensitivity analyses were also conducted, with the most significant of these appearing to be related to the duration of ESA treatment.

Chapter 6 Discussion

Aim

The remit for this report has been to update the evidence used to inform the previous NICE guidance on ESAs for the treatment of anaemia in cancer patients, particularly as laid out in the report by the West Midlands Health Technology Assessments Centre (WMHTAC).[2] In general, they considered evidence up to 2004, which is the start date we have used for this report.

Based on the previous assessment,[2] NICE guidance (TA142)[1] recommended the use of ESAs in combination with intravenous iron for the treatment of CIA in women with ovarian cancer receiving platinum-based chemotherapy with symptomatic anaemia (Hb ≤ 8 g/dl). The recommendation made in TA142 did not prohibit the use of other management strategies for the treatment of CIA, for example blood transfusion.[1] In addition, guidance set out in TA142 recommended ESAs in combination with intravenous iron for people with profound CIA who cannot be given blood transfusions.[1] The ESA with the lowest acquisition cost should be used.[1]

Initially, all ESAs were recommended for use at a Hb level of ≤ 11 g/dl, with target Hb levels not exceeding 13 g/dl. Following a safety review by the Pharmacovigilance Working Party at the request of the Committee for Medicinal Products for Human Use in 2008, changes were made to the SPCs for all ESAs at the EMA's request. These changes came into effect in 2008 – after the previous guidance was issued – and included a decrease in the Hb value for treatment initiation to ≤ 10 g/dl (to either increase Hb or to prevent further decline); an amendment to the Hb target values to 10–12 g/dl; and an amendment to the Hb level for stopping treatment to > 13 g/dl.

The scope of this update review differed from that of the previous HTA review[2] in respect of the population under consideration. Whereas the review conducted by Wilson and colleagues[2] considered cancer-related anaemia, the population covered in the PenTAG review is narrower, being restricted to cancer patients with treatment-induced anaemia (specifically chemotherapy treatment). Similarly, the recent Cochrane review[11] considered the broader population. In light of the publication of the Cochrane review, the PenTAG review aimed to include only studies evaluating ESAs as close to the licensed recommendations as possible. This was defined in the first instance, based on the start dose administered, irrespective of the other criteria specified in the licence, for example start and target Hb levels. In sensitivity analyses the definition of 'within licence' was tightened to (1) a licensed start dose plus an inclusion Hb level of ≤ 11 g/dl and (2) a licensed start dose plus an inclusion Hb level of ≤ 11 g/dl plus a target Hb level of ≤ 13 g/dl.

Clinical effectiveness

A total of 1515 titles/abstracts were screened. In total, 23 primary studies[17,48,50–53,62–70,72–79] reported in 34 publications[17,48,50–53,58–60,62–86] were judged to meet the inclusion criteria for the review. These included studies eligible for inclusion from the previous HTA review[2] and more recent studies identified by the PenTAG review team. Included studies were cross-checked with the recent Cochrane review[11] to ensure completeness. Only one study[62] was identified that was not included in the Cochrane review;[11] however, it had been included in abstract format.[33]

Taken as a whole, the quality of the studies ranged from moderate to poor. For most of the trials it was difficult to make a general assessment about study quality because of omissions in study reporting. Most notably, all trials lacked clarity in the reporting of allocation methods (the procedure for randomisation and/or allocation concealment).

All of the included trials evaluated ESAs as administered in accordance with the start dose recommended in the current licence specifications. However, none of the included studies evaluated ESAs entirely within the remit of their marketing authorisation; in particular, start and target Hb levels and stopping levels were all generally higher than specified in the licence. Twelve studies[17,48,50,53,63,66,69–71,73,74,77] compared ESAs plus supportive care (including transfusions) with placebo plus supportive care (including transfusions). The remaining studies[51,52,62,64,65,67,68,72,75,76,78] compared ESAs plus supportive care (including transfusions) with supportive care (including transfusions) alone.

Analysis of haematological response (defined as an improvement in Hb of ≥ 2 g/dl or an increase in haematocrit of ≥ 6 percentage points) showed that there was a statistically significant difference in Hb response in favour of treatment (RR 3.29, 95% CI 2.84 to 3.81; 12 trials, $n = 2228$). In total, 63% (759/1213) of participants who received ESAs achieved a haematological response, compared with 18% (182/1015) of participants who did not receive ESAs. Subgroup analyses were inconclusive. This and previous analyses provide consistent evidence that ESAs reduced the requirement for RBCT by an estimated 37%. The point estimate generated in the current update is in line with previous and other systematic reviews and meta-analyses. The analysis also provides consistent evidence that ESAs reduce the average number of RBC units transfused.

We identified no evidence for a beneficial effect of ESAs on tumour response (RR 1.10, 95% CI 0.86 to 1.41; seven trials, $n = 1909$). The results of previous reviews with respect to survival have varied and there is much debate surrounding the impact of ESAs on survival. The HR was 0.97 (95% CI 0.83 to 1.13; 18 trials, $n = 4455$). Although this estimate differed from those reported by Wilson and colleagues[2] and Tonia and colleagues[11] (1.05, 95% CI 1.00 to 1.11; 80 trials, $n = 19{,}003$, and 1.03, 95% CI 0.83 to 1.13; 28 trials, $n = 5308$ respectively), there was considerable uncertainty around the estimate (statistically significant heterogeneity identified: $I^2 = 42.4\%$; $p = 0.03$). In addition, subgroup analyses could not identify groups at lower or higher risk. In summary, the data with respect to OS remain inconclusive.

On-study mortality was defined as death occurring up to 30 days after the active study period. Data extracted from the Cochrane review[11] were available for 21 studies including 5085 participants. Analyses suggest that treatment with ESAs in patients with CIA did not have a significant effect on mortality (HR 0.86, 95% CI 0.67 to 1.11; 14 trials, $n = 2967$). In total, 11% (174/1586) of participants who received ESAs had died within 30 days of the active study period, compared with 12% (164/1381) of patients in the control groups.

In agreement with the Cochrane review[11] there was a statistically significant difference between patients treated with ESAs and control patients when combining HRQoL parameters, although this is probably not clinically important. Univariate subgroup analyses conducted for FACT-F outcomes according to chemotherapy type, malignancy type, intervention (epoetin or darbepoetin) and study duration also showed similarly statistically significant differences between the intervention group and the control group; however, the number of included studies was small, therefore the results must be treated with caution.

All AEs were relatively rare compared with the other outcomes considered in this report. The AE with the highest rate was thrombocytopenia/haemorrhage: 6% (55/877) of participants who received ESA treatment reported thrombocytopenia/haemorrhage and 6% (54/838) of participants in the control groups reported thrombocytopenia/haemorrhage. The summary estimate from the random-effects meta-analysis for thrombocytopenia/haemorrhage in the PenTAG review was a RR of 0.93 (95% CI 0.65 to 1.34) compared with a RR of 1.21 (95% CI 1.04 to 1.42) in the Cochrane review.[11] The data are insufficient to rule out detrimental effects of ESAs. Overall, the data suggest that there is an increased risk for thromboembolic events (RR 1.46, 95% CI 1.08 to 1.99), hypertension (RR 1.80, 95% CI 1.14 to 2.85), seizures (RR 1.19, 95% CI 0.33 to 4.38) and pruritus (skin rash, irritation and pruritus were combined in the analyses) (RR 2.04, 95% CI 1.11 to 3.75), consistent with previous estimates.

Important gaps in the evidence remain with respect to survival, mortality, AEs and impact on quality of life.

Subgroup analyses

Two of the subgroups evaluated corresponded with the current NICE recommendations:[1] women with ovarian cancer receiving platinum-based chemotherapy and people unable to receive a RBCT.

Only one included trial[51] evaluated the use of ESAs in women with ovarian cancer; all participants received platinum-based chemotherapy. The data confirm the results from previous analyses that ESAs reduce the risk of a RBCT (RR 0.11, 95% CI 0.03 to 0.47) and improve physiological parameters, such as Hb level (Hb change WMD 1.23, 95% CI 0.48 to 1.98), but increase the risk of thromboembolic events (RR 3.70, 95% CI 0.18 to 74.51). OS was not measured in this study.

No trials were identified that evaluated people unable to receive blood transfusions. However, it is reasonable to generalise from the wider RCT pool that ESAs are likely to work in improving Hb levels in this subpopulation. It is also reasonable to believe that, if people can be supported through the period of life-threatening anaemia, their Hb level will recover; if ESAs are not allowed they run the risk of death in the absence of a RBCT.

In addition, subgroup analyses considering any type of cancer and platinum-based chemotherapy, platinum-based chemotherapy in head and neck malignancies and iron supplementation were conducted. Five trials[48,51,63,64,73] evaluated the use of ESAs in people with any type of cancer receiving platinum-based chemotherapy. Results from this subgroup analysis are consistent with findings from the overall analysis for the anaemia-related outcomes, that is, an improved haematological response and a reduction in RBCT requirements, and are different from the results reported in the Cochrane review.[11] Similar to the overall analysis, the results for the malignancy-related outcomes (OS and on-study mortality) suggest that there are less detrimental effects for people with chemotherapy-induced anaemia treated with ESAs. These effects are also reflected in the decrease in the number of people experiencing thromboembolic events. However, these results should be interpreted with caution. The number of studies per subgroup is small, some of the changes are not statistically significant and the CIs remain wide. It is also important to remember that multiple testing issues arise when subgroups are tested and that the CIs presented here have not been adjusted for this.

Subgroup analyses for the use of ESAs plus iron supplementation did not identify any significant differences between groups. Use of iron supplementation varied between the studies, hindering comparison of the results. No trials were identified that considered the use of ESAs in people with head and neck malignancies receiving platinum-based chemotherapy.

The impact of administering erythropoiesis-stimulating agents 'within licence'

In addition, post-hoc sensitivity analyses considered the impact of administering ESAs 'closer to licence'. For the purposes of these analyses this was defined as a licensed start dose plus an inclusion Hb level of ≤ 11 g/dl and a licensed start dose plus an inclusion Hb level of ≤ 11 g/dl plus a target Hb level of ≤ 13 g/dl. It appeared that the effectiveness of some outcomes was improved when ESAs were evaluated closer to their licensed indications. Anaemia-related outcomes showed improvements consistent with previous analyses. Malignancy-related outcomes appeared to be affected by the licence application and point estimates were notably lower than those reported in previous analyses when ESAs were administered in accordance with licence recommendations (licensed start dose plus inclusion Hb level of ≤ 11 g/dl). Importantly, although the results for thromboembolic events from the PenTAG review agree with those from the Cochrane review,[11] suggesting an increase in thromboembolic events in patients undergoing ESA therapy compared with control patients, the closer the studies were to the licence recommendations, the smaller the point estimates (suggesting fewer detrimental effects of ESA).

Although the evidence is uncertain, some researchers have hypothesised that anaemia in cancer patients is associated with a worse prognosis. According to Bohlius and colleagues,[7] one explanation may be that, as a result of a low Hb level, tumour cells become hypoxic and are subsequently less sensitive to cytotoxic drugs, in particular oxygen-dependent chemotherapies.[9,10,193] Evidence for this, as reported in Tonia and colleagues,[11] exists in studies in which tumour control and OS are improved in solid tumour patients with better tumour oxygenation.[10,12] There is also the practical implication that severe anaemia may require a dose reduction or delay of chemotherapy, subsequently leading to a poorer outcome. It is therefore plausible that efforts taken to reduce anaemia may improve tumour response and OS.[7] That said, it should be noted that Hb levels elevated to > 14 g/dl in women and > 15 g/dl in men are undesirable and may lead to increased viscosity and impaired tumour oxygenation.[186]

As an intervention used to increase Hb, and by association improve prognosis, some studies actually report a detrimental effect of ESAs on survival and tumour progression.[14–20] This effect is postulated to result from the presence of erythropoietin receptors on various cancers,[21,22,24,25,194] whereby the endogenously produced or exogenously administered erythropoietin promotes the proliferation and survival of erythropoietin receptor-expressing cancer cells.[7] However, controversy about the functionality of these receptors remains[26–30] and there are several studies that show no effect on tumour progression for patients receiving ESAs.[17,31–33]

It should be noted that the majority of studies examined in the systematic reviews by Bohlius and colleagues[7] and Tonia and colleagues[11] used a wide range of administration frequencies and dosages of ESAs (generally exceeding the licences), which may cause a rise in the number of AEs and a rise in mortality. This knowledge, along with the generally poor reporting and omission of data on factors such as tumour stage and method of assessment, has led to the conclusion by Tonia and colleagues[11] that no clear evidence was found to either exclude or prove a tumour-promoting effect of ESAs.

Importantly, all subgroup analyses must be interpreted with caution. The number of studies per subgroup is small and the CIs remain wide. The analyses may not have the statistical power to detect the effects of licence application on the effectiveness of outcomes, if such effects exist. Furthermore, we have not sought to address multiple testing issues that arise when considering subgroups, therefore inference is not straightforward.

Cost-effectiveness

Published economic evaluations

Ten cost–utility analyses[2,88,114–116,121,156] and two systematic reviews[88,156] were identified by updating an existing review by Wilson and colleagues.[2] Five cost–utility analyses suggested that ESA therapy is cost-effective; these were all funded by industry[116,156] or conducted by industry (submissions by Amgen Inc., Roche and Ortho Biotec, as reported by Wilson and colleagues[2]).

The inclusion of survival benefits was common to four favourable analyses (that by Martin and colleagues[116] and the industry submissions as reported by Wilson and colleagues[2]), although no statistically significant survival benefit has been shown. The fifth favourable analysis[156] may suffer from problems of internal validity, as it appears that the cumulative dose of epoetin alfa in the analysis was less than half that in the clinical study informing the effectiveness estimates; this would account for the lower than usual incremental drug acquisition costs.

A key assumption in almost all of the analyses was that raising Hb levels would improve HRQoL, although in no case was this assumption based on published RCT evidence using a preference-based quality-of-life measure.

A number of studies assumed a period following treatment over which Hb levels would gradually return to normal (termed normalisation), during which patients in the ESA arm would continue to accrue incremental benefits in quality of life over patients in the no ESA arm; however, no evidence for or against normalisation has been presented.

In the absence of a survival benefit the expected health gain from ESA therapy is small (up to 0.035 QALYs) and is subject to uncertainty.

Studies did not incorporate current list prices or wholesale acquisition costs, which could reduce the drug acquisition cost component of ESA therapy and improve cost-effectiveness.

Strengths and limitations of the systematic review of studies of clinical effectiveness

The systematic review of studies of clinical effectiveness was conducted by an independent experienced research team using the latest evidence and working to a prespecified protocol (registered as PROSPERO CRD42013005812). This technology assessment builds on existing secondary research and economic evaluations. However, there are some important sources of uncertainty that impact on the conclusions:

- *Relative effectiveness*. We did not address the relative effectiveness of different ESAs. The lack of head-to-head RCT evidence would have been an important limitation if we had tried to do this.
- *Dose*. The protocol stated that ESAs should be evaluated in accordance with their UK marketing authorisations. However, given the fact that no studies were completely aligned with their current UK marketing authorisation, we identified studies that were closest to the current UK marketing authorisations, focusing initially on the starting dose. It is important to note that beyond the start dose there were still significant differences from the current licence recommendations in the included studies. Also, we did not prespecify the criteria used to define 'closest to the current UK authorisation', but we did explore alternative, stricter ways of making this definition.
- *Generalisability*. There may be other challenges to the applicability of the included trials, which were carried out up to 20 years ago. Chemotherapy has changed during this period, as has the quality of supportive treatment.
- *Study quality*. The included trials were of variable quality but all were flawed to some degree. Most notably, all trials lacked clarity about randomisation and allocation concealment. The general problem of poor reporting of trials on this topic was greatly assisted by the recent Cochrane review.[11] The authors had gathered further information from investigators and manufacturers, which was used in the meta-analysis for the current review.
- *Heterogeneity*. There is considerable unexplained statistical heterogeneity for a number of outcomes, particularly survival.
- *Publication bias*. There was some evidence in both the previous review[2] and the Cochrane review[11] that the results from small negative trials may not be available for inclusion in the systematic reviews, suggesting the possibility of publication bias. For some outcomes in this review, for example HRQoL, this could not be further investigated because of the small number of included studies; for others, such as survival, there was continuing support for the possibility of publication bias. Industry-sponsored trials predominate.
- *Precision*. Although there is an apparent wealth of RCTs, only a minority of these were included because of the desire to address effectiveness as closely as possible to current UK marketing authorisations. In consequence, 95% CIs were often wide and included values indicating no difference in effect. In addition, it is not clear whether the total number of patients in the trials included was sufficient to establish the true presence or absence of an effect, either because events are uncommon, such as AEs, or because the effect size that would be deemed to be clinically important is small, as would be the case with survival.
- *Multiple testing*. Although we were aware of the possibility of spuriously positive tests for statistical significance arising because of the multiple subgroup analyses carried out, we did not formally make adjustments for this.

The limitations identified here impact on the key outcomes as follows:

- Haematological response and numbers transfused seem to be robust estimates, with no marked heterogeneity or subgroup effects.
- Hb change does have important heterogeneity, which may possibly indicate subgroup effects; however, analyses in this respect were inconclusive.
- HRQoL is affected by the variability of instruments used and study quality.
- AEs are mainly affected by the quality of information available, the variability in the definitions of individual AEs used and the width of the CIs.
- Survival is subject to all of the limitations outlined above. Marked heterogeneity was identified for which no explanation could be provided. In addition, OS was calculated from the longest follow-up available and, as a result, there was a mix of short- and long-term studies.

Strengths and limitations of the systematic review of studies of cost-effectiveness

The systematic review of cost-effectiveness evidence was conducted by an independent research team using the latest evidence and to a prespecified protocol. Two new systematic reviews[88,156] were identified, neither of which identified studies that would have been eligible for this review, but which were not included.

Limitations were identified as follows:

- The searches were limited to English-language studies because of resource limitations.
- Only systematic reviews and cost–utility studies were fully critically appraised and considered in the narrative synthesis.
- Records from database searches published pre 2004 were excluded, although it was not possible to assess whether these had been screened for eligibility in the systematic review presented by Wilson and colleagues.[2] Studies using darbepoetin alfa once every 2 weeks were excluded as being out of licence, although these could have usefully contributed to the review.

Strengths and limitations of the economic modelling by Peninsula Technology Assessment Group

The PenTAG model is an independent model that is not sponsored by any of the manufacturers producing ESAs. We have used up-to-date clinical effectiveness data that have been acquired through a systemic review of current evidence. As such, although we have built on past economic analyses of ESAs, we have also been able to identify key areas where information is scarce or uncertain and, when possible, have attempted to address some of these limitations. These limitations are discussed in the following sections.

Data quality for erythropoiesis-stimulating agent dose

According to licence, the dose of ESAs can be varied in a number of situations. Doses may be escalated if patients do not achieve an adequate response or may be reduced or withdrawn if a patient's Hb level rises at an unacceptable pace or to an unacceptable level.

We estimated the mean weekly dose for patients on an ITT basis to ensure consistency between modelled costs and benefits. The mean weekly dose was estimated by pooling estimates from a number of studies, which could improve external validity, but the individual estimates from studies typically required assumptions such as a uniform withdrawal rate. As a result, estimates from individual studies may not be accurate.

We estimated a mean weekly dose for epoetin alfa of 24,729 IU over a course of 12 weeks, resulting in a modelled cumulative dose of approximately 297,000 IU. Tonelli and colleagues[88] estimate a weekly dose of 30,150 IU over a course of 15 weeks, resulting in a modelled cumulative dose of approximately 452,000 IU (52% larger than our cumulative dose). Tonelli and colleagues[88] did not attempt to model dose adjustment and this, combined with the assumption of 3 weeks of extra treatment, may explain the difference.

Uncertainty in overall survival

Differing assumptions regarding OS for patients receiving and not receiving ESA therapy have a significant impact on the estimated cost-effectiveness of ESAs.

Systematic reviews of the clinical effectiveness of ESAs (including our own) have included meta-analyses of HRs for OS but, to our knowledge, the assumption of proportional hazards (which must be made when calculating HRs) has never been formally tested. Furthermore, it is likely that follow-up for a number of trials for which HRs have been estimated has been very short, therefore there is considerable uncertainty as to the effect of ESA therapy on long-term mortality. IPD have been shared with the Cochrane review group[7] on this subject and these could potentially be scrutinised to address these concerns.

Even when the assumption of proportional hazards is made and the random-effects meta-analysis HR is used, there remains significant parameter and structural uncertainty.

Parameter uncertainty exists in that the CI for the OS HR is very wide (95% CI 0.83 to 1.13). There have not been many studies that are sufficiently powered to detect differences in OS for this parameter to be estimated precisely. Parameter uncertainty also exists in that the OS HR appears to be somewhat sensitive to the choice of inclusion criteria for studies. Further parameter uncertainty exists regarding the OS estimated for patients not receiving ESA therapy. This also has a significant impact on cost-effectiveness, but it is uncertain and likely to differ according to the patient population.

Structural uncertainty exists in that even when assuming proportional hazards there are a number of distributions that permit the proportional hazards assumption: exponential, Weibull and Gompertz distributions. These distributions allow for quite different mortality rates over time, but none appears to be compatible with all reported survival data.

We have demonstrated that uncertainty surrounding OS is the principal contributor to the uncertainty regarding cost-effectiveness by exploring cost-effectiveness when exactly no difference in OS is assumed. This should not be seen as advocacy of the view that there is exactly no difference in OS, as there are biologically plausible explanations for beneficial and detrimental effects of ESA therapy on OS and there is no reason to suppose that these would cancel out.

Normalisation of haemoglobin levels

Clinical expert opinion seems to be in agreement that following chemotherapy cessation Hb levels will gradually increase, potentially up to pre-chemotherapy levels. Unfortunately, we have not found any published clinical studies documenting normalisation, therefore the modelled behaviour of Hb levels during normalisation is based entirely on clinical expert opinion.

Our economic evaluation suggests that the QALY gain from normalisation accounts for approximately one-third of the short-term QALY gain and 6% of the total QALY gain estimated in the base case. This is a significant proportion of the predicted benefits to be largely based on clinical expert opinion, even though the expert opinion was at least not conflicting.

Exclusion of transfusion-dependent haemoglobin measurements

Some clinical studies (e.g. Tjulandin and colleagues[48]) excluded Hb measurements from certain statistical analyses if the patient had received a transfusion in the previous 28 days. The rationale for this exclusion is that transfusions are assumed to increase Hb levels temporarily and that including measurements that could be affected by transfusion could lead to biased estimates of effectiveness.

Our economic evaluation assumes that Hb outcomes reported in trials are unbiased estimates of Hb outcomes for patients in clinical practice where transfusions may be used. Transfusion costs are modelled to 'pay' for the transient benefits in terms of Hb level; if the impact of transfusions on Hb level is stripped from the

effectiveness results then we are modelling the costs but not the benefits of transfusion. As there is greater utilisation of transfusions in patients not receiving ESA therapy, it is possible that the cost-effectiveness of ESA therapy has been overestimated.

Ideally, we would ensure that all outcomes relating to Hb levels used in the model are based on Hb levels from all patients (i.e. not excluding patients who had recently received a transfusion), but there are insufficient data reported in clinical studies to achieve this.

Ultimately, the QALY gains from short-term correction of anaemia are dwarfed by the highly uncertain impact of ESAs on OS, so small biases such as these in the estimation of short-term QALYs are unlikely to materially affect cost-effectiveness.

Haemoglobin to utility mapping

The short-term QALYs associated with anaemia require mapping of Hb levels to utility. This is a surrogate outcome and requires several assumptions. First, the relationship between Hb level and utilities is assumed to be linear. Although our review of previous studies suggests that this is appropriate for Hb levels of < 12 g/dl, the model does allow for normalisation at Hb levels > 12 g/dl in the PSA, in which this assumption of linearity no longer seems to hold. Furthermore, the review of previous studies showed that the evidence base for mapping Hb levels to utility appears to include many different measurement tools for utility (SF-6D, EQ-5D, health state vignettes, LASA), suggesting that if all studies could be mapped to the same scale then this linear relationship may not hold. However, as linear scaling was used to scale the SF-6D results to the EQ-5D, this was not a problem in our base case. To assess the impact of scaling this utility, we also conducted a sensitivity analysis using the unscaled SF-6D value and a sensitivity analysis using an unscaled EQ-5D value from a population of CKD patients. In both instances the QALY gains for ESA use were lower and the ICERs compared with no ESA use increased.

There were several additional problems with the base-case source of our utility estimate associated with a change in Hb level. Aside from having to map the reported outcomes to the EQ-5D, the patient population was restricted to female cancer patients and did not include patients on ESA therapy. This meant that the study examined the association of anaemia and utility rather than the association of anaemia correction and utility improvement, which our analysis was attempting to model. Furthermore, the study design was observational, although this appeared to be the case for most of the studies identified in our review. This does mean that the estimated relationship between utility and Hb level may be biased because of unmeasured confounding variables. As discussed in *Methods*, the results from Tonelli and colleagues[114] suggest that this would likely bias the results in favour of the ESA arm compared with the no ESA arm. Bias may also have occurred in the mapping study of the SF-6D to the EQ-5D because of measurement error in the SF-6D values, which would result in an underestimation of the relationship between the two measures (i.e. attenuation bias).

Chemotherapy costs

The PenTAG model assumes that chemotherapy costs are equal between the groups both in the short term and in the long term, regardless of ESA use. Short-term chemotherapy costs may differ in accordance with on-study mortality or with compliance to chemotherapy treatments, whose effects are not captured in the short term. Although the review of clinical effectiveness studies did not identify any statistically significant difference between the ESA arm and the control arm for on-study mortality, the overall estimate (HR 0.87, 95% CI 0.70 to 1.09) suggests a trend in favour of improved survival with ESA therapy. There is also the possibility that ESA use may affect adherence to a chemotherapy regimen: ESA use appears to reduce the time in hospital for RBCT and this may impact patient attitudes to their treatment. However, it is difficult to speculate about the possible impact that this may have on costs as there appears to be no evidence currently with which to make any claim. Furthermore, in the long term, if an impact on OS is assumed then the chemotherapy costs are likely to differ between groups. Again, is difficult to speculate how these costs might differ, as a longer survival might mean a longer follow-up and larger chemotherapy costs, a better prognosis and therefore fewer chemotherapy costs or a different approach to treatment.

There may also be a follow-on cost difference according to the effects of chemotherapy adherence in the short term. Without a clear clinical understanding of the impact of ESAs on survival and patient preferences, it is difficult to address how chemotherapy costs may alter, which is why they are assumed to be equal in both arms for the base case.

Adverse events

Adverse event rates associated with ESAs are also highly uncertain. The level of severity and specificity of each AE is not well reported. The model specifically does not include rash or seizure as an AE, even though they are reported in the clinical effectiveness systematic review, as these cover a wide, non-specific symptom base. The model included thromboembolic events, hypertension and thrombocytopenia, which cover a more specific symptom base, but these are still not well defined within or across the studies in the review of clinical effectiveness. As such, the review of clinical effectiveness included all definitions of AEs at all levels of severity. This makes it problematic to assign either costs or disutilities to these AEs in the model. Base-case costs were extracted from the NHS reference costs 2012–13 for events likely to fall into the categories of AEs, but these costs are averages from a wide variety of scenarios and as such are highly uncertain. Our sensitivity analyses (doubling and halving the costs) did not appear to make a significant difference to the results, but this assumes that the underlying event costs for AEs are the same in both arms. The model identifies only the proportion of patients who had at least one AE, regardless of severity or number. As such, the costs in the model reflect only one AE and do not account for the possibility that AEs may be more severe in one arm than the other. It is therefore probable that the unit cost for an AE is less likely to have an impact on the overall costs than the number of events or the cost according to severity.

Assigning utilities to the AEs is even more problematic, in terms of both estimating the utility and estimating the time that the disutility should apply for. As such, the model does not account for utility loss associated with AEs and the disbenefit of AEs is reflected only in their costs. Given the sensitivity of the model to changes in QALYs, this could have a significant impact on the overall results. The findings from the clinical effectiveness review were mostly in favour of the control arm: thromboembolic events and hypertension occurred more frequently in patients on ESA therapy, but thrombocytopenia appeared to be more common in the control arm. As such, the addition of AE utilities into the model would likely worsen the cost-effectiveness of ESAs. However, this situation would also lead to the slightly unusual result that the group with the highest risk of AEs has a better survival outcome. This could be explained by the lack of detail on AEs (the higher risk may not actually correspond to the more severe AEs) or by the possible spurious nature of the survival benefit. Again, without a clear clinical understanding of the possible difference in OS, it is difficult to speculate.

Other considerations

The base-case cost for each of the ESAs may not be representative of the actual cost currently paid by individual organisations within the NHS. We therefore used the data collected on wholesale acquisition prices in a sensitivity analysis, with the caveat that these prices cannot be guaranteed.

The cost of administering ESAs was not adjusted in the model for missed doses, which therefore gives an increased cost for patients in the ESA arm. The sensitivity analysis in which alternative dosing schedules were considered does not address this issue directly, but does demonstrate that altering these costs does not have a big impact on the model. Similarly, although it appears that there is debate among clinicians over how ESAs are administered or who should administer them, our results demonstrate that administering ESAs in a similar way to how they are administered for CKD patients has little impact on the overall results.

There is also uncertainty over the implications of other tests that may occur during ESA use. Some clinicians advise that additional blood tests should be carried out and one of the manufacturer submissions from the previous HTA review[2] costed for additional blood pressure checks, but other clinicians believe that no additional tests are required as patients will be under fairly high surveillance during their cancer treatment. However, the impact of this cost seems minimal and the base-case results of the model seem fairly insensitive to changes in this cost.

The model also does not include AEs associated with RBCTs. However, we believe this risk to be minimal and the consequences are not easily defined or accounted for.

The cost of RBCTs has been updated from a particularly old source, making it unlikely to be representative of current costs. Without current information to better inform this cost, we altered it in sensitivity analyses to show the potential impact that changing this cost may have. Again, the results demonstrate that the model is not overly sensitive to this cost, particularly if the cost is reduced.

The model also assumed that the number of RBC units per transfusion is equal in both arms, as we found no evidence to inform a difference between arms. This may not be an accurate representation of the actual number of RBCs per transfusion. If the number of units transfused per transfusion is less for the ESA arm than for the no ESA arm, then the number of transfusions for the ESA arm will increase and the cost-effectiveness of the ESAs will be reduced.

Chapter 7 Assessment of factors relevant to the NHS and other parties

Existing safety concerns

When seeking clinical experts to advise us in this assessment we found that most relevant clinicians (i.e. oncologists, haematologists and gynaecologists) did not use ESA therapy in their clinical practice. This was generally because of concerns about their safety and effectiveness (OS), in addition to restrictions set by the previous NICE guidance (TA142).[1]

As this assessment is unlikely to have reduced any safety concerns, it is relevant to the NHS that many clinicians appear to have judged that the potential risks of ESAs outweigh their potential benefits.

Current usage

It is difficult to assess how frequently ESA therapy is used within the indication of CIA because prescription records do not routinely link medication with indication and ESA therapy is widely used in individuals with CKD. Some indirect evidence of the use of ESA therapy for CIA is available from recorded costs for ESAs, which are categorised by cost centre (in particular, oncology and haematology).

We were provided with data (South East England Specialist Pharmacy Services, 3 October 2013, personal communication) detailing how much had been spent on erythropoietin and darbepoetin alfa by hospital trusts (anonymised) in the East of England. These data were provided for the haematology and oncology cost centres. The oncology cost centre would be unlikely to include CKD patients but would not necessarily include all patients with CIA. The haematology cost centre could include CKD patients. By including only the haematology and oncology cost centres, 87.4% of ESA expenditure was excluded, although the proportion varied according to hospital trust (*Figure 69*), which suggests that trusts may record ESA prescriptions differently. Total ESA expenditure is highly variable but appears to be somewhat correlated with the size of population served (*Figure 70*). This correlation disappears when only haematology and oncology are considered (*Figure 71*). This is suggestive of significant variability in current usage, consistent with the experience that many clinicians do not use ESAs because of safety concerns, although data quality is low and interpretation challenging.

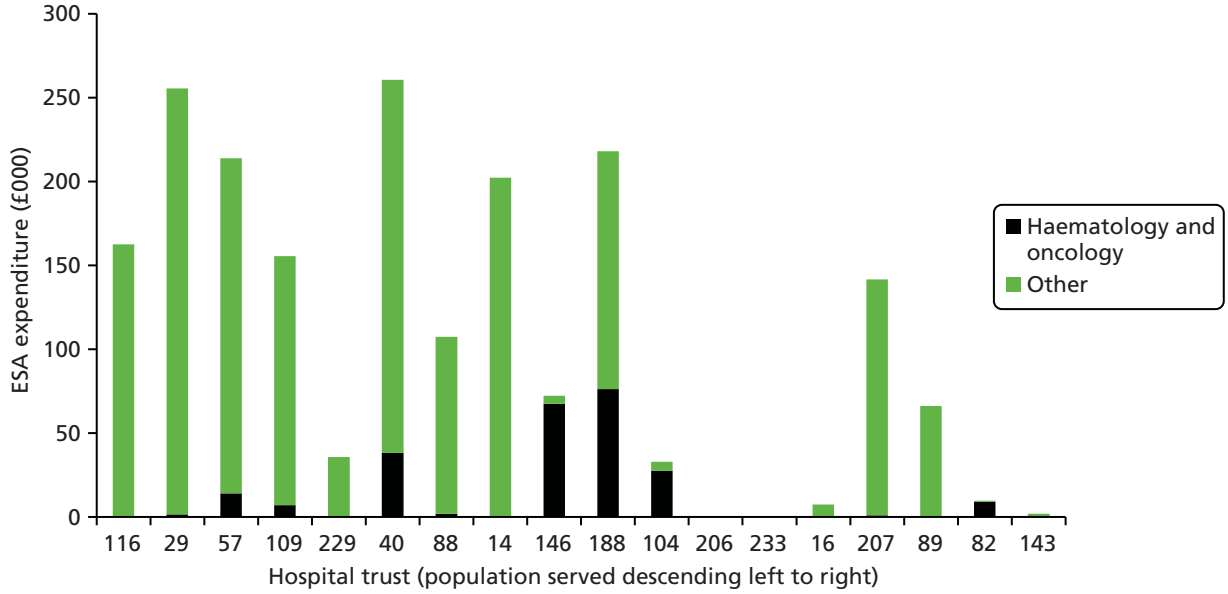

FIGURE 69 Total ESA expenditure for hospital trusts in the East of England.

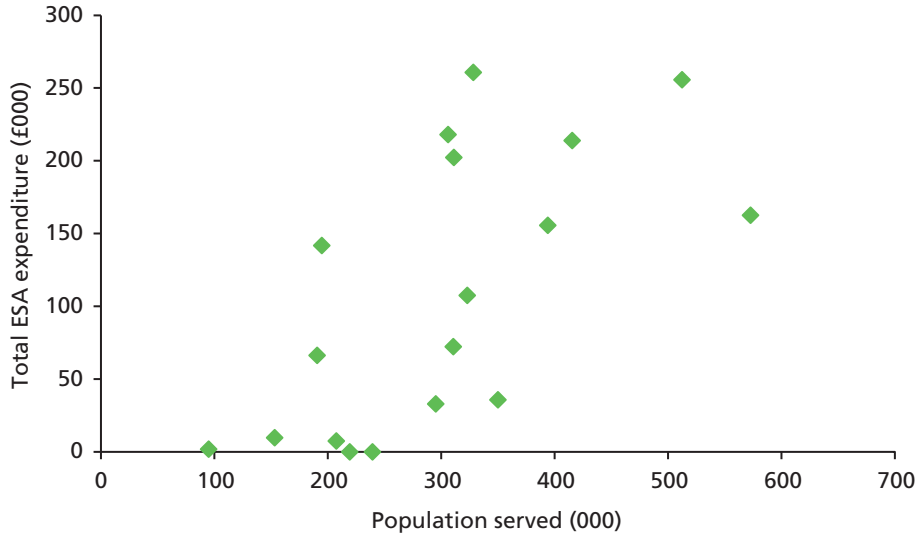

FIGURE 70 Comparison of total ESA expenditure with population served.

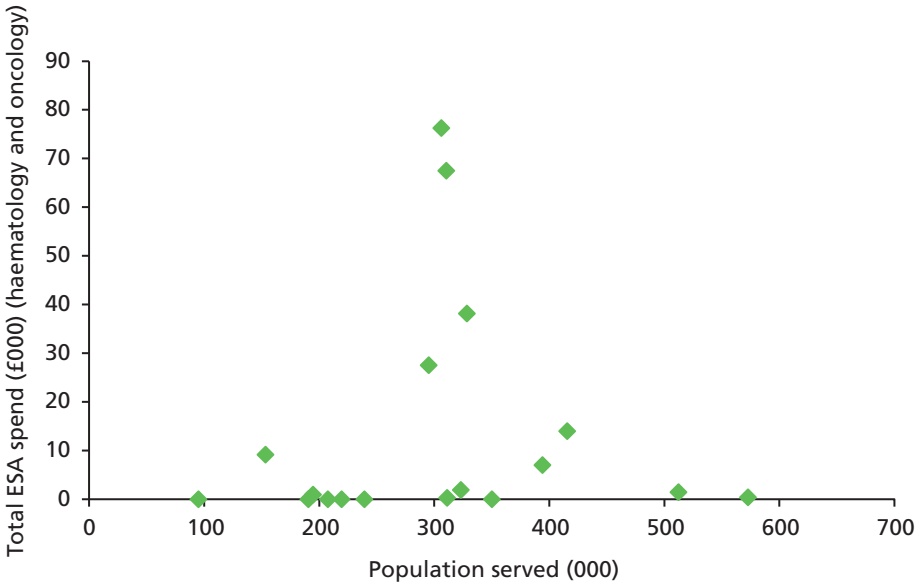

FIGURE 71 Comparison of ESA expenditure in haematology and oncology with population served.

Acquisition cost of erythropoiesis-stimulating agents

As noted in *Chapter 5*, the cost at which hospitals acquire ESAs may be significantly lower than the list price for these drugs. These prices are the subject of confidential negotiations and are commercially sensitive.

The NICE methods guide[169] states that in the reference case analysis, prices should be chosen to best reflect those relevant to the NHS, if these are transparent and consistently applied across the NHS, and can be guaranteed for a period. In the absence of such conditions, prices from the Commercial Medicines Unit Electronic Marketing Information Tool, or public list prices, should be used in the reference case.

At the time of writing no manufacturer has agreed a Patient Access Scheme with the Department of Health and no contracts have been negotiated by the NHS Commercial Medicines Unit. Current acquisition prices are confidential and therefore not transparent and there are no guarantees that current prices will continue into the future.

At present, acquisition prices will largely be driven by demand for ESAs for individuals with CKD. Current prices could be disturbed if there are developments in the management of CKD or if demand for ESAs increases for patients with CIA.

Chapter 8 Conclusions

The previous HTA review[2] concluded that 'Epo is effective in improving haematological response and reducing RBCT requirements. It also appears to improve HRQoL. Its impact on side-effects and survival remains highly uncertain. If there is no impact on survival, it seems highly unlikely to be considered that epo is a cost-effective use of healthcare resources' (p. iv).

Additional clinical effectiveness evidence identified in this updated systematic review continues to suggest that there is clinical benefit from ESAs with respect to anaemia-related outcomes; that is, improvements in haematological response and a reduction in RBCT requirements. Data also suggest that there is an improvement in HRQoL and this is better quantified than in the previous HTA review.[2] The impact on side effects and survival, however, remains highly uncertain. Although the point estimates for both survival and thromboembolic events are lower than previously reported estimates, the 95% CIs are wide and not statistically significant.

Conclusions concerning cost-effectiveness are also no clearer. Base-case ICERs for ESA treatment compared with no ESA treatment ranged from £19,429 to £35,018 per QALY gained, but sensitivity and scenario analyses demonstrate that there is considerable uncertainty in these ICERs. In line with the previous HTA review,[2] survival was an influential parameter. If the survival benefit reported in the clinical effectiveness review (HR 0.97, 95% CI 0.83 to 1.13) is used, ESAs appear to be cost-effective on average, but this is highly uncertain and QALY losses cannot be ruled out (31.4% of simulations in the base case had a QALY loss from ESA therapy). However, if exactly equal survival is assumed in both groups, regardless of ESA therapy, ESAs are predicted not to be cost-effective unless wholesale acquisition costs are used, in which case ESAs are predicted to be cost-effective on average, although approximately one in three simulations give an ICER of > £20,000 per QALY.

In summary, ESAs could be cost-effective but there is considerable uncertainty, mainly because of unknown impacts on OS.

Suggested research priorities

- If ESAs are thought to have a major potential for improving cancer care, large RCTs meeting current methodological and reporting standards with adequate follow-up are needed to evaluate ESAs as administered in line with current marketing authorisations (including licence criteria for Hb levels).
- There is a need for improved estimates of the impact of ESAs on tumour response and mortality; if these estimates are neutral or slightly beneficial it is plausible that ESAs could be cost-effective.
- There should be assessment of the frequency of the key potential AEs related to ESA administration.
- More data are needed to assess the impact of ESAs on HRQoL. Such studies should include the effect of ESAs on the EQ-5D.
- More evidence is needed to assess the impact of Hb normalisation on utility. If clinical studies of normalisation are conducted it would also be valuable for HRQoL outcomes to be measured, preferably using the EQ-5D or another universal HRQoL questionnaire, so that incremental QALYs resulting from normalising from a higher Hb level can be modelled directly rather than by using the surrogate of Hb level.
- In addition to new trials it may be valuable to revisit the Cochrane IPD meta-analysis[7] and select studies that better fit 'licensed recommendations' with respect to Hb criteria and dose administered.
- It may also be helpful to explore reasons why improved anaemia may lead to better outcomes; that is, whether ESAs allow better compliance with chemotherapy.

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Contribution of authors

Louise Crathorne provided overall project management and led the systematic review of clinical effectiveness, including the assessment of all abstracts and titles for possible inclusion and the meta-analysis for the clinical effectiveness outcomes. She also drafted and/or edited all sections of the report.

Nicola Huxley led the development and execution of the economic model and wrote the sections on the design and results of the economic model. She also assessed titles and abstracts for inclusion in the cost-effectiveness review.

Marcela Haasova assessed titles and abstracts for inclusion in the systematic review of clinical effectiveness, led the meta-analysis for the clinical effectiveness review and contributed to the writing and editing of the report.

Tristan Snowsill led the systematic review of economic evaluations, contributed to the design and parameterisation of the model and performed model checking. He also contributed to the writing and editing of all sections of the report.

Tracey Jones-Hughes led the systematic review of quality-of-life outcomes, including the assessment of all abstracts and titles for possible inclusion, and contributed to the writing and editing of the report.

Martin Hoyle led the design of the economic model and contributed to the write-up of the economic model.

Simon Briscoe designed and carried out the literature searches for the systematic reviews and identification of model parameters and contributed to the writing and editing of the report.

Helen Coelho contributed to the clinical effectiveness, quality-of-life and cost-effectiveness systematic reviews and to the editing of the report.

Linda Long assessed abstracts and titles for inclusion in the systematic review of quality-of-life outcomes, assessed the quality of the included systematic reviews, compiled the summary table of review characteristics and conducted the GRADE assessment. She also contributed to the editing of the report.

Antonieta Medina-Lara provided advice on the cost-effectiveness (utilities) and quality-of-life systematic reviews and contributed to the writing and editing of the report.

Ruben Mujica-Mota provided advice on the cost-effectiveness systematic review and the design and results of the cost-effectiveness modelling and contributed to the writing and editing of the report.

Mark Napier provided clinical input into the design of the model and advised on clinical matters.

Chris Hyde contributed to the clinical effectiveness, quality-of-life and cost-effectiveness reviews, the design of the model and the writing and editing of the report and was overall director of the project and guarantor of the report.

Data-sharing statement

This is a systematic review; therefore, there is no primary data to share. Further information can be obtained from the lead author if required.

References

1. National Institute for Health and Care Excellence. *Epoetin Alfa, Epoetin Beta and Darbepoetin Alfa for Cancer Treatment-Induced Anaemia*. NICE technology appraisal guidance TA142. London: NICE; 2008.
2. Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al.* A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007;**11**(13). http://dx.doi.org/10.3310/hta11130
3. Schrijvers D, De Samblanx H, Roila F. Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO Clinical Practice Guidelines for use. *Ann Oncol* 2010;**21**:v244–7. http://dx.doi.org/10.1093/annonc/mdq202
4. Mercadante S, Gebbia V, Marrazzo A, Filosto S. Anaemia in cancer: pathophysiology and treatment. *Cancer Treat Rev* 2000;**26**:303–11. http://dx.doi.org/10.1053/ctrv.2000.0181
5. Schrijvers D, Roila F, Esmo Guidelines Working Group. Erythropoiesis-stimulating agents in cancer patients: ESMO recommendations for use. *Ann Oncol* 2009;**20**(Suppl. 4):159–61.
6. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst* 1999;**91**:1616–34. http://dx.doi.org/10.1093/jnci/91.19.1616
7. 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 Syst Rev* 2009;**3**:CD007303. http://dx.doi.org/10.1002/14651858.cd007303.pub2
8. Vaupel P, Mayer A. Hypoxia and anemia: effects on tumour biology and treatment resistance. *Transfus Clin Biol* 2005;**12**:5–10. http://dx.doi.org/10.1016/j.tracli.2004.11.005
9. Schrijvers D, Highley M, De Bruyn E, Van Oosterom A, Vermorken J. Role of red blood cells in pharmacokinetics of chemotherapeutic agents. *Anticancer Drugs* 1999;**10**:147–53. http://dx.doi.org/10.1097/00001813-199902000-00002
10. Hockel M, Knoop C, Schlenger K, Vorndran B, Baussmann E, Mitze M, *et al.* Intratumoral pO2 predicts survival in advanced cancer of the uterine cervix. *Radiother Oncol* 1993;**26**:45–50. http://dx.doi.org/10.1016/0167-8140(93)90025-4
11. Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, *et al.* Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2012;**12**:CD003407. http://dx.doi.org/10.1002/14651858.cd003407.pub5
12. Knocke TH, Weitmann HD, Feldmann HJ, Selzer E, Potter R. Intratumoral pO2-measurements as predictive assay in the treatment of carcinoma of the uterine cervix. *Radiother Oncol* 1999;**18**:156–69. http://dx.doi.org/10.1016/s0167-8140(99)00139-5
13. Vaupel P, Thews O, Mayer A, Hockel S, Hockel M. Oxygenation status of gynecologic tumors: what is the optimal hemoglobin level? *Strahlenther Onkol* 2002;**178**:727–31. http://dx.doi.org/10.1007/s00066-002-1081-x
14. Leyland-Jones B. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet* 2003;**4**:459–60. http://dx.doi.org/10.1016/S1470-2045(03)01163-X
15. Henke M, Laszig R, Rube C, Schafer 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. http://dx.doi.org/10.1016/S0140-6736(03)14567-9

16. Smith RE Jr, 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. *J Clin Oncol* 2008;**26**:1040–50. http://dx.doi.org/10.1200/JCO.2007.14.2885

17. 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. *Br J Haematol* 2003;**122**:394–403. http://dx.doi.org/10.1046/j.1365-2141.2003.04448.x

18. Overgaard J, Hoff C, Sand Hansen H, Specht L, Overgaard M, Grau C. 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. *Eur J Cancer Suppl* 2007;**5**:6LB.

19. 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. *J Clin Oncol* 2007;**25**:1027–32. http://dx.doi.org/10.1200/JCO.2006.07.1514

20. Goss G, Feld R, Bezjak A, Perry G, Melosky Y, 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. *Lung Cancer* 2005;**49**:S53. http://dx.doi.org/10.1016/S0169-5002(05)80288-0

21. McBroom JW, Acs G, Rose GS, Krivak TC, Mohyeldin A, Verma A. Erythropoeitin receptor function and expression in epithelial ovarian carcinoma. *Gynecol Oncol* 2005;**99**:571–7. http://dx.doi.org/10.1016/j.ygyno.2005.06.038

22. Arcasoy MO, Jiang X, Haroon ZA. Expression of erythropoietin receptor splice variants in human cancer. *Biochem Biophys Res Comm* 2003;**307**:999–1007. http://dx.doi.org/10.1016/S0006-291X(03)01303-2

23. Arcasoy MO, Amin K, Vollmer RT, Jiang X, Demark-Wahnefried W, Haroon ZA. Erythropoietin and erythropoietin receptor expression in human prostate cancer. *Mod Pathol* 2005;**18**:421–30. http://dx.doi.org/10.1038/modpathol.3800288

24. Dagnon K, Pacary E, Commo F, Antoine M, Bernaudin M, Bernaudin JF, *et al.* Expression of erythropoietin and erythropoietin receptor in non-small cell lung carcinomas. *Clin Cancer Res* 2005;**11**:993–9.

25. Leo C, Horn LC, Rauscher C, Hentschel B, Liebmann A, Hildebrandt G, *et al.* Expression of erythropoietin and erythropoietin receptor in cervical cancer and relationship to survival, hypoxia, and apoptosis. *Clin Cancer Res* 2006;**12**:6894–900. http://dx.doi.org/10.1158/1078-0432.CCR-06-1285

26. Feldman L, Wang Y, Rhim JS, Bhattacharya N, Loda M, Sytkowski AJ. Erythropoietin stimulates growth and STAT5 phosphorylation in human prostate epithelial and prostate cancer cells. *Prostate* 2006;**66**:135–45. http://dx.doi.org/10.1002/pros.20310

27. Yasuda Y, Fujita Y, Matsuo T, Koinuma S, Hara S, Tazaki A, *et al.* Erythropoietin regulates tumour growth of human malignancies. *Carcinogenesis* 2003;**24**:1021–9. http://dx.doi.org/10.1093/carcin/bgg060

28. Mohyeldin A, Lu H, Dalgard C, Lai SY, Cohen N, Acs G, *et al.* Erythropoietin signaling promotes invasiveness of human head and neck squamous cell carcinoma. *Neoplasia* 2005;**7**:537–43. http://dx.doi.org/10.1593/neo.04685

29. Henke M, Mattern D, Pepe M, Bezay C, Weissenberger C, Werner M, *et al.* Do erythropoietin receptors on cancer cells explain unexpected clinical findings? *J Clin Oncol* 2006;**24**:4708–13. http://dx.doi.org/10.1200/JCO.2006.06.2737

30. Jelkmann W, Bohlius J, Hallek M, Sytkowski AJ. The erythropoietin receptor in normal and cancer tissues. *Crit Rev Oncol Hematol* 2008;**67**:39–61. http://dx.doi.org/10.1016/j.critrevonc.2008.03.006

31. 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). *Int J Radiat Oncol Biol Phys* 2007;**69**:1008–17. http://dx.doi.org/10.1016/j.ijrobp.2007.04.063

32. Chang J, Couture F, Young S, McWatters KL, Lau CY. Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. *J Clin Oncol* 2005;**23**:2597–605. http://dx.doi.org/10.1200/JCO.2004.12.027

33. Moebus V, Lueck H, Thomssen C, Harbeck N, Nitz U, Kreienberg R. 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). *J Clin Oncol* 2007;**25**(18 Suppl.):569.

34. Schrijvers D. Management of anemia in cancer patients: transfusions. *Oncologist* 2011;**16**(Suppl. 3):12–18. http://dx.doi.org/10.1634/theoncologist.2011-S3-12

35. Janssen-Cilag Ltd. *Summary Product Characteristics: Eprex 40,000 IU/ml Solution for Injection in Pre-Filled Syringe*. High Wycombe: Janssen-Cilag; 2012.

36. Sandoz Ltd. *Summary of Product Characteristics: Binocrit Solution for Injection in a Pre-Filled Syringe*. Camberley: Sandoz Ltd; 2012.

37. Hospira UK Ltd. *Summary of Product Characteristics: Retacrit Solution for Injection in Pre Filled Syringe*. Leamington Spa: Hospira UK Ltd; 2012.

38. Roche Products Ltd. *Summary of Product Characteristics: Neorecormon Solution for Injection in Pre-Filled Syringe*. Welwyn Garden City: Roche Products Ltd; 2012.

39. Teva Pharmaceuticals Ltd. *Summary of Product Characteristics: Eporatio 1,000 IU/0.5 ml Solution for Injection in Pre-Filled Syringe*. Harlow: Teva Pharmaceuticals Ltd; 2012.

40. Amgen Inc. *Summary of Product Characteristics: Aranesp PFS*. Cambridge: Amgen Inc.; 2012.

41. Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Österborg A, *et al.* EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur J Cancer* 2007;**43**:258–70. http://dx.doi.org/10.1016/j.ejca.2006.10.014

42. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spicak JL, *et al.* American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *J Clin Oncol* 2010;**28**:4996–5010. http://dx.doi.org/10.1200/JCO.2010.29.2201

43. British Columbia Cancer Agency. *BCCA Protocol Summary Guidelines for the Use of Erythropoiesis-Stimulating Agents (ESAs) in Patients with Cancer*. Vancouver, BC: British Columbia Cancer Agency; 2012.

44. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535. http://dx.doi.org/10.1136/bmj.b2535

45. Bohlius J, Langensiepen S, Schwarzer G, Seidenfeld J, Piper M, Bennett C, *et al.* Erythropoietin for patients with malignant disease. *Cochrane Database Syst Rev* 2004;**3**:CD00340. http://dx.doi.org/10.1002/14651858.cd003407.pub2

46. NICE. *Final Scope: Anaemia (Cancer-Treatment Induced) – Erythropoiesis-Stimulating Agents (Epoetin and Darbepoetin)*. London: NICE; 2014.

47. Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, *et al. Mortality in Cancer Patients Receiving Recombinant Human Erythropoiesis-Stimulating Agents: Individual Patient Data Meta-Analysis Based on Randomized Trials*. 8th International Luebeck Conference Pathophysiology and Pharmacology of Erythropoietin and other Hemopoietic Growth Factors, Luebeck, Germany, 2009.

48. Tjulandin SA, Bias P, Elsasser R, Gertz B, Kohler E, Buchner A. Epoetin theta in anaemic cancer patients receiving platinum-based chemotherapy: a randomised controlled trial. *Arch Drug Inf* 2010;**3**:45–53. http://dx.doi.org/10.1111/j.1753-5174.2010.00030.x

49. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;**17**:2815–34. http://dx.doi.org/10.1002/(SICI)1097-0258(19981230)17:24<2815::AID-SIM110>3.0.CO;2-8

50. 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. *Eur J Cancer* 2003;**39**:2026–34. http://dx.doi.org/10.1016/S0959-8049(03)00456-8

51. ten Bokkel Huinink WW, de Swart CA, van Toorn DW, Morack G, Breed WP, Hillen HF. 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. *Med Oncol* 1998;**15**:174–82. http://dx.doi.org/10.1007/BF02821936

52. 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. *Br J Cancer* 1999;**80**:396–402. http://dx.doi.org/10.1038/sj.bjc.6690369

53. 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. *Br J Haematol* 2002;**119**:79–86. http://dx.doi.org/10.1046/j.1365-2141.2002.03774.x

54. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Updated March 2011]*. The Cochrane Collaboration; 2011.

55. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 1: Introduction to evidence Synthesis for Decision Making.* April 2011 (last updated April 2012). URL: www.nicedsu.org.uk (accessed 31 August 2015).

56. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34. http://dx.doi.org/10.1136/bmj.315.7109.629

57. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;**25**:3443–57. http://dx.doi.org/10.1002/sim.2380

58. Henry DH, Brooks BJ Jr, Case DC Jr, Fishkin E, Jacobson R, Keller AM, *et al.* Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy. *Canc J Sci Am* 1995;**1**:252–60.

59. Abels RI, Larholt KM, Krantz KD, Bryant EC. Recombinant human erythropoietin (rHuEPO) for the treatment of the anemia of cancer. *Oncologist* 1996;**1**:140–50.

60. Patrick DL, Gagnon DD, Zagari MJ, Mathijs R, Sweetenham J, Epoetin Alfa Study Group. Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients receiving epoetin alfa. *Eur J Cancer* 2003;**39**:335–45. http://dx.doi.org/10.1016/S0959-8049(02)00628-7

61. Wagner LM, Billups CA, Furman WL, Rao BN, Santana VM. Combined use of erythropoietin and granulocyte colony-stimulating factor does not decrease blood transfusion requirements during induction therapy for high-risk neuroblastoma: a randomized controlled trial. *J Clin Oncol* 2004;**22**:1886–93. http://dx.doi.org/10.1200/JCO.2004.01.002

62. 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. *J Natl Cancer Inst* 2013;**105**:1018–26. http://dx.doi.org/10.1093/jnci/djt145

63. Abels R. Erythropoietin for anaemia in cancer patients. *Eur J Cancer* 1993;**29A**(Suppl. 2):S2–8. http://dx.doi.org/10.1016/S0959-8049(05)80281-3

64. 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. *J BUON* 2003;**8**:127–32.

65. Boogaerts M, Coiffier B, Kainz C. Impact of epoetin beta on quality of life in patients with malignant disease. *Br J Cancer* 2003;**88**:988–95. http://dx.doi.org/10.1038/sj.bjc.6600801

66. Dammacco F, Castoldi G, Rodjer S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. *Br J Haematol* 2001;**113**:172–9. http://dx.doi.org/10.1046/j.1365-2141.2001.02715.x

67. 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. *J Clin Oncol* 1997;**15**:2715–21.

68. Dunphy FR, Harrison BR, Dunleavy TL, Rodriguez JJ, Hilton JG, Boyd JH. Erythropoietin reduces anemia and transfusions: a randomized trial with or without erythropoietin during chemotherapy. *Cancer* 1999;**86**:1362–7. http://dx.doi.org/10.1002/(SICI)1097-0142(19991001)86:7<1362::AID-CNCR36>3.0.CO;2-T

69. 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. *Gynecol Oncol* 1997;**65**:461–6. http://dx.doi.org/10.1006/gyno.1997.4675

70. Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B, Epoetin Alfa Study Group. 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. *J Clin Oncol* 2001;**19**:2865–74.

71. Österborg 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. *J Clin Oncol* 2002;**20**:2486–94. http://dx.doi.org/10.1200/JCO.2002.08.131

72. Silvestris F, Romito A, Fanelli P, Vacca A, Dammacco F. Long-term therapy with recombinant human erythropoietin (rHu-EPO) in progressing multiple myeloma. *Ann Hematol* 1995;**70**:313–18. http://dx.doi.org/10.1007/BF01696618

73. 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. *J Natl Cancer Inst* 2002;**94**:1211–20. http://dx.doi.org/10.1093/jnci/94.16.1211

74. Grote T, Yielding 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. *J Clin Oncol* 2005;**23**:9377–86. http://dx.doi.org/10.1200/JCO.2005.01.8507

75. 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. *Ann Oncol* 2009;**20**:1105–12. http://dx.doi.org/10.1093/annonc/mdn750

76. Strauss HG, Haensgen G, Dunst J, Hayward CR, Burger HU, Scherhag A, *et al.* Effects of anemia correction with epoetin beta in patients receiving radiochemotherapy for advanced cervical cancer. *Int J Gynecol Cancer* 2008;**18**:515–24. http://dx.doi.org/10.1111/j.1525-1438.2007.01032.x

77. Tjulandin SA, Bias P, Elsasser 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. *Arch Drug Inf* 2011;**4**:33–41. http://dx.doi.org/10.1111/j.1753-5174.2011.00035.x

78. 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 +/– darbepoetin alfa in primary breast cancer – results at the time of surgery. *Ann Oncol* 2011;**22**:1988–98. http://dx.doi.org/10.1093/annonc/mdq709

79. Österborg AB, Brandberg Y, Hedenus M. Impact of epoetin-beta on survival of patients with lymphoproliferative malignancies: long-term follow up of a large randomized study. *Br J Haematol* 2005;**129**:206–9. http://dx.doi.org/10.1111/j.1365-2141.2005.05440.x

80. Untch M, Minckwitz G, Konecny GE, Conrad U, Fett W, Kurzeder C, *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 with or without darbepoetin alfa in primary breast cancer – outcome on prognosis. *Ann Oncol* 2011;**22**:1999–2006. http://dx.doi.org/10.1093/annonc/mdq713

81. Bajetta E, Vercammen E, Reinhardt U, Janmohamed R, da Costa RM, Matulonis U, *et al.* Efficacy of epoetin alfa in a retrospective non-stratified subgroup analysis of a breast cancer cohort receiving non-platinum chemotherapy. *Tumori* 2004;**90**:449–57.

82. Aapro M, Bajetta E, Freund M, Littlewood TJ, Nortier JWR, Rapoport B. Is there a possible survival benefit to increasing hemoglobin levels with epoetin alfa during chemotherapy? *Eur J Cancer Suppl* 2004;**2**:20–8. http://dx.doi.org/10.1016/S1359-6349(03)00104-6

83. 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. *J Pain Symptom Manage* 2006;**31**:317–25. http://dx.doi.org/10.1016/j.jpainsymman.2005.08.013

84. 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. *Support Care Cancer* 2004;**12**:253–62. http://dx.doi.org/10.1007/s00520-003-0583-0

85. 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. *Semin Oncol* 1994;**21**:21–8.

86. Case DC Jr, Bukowski RM, Carey RW, Fishkin EH, Henry DH, Jacobson RJ, *et al.* Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *J Natl Cancer Inst* 1993;**85**:801–6. http://dx.doi.org/10.1093/jnci/85.10.801

87. Coiffier B, Boogaerts M, Kaine C, editors. *Impact of Epoetin Beta Versus Standard Care on Quality of Life in Patients with Malignant Disease*. 6th Congress of the European Haematology Association, Frankfurt, Germany, June 2001. Abstract no. 194.

88. Tonelli M, Lloyd A, Weibe N, Hemmelgarn B, Reiman T, Manns B, *et al. Erythropoiesis-Stimulating Agents for Anemia of Cancer or of Chemotherapy: Systematic Review and Economic Evaluation*. Technology report number 119. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

89. Grant MD, Piper M, Bohlius J, Tonia T, Nadege R, Vikrant V, *et al. Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update*. Chicago, IL: Blue Cross and Blue Shield Association Technology Evaluation Center; 2013.

90. Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J Natl Cancer Inst Monogr* 2004; (32):40–50. http://dx.doi.org/10.1093/jncimonographs/lgh027

91. Ross SD, Allen IE, Probst CA, Sercus B, Crean SM, Ranganathan G. Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: a systematic review and meta-analysis. *Oncologist* 2007;**12**:1264–73. http://dx.doi.org/10.1634/theoncologist.12-10-1264

92. Shehata N, Walker I, Meyer R, Haynes AE, Imrie K, Cancer Care Ontario Hematology Disease Site Group. The use of erythropoiesis-stimulating agents in patients with non-myeloid hematological malignancies: a systematic review. *Ann Hematol* 2008;**87**:961–73. http://dx.doi.org/10.1007/s00277-008-0525-5

93. Kvam AK, Fayers P, Hjermstad M, Gulbrandsen N, Wisloff F. Health-related quality of life assessment in randomised controlled trials in multiple myeloma: a critical review of methodology and impact on treatment recommendations. *Eur J Haematol* 2009;**83**:279–89. http://dx.doi.org/10.1111/j.1600-0609.2009.01303.x

94. Minton O, Stone P, Richardson A, Sharpe M, Hotopf M. Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev* 2010;**1**:CD006704. http://dx.doi.org/10.1002/14651858.cd006704.pub3

95. Bohlius JS, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, *et al.* Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet* 2009;**373**:1532–42. [Erratum published in *Lancet* 2009;**374**:28.] http://dx.doi.org/10.1016/S0140-6736(09)60502-X

96. Amgen Inc. *Erythropoiesis-Stimulating Agents (Epoetin and Darbepoetin) for Treating Cancer-Treatment Induced Anaemia (Including Review of TA 142): Aranesp® (Darbepoetin Alfa)*. Report presented to NICE as part of the MTA review. Cambridge: Amgen Inc. 2013.

97. Sandoz Ltd. *Erythropoiesis Agents for Treatment of Cancer-Treatment Induced Anaemia (Incl Review of TA 142): Binocrit® (Epoetin Alfa)*. Report presented to NICE as part of the MTA review. Camberley: Scandoz Ltd; 2013.

98. Sorgel F, Thyroff-Friesinger U, Vetter A, Vens-Cappell B, Kinzig M. Bioequivalence of HX575 (recombinant human epoetin alfa) and a comparator epoetin alfa after multiple intravenous administrations: an open-label randomised controlled trial. *BMC Clin Pharmacol* 2009;**9**:10. http://dx.doi.org/10.1186/1472-6904-9-10

99. Sorgel F, Thyroff-Friesinger U, Vetter A, Vens-Cappell B, Kinzig M. Bioequivalence of HX575 (recombinant human epoetin alfa) and a comparator epoetin alfa after multiple subcutaneous administrations. *Pharmacology* 2009;**83**:122–30. http://dx.doi.org/10.1159/000189027

100. Sorgel F, Thyroff-Friesinger U, Vetter A, Vens-Cappell B, Kinzig M. Biosimilarity of HX575 (human recombinant epoetin alfa) and epoetin beta after multiple subcutaneous administration. *Int J Clin Pharmacol Ther* 2009;**47**:391–401. http://dx.doi.org/10.5414/CPP47391

101. Weigang-Köhler K, Vetter A, Thyroff-Friesinger U. HX575, recombinant human epoetin alfa, for the treatment of chemotherapy-associated symptomatic anaemia in patients with solid tumours. *Onkologie* 2009;**32**:168–74. http://dx.doi.org/10.1159/000200783

102. Haag-Weber M, Vetter A, Thyroff-Friesinger U, INJ-Study Group. Therapeutic equivalence, long-term efficacy and safety of HX575 in the treatment of anemia in chronic renal failure patients receiving hemodialysis. *Clin Nephrol* 2009;**72**:380–90.

103. Desrame J, Stamerra O, Labourey JL, Toledano A, Dauriac C, Ianotto JC, *et al.*, editors. *Haemoglobin Outcomes with Biosimilar Epoetin Alfa in the Management of Chemotherapy-Induced Anaemia in Cancer Patients: First Results From OnCoBOS, A French Observational Study*. European Cancer Congress, Amsterdam, the Netherlands, 2013, abstract 1312.

104. Rodriguez Garzotto A, Cortijo Cascajares S, Pernaut Sanchez C, Otero Blas I, Ruiz Ares G, Rebollo Laserna FJ, *et al.*, editors. *Use of Erythropoiesis-Stimulating Agents and Comparison of Different Products for the Treatment of Chemotherapy-Induced Anaemia (CIA)*. European Cancer Congress, Amsterdam, the Netherlands, 2013, abstract 1320.

105. Lorenz A, Heine O, editors. *First Comparison of Biosimilar Epoetin Alfa and Darbepoetin Alfa for the Treatment of Chemotherapy-Induced Anaemia*. European Cancer Congress, Amsterdam, the Netherlands, 2013, abstract 1392.

106. Kerkhofs L, Boschetti G, Lugini A, Stanculeanu DL, Palomo AG. Use of biosimilar epoetin to increase haemoglobin levels in patients with chemotherapy-induced anemia: real-life clinical experience. *Future Oncol* 2012;**8**:751–6. http://dx.doi.org/10.2217/fon.12.39

107. Delarue R, Haioun C, Coiffier B, Fornecker L, Fournier M, Mounier N, *et al.* Survival effect of darbepoetin alfa in patients with diffuse large B-cell lymphoma (DLBCL) treated with immunochemotherapy: the LNH03-6B study. *J Clin Oncol* 2011;**29**(15 Suppl. 1):9048.

108. Hartmann JT, Metzner B, Binder C, Mergenthaler HG, Rick O, Sayer HG, *et al.* Addition of darbepoetin alfa to sequential high-dose VIP chemotherapy for patients with advanced metastatic germ cell cancer. *J Clin Oncol* 2012;**30**(Suppl. 1):e15026.

109. 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*. 20th Regional Congress of the International Society of Blood Transfusion, Nagoya, Japan, November 2009.

110. Nitz U, Oberhoff C, Reimer T, Schumacher C, Hackmann J, Warm M, *et al.* Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: a safety analysis from the Phase III ARA plus trial. *Cancer Res* 2009;**69**(Suppl.):4100. http://dx.doi.org/10.1158/0008-5472.SABCS-4100

111. 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 chemotherapyinduced anemia (CIA). 34th Congress of the European Society for Medical Oncology (ESMO), Stockholm, Sweden, September 2008. *Ann Oncol* 2008;**19**:viii277.

112. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;**24**:547–61. http://dx.doi.org/10.1016/S0885-3924(02)00529-8

113. Drummond MF, Sculpher MJ, Forrance GN, O'Brien BS, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd edn. Oxford: Oxford University Press; 2005.

114. Barosi G, Marchetti M, Liberato NL. Cost-effectiveness of recombinant human erythropoietin in the prevention of chemotherapy-induced anaemia *Br J Cancer* 1998;**78**:781–7. http://dx.doi.org/10.1038/bjc.1998.579

115. Cremieux PY, Finkelstein SN, Berndt ER, Crawford J, Slavin MB. Cost effectiveness, quality-adjusted life-years and supportive care: recombinant human erythropoietin as a treatment of cancer-associated anaemia. *Pharmacoeconomics* 1999;**16**:459–72. http://dx.doi.org/10.2165/00019053-199916050-00004

116. Martin SC, Gagnon DD, Zhang L, Bokemeyer C, Van Marwijk Kooy M, van Hout B. Cost-utility analysis of survival with epoetin-alfa versus placebo in stage IV breast cancer. *Pharmacoeconomics* 2003;**21**:1153–69. http://dx.doi.org/10.2165/00019053-200321160-00002

117. Ortega A, Dranitsaris G, Puodziunas AL. What are cancer patients willing to pay for prophylactic epoetin alfa? A cost–benefit analysis. 1998;**83**:2588–96.

118. Sheffield RE, Sullivan SD, Saltiel E, Nishimura L. Cost comparison of recombinant human erythropoietin and blood transfusion in cancer chemotherapy-induced anemia. *Ann Pharmacother* 1997;**31**:15–22.

119. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5.

120. Philips Z, Ginnely L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Health Technol Assess* 2004;**8**(36). http://dx.doi.org/10.3310/hta8360

121. Fagnoni P, Limat S, Chaigneau L, Briaud S, Schmitt B, Merrouche Y, *et al.* Clinical and economic impact of epoetin in adjuvant-chemotherapy for breast cancer. *Support Care Cancer* 2006;**14**:1030–7. http://dx.doi.org/10.1007/s00520-006-0062-5

122. Glaspy J, Tchekmedyian N, Gupta S. PCN17: comparing the cost-effectiveness of 3 mcg/kg Q2W darbepoetin alfa with standard dose epoetin alfa for anemia management in chemotherapy-treated cancer patients in United States. *Value Health* 2002;**5**:543. http://dx.doi.org/10.1016/S1098-3015(10)61433-7

123. Borget I, Tilleul P, Joly AC, Chouaid C. Incremental cost-effectiveness ratio of darbepoetin alfa (Aranesp (R)) in the treatment of chemotherapy-induced anemia in lung cancer patients. *Value Health*. 2006;**9**:A278–9. http://dx.doi.org/10.1016/S1098-3015(10)63440-7

124. Ben-Hamadi R, Duh MS, Aggarwal J, Henckler A, McKenzie RS, Tak Piech C. The cost-effectiveness of weekly epoetin alfa relative to weekly darbepoetin alfa in patients with chemotherapy-induced anemia. *Curr Med Res Opin* 2005;**21**:1677–82. http://dx.doi.org/10.1185/030079905X65501

125. Persson U, Borg S, Jansson S, Ekman T, Franksson L, Friesland S, *et al.* Epoetin alfa and darbepoetin alfa for the treatment of chemotherapy-related anemia in cancer patients in Sweden: comparative analysis of drug utilization, costs, and hematologic response. *Adv Ther* 2005;**22**:208–24. http://dx.doi.org/10.1007/BF02849930

126. Spaepen E, Demarteau N, Van Belle S, Annemans L. Health economic evaluation of treating anemia in cancer patients receiving chemotherapy: a study in Belgian hospitals. *Oncologist* 2008;**13**:596–607. http://dx.doi.org/10.1634/theoncologist.2007-0219

127. Pashos CL, Larholt K, Fraser KA, McKenzie RS, Senbetta M, Piech CT. Outcomes of erythropoiesis-stimulating agents in cancer patients with chemotherapy-induced anemia. *Support Care Cancer*. 2012;**20**:159–65. http://dx.doi.org/10.1007/s00520-010-1083-7

128. Cornes P, Coiffier B, Zambrowski JJ. Erythropoietic therapy for the treatment of anemia in patients with cancer: a valuable clinical and economic option. *Curr Med Res Opin* 2007;**23**:357–68. http://dx.doi.org/10.1185/030079906X167282

129. Herrmann R. Erythropoietin therapy in cancer-related anaemia, yes or no? *Intern Med J* 2008;**38**:749–50. http://dx.doi.org/10.1111/j.1445-5994.2008.01767.x

130. Marchetti M, Barosi G. Clinical and economic impact of epoetins in cancer care. *Pharmacoeconomics* 2004;**22**:1029–45. http://dx.doi.org/10.2165/00019053-200422160-00001

131. Reeder CE. Anemia in cancer and critical care patients: pharmacoeconomic considerations. *Am J Health Syst Pharm* 2007;**64**:S22–7. http://dx.doi.org/10.2146/ajhp060603

132. Stasi R, Amadori S, Littlewood TJ, Terzoli E, Newland AC, Provan D. Management of cancer-related anemia with erythropoietic agents: doubts, certainties, and concerns. *Oncologist* 2005;**10**:539–54. http://dx.doi.org/10.1634/theoncologist.10-7-539

133. Repetto L, Moeremans K, Annemans L. European guidelines for the management of chemotherapy-induced anaemia and health economic aspects of treatment. *Cancer Treat Rev* 2006;**32**:S5–9. http://dx.doi.org/10.1016/j.ctrv.2006.04.007

134. Roungrong J. Cost utility analysis of recombinant human erythropoietin in anemic cancer patients induced by chemotherapy in Thailand. *J Med Assoc Thai* 2008;**91**(Suppl. 2):S119–25.

135. Roungrong J, Teerawattananon Y, Chaikledkaew U. Cost–utility analysis of recombinant human erythropoietin in anaemic cancer patients induced by chemotherapy in Thailand. *J Med Assoc Thailand* 2008;**91**(Suppl. 2):S119–25.

136. Griggs JJ. Cost–utility of erythropoietin in the treatment of cancer-related anemia. *Med Decis Making* 1997;**17**:529.

137. Griggs JJ. Recombinant erythropoietin and blood transfusions in cancer chemotherapy-induced anemia. *Anticancer Drugs* 1998;**9**:925–32. http://dx.doi.org/10.1097/00001813-199811000-00012

138. Malonne H, editor. *Cost evaluation of erythropoiesis stimulating agents in the treatment of platinum chemotherapy induced anaemia*. 20th Annual Meeting of the Belgian Hematology Society, Genval, Belgium, January 2005.

139. Borget I, Tilleul P, Baud M, Joly AC, Chouaid C. Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. *Pharm World Sci* 2007;**29**:454.

140. Chouaid C, Borget I, Baud M, Joly AC, Daguenel A, Tilleul P. Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. *Lung Cancer* 2005;**49**:S23. http://dx.doi.org/10.1016/S0169-5002(05)80192-8

141. Finek J, Holubec L, Wiesnerova A, Pav Z, Dusek V. Darbepoetin alfa versus epoetin alfa for treatment of chemotherapy-induced anemia: a health economic evaluation. *Ann Oncol* 2010;**21**(Suppl. 8):344.

142. Klarenbach S, Manns B, Reiman T, Reaume MN, Lee H, Lloyd A, *et al.* Economic evaluation of erythropoiesis-stimulating agents for anemia related to cancer. *Cancer* 2010;**116**:3224–32. http://dx.doi.org/10.1002/cncr.25052

143. Szucs TD, Boogaerts M, Coiffier B, Kainz C. Cost-effectiveness of epoetin beta in the management of cancer-related anaemia. 6th Annual Congress of the European Haematology Association, Frankfurt, Germany, 21–24 June 2001.

144. Cremieux P, Greenberg P, Piech CT. Epoetin alfa is more effective and less costly relative to darbepoetin alfa in lung cancer patients receiving treatment for chemotherapy-induced anemia. *Proc Am Soc Clin Oncol* 2003;**22**:559.

145. Fragoulakis V, Maniadakis N. Economic evaluation of darbepoetin alpha in the management of patients with chemotherapy induced anemia (CIA) in Greece. *Value Health* 2011;**14**:A440. http://dx.doi.org/10.1016/j.jval.2011.08.1139

146. Mark TL, McKenzie SR, Piech CT. Better early and overall hematologic outcomes and lower drug cost with epoetin alfa (EPO) compared with darbepoetin alfa (DARB). *Blood* 2003;**102**:510B.

147. van Hout BA, Gagnon DD. The cost-effectiveness of epoetin alfa (Eprex) and darbepoetin alfa (Aranesp) in the treatment of chemotherapy-related anemia. *Hematol J* 2004;**5**:S176–7.

148. Ben-Hamadi R, Duh MS, Henckler A, McKenzie S, Fastenau J, Piech CT. Cost-effectiveness of once weekly epoetin alfa and darbepoetin alfa in treating chemotherapy-induced anemia. *J Clin Oncol* 2005;**23**:551S. http://dx.doi.org/10.1016/s1098-3015(10)62574-0

149. Van Bellinghen LA, Demarteau N, Annemans L, Bracco A. A cost–consequence analysis of darbepoetin alfa administered every 3 weeks (Q3W_DA) compared to weekly epoetin alfa (QW_EA) or epoetin beta (QW_EB) in patients with chemotherapy-induced anemia (CIA): a retrospective study. *Value Health* 2006;**9**:A286. http://dx.doi.org/10.1016/S1098-3015(10)63463-8

150. Esposito G, Lamotte M, Annemans L, Bracco A. Cost–consequence analysis of darbepoetin alfa administered every 3 weeks (Q3W_DA) compared to weekly epoetin alfa (QW_EA) or epoetin beta (QW_EB) in patients with chemotherapy-induced anemia (CIA): the Italian case. *Value Health* 2007;**10**:A324. http://dx.doi.org/10.1016/S1098-3015(10)65166-2

151. Van Bellinghen LA, Esposito G, Lamotte M, Bracco A, Goertz A, Annemans L. A cost–consequence analysis of darbepoetin alfa administered every 3 weeks (Q3W_DA) compared to weekly epoetin alfa (QW_EA) or epoetin beta (QW_EB) in patients with chemotherapy-induced anemia (CIA): the German case. *Value Health* 2007;**10**:A328. http://dx.doi.org/10.1016/S1098-3015(10)65177-7

152. Finek J, Holubec L, Wiesnerova A, Pav Z, Dusek L. Darbepoetin alfa versus epoetin alfa for treatment of chemotherapy-induced anemia: a health economic evaluation. *Value Health* 2010;**13**:A465. http://dx.doi.org/10.1016/S1098-3015(11)72978-3

153. Liwing J, Nasman P, Kernell H, Gagnon DD, Wu Y. Cost-effectiveness modelling of epoetin alfa and darbepoetin alfa in the treatment of chemotherapy-related anaemia in Sweden. *Value Health*. 2010;**13**:A38. http://dx.doi.org/10.1016/S1098-3015(10)72167-7

154. Walter E, Ribnicsek E, Kutikova L. Economic evaluation of darbepoetin alfa (Aranesp) compared to epoetin alfa (Erypo) and epoetin beta (NeoRecormon) in the treatment of chemotherapy-induced anemia (CIA) in Austria. *Value Health*. 2010;**13**:A377. http://dx.doi.org/10.1016/S1098-3015(11)72530-X

155. Duh MS, Weiner JR, White LA, Lefebvre P, Greenberg PE. Management of anaemia: a critical and systematic review of the cost effectiveness of erythropoiesis-stimulating agents. *Pharmacoeconomics* 2008;**26**:99–120. http://dx.doi.org/10.2165/00019053-200826020-00002

156. Borg S, Glenngard AH, Österborg A, Persson U. The cost-effectiveness of treatment with erythropoietin compared to red blood cell transfusions for patients with chemotherapy induced anaemia: a Markov model. *Acta Oncol* 2008;**47**:1009–17. http://dx.doi.org/10.1080/02841860701744498

157. Borget I, Tilleul P, Baud M, Joly AC, Daguenel A, Chouaid C. Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. *Lung Cancer* 2006;**51**:369–76. http://dx.doi.org/10.1016/j.lungcan.2005.10.024

158. Aapro M, Cornes P, Sun D, Abraham I. Comparative cost efficiency across the European G5 countries of originators and a biosimilar erythropoiesis-stimulating agent to manage chemotherapy-induced anemia in patients with cancer. *Ther Adv Med Oncol* 2012;**4**:95–105. http://dx.doi.org/10.1177/1758834012444499

159. Ossa DF, Briggs A, McIntosh E, Cowell W, Littlewood T, Sculpher M. Recombinant erythropoietin for chemotherapy-related anaemia: economic value and health-related quality-of-life assessment using direct utility elicitation and discrete choice experiment methods. *Pharmacoeconomics* 2007;**25**:223–37. http://dx.doi.org/10.2165/00019053-200725030-00005

160. Reed SD, Radeva JI, Daniel DB, Mody SH, Forlenza JB, McKenzie RS, *et al.* Economic evaluation of weekly epoetin alfa versus biweekly darbepoetin alfa for chemotherapy-induced anaemia: evidence from a 16-week randomised trial. *Pharmacoeconomics* 2006;**24**:479–94. http://dx.doi.org/10.2165/00019053-200624050-00006

161. Casadevall N, Durieux P, Dubois S, Hemery F, Lepage E, Quarre MC, *et al.* Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. *Blood* 2004;**104**:321–7. http://dx.doi.org/10.1182/blood-2003-07-2252

162. Crawford J, Cella D, Cleeland CS, Cremieux PY, Demetri GD, Sarokhan BJ, *et al.* Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer* 2002;**95**:888–95. http://dx.doi.org/10.1002/cncr.10763

163. Evers S. *CHEC Project*. The Netherlands: Maastricht University; 2015. URL: www.maastrichtuniversity.nl/web/Institutes/Theme/DepartmentsCAPHRI/HealthServicesResearch/ResearchHSR/CHECProject.htm (accessed 12 November 2015).

164. Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S, Vadhan-Raj S. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community Oncology practice. Procrit Study Group. *J Clin Oncol* 1997;**15**:1218–34.

165. Abels RI. Recombinant human erythropoietin in the treatment of the anaemia of cancer. *Acta Haematol* 1992;**87**(Suppl. 1):4–11. http://dx.doi.org/10.1159/000204780

166. Joint Formulary Committee. *British National Formulary*. 66 ed. London: BMJ Group and Pharmaceutical Press; 2013.

167. Witzig TE, Silberstein PT, Loprinzi CL, Sloan JA, Novotny PJ, Mailliard JA, *et al.* Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. *J Clin Oncol* 2005;**23**:2606–17. http://dx.doi.org/10.1200/JCO.2004.10.020

168. Kotasek D, Canon J-L, San Miguel J, Hedenus M, Hendricks L, Rossi G, *et al*. Correction/maintenance dosing (front loading) of darbepoetin alfa: final results from a randomized Phase 3 active controlled trial. *Blood* 2004;**104**:1636.

169. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal*. London: NICE; 2013.

170. Latimer N. *NICE DSU Technical Support Document 14: Undertaking Survival Analysis for Economic Evaluations Alongside Clinical Trials – Extrapolation with Patient-Level Data*. 2011 (last updated March 2013). URL: www.nicedsu.org.uk/ (accessed 16 August 2015).

171. Latimer NR. Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Med Decis Making* 2013;**33**:743–54. http://dx.doi.org/10.1177/0272989X12472398

172. Varney SJ, Guest JF. The annual cost of blood transfusions in the UK. Transfusion medicine (Oxford, England). 2003;**13**:205–18. http://dx.doi.org/10.1046/j.1365-3148.2003.00443.x

173. Office for National Statistics. *Interim Life Tables, 2010–2012*. London: ONS; 2013. URL: www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2010-2012/index.html (accessed 8 August 2015).

174. Ossa DF, Briggs A, Cowell W, Littlewood T, Sculpher M. Utility associated with severity of cancer-related anaemia (CRA): a societal valuation. *Value Health* 2004;**7**:680. http://dx.doi.org/10.1016/s1098-3015(10)65767-1

175. Papaioannou D, Brazier J, Paisley S. *NICE DSU Technical Support Document 9: the Identification, Review and Synthesis of Health State Utility Values from the Literature*. October 2010. URL: www.nicedsu.org.uk/ (accessed 16 August 2015).

176. Harrow BS, Eaton CB, Roberts MB, Assaf AR, Luo X, Chen Z. Health utilities associated with hemoglobin levels and blood loss in postmenopausal women: the Women's Health Initiative. *Value Health* 2011;**14**:555–63. http://dx.doi.org/10.1016/j.jval.2010.11.008

177. Lloyd A, van Hanswijck de Jonge P, Doyle S, Cornes P. Health state utility scores for cancer-related anemia through societal and patient valuations. *Value Health* 2008;**11**:1178–85. http://dx.doi.org/10.1111/j.1524-4733.2008.00394.x

178. Tajima R, Kondo M, Kai H, Saito C, Okada M, Takahashi H, *et al.* Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D). *Clin Exp Nephrol* 2010;**14**:340–8. http://dx.doi.org/10.1007/s10157-010-0304-1

179. Wisloff F, Gulbrandsen N, Hjorth M, Lenhoff S, Fayers P. Quality of life may be affected more by disease parameters and response to therapy than by haemoglobin changes. *Eur J Haematol* 2005;**75**:293–8. http://dx.doi.org/10.1111/j.1600-0609.2005.00509.x

180. Dakin H. Review of studies mapping from quality of life or clinical measures to EQ-5D: an online database. *Health Qual Life Outcomes* 2013;**11**:151. http://dx.doi.org/10.1186/1477-7525-11-151

181. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Econ* 2004;**13**:873–84. http://dx.doi.org/10.1002/hec.866

182. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. 2010;**13**:509–18. http://dx.doi.org/10.1111/j.1524-4733.2010.00700.x

183. Office for National Statistics. *Statistical Bulletin: Cancer Registration Statistics, England, 2011*. London: ONS; 2011. URL: www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations–england–series-mb1-/no–42–2011/stb-cancer-statistics-registrations-2011.html (accessed 8 August 2015).

184. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care* 2000;**38**:583–637. http://dx.doi.org/10.1097/00005650-200006000-00004

185. Hoyle M, Crathorne L, Peters J, Jones-Hughes T, Cooper C, Napier M, *et al.* The clinical effectiveness and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal no.150 and part review of technology appraisal no. 118): a systematic review and economic model. *Health Technol Assess* 2013;**17**(14). http://dx.doi.org/10.3310/hta17140

186. Pavey T, Hoyle M, Ciani O, Crathorne L, Jones-Hughes T, Cooper C, *et al.* Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. *Health Technol Assess* 2012;**16**(42). http://dx.doi.org/10.3310/hta16420

187. Curtis L. *Unit Costs of Health and Social Care 2012*. Canterbury: Personal Social Services Research Unit; 2012.

188. Curtis L. *Unit Costs of Health and Social Care 2013*. Canterbury: Personal Social Services Research Unit; 2013.

189. Information Centre. *2006/07 UK General Practice Workload Survey*. Leeds: The Information Centre; 2007.

190. Department of Health. *NHS Reference Costs 2012–2013*. London: Department of Health; 2013.

191. NHS Blood and Transplant. *NHSBT Price List 2013/2014*. London: Department of Health; 2013.

192. National Commissioning Group for Blood. *Update on the Cost of Blood Components and Prices for the Provision of Diagnostic Services for 2008/09 from the National Blood Service (NBS)*. London: Department of Health; 2007.

193. Vaupel P. Hypoxia and aggressive tumor phenotype: implications for therapy and prognosis. *Oncologist* 2008;**13**:21–6. http://dx.doi.org/10.1634/theoncologist.13-S3-21

194. Arcasoy MO, Amin K, Chou SC, Haroon ZA, Varia M, Raleigh JA. Erythropoietin and erythropoietin receptor expression in head and neck cancer: relationship to tumor hypoxia. *Clin Cancer Res* 2005;**11**:20–7.

195. Nunnaly JC. *Psychometric Theory*, 2nd edn. New York, NY: McGraw Hill; 1978.

196. Cazzola M, Beguin Y. New tools for clinical evaluation of erythron function in man. *Br J Haematol* 1992;**80**:278–84. http://dx.doi.org/10.1111/j.1365-2141.1992.tb08133.x

197. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 1975;**36**:842–54. http://dx.doi.org/10.1002/1097-0142(197509)36:3<842::AID-CNCR2820360303>3.0.CO;2-U

198. Moebus V, Jackisch C, Lueck HJ, du Bois A, Thomssen C, Kurbacher C, *et al.* Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol* 2010;**28**:2874–80. http://dx.doi.org/10.1200/JCO.2009.24.7643

199. Moebus V, Untch M, du Bois A, Lueck HJ, 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. *J Clin Oncol* 2004;**22**(Suppl.):abstract 513.

200. Moebus VJ, Lueck HJ, Thomssen C, Kuhn W, Kurbacher C, Nitz U, *et al.* Dose-dense sequential chemotherapy with epirubicin (E), paclitaxel (T) and cyclophosphamide (C) (ETC) in comparison to conventional dosed chemotherapy in high-risk breast cancer patients (≥ 4 + LN). Mature results of an AGO-trial. *Breast Cancer Res Treat* 2007;**103**:abstract 43.

201. Ray-Coquard I, Le Cesne A, Rubio MT, Mermet J, Maugard C, Ravaud A, *et al.* Risk model for severe anemia requiring red blood cell transfusion after cytotoxic conventional chemotherapy regimens. The Elypse 1 Study Group. *J Clin Oncol* 1999;**17**:2840–6.

202. Tchekmedyian NS, Kallich J, McDermott A, Fayers P, Erder MH. The relationship between psychologic distress and cancer-related fatigue. *Cancer* 2003;**98**:198–203. http://dx.doi.org/10.1002/cncr.11463

203. Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Österborg A, *et al.* EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. *Eur J Cancer* 2004;**40**:2201–16. http://dx.doi.org/10.1016/j.ejca.2004.07.015

204. Minton O, Stone P, Richardson A, Sharpe M, Hotopf M. Drug therapy for the management of cancer related fatigue. *Cochrane Database Syst Rev* 2008;**1**:CD006704. http://dx.doi.org/10.1002/14651858.cd006704.pub2

205. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. *J Natl Cancer Inst* 2008;**100**:1155–66. http://dx.doi.org/10.1093/jnci/djn250

206. Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, *et al.* Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2006;**3**:CD003407. http://dx.doi.org/10.1002/14651858.cd003407.pub4

207. Bohlius J, Langensiepen S, Schwarzer G, Seidenfeld J, Piper M, Bennett C, *et al.* Recombinant human erythropoietin and overall survival in cancer patients: results of a comprehensive meta-analysis. *J Natl Cancer Inst* 2005;**97**:489–98. http://dx.doi.org/10.1093/jnci/dji087

208. 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. *J Natl Cancer Inst* 2006;**98**:708–14. http://dx.doi.org/10.1093/jnci/djj189

209. Bohlius JF, Langensiepen S, Engert A, Schwarzer G, Bennett CL. Effectiveness of erythropoietin in the treatment of patients with malignancies: methods and preliminary results of a Cochrane review. *Best Pract Res Clin Haematol* 2005;**18**:449–54. http://dx.doi.org/10.1016/j.beha.2005.01.022

210. 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**:102–10. http://dx.doi.org/10.1159/000067766

211. Cascinu S, Fedeli A, Del Ferro E, Luzi Fedeli S, Catalano G. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double-blind trial with placebo. *J Clin Oncol* 1994;**12**:1058–62.

212. 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**:4446–53.

213. 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. *J Pain Symptom Manage* 2003;**25**:512–18. http://dx.doi.org/10.1016/S0885-3924(03)00070-8

214. 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. *Int J Clin Oncol* 2001;**6**:296–301. http://dx.doi.org/10.1007/s10147-001-8031-y

215. 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. *Ann Oncol* 1998;**9**:255–60. http://dx.doi.org/10.1023/A:1008296622469

216. Österborg 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. The European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma. *Blood* 1996;**87**:2675–82.

217. 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. *Clin Cancer Res* 2003;**9**:1689–97.

218. Throuvalas N, Antonadu D, Boufi M, Lavey RS, Malamos N, editors. *Erythropoietin decreases transfusion requirements during radiochemotherapy*. American Society of Clinical Oncology Annual Meeting, New Orleans, LA, USA, May 2000, abstract 1558.

219. Welch RS, James RD, Wilkinson PM, Belli F, Cowan RA. Recombinant human erythropoietin and platinum-based chemotherapy in advanced ovarian cancer. *Canc J Sci Am* 1995;**1**:261–6.

220. Aapro M, Scherhag A, Burger HU. Effect of treatment with epoetin-beta on survival, tumour progression and thromboembolic events in patients with cancer: an updated meta-analysis of 12 randomised controlled studies including 2301 patients. *Br J Cancer* 2008;**99**:14–22. http://dx.doi.org/10.1038/sj.bjc.6604408

221. Aapro M, Scherhag A, Osterwalder B, Ukarma L, Burger HU. Epoetin beta treatment in patients with cancer chemotherapy induced anaemia: the impact of initial haemoglobin and target haemoglobin levels on survival, tumour progression and thromboembolic events. International MASCC/IS00 Symposium, Rome, June 2009. *Support Care Cancer* 2009;**17**:1036–7.

222. Berndt E, Kallich J, McDermott A, Xu X, Lee H, Glaspy J. Reductions in anaemia and fatigue are associated with improvements in productivity in cancer patients receiving chemotherapy. *Pharmacoeconomics* 2005;**23**:505–14. http://dx.doi.org/10.2165/00019053-200523050-00009

223. Blohmer JU, Paepke S, Sehouli J, Boehmer D, Kolben M, Wurschmidt 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. *J Clin Oncol* 2011;**29**:3791–7. http://dx.doi.org/10.1200/JCO.2010.30.4899

224. 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**:848–55. http://dx.doi.org/10.1002/cncr.26341

225. Chang J, Couture FA, Young SD, Lau CY, McWatters KL. Weekly administration of epoetin alfa improves cognition and quality of life in patients with breast cancer receiving chemotherapy. *Support Cancer Ther* 2004;**2**:52–8. http://dx.doi.org/10.3816/SCT.2004.n.023

226. 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**:727–37. http://dx.doi.org/10.1634/theoncologist.12-6-727

227. Christodoulou C, Dafni U, Aravantinos G, Koutras A, Samantas E, Karina M, *et al.* Effects of epoetin-alpha on quality of life of cancer patients with solid tumors receiving chemotherapy. *Anticancer Res* 2009;**29**:693–702.

228. Engert A, Josting A, Haverkamp H, Villalobos M, Lohri A, Sokler M, *et al.* Epoetin alfa in patients with advanced-stage Hodgkin's lymphoma: results of the randomized placebo-controlled GHSG HD15EPO trial. *J Clin Oncol* 2010;**28**:2239–45. http://dx.doi.org/10.1200/JCO.2009.25.1835

229. Fujisaka Y, Sugiyama T, Saito H, Nagase S, Kudoh S, Endo M, *et al.* Randomised, Phase III trial of epoetin-beta to treat chemotherapy-induced anaemia according to the EU regulation. *Br J Cancer* 2011;**105**:1267–72. http://dx.doi.org/10.1038/bjc.2011.395

230. Glaspy J, Vadhan-Raj S, Patel R, Bosserman L, Hu E, Lloyd RE, *et al.* Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia: the 20030125 study group trial. *J Clin Oncol* 2006;**24**:2290–7. http://dx.doi.org/10.1200/JCO.2005.03.8570

231. Gupta S, Singh PK, Bisth SS, Bhatt ML, Pant M, Gupta R, *et al.* Role of recombinant human erythropoietin in patients of advanced cervical cancer treated 'by chemoradiotherapy.' *Cancer Biol Ther* 2009;**8**:13–17. http://dx.doi.org/10.4161/cbt.8.1.7089

232. 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. *Curr Med Res Opin* 2009;**25**:2109–20. http://dx.doi.org/10.1185/03007990903084164

233. 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. *J Clin Oncol* 2005;**23**:5960–72. http://dx.doi.org/10.1200/JCO.2005.06.150

234. Milroy R, Bajetta E, van den Berg PM, O'Brien MER, 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. *Eur J Clin Med Oncol* 2011;**3**:49–56.

235. Nagel S, Kellner O, Engel-Riedel W, Guetz S, Schumann C, Gieseler F, *et al.* Addition of darbepoetin alfa to dose-dense chemotherapy: results from a randomized Phase II trial in small-cell lung cancer patients receiving carboplatin plus etoposide. *Clin Lung Cancer* 2011;**12**:62–9. http://dx.doi.org/10.3816/CLC.2011.n.009

236. 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. *Clin Breast Cancer* 2005;**5**:439–46. http://dx.doi.org/10.3816/CBC.2005.n.002

237. 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. *J Clin Oncol* 2008;**26**:2342–9. http://dx.doi.org/10.1200/JCO.2007.15.0748

238. 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**:935–43. http://dx.doi.org/10.1634/theoncologist.2009-0279

239. 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. *J Clin Oncol* 2006;**24**:3583–9. http://dx.doi.org/10.1200/JCO.2005.03.4371

240. Reed SD, Radeva JI, Daniel DB, Fastenau JM, Williams D, Schulman KA. Early hemoglobin response and alternative metrics of efficacy with erythropoietic agents for chemotherapy-related anemia. *Curr Med Res Opin* 2005;**21**:1527–33. http://dx.doi.org/10.1185/030079905X65394

241. Waltzman R, Croot C, Justice GR, Fesen MR, Charu V, Williams D. Randomized comparison of epoetin alfa (40,000 U weekly) and darbepoetin alfa (200 microg every 2 weeks) in anemic patients with cancer receiving chemotherapy. *Oncologist* 2005;**10**:642–50. http://dx.doi.org/10.1634/theoncologist.10-8-642

242. Rosenzweig MQ, Bender CM, Lucke JP, Yasko JM, Brufsky AM. The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. *J Pain Symptom Manage* 2004;**27**:185–90. http://dx.doi.org/10.1016/j.jpainsymman.2003.06.010

243. 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**:197–205. http://dx.doi.org/10.1634/theoncologist.11-2-197

244. Savonije JH, van Groeningen CJ, Wormhoudt LW, Giaccone G. Early intervention with epoetin alfa during platinum-based chemotherapy: an analysis of the results of a multicenter, randomized, controlled trial based on initial hemoglobin level. *Oncologist* 2006;**11**:206–16. http://dx.doi.org/10.1634/theoncologist.11-2-206

245. Savonije JH, van Groeningen CJ, van Bochove A, Honkoop AH, van Felius CL, Wormhoudt LW, *et al.* 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. *Eur J Cancer* 2005;**41**:1560–9. http://dx.doi.org/10.1016/j.ejca.2005.03.024

246. Schwartzberg LS, Yee LK, Senecal FM, Charu V, Tomita D, Wallace J, *et al.* A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. *Oncologist* 2004;**9**:696–707. http://dx.doi.org/10.1634/theoncologist.9-6-696

247. Senecal FM, Yee L, Gabrail N, Charu V, Tomita D, Rossi G, *et al.* Treatment of chemotherapy-induced anemia in breast cancer: results of a randomized controlled trial of darbepoetin alfa 200 microg every 2 weeks versus epoetin alfa 40,000 U weekly. *Clin Breast Cancer* 2005;**6**:446–54. http://dx.doi.org/10.3816/CBC.2005.n.050

248. Thomas G, Ali S, Hoebers FJ, 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. *Gynecol Oncol* 2008;**108**:317–25. http://dx.doi.org/10.1016/j.ygyno.2007.10.011

249. 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. *Jpn J Clin Oncol* 2009;**39**:163–8. http://dx.doi.org/10.1093/jjco/hyn151

250. Wilkinson PM, Antonopoulos M, Lahousen M, Lind M, Kosmidis P. Epoetin alfa in platinum-treated ovarian cancer patients: results of a multinational, multicentre, randomised trial. *Br J Cancer* 2006;**94**:947–54. http://dx.doi.org/10.1038/sj.bjc.6603004

251. 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. *J Clin Oncol* 2009;**27**:644–6. http://dx.doi.org/10.1200/JCO.2008.20.4966

252. Strauss HG, Haensgen G, Dunst J, Hayward C, Koelbl H. Effects of anaemia correction with epoetin beta in patients with advanced cervical cancer and radiochemotherapy. *J Clin Oncol* 2005;**23**(Suppl.):5121.

253. Delarue R, Tilly H, Mounier N, Petrella T, Salles G, Thieblemont C, *et al.* Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol* 2013;**14**:525–33. http://dx.doi.org/10.1016/S1470-2045(13)70122-0

254. Boccia R, Malik IA, Raja V, Kahanic S, Liu R, Lillie T, *et al.* Darbepoetin alfa administered every three weeks is effective for the treatment of chemotherapy-induced anemia. *Oncologist* 2006;**11**:409–17. http://dx.doi.org/10.1634/theoncologist.11-4-409

255. Boccia R, Lillie T, Tomita D, Balducci L. The effectiveness of darbepoetin alfa administered every 3 weeks on hematologic outcomes and quality of life in older patients with chemotherapy-induced anemia. *Oncologist* 2007;**12**:584–93. http://dx.doi.org/10.1634/theoncologist.12-5-584

256. Glaspy J. Assessment of early and standard intervention with procrit® (epoetin alfa) 120,000 units once every three weeks (q3w) in patients with cancer receiving chemotherapy. *Blood* 2006;**108**:abstract 3774.

257. Gregory SA. Efficacy of darbepoetin alfa in the treatment of chemotherapy-induced anemia in non-Hodgkin's lymphoma. *Support Cancer Ther* 2006;**3**:232–9. http://dx.doi.org/10.3816/SCT.2006.n.021

258. Gabrilove JL, Perez EA, Tomita DK, Rossi G, Cleeland CS. Assessing symptom burden using the MD Anderson symptom inventory in patients with chemotherapy-induced anemia: results of a multicenter, open-label study (SURPASS) of patients treated with darbepoetin-alpha at a dose of 200 microg every 2 weeks. *Cancer* 2007;**110**:1629–40. http://dx.doi.org/10.1002/cncr.22943

259. Larholt K, Pashos CL, Wang Q, Bookhart B, McKenzie RS, Piech CT. Dosing and Outcomes Study of Erythropoiesis-Stimulating Therapies (DOSE): a registry for characterizing anaemia management and outcomes in oncology patients. *Clin Drug Investig* 2008;**28**:159–67. http://dx.doi.org/10.2165/00044011-200828030-00003

260. Dammacco F. *A Placebo-Controlled Study on the Effect of Epoetin Alfa in Subjects with Multiple Myeloma Followed by an Open-Label Extension*. XIVth Meeting of the International Society of Haematology, Oral Session 10. Stockholm: 1997;**O-046**:49.

261. Dammacco F. A placebo-controlled study on the effect of epoetin alfa in subjects with multiple myeloma followed by an open-label extension. *Eur J Cancer* 1997;**33**(Suppl. 8):394. http://dx.doi.org/10.1016/S0959-8049(97)84828-9

262. Dammacco F, Castoldi G, Roedjer S. A placebo-controlled study on the effect of epoetin alfa in subjects with multiple myeloma followed by an open-label extension. *Blood* 1997;**90**(Suppl. 1):358a.

263. Reddy PK, Williams D, Wilhelm FE. An open-label pilot to evaluate a flexible dosing regimen of epoetin alfa for the treatment of chemotherapy-induced anemia: 60,000 units weekly followed by 60,000 units every 2 weeks. *Support Cancer Ther* 2006;**4**:56–62. http://dx.doi.org/10.3816/SCT.2006.n.032

264. Justice G, Kessler JF, Jadeja J, Campos L, Weick J, Chen CF, *et al.* A randomized, multicenter study of subcutaneous and intravenous darbepoetin alfa for the treatment of chemotherapy-induced anemia. *Ann Oncol* 2005;**16**:1192–8. http://dx.doi.org/10.1093/annonc/mdi218

265. Kotasek D, Canon JL, Mateos MV, Hedenus M, Rossi G, Taylor K. A randomized, controlled trial comparing darbepoetin alfa correction/maintenance dosing with weekly dosing for treating chemotherapy-induced anemia. *Curr Med Res Opin* 2007;**23**:1387–401. http://dx.doi.org/10.1185/030079907X188053

266. 20030125 Study Group Trial, Glaspy J, Vadhan-Raj S, Patel R, Bosserman L, Hu E, *et al.* Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia: the 20030125 Study Group Trial. *J Clin Oncol* 2006;**24**:2290–7. http://dx.doi.org/10.1200/JCO.2005.03.8570

267. Montoya VP, Xie J, Williams D, Woodman RC, Wilhelm FE. An extended maintenance dosing regimen of epoetin alfa 80,000 U every 3 weeks in anemic patients with cancer receiving chemotherapy. *Support Care Cancer* 2007;**15**:1385–92. http://dx.doi.org/10.1007/s00520-007-0263-6

268. Charu V, Saidman B, Ben-Jacob A, Justice GR, Maniam AS, Tomita D, *et al.* A randomized, open-label, multicenter trial of immediate versus delayed intervention with darbepoetin alfa for chemotherapy-induced anemia. *Oncologist* 2007;**12**:1253–63. http://dx.doi.org/10.1634/theoncologist.12-10-1253

269. Bastit L, Vandebroek A, Altintas S, Gaede B, Pintér 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. *J Clin Oncol* 2008;**26**:1611–18. http://dx.doi.org/10.1200/JCO.2006.10.4620

270. Gregory SA, Williams D. Epoetin alfa 60,000 U QW followed by Q2W maintenance dosing corrects anemia and maintains hemoglobin (Hb) in anemic patients with cancer receiving chemotherapy. *Blood* 2003;**102**:166b (abstract 4373).

271. Baltz B, Gregory SA, Ehmann WC, Williams D. Initial dosing of epoetin alfa 60,000 U qw followed by q2w maintenance for anemic patients with cancer receiving chemotherapy. *J Clin Oncol* 2004;**22**(Suppl. 14):abstract 8212.

272. Gregory SA, Baltz B, Williams D. Every-two-week (Q2W) maintenance dosing with epoetin alfa in anemic patients with cancer receiving chemotherapy: 60,000 U qw to target Hb 12 g/dl, followed by 60,000 U q2w. *Blood* 2004;**104**:144b (abstract 4233.5).

273. Gregory SA, Xie J, Woodman RC. Maintenance dosing with epoetin alfa every two weeks (q2w) in anemic patients with cancer receiving chemotherapy every one or four weeks: final results. *Blood* 2005;**106**:abstract 3770.

274. Glaspy JA, Charu V, Luo D, Moyo V, Kamin M, Wilhelm FE. Initiation of epoetin-alpha therapy at a starting dose of 120,000 units once every 3 weeks in patients with cancer receiving chemotherapy: an open-label, multicenter study with randomized and nonrandomized treatment arms. *Cancer* 2009;**115**:1121–31. http://dx.doi.org/10.1002/cncr.24127

275. Steensma DP, Molina R, Sloan JA, Nikcevich DA, Schaefer PL, Rowland KM Jr, *et al.* Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. *J Clin Oncol* 2006;**24**:1079–89. http://dx.doi.org/10.1200/JCO.2005.02.7276

276. Steensma DP, Molina R, Sloan JA, Nikcevich DA, Schaefer PL, Roland KM Jr, *et al.* A Phase III randomized trial of two different dosing schedules of erythropoietin (EPO) in patients with cancer-associated anemia: North Central Cancer Treatment Group (NCCTG) study N02C2. *J Clin Oncol* 2005;**23**(Suppl. 16):A-8031.

277. Straus DJ, Testa MA, Sarokhan BJ, Czuczman MS, Tulpule A, Turner RR, *et al*. Quality-of-life and health benefits of early treatment of mild anemia: a randomized trial of epoetin alfa in patients receiving chemotherapy for hematologic malignancies. *Cancer* 2006;**107**:1909–17. http://dx.doi.org/10.1002/cncr.22221

278. Glaspy J, Henry D, Patel R, Tchekmedyian S, Applebaum S, Berdeaux D, *et al.* Effects of chemotherapy on endogenous erythropoietin levels and the pharmacokinetics and erythropoietic response of darbepoetin alfa: a randomised clinical trial of synchronous versus asynchronous dosing of darbepoetin alfa. *Eur J Cancer* 2005;**41**:1140–9. http://dx.doi.org/10.1016/j.ejca.2005.01.021

279. 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**:715–24. http://dx.doi.org/10.1634/theoncologist.2007-0241

280. Canon JL, Vansteenkiste J, Bodoky G, Mateos MV, Bastit L, Ferreira I, *et al.* Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. *J Natl Cancer Inst* 2006;**98**:273–84. http://dx.doi.org/10.1093/jnci/djj053

281. Canon JL, Vansteenkiste J, Hedenus M, Gascon P, Bokemeyer C, Ludwig H, *et al.* Transfusion risk in cancer patients with chemotherapy-induced anemia when initiating darbepoetin alfa therapy at a baseline hemoglobin level of < 9 g/dl versus 9 to < 10 g/dl versus ≥ 10 g/dl: an exploratory analysis of a phase 3 trial. *Med Oncol* 2012;**29**:2291–9. http://dx.doi.org/10.1007/s12032-011-0103-x

282. Vansteenkiste J, Hedenus M, Gascon P, Bokemeyer C, Ludwig H, Vermorken J, *et al.* Darbepoetin alfa for treating chemotherapy-induced anemia in patients with a baseline hemoglobin level < 10 g/dl versus > or = 10 g/dl: an exploratory analysis from a randomized, double-blind, active-controlled trial. *BMC Cancer* 2009;**9**:311. http://dx.doi.org/10.1186/1471-2407-9-311

283. Schwartzberg L, Burkes R, Mirtsching B, Rearden T, Silberstein P, Yee L, *et al.* Comparison of darbepoetin alfa dosed weekly (QW) vs. extended dosing schedule (EDS) in the treatment of anemia in patients receiving multicycle chemotherapy in a randomized, phase 2, open-label trial. *BMC Cancer* 2010;**10**:581. http://dx.doi.org/10.1186/1471-2407-10-581

284. Schouwink JH, Codrington H, Sleeboom HP, Kerkhofs LG, Wormhoudt LW. Prevention of anaemia by early intervention with once weekly epoetin alfa during chemotherapy. *Eur J Cancer* 2008;**44**:819–29. http://dx.doi.org/10.1016/j.ejca.2008.02.017

285. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, *et al.* The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;**11**:570–9.

286. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83. http://dx.doi.org/10.1097/00005650-199206000-00002

287. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. *J R Coll Gen Pract* 1985;**35**:185–8.

288. Bowling A. *Measuring Health, A Guide to Rating Scales and Questionnaires*. Buckingham: Oxford University Press; 1997.

289. Bretscher M, Rummans T, Sloan J, Kaur J, Bartlett A, Borkenhagen L, *et al.* Quality of life in hospice patients. A pilot study. *Psychosomatics* 1999;**40**:309–13. http://dx.doi.org/10.1016/S0033-3182(99)71224-7

290. Sloan JA, Loprinzi CL, Kuross SA, Miser AW, O'Fallon JR, Mahoney MR, *et al.* Randomized comparison of four tools measuring overall quality of life in patients with advanced cancer. *J Clin Oncol* 1998;**16**:3662–73.

291. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med* 1983;**13**:595–605. http://dx.doi.org/10.1017/S0033291700048017

292. Morasso G, Costantini M, Baracco G, Borreani C, Capelli M. Assessing psychological distress in cancer patients: validation of a self-administered questionnaire. *Oncology* 1996;**53**:295–302. http://dx.doi.org/10.1159/000227576

293. de Haes J, Curran D, Young T, Bottomley A, Flechtner H, Aaronson N, *et al.* Quality of life evaluation in oncological clinical trials – the EORTC model. The EORTC Quality of Life Study Group. *Eur J Cancer* 2000;**36**:821–5. http://dx.doi.org/10.1016/S0959-8049(00)00007-1

294. Michallet M, Goldet K, Sobh M, Morisset S, Chelghoum Y, Thomas X, *et al.* Prospective study of erythropoietin use on quality of life and cost effectiveness in acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation patients. *Cancer* 2013;**119**:107–14. http://dx.doi.org/10.1002/cncr.27686

Appendix 1 Literature search strategies

Clinical effectiveness

MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to May Week 3 2013.

Date searched: 24 May 2013.

Searcher: SB.

Hits: 342.

Strategy

1. (erythropoietin* or EPO).tw.
2. Erythropoietin/
3. Receptors, erythropoietin/
4. erythropoiesis.tw.
5. Erythropoiesis/
6. (epoetin adj1 (alfa or beta or theta or zeta)).tw.
7. darbepoetin.tw.
8. CERA.tw.
9. (eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp).tw.
10. or/1-9
11. an?emi?.tw.
12. exp anemia/
13. 11 or 12
14. (cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumo?r* or myelo* or lymphoma* or oncolog* or chemotherap*).tw.
15. exp neoplasms/
16. 14 or 15
17. (random* or rct* or "controlled trial*" or "clinical trial*").tw.
18. randomized controlled trial.pt.
19. 17 or 18
20. 10 and 13 and 16 and 19
21. limit 20 to (english language and yr="2004 -Current")

MEDLINE(R) In-Process & Other Non-Indexed Citations

Host: Ovid.

Data parameters: 23 May 2013.

Date searched: 24 May 2013.

Searcher: SB.

Hits: 28.

Strategy

1. (erythropoietin* or EPO).tw.
2. erythropoiesis.tw.
3. (epoetin adj1 (alfa or beta or theta or zeta)).tw.
4. darbepoetin.tw.
5. CERA.tw.
6. (eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp).tw.
7. or/1-6
8. an?emi?.tw.
9. (cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumo?r* or myelo* or lymphoma* or oncolog* or chemotherap*).tw.
10. (random* or rct* or "controlled trial*" or "clinical trial*").tw.
11. 7 and 8 and 9 and 10
12. limit 11 to yr="2004 -Current"

EMBASE

Host: Ovid.

Data parameters: 1980 to Week 21 2013.

Date searched: 29 May 2013.

Searcher: SB.

Hits: 865.

Strategy

1. (erythropoietin* or EPO).tw.
2. Erythropoietin/
3. Receptors, erythropoietin/
4. recombinant erythropoietin/
5. erythropoiesis.tw.
6. Erythropoiesis/
7. (epoetin adj1 (alfa or beta or theta or zeta)).tw.
8. darbepoetin.tw.
9. novel erythropoiesis stimulating protein/
10. CERA.tw.
11. continuous erythropoiesis receptor activator/
12. (eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp).tw.
13. or/1-12
14. an?emi?.tw.
15. exp anemia/
16. 14 or 15
17. (cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumo?r* or myelo* or lymphoma* or oncolog* or chemotherap*).tw.
18. exp neoplasms/
19. 17 or 18
20. (random* or rct* or "controlled trial*" or "clinical trial*").tw.
21. 13 and 16 and 19 and 20
22. limit 21 to (english language and yr="2004 -Current")

Cochrane Central Register of Controlled Trials

Host: The Cochrane Library.

Data parameters: Issue 4 of 12, April 2013.

Date Searched: 24 May 2013.

Searcher: SB.

Hits: 219.

Strategy

1. (erythropoietin* or EPO):ti or (erythropoietin* or EPO):ab from 2004, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations
2. MeSH descriptor: [Erythropoietin] explode all trees
3. MeSH descriptor: [Receptors, Erythropoietin] explode all trees
4. erythropoiesis:ti or erythropoiesis:ab from 2004, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations
5. MeSH descriptor: [Erythropoiesis] explode all trees
6. (epoetin near/1 (alfa or beta or theta or zeta)):ti or (epoetin near/1 (alfa or beta or theta or zeta)):ab from 2004, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations
7. darbepoetin:ti or darbepoetin:ab from 2004, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations
8. CERA:ti or CERA:ab from 2004, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations
9. (eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp):ti or (eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp):ab from 2004, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations
10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
11. anemi? or anaemi?:ti or anemi? or anaemi?:ab from 2004, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations
12. MeSH descriptor: [Anemia] explode all trees
13. #11 or #12
14. (cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumour* or tumor* or myelo* or lymphoma* or oncolog* or chemotherap*):ti or (cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumour* or tumor* or myelo* or lymphoma* or oncolog* or chemotherap*):ab from 2004, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations
15. MeSH descriptor: [Neoplasms] explode all trees
16. #14 or #15
17. #10 and #13 and #16 from 2004, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations

Web of Science

Host: Thomson Reuters.

Data parameters: not applicable.

Date searched: 28 May 2013.

Searcher: SB.

Hits: 745.

Strategy

1. Title=((erythropoietin* or EPO)) OR Topic=((erythropoietin* or EPO))
2. Title=(erythropoiesis) OR Topic=(erythropoiesis)
3. Title=((epoetin near/0 (alfa or beta or theta or zeta))) OR Topic=((epoetin near/0 (alfa or beta or theta or zeta)))
4. Title=(darbepoetin) OR Topic=(darbepoetin)
5. Title=(CERA) OR Topic=(CERA)
6. Title=((eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp)) OR Topic=((eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp))
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. Title=(anemi* OR anaemi*) OR Topic=(anemi* OR anaemi*)
9. TI=((cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumour* or tumor* or myelo* or lymphoma* or oncolog* or chemotherap*)) OR TS=((cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumour* or tumor* or myelo* or lymphoma* or oncolog* or chemotherap*))
10. Title=((random* or rct* or "controlled trial*" or "clinical trial*")) OR Topic=((random* or rct* or "controlled trial*" or "clinical trial*"))
11. #7 AND #8 AND #9 AND #10 Timespan=2004-2013

Cumulative Index to Nursing and Allied Health Literature

Host: EBSCO*host*.

Data parameters: not applicable.

Date searched: 29 May 2013.

Searcher: SB.

Hits: 79.

Strategy

1. TI(erythropoietin* or EPO) OR AB(erythropoietin* or EPO)
2. (MH "Erythropoietin")
3. TI(erythropoiesis) OR AB(erythropoiesis)
4. (MH "Erythropoiesis")
5. TI(epoetin n0 (alfa or beta or theta or zeta)) OR AB(epoetin n0 (alfa or beta or theta or zeta))
6. TI(darbepoetin) OR AB(darbepoetin)
7. TI(CERA) OR AB(CERA)

8. TI(eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp) OR AB(eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp)
9. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
10. TI(anemi* or anaemi*) OR AB(anemi* or anaemi*)
11. (MH "Anemia+")
12. S10 OR S11
13. TI(cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumor* or tumour* or myelo* or lymphoma* or oncolog* or chemotherap*) OR AB(cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumor* or tumour* or myelo* or lymphoma* or oncolog* or chemotherap*)
14. (MH "Neoplasms+")
15. S13 OR S14
16. TI(random* or rct* or "controlled trial*" or "clinical trial*") OR AB(random* or rct* or "controlled trial*" or "clinical trial*")
17. PT(randomized controlled trial)
18. S16 OR S17
19. S9 AND S12 AND S15 AND S18

Date limited 2004–current.

Numbers of references retrieved and deduplicated: clinical effectiveness review

Database	Hits
MEDLINE	342
MEDLINE In-Process & Other Non-Indexed Citations	28
EMBASE	865
CENTRAL	219
Web of Science	745
CINAHL	79
Total	2278
Automatically deduplicated	845
Manually deduplicated	97
Total records to screen	1336

Cost-effectiveness

MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to May Week 3 2013.

Date searched: 29 May 2013.

Searcher: SB.

Hits: 144.

Strategy

Lines 1–16: see MEDLINE clinical effectiveness strategy.

17. (pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money").tw.
18. (fiscal or funding or financial or finance* or expenditure* or budget*).tw.
19. ("resource* alloca*" or "resource* use").tw.
20. exp Economics/
21. exp models, economic/
22. exp "Costs and Cost Analysis"/
23. Cost of illness/
24. ec.fs.
25. (decision adj2 (model* or tree* or analy*)).tw.
26. markov.tw.
27. decision trees/
28. or/17-27
29. 10 and 13 and 16 and 28
30. limit 29 to (english language and yr="2004 -Current")

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Host: Ovid.

Data parameters: 28 May 2013.

Date searched: 29 May 2013.

Searcher: SB.

Hits: 13.

Strategy

Lines 1–9: see MEDLINE In-Process & Other Non-Indexed Citations clinical effectiveness strategy.

10. (pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money").tw.
11. (fiscal or funding or financial or finance* or expenditure* or budget*).tw.
12. ("resource* alloca*" or "resource* use").tw.
13. (decision adj2 (model* or tree* or analy*)).tw.
14. markov.tw.
15. or/10-14
16. 7 and 8 and 9 and 15
17. limit 16 to yr="2004 -Current"

EMBASE

Host: Ovid.

Data parameters: 1980 to Week 21 2013.

Date searched: 29 May 2013.

Searcher: SB.

Hits: 677.

Strategy
Lines 1–19: see EMBASE clinical effectiveness strategy.

20. (pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money").tw.
21. (fiscal or funding or financial or finance* or expenditure* or budget*).tw.
22. ("resource* alloca*" or "resource* use").tw.
23. exp Economics/
24. models, economic/
25. exp health economics/
26. exp "Costs and Cost Analysis"/
27. Cost of illness/
28. resource allocation/
29. pe.fs.
30. (decision adj2 (model* or tree* or analy*)).tw.
31. markov.tw.
32. decision trees/
33. or/20-32
34. 13 and 16 and 19 and 33
35. limit 34 to (english language and yr="2004 -Current")

NHS Economic Evaluation Database
Host: The Cochrane Library.

Data parameters: Issue 2 of 4, April 2013.

Date searched: 24 May 2013.

Searcher: SB.

Hits: 10.

Strategy
See CENTRAL clinical effectiveness strategy.

Web of Science
Host: Thomson Reuters.

Data parameters: not applicable.

Date searched: 29 May 2013.

Searcher: SB.

Hits: 173.

Strategy

Lines 1–9: see Web of Science clinical effectiveness strategy.

10. TI=((pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money")) OR TS=((pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money"))
11. Title=((fiscal or funding or financial or finance* or expenditure* or budget*)) OR Topic=((fiscal or funding or financial or finance* or expenditure* or budget*))
12. Title=(("resource* alloca*" or "resource* use")) OR Topic=(("resource* alloca*" or "resource* use"))
13. Title=((decision near/1 (model* or tree* or analy*))) OR Topic=((decision near/1 (model* or tree* or analy*)))
14. Title=(markov) OR Topic=(markov)
15. #14 OR #13 OR #12 OR #11 OR #10
16. #15 AND #9 AND #8 AND #7 Timespan=2004-2013

Cumulative Index to Nursing and Allied Health Literature

Host: EBSCO*host*.

Data parameters: not applicable.

Date searched: 29 May 2013.

Searcher: SB.

Hits: 81.

Strategy

Lines 1–15: see CINAHL clinical effectiveness strategy.

16. TI(pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money") OR AB(pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money")
17. TI(fiscal or funding or financial or finance* or expenditure* or budget*) OR AB(fiscal or funding or financial or finance* or expenditure* or budget*)
18. TI("resource* alloca*" or "resource* use") OR AB("resource* alloca*" or "resource* use")
19. (MH "Economics+")
20. TI(decision n1 (model* or tree* or analy*)) OR AB(decision n1 (model* or tree* or analy*))
21. TI(markov) OR AB(markov)
22. (MH "Decision Trees")
23. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
24. S9 AND S12 AND S15 AND S23

Date limited 2004–current.

Health Economic Evaluations Database

Host: The Cochrane Library.

Data parameters: not applicable.

Date searched: 29 May 2013.

Searcher: SB.

Hits: 33.

Strategy

1. TI=(erythropoietin* or EPO)
2. TI=erythropoiesis
3. TI=(epoetin alfa or epoetin beta or epoetin theta or epoetin zeta)
4. TI=darbepoetin
5. TI=CERA
6. TI=(eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp)
7. AB=(erythropoietin* or EPO)
8. AB=erythropoiesis
9. AB=(epoetin alfa or epoetin beta or epoetin theta or epoetin zeta)
10. AB=darbepoetin
11. AB=CERA
12. AB=(eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp)
13. CS=(1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12)
14. TI=(anaemi* or anemi*)
15. AB=(anaemi* or anemi*)
16. CS=(14 or 15)
17. TI=(cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumor* or tumour* or myelo* or lymphoma* or oncolog* or chemotherap*)
18. AB=(cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumor* or tumour* or myelo* or lymphoma* or oncolog* or chemotherap*)
19. CS=(17 or 18)
20. CS=(13 and 16 and 19)

Numbers of references retrieved and deduplicated: cost-effectiveness review

Database	Hits
MEDLINE	144
MEDLINE In-Process & Other Non-Indexed Citations	13
EMBASE	677
NHS EED	10
Web of Science	173
CINAHL	81
HEED	33
Total	1131
Automatically de-duplicated	279
Manually de-duplicated	38
Total records to screen	814

Quality of life

MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to May Week 4 2013.

Date searched: 30 May 2013.

Searcher: SB.

Hits: 369.

Strategy

Lines 1–16: see MEDLINE clinical effectiveness strategy.

17. ("quality of life" or QoL or HRQL or HRQoL).tw.
18. quality of life/
19. ("quality adjusted life year*" or QALY*).tw.
20. quality-adjusted life years/
21. "activities of daily living".tw.
22. activities of daily living/
23. ("quality of wellbeing" or QWB or "QWB SA").tw.
24. ("health* year* equivalent*" or HYE*).tw.
25. "health status".tw.
26. health status/
27. health status indicators/
28. Psychometrics/
29. psychometric*.tw.
30. ("short form 36" or "SF-36" or SF36).tw.
31. ("short form 20" or "SF-20" or SF20).tw.
32. ("short form 12" or "SF-12" or SF12).tw.
33. ("short form 8" or "SF-8" or SF8).tw.
34. (Euroqol or "EQ-5D").tw.
35. exp Questionnaires/
36. or/17-35
37. 10 and 13 and 16 and 36
38. limit 37 to (english language and yr="2004 -Current")

MEDLINE(R) In-Process & Other Non-Indexed Citations

Host: Ovid.

Data parameters: 29 May 2013.

Date searched: 30 May 2013.

Searcher: SB.

Hits: 19.

Strategy

Lines 1–9: see MEDLINE In-Process & Other Non-Indexed Citations clinical effectiveness strategy.

10. ("quality of life" or QoL or HRQL or HRQoL).tw.
11. ("quality adjusted life year*" or QALY*).tw.
12. "activities of daily living".tw.
13. ("quality of wellbeing" or QWB or "QWB SA").tw.
14. ("health* year* equivalent*" or HYE*).tw.
15. "health status".tw.
16. psychometric*.tw.
17. ("short form 36" or "SF-36" or SF36).tw.
18. ("short form 20" or "SF-20" or SF20).tw.
19. ("short form 12" or "SF-12" or SF12).tw.
20. ("short form 8" or "SF-8" or SF8).tw.
21. (Euroqol or "EQ-5D").tw.
22. or/10-21
23. 7 and 8 and 9 and 22
24. limit 23 to yr="2004 -Current"

EMBASE

Host: Ovid.

Data parameters: 1980 to Week 21 2013.

Date searched: 30 May 2013.

Searcher: SB.

Hits: 952.

Strategy

Lines 1–19: see EMBASE clinical effectiveness strategy.

20. ("quality of life" or QoL or HRQL or HRQoL).tw.
21. exp quality of life/
22. ("quality adjusted life year*" or QALY*).tw.
23. "activities of daily living".tw.
24. daily life activity/
25. ("quality of wellbeing" or QWB or "QWB SA").tw.
26. ("health* year* equivalent*" or HYE*).tw.
27. "health status".tw.
28. health status/
29. health status indicators/
30. psychometric*.tw.
31. psychometry/
32. ("short form 36" or "SF-36" or SF36).tw.
33. ("short form 20" or "SF-20" or SF20).tw.
34. ("short form 12" or "SF-12" or SF12).tw.
35. ("short form 8" or "SF-8" or SF8).tw.
36. exp questionnaire/
37. or/20-36
38. 13 and 16 and 19 and 37
39. limit 38 to (english language and yr="2004 -Current")

Web of Science

Host: Thomson Reuters.

Data parameters: not applicable.

Date searched: 30 May 2013.

Searcher: SB.

Hits: 646.

Strategy

Lines 1–9: see Web of Science clinical effectiveness strategy.

10. Title=(("quality of life" or QoL or HRQL or HRQoL)) OR Topic=(("quality of life" or QoL or HRQL or HRQoL))
11. Title=(("quality adjusted life year*" or QALY*)) OR Topic=(("quality adjusted life year*" or QALY*))
12. Title=("activities of daily living") OR Topic=("activities of daily living")
13. Title=(("quality of wellbeing" or QWB or "QWB SA")) OR Topic=(("quality of wellbeing" or QWB or "QWB SA"))
14. Title=(("health* year* equivalent*" or HYE*)) OR Topic=(("health* year* equivalent*" or HYE*))
15. Title=("health status") OR Topic=("health status")
16. Title=(psychometric*) OR Topic=(psychometric*)
17. Title=(("short form 20" or "SF-20" or SF20)) OR Topic=(("short form 20" or "SF-20" or SF20))
18. Title=(("short form 12" or "SF-12" or SF12)) OR Topic=(("short form 12" or "SF-12" or SF12))
19. Title=(("short form 8" or "SF-8" or SF8)) OR Topic=(("short form 8" or "SF-8" or SF8))
20. Title=((Euroqol or "EQ-5D")) OR Topic=((Euroqol or "EQ-5D"))
21. #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10
22. #21 AND #9 AND #8 AND #7 Timespan=2004-2013

Cumulative Index to Nursing and Allied Health Literature

Host: EBSCO*host*.

Data parameters: not applicable.

Date searched: 30 May 2013.

Searcher: SB.

Hits: 111.

Strategy

Lines 1–15: see CINAHL clinical effectiveness strategy.

16. TI("quality of life" or QoL or HRQL or HRQoL) OR AB("quality of life" or QoL or HRQL or HRQoL)
17. (MH "Quality of Life+")
18. TI("quality adjusted life year*" or QALY*) OR AB("quality adjusted life year*" or QALY*)
19. (MH "Quality-Adjusted Life Years")
20. TI("activities of daily living") OR AB("activities of daily living")
21. (MH "Activities of Daily Living+")
22. TI("quality of wellbeing" or QWB or "QWB SA") OR AB("quality of wellbeing" or QWB or "QWB SA")
23. TI("health* year* equivalent*" or HYE*) OR AB("health* year* equivalent*" or HYE*)
24. TI("health status") OR AB("health status")

25. (MH "Health Status+")
26. (MH "Health Status Indicators")
27. TI(psychometric*) OR AB(psychometric*)
28. (MH "Psychometrics")
29. TI("short form 36" or "SF-36" or SF36) OR AB("short form 36" or "SF-36" or SF36)
30. TI("short form 20" or "SF-20" or SF20) OR AB("short form 20" or "SF-20" or SF20)
31. TI("short form 12" or "SF-12" or SF12) OR AB("short form 12" or "SF-12" or SF12)
32. TI("short form 8" or "SF-8" or SF8) OR AB("short form 8" or "SF-8" or SF8)
33. TI(Euroqol or "EQ-5D") OR AB(Euroqol or "EQ-5D")
34. (MH "Questionnaires+")
35. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
36. S9 AND S12 AND S15 AND S35

Date limited 2004-current.

British Nursing Index

Host: ProQuest.

Data parameters: not applicable.

Date searched: 31 May 2013.

Searcher: SB.

Hits: 43.

Strategy

(TI,AB((erythropoietin* or EPO or erythropoiesis) OR (epoetin near/1 (alfa or beta or theta or zeta)) OR (eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp))) AND (TI,AB(anaemi* or anemi*)) AND (TI,AB(cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumo?r* or myelo* or lymphoma* or oncolog* or chemotherap*))

Date limited 2004–current.

Numbers of references retrieved and deduplicated: quality of life

Database	Hits
MEDLINE	369
MEDLINE In-Process & Other Non-Indexed Citations	19
EMBASE	952
Web of Science	646
CINAHL	111
British Nursing Index	43
Total	2140
Automatically deduplicated	805
Manually deduplicated	67
Total records to screen	1268

Update searches

Numbers of references retrieved and deduplicated

All update searches were run on 2 December 2013 and date limited from 1 January 2013 to 2 December 2013.

Database	Hits
Clinical effectiveness	
MEDLINE	11
MEDLINE In-Process & Other Non-Indexed Citations	8
EMBASE	44
CENTRAL	2
Web of Science	32
CINAHL	1
Total	98
Automatically deduplicated	30
Manually deduplicated	0
Total records to screen	68
Cost-effectiveness	
MEDLINE	8
MEDLINE In-Process & Other Non-Indexed Citations	5
EMBASE	47
NHS EED	2
Web of Science	11
CINAHL	0
HEED	0
Total	73
Automatically deduplicated	17
Manually deduplicated	5
Total records to screen	51
Quality of life	
MEDLINE	9
MEDLINE In-Process & Other Non-Indexed Citations	8
EMBASE	46
Web of Science	25
CINAHL	0
British Nursing Index	0
Total	88
Automatically deduplicated	24
Manually deduplicated	3
Total records to screen	61

Supplementary searches (1): reviews and reports

Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database

Host: The Cochrane Library.

Data parameters: CDSR: Issue 4 of 12, April 2013; DARE and HTA database: Issue 2 of 4, April 2013.

Date searched: 24 May 2013.

Searcher: SB.

Hits: CDSR = 8; DARE = 16; HTA database = 6.

Strategy

See CENTRAL clinical effectiveness strategy.

Health Management Information Consortium

Host: Ovid.

Data parameters: 1979 to March 2013.

Date searched: 30 May 2013.

Searcher: SB.

Hits: 2.

Strategy

1. (erythropoietin* or EPO).tw.
2. erythropoiesis.tw.
3. (epoetin adj1 (alfa or beta or theta or zeta)).tw.
4. darbepoetin.tw.
5. CERA.tw.
6. (eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp).tw.
7. or/1-6
8. an?emi?.tw.
9. (cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumo?r* or myelo* or lymphoma* or oncolog* or chemotherap*).tw.
10. 7 and 8 and 9
11. limit 10 to yr="2004 -Current"

Numbers of references retrieved and deduplicated: reviews and reports

Database	Hits
CDSR	8
DARE	16
HTA	6
HMIC	2
Total	32
Manually deduplicated	3
Total records to screen	29

Supplementary searches (2): haemoglobin level

The references retrieved for these two searches were not deduplicated because the searches were carried out only in MEDLINE and each search was sent to the review team as a separate EndNote file.

Haemoglobin level over time after stopping chemotherapy

MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to September Week 1 2013.

Date searched: 17 September 2013.

Searcher: SB.

Hits: 159.

Strategy

1. (haemoglobin* or hemoglobin*).tw.
2. exp Hemoglobins/
3. (hgb or hb).tw.
4. or/1-3
5. ((post or after* or subsequent* or following) adj5 chemo*).tw.
6. postchemo*.tw.
7. or/5-6
8. an?emi?.tw.
9. exp anemia/
10. or/8-9
11. 4 and 7 and 10

Utilities as a function of haemoglobin level

MEDLINE(R)
Host: Ovid.

Data parameters: 1946 to September Week 1 2013.

Date searched: 18 September 2013.

Searcher: SB.

Hits: 258.

Strategy

1. (haemoglobin* or hemoglobin*).tw.
2. exp hemoglobins/
3. (hgb or hb).tw.
4. or/1-3
5. an?emi?.tw.
6. exp anemia/
7. or/5-6
8. (utility or utilities or "EQ-5D" or "SF-6D" or "EORTC-QLQ-C30" or HUI2 or "time trade-off" or TTO or "standard gamble" or SG or "quality-adjusted life year*" or QALY? or "discrete choice" or "stated preference").tw.
9. Quality-Adjusted Life Years/
10. 8 or 9
11. 4 and 7 and 10

Appendix 2 Data extraction forms

Clinical effectiveness and health-related quality-of-life review: data extraction forms (primary studies)

EndNote ref. ID: 2706	Malignancy type: anaemic cancer (primary myeloid malignancies and acute leukaemias excluded) Treatment: rHuEPO (Amgen Inc.; assumed epoetin alfa)

Study design		Participants
Author, year	Abels 1993[63]	$n = 413$. Three populations: cyclic non-cisplatin-containing chemotherapy ($n = 157$), cyclic cisplatin-containing chemotherapy ($n = 132$) and no chemotherapy ($n = 124$) vs. placebo ($n = 200$)[a]
Objective	To examine the safety of rHuEPO treatment and its impact on haematocrit, transfusion requirements and quality of life	Inclusion criteria: > 18 years of age; biopsy-proven diagnosis of cancer (with primary myeloid malignancies and acute leukaemias excluded); anaemia: haematocrit of ≤ 32% or Hb level ≤ 10.5 g/dl; ECOG score of ≤ 3; life expectancy ≥ 3 months; cyclic cisplatin- and non-cisplatin-containing chemotherapy administered < 5 days every 3–4 weeks Exclusion criteria: known cerebral metastases; uncontrolled hypertension; acute illness within 7 days of study entry; radiation or surgery within 30 days of study entry; experimental therapy within 30 days of study entry; androgen therapy within 2 months of study entry; evidence of renal insufficiency (i.e. serum creatinine ≥ 2 mg/dl); evidence of folate, B_{12} and/or iron deficiency, autoimmune haemolysis or presence of gastrointestinal bleeding
No. of centres	NR	
Other references/ aliases	Abels 1996,[59] Henry 1994,[85] Henry 1995,[58] Case 1993,[86] see note for more details	
Geographical setting	NR	
Duration of treatment	12 weeks	
Length of follow-up (if different)	After completion of double-blind therapy, patients were eligible to receive rHuEPO on an open-label basis. Henry and colleagues[85] provide results for the first 6 months of epoetin therapy (combined double-blind and open-label data: the mean duration of epoetin therapy was 17.1, 18.2 and 15.8 weeks for no chemotherapy, non-cisplatin-containing chemotherapy and cisplatin-containing chemotherapy respectively	
Country of corresponding author	USA	
Language of publication	English	
Sources of funding	NR	
Randomisation and allocation	Series of double-blind, placebo-controlled trials: three populations of anaemic cancer patients were randomised to rHuEPO or placebo. The three populations were (1) patients not receiving concomitant chemotherapy, (2) patients receiving chemotherapeutic regimens that did not contain cisplatin and (3) patients receiving chemotherapeutic regimens that contained cisplatin	

a Prior to study completion, a decision was made to pool data within each study type (according to type of cancer treatment). Thus, data in each category were pooled and reported as a single entity as follows: no chemotherapy treatment (protocols H87 032, 87–014, 87–015), treatment with non-cisplatin chemotherapy (protocols I88–037, 87–016, 87–017) and treatment with cisplatin chemotherapy (protocols I88–036, 87–018, 87–019).

Note

Abels and colleagues[59] report pooled data from the three chemotherapy populations. Henry and colleagues:[85] after completion of double-blind therapy, patients were offered rHuEPO on an open-label basis; this paper reports the open-label follow-up data. Case and colleagues[86] report analysis of the non-cisplatin-containing chemotherapy subgroup. Henry and colleagues[58] report analysis of the cisplatin-containing chemotherapy subgroup.

Treatment arms		
Arm drug name(s)	Epoetin	Placebo
n	206 (efficacy population)	190 (efficacy population)
Dose and frequency (once daily, twice daily, etc.)	150 U/kg three times a week	150 U/kg three times a week
Dose adjustment (yes/no)	Yes	
Route of administration	Subcutaneously	Subcutaneously
Duration of epoetin treatment		
Adjuvant anaemia treatment	NR	NR
Transfusion trigger	NR	NR

Outcomes	
Primary outcome	–
Other outcomes	RBCT (number of units of blood transfused per patient and the proportion of patients transfused requirements); haematological response (haematocrit: change from baseline, mean weekly haematocrit, number of correctors and responders,[a] neutrophil analyses; platelet analyses; HRQoL (100-mm VAS: energy level, ability to perform daily activities and overall quality of life)

a Correctors = patients who attained a haematocrit ≥ 38% unrelated to transfusion; responders = patients whose haematocrit increased by ≥ 6% unrelated to transfusion. 'Unrelated to transfusion' meant that no transfusion was administered in the month before documenting attainment of the criterion.

Note

Other analyses included the determination of whether tumour type (haematological vs. non-haematological) or tumour in filtration of the bone marrow influenced the response to therapy.

Analysis	
Statistical technique used	Fischer's exact test was used for statistical inference for dichotomous variables (e.g. sex by treatment group) formulated as 2 × 2 tables. The extended Mantel–Haenszel test with integer scores was used for other types of discrete data. Between-group comparisons of means were analysed with two-sample *t*-tests and changes from baseline to final value were analysed with paired *t*-tests. A linear model approach was used for inference on major efficacy variables such as transfusion requirements. These models were constructed with treatment group and covariant factors such as endogenous serum erythropoietin level, haematocrit, performance score, etc. All statistical tests were two-sided, with $\alpha = 0.05$
ITT analysis?	Patients were considered evaluable for efficacy if they completed > 15 days on the study. All patients were evaluable for safety
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	Unclear: ITT $n = 413$ (epoetin $n = 213$ and placebo $n = 200$); efficacy population $n = 396$ (epoetin $n = 206$, placebo $n = 190$)
Was attrition rate adequately dealt with?	NR
No. (%) followed up from each condition?	Unclear; Henry and colleagues[85] provide results for the first 6 months of epoetin therapy (combined double-blind and open-label data): $n = 363$, efficacy population $n = 347$

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/myelodysplastic syndrome/mixed)		Anaemic cancer (primary myeloid malignancies and acute leukaemias excluded)
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Cyclic non-cisplatin chemotherapy ($n = 157$) and cyclic cisplatin chemotherapy ($n = 132$)
Adjuvant anaemia treatment	Iron	NR
	G-CSF	NR
	Transfusion trigger	NR
	Hb inclusion criterion level	Anaemia: haematocrit of $\leq 32\%$ or a Hb level ≤ 10.5 g/dl

	Arm 1 = epoetin ($n = 213$)	Arm 2 = placebo ($n = 200$)	*p*-value
Baseline demographics and clinical characteristics are reported for the entire enrolled patient population and are not separated out by chemotherapy treatment			
Sex			
Male, *n*	102	95	
Female, *n*	111	105	
Age (years), mean (SD)	61.2 (13)	62.5 (14.1)	
Patients evaluable for efficacy	$n = 206$	$n = 190$	
Patients transfused, %	44.7	48.4	
No. of RBC units transfused per patient per month prior to the study, mean (SD)	0.67 (1.08)	0.73 (1.04)	
Mean haematocrit, mean (SD)	29.1 (4)	28.5 (3.8)	
Haematocrit, mean (SD)			
Non-cisplatin chemotherapy	($n = 79$) 28.6 (3.9)	($n = 74$) 29.4 (3)	
Cisplatin chemotherapy	($n = 64$) 29.4 (4)	($n = 61$) 28.4 (14.5)	
Endogenous serum erythropoietin level (mU/ml), mean (SD) [median]	146 (260) [76]	149 (217) [85]	
Median serum erythropoietin level (mU/ml)	NR	NR	
Overall quality of life (mm), mean (SD)	50 (24)	50.4 (26)	
Tumour type			
Haematological, %	32	32.1	
Non-haematological, %	68	67.9	
Prostate	11.2	9	
Breast	10.7	12.6	
Gastrointestinal	10.2	5.3	
Lung, non-small cell	10.2	9	

	Arm 1 = epoetin ($n = 213$)	Arm 2 = placebo ($n = 200$)	p-value
Gynaecological	9.2	12.1	
Lung, small cell	3.9	8	
Head and neck	2.4	1.6	
Oesophagus	1.0	1.6	
Unknown primary	3.4	1.1	
Other	5.8	7.9	
Were intervention and control groups comparable?	No p-values reported; authors stated that 'Pooling patients across all trials shows equivalent demographic characteristics between the patients randomised to r-HuEPO and the patients randomised to placebo' (p. S3)		

Results (reported for platinum-based chemotherapy and non-platinum-based chemotherapy; data available for no chemotherapy but outside the scope of this appraisal)				
Patients evaluable for efficacy	$n = 206$	$n = 190$	Notes	p-value
Response of haematocrit to therapy				
Non-cisplatin chemotherapy	$n = 79$	$n = 74$		
Change in haematocrit (%), mean (SE)	6.9 (6)	1.1 (4.3)	Figure 2 represents mean (SE) weekly haematocrit comparing epoetin and placebo in all three populations	< 0.004
Final haematocrit (%), mean (SE)	35.5 (6)	30.5 (4)		
Correctors (%)	40.5	4.1		< 0.008
Responders (%)	58.2	13.5		< 0.008
Area under the curve for neutrophil count vs. time (cells × week/μl)	30,203	34,189	As reported in Case and colleagues[86]	
Platelet counts/μl (% change from baseline to final value)	–39	–48		
Rise in haematocrit to ≥ 38% unrelated to transfusion, n (%)	32 (40.5)	3 (4.1)		
≥ 6% point rise in haematocrit from baseline unrelated to transfusion, n (%)	46 (58.2)	10 (13.5)		
Cisplatin chemotherapy	$n = 64$	$n = 61$		
Change in haematocrit (%), mean (SE)	6 (7)	1.3 (5)	Figure 2 represents mean (SE) weekly haematocrit comparing epoetin and placebo in all three populations	< 0.004
Final haematocrit (%), mean (SE)	35.4 (7)	29.7 (4.5)		
Correctors (%)	35.9	1.6		< 0.008
Responders (%)	48.4	6.6		< 0.008
Haematological response (≥ 6 percentage points without a transfusion in the 4 weeks prior to that haematocrit value), change from baseline (mean ± SD)	6.0 ± 7.0	1.3 ± 5.0 Difference 4.7; $p < 0.0001$ (favours epoetin)	As reported in Henry and colleagues;[58] also reports baseline haematocrit 29.4 ± 4.0% (rHuEPO) and 28.4 ± 4.5% (placebo)	

Results (reported for platinum-based chemotherapy and non-platinum-based chemotherapy; data available for no chemotherapy but outside the scope of this appraisal)				
Transfusions				
Non-cisplatin chemotherapy	$n = 79$	$n = 74$		
Proportion of patients transfused (%), overall	40.5	48.6	When the non-cisplatin and cisplatin chemotherapy populations were combined there was a significant difference for the proportion of patients transfused at months 2–3 ($p \leq 0.005$) and the mean units per patients at months 2–3 ($p = 0.009$)	
Mean units transfused per patient, overall (unclear whether SD or SE)	2.03 (3.88)	2.75 (4.15)		
Proportion of patients transfused (%), month 1	25.3 ($n = 70$)	27 ($n = 68$)		
Mean units per patient, month 1	0.69	0.71		
Proportion of patients transfused (%), months 2–3	28.6 ($n = 70$)	36.8 ($n = 68$)		
Mean units per patient, months 2–3	0.91	1.65		0.056
Patients transfused, *n* (%)			As reported in Case and colleagues[86]	
Month 1 ($n = 79$)	20 (25.3)	20 (27.0)		
Months 2–3 ($n = 70$)	20 (28.6)	25 (36.8)		
Transfusion rate (least-squares mean from linear analysis), mean ± SE				
Month 1 ($n = 79$)	0.69 ± 0.16	0.71 ± 0.16		
Months 2–3 ($n = 70$)	0.91 ± 0.27	1.65 ± 0.27		0.056
Cisplatin chemotherapy	$n = 64$	$n = 61$		
Proportion of patients transfused (%), overall	53.1	68.9	When the non-cisplatin and cisplatin chemotherapy populations were combined there was a significant difference for the proportion of patients transfused at months 2–3 ($p \leq 0.005$) and the mean units per patients at months 2–3 ($p = 0.009$)	
Mean units transfused per patients, overall, mean (unclear whether SD or SE)	3.56 (7.01)	4.01 (4.87)		
Proportion of patients transfused (%), month 1	43.8	44.3		
Mean units per patients, month 1	1.71	1.2		
Proportion of patients transfused (%), months 2–3	26.8 ($n = 56$)	56.4 ($n = 55$)		≤ 0.005
Mean units per patients, months 2–3	1.2	2.02		0.089

Note
Neutrophil and platelet analyses and mean haematocrit were similar across all groups at the time of transfusion.

RBCT least-squares mean						
	All participants, n	*Patients transfused, n (%)*	*All participants, n*	*Patients transfused, n (%)*		
Patients transfused						
n	64	34 (53.1)	61	42 (68.9)	As reported in Henry and colleagues[58]	
Month 1	64	28 (43.8)	61	27 (44.3)		> 0.05
Month 2	56	12 (21.4)	55	27 (49.1)		< 0.005
Month 3	47	8 (17.0)	46	13 (28.3)		
Months 2–3	56	15 (26.8)	55	31 (56.4)		
Units transfused, mean ± SE						
n	56		53			
Units transfused	4.01 ± 0.85		3.95 ± 0.84			> 0.05
Month 1	1.71 ± 0.28		1.20 ± 0.29			> 0.05
Month 2	0.71 ± 0.22		1.30 ± 0.22			0.0572
Month 3	0.42 ± 0.16		0.62 ± 0.16			–
Months 2–3	1.20 ± 0.33		2.02 ± 0.33			0.0893
Haematological vs. non-haematological tumour						
Change in haematocrit from baseline to final value by tumour type (%)						
Chronic lymphocytic leukaemia	6.0 ($n = 7$)		0.9 ($n = 9$)		As the data for any turnout type may include patients from the no chemotherapy, non-cisplatin-containing chemotherapy and cisplatin-containing chemotherapy treatment groups, duration of therapy can range from 8 weeks (no chemotherapy) to 12 weeks (non-cisplatin-containing chemotherapy, cisplatin-containing chemotherapy)	0.077
Myeloma	3.7 ($n = 19$)		0.3 ($n = 23$)			0.058
Lymphoma	6.0 ($n = 40$)		0.5 ($n = 29$)			≤ 0.05
Breast cancer	6.5 ($n = 22$)		1.6 ($n = 24$)			≤ 0.05
Lung cancer	6.4 ($n = 29$)		1.1 ($n = 32$)			≤ 0.05
Prostate cancer	2.3 ($n = 23$)		0.1 ($n = 17$)			
Gastrointestinal cancer	5.8 ($n = 21$)		1.6 ($n = 10$)			≤ 0.05
Gynaecological cancer	7.7 ($n = 18$)		–0.3 ($n = 23$)			≤ 0.05

Note
Tumour type and bone marrow infiltration were similar at baseline and among responders (table 10).

HRQoL

Reported for the entire enrolled patient population and not separated by chemotherapy treatment. Data presented graphically (Figures 3 and 4)

As reported in Case and colleagues:[86] Pre-study and post-study quality-of-life assessments were available for 124 patients (rHuEPO $n = 63$; placebo $n = 61$); the rHuEPO-treated population as a whole had a statistically significant ($p \leq 0.05$) increase in the baseline to final evaluation for energy level and ability to perform daily activities, as well as a near statistically significant ($p = 0.86$) improvement for overall quality of life. No similar improvements in quality-of-life assessments were seen in placebo-treated patients. The changes in quality-of-life scores were of somewhat greater magnitude in the rHuEPO-treated populations, with an increase in haematocrit to ≥ 38% or an increase of ≥ 6 percentage points (both unrelated to transfusion), than in the rHuEPO-treated population as a whole

As reported in Henry and colleagues:[58] patients in the rHuEPO-treated group experienced a significant ($p \leq 0.05$) pre-study to post-study improvement in energy level, ability to perform daily activities and overall quality of life. Patients in the placebo group also experienced a significant ($p \leq 0.05$) pre-study to post-study improvement in energy level, but not in ability to perform daily activities or overall quality of life. Comparing the two treatment arms there was a significantly greater pre-study to post-study change in overall quality of life for the rHuEPO-treated group than for the placebo-treated group ($p = 0.013$). When only responders in the rHuEPO-treated group were compared with the placebo-treated group, the quality-of-life changes were even greater in favour of the rHuEPO group but did not achieve significance because of the smaller numbers involved

Adverse effects of treatment (%)

Reported for the entire enrolled patient population and not separated out by chemotherapy treatment

Reported by at least 10% of patients	$n = 213$	$n = 200$	
Nausea	23	29	
Pyrexia	22	21	
Asthenia	17	16	
Fatigue	15	20	
Vomiting	15	18	
Diarrhoea	15	9	
Oedema	14	8	
Dizziness	10	9	
Skin reaction at medication site	10	10	
Constipation	10	9	
Shortness of breath	8	15	< 0.03
Decreased appetite	8	12	
Chills	7	10	
Trunk pain	8	12	

Note

No antibodies against rHuEPO developed during the course of therapy.

Hypertension	5	3.5		> 0.05
Non-cisplatin chemotherapy				
ITT population	$n = 81$	$n = 76$	As reported in Case and colleagues[86]	> 0.05
No. (%) of patients completing the study	63 (78)	63 (83)		> 0.05
No. (%) of patients who discontinued the study prematurely because of an adverse experience, death or disease progression	13 (16)	8 (11)		
Diarrhoea, *n* (%)	18 (22)	8 (10)		0.05
Diaphoresis, *n* (%)	9 (11)	1 (1)		< 0.05
Hypertension, *n*[a]	4	2		
Seizure, *n*[b]	2	2		
Thromboembolic events, *n*	4	4		

a Hypertension in the rHuEPO-treated patients tended to be more severe than in the placebo-treated patients, with the diastolic blood pressure in one of the rHuEPO-treated patients reaching 140 mmHg. The haematocrit in this patient increased from 31% at baseline to 43% at the time that the hypertension was reported (Day 57).

b Seizures occurred in the context of a substantial increase in haematocrit and blood pressure. However, these patients also had structural abnormalities of the central nervous system (cerebral metastases and/or abnormal cells in the cerebrospinal fluid and increased cerebrospinal fluid protein).

Note

There was no statistically significant difference in the incidence of any adverse experience between the rHuEPO-treated patients and the placebo-treated patients except for diarrhoea ($p = 0.05$) and diaphoresis ($p < 0.05$).

Cisplatin chemotherapy			
n	67	65	As reported in Henry 1995[58]
Overall, *n* (%)	58 (87)	58 (89)	
≥ 10% of patients, *n* (%)			
Fever	16 (24)	17 (26)	
Nausea	15 (22)	25 (28)	
Vomiting	13 (19)	17 (26)	
Fatigue	11 (16)	12 (18)	
Diarrhoea	10 (15)	4 (6)	
Abdominal/trunk pain	10 (15)	12 (18)	
Asthenia	9 (13)	9 914)	
Oedema	9 (13)	6 (9)	
Anorexia	7 (10)	10 (15)	
Bacterial infection	7 (10)	7 (11)	
Paraesthesia	7 (10)	5 (8)	
Skin reaction at medication site	7 (10)	4 (6)	
Constipation	7 (10)	3 (5)	
Rash	7 (10)	2 (3)	
Shortness of breath	5 (7)	13 (20)	
Arthralgia	5 (7)	7 (11)	
< 10% of patients, selected AEs, *n* (%)			
Thrombosis	6 (9)	2 (3)	
Headache	5 (7)	3 (5)	
Seizure	3 (4)	2 (3)	
Hypertension	2 (3)	4 (6)	

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear (states randomised but no details given)
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear; no *p*-values reported, authors stated that 'Pooling patients across all trials shows equivalent demographic characteristics between the patients randomised to r-HuEPO and the patients randomised to placebo' (p. S3)
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes (states double blind)
6. Were the outcome assessors blind to treatment allocation?	Yes (states double blind)
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Unclear
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	After completion of double-blind therapy, patients were eligible to receive rHuEPO on an open-label basis

Other	
Generalisability	
Author conclusions	rHuEPO increases the haematocrit and corrects anaemia in cancer patients whether or not they are receiving chemotherapy and apparently without regard to type of cancer. With a dose of 150 U/kg three times weekly, rHuEPO appears to decrease transfusion requirements after the first month of therapy but not earlier. This therapy also appears to improve functional capacity in those anaemic cancer patients who show a significant increase in haematocrit in response to therapy. rHuEPO also appears to be well tolerated in this patient population
Reviewer comments	

ECOG, Eastern Cooperative Oncology Group; NR, not reported.

EndNote ref. ID: 2685	Malignancy type: solid (ovarian, lung and stomach) Treatment: rHuEPO (epoetin alfa)	
Study design		**Participants**
Author, year	Aravantinos 2003[64]	*n* = 47
Objective	To evaluate the safety and efficacy of rHuEPO for the management of anaemia in cancer patients receiving platinum-based chemotherapy	Inclusion criteria: Adults with confirmed (histologically proven) malignancies about to start or already receiving platinum-based chemotherapy. Diagnosis of recent-onset anaemia as a result of malignant disease, performance status of 0–2 according to ECOG and life expectancy ≥ 3 months. Patients with Hb values < 10.5 g/dl before initiation or during chemotherapy, receiving platinum-based combinations on a 3- to 4-weekly schedule lasting for not more than 5 days per cycle. Laboratory requirements: white blood cell count > 3500/µl, platelet count > 100,000/µl, serum creatinine < 2 mg/dl, negative direct Cooms reaction (to exclude haemolytic anaemia) and normal iron levels (to exclude iron-deficiency anaemia) Exclusion criteria: Uncontrolled hypertension (diastolic blood pressure > 100 mmHg) and suspicion of iron, folic acid or vitamin B_{12} deficiency; patients who had received radiotherapy, who had undergone surgery 2 weeks prior to study entry or who had received a RBCT the week before
No. of centres	1	
Other references/ aliases	NA	
Geographical setting	Greece	
Duration of treatment	Unclear; median five cycles	
Length of follow-up (if different)	NR	
Country of corresponding author	Greece	
Language of publication	English	
Sources of funding	NR	
Randomisation and allocation	Randomised, unblinded, single-centre study. Stratified by type of malignancy, type of platinum compound (cisplatin or carboplatin) and chemotherapy cycle number at study entry (first vs. second vs. third)	

Treatment arms		
Arm drug name(s)	rHuEPO	Control: no rHuEPO
n	24	23
Dose and frequency (once daily, twice daily, etc.)	150 IU/kg Q3W	NA
Dose adjustment (yes/no)	Yes: Hb value > 14 g/dl rHuEPO administration was interrupted and reinitiated in a dose reduced by 25% when Hb was < 12.5 g/dl. No escalation of the rHuEPO dose was attempted in case of failure to increase Hb by > 1 g/dl in a month. Dose adjustments were made according to body weight on the first day of the following chemotherapy cycle	NA
Route of administration	Subcutaneous	NA
Duration of epoetin treatment	NR	NR
Adjuvant anaemia treatment	200 mg elementary iron daily	200 mg elementary iron daily
Transfusion trigger	Discretion of treating physician but avoided if Hb level > 9 g/dl	Discretion of treating physician but avoided if Hb level > 9 g/dl

Outcomes	
Primary outcome	Reduction in transfusion requirement, number of transfusions (per group and per patient)
Other outcomes	Hb level (change per cycle), haematocrit level (change per cycle), number of RBCTs required (change per cycle), number of patients requiring transfusion

Analysis	
Statistical technique used	ANOVA with two parameters was used for the administration of epoetin, follow-up, RBCTs and cycle number. Statistical significance was tested in relation to epoetin administration (with or without epoetin) and in relation to cycle number. ANOVA with one parameter was used to identify statistically significant differences in relation to the use of epoetin and cycle number. Post-hoc comparisons and Scheffe tests followed in order to assess the statistical significance of differences between the two groups. Independent Mann–Whitney tests were performed to study the differences concerning the number of transfusions and all data were also studied with descriptive statistics. A p-value < 0.05 was considered significant
ITT analysis?	Unclear; likely ITT analysis as no crossover and results were reported for the full data set but not mentioned in the study write-up
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)	NR
Attrition rate (loss to follow-up)?	NR
Was attrition rate adequately dealt with?	Unclear; attrition rate not reported
No. (%) followed up from each condition?	NA

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		Solid – ovarian, lung, stomach, other
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Platinum based (cisplatin or carboplatin)
Adjuvant anaemia treatment	Iron	200 mg elementary iron daily
	G-CSF	NR
	Transfusion trigger	Discretion of treating physician but avoided if Hb level > 9 g/dl
	Hb inclusion criterion level	< 10.5 g/dl

	Arm 1 = rHuEPO ($n = 24$)	Arm 2 = no rHuEPO ($n = 23$)	Notes	p-value
Sex, n (%)				
Male	2 (8)	7 (30)		
Female	22 (92)	16 (70)		
Age (years), median (range)	59 (18–76)	64 (23–75)		
Performance status: ECOG score, n (%)				
0	11 (45.8)	14 (60.9)		
1	8 (33.3)	4 (17.4)		
2	5 (20.9)	5 (21.7)		

	Arm 1 = rHuEPO ($n = 24$)	Arm 2 = no rHuEPO ($n = 23$)	Notes	p-value
Type of solid tumour, *n* (%)				
Ovarian	16 (67)	10 (43)		
Lung	3 (12.5)	5 (22)		
Stomach	2 (8)	2 (9)		
Other	3 (12.5)	6 (26)		
No. of chemotherapy cycle at study entry, *n* (%)				
1	9 (37.5)	5 (21.7)		
2	9 (37.5)	13 (56.5)		
3	3 (12.5)	2 (8.6)		
4	3 (12.5)	3 (13.0)		
Hb at baseline (g/dl)	NR	NR		
Hb at cycle 1 (g/dl)	9.8 (0.5)	9.32 (0.8)	Reported values are assumed to be means and SDs	
Iron at baseline (U/l)	NR	NR		
Epoetin at baseline (mU/ml)	NR	NR		
Target Hb	NR	NR		
Were intervention and control groups comparable?	No p-values reported; authors stated that 'all characteristics were well-balanced between the two groups' (p. 129)			

Results				
Median no. of chemotherapy cycles	5	5		
Mean Hb level by cycle				
Cycle 1	9.8 ± 0.5	9.32 ± 0.8	Reported values are assumed to be means and SDs	p-value for all cycles: < 0.0002
Cycle 2	10.36 ± 1.08	10.2 ± 1.01		
Cycle 3	10.66 ± 1.3	10.07 ± 1.32		
Cycle 4	11.47 ± 1.67; Hb increase compared with control group: $p < 0.03$	10.31 ± 1.56		
Cycle 5	12.11 ± 1.39; Hb increase compared with control group: $p < 0.03$	10.55 ± 1.83		
Mean haematocrit by cycle				
Cycle 1	28.56 ± 4.92	28.74 ± 2.68	Reported values are assumed to be means and SDs	
Cycle 2	31.5 ± 0.47	31.09 ± 3.14		
Cycle 3	32 ± 4.06	30.57 ± 4.21		
Cycle 4	34.9 ± 4.48; haematocrit increase compared with control group: $p < 0.002$	31.58 ± 4.54		
Cycle 5	36.43 ± 4.33	32.2 ± 5.63		

Results				
RBC count ($\times 10^4$/mm^3) by cycle				
Cycle 1	3.46 ± 0.42	3.46 ± 0.59	Reported values are assumed to be means and SDs	
Cycle 2	3.62 ± 0.50	3.71 ± 0.59		
Cycle 3	3.64 ± 0.57	3.61 ± 0.62		
Cycle 4	3.77 ± 0.55	3.54 ± 0.66		
Cycle 5	4.01 ± 0.4	3.61 ± 0.61		
RBCT				
No. (%) of patients requiring a RBCT	9 (37.5)	23 (100%)		< 0.0001
No. of transfusions				
Total	20	73		< 0.04
Per patient	2.22	3.17		

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear; stratification
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear; *p*-values NR; authors stated that 'all characteristics were well-balanced between the two groups' (p. 129)
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No
6. Were the outcome assessors blind to treatment allocation?	No
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially (variability can be calculated from data presented in the paper)
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes; results reported for full population and no crossover, so appears to be ITT analysis but not mentioned in study description
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	NR

Notes

Hb levels within the rHuEPO group increased with cycle number, becoming statistically significant in cycle 5. Similarly, there was a trend for an increase in the no rHuEPO group (< 0.06).
There was a statistically significant increase in haematocrit level in the rHuEPO group compared with the no rHuEPO group, especially in cycle 4 ($p < 0.002$), with a statistically significant increase in haematocrit level during the cycles (more significant in cycles 4 and 5).
There was a tendency towards higher RBC numbers per cycle in the rHuEPO group.
Detailed analysis per group and per cycle of treatment showed that for rHuEPO there was a decrease in the transfusion requirements from cycle to cycle (20.1% in cycle 2 vs. 4.2% in cycle 5). Similarly, for no rHuEPO there was a decrease in transfusion requirements, from 65.2% in cycle 2 to 30.4% in cycle 5. This was not statistically significant for either group.
Of the nine patients in the rHuEPO group requiring transfusion, 56% received their first transfusion in cycle 2, whereas only 22.2% received their first transfusion in cycles 3 or 4. There was a significant fluctuation in the percentage of patients requiring a transfusion per cycle (21.7% cycle 1; 47.8% cycle 2; 8.7% cycle 3; 13% cycle 4).

Other	
Generalisability	Mixed population – majority women (81%) (majority of women had ovarian cancer); other solid tumours included lung and stomach cancer
Author conclusions	Administration of rHuEPO is an effective intervention for the management of chemotherapy-induced anaemia, significantly reducing RBCT requirements in patients receiving platinum-based chemotherapy. Hb and haematocrit levels proved reliable indicators for the response to rHuEPO treatment
Reviewer comments	Trial unblinded

ANOVA, analysis of variance; ECOG, Eastern Cooperative Oncology Group; NR, not reported; Q3W, once every 3 weeks.

EndNote ref. ID: 2710	Malignancy type: haematological and solid Treatment: epoetin beta	
Study design		**Participants**
Author, year	Boogaerts 2003[65]	$n = 262$
Objective	To assess the impact of epoetin beta on quality of life compared with standard care in anaemic patients with lymphoid or solid tumour malignancies	Inclusion criteria: Adult outpatients; Hb level ≤ 11 g/dl associated with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia and any solid tumour treated with myelosuppressive chemotherapy with at least three cycles remaining; WHO performance status of ≤ 2 and a life expectancy of 6 months Exclusion criteria: Anaemia arising for other reasons (iron or vitamin B_{12} deficiency, acute bleeding, haemolytic anaemia); refractory hypertension; severe renal insufficiency [serum creatinine of > 2.5 mg/dl (> 220 µmol/l)]; epilepsy or acute infection; pregnant or lactating women and women of childbearing age practising unreliable contraception; any patient scheduled to undergo bone marrow or peripheral stem cell transplantation during the study period or 4 weeks prior to the study
No. of centres	Multicentre; conducted between October 1996 and September 1998	
Other references/ aliases	Coiffier 2001[87] (abstract) (see note)	
Geographical setting	Eight countries: Austria, Belgium, France, Germany, Italy, South Africa, Sweden, UK	
Duration of treatment	12 weeks (plus run-in period of up to 2 weeks)	
Length of follow-up (if different)	26 weeks?	
Country of corresponding author	Belgium	
Language of publication	English	
Sources of funding	NR	
Randomisation and allocation	Patients were randomised 1 : 1, stratified according to centre to receive either epoetin beta or standard care with transfusion support	

Note
Results also presented in abstract form[87] (this reference was included in the Wilson and colleagues[2] review).

Treatment arms		
Arm drug name(s)	Epoetin beta	Standard care
n	133	129
Dose and frequency (once daily, twice daily, etc.)	150 U/kg Q3W. Average dose of epoetin over the study period was 174 IU/kg per administration	NA
Dose adjustment (yes/no)	Dose increased to 300 U/kg Q3W for those patients in whom Hb level increased by < 0.5 g/dl after 3–4 weeks or by < 1 g/dl after 6–8 weeks. The dose was reduced by 50% if the Hb level increased by > 2 g/dl per month, whereas treatment was interrupted if the Hb level increased to > 14 g/dl. Treatment was recommenced at half the previous dose once the Hb level had declined to < 12 g/dl	NA
Route of administration	Subcutaneous	NA
Duration of epoetin treatment	12 weeks	NR
Adjuvant anaemia treatment	Oral iron supplementation (200–300 mg elemental iron per day) as indicated (transferrin saturation < 15%)	Oral iron supplementation (200–300 mg elemental iron per day) as indicated (transferrin saturation < 15%)
Transfusion trigger	Hb 8.5 g/dl was a guide to initiate transfusion throughout the centres	Hb 8.5 g/dl was a guide to initiate transfusion throughout the centres

Outcomes	
Primary outcome	HRQoL (change from baseline to week 12 in SF-36, FACT-An and FACT-F)
Other outcomes	Haematological response [defined as an increase in Hb level of ≥ 2 g/dl without transfusion requirement after the first 4 weeks (also measured haematological response as an increase in Hb level of ≥ 2 g/dl or an increase in Hb level to ≥ 12 g/dl)]; change in Hb from baseline to week 12 (plus changes in Hb and corresponding changes in quality of life); RBCTs; HRQoL[a] (change from baseline to week 12 in VAS and FACT-An Global); AEs[b] (including no. of hospitalisations)

a All quality-of-life assessments were performed immediately before the clinic visits so that patients could not be influenced by reference to Hb levels.

b Defined as any undesired, noxious or pathological change in a patient, as indicated by signs, symptoms and/or laboratory changes that occurred in association with the use of a drug or placebo, whether considered to be drug related or not.

Notes

Clinic visits were every 3 or 4 weeks for patients off chemotherapy. Clinical outcomes were collected at each post-baseline visit. Quality of life was assessed at baseline, after 3–4 weeks, after 6–8 weeks and at the end of the study.

Analysis		
Statistical technique used		Psychometric evaluation was performed to evaluate how well the quality-of-life scale items satisfied the assumptions underlying the Likert method for summated rating. The internal consistency reliability of each scale score was estimated using Cronbach's alpha. Cronbach's alpha, which ranges from 0 to 1, where '1' equals perfect reliability, is based on the average inter-item correlation and the number of items. Minimum values ≥ 0.70 have been recommended for group-level comparisons.[195] For quality-of-life assessments only patients for whom values were available at baseline and at least one follow-up visit were included in the analysis. The data are presented in their raw form and using the LOCF approach for patients with missing values at the final visit. For the percentage of clinical responders, Kaplan–Meier estimates and CIs for time to treatment response were determined and curves were compared using the log-rank test. The observed/predicted log serum erythropoietin ratio was derived from reference regression at the particular haematocrit or Hb level and was calculated for responders and non-responders to epoetin beta. The relation between endogenous erythropoietin level and response to treatment was explored using the OR and RRs.[196] Appropriate parametric and non-parametric tests were used to analyse between-group differences for continuous and categorical variables respectively. All tests were two-sided and $p < 0.05$ was considered significant. Assessment of statistical significance was not adjusted for multiple comparisons
ITT analysis?		Yes; ITT = 262
Does statistical technique adjust for confounding?		NR
Power calculation (a priori sample calculation)?		Based on expected change in SF-36 PCS score. To detect a between-group difference in SF-36 PCS score of at least 4 points, assuming a SD of 10 using a two-sided test with a statistical power of 80% and $\alpha = 2.5\%$, at least 121 patients/group were required to complete the study and be evaluable for efficacy. To allow for dropouts approximately 310 patients were to be enrolled; however, this was not achieved
Attrition rate (loss to follow-up)?		51 patients were withdrawn from the study (epoetin beta $n = 30$; control $n = 21$); 20 were withdrawn because of AEs (epoetin beta $n = 15$; control $n = 5$). Other reasons for withdrawal included death, loss to follow-up, withdrawal of consent and protocol violation
Was attrition rate adequately dealt with?		LOCF for patients with missing values at final visit
No. (%) followed up from each condition?		NR
Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		Haematological and solid
Treatment (e.g. chemotherapy platinum/ non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Chemotherapy, NR
Adjuvant anaemia treatment	Iron	Oral iron supplementation (200–300 mg elemental iron per day) was indicated (transferrin saturation < 15%)
	G-CSF	NR
	Transfusion trigger	Hb 8.5 g/dl
	Hb inclusion criterion level	≤ 11 g/dl

	Arm 1 = epoetin	Arm 2 = control	Notes	*p*-value
Evaluable population	*n* = 133	*n* = 129		
Sex				
Male, *n* (%)	46 (35)	52 (40)		
Female, *n* (%)	87 (65)	77 (60)		
Age (years), median (range)	62 (24–85)	62 (24–85)		
Hb (g/dl), median (range)	9.0 (5–13)	9.2 (5–12)		
Erythropoietin (mU/ml), median (range) (*n* = 25)	54 (7–1650)	58 (5–4300)		
Iron, serum (µg/dl), median (range) (*n* = 26)	63.7 (6–472)	78.8 (4–510)		
Iron saturation (%), median (range) (*n* = 26)	20.6 (1–97)	29.0 (2–100)		
Folic acid (mg/ml), mean (SD) (*n* = 25)	NR	NR		
Vitamin B_{12} (pg/ml), mean (SD) (*n* = 24)	NR	NR		
Baseline quality-of-life score				
SF-36 PCS, mean (SD); median (range)	35 (8.4); 35 (17–60)	38 (9.5); 38 (15–60)		
FACT-F, mean (SD); median (range)	27 (12); 28 (1–49)	31 (11); 33 (2–51)		0.02[a]
FACT-AN, mean (SD); median (range)	20 (3.8); 21 (6–27)	21 (4.4); 22 (2–28)		
VAS, mean (SD); median (range)	56 (17); 53 (11–96)	62 (17); 60 (18–96)		
Were intervention and control groups comparable?	Authors report that 'Overall, there were no significant differences between groups in baseline demographics and clinical characteristics, except for a significantly higher proportion of patients in the control group having received prior chemotherapy 80 vs. 68%; *p* = 0.025)' (p. 990). With respect to quality-of-life measures, baseline scores on the FACT-An subscale were comparable between treatment groups, although those randomised to epoetin beta therapy had a lower FACT-F subscale score relative to the control group (*p* = 0.02)			

a *p* = 0.02 vs. epoetin beta group.

Results				
Haematological response, *n* (%)				
Responders: increase ≥ 2 g/dl	63 (47)	17 (13)	Figure 2 provides a graph showing response	< 0.001
Responders: increase ≥ 2 g/dl or increase to ≥ 12 g/dl	65 (49)	19 (15)		
Hb baseline to week 12, median increase (range)				
All patients	2.1 (–3 to 8) (*n* = 112)	0.9 (–3 to 6) (*n* = 112)	Figure 3 provides a graph showing Hb change	< 0.001
Patients with solid tumours	2.1 (–1 to 8) (*n* = 45)	0.9 (–3 to 4) (*n* = 51)		No *p*-values provided for subgroup analyses
Patients with lymphoid tumours	1.9 (–3 to 8) (*n* = 67)	0.9 (–3 to 6) (*n* = 61)		
With chemotherapy	2.1 (NR) (*n* = 74)	(NR) (*n* = 88)		
Without chemotherapy	2.0 (NR) (*n* = 38)	0.2 (NR) (*n* = 24)		

Results				
Haematological response, *n* (%)				
Transfusions				
Hb level before transfusion (g/dl), median	7.64	7.8	Units transfused per patient reduced by 45% during the treatment period with epoetin beta	
Patients transfused in last 8 weeks of study (%)	22	43		< 0.001
Patients transfused overall (%)	32	52		0.001
HRQoL				
Cronbach's alpha: reliabilities for SF-36 subscales varied from 0.83 to 0.90 for the pooled population, apart from the general health subscale (0.75). The FACT-F subscale and the FACT-An global scale showed high consistency (> 0.9), whereas the FACT-An seven-item subscale reached 0.68 using the pooled population				
Median change baseline to week 12, LOCF data				
SF-36 PCS	+3.1 ($n = 104$)	NR ($n = 109$)	*p*-value vs. control	< 0.05
FACT-F	+3.0 ($n = 104$)	NR ($n = 109$)		< 0.05
FACT-AN	+1.0 ($n = 104$)	NR ($n = 109$)		0.076
VAS	+10.0 ($n = 111$)	+1.0 ($n = 112$)		0.004
Median change baseline to week 12, data without LOCF				
SF-36 PCS	+3.3 ($n = 77$)	NR	*p*-value vs. control	0.01
FACT-F	+4.0 ($n = 90$)	NR		0.001
FACT-AN	+1.0 ($n = 89$)	NR		0.068
VAS	+10.0 ($n = 89$)	+3.0 ($n = 98$)		0.001

Note
Patients with lymphoproliferative malignancies derived at least as much quality-of-life benefit from epoetin beta therapy as patients with solid tumours; likewise, patients previously exposed to chemotherapy showed similar quality of life benefits with epoetin beta as chemotherapy-naive patients (data not shown). However, patients who responded to epoetin beta therapy (i.e. achieved the target Hb response) experienced a greater improvement in quality of life from baseline to the final visit than patients who were non-responders (i.e. did not achieve the target Hb response). Patients who responded to epoetin beta therapy had a mean increase of 3.7 points in their SF-36 score, 7.2 points in their FACT-F score and 1.2 points in their FACT-An subscale score; the corresponding improvements in the non-responder group were 3.1, 3.4 and 0.5 points, respectively. Changes in SF-36 PCS and FACT-F scores were mediated through changes in Hb level ($p < 0.01$), as shown by a path analysis in which epoetin beta treatment, quality of life increase and Hb increase were used as dependent variables in turn. Mean change in quality-of-life scores from baseline in the epoetin beta and control groups for the without LOCF population are reported graphically.

AEs in ≥ 5% of patients in at least one treatment group, n (%)			
Malignancy progression	33 (25)	42 (33)	
Anaemia	18 (14)	33 (26)	
Leucopenia	20 (15)	19 (15)	
Thrombocytopenia	8 (6)	13 (10)	
Bronchitis	7 (5)	8 (6)	
Fever	5 (4)	10 (8)	
Nausea	6 (5)	8 (6)	
Pain	9 (7)	5 (4)	
Pneumonia	9 (7)	5 (4)	
Asthenia	6 (5)	7 (5)	
Diarrhoea	11 (8)	2 (2)	
Infection	8 (6)	4 (3)	
Sepsis	3 (2)	7 (5)	
Vomiting	9 (7)	1 (< 1)	
Depression	8 (6)	1 (< 1)	
Headache	7 (5)	2 (2)	
No. of hospitalisations per patient, mean (SD)	3.8 (4.5)	4.1 (4.9)	0.52
No. of hospital days, mean (SD)	11.7 (13.7)	9.4 (10.3)	0.46
Admissions related to anaemia, mean (SD)	0.8 (2.2)	1.5 (3.6)	0.043
Iron			
Iron supplementation (mostly oral), *n*	30	28	
Parenteral iron, *n*	9	2	
Serum iron deficit, baseline to study end	4.5 µg/dl[a]	16.8 mg/dl[a]	< 0.01

a On reported on p. 993.

Note

No clinically relevant changes in transferrin saturation were observed for either group between baseline and study end (data not shown).

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear; randomised but method not specified
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	No; higher proportion of participants in the control group had received chemotherapy previously (80% vs. 68%; $p = 0.025$); participants randomised to epoetin beta had lower FACT-F scores relative to the control group ($p = 0.02$)
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No (open label)
6. Were the outcome assessors blind to treatment allocation?	No (open label)
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Yes
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Partially; total number and number withdrawing because of AEs reported per group. Other reasons stated but numbers not reported

Other	
Generalisability	
Author conclusions	Compared with transfusion therapy, epoetin beta produced a clinically significant improvement in quality of life in patients with anaemia associated with malignancy. Epoetin beta improved physical function and well-being as a result of diminished anaemia-related symptoms as measured by the FACT-An and FACT-F questionnaires. These improvements in quality of life accompany and are mediated through improvements in Hb concentration and can be achieved after a few weeks of epoetin beta therapy. In addition, baseline erythropoietin serum levels and the observed/predicted ratio might identify those patients with lymphoproliferative malignancies who are more likely respond to epoetin beta; however, this requires further study
Reviewer comments	Abstract by Coiffier and colleagues included in the Wilson and colleagues[2] review. We have included the full paper in this review

LOCF, last observation carried forward; NR, not reported; PCS, physical component summary; Q3W, once every 3 weeks.

EndNote ref. ID: 2689	Malignancy type: haematological (multiple myeloma) Treatment: epoetin alfa

Study design		Participants
Author, year	Dammacco 2001[66]	*n* (ITT) = 145
Objective	To evaluate the efficacy of epoetin alfa in correcting anaemia in patients with multiple myeloma thereby decreasing transfusion requirements	Inclusion criteria: Men and women aged 40–80 years with multiple myeloma; life expectancy of at least 3 months and an ECOG score of 0–3; receiving chemotherapy for at least 6 months; baseline Hb level < 11.0 g/dl Exclusion criteria: Patients with uncontrolled hypertension or evidence of untreated iron, folate or vitamin B_{12} deficiency; received a blood transfusion within 7 days of study entry; major infection within 1 month or an acute illness within 7 days of study entry
No. of centres	31	
Other references/ aliases	None	
Geographical setting	12 countries (Italy, Poland, UK, Norway, Sweden, Czech Republic, Hungary, Belgium, Israel, Denmark, Spain, Switzerland)	
Duration of treatment	12 weeks double blind	
Length of follow-up (if different)	12 weeks open label optional	
Country of corresponding author	Italy	
Language of publication	English	
Sources of funding	Supported by a grant from the RW Johnson Pharmaceutical Research Institute, Bassersdorf, Switzerland	
Randomisation and allocation	Stratified according to receipt of blood transfusion within the preceding 3 months. Patients within each transfusion stratum were then randomised to treatment or control. Patients in both arms who completed the 12 weeks had an option to receive epoetin for up to 12 weeks in the open-label extension of the study	

Treatment arms		
Arm drug name(s)	Epoetin alfa	Placebo
n	69	76
Dose and frequency (once daily, twice daily, etc.)	150 IU/kg Q3W (each dose separated by at least 1 day)	Matched to epoetin alfa dose
Dose adjustment (yes/no)	Yes: if Hb level had not increased by ≥ 1 g/dl after 4 weeks of treatment the dose was doubled to 300 IU/kg Q3W for the remaining 8 weeks of the study; if Hb level increased to > 14 g/dl treatment was withheld until Hb level was < 12 g/dl and was then reinitiated at a dose approximately 25% lower than the start dose; if Hb level increased by ≥ 2 g/dl within a 4-week period the dose was reduced by approximately 25% to maintain an increase of < 2 g/dl	Matched to epoetin alfa dose
Route of administration	Subcutaneous	Subcutaneous
Duration of epoetin treatment	12 weeks (double blind)	12 weeks (double blind)
Adjuvant anaemia treatment	NR	NR
Transfusion trigger	< 8 g/dl; to be avoided if possible if Hb > 8 g/dl	To be avoided if possible if Hb > 8 g/dl

Outcomes	
Primary outcome	Transfusion requirement stratified by baseline transfusion status
Other outcomes	HRQoL (change in quality-of-life scores: NHP and CLAS/LASA). AEs reported (by questioning patients at study visits); all AEs together with investigators' assessments of their seriousness, severity and presumed relationship to study medication were recorded

Notes

Vital signs, clinical laboratory tests (e.g. complete blood and reticulocyte count), serum chemistry and urinalysis were competed 7 days before study entry, on day 1 and weekly. Serum erythropoietin was evaluated before study entry, on day 1 and at weeks 2, 4 and 8. Serum iron, transferrin, total iron-binding capacity and ferritin were evaluated before study entry, on day 1 and every 4 weeks.
Responders: proportion of patients during double-blind phase with an increase in Hb level of ≥ 2 g/dl.
Correctors: achieved a Hb level of ≥ 12 g/dl without receiving a transfusion within the previous month.
NHP: 38 questions combined to form six separate scales: emotional reactions, pain, energy, sleep, social isolation and physical mobility. Patients respond yes/no. Scale calculated by counting the number of items rated as 'yes' within each scale. Scale is then converted to a scale from 0 (good) to 100 (bad).
CLAS: 100 mm scale separately evaluates energy level, ability to carry out daily activities and overall quality of life.
Also carried out/measured pre study and at the end of the study: complete physical examination, clinical signs and symptoms of multiple myeloma, bone marrow biopsy, skeletal radiography, serum M-component, urine light-chain M-component, folate, vitamin B_{12}, myeloma staging and physician's performance score and global assessment.

Analysis	
Statistical technique used	Proportion of patients transfused stratified by pre-study transfusion history was analysed with the Cochran–Mantel–Haenszel test. Only data for months 2 and 3 were analysed (effects not expected before this time).[156] Between-group changes in haematological parameters from baseline to last determination were compared using *t*-tests; between-group differences in the proportions of responders and correctors were compared using Fisher's exact test. For quality of life, the Kruskal–Wallis test was performed to ensure that no bias had been introduced by deleting patients. Assessments were evaluated in univariate analyses using *t*-tests; multivariate analyses were also performed. Changes in performance scores between treatment groups, categories of response to chemotherapy and the treatment groups stratified by response to chemotherapy were analysed using Kruskal–Wallis and Cochran–Mantel–Haenszel tests. Between-group differences in the physician's global assessment were analysed using the Kruskal–Wallis test. All statistical tests were two-sided
ITT analysis?	Results for the primary efficacy evaluation of transfusion requirements and safety are reported for the ITT population. Results for the secondary efficacy parameters are reported for the efficacy population (patients randomised to a treatment group who remained in the study for at least 2 months – it was believed that this duration would allow patients, including those who required a dose increase at week 4, sufficient time to respond). Quality-of-life analyses were performed for the ITT population minus patients who died during the double-blind phase of the study, for whom quality-of-life data were incomplete
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)	NR
Attrition rate (loss to follow-up)?	Yes. Five epoetin patients discontinued [$n = 2$ AEs (death from septic shock $n = 1$ and disease progression $n = 1$); $n = 3$ for personal reasons]. 15 placebo patients discontinued [$n = 3$ AEs (pneumonia $n = 1$, death from septic shock $n = 1$, death from acute renal failure $n = 1$); $n = 6$ disease progression; $n = 3$ personal reasons; $n = 3$ other unspecified reasons]
Was attrition rate adequately dealt with?	Partially: ITT population was not used for secondary efficacy parameters and HRQoL data
No. (%) followed up from each condition?	NA

Baseline characteristics					
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		Haematological: multiple myeloma			
Treatment (e.g. chemotherapy platinum/ non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Unclear, although most commonly used non-platinum-based chemotherapy			
Adjuvant anaemia treatment	Iron	NR			
	G-CSF	NR			
	Transfusion trigger	To be avoided if possible if Hb > 8 g/dl			
	Hb inclusion criterion level	< 11.0 g/dl			
		Arm 1 = epoetin alfa (*n* = 69)	**Arm 2 = placebo (*n* = 76)**	**Notes**	***p*-value**
Sex					
Male, *n* (%)		34 (49%)	31 (41%)		
Female, *n* (%)		35 (51%)	45 (59%)		
Age (years), median (range)		67.3 (43.0–80.4)	65.0 (38.2–88.9)		
ECOG performance score (0–4; higher score indicates worse the performance status), (%)					
Missing		1	0		
0		9	8		
1		51	50		
2		33	34		
3		6	8		
Creatinine (μmol/l), mean ± SD		106.3 ± 42.29	102.4 ± 35.60		
No. of chemotherapy cycles within 6 months prestudy, mean ± SD (range)		3 ± 2.5 (0–15) (*n* = 68)	4 ± 2.0 (0–8) (*n* = 75)		
Malignancy staging (%)[197]					
IA		4	5		
IB		0	1		
IIA		33	34		
IIB		4	0		
IIIA		46	54		
IIIB		12	5		
Hb baseline (g/dl), mean ± SD (median; range)		9.3 ± 1.27 (9.6; 5.7–11.5)	9.6 ± 0.95 (9.7; 7.4–11.8)		
Hb level (g/dl) at transfusion (for patients receiving transfusions at baseline), mean ± SD		8.1 ± 1.08 (*n* = 25)	8.1 ± 0.93 (*n* = 28)		
Serum erythropoietin level (mU/ml), median (range)		116 (18–5220) (*n* = 36)	93 (10–408) (*n* = 36)		
Were intervention and control groups comparable?		No *p*-values reported but authors state that 'baseline demographic and clinical characteristics were comparable between treatment groups' (p. 174). Based on the reported values the groups appear comparable			

Results			
ITT population	*n* = 69	*n* = 76	
RBCT			
Patients transfused during months 2 and 3 (double-blind study), *n* (%)	19 (27.5)	36 (47.4)	0.017
Transfused (by transfusion history) (either having or not having received one or more transfusions during the previous 3 months)			
Transfused pre study, *n* (%)	14 (56.0)	22 (78.6)	0.006
Not transfused pre study, *n* (%)	5 (11.4)	14 (29.2)	
Hb level (g/dl) triggering RBCT, mean (range)	7.66 (6.1–9.7)	7.89 (6.47–9.45)	
Adverse effects of treatment (reported in ≥ 10% of patients in any treatment group),* n *(%)			
Any AE	50 (72.5)	57 (75.0)	
Fever	5 (7.2)	10 (13.2)	
Pain	9 (13.0)	3 (3.9)	
Skeletal pain	5 (7.2)	2 (2.6)	
Leukopenia	9 (13.0)	6 (7.9)	
Granulocytopenia	3 (4.3)	4 (5.3)	
Dyspnoea	2 (2.9)	3 (3.9)	
Hypertension	3 (4.3)	1 (1.3)	
Infection	1 (1.4)	4 (5.3)	
Deaths, *n*[a]	1	7	

a No deaths were attributed to the study drug (reasons reported for double-blind and open-label phases not reported separately). Reasons for death included disease progression (50% of deaths for both periods), septic shock/infection, acute renal failure or cardiogenic shock.

Note

Disease response comparable between patients receiving epoetin alfa and those receiving placebo (epoetin alfa did not appear to influence effects of chemotherapy, treatment or disease status) (data not reported).

ECOG score	*n* = 66	*n* = 66	
Change from baseline	NR	NR	0.038
1-point improvement, *n* (%)	13 (19.7)	4 (6.1)	
2-point deterioration, *n* (%)	1 (1.5)	5 (7.6)	

Response to anaemia treatment (rated by physician) (%)[a]		
Excellent	19.7	0.0
Very good	19.7	3.0
Good	13.6	9.1
Fair	18.2	24.2
Poor	28.8	63.6

a Not clear if results are provided for the double-blind phase of the study only.

Efficacy population	$n = 66$	$n = 66$	
Hb			
Change in Hb level (g/dl) baseline to last value, mean ± SD	1.8 ± 2.05	0.0 ± 1.18	< 0.001
Mean Hb level (g/dl) week 12	11.2	9.7	
Responders, *n* (%)	38 (57.6)	6 (9.1)	< 0.001
Mean time (days) for responders to achieve Hb level ≥ 2 g/dl above baseline	46	35[a]	
Correctors, *n* (%)	30 (45.5)	2 (3)	< 0.001
Mean time (days) for correctors to achieve Hb level ≥ 12 g/dl	50	23[a]	

a Most likely because of the small numbers of placebo-treated responders and correctors.

HRQoL			
Quality of life population	$n = 66$	$n = 72$	

Notes
Health state utility scale = NHP and CLAS.
Data not reported.
Both treatment groups showed some improvement in quality of life but multivariate analysis did not show a significant difference between the groups for week 12 change scores, although nearly all trends favoured patients treated with epoetin alfa (data NR).
Univariate analyses of within-group mean changes from baseline to week 12 indicated a significant improvement in four quality-of-life scales for the epoetin alfa group [NHP scales for emotional reaction $p < 0.001$ and social isolation $p = 0.05$ and CLAS scales for energy level ($p = 0.01$) and ability to carry out daily activities ($p < 0.001$)] and one quality-of-life scale for the placebo group (NHP sleep scale $p = 0.03$). A trend towards improvement was also noted for CLAS overall quality of life for the epoetin alfa-treated group, whereas for the placebo group scores were virtually unchanged from baseline.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear; no *p*-values reported but groups appear comparable based on the values reported
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes (although not blinded to dose – placebo dose matched epoetin alfa dose)
6. Were the outcome assessors blind to treatment allocation?	Yes (although not blinded to dose – placebo dose matched epoetin alfa dose)
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially (variability can be calculated from data presented in the paper)
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Partially: primary end point and HRQoL only
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes

Other	
Generalisability	Haematological cancer
Author conclusions	Epoetin alfa is an effective and well-tolerated agent for the management of myeloma-associated anaemia. Benefits include prevention or amelioration of anaemia, reduction in transfusion requirements and improvements in quality of life
Reviewer comments	

CLAS, Cancer Linear Analogue Scale; ECOG, Eastern Cooperative Oncology Group; NHP, Nottingham Health Profile; NR, not reported; Q3W, once every 3 weeks.

EndNote ref. ID: 2700	Malignancy type: solid (breast) Treatment: epoetin (assumed epoetin alfa)	
Study design		**Participants**
Author, year	Del Mastro 1997[67]	*n* = 62
Objective	To evaluate the ability of epoetin to prevent the development of clinically significant anaemia in patients treated with chemotherapy	Inclusion criteria: Stage II breast cancer patients receiving accelerated (every 14 days) adjuvant chemotherapy after radical mastectomy or breast-conserving surgery; Hb ≤ 12 g/dl; normal mean corpuscular volume of RBCs (within 80–100 fl) Exclusion criteria: Uncontrolled hypertension; inadequate iron reserves as evidenced by serum iron level less than normal (37 µg/dl) associated with a ferritin level < 10 ng/ml and/or transferrin saturation < 20%
No. of centres	1 (February 1993–June 1995)	
Other references/aliases	None	
Geographical setting	Italy	
Duration of treatment	12 weeks: 6 cycles plus 2 weeks (starting on day 1 of chemotherapy until 2 weeks after the last chemotherapy cycle); 36 administrations planned per participant	
Length of follow-up (if different)	A blood count was performed 6 months after the last chemotherapy cycle	
Country of corresponding author	Italy	
Language of publication	English	
Sources of funding	Supported in part by a grant from the Associazione Italiana per la Ricerca sul Cancro, Milan, Italy	
Randomisation and allocation	Randomisation was performed by a telephone call to a central office. Randomisation was balanced with blocks of variable size. No stratification was planned. Two-arm Phase III study	
Treatment arms		
Arm drug name(s)	Epoetin	Best supportive care
n	31	31
Dose and frequency (once daily, twice daily, etc.)	150 U/kg Q3W	NA
Dose adjustment (yes/no)	Yes. If Hb increased to 15 g/dl in two consecutive weekly assays, epoetin treatment was stopped until Hb < 13 g/dl (*n* = 4)	NA
Route of administration	Subcutaneous	NA
Duration of epoetin treatment	12 weeks: 6 cycles plus 2 weeks (starting on day 1 of chemotherapy until 2 weeks after last chemotherapy cycle); 36 administrations planned per patient	12 weeks

Treatment arms		
Adjuvant anaemia treatment	G-CSF 5 µg/kg SC day 4 to day 11 during the first 5 cycles; it was withdrawn after the sixth cycle. Oral iron supplement (ferrous sulphate 325 mg/d) was started at the occurrence of serum iron < 37 µg/dl; serum ferritin < 10 ng/ml; or transferrin saturation < 20% ($n = 4$)	G-CSF 5 µg/kg SC day 4 to day 11 during the first 5 cycles; it was withdrawn after the sixth cycle. Oral iron supplement (ferrous sulphate 325 g/d) was started at the occurrence of serum iron < 37 µg/dl; serum ferritin < 10 ng/ml; or transferrin saturation < 20% ($n = 3$)
Transfusion trigger	Hb < 8 g/dl or in presence of anaemia-related symptoms (dyspnea, tachycardia, severe asthenia)	Hb < 8 g/dl or in presence of anaemia-related symptoms (dyspnea, tachycardia, severe asthenia)

Outcomes	
Primary outcome	Unclear
Other outcomes	RBC count (mean corpuscular volume, mean corpuscular Hb level, mean corpuscular Hb concentration); haematocrit; reticulocyte count; HRQoL (PDI)

On day 1 of each cycle: blood cell count, reticulocyte count, serum iron, transferrin, ferritin and total iron-binding capacity. Assay of erythropoietin serum at baseline and 2 weeks post last chemotherapy cycle only for the first 15 patients in each arm.

Notes

PDI: 5-point, 13-item self-assessment scale, developed and validated in Italy to measure psychological distress in cancer patients. Measured before randomisation, after the third cycle of chemotherapy and at the first follow-up visit (approx. 6 months after randomisation).

AE severity assessed using WHO criteria. Worst toxicity for each patient during all cycles was documented.

Other measures: iron metabolism – serum iron, transferrin, ferritin and total iron-binding capacity; serum erythropoietin: observed/predicted ratio (predicted was derived from regression equations for haematocrit ≤ 38% and > 38%).

Analysis	
Statistical technique used	Student's *t*-test for dependent and independent samples was used. ANCOVA for repeated measures was used to evaluate differences in terms of Hb, iron-related parameters and psychological distress after adjustment for baseline values. The probability of maintaining Hb levels at > 10 g/dl was calculated using the Kaplan–Meier method. The log-rank test was used to assess the difference between the curves. Patients who did not develop anaemia were censored at the cycle at which they were taken off treatment. Patients who received a RBCT were considered as events
ITT analysis?	Yes [HRQoL: PDI available only for 53 (85.5%) patients]
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)?	Yes. Previous study indicated that 50% of patients treated with accelerated CEF chemotherapy developed clinically significant anaemia defined as Hb level ≤ 10 g/dl. Study interested in reducing anaemia occurrence to 10% of patients; 30 patients per arm had to be randomised to ensure a significance of 0.05 (two-sided) and a power of 0.90
Attrition rate (loss to follow-up)?	Partially: two patients in the control group and three in the epoetin group did not complete all six cycles of chemotherapy. Two patients refused accelerated chemotherapy and epoetin treatment. They were treated with CEF chemotherapy at the same doses but every 3 weeks. No attrition rate provided for the last measurement (2 weeks post sixth cycle) or for HRQoL data
Was attrition rate adequately dealt with?	Unclear as attrition rate not fully reported
No. (%) followed up from each condition?	Yes

Baseline characteristics					
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/ haematological/myelodysplastic syndrome/mixed)		Solid (breast)			
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Chemotherapy: six cycles of CEF, cycles repeated every 2 weeks (unless delayed until hematological recovery)			
Adjuvant anaemia treatment	Iron	Oral iron supplement (ferrous sulphate 325 mg/day) started on occurrence of serum iron < 37 µg/dl, serum ferritin < 10 ng/ml or transferrin saturation < 20%			
	G-CSF	G-CSF 5 µg/kg subcutaneously from day 4 to day 11 during the first five cycles; withdrawn after the sixth cycle			
	Transfusion trigger	Hb < 8 g/dl or in presence of anaemia-related symptoms (dyspnoea, tachycardia, severe asthenia)			
	Hb inclusion criterion level	≤ 12 g/dl			
		Arm 1 = epoetin (*n* = 31)	**Arm 2 = control (*n* = 31)**	**Notes**	***p*-value**
Age (years), median (range)		54 (31–68)	56 (29–68)		
Hb (g/dl), mean ± SD		13.0 ± 0.7	13.1 ± 0.6		
White blood cell count ($\times 10^9$/l), mean ± SD		7.2 ± 2.0	7.1 ± 2.0		
Platelet count ($\times 10^9$/l), mean ± SD		247 ± 60.7	241 ± 51.3		
RBC count ($\times 10^{12}$/l), mean ± SD		4.4 ± 0.2	4.4 ± 0.3		
Haematocrit (%), mean ± SD		39.8 ± 2.2	40.0 ± 2.0		
Reticulocyte count (%), mean ± SD		8.8 ± 6.8	7.0 ± 5.6		
Corpuscular volume (fl), mean ± SD		91.2 ± 3.7	90.7 ± 4.7		
Corpuscular Hb (pg), mean ± SD		29.9 ± 1.1	29.8 ± 1.6		
Corpuscular Hb concentration (g/dl), mean ± SD		32.7 ± 1.1	32.8 ± 1.0		
Serum iron (mmol/l), mean ± SD		77.3 ± 46.2	93.1 ± 37.0		
Transferrin saturation (%), mean ± SD		20.7 ± 14.5	27.1 ± 11.4		
Ferritin (ng/ml)		61.2 ± 48.1	45.1 ± 35.1		
Total iron-binding capacity (µg/dl), mean ± SD		348 ± 55.6	352 ± 51.3		
Serum erythropoietin (mU/ml), median (range)		21.0 (0–512)	25.5 (0–800)	Evaluated in 16 patients per arm; note that methods section states 15 patients	
Observed/predictive ratio, median (range)		1.13 (0.82–1.31)	1.19 (0.87–2.34)		
No. (%) receiving conservative surgery		22 (71)	26 (84)		
HRQoL: PDI, mean ± SD		27.5 ± 8.6 (*n* = 27)	27.1 ± 7.3 (*n* = 26)		
Were intervention and control groups comparable?		Unclear. *p*-values NR but authors state that there was 'no statistically significant difference in baseline haematological and iron-related parameters' (p. 2717)			

Results				
RBC-related parameters at end of treatment period, mean ± SD				
RBC count (×10^{12}/l)	4.1 ± 0.5	3.3 ± 0.4		0.000
Hb (g/dl)	12.2 ± 1.2	10.0 ± 1.1		0.000
Hb decrease at the end of chemotherapy[a]	0.8 ± 1.4 (95% CI 0.3 to 1.4)	3.05 ± 1 (95% CI 2.6 to 3.5)		< 0.001
Hb (g/dl) at 6 months' follow-up	13.2 ± 0.87	13.2 ± 0.61		> 0.05
Anaemia (Hb level ≤ 10 g/dl), *n* (%)[b]	0 (0) (95% CI 0 to 14)	16 (52) (95% CI 33 to 69)		0.00001
RBCT (no. of patients requiring)		2		
Haematocrit (%)	37.8 ± 3.9	31.0 ± 3.8		0.000
Reticulocyte count (%)	10.1 ± 9.8	11.8 ± 8.7		0.6
Mean corpuscular volume (fl)	91.9 ± 6.7	94.7 ± 4.3		0.08
Mean corpuscular Hb level (pg)	29.6 ± 2.3	30.7 ± 1.8		0.07
Mean corpuscular Hb concentration (g/dl)	32.3 ± 1.3	32.4 ± 1.2		0.8
Observed/predictive ratio, median (range)	1.32 (0.85–2.19)	1.05 (0.63–2.14)	Evaluated in 16 patients per arm; note that methods section states 15 patients	
Serum erythropoietin (mU/ml), median (range)[a]	83 (18–774)	66 (14.5–469)		
O/P ratio < 1, %	1	37		

O/P, observed/predictive ratio.
a RBC and haematocrit values showed a similar course to Hb data, but data NR in the paper.
b In the control group, patients developing anaemia had a mean baseline Hb level that was significantly lower than that in those who did not (12.8 g/dl ± 0.6 g/dl treatment group vs. 13.4 ± 0.5 control group; $p = 0.005$). The probability of maintaining a Hb level > 10 g/dl was significantly lower in the control group than in the epoetin group ($p < 0.0001$ (data reported graphically; see Figure 3).

Note
Reticulocytes increased in both arms from baseline to week 2 (treatment arm from 8% to 17%, control arm from 7% to 11%). After this early increase reticulocytes decreased and in both arms the final value was not significantly different from the baseline value (treatment arm 10%, control arm 12%).

Iron metabolism	Throughout six cycles of treatment, serum iron ($p < 0.001$) and transferrin saturation ($p = 0.0002$) significantly decreased, regardless of the treatment arm. Differences between the two arms for serum iron ($p = 0.33$) and transferrin saturation ($p = 0.79$) were not statistically significant. After the first cycle of chemotherapy a sharp increase in mean serum ferritin was observed in both arms. After this time ANCOVA showed that the ferritin values did not change significantly ($p = 0.14$) during treatment, but levels were significantly lower in the epoetin group than in the control group ($p = 0.0015$). Results were presented graphically	
Total iron-binding capacity at the end of chemotherapy, mean ± SD	356.4 ± 62.0	338.5 ± 58.6
HRQoL		
Health state utility scale: PDI score	*n* = 27	*n* = 26
During treatment, mean ± SD	30.6 ± 10.4	28.3 ± 8.0
Follow-up, mean ± SD	27.4 ± 11.2	26.3 ± 9.8

Notes
Psychological distress increased during treatment and decreased at the first follow-up visit ($p = 0.03$).
Treatment groups did not differ in terms of psychological distress ($p = 0.4$).

Adverse effects of treatment*, n *(%)				
	WHO grade			
Leukopenia	I–II	–	4 (13)	No grade IV toxicity reported. No statistically significant differences in the main toxicities were observed between the two arms
	III	2 (7)	–	
Thrombocytopenia	I	4 (13)	4 (13)	
Nausea/vomiting	I–II	22 (71)	23 (74)	
	III	6 (19)	3 (10)	
Alopecia	III	31 (100)	31 (100)	
Mucositis	I–II	16 (52)	15 (48)	
	III	3 (10)	4 (13)	
Diarrhoea	I–II	1 (3)	3 (10)	
	III	1 (3)	1 (3)	
Bone pain	I–II	12 (39)	10 (32)	
	III	4 (13)	4 (13)	
Fatigue	I–II	18 (58)	19 (61)	
	III	1 (3)	1 (3)	
Fever	I–II	5 (16)	5 (16)	
	III	–	1 (3)	

Note
Epoetin-related toxicities included facial rash ($n = 2$) after the first administrations. In one of these patients, dyspnoea and headache requiring dose reduction also occurred. Almost all patients experienced mild or moderate local burning during epoetin administration.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Yes
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	Unclear; randomisation was performed by a telephone call to a central office
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear: no *p*-values reported but authors state that there were no significant differences between groups
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No
6. Were the outcome assessors blind to treatment allocation?	NR
7. Were the point estimates and measure of variability presented for the primary outcome measure?	No; no primary outcome stated
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	Partial; some evidence, e.g. white blood cell count mentioned but data NR
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes; however, for HRQoL only 87% and 84% of participants were analysed in the epoetin and control groups respectively
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Partially

Other	
Generalisability	Women only (breast cancer patients)
Author conclusions	Epoetin prevents anaemia in patients undergoing chemotherapy. Further trials are required to identify subsets of patients in which the preventative use of this drug could be cost-effective
Reviewer comments	

ANCOVA, analysis of covariance; CEF, cyclophosphamide, epirubicin and fluorouracil; NR, not reported; Q3W, once every 3 weeks.

EndNote ref. ID: 2701	Malignancy type: advanced head and neck or lung carcinoma Treatment: epoetin (assumed epoetin alfa)	
Study design		**Participants**
Author, year	Dunphy 1999[68]	$n = 30$
Objective	The effects of paclitaxel and carboplatin with or without concurrent epoetin in the treatment of patients with head and neck carcinoma and lung carcinoma on anaemia and the number of transfusions required	Inclusion criteria: Patients with head and neck carcinoma and lung carcinoma treated at Saint Louis University Health Sciences Center in a Phase II trial using paclitaxel and carboplatin; histologically confirmed advanced head and neck carcinoma (clinical stage III and IV) or advanced non-small cell lung carcinoma (stage IV); no previous therapy was permitted and all patients had measurable or evaluable disease; serum iron saturation ≥ 15%; Zubrod performance status of ≤ 2; serum creatinine < 3 mg/dl; serum bilirubin < 1.5 mg/dl; granulocyte count > 1500/µl; platelet count > 100,000/µL; life expectancy > 4 months; Hb level NR (see dose adjustment)
No. of centres	1	
Other references/aliases		
Geographical setting	USA	
Duration of treatment	Unclear – while on chemotherapy. The mean number of chemotherapy courses administered was three for each group (6 weeks?)	
Length of follow-up (if different)	NR	
Country of corresponding author	USA	Exclusion criteria: NR (see inclusion criteria)
Language of publication	English	
Sources of funding	NR	
Randomisation and allocation	Patients were randomised in a non-blinded fashion either to receive epoetin or to not receive epoetin	

Treatment arms		
Arm drug name(s)	Epoetin	Control
n	15	15
Dose and frequency (once daily, twice daily, etc.)	150 U/kg three times per week	NA
Dose adjustment (yes/no)	Yes. If the Hb fell by ≥ 1 g/dl (course 1) the dose was escalated to 300 U/kg (course 2); if the Hb fell by ≥ 1 g/dl the dose was escalated to 450 U/kg (course 3). Epoetin was not initiated if the Hb level was ≥ 16 g/dl. Once epoetin was initiated the Hb level was checked weekly. If the Hb level rose to 18 g/dl, epoetin was discontinued until it fell to 16 g/dl, at which point treatment was reinitiated	NA
Route of administration	NR	NR
Duration of epoetin treatment	NR	NR
Adjuvant anaemia treatment	Oral iron and folic acid for the duration of chemotherapy (ferrous sulfate, 325 mg orally, three times per day and folic acid, 1 mg orally, twice per day)	Oral iron and folic acid for the duration of chemotherapy (ferrous sulfate, 325 mg orally, three times per day and folic acid, 1 mg orally, twice per day)
Transfusion trigger	Hb < 8.0 g/dl or development of cardiovascular symptoms of anaemia	Hb < 8.0 g/dl or development of cardiovascular symptoms of anaemia

Outcomes	
Primary outcome	
Other outcomes	Haematological response, RBCT

Note
Complete blood count with differential and platelet counts was obtained at enrolment and every week during chemotherapy.

Analysis	
Statistical technique used	Accrual was limited by the number of patients who were to be enrolled in local phase II protocols for the treatment of carcinoma of the head and neck and lung carcinoma with paclitaxel and carboplatin. Therefore, the sample size was insufficient to ensure adequate power for subset analyses. Repeated analysis of variance was used to compare the difference in post-chemotherapy Hb levels between the two groups during the first two courses of chemotherapy. Fisher's exact test was used to compare the difference in the rate of transfusion between the two groups. The Mann–Whitney *U*-test and Fisher's exact test were used to compare characteristics between the two groups. An a priori level of significance of 0.05 was used for all comparisons
ITT analysis?	Of 30 people randomised, three were not evaluable [$n = 2$ in the epoetin group ($n = 1$ non-compliance and $n = 1$ epoetin initiated on day 8) and $n = 1$ in the control group (early death)]
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)	Yes. A minimum of 20 evaluable patients was required to detect a difference of 2.5 g/dl in post-chemotherapy Hb levels between epoetin and control participants with a power of > 90% at a significance level of 0.05
Attrition rate (loss to follow-up)?	Partially: two participants (non-compliance and epoetin was initiated on day 8) in the epoetin group and one participant (early death) in the control group were not evaluable
Was attrition rate adequately dealt with?	NR
No. (%) followed up from each condition?	NR

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/ haematological/myelodysplastic syndrome/mixed)		Advanced head and neck or lung carcinoma
Treatment (e.g. chemotherapy platinum/ non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Paclitaxel and carboplatin, repeated every 21 days. Patients with advanced lung carcinoma were treated until best response or for six courses of chemotherapy. After two to three preoperative chemotherapy courses, patients with head and neck carcinoma were treated with radiation if they were observed to have a > 50% response or surgery if a < 50% response was observed. They were then followed up with no further treatment until they developed a recurrence
Adjuvant anaemia treatment	Iron	Oral iron and folic acid for the duration of chemotherapy (ferrous sulfate, 325 mg orally, three times per day and folic acid, 1 mg orally, twice per day)
	G-CSF	NR
	Transfusion trigger	Hb < 8.0 g/dl or development of cardiovascular symptoms of anaemia
	Hb inclusion criterion level	NR

Evaluable population	Arm 1 = epoetin ($n = 13$)	Arm 2 = control ($n = 14$)	Notes	p-value
Sex				
Male, *n* (%)	12 (92)	7 (50)	Gender was not distributed equally between the two treatment groups	0.003
Female, *n* (%)	1 (8)	7 (50)		
Age (years), median (range)	59 (42–76)	67 (32–82)		
Hb g/dl mean (SD)	14.1 (2.1)	14.1 (1.6)		0.68
Epoetin (mU/ml), mean (SD) ($n = 25$)	8.8 (5.1)	7.3 (4.4)		
Iron, serum (mg/dl), mean (SD) ($n = 26$)	67.2 (22.9)	75.7 (51.1)		
Iron saturation (%), mean (SD) ($n = 26$)	26.8 (8.7)	31.9 (24.3)		
Folic acid (mg/ml), mean (SD) ($n = 25$)	8.3 (4.2)	6.1 (3.1)		
Vitamin B_{12} (pg/ml), mean (SD) ($n = 24$)	552 (243)	445 (139)		
Type of solid tumour, randomised participants				
Head and neck, *n* (%)	10 (66.7)	11 (77.3)		
Lung, *n* (%)	5 (33.3)	4 (26.7)		
Were intervention and control groups comparable?	No			
Results				
Hb				
Change in Hb (g/dl) after two courses of chemotherapy	1.2	2.8		0.037
Note There was a highly significant decrease in Hb over time (two courses of chemotherapy or 6 weeks) in patients who did not receive epoetin compared with those who did ($p = 0.008$) (see Figure 1).				
Transfusions				
No. (%) transfused during two courses of chemotherapy	1 (8)	2 (14)		> 0.05
No. (%) of transfused participant at four courses of chemotherapy	2 (15)	5 (36)	These differences were not compared statistically because after the second chemotherapy session fewer patients were treated in subsequent courses (see Figure 2)	
Units received per participant at four courses of chemotherapy	3	2.8		
Serum epoetin, *n*	10	10	Three epoetin and four control participants had no follow-up serum epoetin data. Epoetin levels increased significantly over time for both groups ($p = 0.007$); however, the increase in the group treated with epoetin was significantly greater than the increase in the control group ($p = 0.002$) (see Figure 3)	
HRQoL				
NR				
Adverse effects of treatment				
NR				

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear; not specified
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Gender was not distributed equally between the two treatment groups ($p = 0.003$)
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No
6. Were the outcome assessors blind to treatment allocation?	NR
7. Were the point estimates and measure of variability presented for the primary outcome measure?	NA; no primary outcome specified
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	No
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes

Other	
Generalisability	Gender was not distributed equally between the two treatment groups ($p = 0.003$)
Author conclusions	There was significantly less anaemia and transfusions were reduced by 50% in patients randomised to receive epoetin during chemotherapy with paclitaxel and carboplatin
Reviewer comments	No Hb inclusion criterion; epoetin was not initiated if the Hb level was ≥ 16 g/dl. In addition, after two to three preoperative chemotherapy courses, patients with head and neck carcinoma were treated with radiation if they were observed to have a > 50% response or surgery if a < 50% response was observed. They were then followed up with no further treatment until they developed a recurrence

NR, not reported.

EndNote ref. ID: 362	Malignancy type: SCLC Treatment: epoetin alfa	
Study design		**Participants**
Author, year	Grote 2005[74]	*n* = 224
Objective	To evaluate the effects of epoetin alfa on tumour response to chemotherapy and survival in patients with SCLC	Inclusion criteria: Age ≥ 18 years; newly diagnosed both extensive-stage and limited-stage SCLC scheduled for at least three chemotherapy cycles; ECOG score 0–2; life expectancy ≥ 3 months; Hb ≤ 14.5 g/dl
No. of centres	35 sites	
Other references/aliases	N93–004	
Geographical setting	USA	Exclusion criteria: Previous cytotoxic chemotherapy or radiotherapy or scheduled curative-intent radiotherapy during the first three chemotherapy cycles; uncontrolled underlying disease not attributable to malignancy; uncontrolled hypertension; evidence of untreated iron, folate or vitamin B_{12} deficiency or ongoing haemolysis
Duration of treatment	12 weeks = from start of treatment until 3 weeks after chemotherapy completed (the mean number of chemotherapy cycles was 4 and 4.1 in the epoetin and placebo groups respectively; duration of a cycle = 3 weeks)	
Length of follow-up (if different)	3 years after treatment	
Country of corresponding author	USA	
Language of publication	English	
Sources of funding	Johnson & Johnson LLC	
Randomisation and allocation	Randomised double-blind, parallel-group, placebo-controlled trial; 1 : 1 computer-generated randomisation, no details provided on allocation concealment	

Treatment arms		
Arm drug name(s)	Epoetin alfa	Placebo
n	109	115
Dose and frequency (once daily, twice daily, etc.)	150 U/kg three times a week	150 U/kg three times a week
Dose adjustment (yes/no)	Yes. Epoetin stopped if Hb level was > 16 g/dl until Hb level was < 14 g/dl and resumed at 75 U/kg; no dose escalation	
Route of administration	Subcutaneous	Subcutaneous
Duration of epoetin treatment	Until approximately 3 weeks after final chemotherapy cycle	Until approximately 3 weeks after final chemotherapy cycle
Adjuvant anaemia treatment	NR	NR
Transfusion trigger	NR	NR

Outcomes	
Primary outcome	
Other outcomes	Haematological response (weekly Hb, after three cycles and after final cycle); RBCT (proportion of patients transfused, no. of units transfused, time to first transfusion); tumour response (after three cycles and final cycle); survival (up to 3 years); AEs

Note
Study terminated early because of slow recruitment and suboptimal enrolment: enrolled 224 of 400 planned participants and thus there were some power issues.

Analysis	
Statistical technique used	Overall tumour response rate CR[a] plus PR[b] and 95% CIs reported. Kaplan–Meier estimates for survival data
ITT analysis?	Yes for all efficacy data. Safety population consisted of all patients receiving at least one dose of study drug with available safety data
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)	Yes (based on 15% one-sided decrease in overall tumour response rate in the epoetin arm). However, the trial was terminated early and thus there were power issues
Attrition rate (loss to follow-up)?	No. of patients and reasons for treatment discontinuation reported for both arms
Was attrition rate adequately dealt with?	NR except to say that ITT analysis was conducted
No. (%) followed up from each condition?	NR

NR, not reported.
a CR = total disappearance of all known malignant disease.
b PR = defined as a ≥ 50% decrease in total tumour area (added products of bidimensional measurements of all measurable disease), as no growth of any measurable lesion by > 25% and no estimated growth of any unmeasurable but assessable lesions by > 25% and as no new lesions.

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/myelodysplastic syndrome/mixed)		SCLC
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Etoposide and cisplatin
Adjuvant anaemia treatment	Iron	NR
	G-CSF	NR
	Transfusion trigger	NR
	Hb inclusion criterion level	≤ 14.5

	Arm 1 = epoetin (*n* = 109)	Arm 2 = placebo (*n* = 115)	Notes	*p*-value
Sex, *n* (%)				
Male	59 (54.1)	64 (55.7)		
Female,	50 (45.9)	51 (44.3)		
Age (years), mean (SD) [range]	64.4 (8.7) [37–78]	63.2 (8.9) [37–78]		
Performance status: ECOG score, *n* (%)				
0–1	73 (67)	83 (72.2)		
2	34 (31.2)	32 (27.8)		
3	1 (0.9)	0 (0)		
4	0 (0)	0 (0)		
Missing	1 (0.9)	0 (0)		
Baseline Hb (g/dl), mean (SD)	12.8 (1.5)	13 (1.5)		
Baseline iron (U/l), mean (SD)	75.3 (65.41)	81.6 (66.35)		
Ferritin (ng/dl), mean (SD)	471.7 (856.3)	460.3 (632.9)		

	Arm 1 = epoetin ($n = 109$)	Arm 2 = placebo ($n = 115$)	Notes	*p*-value
No. of chemotherapy cycles received, mean (SD); median (range)	4 (2.1); 4 (1–10)	4.1 (2.2); 4 (1–12)		
Received radiotherapy, all cycles, *n* (%)	16 (14.7)	14 (12.2)		
Extensive-stage SCLC, *n* (%)	72 (66.1)	68 (59.1)		
Were intervention and control groups comparable?	No *p*-values reported; authors stated that the 'demographics and clinical characteristics were generally similar between groups' (p. 9379)			

Results				
			Difference epoetin – placebo	95% CI
Tumour response				
Tumour response: CR or PR at final cycle, *n* (%)	65 (59.6)	64 (55.7)	4%	–9 to 17%
Tumour response: CR at final cycle, *n* (%)	20 (18.3)	21 (18.3)		
Hb				
Mean Hb at cycle 3 (g/dl)	12.5	10.6	1.9	1.4 to 2.4
Mean Hb at final cycle (g/dl)	12.2	10.3	1.9	1.4 to 2.4
Mean change in Hb from baseline to end of treatment (g/dl)	–0.6	–2.7		
Mean change in Hb at time of median exposure to study drug (13 weeks) (g/dl)	–0.2	–2.9		
Hb at 13 weeks estimated from Figure 2, mean (SD)	12.5 (0.6) ($n = 64$)	10.24 (0.4) ($n = 58$)		
HRQoL				
NR				
OS				
Median survival (Kaplan–Meier) (months)[a]	10.5	10.4		
Transfusions				
Participants, *n* (%)	26 (24)	42 (37)		HR 0.597, 95% CI 0.365 to 0.977
No. of units, mean (SD)	0.5 (3.6)[b]	0.4 (0.7)		

a Figure 1: Kaplan-Meier plot of survival over time (1 month = 28 days).
b One patient in the epoetin arm had an abdominal aortic aneurysm requiring 37 units of blood.
Note
Difference in Kaplan–Meier estimates of time to first transfusion showed that probability of transfusion was greater in the placebo group starting at month 3.

Safety data[a]		
Discontinued chemotherapy because of AEs, *n* (%)	23 (21)	32 (28)
Deaths (at 3 years' follow-up), *n* (%)	100 (91.7)	101 (87.8)
Cause of death = disease progression, %	91	84
Nausea, *n* (%)	80 (73.4)	79 (68.7)
Vomiting, *n* (%)	56 (51.4)	58 (50.4)
Fatigue, *n* (%)	32 (29.4)	40 (34.8)
Constipation, *n* (%)	34 (31.2)	40 (34.8)
Clinically relevant thrombovascular events, *n* (%)	12 (11)	11 (9.6)
Thromboembolic events, *n* (%)	1 (0.9)	0 (0.9)
Hypertension	NR; patients with uncontrolled hypertension were excluded	
ECOG score	At baseline 98% and 100% patients had an ECOG score of ≤ 2 in the epoetin and placebo groups, respectively; at the end of treatment 71% of patients had an ECOG score of ≤ 2 in both groups	

a Data for all 224 participants available.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Yes
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear; no *p*-values reported
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes
6. Were the outcome assessors blind to treatment allocation?	Yes
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Yes
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes, during treatment period only

Note
Patients without a date of death were censored on the date that they were last known to be alive.

Other	
Generalisability	
Author conclusions	Results suggest that in newly diagnosed patients with SCLC epoetin alfa does not affect tumour response to chemotherapy or survival. However, the early trial closure makes these conclusions preliminary
Reviewer comments	Divergence in survival curves after 12 months (see Figure 1). The authors note that there is no information on patients' medication after the end of treatment, nor on the possible differences in the proportion of patients with extensive-stage SCLC. However, the paper does not report whether any significant differences were found for outcomes measured at baseline. In addition, although unknown, the medication could be expected to be similar for all patients

CR, complete response; ECOG, Eastern Cooperative Oncology Group; NR, not reported; PR, partial response; SCLC, small-cell lung cancer.

EndNote ref. ID: 2703	Malignancy type: lymphoproliferative Treatment: darbepoetin alfa	
Study design		**Participants**
Author, year	Hedenus 2002[53]	$n = 66$
Objective	To assess the safety and dose–response relationship of darbepoetin alfa in patients with different types of lymphoproliferative malignancies receiving multicycle chemotherapy	Inclusion criteria: Patients with a diagnosis of lymphoproliferative malignancy (multiple myeloma, low- and intermediate-grade non-Hodgkin's lymphoma, Hodgkin's disease or chronic lymphocytic leukaemia); life expectancy ≥ 6 months; ECOG performance status 0–2; at least 12 more weeks of chemotherapy; adequate iron stores (transferrin saturation ≥ 15% or ferritin ≥ 10 µg/l); normal serum vitamin B_{12} and folate concentrations; adequate liver function (serum bilirubin ≤ 1.5 times the upper limit of the normal range); adequate renal function (serum creatinine ≤ 177 µmol/l); not received two RBCTs within 4 weeks of randomisation or any RBCT within 2 weeks of randomisation; Hb level: ≤ 11.0 g/dl Exclusion criteria: High-grade non-Hodgkin's lymphoma; myeloablative chemotherapy or radiotherapy for transplantation or chemotherapy regimens using investigational agents; primary or metastatic malignancy involving the central nervous system; clinical evidence of active infection or inflammatory disease; other disorders that could potentially interfere with the response of darbepoetin
No. of centres	15	
Other references/ aliases	NR	
Geographical setting	Europe/Australia	
Duration of treatment	12 weeks	
Length of follow-up (if different)	4 weeks after treatment period	
Country of corresponding author	Sweden	
Language of publication	English	
Sources of funding	Amgen, Inc.	
Randomisation and allocation	Multicentre, randomised (1 : 2 : 2 : 1 ratio[a]), double-blind, placebo-controlled, dose-finding study. Randomisation was performed using a central computerised system and was stratified to balance the treatment groups with respect to malignancy type (myeloma vs. lymphoma)	

a Four study groups: darbepoetin 1.0 µg/kg ($n = 11$); darbepoetin 2.25 µg/kg ($n = 22$); darbepoetin 4.5 µg/kg ($n = 22$); placebo ($n = 11$). Only the darbepoetin 2.25 µg/kg ($n = 22$) and placebo ($n = 11$) groups were relevant to this review.

Treatment arms		
Arm drug name(s)	Darbepoetin alfa	Placebo
n	22	11
Dose and frequency (once daily, twice daily, etc.)	2.25 µg/kg once weekly	NR
Dose adjustment (yes/no)	Yes; doses reduced by 50% for patients who had a ≥ 2 g/dl increase in Hb during any 28-day period in the absence of RBCT; withheld for patients with Hb concentrations > 15.0 g/dl (men) or > 14.0 g/dl (women) and reinstated at 50% of weekly dose once Hb concentrations decreased to ≤ 13.0 g/dl	NR
Route of administration	Subcutaneous	Subcutaneous
Duration of epoetin treatment	12 weeks	12 weeks
Adjuvant anaemia treatment	NR	NR
Transfusion trigger	RBCTs were recommended for patients with Hb concentrations ≤ 8.0 g/dl	NR but assumed to match darbepoetin group

Outcomes	
Primary outcome	Haematological response (defined as an increase in Hb of ≥ 2.0 g/dl from baseline in the absence of RBCT; haematopoietic response defined as Hb response or increase in Hb concentration to ≥ 12.0 g/dl in the absence of RBCT; sustained Hb response defined as Hb response maintained for 28 days or until the end of treatment; Hb concentrations measured weekly
Other outcomes	RBCT (from week 5 until the end of the treatment period); AEs (AEs, excess increases in Hb, changes in laboratory variables and vital signs, antibody formation resulting from darbepoetin administration)

Analysis	
Statistical technique used	Rates of Hb response and haematopoietic response estimated using the Kaplan–Meier method. Logistic regression was used to assess treatment effect, dose–response relationships and the effect of covariates
ITT analysis?	Described as ITT analysis but defined as all randomised who received at least one dose of study drug, so not strict ITT analysis
Does statistical technique adjust for confounding?	Covariates included in models were malignancy type, sex, baseline Hb (categorical variable), RBCTs in the 4 weeks before randomisation, baseline serum endogenous erythropoietin concentration (categorical variable)
Power calculation (a priori sample calculation)	NR
Attrition rate (loss to follow-up)?	Three of the 66 patients recruited to the four study groups (two patients in the darbepoetin groups withdrawn because of a delay in chemotherapy;[a] one in the placebo group withdrew consent)
Was attrition rate adequately dealt with?	Not clear, although attrition rate low
No. (%) followed up from each condition?	NR

a Withdrawals given for the three darbepoetin groups combined ($n = 2$), although only one of these groups (darbepoetin alfa 2.25 µg/kg/week) is relevant to this review.

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		Lymphoproliferative
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Chemotherapy (type NR)
Adjuvant anaemia treatment	Iron	NR
	G-CSF	NR
	Transfusion trigger	RBCTs were recommended for patients with Hb concentrations ≤ 8.0g/dl
	Hb inclusion criterion level	≤ 11.0 g/dl

	Arm 1 = darbepoetin ($n = 22$)	Arm 2 = placebo ($n = 11$)	Notes	*p*-value
Sex, *n* (%)				
Male	14 (64)	2 (18)		
Female	8 (36)	9 (82)		
Age (years), median (range)	69 (20–84)	63 (25 –80)		
Neutrophil count (×10^9/l), mean (SD)	2.9 (2.2)	7.0 (7.5)		
RBCT during 4 weeks pre randomisation, *n* (%)	4 (18)	2 (18)		
Hb (g/dl), mean (SD)	9.4 (1.3)	9.5 (1.0)		
Platelet count (×10^9/l), mean (SD)	232.4 (157.6)	283.1 (188.6)		
Endogenous serum erythropoietin (U/l), median (range)	69 (12–1362)	45 (12–132)		
Lymphoma, *n* (%)				
Hodgkin's disease	4 (18)	3 (27)		
Non-Hodgkin's lymphoma	11 (50)	3 (27)		
Chronic lymphocytic leukaemia	1 (5)	2 (18)		
Multiple myeloma	6 (27)	3 (27)		
Serum ferritin (µg/l), median (range)	430 (15–1288)	524 (14–2178)		
Transferrin saturation (%), median (range)	25 (6–71)	18 (9–37)		
Were intervention and control groups comparable?	No; stated that there was a higher proportion of women in the placebo group and that neutrophil and platelet counts were higher in the placebo group. No analyses presented to support these statements			

Results			
Haematology			
Proportion of participants with a haematological response	55	10	Analysis comparing these two groups NR
Time to response (weeks), median (range)	13 weeks (1–13)	Not estimated	
Proportion of participants with a haematopoietic response (95% CI)	60 (39 to 81)	19 (0 to 43)	
Mean change (95% CI) in Hb from baseline to week 13	1.64 (1.05 to 2.24)	1.00 (0.55 to 1.45)	

Results		
Transfusions		
Proportion of patients transfused (95% CI)	27 (9 to 46)	45 (16 to 75)
HRQoL		
NR		
Adverse effects of treatment		
	Darbepoetin ($n = 55$)	Placebo ($n = 11$)
At least one AE during the study period, *n* (%)	52 (95)	10 (91)
Rapid rise in Hb of ≥ 2g/dl within 28-day period, *n* (%)	22 (40)	1 (9)

Note
Safety data given for all three darbepoetin groups combined vs. placebo. Most AEs are presented graphically (bar chart) and it was not possible to extract exact data from the chart.
Changes in laboratory measures and vital signs were reported as 'similar between patients receiving darbepoetin alpha and placebo' (p. 83).

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Yes, computerised stratified system
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	Unclear; stated as central computer but further details not provided
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Higher proportion of women in the placebo group (but sex included as confounder in models); neutrophil and platelet counts higher in the placebo group
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes
6. Were the outcome assessors blind to treatment allocation?	Yes
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Yes
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes

Quality appraisal	
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Partially. No CONSORT flow chart, but withdrawals and reasons are noted in the text: 'Two patients receiving darbepoetin alfa were withdrawn. However, it is unclear from which of the three darbepoetin alfa groups the participants withdrew. In addition, one patient randomised to receive placebo withdrew consent' (p. 81)
Other	
Generalisability	Small sample sizes. Analyses conducted using combined data from the three darbepoetin groups vs. placebo, but only one of the darbepoetin groups is relevant to this review
Author conclusions	The results of the study indicated that darbepoetin alfa, administered once weekly at doses of 1.0 µg/kg, 2.25 µg/kg and 4.5 µg/kg, was associated with greater effects on Hb levels than placebo in patients with lymphoproliferative malignancies
Reviewer comments	Difficult to interpret results specifically for the dosage relevant to this review

CONSORT, Consolidated Standards of Reporting Trials; ECOG, Eastern Cooperative Oncology Group; NR, not reported.

EndNote ref. ID: 2704

Malignancy type: lymphoproliferative

Treatment: darbepoetin alfa

Study design		Participants
Author, year	Hedenus 2003[17]	$n = 344$
Objective	To evaluate the efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies. The study included patients with myeloma and lymphoma and was stratified to enable a comparison of darbepoetin alfa and placebo within each malignancy type	Inclusion criteria: Men and women aged ≥ 18 years; lymphoproliferative malignancies (Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia or multiple myeloma); anaemia (Hb ≤ 11 g/dl), primarily because of cancer or chemotherapy (i.e. serum folate ǂ 4.5 nmol/l and vitamin B_{12} ǂ 148 pmol/l, no haemolysis, and no gastrointestinal bleeding); ECOG performance status 0–3; scheduled to receive cytotoxic chemotherapy for at least 12 additional weeks; adequate renal and liver function (serum creatinine concentration ≤ 177 µmol/l, serum bilirubin ≤ 1.5 times the central laboratory upper limit of normal); life expectancy of ≥ 4 months Exclusion criteria: Burkitt's or lymphoblastic lymphoma; scheduled to receive a stem cell transplant within 16 weeks of randomisation; received myeloablative chemotherapy, radiotherapy for transplantation or chemotherapy regimens containing investigational agents; transferrin saturation < 15% and ferritin < 10 µg/l; significant central nervous system, cardiac or inflammatory diseases; any known primary haematological disorders that could cause anaemia; patients not to have received epoetin within 8 weeks, more than two RBCTs within 4 weeks or any RBCT within 2 weeks of randomisation
No. of centres	49	
Other references/aliases	Secondary analysis in Littlewood 2006[83] (see note)	
Geographical setting	Europe, Australia and Canada	
Duration of treatment	12 weeks	
Length of follow-up (if different)	Unclear; a median follow-up period of approximately 11 months	
Country of corresponding author	Sweden	
Language of publication	English	
Sources of funding	This study was supported by Amgen, Inc., Thousand Oaks, CA, USA	
Randomisation and allocation	Central randomisation 1 : 1 to receive darbepoetin alfa or placebo. Randomisation was stratified to balance the treatment groups with respect to malignancy type (lymphoma vs. myeloma), region (Australia vs. Canada vs. Western Europe) and chemotherapy before randomisation (heavily pretreated vs. not heavily pretreated; note: patients were considered to have been heavily pretreated if they had received two or more lines of chemotherapy or one line of chemotherapy and a stem cell transplant)	

Note

Littlewood and colleagues[83] investigate the effects of Hb levels on fatigue and examine the relationship between improvement in fatigue and HRQoL.

Treatment arms		
Arm drug name(s)	Darbepoetin alfa	Placebo
n	174	170
Dose and frequency (once daily, twice daily, etc.)	2.25 µg/kg, QW	NA, QW
Dose adjustment (yes/no)	Yes. Dose doubled for patients who had a ≤ 1 g/dl increase in Hb from baseline after 4 weeks of treatment. It was withheld if Hb value increased to > 15 g/dl for men or > 14 g/dl for women and was reinstated at 50% once Hb level was ≤ 13 g/dl	
Route of administration	Subcutaneous	
Duration of epoetin treatment	12 weeks	
Adjuvant anaemia treatment	Iron therapy was at the discretion of the investigators	
Transfusion trigger	Transfusion policies were left to the discretion of the investigators; recommended if Hb ≤ 8 g/dl	
Outcomes		
Primary outcome	Haematological response (proportion of participants with a Hb response[a])	
Other outcomes	Haematological response (proportion of participants with a haematopoietic response[b]); RBCT [incidence of transfusions from week 5 to the end of the treatment (and from week 1 to the end of the treatment)]; tumour response (continued to be collected during a long-term follow-up period); survival (continued to be collected during a long-term follow-up period); AEs (AEs and antibody formation); HRQoL (FACT-F every 4 weeks on day 1 of each cycle of chemotherapy, before any other study procedures)	

QW, once weekly.
a Hb response defined as an increase in Hb of ≥ 2 g/dl from baseline in the absence of any RBCTs during the previous 28 days.
b Haematopoietic response defined as a Hb response or a Hb concentration of ≥ 12 g/dl in the absence of any RBCTs during the previous 28 days.

Analysis	
Statistical technique used	The Kaplan–Meier method was used to estimate the percentages of patients with a Hb response, haematopoietic response or RBCT because of the anticipated withdrawal rate and approximate 95% CIs were calculated using Greenwood's formula. Statistical comparisons of these percentages between treatment groups were based on the chi-squared test. Cox proportional hazards modelling was performed as an exploratory analysis to evaluate the effect of baseline serum erythropoietin (≤ 100 vs. > 100 IU/l) on the time to Hb response. The mean ($\pm$ SEM) change in Hb concentration was assessed in two ways: first, by subtracting the baseline Hb value from the last value during the treatment phase and, second, by evaluating the completers analysis.[a] Efficacy end points were analysed with and without adjusting for the stratification factors of malignancy type, region and chemotherapy before randomisation. Results of these analyses were similar; thus, only the results of the unadjusted analyses are presented. Exploratory analyses of changes in the FACT-F subscale were conducted using analysis of variance. The relationship between the change in the FACT-F subscale and the change in Hb was investigated using simple linear regression
ITT analysis?	Yes. All patients who received at least one dose of the study drug were included in the analyses of efficacy and safety (ITT analysis set $n = 344$), with the exception of transfusion end points, valuated during week 5 to the end of the treatment phase. For these end points, patients who did not complete the first 4 weeks of treatment were excluded from the analysis ($n = 332$). For Hb and haematopoietic response, patients who withdrew from the study early for any reason were censored at the time of withdrawal. For the RBCT end points, patients who withdrew from the study before the completion of the treatment period were considered to have been transfused and patients who withdrew because of either disease progression or death were censored at the time of withdrawal
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)	Yes. Sample size to detect an increase in Hb response rate from 25% in the placebo group to 50% in the darbepoetin alfa group within each malignancy type, with 90% power at a two-sided significance level of 0.05 (estimated withdrawal rate of 10% during the 12-week study)
Attrition rate (loss to follow-up)?	Yes, until the end of treatment
Was attrition rate adequately dealt with?	Yes
No. (%) followed up from each condition?	NR

a Completers analysis = participants with ≥ 12 weeks of treatment (had a week 13 Hb level with no transfusions during the preceding 28 days).

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		Lymphoproliferative
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Chemotherapy – no further details given
Adjuvant anaemia treatment	Iron	Iron therapy was at the discretion of the investigators
	G-CSF	None
	Transfusion trigger	At the discretion of the investigators; recommended if Hb ≤ 8 g/dl
	Hb inclusion criterion level	≤ 11 g/dl

	Darbepoetin alfa ($n = 174$)	Placebo ($n = 170$)	Difference	*p*-value
Sex				
Male (%)	87 (50)	78 (46)		
Female (%)	87 (50)	92 (54)		
Age (years), mean (SD)	64.8 (13.8)	64.6 (12.2)		
ECOG score, *n* (%)				
0	54 (31)	43 (25)		
1	80 (46)	92 (54)		
2	32 (18)	28 (16)		
> 2	8 (5)	6 (4)		
Missing	0 (0)	1 (1)		
Hb baseline (g/dl), mean (SD)	9.59 (1.22)	9.5 (1.21)		
Ferritin (µg/l), median (range)	324.5 (5–5352)	253.5 (15–5027)		
Transferrin saturation (%), median (range)	26.5 (5–95)	25 (4–95)		
Serum erythropoietin baseline (mU/ml), median (range)	68.99 (2.3–1522.7)	54.49 (10.9–3169.1)		
Previous chemotherapy, *n* (%)				
Heavily pretreated[a]	46 (26)	47 (28)		
Not heavily pretreated	128 (74)	123 (72)		
Malignancy type, *n* (%)				
Lymphoma (Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia)	85 (49)	86 (51)		
Multiple myeloma	89 (51)	84 (49)		
Were intervention and control groups comparable?	No *p*-values reported; authors stated that 'baseline demographic and clinical characteristics were generally well balanced between the treatment groups' (p. 397)			

a Two or more lines of chemotherapy or one line of chemotherapy and a stem cell transplant.

Results				
Hb response (%) (95% CI)	60 (52 to 68)	18 (12 to 24)	42 (32 to 52)	< 0.001
Haematopoietic response (%)[a] (95% CI)	65 (57 to 73)	24 (18 to 31)		< 0.001
Mean change in Hb (SEM); ITT[b]	1.8 (0.17)	0.19 (0.1)		< 0.001
Mean change in Hb (SEM); completer's analysis[b]	2.66 (0.2)	0.69 (0.14)		< 0.001
Lymphoma subgroup				
Hb response (%)	64 ($n = 85$)	13 ($n = 86$)	51	< 0.001
Myeloma subgroup				
Hb response (%)	56 ($n = 89$)	23 ($n = 84$)	33	< 0.001
Baseline serum erythropoietin levels ≤ 100 IU/l				
Hb response (%) (95% CI)	69 (60 to 79) ($n = 89$)	16 (9 to 22) ($n = 84$)		
Baseline serum erythropoietin levels > 100 IU/l				
Hb response (%) (95% CI)	44 (31 to 58) ($n = 89$)	25 (11 to 39) ($n = 84$)	19 (0 to 38)	
Transfusions; from week 5 to end of treatment (%) (95% CI)[c]	31 (24 to 38) ($n = 167$)	48 (41 to 56) ($n = 165$)		< 0.001
Transfusions; from week 1 to end of treatment (%) (95% CI)[d]	($n = 167$)	($n = 165$)	17 (6 to 27)	< 0.001

a Percentages calculated using Kaplan–Meier estimates.
b The mean change in Hb concentration was assessed in two ways: (1) subtracting the baseline Hb value from the last value during the treatment phase (ITT analysis); and (2) by evaluating participants who completed at least 12 weeks of treatment (completer's analysis). Hb values within 28 days after a RBCT were excluded from the analysis.
c When the data were analysed within each malignancy type, darbepoetin was associated with a reduction in transfusions compared with placebo both in patients with lymphoma (27% vs. 49%; $p = 0.002$) and in patients with myeloma (35% vs. 48%; $p = 0.042$).
d This reduction in transfusions with darbepoetin compared with placebo was observed both in patients with lymphoma ($p = 0.011$) and in patients with myeloma ($p = 0.018$).

Change in FACT-F subscale score from baseline to end of treatment period (84% of patients completed the FACT-F subscale at week 13): improvement in FACT-F subscale score compared with placebo regardless of level of fatigue at baseline. Patients with the lowest baseline FACT-F subscale scores reported the largest improvement in FACT-F subscale score at EOTP. After adjusting for the effect of baseline score, increases in FACT-F subscale scores with darbepoetin alfa treatment were significantly greater than those observed with placebo ($p = 0.032$). For every 1 g/dl increase in Hb, the estimated mean increase in FACT-F subscale score was 1.39 (95% CI 0.83 to 1.94; $p < 0.001$). For FACT-F change scores in the lymphoma and myeloma subgroups, see Littlewood and colleagues[83]

Adverse effects		
Deaths (during the study or within 30 days of the last dose of study drug), *n* (%)	10 (6)	4 (2)
Withdrawal because of adverse effects (not including death) (%)	3	4
No evidence of neutralising antibodies to darbepoetin alfa was detected for any patient		
Iron supplementation received (%)		
Oral	6	7
Subcutaneous	0	1
Survival (median follow-up period of approximately 11 months)		
PFS, *n* (%)	82 (47)	76 (45)

EOTP, end of the treatment period.
Note
One patient was randomised to receive placebo but received darbepoetin alfa as the result of an error at the study centre. Efficacy data for this patient were analysed in the placebo group and safety data were analysed in the darbepoetin alfa group.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Yes
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	No *p*-values reported; authors stated that 'baseline demographic and clinical characteristics were generally well balanced between the treatment groups' (p. 397)
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes
6. Were the outcome assessors blind to treatment allocation?	Yes
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Yes
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes, ITT defined as all randomised who received one or more dose of the study drug
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes, until the end of treatment

Other	
Generalisability	Yes
Author conclusions	The efficacy of darbepoetin alfa was consistent for patients with lymphoma or myeloma. Improvements in quality of life were also observed with darbepoetin alfa. The overall safety profile of darbepoetin alfa was consistent with that expected for this patient population. Darbepoetin alfa significantly increased Hb levels and reduced RBCTs in patients with lymphoproliferative malignancies receiving chemotherapy. Darbepoetin alfa demonstrated clinically important improvements in response rate relative to placebo, regardless of baseline endogenous erythropoietin level
Reviewer comments	

ECOG, Eastern Cooperative Oncology Group; NR, not reported; SEM, standard error of the mean.

EndNote ref. ID: 2705	Malignancy type: solid – breast, gynaecological, gastrointestinal, lung, other Treatment: chemotherapy, darbepoetin alfa	
Study design		**Participants**
Author, year	Kotasek 2003[50]	*n* = 249
Objective	To assess the safety of darbepoetin alfa in patients with cancer receiving chemotherapy, to assess the feasibility of administering darbepoetin alfa Q3W and to characterise the dose–response relationships for darbepoetin alfa when given Q3W	Inclusion criteria: Age ≥ 18 years with solid tumours receiving cyclic chemotherapy; life expectancy ≥ 6 months; ECOG performance status 0–2; adequate liver and renal function; anaemia (Hb level ≤ 11.0 g/dl) because of cancer and/or chemotherapy Exclusion criteria: Iron deficient (transferrin saturation < 15% and ferritin < 10 µg/l); received recombinant human erythropoietin within 8 weeks of randomisation; more than two RBCTs within 4 weeks of randomisation; any RBCT within 2 weeks of randomisation; known primary haematological disorders that could cause anaemia and central nervous system, cardiac or inflammatory diseases
No. of centres	26	
Other references/aliases	None	
Geographical setting	Australia, Canada, Costa Rica and Europe	
Duration of treatment	12 weeks (double-blind treatment). NB: study in two parts (part B open-label treatment period weeks 12–24)	
Length of follow-up (if different)	Unclear: 8-week observation period after last dose of study drug at week 12 (Figure 1 shows part A of study has observation period running to week 18, thus 6 weeks); however, results for the observation period are not reported	
Country of corresponding author	Australia	
Language of publication	English	
Sources of funding	Supported by Amgen, Inc., USA	
Randomisation and allocation	Randomised, double-blind, placebo-controlled, dose-finding study of darbepoetin alfa. Randomised 4 : 1 to receive darbepoetin alfa (4.5 µg/kg, 6.75 µg/kg, 9.0 µg/kg or 13.5 µg/kg) or placebo. Later, after review of data by the safety monitoring committee, dose cohorts of 12.0 µg/kg and 15.0 µg/kg were added	

Treatment arms		
Arm drug name(s)	Darbepoetin alfa	Placebo
n	17	51
Dose and frequency (once daily, twice daily, etc.)	6.75 µg/kg Q3W[a] (2.2 µg/kg QW) The mean administered number of darbepoetin alfa doses over the 12-week treatment phase was 3.6	NR
Dose adjustment (yes/no)	Yes. No dose increase for inadequate response was allowed in the double-blind part of the study. If Hb level increased to > 15.0 g/dl for men or ≥ 14.0 g/dl for women, treatment was interrupted and reinstated at a lower dose when Hb level was ≤ 13.0 g/dl	NR
Route of administration	Subcutaneous	NR
Duration of epoetin treatment	12 weeks	12 weeks
Adjuvant anaemia treatment	NR	NR
Transfusion trigger	NR	NR

a Six darbepoetin alfa doses were evaluated (4.5 µg/kg, 6.75 µg/kg, 9.0 µg/kg, 12.0 µg/kg, 13.5 µg/kg and 15.0 µg/kg Q3W). Only the 6.75 µg/kg dose was eligible for inclusion in this review.

Outcomes	
Primary outcome	AEs[a] (incidence of AE by dose and treatment group and formation of antibodies)
Other outcomes	Haematological response [responders;[b] haematopoietic response;[c] Hb level (change from baseline); RBCT (week 5 to end of treatment period); HRQoL (FACT-G, FACT-F)]

a AEs classified using a modified WHO AE term dictionary.
b Responders = increase in Hb of ≥ 2.0 g/dl during the treatment phase in the absence of any RBCTs in the previous 28 days.
c Haematopoietic response = haematological response and/or Hb concentration of ≥ 12.0 g/dl during the treatment phase in the absence of any RBCT in the previous 28 days.

Note
Pre-dose and 48-hour post-dose serum samples (darbepoetin concentration) were collected at weeks 1, 4 and 10; quality-of-life assessments were carried out at weeks 1, 4, 7 and10 (to assess the feasibility, reliability, validity, sensitivity and timing of quality-of-life assessments rather than to evaluate fatigue).

Analysis	
Statistical technique used	Proportion of patients per dose group (Hb response, haematopoietic response) estimated by taking 1 minus the Kaplan–Meier estimate of the survivor function at the time of the last observed end point. Approximate 95% CIs for the Kaplan–Meier estimate of the proportion were calculated using Greenwood's estimate of the variance and assuming a normal distribution for the Kaplan–Meier estimate. For the incidence of RBCT a subset was used (transfusions from week 5 to end of treatment period) including all patients who received at least one dose of study drug and who ended their treatment phase during week 5 or later. Patients who had more than one transfusion were counted only once in calculating the incidence of transfusions Change in Hb from baseline: • If a patient had a RBCT within 28 days of the last treatment-phase Hb value, then the last pre-transfusion Hb value was substituted to discount the effect of RBCT on the change in Hb. All patients had an observed or imputed value for this analysis (patients who withdrew after one dose were given a change score of zero) • Using the set of patients who completed at least 12 weeks of treatment Established post-hoc tests (not specified in protocol): trend tests were conducted using a distribution-free test (asymptotic *p*-values were obtained using the two-sided Jonckheere–Terpstra test) to investigate the dose relationship of darbepoetin alfa: • mean change in Hb at EOTP across dose groups • mean change in FACT-F across categorised change in Hb (change in Hb at last available quality-of-life assessment)
ITT analysis?	Analyses conducted on patients randomised to study drug who received at least one dose
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)	Sample size was statistically based on the secondary objectives to determine a clinically effective dose, by means of estimating Hb response rates. The 4 : 1 randomisation allowed for 36 darbepoetin alfa patients per dose cohort. Anticipated premature withdrawal rate of approximately 20%, and therefore a sample size of 29, allows estimation of the Hb response rate within a SE of 0.09. The exact number of patients in each cohort was determined by the rate of enrolment and how long it took the data monitoring committee to determine safety before allowing dose escalation
Attrition rate (loss to follow-up)?	Yes (detailed in patient flow chart in Figure 2)
Was attrition rate adequately dealt with?	Yes
No. (%) followed up from each condition?	NR

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		Solid – breast, gynaecological, gastrointestinal, lung, other
Treatment (e.g. chemotherapy platinum/ non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Chemotherapy: NR
Adjuvant anaemia treatment	Iron	NR
	G-CSF	NR
	Transfusion trigger	NR
	Hb inclusion criterion level	≤ 11.0 g/dl

	Arm 1 = darbepoetin alfa ($n = 198$)	Arm 2 = placebo ($n = 51$)	Notes	p-value
Baseline demographics and clinical characteristics reported for all darbepoetin alfa patients not separated out by dose				
Sex, *n* (%)				
Male	56 (28)	16 (31)		
Female	142 (72)	35 (69)		
Age (years), mean (SD)	58.3 (11.9)	56.2 (12.4)		
ECOG performance status, *n* (%)				
< 2	180 (91)	45 (88)		
Type of solid tumour, *n* (%)				
Breast	61 (31)	13 (25)		
Gynaecological	46 (23)	9 (18)		
Gastrointestinal	34 (17)	13 (25)		
Lung	33 (17)	10 (20)		
Other	24 (12)	6 (12)		
Hb (g/l), mean (SD)	99.3 (10.0)	98.7 (11.2)		
Hb (g/dl), mean (SD) (PenTAG calculated)	9.93 (1.00)	9.87 (1.12)		
Ferritin (µg/l) < 50, mean (SD)	21 (11)	3 (6)		
Endogenous erythropoietin baseline (patients with ≥ 100 mU/ml), *n* (%)	32 (17) ($n = 183$)	7 (15) ($n = 47$)		
FACT-F score, mean (SD) (darbepoetin and placebo groups combined; $n = 239$)	27.2 (12.4)			
Were intervention and control groups comparable?	No *p*-values reported; authors stated that 'In general, baseline demographic and clinical characteristics of patients were well balanced between the darbepoetin alfa and placebo groups (p. 2029). Some imbalances were noted in the 12.0 µg/kg group in respect of disease type and mean Hb concentration at baseline. In addition, the authors state that 'No clinically meaningful differences in pretreatment chemotherapy were seen between the darbepoetin alfa and placebo patients (data not shown)' (p. 2029)			

Results (data extraction for 6.75 µg/kg Q3W and placebo arms only)	Arm 1 = darbepoetin alfa 6.75 µg/kg Q3W [*n* = 17 (of total 198]	Arm 2 = placebo (*n* = 51)	
Hb			
Responders, Kaplan–Meier proportion (95% CI)	52 (27 to 78)	31 (16 to 45)	Hb values within 28 days of a RBCT have been omitted
Change in Hb from baseline to EOTP (g/l), mean (SE)	8.6 (3.8)	–0.2 (2.0)	
Change in Hb from baseline to EOTP (g/dl), mean (SE) (PenTAG calculated)	0.86 (0.38)	–0.02 (0.2)	
Change in Hb from baseline after 12 weeks (g/l),[a] mean (SE)	10.2 (5.4) (*n* = 11)	3.1 (2.4) (*n* = 37)	
Change in Hb from baseline after 12 weeks (g/dl), mean (SE) (PenTAG calculated)	1.02 (0.54) (*n* = 11)	0.31 (0.24) (*n* = 37)	

a Change after 12 weeks: a window was used allowing week 12 or week 14 to be used in the absence of an evaluable week 13 Hb value (using the set of patients who completed at least 12 weeks of treatment).

Safety: withdrawal because of, *n* (%)		
Deaths	7 (4)[a]	3 (6)
Tumour progression	6 (3)[a]	0
AEs[b]	1 (1)[a]	0
RBCT (week 5 to end of treatment period)[c]	*n* = 188	*n* = 50
HRQoL: change in FACT-F score from baseline to EOTP by change in Hb[d]		

EOTP, end of the treatment period.

a All darbepoetin alfa doses (withdrawal not reported by darbepoetin alfa dose).

b AEs reported for all patients receiving darbepoetin alfa and not reported by dose (results for AEs occurring with ≥ 15% incidence are presented graphically in Figure 3). The authors state that 'No relationship between the dose and adverse events was noted' (p. 2030) and 'AEs reported were comparable between the darbepoetin alfa and placebo patients and generally consistent with those expected for patients being treated with myelosuppressive chemotherapy' (p. 2029).

c Results presented graphically. For all doses: a lower percentage of patients in the darbepoetin alfa group required a RBCT from week 5 to EOTP than in the placebo group (46%; 95% CI 32% to 61%). No differences between the darbepoetin alfa groups could be observed: transfusion rates varied from 19% (95% CI 6% to 32%) to 30% (95% CI 16% to 44%).

d Results presented graphically. For all doses: mean change in FACT-F score appeared to increase with increasing Hb concentration, from roughly no change in patients who had no improvement in their Hb to an approx. 5-point improvement in patients whose Hb increased by > 2.0 g/dl. A trend test of the relationship between FACT-F score and Hb concentration was significant at a level of $p = 0.0023$.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear; process not described
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	No.[a] 'In general, baseline demographic and clinical characteristics of patients were well balanced between the darbepoetin alfa and placebo groups' (p. 2029). Some imbalances were noted in the 12.0 µg/kg group in respect of disease type and mean Hb concentration at baseline. In addition, the authors state that 'No clinically meaningful differences in pretreatment chemotherapy were seen between the darbepoetin alfa and placebo patients (data not shown)' (p. 2029)
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes
6. Were the outcome assessors blind to treatment allocation?	Yes
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially: results for AEs occurring with ≥ 15% incidence are presented graphically in Figure 3, not separated out by dose
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes, all randomised who received one or more dose of study drug were analysed (100% and 95% of participants in darbepoetin alfa and placebo groups respectively)
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Partially; only until the end of the double-blind study

a Yes for the placebo group and the 6.75 µg/kg Q3W (2.2 µg/kg QW) darbepoetin alfa subgroup.

Other	
Generalisability	Dose-finding study
Author conclusions	Darbepoetin alfa Q3W is well tolerated and effective in the treatment of anaemic patients receiving chemotherapy. Need for further research to investigate the proportion of patients responding to treatment and the time to achieve a response in this setting. Ability to administer Q3W as well as the possibility of administering darbepoetin alfa to coincide with chemotherapy that is administered Q3W represents an opportunity to simplify the treatment of anaemia and fatigue in cancer patients undergoing chemotherapy
Reviewer comments	

ECOG, Eastern Cooperative Oncology Group; NR, not reported; Q3W, once every 3 weeks; QW, once weekly.

EndNote ref. ID: 2691	Malignancy type: solid Treatment: rHuEPO, assume epoetin alfa	
Study design		**Participants**
Author, year	Kurz 1997[69]	*n* = 35
Objective	To evaluate the effectiveness of rHuEPO with respect to increasing Hb levels and decreasing RBCT requirements and to assess its influence on quality-of-life parameters	Inclusion criteria: Age 18–75 years; Hb level < 11 g/dl; ferritin serum level > 29 ng/ml; stool negative for occult blood; life expectancy > 3 months Exclusion criteria: Clinically significant disease or dysfunction of the pulmonary, cardiovascular, endocrine, neurological, gastrointestinal or genitourinary system not attributable to the underlying malignancy; uncontrolled hypertension (diastolic blood pressure > 100 mmHg); anaemia attributable to factors other than chronic neoplastic disease, such as vitamin B_{12} deficiency, iron deficiency and ferritin serum levels < 29 ng/ml; gastrointestinal bleeding or autoimmune haemolysis; acute illness within the last 7 days; creatinine > 2.5 mg/dl
No. of centres	4	
Other references/aliases	None	
Geographical setting	Austria	
Duration of treatment	12 weeks	
Length of follow-up (if different)	NR	
Country of corresponding author	Austria	
Language of publication	English	
Sources of funding	Supported in part by Janssen-Cilag Austria	
Randomisation and allocation	Random permuted blocks and a corresponding randomisation list was used in the randomisation office at Janssen-Cilag. A 2 : 1 ratio between rHuEPO and placebo was implemented. The randomisation code was broken after documentation of all data	

Treatment arms		
Arm drug name(s)	rHuEPO (Erypo; epoetin alfa)	Placebo
n	23	12
Dose and frequency (once daily, twice daily, etc.)	150 U/kg Q3W	150 U/kg Q3W
Dose adjustment (yes/no)	Yes. If Hb levels at week 4 were < 1 g/dl above the baseline value each dose was increased to 300 U/kg Q3W. If at week 4 Hb levels were > 1 g/dl above the baseline value but still within the anaemic range, the patient received 150 U/kg subcutaneously Q3W for the next 8 weeks	Yes. If Hb levels at week 4 were < 1 g/dl above the baseline value each dose was increased to 300 U/kg Q3W. If at week 4 Hb levels were > 1 g/dl above the baseline value, but still within the anaemic range, the patient received 150 U/kg subcutaneously Q3W for the next 8 weeks
Route of administration	Subcutaneous	Subcutaneous
Duration of epoetin treatment	12 weeks	12 weeks
Adjuvant anaemia treatment	Iron saccharate substitution following each dose of chemotherapy beginning with the next cycle	Iron saccharate substitution following each dose of chemotherapy beginning with the next cycle
Transfusion trigger	Hb < 8 g/dl	Hb < 8 g/dl

Outcomes	
Primary outcome	
Other outcomes	Haematological response (Hb levels measured every 4 weeks); RBCT (number of transfusions documented); HRQoL (beginning of treatment and then every 4 weeks before receiving chemotherapy patients completed a standardised questionnaire (10 items) – VAS (1–5); self-administration – collected by a nurse but results not read immediately and physician did not comment on the results)

Analysis	
Statistical technique used	Significance of the number of responders and the number of transfusions evaluated using chi-squared test. Differences between the treatment group and the control group shown using Kruskall–Wallis test for variables with a non-parametric distribution. Quality of life described per patient by 10 different scores, each of which was calculated as the average value of the scores for weeks 4, 8 and 12 minus the pretreatment value. Described the average of these 10 scores separately for each treatment and evaluated the significance in an exploratory mode using the Student's *t*-test for unpaired samples. A multivariate evaluation of all 10 different scores was carried out using Hotelling's T^2 test. The effect of achieving a response from a state of non-response was described for each responding patient ($n = 13$) by the difference in average quality-of-life score values for the items for feeling of well-being, level of activity, physical ability and social activities under response and non-response
ITT analysis?	Assumed ITT but unclear. Results reported for the total patient population and no reported crossover; however, not reported explicitly in the paper
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)	NR
Attrition rate (loss to follow-up)?	NR
Was attrition rate adequately dealt with?	Unclear as attrition rate NR
No. (%) followed up from each condition?	NA

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/myelodysplastic syndrome/mixed)		Solid – ovarian, cervical, uterine
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Platinum-based chemotherapy [$n = 28$ ($n = 17$ epoetin; $n = 11$ placebo)] and non-platinum-based chemotherapy [$n = 7$ ($n = 6$ epoetin; $n = 1$ placebo)]
Adjuvant anaemia treatment	Iron	Iron saccharate substitution following each dose of chemotherapy beginning with the next cycle
	G-CSF	NR
	Transfusion trigger	Hb < 8 g/dl
	Hb inclusion criterion level	< 11 g/dl

APPENDIX 2

	Arm 1 = rHuEPO (epoetin alfa) ($n = 23$)	Arm 2 = placebo ($n = 12$)	Notes	p-value
Age (years), mean ± SD (range)	54.4 ± 9.7 (32–68)	52.7 ± 7.5 (43–63)		0.36[a]
WHO performance status, *n*				
0–1	17	9		0.88[b]
1–2	6	3		
Type of solid tumour, *n*				
Ovarian	17	8		0.64[b]
Uterine sarcoma	3	1		
Cervical carcinoma	3	3		
Hb baseline (g/dl), mean ± SD	9.88 ± 0.889	9.85 ± 0.60		0.63[a]
Haematocrit baseline (ng/ml), mean ± SD	29.9 ± 3.1	29.9 ± 1.7		
Ferritin baseline (ng/ml), mean ± SD	300 ± 255	245 ± 196		
Were intervention and control groups comparable?	Yes; no statistically significant differences between the groups were reported			

a Kruskall–Wallis test.
b Chi-squared text.

Results				
Hb level (g/dl), mean				
Week 4	11.3	No change		
Week 8	11.9	No change		
Week 12	13.1	No change		
Haematological response, *n* (%)[a]				
Yes	13 (56.5)[b]	0 (0)	$\chi^2 = 10.79$	0.001
No	10 (43.5)	12 (100)		

Note
a Responder = if Hb level at weeks 4, 8 and 12 was > 2 g/dl above the baseline value and/or > 12 g/dl the patient was classified as a responder. Non-responder = patient receiving RBCT (Hb level < 8 g/dl; erythrocytes < 3×10^6/ml; or clinical symptoms of anaemia that made transfusion necessary).
b Of the 13 responders in the epoetin alfa arm, nine responded after 4 weeks of treatment, two after 8 weeks of treatment and two after 12 weeks of treatment.
Values estimated from:

Hb		Epoetin alfa ($n = 23$)		Placebo ($n = 12$)
4 weeks, mean (SD)		11.34 (1.75)		9.82 (1.75)
8 weeks, mean (SD)		11.87 (2.25)		10.32 (2.25)
12 weeks, mean (SD)		13.14 (2.25)		10.1 (2.25)
RBCT				
RBCT requirement, *n* (%)[a]	5 (21.7)	8 (66.6)	$\chi^2 = 6.81$	0.009

a The five patients receiving a RBCT in the treatment group received 33 units for transfusion, whereas the eight patients receiving a RBCT in the placebo group received 44 blood units. None of the responding patients had to be transfused during the study period. There was a 2.5 times increased demand for transfusions in the placebo-treated group compared with the epoetin alfa group.

HRQoL (not validated questionnaire)

	rHuEPO ($n = 23$)	Placebo ($n = 12$)	t-test, p-value[a]
Health state utility scale (see notes in *Outcomes* regarding the questionnaire used)			
Feeling of well-being	0.004	–0.16	0.77
Mood	–0.21	–0.18	0.94
Level of activity	0.26	0.58	0.71
Pain	0.37	–0.26	0.32
Nausea	–0.11	–0.43	0.17
Appetite	–0.32	–0.07	0.61
Physical ability	–0.33	–0.32	0.53
Social activities	–0.04	–0.51	0.89
Anxiety	1.92	2.45	0.38
Treatment is helping	1.76	2.34	0.11
Adverse effects			
Adverse effects of treatment	Well tolerated without any significant side effects (data not reported). No local reactions at the injection area nor any dermatitis or eruption could be observed		

a Multivariate Hotelling's T^2: $p = 0.34$.

Quality appraisal

1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Yes
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	Unclear; randomisation was performed in the randomisation office but details of allocation concealment were not reported
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Yes
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes
6. Were the outcome assessors blind to treatment allocation?	Yes
7. Were the point estimates and measure of variability presented for the primary outcome measure?	No; variability measure NR, unclear what the primary end point was
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes; results include response for all patients and no crossovers so assume ITT
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	NR

Other	
Generalisability	Women only
Author conclusions	rHuEPO significantly increases Hb levels and decreases RBCT requirements while maintaining quality of life in patients with gynaecological malignancies who are undergoing polychemotherapy
Reviewer comments	rHuEPO is epoetin alfa (Erypo, Janssen-Cilag)

NR, not reported; Q3W, once every 3 weeks.

EndNote ref. ID: 2692	Malignancy type: solid or non-myeloid haematological malignancies Treatment: epoetin alfa	
Study design		**Participants**
Author, year	Littlewood 2001[70]	$n = 375$
Objective	To assess the effects of epoetin alfa on RBCT requirements, haematopoietic parameters, quality of life and safety in patients receiving non-platinum-based chemotherapy	Inclusion criteria: Age ≥ 18 years; confirmed diagnosis of solid or non-myeloid hematological malignancy and receiving or scheduled to receive non-platinum-based chemotherapy (with a minimum cycle duration of 3 weeks); life expectancy ≥ 6 months; Hb level ≤ 10.5 g/dl or > 10.5 g/dl but ≤ 12.0 g/dl with at least a 1.5-g decrease in Hb per cycle/month since beginning chemotherapy
No. of centres	73 sites	
Other references/aliases	Patrick 2003,[60] Aapro 2004[82] and Bajetta 2004[81] and all retrospective analyses of this trial	
Geographical setting	15 countries (Germany, the Netherlands, UK, Ireland, Belgium, Luxembourg, Italy, South Africa, France, Greece, Switzerland, Poland, Portugal, Hungary, Czech Republic)	Exclusion criteria: Patients with acute leukaemia and myeloid malignancies; uncontrolled hypertension or untreated iron, folate or vitamin B_{12} deficiency; previous myeloablative chemotherapy; acute major infection or bleeding within 1 month; radiotherapy or allogeneic blood transfusion within 14 days; severe illness or surgery within 7 days of study entry
Duration of treatment	Up to 28 weeks: 12–24 weeks (three to six cycles) of chemotherapy and a 4-week period after the last dose of chemotherapy	
Length of follow-up (if different)	Survival rates were determined based on data collected during the 12-month period after the study was completed by the last patient	
Country of corresponding author	UK	
Language of publication	English	
Sources of funding	Supported by a research grant from RW Johnson Pharmaceutical Research Institute and Ortho Biotech Europe/Janssen-Cilag	
Randomisation and allocation	Stratified by tumour stratum (solid or haematological) and Hb level (≤ 10.5 g/dl or ≤ 12.0 g/dl but > 10.5 g/dl). Double-blind trail but concealed allocation not reported	

Treatment arms		
Arm drug name(s)	Epoetin alfa	Placebo
n	251	124
Dose and frequency (once daily, twice daily, etc.)	150 IU/kg three times a week	Matching volume to epoetin alfa
Dose adjustment (yes/no)	Yes, at 4 weeks. Dose was doubled if Hb increase was < 1 g/dl and the reticulocyte count increase was < 40,000 above baseline. Dose reduction by 25% if Hb increased by ≥ 2 g/dl per month or cycle. If at any time the Hb level was > 15 g/dl, medication was interrupted until the Hb level was < 12g/dl and restarted with a 25% dose reduction	

Treatment arms		
Route of administration	Subcutaneously	Subcutaneously
Duration of epoetin treatment	Up to 28 weeks	Up to 28 weeks
Adjuvant anaemia treatment	Oral daily dose of 200 mg of elemental iron daily	Oral daily dose of 200 mg of elemental iron daily
Transfusion trigger		
Outcomes		
Primary outcome	RBCT (proportion of patients transfused after first 4 weeks of treatment)	
Other outcomes	Haematological response[a] [change in Hb level (baseline to last value); proportion of responders]; survival; HRQoL [change in quality-of-life score (baseline to last value) on five cancer-specific scales: FACT-An, FACT-G Total, FACT-An Fatigue, CLAS, LASA])	

a Responders = patients with an increase in Hb level of ≥ 2 g/dl unrelated to transfusion, i.e. no transfusion within 28 days before measurement.

Analysis	
Statistical technique used	Primary end point analysed for ITT and efficacy populations (see below). Patients on study for ≤ 28 days were counted as transfused for the ITT analysis. The analyses were performed using a logistic regression model that included terms correcting for the main effects of treatment group, primary tumour stratum (solid or haematological) and haematological stratum (Hb ≤ 10.5 g/dl or > 10.5 g/dl). As the interaction terms for treatment by tumour stratum and treatment by Hb stratum were not significant at the 10% level, they were not included in the model. Secondary efficacy variables (other than quality of life) were analysed for the efficacy population. Changes in Hb level from baseline to last value were compared using *t*-tests and the proportions of responders were compared using the Fisher's exact test Univariate analysis was performed to test within-group mean quality-of-life change scores for differences from 0 with a paired *t*-test and differences in mean change scores between the treatment groups were examined using independent-sample *t*-tests (two-sided). The *p*-values for the primary quality-of-life measures were adjusted for multiple comparisons using a sequentially rejective version of the Bonferroni procedure. All hypothesis tests were performed on the adjusted *p*-values. In a separate analysis Pearson correlation coefficients were calculated to assess the relationship between change in Hb level and quality-of-life scores for each primary quality-of-life measure Protocol not designed or powered for survival, was amended before unblinding and study end to permit prospective analysis of survival. Information for this analysis was collected 12 months after the study end and survival distributions were estimated using Kaplan–Meier curves, which were compared by means of log-rank tests. In addition, to compensate for the variable survival times associated with different malignancies, Kaplan–Meier estimates of survival by tumour strata (haematological vs. solid) were also performed. Further analysis with the Cox regression model was performed using a stepwise selection procedure to correct for effects of potential prognostic factors on patient survival. Eight factors were tested for; four – tumour stratum, baseline Hb level, age and area under the curve for neutrophils – were found to be significant and were included in the model For all analyses $p < 0.05$ was considered significant. The study was not powered for subgroups
ITT analysis?	Partially. Three populations were used for the efficacy analyses: the ITT population, which included all randomised patients; the efficacy group, which included all randomised patients on study for > 28 days (efficacy); and the quality of life population, which was defined as all patients who had been randomised, received the study drug and had a baseline and at least one follow-up quality-of-life assessment. Safety population was the same as for the ITT population Baseline demographics and primary efficacy variable were analysed for both the ITT population and the efficacy population. Secondary variables other than quality of life domains were analysed for the efficacy population

Analysis	
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)	NR
Attrition rate (loss to follow-up)?	Yes; 16 patients (seven receiving epoetin alfa and nine receiving placebo) were excluded from the efficacy evaluation, 14 (six receiving epoetin alfa and eight receiving placebo) because they discontinued before completing treatment (no reasons reported) and two (one per patient group) because the blind on their treatment codes was broken permanently. The remaining 359 patients were assessable for efficacy. Numbers were also reported for the quality-of-life data set
Was attrition rate adequately dealt with?	Yes; patients on study for ≤ 28 days were counted as transfused for the ITT analysis (although no sensitivity analysis was performed)
No. (%) followed up from each condition?	Yes; two epoetin alfa patients and one placebo patient were lost to follow-up for the 12-month survival analysis

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		Solid: breast
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Non-platinum-based chemotherapy
Adjuvant anaemia treatment	Iron	An oral daily dose of 200 mg of iron was recommended if transferrin saturation was ≤ 20%; intravenous iron was recommended, use of iron dextran was not allowed
	G-CSF	No
	Transfusion trigger	At the discretion of the physician, with a recommended Hb level of < 8 g/dl unless clinically indicated
	Hb inclusion criterion level	≤ 10.5 g/dl or > 10.5 g/dl but ≤ 12.0 g/dl after a ≥ 1.5 g/dl decrease in Hb level per cycle or month since beginning chemotherapy

	Arm 1 = epoetin alfa (*n* = 251)	Arm 2 = placebo (*n* = 124)	Notes	*p*-value
Sex, *n* (%)				
Male	85 (34)	39 (31)		
Female	166 (66)	85 (69)		
Age (years), mean ± SD	58.3 ± 14.2	59.5 ± 13.9		
WHO/ECOG performance status	NR	NR		
Hb baseline (g/dl), mean ± SD	9.9 ± 1.1	9.7 ± 1.1		
Hb stratum, *n* (%)				
≤ 10.5 g/dl	209 (83)	109 (88)		
> 10.5 g/dl	42 (17)	15 (12)		
Chemotherapy within 3 months of study start, *n* (%)	231 (92)	114 (92)		
Pre-study transfusions within 3 months of study start, *n* (%)	71 (28)	44 (35)		
Iron baseline (U/l), median (range)	NR	NR		
Erythropoietin baseline (mU/ml)	NR	NR		
Target Hb	NR	NR		

	Arm 1 = epoetin alfa ($n = 251$)	Arm 2 = placebo ($n = 124$)	Notes	*p*-value
Tumour stratum, *n* (%)[70]				
Solid	136 (54)	66 (53)		
Haematological	115 (46)	58 (47)		
Were intervention and control groups comparable?	No *p*-values reported; authors stated that 'Demographic and baseline characteristics of the patients in the ITT population were generally comparable between the epoetin alfa and placebo treatment groups (p. 2867). However, there were proportionally fewer previously transfused patients at baseline in the epoetin alfa group than in the placebo group (28% vs. 36% respectively) (p. 2867)'			
Results: ITT and efficacy populations				
Patients transfused, *n/N* (%) (ITT population)				
Overall	62/251 (24.7)	49/124 (39.5)	0.0057 (adjusted)	
Solid tumour	33/136 (24.3)	24/66 (36.4)		
Haematological tumour	29/155 (25.2)	25/58 (43.1)		
Change in Hb after 28 weeks (g/dl), mean (SD) (efficacy population)[a]	2.2 (2.18) ($n = 244$)	0.5 (1.79) ($n = 115$)	< 0.001	
Responders (increase in Hb level of 2 g/dl during the study without transfusion in the previous 30 days), *n/N* (%) (efficacy population)				
Overall	172 (70.5) ($n = 244$)	22 (19.1) ($n = 115$)	< 0.001 (Fisher's exact test)	
Solid tumour	87/131 (66.4)	13/61 (21.3)		
Haematological tumour	85/113 (75.2)	9/54 (16.7)		
Hb ≤ 10.5 g/dl	139/203 (68.5)	22/100 (22.0)		
Hb > 10.5 g/dl	33/41 (80.5)	0/15 (0.0)		
Survival 12 months after the last patient enrolled completed the study (median follow-up 26 months)				
OS at 12-month assessment (safety population), *n* (%)	$n = 251$	$n = 124$		
Alive	94 (37)	41 (33)		
Dead	155 (62)	82 (66)		
Lost to follow-up	2 (1)	1 (1)		
Median survival (months) (ITT population)	17	11		
OS (note study insufficiently powered for this outcome) Kaplan–Meier 12-month survival estimates (ITT population) (%)	60	49	0.13	
Estimated HR (placebo vs. epoetin alfa)	1.309[b]		0.052	

OS at 12-month assessment (safety population), *n* (%)			
Haematological malignancies (*n* = 173)	*n* = 115	*n* = 58	
Alive	60 (52)	28 (48)	
Dead	54 (47)	30 (52)	
Lost to follow-up	1 (1)	0 (0)	
Solid tumours (*n* = 202)	*n* = 136	*n* = 66	
Alive	34 (25)	13 (20)	
Dead	101 (74)	52 (79)	
Lost to follow-up	1 (1)	1 (2)	
Health state utility scale	Of the 375 ITT patients, 349 were evaluated for changes in quality-of-life parameters. Presented as change from baseline to last assessment (unclear when)		
Results for FACT and CLAS			
Mean change score: FACT-An Fatigue	3.0 (*n* = 200)	–2.2 (*n* = 90)	0.004
Mean change score: FACT-An Anaemia	4 (*n* = 200)	–2.6 (*n* = 90)	0.0007 (not adjusted for multiple comparisons)
Mean change score FACT-G	2.5 (*n* = 194)	–3.6 (*n* = 88)	0.004
CLAS-Energy	8.1 (*n* = 228)	–5.8 (*n* = 108)	0.0007
CLAS-Daily activities	7.5 (*n* = 228)	–6.0 (*n* = 108)	0.0018
CLAS-Overall quality of life	4.8 (*n* = 228)	–6.0 (*n* = 107)	0.0048
Adverse effects of treatment (safety population), *n* (%)[c]	*n*= 251	*n* = 124	
Any AE	216 (86)	101 (81)	
Fever	55 (22)	21 (17)	
Granulocytopenia	49 (20)	16 (13)	
Disease progression	44 (18)	27 (22)	
Nausea	46 (18)	17 (14)	
Abdominal pain	30 (12)	13 (10)	
Constipation	30 (12)	16 (13)	
Leukopenia	31 (12)	13 (10)	
Diarrhoea	27 (11)	10 (8)	
Vomiting	24 (10)	13 (10)	
Fatigue	17 (7)	15 (12)	
Dyspnoea	15 (6%)	14 (11%)	

a Hb levels increased for the first 10–14 weeks on epoetin alfa, whereas the Hb levels in the placebo group did not differ significantly from baseline over the same period.
b HR in favour of epoetin alfa; during the entire follow-up period the risk of dying was approximately 31% higher for placebo-treated patients than for epoetin alfa-treated patients.
c AEs were reported in at least 10% of patients in either treatment group.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear: stratified by tumour stratum (solid or haematological) and Hb level (≤ 10.5 g/dl or ≤ 12.0 g/dl but > 10.5 g/dl)
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear[a]
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes
6. Were the outcome assessors blind to treatment allocation?	Yes
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially, no variability
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes, apart from HRQoL (only 80% and 73% of participants analysed in the epoetin and placebo groups, respectively)[b]
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes, numbers given but detailed reasons not provided

a No *p*-values reported; authors report that 'Demographic and baseline characteristics of the patients in the ITT population were generally comparable between the epoetin alfa and placebo treatment groups' (p. 2867).
b Secondary end point (other than quality of life) analyses using the efficacy population (see Analysis section).

Other	
Generalisability	Yes – broad population
Author conclusions	Epoetin alfa safely and effectively ameliorates anaemia and significantly improves quality of life in cancer patients receiving non-platinum-based chemotherapy. Encouraging results regarding increased survival warrant another trial designed to confirm these findings
Reviewer comments	Caution required with regard to survival results because of being underpowered. Also, concern over lack of explanation for dropouts/withdrawals; some explanation reported in Littlewood and colleagues[70] but reasons for withdrawals not specified in detail

CLAS, Cancer Linear Analogue Scale; ECOG, Eastern Cooperative Oncology Group; NR, not reported.

EndNote ref. ID: 2680	Malignancy type: breast cancer Treatment: epoetin alfa	
Study design		**Participants**
Author, year	Moebus 2013[62]	$n = 1284$, of whom 643 in the intense dose-dense arm sequential chemotherapy (IDD-ETC) arm were randomised to epoetin alfa ($n = 324$) or epoetin alfa ($n = 319$)
Objective	The AGO-ETC trial compared intense dose-dense sequential chemotherapy every 2 weeks with conventional scheduled therapy in high-risk breast cancer patients. The objective of this study was to evaluate the safety and efficacy of epoetin alfa in a second randomisation of the IDD-ETC arm	Inclusion criteria: Age 18–65 years; histologically confirmed primary breast cancer of stages II–IIIa with four or more tumour-infiltrated axillary lymph nodes, M0 status and R0 resection of the primary tumour and axilla with a minimum of 10 axillary lymph nodes removed; ECOG performance status of 0–1; normal left ventricular ejection fraction; neutrophils ≥ 1,500/µl; platelets ≥ 100,000/µl; serum creatinine, transaminases and total bilirubin < 1.25; alkaline phosphatase < 3.0 times the institutional upper normal limit Exclusion criteria: History of severe cardiac disease; previous systemic tumour therapy; simultaneous contralateral breast cancer or any other cancer except for basal cell skin carcinoma
No. of centres	165 (recruitment between November 1998 and April 2003)	
Other references/aliases	EPO-GER-10, AGO-ETC trial, Moebus 2010[198] and presented in part at the 40th Annual Meeting of the American Society of Clinical Oncology, New Orleans, LA, 5–8 June 2004,[199] and at the 29th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, 14–17 December 2006[200]	
Geographical setting	Germany	
Duration of treatment	Median 18 weeks (mean 16.9 weeks)	
Length of follow-up (if different)	Median follow-up was 62 months but the study is ongoing for continued 10-year follow-up	
Country of corresponding author	Germany	
Language of publication	English	
Sources of funding	Bristol-Myers Squibb, Amgen Inc., Pharmacia and Johnson & Johnson	
Randomisation and allocation	Patients stratified by centre, menopausal status (pre- vs. post menopausal) and the number of affected lymph nodes (4–9 vs. ≥ 10) at central fax randomisation. Computer-generated lists with permuted blocks of randomly variable size were used	
Treatment arms		
Arm drug name/s	Epoetin alfa	Control, standard care
n	324	319
Dose and frequency (once daily, twice daily, etc.)	150 IU/kg three times weekly	NA
Dose adjustment (yes/no)	To maintain Hb level of 12.5–13.0 g/dl. Dose doubled if Hb dropped > 2 g/dl within a 4-week period. Epoetin was withdrawn when Hb > 14.0 g/dl and was restarted when Hb < 13.0 g/dl	NA
Route of administration	Subcutaneously	NA
Duration of epoetin treatment	Started on day 1 and continued up to 14 days after the last dose of cyclophosphamide	NA

Treatment arms		
Adjuvant anaemia treatment	200 mg/day oral iron	200 mg/day oral iron
Transfusion trigger	Patients with a Hb level < 9.0 g/dl were evaluated for transfusion by the physician. The indication for RBCT depended on the symptoms of the patients and was at the discretion of the physician	Patients with a Hb level < 9.0 g/dl were evaluated for transfusion by the physician

Outcomes	
Primary outcome	Hb levels baseline to cycle 9
Other outcomes	RBCT (no. of blood transfusions); survival (OS, recurrence-free survival); HRQoL (EORTC QLQ, version 3 [assessed before the start of treatment, at every second cycle, at the end of treatment and at each follow-up visit)]; AEs

Notes
Complete blood counts were obtained at each cycle and Hb level was measured at least weekly during chemotherapy.
Follow-up visits were performed every 3 months for 3 years, every 6 months during years 4 and 5 and annually thereafter.
M0 status: i.e. normal findings on chest radiography, liver ultrasonography and bone scan.
Radiation of the supraclavicular, infraclavicular and parasternal lymph nodes, as well as radiation of the breast in patients with partial mastectomy or to the chest wall in case of mastectomy, was recommended in all patients.

Analysis	
Statistical technique used	All statistical tests were two-sided except for the primary end point of transfusion, for which a one-sided hypothesis was prospectively defined. Comparison of Hb levels was evaluated with ANOVA and Wilcoxon tests. Numbers with at least one on-study RBCT were compared between the two groups using Fisher's exact test. On-study was defined as the period from randomisation to the date of the last cycle of chemotherapy plus 14 days or the date of withdrawal, whichever occurred first. Kaplan–Meier estimates of the relapse-free survival rate were compared using a two-sided log-rank test with and without the stratification factors for menopausal status and number of positive lymph nodes. Cox regression models, with and without adjustment for the stratification factors, were performed to calculate HRs and 95% CIs
ITT analysis?	Yes, ITT and per-protocol analyses for primary outcomes and relapse-free survival. The safety population included 627 subjects (309 epoetin arm, 318 control arm): all epoetin patients receiving epoetin and all control subjects with no epoetin treatment. The per-protocol population included 511 subjects (258 epoetin arm, 253 control arm). Patients were excluded if unknown ECOG/WHO performance status; less than four positive lymph nodes at baseline; not receiving the assigned treatment (the majority of patients were excluded if they failed to receive nine cycles of chemotherapy)
Does statistical technique adjust for confounding?	NA
Power calculation (a priori sample calculation)?	Yes, based on the size needed to detect any difference in Hb levels and proportions needing transfusion. In addition, the sample size had approx. 85% power to detect a 10% difference in the 5-year relapse-free survival rate after a median follow-up of 5 years using a log-rank test
Attrition rate (loss to follow-up)?	Yes
Was attrition rate adequately dealt with?	Yes
No. (%) followed up from each condition?	Yes

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/ haematological/myelodysplastic syndrome/mixed)		Solid tumour: breast cancer
Treatment (e.g. chemotherapy platinum/ non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Nine cycles of three sequential cycles of epirubicin (150 mg/m^2), paclitaxel (225 mg/m^2) and cyclophosphamide (2500 mg/m^2) every 2 weeks (IDD arm A)
Adjuvant anaemia treatment	Iron	200 mg/day oral iron
	G-CSF	All cycles were administered in 3-week intervals without growth factor support
	Transfusion trigger	Patients with a Hb level < 9.0 g/dl were evaluated for transfusion by the physician
	Hb inclusion criterion level	NR

	Arm 1 = epoetin alfa (n = 324)	Arm 2 = control (n = 319)	Notes	p-value
Age (years), median (range)	50 (29–65)	52 (28–67)		
ECOG performance status, n (%)	(n = 315)	(n = 312)		
0	254 (81)	260 (83)		
1	61 (19)	52 (17)		
Body mass index (kg/m^2), median (range)	24.5 (17–42)	24.4 (17–48)		
Hb baseline (g/dl), median (IQR)	12.4 (11.7–13.3) (n = 313)	12.8 (12.2–13.6) (n = 303)		
Tumour stage, n (%)				
pT1	81 (25)	100 (31)		
pT2	190 (59)	172 (54)		
pT3	50 (15)	46 (14)		
Were intervention and control groups comparable?	No p-values reported; authors stated that 'the two treatment groups were generally similar with respect to the demographic and baseline characteristics' (p. 1020)			

Results				
Change in Hb (cycle 9)[a]	0	–2.2		< 0.001
No. of transfusions, assessed during the period from randomisation to the date of the last cycle of chemotherapy plus 14 days or the date of withdrawal, whichever occurred first (ITT)[b]	41 (12.8)	86 (28.1)	HR 0.37 (95% CI 0.25 to 0.57)	< 0.0001
HRQoL[c]				
Survival (ITT), *n*	324	317		
5-year relapse-free survival (%) (95% CI)	71 (66 to 76)	72 (67 to 77)	HR 1.03 (95% CI 0.77 to 1.37)	*p* = 0.86
5-year OS (%) (95% CI)	81 (76 to 86)	83 (78 to 87)	HR 0.97 (95% CI 0.67 to 1.41)	*p* = 0.89
Safety[d]	(*n* = 309)	(*n* = 318)		
Total no. of subjects with AEs	10 (3)	22 (7)		
Embolism, *n* (%)	1 (< 1)	0 (0)		
No. (%) of patients with thromboembolic vascular event while on chemotherapy	39 (13)	22 (7)		
No. (%) of patients with clinically relevant thromboembolic vascular events	22 (7)	10 (3)		*p* = 0.03
Vascular disorders, *n* (%)				
Thrombosis	21 (7)	9 (3)		
Venous thrombosis	2 (1)	0 (0)		
Arterial thrombosis	1 (< 1)	0 (0)		
Deep-vein thrombosis	1 (< 1)	0 (0)		
Embolism	0 (0)	1 (< 1)		
Subclavian vein thrombosis	0 (0)	1 (< 1)		
Respiratory, thoracic, and mediastinal disorders, *n* (%)				
Pulmonary embolism	0 (0)	1 (< 1)		
Serious AE (%)	10%	13%		

a Mean Hb values presented graphically.
b Similar results were obtained when the per-protocol population was analysed. Most transfusions, regardless of treatment group, occurred during cycles 7–9. The number of subjects in the control group who received transfusions increased steadily from cycle 1 to cycle 9; the number of subjects in the epoetin alfa group who received transfusions increased mainly during cycles 7–9.
c Results for health-related patient-reported outcome analyses are not presented because of the large number of missing baseline data (in excess of 40% of baseline measurements were missing).
d Incidence is based on the number of patients experiencing at least one AE, not the number of AEs.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Yes
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	Unclear
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear; no *p*-values reported
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No
6. Were the outcome assessors blind to treatment allocation?	NR
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Yes
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	Yes; this study had a Latin square design and this paper reports second randomisation (first randomisation results published in an alternative reference,[198] excluded as epo vs. epo not measured)
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes

Other	
Generalisability	Females only (breast cancer)
Author conclusions	Epoetin alfa resulted in improved Hb levels and decreased transfusions without an impact on relapse-free or OS. However, epoetin alfa had an adverse effect, resulting in increased thrombosis
Reviewer comments	Although epoetin alfa dosing information had to be reported in the case report form as the number of units administered per kilogram of body weight, a fixed dose of 10,000 IU was specified for some subjects. In these instances, a per-kg dose was calculated using the subject's body weight

AGO, Arbeitsgemeinschaft für Gynäkologische Onkologie; ANOVA, analysis of variance; ECOG, Eastern Cooperative Oncology Group; EPO-GER-10, EPO Germany 10; ETC, epirubicin, paclitaxel and cyclophosphamide; IDD, intense dose-dense; IQR, interquartile range; NR, not reported.

EndNote ref. ID: 2693	Malignancy type: lymphoproliferative malignancies – NHL, CLL, MM Treatment: ESA – epoetin beta	
Study design		**Participants**
Author, year	Österborg 2005[79]	$n = 349$ (ITT $n = 343$)
Objective	To investigate the efficacy of epoetin beta in eliminating severe anaemia and transfusion dependency and concomitant effects on quality of life using the FACT scale in participants with advanced MM, low-grade NHL and CLL	Inclusion criteria: Age ≥ 18 years; confirmed diagnosis of NHL, CLL or MM; Hb < 10 g/dl with a transfusion requirement of ≥ 2 units of RBCs in the 3 months before the study; inadequately low endogenous serum erythropoietin concentration ≤ 100 IU/l if Hb > 9 g/dl to < 10 g/dl) ≤ 180 IU/l if Hb level > 8 g/dl to ≤ 9 g/dl or ≤ 300 IU/l if Hb level ≤ 8 g/dl; scheduled to receive antitumour therapy for the next 4 months; life expectancy > 4 months; WHO performance score 0–3. Exclusion criteria: Therapy-resistant hypertension; relevant acute or chronic bleeding in 3 months before study commencement; thrombocytopenia or thrombocytosis (platelets < 20 and > 450 × 10^9/l respectively); vitamin B_{12} or folic acid deficiency; creatinine level > 2.5 mg/dl; haemolysis (haptoglobin level < 50 mg/dl); epilepsy; known hypersensitivity to preservatives used in study medication injection formulation; evidence of functional iron deficiency (transferrin < 25%)
No. of centres	63, conducted between June 1997 and July 1999	
Other references/aliases	Österborg 2002[71]	
Geographical setting	12 countries	
Duration of treatment	16 weeks	
Length of follow-up (if different)	Participants followed up for at least 1 year after the end of the treatment period. The minimum length of follow-up was approx. 17.5 months in both treatment groups, with only 4 participants in each group having a shorter follow-up (reported in Österborg and colleagues[79])	
Country of corresponding author	Sweden	
Language of publication	English	
Sources of funding	F. Hoffmann-La Roche	
Randomisation and Allocation	Randomised, double-blind, placebo-controlled trial. Stratified according to malignancy type and study centre. After a run-in period of approximately 2 weeks, patients suitable for inclusion were randomised	
Treatment arms		
Arm drug name(s)	Epoetin beta	Placebo
n	170	173
Dose and frequency (once daily, twice daily, etc.)	150 IU/kg three times a week	
Dose adjustment (yes/no)	The dose was increased to 300 IU/kg if Hb level was < 8.5 g/dl or if increase in Hb from baseline was < 0.5 g/dl after 4 weeks. Dose was decreased by 50% if Hb increased by > 2 g/dl within this period. If Hb was > 14 g/dl, the study medication was suspended until Hb level declined to ≤ 13 g/dl, when epoetin beta was reinstated at 50% of the previous dose	
Route of administration	Subcutaneous	Subcutaneous
Duration of epoetin treatment	16 weeks	16 weeks

Treatment arms		
Adjuvant anaemia treatment	Enrolled participants with a baseline transferrin saturation of < 25% received intravenous iron substitution (100 mg iron) before the start of study treatment. When the transferrin saturation level decreased to < 25% during the course of the study, intravenous iron substitution therapy was administered at a dose of 100 mg of iron per week until transferrin saturation reached ≥ 25%. Oral iron substitution therapy (200–300 mg) was administered to those in whom intravenous iron was precluded	Enrolled participants with a baseline transferrin saturation of < 25% received intravenous iron substitution (100 mg iron) before the start of study treatment. When the transferrin saturation level decreased to < 25% during the course of the study, intravenous iron substitution therapy was administered at a dose of 100 mg of iron per week until transferrin saturation reached ≥ 25%. Oral iron substitution therapy (200–300 mg) was administered to those in whom intravenous iron was precluded
Transfusion trigger	Hb < 8.5 g/dl or at higher levels if medically indicated, i.e. the presence of marked anaemic symptoms such as angina pectoris	Hb < 8.5 g/dl or at higher levels if medically indicated, i.e. the presence of marked anaemic symptoms such as angina pectoris
Outcomes		
Primary outcome	Transfusion-free survival (during weeks 5–16 of the study). Also analysed severe anaemia-free survival (Hb ≥ 8.5 g/dl) during weeks 5–16. Death without a previous event was considered a failure	
Other outcomes	Haematological response (increase in Hb level of ≥ 2 g/dl above baseline without the need for a blood transfusion in the previous 6 weeks); Hb nadir (measured at 4-week long intervals); HRQoL (subjective quality of life was assessed at baseline and every 4 weeks during the study using FACT-An;[a] questionnaires were completed before any examination or treatment so that participant assessments could not be influenced by references to current Hb level); AEs (AEs, hematological parameters, concomitant medications, blood transfusions and antitumour therapy were documented throughout the course of the study)	

a Although the anaemia and fatigue subscales were part of the original study plan, the FACT-G questionnaire was introduced by an amendment to the study protocol in January 1998.

Analysis	
Statistical technique used	Subgroup analyses with a one-sided Wald chi-squared test ($\alpha = 0.05$) performed if the difference in the total study population was significant and no significant interaction between study treatment and strata was present ($p > 0.1$). HRs were calculated to estimate the relative risk of failure and event-free curves were displayed that were based on Kaplan–Meier estimates. Multivariate Cox proportional hazard methods were used to assess the contribution of other baseline characteristics to event-free rates. Cumulative response rates were analysed by the stratified log-rank test and displayed as Kaplan–Meier curves. Analysis of covariance techniques were used to analyse the changes from baseline in quality of life and Hb data, with baseline values considered as covariates Long-term survival data (Österborg 2005[79]): Survival data were analysed by standard Kaplan–Meier methods and differences in survival between groups were assessed using a log-rank test. The median time to patients being censored was 27.8 months in the epoetin beta group and 27.5 months in the placebo group
ITT analysis?	Yes; the primary efficacy variable was analysed on an ITT basis via a Cox proportional hazard model adjusted for the type of underlying malignant disease at a significance level of 5%, although the ITT population is defined as all participants receiving study treatment ($n = 343$), whereas 349 participants were randomised. ITT population = safety population in this study ($n = 343$)
Does statistical technique adjust for confounding?	Yes

Analysis		
Power calculation (a priori sample calculation)?		Yes; 150 patients with low-grade NHL, CLL or MM needed to detect an improvement in the primary variable from 25% to 50% with a power of 85% via a Cox proportional hazard model. In an amendment to the study protocol, the sample size was increased: enrol at least 100 participants per stratum (MM, NHL, CLL; 50 participants per treatment group) to achieve a power of 80% for the three corresponding subgroup analyses). A lost-to follow-up rate of ≤ 10% in weeks 5–16 weeks was assumed
Attrition rate (loss to follow-up)?		Three participants in each treatment group were withdrawn before receiving study medication because of withdrawal of consent ($n = 5$) and protocol violation ($n = 1$). In total, of 349 participants, 281 completed the study. The main reasons for withdrawal were death ($n = 35$), withdrawal of consent ($n = 12$) and AEs ($n = 11$)
Was attrition rate adequately dealt with?		In case of premature withdrawal from study treatment, participants were observed and Hb level, number of blood transfusions and vital status were recorded whenever possible until study week 16
No. (%) followed up from each condition?		Yes, until the end of treatment only
Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/ haematological/myelodysplastic syndrome/mixed)		NHL, CLL, MM
Treatment (e.g. chemotherapy platinum/ non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Non-platinum-based chemotherapy
Adjuvant anaemia treatment	Iron	Yes, see treatment description above for more details
	G-CSF	NR
	Transfusion trigger	Hb < 8.5 g/d or at higher levels if medically indicated, i.e. the presence of marked anaemic symptoms such as angina pectoris
	Hb inclusion criterion level	< 10 g/dl

	Arm 1 = epoetin beta ($n = 170$)	Arm 2 = placebo ($n = 173$)	Notes	*p*-value
Sex, *n* (%)				
Male	91 (54.0)	82 (47.0)		
Female	79 (46.0)	91 (53.0)		
Age (years), median (range)	63 (32–86)	64 (28–83)		
WHO performance status, *n* (%)				
0	10 (6.0)	13 (7.5)		
1	57 (33.5)	62 (36.0)		
2	73 (43.0)	68 (39.0)		
3	30 (17.5)	30 (17.5)		
Body weight (kg), mean ± SD	69 ± 12	69 ± 13		
Underlying malignancy, *n* (%)				
CLL	59 (35.0)	66 (38.0)		
MM	58 (34.0)	58 (33.5)		
NHL	53 (31.0)	49 (28.5)		

	Arm 1 = epoetin beta ($n = 170$)	Arm 2 = placebo ($n = 173$)	Notes	*p*-value
Transfusion requirement, *n* (%)				
None	11 (6.5)	6 (3.5)		
1 unit	4 (2.5)	6 (3.5)		
2–5 units	126 (74.0)	131 (76.0)		
≥ 6 units	29 (17.0)	30 (17.0)		
Haematological parameters				
Hb (g/dl), mean ± SD	9.2 ± 1.1	9.3 ± 1.0		
Haematocrit (%), mean ± SD	28.2 ± 4.7	28.6 ± 4.2		
Neutrophil count ($\times 10^9$/l), mean ± SD	2.8 ± 2.5	3.0 ± 3.1		
Platelet count, ($\times 10^9$/l), mean (IQR)	149 (100–195)	141 (94–190)		
Serum erythropoietin (IU/l), median (IQR)	38 (20–72)	41 (21–77)		
Serum ferritin (ng/ml), median (IQR)	586 (235–1121)	514 (195–1183)		
Transferrin saturation (%), mean ± SD	38 ± 22	39 ± 23		
Quality-of-life scores, mean ± SD				
FACT-An	115.2 ± 28.0	114.0 ± 28.3		
FACT-G	69.1 ± 14.4	68.5 ± 15.0		
FACT-F	28.8 ± 10.7	29.2 ± 11.0		
FACT-An subscale	17.3 ± 4.6	17.0 ± 5.0		
Were intervention and control groups comparable?	Unclear: no *p*-values reported; author states that 'There were no major differences in the demographics and clinical characteristics of the two treatment groups' (p. 207)			

Results				
Haematological				
Hb response (≥ 2 g/dl increase in Hb without transfusion) at 16 weeks (%)[a]		67	27	< 0.0001
Hb response MM patients ($n = 116$) (%)		76	29	< 0.0001
Hb response NHL patients ($n = 102$) (%)		62	24	< 0.0001
Hb response CLL patients ($n = 125$) (%)		63	26	< 0.0001
Hb nadir (g/dl), mean ± SD[b]				
1–4 weeks		9.1 ± 1.4 ($n = 169$)	8.7 ± 1.2 ($n = 173$)	0.0003
5–8 weeks		10.0 ± 1.9 ($n = 161$)	8.8 ± 1.5 ($n = 165$)	0.0001
9–12 weeks		10.5 ± 2.0 ($n = 152$)	8.9 ± 1.5 ($n = 153$)	0.0001
13–16 weeks		10.8 ± 2.0 ($n = 146$)	9.2 ± 1.6 ($n = 147$)	0.0001
Prediction of response (Cox's multivariate regression analysis of factors in transfusion-free survival during weeks 5–16)[c]				
Treatment, epoetin beta vs. placebo		HR 0.555, 95% CI 0.369 to 0.776; $p = 0.0006$		
Platelet count, ≥ 100 vs. < 100×10^9 g/l		HR 0.416, 95% CI 0.292 to 0.592; $p = 0.0001$		
Hb level, ≥ 9 g/dl vs. < 9 g/dl		HR 0.589, 95% CI 0.423 to 0.821; $p = 0.0018$		
Pretreatment transfusion requirement, ≤ 2 vs. 3 units		HR 0.645, 95% CI 0.458 to 0.909; $p = 0.0123$		
Underlying malignancy		HR 0.803, 95% CI 0.565 to 1.140; $p = 0.2198$		
Severe anaemia and transfusion-free survival				
Participants with blood transfusions in first 4 weeks of study treatment (%)	29.0	27.2		0.707
Transfusion-free survival during 16 weeks of treatment (%)	66.7	47.6	Risk reduction of 43% favouring epoetin beta	0.0012
Severe anaemia- and transfusion-free survival[d]			Risk reduction of 51% favouring epoetin beta	0.0001
Interaction between underlying malignant disease and treatment				> 0.1
Survival (long-term follow-up) ([e]Österborg and colleagues[79])				
No. (%) of deaths	110 (65%), censored $n = 60$	109 (63%), censored $n = 64$		
Kaplan–Meier: survival (months), median (95% CI)	17.4 (15.0 to 20.5)	18 (16 to 22.3)	HR 1.04 (0.8 to 1.36)	0.76

a Figure 2 presents time to response graphically.
b The difference in mean Hb nadir was 0.4 g/dl at weeks 1–4, increasing to 1.6 g/dl at weeks 13–16 ($p = 0.001$ vs. placebo). Similar findings were observed for mean Hb levels and haematocrit, which increased significantly in the epoetin beta group from week 2 onward (both $p < 0.005$ vs. placebo) during the course of the study.
c Baseline platelet count ≥ 100×10^9/l, Hb level ≥ 9 g/dl and a lower prestudy transfusion requirement (≤ 2 units) were the factors strongly associated with a low risk of failure. Subgroup analyses also demonstrated that risk reduction in epoetin beta participants vs. placebo participants was stronger in participants with a high platelet count (55%) and high Hb levels (51%) than in participants with a low platelet count (21%) and low Hb levels (26%).The type of underlying malignancy (MM, NHL or CLL), sex, age, baseline neutrophil count, transferrin saturation, WHO performance score or quality-of-life score had no significant effect in either analysis.
d Figure 1 represents severe anaemia- and transfusion-free survival graphically. The difference in transfusion- and severe anaemia-free survival was statistically significant across all malignancy subtypes and was particularly apparent in participants with MM ($p = 0.0001$), with a risk reduction of 66% in those receiving epoetin beta compared with placebo. In those with NHL and CLL, the risk was reduced by approx. 40% in both groups ($p = 0.02$ and $p = 0.03$ respectively).
e Figure 1 represents OS graphically.

HRQoL

Baseline and change from baseline in quality-of-life questionnaires

	Baseline		Week 4		Week 8		Week 12		Week 16	
Variable	Score, mean ± SD	No. of participants	Score, mean ± SD	No. of participants	Score, mean ± SD	No. of participants	Score, mean ± SD	No. of participants	Score, mean ± SD	No. of participants
FACT-An, 49 items, range 0–196										
Epoetin beta	115.2 ± 28.0	128	4.9 ± 21.4	127	7.9 ± 25.7	118	13.1 ± 27.6[a]	114	14.8 ± 28.0[a]	105
Placebo	114.0 ± 28.3	121	5.3 ± 19.5	119	7.4 ± 22.7	110	7.1 ± 26.3	102	8.7 ± 28.9	101
FACT-G, 29 items, range 0–116										
Epoetin beta	69.1 ± 14.4	129	1.7 ± 11.8	128	3.7 ± 13.0	118	5.9 ± 14.5[a]	114	6.5 ± 13.8[a]	106
Placebo	68.5 ± 15.0	122	2.2 ± 10.1	120	2.9 ± 11.5	112	2.6 ± 12.9	104	3.1 ± 14.4	103
FACT-F subscale, 13 items, range 0–52										
Epoetin beta	28.8 ± 10.7	160	2.2 ± 8.7	157	2.8 ± 10.8	148	4.2 ± 11.7	145	5.2 ± 12.2	133
Placebo	29.2 ± 11.0	157	1.8 ± 8.4	157	1.9 ± 9.8	145	2.5 ± 10.9	135	3.0 ± 12.1	130
FACT-An subscale, seven items, range 0–28										
Epoetin beta	17.3 ± 4.6	160	0.9 ± 3.3	157	1.2 ± 4.2	148	1.7 ± 4.4	145	2.0 ± 4.3	133
Placebo	17.0 ± 5.0	157	0.8 ± 3.5	157	1.2 ± 4.1	145	1.2 ± 4.5	135	1.7 ± 5.2	130

a $p < 0.5$ (after 12 and 16 weeks, the improvement in FACT-An and FACT-G scores was greater in the epoetin beta arm).

Note

Analysis of the dimensions of the FACT-G scale revealed statistically significant differences after 12 weeks: $p < 0.01$ and $p < 0.05$ favouring epoetin beta for social and family well-being and emotional well-being respectively.

Quality of life results at baseline and change from baseline in epoetin beta responders and non-responders

Variable	Baseline		Week 4		Week 8		Week 12		Week 16	
	Score, mean ± SD	No. of participants	Score, mean ± SD	No. of participants	Score, mean ± SD	No. of participants	Score, mean ± SD	No. of participants	Score, mean ± SD	No. of participants
FACT-An, 49 items, range 0–196										
Responder	118.9 ± 25.1	92	5.1 ± 21.6	91	9.7 ± 25.2[a]	87	15.2 ± 26.3[a]	88	17.4 ± 25.9[a]	82
Non-responder	105.7 ± 32.9	36	4.3 ± 21.0	36	3.0 ± 27.0	31	5.8 ± 31.0	26	5.8 ± 33.7	23
FACT-G, 29 items, range 0–116										
Responder	70.6 ± 12.9	92	1.5 ± 12.2	91	4.9 ± 12.4[a]	87	6.9 ± 14.3[a]	88	7.8 ± 13.4[a]	83
Non-responder	65.6 ± 17.2	37	2.0 ± 10.8	37	0.5 ± 14.2	31	2.6 ± 14.7	26	1.9 ± 14.5	23
FACT-F subscale, 13 items, range 0–52										
Responder	30.4 ± 10.1	114	2.5 ± 8.3*	112	3.8 ± 10.5[a]	108	5.3 ± 10.5[a]	110	6.3 ± 10.5[a]	102
Non-responder	24.8 ± 11.2	46	1.3 ± 9.5	45	0.2 ± 11.4	40	0.5 ± 14.3	35	1.7 ± 15.0	31
FACT-An subscale, seven items, range 0–28										
Responder	17.8 ± 4.4	114	1.0 ± 3.2	112	1.3 ± 4.3	108	2.1 ± 3.9[a]	110	2.2 ± 4.0[a]	102
Non-responder	16.0 ± 4.7	46	0.7 ± 3.5	45	1.2 ± 4.2	40	0.4 ± 5.4	35	1.3 ± 5.2	31

a $p < 0.05$.

Note

Analysis of the relationship between the final Hb level in week 16 and change in the total FACT-An score from baseline in the epoetin beta group was undertaken by regression analysis. A statistically significant correlation was found on the basis of a log-linear relationship regression ($r = 0.3167$; $p = 0.001$), but the variability between participants was considerable and a uniform target Hb value associated with an optimal quality of life could not be identified.

AEs			
Participants reporting at least one AE, *n* (%)	122 (72)	132 (76)	
Hypertension (%)	9	5	
Local transient reaction after injection (%)	1	0	
Serious AE, *n* (%)	57 (33)	55 (32)	
Deaths, *n* (%)	28 (16)	22 (13)	
Death from pulmonary embolism, *n*	1	0	
Stable disease or partial remission (%)	68	68	Reported in Österborg and colleagues[79]
Remission, *n* (%)	9 (5)	5 (3)	
Progressive disease, *n* (%)	31 (18)	40 (23)	
Iron			
Note No antibodies to erythropoietin were detected in any patient. The proportion of patients who Id a transferrin saturation of < 25% during the study period was 66% in the epoetin beta group and 63% in the placebo group. The average exposure to intravenous iron supplementation was slightly higher in epoetin beta patients (235 mg elemental iron) than in placebo patients (195 mg elemental iron). The number of patients in each treatment group receiving orally administered iron supplementation was similar (35% and 33% for epoetin beta- and placebo-treated patients respectively).			

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes
6. Were the outcome assessors blind to treatment allocation?	Yes
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially (variability can be calculated from data provided in the paper
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes, until the end of treatment only

Other	
Generalisability	Reasonably sized, broad sample
Author conclusions	This randomised, placebo-controlled study has demonstrated that epoetin beta treatment is effective in relieving anaemia and improving quality of life in severely anaemic, transfusion-dependent patients with advanced-phase NHL, CLL and MM. Overall, the improvement in quality of life was particularly apparent in participants with Hb increases of ≥ 2 g/dl. This suggests that the minimum increase in Hb may be a more important determinant of improved quality of life than a uniform and close to normal target Hb level Österborg 2005: Treatment with epoetin beta was found to have 'no significant effect on the risk of progressive disease or long term survival in patients with lymphoproliferative malignancies. . . . a limitation of these data is that the 16-week treatment period was relatively short compared with the median survival time of patients' (p. 208)
Reviewer comments	

CLL, chronic lymphocytic leukemia; IQR, interquartile range; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; NR, not reported.

EndNote ref. ID: 1119

Malignancy type: solid tumours and hematological cancer

Treatment: epoetin alfa

Study design		Participants
Author, year	Ray-Coquard 2009[75]	$n = 218$
Objective	This randomised Phase III study aimed to identify the effects of epoetin alfa in patients at high risk for anaemia requiring RBCT: patients receiving chemotherapy with a Hb level < 12 g/dl, performance status[a] > 1 and/or lymphocytes ≤ 700/µl (score of ≥ 4 according to the ELYPSE risk model[b])	Inclusion criteria: Histologically documented solid tumours or hematological cancer necessitating chemotherapy; age ≥ 18 years; Hb < 12 g/dl (on day 1 of chemotherapy) and lymphocytes ≤ 700/µl or performance status > 1; negative human immunodeficiency virus test in patients with non–Hodgkin's lymphoma; chemotherapy not requiring haematopoietic stem cell support, chemotherapy planned for at least 3 months and inclusion during first or second course of chemotherapy (regardless of line of treatment) Exclusion criteria: Systematic administration of epoetin during chemotherapy; uncontrolled hypertension (i.e. diastolic blood pressure > 95 mmHg); patient refusal; anaemia in cancer patients not receiving chemotherapy; history of nervous or psychiatric disorder that would preclude informed consent or compliance; anaemia resulting from factors other than cancer or its treatment; untreated folate or vitamin B_{12} deficiency; pregnancy; history of thrombovascular events in the preceding 6 months; current dose-intensification chemotherapy for bone marrow or stem cell transplant in the preceding 8 weeks
No. of centres	Nine sites; September 2000–January 2005	
Other references/aliases	Ray-Coquard 1999[201] (not eligible for inclusion in the review – reports more detail about the development of the ELYPSE model)	
Geographical setting	France	
Duration of treatment	12 weeks	
Length of follow-up (if different)	Median follow-up 12 months (95% CI 12 to 12.4 months)	
Country of corresponding author	France	
Language of publication	English	
Sources of funding	Ministry of Health; Ligue Contre le Cancer (Ain, Rhône and Savoie)	
Randomisation and allocation	Randomisation was centralised and stratified according to the participating centres and the number of prognostic factors for severe anaemia, with two vs. three of the following criteria: Hb level at day 0 < 12 g/dl, lymphocytes ≤ 700/µl and performance status > 1	

a Not clear what performance status score used; assumed ECOG score as ECOG score reported in results section.
b ELYPSE model: score of ≥ 4: scoring based on Hb < 12 g/dl (score of 3) and lymphocyte count ≤ 700/µl or performance status > 1 (score of 1 each).

Treatment arms		
Arm drug name(s)	Epoetin alfa	No treatment
n	110	108
Dose and frequency (once daily, twice daily, etc.)	150 UI/kg three times a week	
Dose adjustment (yes/no)	Decreased to 75% if Hb increase > 2 g/dl. If after 4 weeks Hb level was < 10.5 g/dl with < 1 g/dl decrease and reticulocyte count was < 40,000 cells/µl, dose increased to 60,000 UI weekly. If Hb increased to > 12 g/dl, dose interrupted until Hb is 12 g/dl	
Route of administration	Subcutaneous	NA
Duration of epoetin treatment	12 weeks	
Adjuvant anaemia treatment	Oral iron supplementation was administered to support erythropoiesis in patients with iron deficiency as no information on the improved efficacy of intravenous iron treatment was available at the initiation of the trial	Oral iron supplementation was administered to support erythropoiesis in patients with iron deficiency as no information on the improved efficacy of intravenous iron treatment was available at the initiation of the trial
Transfusion trigger	Incidence of severe anaemia	Incidence of severe anaemia

Note
Severe anaemia = grade III anaemia (Hb < 8 g/dl) or grade II anaemia (Hb < 10 g/dl and ≥ 8 g/dl) in patients with grade III symptomatic cardiopathy, tachycardia (> 100 beats/minute), symptomatic angina with electric signs (modification of ST segment), grade III dyspnoea, symptomatic pneumopathy (*Pa*O2 50–64, diffusion of carboxy oxygen 54–40%, volume capacity 54–40%) and grade III asthenia.

Outcomes	
Primary outcome	
Other outcomes	RBCT[c] (rate of transfusion, number of transfusions); survival (OS, time to disease progression); HRQoL (EORTC QLQ-C30); AEs

Prognostic factors for no RBCT: the final model showed that no previous history of RBCT (OR 0.36, 95% CI 0.135 to 0.978) and Hb level > 10 g/dl at baseline (OR 0.27, 95% CI 0.09 to 0.84) were independent risk factors for no RBCT.

Analysis	
Statistical technique used	OS was the time interval from randomisation to date of death or last follow-up. Kaplan–Meier survival estimates and differences were assessed by the log-rank test. Safety variables were analysed using the safety population (all randomly assigned patients with at least one safety assessment). Quality-of-life scores were compared between the two arms for each chemotherapy cycle and variations from baseline were calculated for each patient and compared between arms after stratification into three levels on the assumption that a 10-point disparity represented a clinically pertinent differential
ITT analysis?	Yes
Does statistical technique adjust for confounding?	NA
Power calculation (a priori sample calculation)?	Yes, to detect a 15% difference in RBCTs with a power of 80% and a one-sided significance level of 5%
Attrition rate (loss to follow-up)?	NR; numbers of patients and reasons for treatment discontinuation reported (but not by study arm)
Was attrition rate adequately dealt with?	NR
No. (%) followed up from each condition?	NR

Baseline characteristics					
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/myelodysplastic syndrome/mixed)		Solid tumours and hematological cancer			
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Unspecified chemotherapy			
Adjuvant anaemia treatment	Iron	Yes; oral supplementation in patients with iron deficiency			
	G-CSF	Yes; could be used in primary or secondary prophylaxis			
	Transfusion trigger	Incidence of severe anaemia			
	Hb inclusion criterion level	< 12 g/dl			
		Arm 1 = epoetin alfa (*n* = 110)	**Arm 2 = control (*n* = 108)**	**Notes**	***p*-value**
Sex, *n* (%)					
Male		52 (47.3)	41 (38)		
Female		58 (52.7)	67 (62)		
Age (years), mean (SD)		62.7 (11.6)	61.7 (11.6)		
ECOG score					
0–1		8 (7.3)	8 (7.4)		
2		87 (79.1)	8 (76.9)		
3–4		15 (13.6)	17 (15.7)		
Hb baseline (g/dl), mean (SD)		10 (1.2)	10 (1.2)		
Haematocrit (%), mean (SD)		30.3 (3.4)	30.4 (3.8)		
Ferritin (µg/dl), mean (SD)		585 (697)	701 (1005)		
Stage, *n* (%)					
Local		16 (14.5)	12 (11.1)		
Metastatic		92 (83.6)	94 (87.0)		
NA		2 (1.8)	2 (1.9)		
Two strata (prognostic factor), *n* (%)		84 (76.4)	79 (73.1)		
Three strata (prognostic factor), *n* (%)		26 (23.6)	29 (26.9)		
Health state utility scale (EORTC QLQ-C30) score					0.048
Were intervention and control groups comparable?		No *p*-values reported apart from HRQoL data; authors stated that 'Patient distribution was well balanced between the two groups of treatments' (p. 1107)			

Results				
HRQoL:[a,b] health state utility scale (EORTC QLQ-C30)				
Baseline				$p = 0.048$
Follow-up				
Survival				
OS[c,d]				
Median survival (months) (95% CI)	7.6 (5.3 to 10.4)	6 (5.0 to 8.0)		$p = 0.148$
Median PFS (months) (95% CI)	5 (4.3 to 6.6)	4.4 (3.8 to 5.2)		$p = 0.17$
Transfusions[c]				
Participants, *n* (%)	39 (36.1)	61 (58)	Relative risk 0.62 (95% CI 0.46 to 0.84)	$p = 0.001$
Safety data				
At least one AE, *n* (%)	59 (53.6)	50 (46.7)		$p = 0.31$
At least one serious AE, *n* (%)	54 (49.1)	49 (45.4)		$p = 0.58$
Fatal AE, *n* (%)	20 (18.2)	20 (18.5)		$p = 0.95$
Deaths	The majority (73%) of patients had died at the time of the final analysis			
Cause of death = thrombovascular events (%)	1.3	0.6		
Cause of death = disease progression (%)	27	22		
Thrombovascular events (%)	4.5	3.7		
Hematological toxic effects (%)	18.2	13		
Serious AEs were considered related to the study drug (%)	4.6	2.9		$p = 0.72$
Incidence of serious AEs, including deaths (%)	50	46.7		$p = 0.63$

a Only 54% of the questionnaires (118) were available for quality of life evaluation, 57% in arm 1 ($n = 63$) and 51% in arm 2 ($n = 55$).
b No statistically detectable differences were noted during the study period, whatever the date of evaluation (at 1, 2, 3 or 4 months or at the end of the study; all $p > 0.2$). Global scores remained stable or slightly increased in both arms during the entire study.
c 213 patients were assessable for primary criteria (rate of RBCTs) and toxicity; five patients (2.3%) were enrolled but did not receive chemotherapy (four died before the beginning of treatment).
d Lymphocytes were found to be correlated with OS, with a median OS of 4.2 months (95% CI 3.0 to 5.5 months) for patients with ≤ 700/µl lymphocytes and 8.3 months (95% CI 6.6 to 10.4) otherwise. Also, patients with two prognostic factors had a significantly better OS than patients with three prognostic factors (median 8.3 vs. 3.6 months; $p < 0.0001$; HR 2.36, 95% CI 1.7 to 3.3). However, Hb level < 10 g/dl vs. ≥ 10 g/dl was not correlated.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear; method was centralised but not reported
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	Unclear
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear; no *p*-values reported but the authors report that patient distribution was well balanced between the two treatment groups (p. 1107). However, significant differences in favour of the epoetin alfa arm were noted for quality-of-life scores at inclusion and so the groups were unbalanced in this respect
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No (open label)
6. Were the outcome assessors blind to treatment allocation?	No (open label)
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Yes
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes, apart from HRQoL (54% and 57% participants analysed in epoetin alfa and control groups respectively)
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	NR; see Analysis section

Other	
Generalisability	A very specific population group
Author conclusions	Patients at high risk for RBCT according to Hb < 12 g/dl and lymphocytes ≤ 700/μl and/or performance status > 1 could be given prophylactic epoetin alfa, with a significantly reduced requirement for RBCT and no significant impact on side effects, PFS or OS
Reviewer comments	Not a very well-reported trial, e.g. data in results and methods section only partially reported

ECOG, Eastern Cooperative Oncology Group; NR, not reported.

EndNote ref. ID: 2695	Malignancy type MM
	Treatment: second induction chemotherapy, rHuEPO – assume epoetin alfa

Study design		Participants
Author, year	Silvestris 1995[72]	$n = 54$
Objective	Not stated – paper reports the results of a long-term trial using rHuEPO in MM patients undergoing second-induction chemotherapy	Inclusion criteria: MM stages I–IIIA, resistant to conventional melphalan-prednisone; chronic anaemia (Hb level ≤ 8.0 g/dl) with or without transfusional supplementation; commencement of second induction chemotherapy; preserved kidney function; Karnofsky performance status < 50 Exclusion criteria: NR
No. of centres	NR	
Other references/aliases	None	
Geographical setting	NR	
Duration of treatment	NR – according to graph 24 weeks	
Length of follow-up (if different)	NR	
Country of corresponding author	Italy	
Language of publication	English	
Sources of funding	This work was supported in part by the Finalised Project 'Clinical Application of Oncology Research' of the Italian National Research Council. No further details provided	
Randomisation and allocation	Randomisation was carried out directly by the biostatistical department of the pharmaceutical company providing the recombinant hormone (Cilag AG, Schaffhausen, Switzerland)	

Treatment arms		
Arm drug name(s)	rHuEPO	Control (assumed as this arm is not mentioned)
n	30	24
Dose and frequency (once daily, twice daily, etc.)	150 IU/kg, three times a week, started within the first month of the conventional cytotoxic protocol	
Dose adjustment (yes/no)	Dose increased to 300 IU/kg by the sixth week of treatment	
Route of administration	Subcutaneous	
Duration of epoetin treatment		
Adjuvant anaemia treatment	Regular iron supplementation was provided throughout the study	
Transfusion trigger	Hb 9.5 g/dl	

Outcomes[a]	
Primary outcome	
Other outcomes	Haematological response (an increase of ≥ 2 g/dl above the original Hb level or no further RBC supplementation in transfusion-dependent participants was taken as response to treatment)

a No outcomes clearly identified in methods.

Note

Weekly controls included a thorough physical examination (including monthly assessment of performance status), a complete blood count, Hb and haematocrit levels, iron, transferrin and ferritin concentrations, electrolytes and kidney function tests.

Analysis	
Statistical technique used	As the majority of laboratory parameter studies are not normally distributed, ANOVA was performed by evaluating the median of each parameter and its range between minimum and maximum. The Wilcoxin test was adopted as a non-parametric method to compare different groups
ITT analysis?	NR
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	Four participants withdrawn although the results table suggests five
Was attrition rate adequately dealt with?	Yes
No. (%) followed up from each condition?	NR

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/myelodysplastic syndrome/mixed)		MM
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Second induction chemotherapy
Adjuvant anaemia treatment	Iron	Regular iron was provided
	G-CSF	NR
	Transfusion trigger	NR
	Hb inclusion criterion level	≤ 8.0 g/dl

	Arm 1 = rHuEPO (*n* = 30)	Arm 2 = control (*n* = 24)	Notes	*p*-value
Sex, *n*				
Male	NR	NR		
Female	NR	NR		
Age (years), median (range)	NR	NR		
Neutrophil count, (cell/μL), median	NR	NR		
Patients transfused, *n* (%)	NR	NR		
No. of RBC units transfused per patient over 3 months prior to study start, mean (range)	NR	NR		
Mean haematocrit, *n* (%)	NR	NR		
Endogenous erythropoietin level (mU/ml), mean (median) [range]	NR	NR		

Baseline characteristics		
Type of solid tumour, *n* (%)		
Haematological	NR	NR
Breast	NR	NR
Gynaecological	NR	NR
Gastrointestinal	NR	NR
Lung (SCLC and NSCLC)	NR	NR
Prostate	NR	NR
Head and neck	NR	NR
Other	NR	NR
Unknown primary	NR	NR

Distribution of patients enrolled into the trial

	Arm 1 = rHuEPO (*n* = 30) (*n* = 27 evaluable)				Arm 2 = control (*n* = 24) (*n* = 22 evaluable)	
Chemotherapy groups	NTD, *n*	Responders[a]/ evaluable patients	TD, *n*	Responders[a]/ evaluable patients	NTD, *n*	TD, *n*
VMCP	11	9/10	9	5/8	12[b]	5[c]
VMCP + α-IFN	5	5/5	–	–	3	–
VED	1		3	2/3	1	2
CTX	–		1	–/1	–	1

CTX, high dose cyclophosphamide; IFN, interferon; NTD, non-transfusion dependant; TD, transfusion dependant; VED, vincristine + epirubicin + dexamethasone; VMCP, vincristine + melphalan + cyclophosphamide + prednisone.
a Response defined as ≥ 2 g/dl increase in Hb concentration.
b Eleven patients were evaluable at the end of the study.
c Four patients were evaluable at the end of the study.

Were intervention and control groups comparable?	No baseline characteristics reported. However, the authors do report the distribution of participants by their chemotherapy protocols, transfusion dependency and response to the recombinant erythropoietin treatment

Results

	Arm 1 = rHuEPO ($n = 30$) ($n = 27$ evaluable)	Arm 2 = control ($n = 24$) ($n = 22$ evaluable)	Notes	p-value
Hb response (≥ 2g/dl), n (%)	21 (77.7) after a median period of 8 weeks			

Median Hb (g%) (approximate interpretation from graphs by PenTAG)

	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
NTD – VMCP + EPO ($n = 9$)	7.6	8.2	9.5	10.5	10.4	10.4	10.2
NTD – VCMP – EPO ($n = 11$)	7.8	7.6	7.5	7.6	7.6	7.6	7.6
TD – VMCP + EPO ($n = 5$)	7.4	9.0	9.5	9.4	9.4	9.2	9.4
TD – VCMP – EPO ($n = 4$)	7.8	8.4	8.1	8.6	9.0	8.9	9.0

EPO, epoetin; NTD, non-transfusion dependant; TD, transfusion dependant; VMCP, vincristine + melphalan + cyclophosphamide + prednisone.

HRQoL	NR	NR		
Adverse effects[a]				

Note

In non-transfusion-dependent patients, rHuEPO promoted a significant ($p < 0.05$) and stable increase in Hb levels by the 12th week compared with initial values.

a Mild hypertension was recorded in four cases. The first of four withdrawals suffered a cerebral vascular stroke during the fifth week. One participant was lost to follow-up at the seventh week and the remaining two participants were excluded at the third and 11th week because of severe pneumonia and multiple bone fractures respectively. No evident Hb increase was observed in the three epoetin dropout patients during their inclusion in the trial.

Quality appraisal

1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	NR
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Unclear
6. Were the outcome assessors blind to treatment allocation?	Unclear
7. Were the point estimates and measure of variability presented for the primary outcome measure?	No
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	No, ≥ 10% of dropouts in the epoetin group
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes

Other	
Generalisability	Unable to assess
Author conclusions	Our data suggest that α-interferon plus rHuEPO treatment in MM patients is effective in restoring normal B-cell function. These results may reflect in vivo the modulation of normal human B-cells and lymphoblasts by rHuEPO observed in vitro
Reviewer comments	Small sample size, no baseline characteristics, poorly reported outcomes

ANOVA, analysis of variance; MM, multiple myeloma; NR, not reported; NSCLC, non-small-cell lung cancers; SCLC, small-cell lung cancer.

EndNote ref. ID: 341

Malignancy type: cervical cancer

Treatment: epoetin beta

Study design		Participants
Author, year	Strauss 2008[76]	$n = 74$
Objective	To investigate whether in patients with cervical cancer the effectiveness and outcome of radiotherapy plus cisplatin could be positively influenced by treatment with epoetin beta. The design of the second stage was to be adapted or rejected depending on the outcome of the first stage of the trial. The primary objective of the first stage was to investigate whether there was a correlation between anaemia correction with epoetin beta and treatment failure in women with cervical cancer receiving radiochemotherapy. After the first stage had been analysed the study protocol outlined a continuation of the study in which a further 450 patients were to be enrolled to investigate the potential impact of anaemia correction with epoetin on survival	Inclusion criteria: Age ≥ 18 years; histologically confirmed diagnosis of cervical cancer; FIGO (International Federation of Gynecology and Obstetrics) stage IIB–IVA (except chorion carcinoma and neuroendocrine small cell carcinoma); Hb levels between 9 and 13 g/dl at screening; WHO performance status of 0–2; life expectancy of at least 3 months; adequate bone marrow function (platelets > 100 × 10^9/l and leucocytes > 3.0 × 10^9/l); adequate liver function (transaminases and/or alkaline phosphatises no greater than 2.5 × upper normal limit; bilirubin no greater than 1.5 × normal limit); adequate renal function (calculated creatinine clearance > 60 ml/minute); no previous systemic antineoplastic therapy or radiotherapy for cervical cancer except previous single brachytherapy fraction of the protocol-prescribed radiotherapy course as clinically indicated Exclusion criteria: Patients with distant metastasis (M1 disease); positive para-aortic lymph nodes; chronic heart failure [New York Heart Association (NYHA ≥ 2]; uncontrolled arterial hypertension (systolic blood pressure ≥ 170 mmHg, diastolic blood pressure ≥ 100 mmHg); known history of deep-vein thrombosis; thrombocytosis; known haemoglobinopathies; vitamin B_{12} and/or folic acid deficiencies; haemolytic anaemia; bleeding requiring transfusion within 3 months before planned start of treatment; acute infection; transferrin saturation < 20%; known presence of other neoplasias within the last five years; pregnancy or lactation; exposure to epoetins within 3 months; contraindications against cisplatin therapy
No. of centres	20	
Other references/aliases	Full paper	
Geographical setting	Europe, Turkey and Thailand	
Duration of treatment	Unclear – participants scheduled to receive radiotherapy over 6 weeks (to a maximum of 50 days) plus concomitant cisplatin	
Length of follow-up (if different)	447–513 days (unclear if this starts after the end of the treatment period)	
Country of corresponding author	Germany	
Language of publication	English	
Sources of funding	F. Hoffman-La Roche	
Randomisation and allocation	Open-label, randomised, two-arm, parallel-group, two-stage adaptive study. Patients were centrally randomised to the epoetin arm or the control arm. No details given on randomisation procedure	

Treatment arms[a]		
Arm drug name(s)	Epoetin beta	Control (standard care)
n	34	40
Dose and frequency (once daily, twice daily, etc.)	450 IU/kg in three divided doses	
Dose adjustment (yes/no)	Yes. If insufficient Hb response (increase in Hb of < 0.5 g/dl after 4 weeks of treatment or requirement for RBCT in the fourth week of treatment) the dose could be doubled to 900 IU/kg. If Hb > 15 g/dl epoetin was stopped and resumed at 50% of the previous dose until Hb ≤ 14 g/dl. If Hb increased by > 2 g/dl in 4 weeks dose reductions of 50% were applied	
Route of administration	Subcutaneous	
Duration of epoetin treatment	Median duration of epoetin beta treatment was 63 days (range 3–98 days)	
Adjuvant anaemia treatment	If transferrin saturation was < 20%, intravenous iron supplementation with a dose of 100 mg of Fe^{3+} was recommended. If contraindicated or not available, daily oral iron supplementation at a dose of 200–300 mg of Fe^{3+} could be used. Iron was received by 27 participants (79%) in the epoetin group. Of these, 15 received iron intravenously and 12 orally. In the control group, iron was received by 22 participants (55%), with 12 receiving iron intravenously and 10 orally	
Transfusion trigger	At physicians' discretion if Hb level < 8.5 g/dl and to be avoided in participants with a Hb level > 8.5 g/dl	

a 2-week pretreatment period to ensure that anaemic patients had an acceptable Hb level at the start of the study.

Outcomes	
Primary outcome	Treatment failures in correlation with Hb change from baseline to study end (defined as participants with no complete response or relapsing within 6 months after initiation of radiochemotherapy)
Other outcomes	Tumour response; progression-/relapse-free survival; OS; overall response rate; AEs

Analysis	
Statistical technique used	The effect of Hb change from baseline on treatment failure (defined as no complete response or relapse within 6 months after initiation of radiochemotherapy) was analysed using a logistical regression analysis (two-sided test at $\alpha = 5\%$ with change in Hb from baseline as main factor in the model). A proof of concept for the first stage of the study was to be accepted if a positive correlation between change in Hb level from baseline to the end of the treatment period and treatment failure could be established and no important safety concerns were raised in an initial group of approximately 80 participants. Progression-free and OS were analysed by log-rank testing and Cox regression analysis. Multivariate analysis was performed using a stepwise Cox regression procedure. The overall response was analysed using the Chi–squared test with Schouten correction and 95% Clopper–Pearson CIs. Change in Hb from baseline at the end of the treatment period was tested in an ANCOVA model, with Hb at baseline as a covariate. Hb change from baseline was assessed at week 4 and at the end of the treatment period
ITT analysis?	Yes; all randomised participants were included in the ITT population and all efficacy results are provided for this population. The safety population consisted of all patients who received at least one dose of the trial medication (radiochemotherapy and/or epoetin in the epoetin beta group and at least one dose of radiochemotherapy in the control group

Analysis	
Does statistical technique adjust for confounding?	NR (only baseline Hb values mentioned as a covariate in ANCOVA)
Power calculation (a priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	See below
Was attrition rate adequately dealt with?	Three participants were excluded from the safety analysis (one from the treatment arm and two from the control arm) as they did not receive the study treatment. A total of 12 participants (16%) were withdrawn prematurely from the study, eight in the epoetin arm and four in the control arm. There were no withdrawals because of AEs in either group. Reasons for withdrawal were death (not related to study medication), refusal of further treatment, failure to return for treatment, inclusion criteria not being met or exclusion criteria being fulfilled
No. (%) followed up from each condition?	Median follow-up for survival was 482 (IQR 447–617) days in the epoetin beta group and 466 (IQR 446–513) days in the control group

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/myelodysplastic syndrome/mixed)		Cervical
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Chemotherapy + radiotherapy
Adjuvant anaemia treatment	Iron	Enrolled participants with a transferrin saturation of < 20% were recommended to receive intravenous iron supplementation with a dose of 100 mg Fe^{3+}. If contraindicated or not available, daily oral iron supplementation at a dose of 200–300 mg Fe^{3+} could be used
	G-CSF	No
	Transfusion trigger	Blood transfusions were given according to decision of physician if Hb level was < 8.5 g/dl and were to be avoided in participants with a Hb level > 8.5 g/dl
	Hb inclusion criterion level	Between 9 and 13 g/dl at screening

	Arm 1 = epoetin beta (n = 34)	Arm 2 = control (n = 40)	Notes	p-value
Sex, *n* (%)				
Male	–	–		
Female (%)	34 (100)	40 (100)		0.957
Age (years), mean (SD)	48.8 (10.2)	49.2 (12.8)		
WHO performance status, *n* (%)				
0	21 (61.8)	27 (67.5)		0.689
1	13 (38.2)	12 (30.0)		0.529
2	0	1 (2.5)		–
3				
4				

Baseline characteristics			
Hb baseline (g/dl), median (IQR)	11.4 (10.8–12.0)	11.6 (10.9–12.4)	0.371
Hb before radiochemotherapy (g/dl), median (IQR)	11.8 (10.6–13.1)	11.7 (10.9–12.4)	0.633
Epoetin baseline (mU/ml)			
Were intervention and control groups comparable?	Yes		

Results			
Haematological outcomes and transfusions			
Median change in Hb (g/dl) (baseline to last value)[a]	1.3	–0.7	
Transfusion-free participants	25 (73.5)	28 (70)	
RBC units received, median (range)	3.3 (0.9–6.4)	12 (0.9–6.0)	Not significant
Survival, *n* (%)			
OS, deaths[b]	8 (23.5)	5(12.5)	0.22
Treatment failures	11 (32.4)	12 (30.0)	0.32
Complete response	18 (52.9)	23 (57.5)	0.86
Partial response	4 (11.8)	6 (15.0)	0.83
Stable disease	0	3 (7.5)	
Progressive disease	7 (20.6)	3 (7.5)	0.12
PFS (%)	10 (29.4)	13 (32.5)	0.96
Tumour response	(*n* = 29)	(*n* = 35)	
Complete response, *n*	18	23	
HRQoL: health state utility scale	Not collected		
Adverse effects, *n* (%)[c]			
Total	19 (58)	26 (68)	0.409
Deaths	8 (23.5)	5 (12.5)	0.22
Thromboembolic events			
Hypertension			
Haemorrhage/thrombocytopenia	1 (3)	4 (11)	0.313
Rash/irritation/pruritus	1 (3)	0 (0)	
Seizures			

a By week 4 after initiation of radiochemotherapy, the median Hb level increased by 1.1 g/dl from baseline in the epoetin group but decreased by 0.6 g/dl in the control group. An ANCOVA showing a difference in least-square means (adjusting for baseline Hb) indicated that the change in Hb from baseline was highly significant between groups ($p < 0.0001$). More participants in the treatment group achieved a target Hb level of 13 g/dl than those in the control group (71% vs. 25%).
b OS: RR 2.0, 95% CI 0.65 to 6.15; $p = 0.22$.
c Seven participants reported a serious AE [epoetin arm: $n = 5$ (15%); control arm: $n = 2$ (5%)]. Only one serious AE was considered by the investigator to be related to study treatment, a deep-vein thrombosis in a participant receiving epoetin beta. This participant had several other risk factors including hypertension, diabetes mellitus and obesity.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	Unclear; although described as 'centrally randomised', further details were not provided
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Yes
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No
6. Were the outcome assessors blind to treatment allocation?	No
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially (variability can be calculated from data presented in the paper)
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes
Other	
Generalisability	
Author conclusions	This study shows that epoetin beta rapidly, effectively and safely increases Hb levels in patients with cervical cancer receiving radiochemotherapy. Because no positive correlation between Hb increase and improvement in clinical outcomes, such as a reduction in treatment failure, could be demonstrated in stage 1 of this study, this study was not expanded to its second stage, which was designed to investigate the potential benefits of anaemia correction on survival. Therefore, this study does not allow any definite conclusions to be drawn with respect to the positive or negative effects of epoetin therapy on survival or disease progression in patients with cervical cancer receiving radiochemotherapy
Reviewer comments	

ANCOVA, analysis of covariance; IQR, interquartile range; NR, not reported.

EndNote ref ID: 2696	Malignancy type: Ovarian carcinoma Treatment: epoetin beta (assumed)	
Study design		**Participants**
Author, year	ten Bokkel Huinink 1998[51]	$n = 122$
Objective	To investigate the influence of rHuEPO on anaemia and transfusion requirement in patients with ovarian carcinoma treated with platinum-based therapy	Inclusion criteria: Age ≥ 18 years; ovarian cancer stage IIb–IV [according to the International Federation of Gynecology and Obstetrics (FIGO) classification]; WHO performance status 0–2; Hb < 13 g/dl prior to treatment; overall life expectancy > 2 months; previously treated patients who had achieved a complete remission (CR) and who had not received treatment for at least 1 year could be enrolled into the study; receiving cisplatin ≥ 75 mg/m^2 or carboplatin ≥ 350 mg/m^2 because lower doses induce anaemia in only a small proportion of patients Exclusion criteria: Previous chemotherapy or radiotherapy for ovarian cancer if requirements for previously treated patients as detailed in the inclusion criteria not met; white blood cell count ≤ 3.5 × 10^9/l; platelet count ≤ 100 × 10^9/l; hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg); impaired liver function (bilirubin > 25 mmol/l); impaired renal function (creatinine > 120 µmol/l); thrombocytosis (≥ 500 × 10^9/l); other reasons for anaemia; severely impaired coagulation; iron deficiency; epilepsy; blood transfusion < 1 week prior to protocol treatment; haemoglobinopathies; acute infections; second primary tumours; administration of an investigational drug within 30 days preceding the first dose of the study drug
No. of centres	NR	
Other references/aliases	None	
Geographical setting	NR	
Duration of treatment	Treatment with epoetin and chemotherapy began 2 days after randomisation in most patients. Epoetin was continued throughout the course of chemotherapy and for a further 3–24 weeks after the last cycle of treatment, depending on the duration of chemotherapy. Median duration of observation (between randomisation and last examination) was 170 days in the control group and 167 days in group 1	
Length of follow-up (if different)		
Country of corresponding author	The Netherlands	
Language of publication	English	
Sources of funding	NR	
Randomisation and allocation	Participants were randomly allocated to three study groups. Randomisation was performed centrally using permuted blocks stratified by institute and previous treatment (previously untreated, first line or recurrent disease)	

Treatment arms	
Arm drug name(s)	Not given – assume epoetin alfa
n	46
Dose and frequency (once daily, twice daily, etc.)	150 µg/kg three times a week
Dose adjustment (yes/no)	The dose of epoetin was reduced by 50% if Hb increased by > 2 g/dl during chemotherapy. If Hb exceeded 15 g/dl at any time, epoetin administration was stopped until Hb returned to < 14 g/dl and was then resumed at half the previous dose. Epoetin was withheld while platelet count was $< 20 \times 10^9$ g/l. If chemotherapy was delayed because of thrombocytopenia but platelet count was $> 20 \times 10^9$ g/l, epoetin was continued
Route of administration	Subcutaneous
Duration of epoetin treatment	Treatment with epoetin and chemotherapy began 2 days after randomisation in most patients. Epoetin continued throughout the course of chemotherapy and for a further 3–24 weeks after the last cycle of treatment, depending on the duration of chemotherapy
Adjuvant anaemia treatment	NR
Transfusion trigger	Hb < 9.7 g/dl

Outcomes	
Primary outcome	Time from randomisation to first erythrocyte transfusion; RBCT (no. of patients in study period)
Other outcomes	No. and volume of RBCTs per patient and per chemotherapy cycle; course of Hb per chemotherapy cycle; response to chemotherapy; number of deaths; AEs[a]

a Serious AE: fatal or life-threatening event; hospitalisation; patient permanently disabled; new cancer diagnosed; congenital abnormality detected. All other AEs defined as non-serious.

Analysis	
Statistical technique used	The time to first erythrocyte transfusion was analysed using failure-time methods (Kaplan–Meier estimates) using log-rank tests based on months from randomisation and number of cycles of chemotherapy. Univariate and multiple failure-time analyses (Cox proportional hazard method, maximum likelihood methods) were also performed. Laboratory parameters were analysed by means of parametric and non-parametric statistics
ITT analysis?	Described as ITT but two patients were excluded from the analysis because of insufficient data
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	Numbers unclear – author states 84 patients completed the protocol. Of 120 patients, one patient in group 1 and one in group 2 dropped out of the study before the start of treatment. Twenty-nine plus seven withdrew (because of death, non-compliance, etc.) to give 82 patients
Was attrition rate adequately dealt with?	Safety was assessed according to ITT analysis, but unclear how missing data were handled
No. (%) followed up from each condition?	NR

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/ haematological/myelodysplastic syndrome/mixed)		Ovarian cancer
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Platinum-based chemotherapy
Adjuvant anaemia treatment	Iron	NR
	G-CSF	NA
	Transfusion trigger	Hb < 9.7 g/dl
	Hb inclusion criterion level	< 13 g/dl

	Arm 2 = rHuEPO ($n = 45$)	Arm 1 = control ($n = 33$)	Notes	p-value
Sex (%)				
Male				
Female	100	100		
Age (years), mean	58.81	58.83		
WHO performance status, *n* (%)				
0	24 (53.3)	20 (60.6)		
1	19 (42.2)	13 (39.4)		
2	2 (4.4)	0		
Previous chemotherapy, *n* (%)				
Carboplatin ≤ 350 mg/m^2	17 (37)	15 (45)		
Carboplatin > 350 mg/m^2	9 (20)	8 (24)		
Cisplatin < 75 mg/m^2	0	1 (3)		
Cisplatin ≥ 75 to < 100 mg/m^2	16 (35)	7 (21)		
Cisplatin ≥ 100 mg/m^2	3 (6)	2 (6)		
Haematological parameters, median (range)				
Hb (g/dl)	12.0 (10.3–12.6)	11.8 (10.6–12.5)	There appears to be a 'typo' in Table 1 for the epoetin baseline Hb value: 12.0 (1.3–12.6) assumed to be 12.0 (10.3–12.6)	
Haematocrit (%)	37.0 (34.2–38.5)	37.0 (33.0–38.0)		
Erythrocytes (×10^9/l)	4.0 (3.7–4.3)	4.0 (3.8–4.3)		
Reticulocytes (%)	10.5 (7.6–14.0)	12.8 (15.7–16.9)		
Platelet count (×10^9/l)	383 (304–433)	395 (302–505)		
Neutrophil count (×10^9/l)	4.3 (3.3–5.7)	5.1 (3.4–6.2)		
Iron (U/l), median (range)	NR	NR		
Epoetin (mU/ml)	NR	NR		
Target Hb (g/dl)	NR	NR		
Were intervention and control groups comparable?	No p-values reported; authors stated that 'The three groups were comparable with respect to age, stage of disease, WHO performance status, primary and recurrent disease, previous chemotherapy and baseline haematological parameters' (p. 176)			

Results			
	Arm 2 = rHuEPO ($n = 44$[a])	Arm 1 = control ($n = 33$)	
Response to chemotherapy, *n*	($n = 40$)	($n = 30$)	
Progression	6	2	
Complete remission	23	19	
Deaths	1	2	
Transfusions			
Time to first transfusion (months)	Longer in epoetin group than in control group		0.0002
No. (%) of patients receiving at least one transfusion	2 (4.4)	(39.4)	
No. of units	15 units in six transfusion events	41 units in 19 transfusion events	
Haematological outcomes			
Patients with Hb < 10 g/dl, *n* (%)			
Cycle 1	2 (4.5)	8 (24.2)	
Cycle 2	1 (2.4)	10 (32.3)	
Cycle 3	1 (2.5)	15 (50)	
Cycle 4	3 (8.1)	15 (53.7)	
Cycle 5	6 (16.7)	13 (50)	
Cycle 6	6 (17.6)	12 (50)	
Serum EPO (mU/ml)			
No. of patients evaluable	31	19	
Median (range)	9 (9–584)	8 (2–29)	
O/P ratio			
No. of patients evaluable	28	18	
O/P ratio[b] ≥ 0.8	16	7	
O/P ratio[b] < 0.8	12	11	
HRQoL	NR	NR	
AEs[c]			
Thromboembolic events, *n*	1		
Hypertension, *n/N* (%)	1/43 (2.3)	1/28 (3.6)	
Participants suffering at least one AE, *n/N* (%)	39/45 (86.7)	28/33 (84.8)	
Participants suffering more than one AE, *n/N* (%)	(20.0)	(15.2)	
Superficial thrombophlebitis, *n*	1		

O/P, observed/predictive ratio.

a One participant withdrew before the start of treatment with epoetin.

b The ratio between the observed serum erythropoietin level and the level predicted from the degree of anaemia (O/P) was selected as a possible predictor of transfusion requirement because a relative erythropoietin deficiency (O/P < 0.8) is considered to indicate an inadequate endogenous erythropoietin concentration.

c Because of AEs, 25 participants in the control group and 34 participants in group 1 completed the planned protocol. Seven participants (15.6%) in group 1 and four (12.1%) in the control group were withdrawn because of AEs.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/ pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Yes
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No
6. Were the outcome assessors blind to treatment allocation?	No
7. Were the point estimates and measure of variability presented for the primary outcome measure?	No
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Partially; number unclear

Other	
Generalisability	Small sample size – all-female population
Author conclusions	The use of rHuEPO should be considered in patients with ovarian cancer receiving platinum-based chemotherapy, particularly if they have an endogenous erythropoietin deficiency, to delay the onset of anaemia and reduce the need for RBCT
Reviewer comments	Some of the results for the two dosing arms (one of which is not applicable to this review) have been combined and therefore not extracted

NR, not reported.

EndNote ref. ID: 2697

Malignancy type: small-cell lung cancer (SCLC)

Treatment: epoetin alfa

Study design		Participants
Author, year	Thatcher 1999[52]	$n = 130$
Objective	To determine the efficacy and safety of epoetin alfa in preventing the decline in Hb level in patients undergoing cyclic chemotherapy for SCLC and to evaluate whether a reduction in RBCT requirements could also be achieved. The impact of epoetin alfa therapy on patients' quality of life was also assessed	Inclusion criteria: Male or female aged 18–75 years; planned treatment with four to six cycles of combination chemotherapy, primarily platinum based; SCLC; required to be ambulatory and capable of self-care (WHO performance status ≤ 2); Hb ≤ 10.5 g/dl; neutrophil count > 3000/µl; platelet count > 100,000/µl; no clinically relevant abnormalities of renal or hepatic function; serum calcium < 10.6 mg/dl; stool samples negative for occult blood Exclusion criteria: Pregnant or of childbearing potential and not taking adequate contraceptive measures; any clinically significant disease; history of primary haematological disease; history of seizures or acute illness within 7 days of study entry; received androgen therapy within 2 months of study entry or received any experimental treatment, immunosuppressive drugs or other agents known to affect haematocrit within 1 month of study entry; receiving haematopoietic growth factors (including epoetin alfa); participating in another trial
No. of centres	NR	
Other references/ aliases	None	
Geographical setting	Unclear	
Duration of treatment	Maximum study duration was 26 weeks	
Length of follow-up (if different)	NR	
Country of corresponding author	UK	
Language of publication	English	
Sources of funding	NR	
Randomisation and allocation	Participants randomised to one of three groups: epoetin alfa 150 IU/kg, epoetin alfa 300 IU/kg (outside licence therefore and therefore not applicable) and control	

Treatment arms		
Arm drug name(s)	Epoetin alfa	Control (standard care)
n	42	44
Dose and frequency (once daily, twice daily, etc.)	150 IU/kg three times a week. Treatment started 1 day after administration of each cycle of chemotherapy and continued until 3 days prior to the following cycle; treatment continued for 1 month after the final cycle	
Dose adjustment (yes/no)	If Hb level exceeded 15 g/dl, epoetin alfa was discontinued until the value had fallen to < 13 g/dl, at which point treatment was reinstated at half the initial dose	
Route of administration	Subcutaneous	
Duration of epoetin treatment	Maximum study duration was 26 weeks	
Adjuvant anaemia treatment	Transfusions were allowed as necessary. No participants received iron supplementation	
Transfusion trigger	NR	

Outcomes	
Primary outcome	Haematological response (prevention of anaemia defined as maintenance of Hb level at ≥ 10 g/dl)
Other outcomes	HRQoL [participant well-being in the week prior to each cycle of chemotherapy was assessed using a quality-of-life questionnaire, in which participant responses to three levels (energy level, daily activity and overall quality of life) were scored on a 100-mm VAS, and WHO performance status score]; AEs [safety assessments included participant discontinuation information, vital signs (recorded in the treated groups only) and the incidence and severity of AEs, laboratory parameters at the start of each cycle and epoetin alfa antibody titre at study end compared with baseline]

Analysis	
Statistical technique used	Comparability of the three groups with regard to demographic and clinical characteristics at baseline was tested by means of ANOVA, Kruskal–Wallis tests or chi-squared tests, as appropriate. Differences between treatment groups for mid-cycle Hb and haematocrit through cycles 1–6 were tested using ANOVA. Within-group differences from baseline for efficacy parameters were tested using a paired Student's *t*-test. The proportion of participants transfused was compared between treatment groups using a Cochran–Mantel–Haenszel analysis. For pairwise comparisons of treatment groups, the sequentially rejective Bonferroni–Holm procedure was applied to adjust for three multiple comparisons. The time to become anaemic or require transfusion was analysed by survival analysis using Kaplan–Meier estimates and the log-rank test. All tests were conducted at the two-sided, 0.05 significance level
ITT analysis?	Yes
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	Reasons for premature study discontinuation

Parameter	Control ($n = 42$)	Epoetin alfa ($n = 44$)
AEs	2	4
Death	3	1
Intercurrent illness	1	1
Other[a]	8	10
Total	14	16

a Including personal reasons, loss to follow-up, non-responder to chemotherapy, disease progression or remission, discontinuation of chemotherapy, toxicity of chemotherapy, elevated Hb, deterioration of general condition and physician decision.

Was attrition rate adequately dealt with?	NR
No. (%) followed up from each condition?	NR

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		SCLC
Treatment (e.g. chemotherapy platinum/ non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Platinum-based chemotherapy
Adjuvant anaemia treatment	Iron	None
	G-CSF	None
	Transfusion trigger	NR
	Hb inclusion criterion level	≥ 10.5 g/dl

	Arm 2 = epoetin alfa ($n = 42$)	Arm 1 = control ($n = 44$)	Notes	*p*-value
Sex, *n*				
Male	26	27		
Female	16	17		
Age (years), median (range)	59.0 (43–72)	60 (39–74)		
Hb (g/dl), median (range)	13.7 (10.7–16.1)	13.4 (10.9–16.4)		
Haematocrit (%), median (range)	41.0 (32.6–50.3)	39.4 (32.3–46.8)		
Reticulocyte count ($\times 10^9$/l), median (range)	40.1 (1.0–76.2)	39.3 (0.1–109.1)		
Neutrophil count ($\times 10^9$/l), median (range)	6.0 (1.7–11.3)	5.9 (2.9–16.4)		
WHO performance status (0–4), median (range)	1.0 (0–3)	1.0 (0–2)		
Quality-of-life scores (0–100 mm), median (range)				
Energy level	47.0 (11–100)	51.0 (0–94)		
Daily activity	46.0 (5–100)	32.0 (0–97)		
Overall quality of life	44.0 (1–100)	49.0 (0–98)		
Chemotherapy regimen, *n*				
Carboplatin based	34	38		
Cisplatin based	2	2		
Other	6	4		
Were intervention and control groups comparable?	No *p*-values reported; authors stated that there were 'no statistically significant between-group differences' (p. 398)			

Results			
Haematological and transfusion outcomes			
Participants experiencing Hb < 10g/dl (%)	48	66	< 0.05
Participants requiring a transfusion, *n/N* (%)	19/42 (45)	26/44 (59)	< 0.05
Total no. of transfusions	41	73	
Cumulative transfusion rate for 6 cycles of chemotherapy, mean ± SD	3.84 ± 5.58	6.13 ± 7.13	< 0.01
Median time (days) to become anaemic/require first transfusion	116/98	59/48	
HRQoL			
Parameters assessed by the quality-of-life questionnaire did not show any marked changes from baseline at the end of the study in any group, with the exception of significant improvement in overall quality of life in the epoetin alfa 150 IU/kg group ($p < 0.05$). There were no significant between-group differences, which may be related to the fact that all groups had similar Hb values at study end. Evaluation of WHO performance status scores revealed similar findings, with no significant between- or within-group differences			
Change in quality-of-life parameter from baseline (0–100 mm), mean ± SD	($n = 33$)	($n = 27$)	
Energy level	–2.3 ± 31.9	1.6 ± 23.9	
Daily activity	3.0 ± 31.7	10.8 ± 35.6	
Overall quality of life	11.7 ± 30.6[a]	7.5 ± 29.1	
Adverse effects reported by ≥ 5% of participants in any treatment group,* n *(%)[b,c,d]			
Anaemia	19 (43)	14 (33)	
Thrombocytopenia	9 (20)	11 (26)	
Bacterial infection	10 (23)	8 (19)	
Nausea	6 (14)	3 (7)	
Neutropenia[c]	8 (18)	5 (12)	
Pyrexia	7 (16)	7 (17)	
Dyspnoea	1 (2)	1 (2)	
Vomiting	5 (11)	5 (12)	
Dizziness	1 (2)	3 (7)	
Cough	0	0	
Headache	1 (2)	2 (5)	
Constipation	1 (2)	2 (5)	
Malaise	0	2 (5)	
Urinary tract infection	0	0	
Alopecia	3 (7)	1 (2)	
Oedema	0	4 (10)	
Diarrhoea	2 (5)	5 (12)	
Rash	4 (9)	5 (12)	
Decreased white blood cell count	3 (7)	1 (2)	
Lethargy	3 (7)	1 (2)	

a $p < 0.05$ vs. baseline.
b There was no evidence of a sustained increase in hypertension in the epoetin alfa arm. One patient had several recordings of a diastolic blood pressure around 105 mmHg and another patient with a history of hypertension experienced an elevation in blood pressure to 180/120 mmHg after the second dose. Overall, there was a significant reduction in mean systolic blood pressure over time in the epoetin alfa treatment group.
c Low serum iron and transferrin saturation values were seen in participants in the treatment group.
d There were no statistically significant differences in neutropenia suggesting no differences in chemotherapy intensity.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Yes
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No
6. Were the outcome assessors blind to treatment allocation?	NR
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially (variability can be calculated from data presented in the paper)
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes (except for quality of life)
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes

Other	
Generalisability	Relatively small sample size
Author conclusions	This study has demonstrated that epoetin alfa is effective and well tolerated in maintaining a Hb level $\geq$ 10 g/dl and reducing transfusion requirements in patients with SCLC undergoing platinum-based cyclic combination chemotherapy
Reviewer comments	Quality of life of limited used because of unvalidated scale. WHO performance status scores were measured

ANOVA, analysis of variance; NR, not reported; SCLC, small-cell lung cancer.

EndNote ref. ID: 435	Malignancy type: solid tumours Treatment: epoetin theta and beta and placebo

Study design		Participants
Author, year	Tjulandin 2010[48]	$n = 223$
Objective	To assess the effects of epoetin theta compared with placebo for efficacy and to compare the efficacy and safety profiles of epoetin theta and epoetin beta	Inclusion criteria: Secondary anaemia (Hb ≤ 11 g/dl) related to platinum-containing chemotherapy; age ≥ 18 years; histologically or cytologically proven diagnosis of a solid tumour; at least one platinum-based chemotherapy cycle as treatment for the current malignancy during the last 4 weeks (Hb concentration of ≤ 11 g/dl after the last chemotherapy); ECOG score of ≥ 3 Exclusion criteria: Head and neck tumours; uncontrolled severe hypertension; receiving concomitant radiotherapy
No. of centres	54 sites; between October 2005 and July 2007	
Other references/aliases	Trial registration: ISRCTN09530309	
Geographical setting	International: 10 countries (Argentina, Belarus, Brazil, Bulgaria, Croatia, India, Moldova, Romania, Russia, Ukraine)	
Duration of treatment	12 weeks. The mean ± SD treatment duration was comparable in all three groups (75.0 ± 16.9 days epoetin theta vs. 71.0 ± 19.7 days epoetin beta vs. 70.5 ± 23.7 days placebo)	
Length of follow-up (if different)	NR	
Country of corresponding author	Germany	
Language of publication	English	
Sources of funding	Sponsored by BioGeneriX AG, a company of the ratiopharm Group SA	
Randomisation and allocation	Randomised using a computer-generated allocation schedule in a 1 : 1: 1 ratio stratified by country to double-blind treatment for 12 weeks with epoetin theta, epoetin beta or placebo. Randomisation list generated by the Department of Biostatistics, Merckle GmbH. Only the person administering the study medication was unblinded (because of the difference in dosing schemes). An unblinded data monitoring committee closely monitored for safety	

Treatment arms			
Arm drug name/s	Epoetin theta	Epoetin beta	Placebo
n	76	73	74
Dose and frequency (once daily, twice daily, etc.)	20,000 IU once per week[a]	450 IU/kg three times per week	Same schedule as epoetin theta for blinding purposes
Dose adjustment (yes/no)	Yes. After 4 weeks increase to 40 000 IU if Hb increase is < 1 g/dl, with a further increase to 60,000 IU if after the next 4 weeks there is still an insufficient response. Reduce by 50% if Hb increase is > 2 g/dl at 4 weeks. If Hb is > 13 g/dl, dose interruption or 50% dose reduction	Yes. After 4 weeks dose doubled if Hb increase is < 1 g/dl. Reductions the same as for epoetin theta	NA
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous
Duration of epoetin treatment	12 weeks	12 weeks	NA

Treatment arms			
Adjuvant anaemia treatment	Iron substitution was allowed during the study	Iron substitution was allowed during the study	Iron substitution was allowed during the study
Transfusion trigger	At the discretion of the investigator but should be avoided if Hb level is ≥ 8.5 g/dl	At the discretion of the investigator but should be avoided if Hb level is ≥ 8.5 g/dl	At the discretion of the investigator but should be avoided if Hb level is ≥ 8.5 g/dl

a In addition, patients randomised to epoetin theta also received the same volume of placebo twice weekly for blinding purposes.

Outcomes	
Primary outcome	Haematological response (increase in Hb of ≥ 2 g/dl from baseline without the benefit of a transfusion within the previous 4 weeks)
Other outcomes	Haematological response (partial Hb response of ≥ 1 g/dl from baseline; number of patients having a complete Hb response with the initial dose; time course of Hb, haematocrit and reticulocytes; dose of epoetin theta or epoetin beta at the time of complete/partial Hb response); RBCT (no. of patients requiring a RBCT; no. of blood units transfused); HRQoL [FACT-An (including FACT-G and FACT-F)]; AEs (safety laboratory variables, vital signs, incidence of AEs, adverse drug reactions, overall tolerability and screening for antidrug antibodies to epoetin theta and epoetin beta at the beginning and end of the study and 60 days after the end of the individual treatment period)

Analysis	
Statistical technique used	Logistic regression analysis with treatment and baseline Hb level as explanatory variables was performed to estimate the difference in the proportion of complete Hb responders for epoetin theta vs. placebo, epoetin beta vs. placebo and epoetin theta vs. epoetin beta in the confirmatory analysis of the primary end point. For other binary secondary efficacy end points the same logistic regression model as for the primary end point was used. Changes in quality of life (FACT score) from baseline to the end of the treatment period were compared pairwise among treatment groups with the Wilcoxon–Mann–Whitney test; treatment groups for other secondary end points were only compared descriptively
ITT analysis?	Yes. Full analysis set used for efficacy end points; no crossovers and end points reported for full patient numbers
Does statistical technique adjust for confounding?	NR; however, logistic regression analysis was adjusted for baseline Hb level to estimate the effects of treatment on Hb response
Power calculation (a priori sample calculation)?	Partial; sample size calculation given for the statistical superiority test comparing epoetin theta and placebo but not overall (two-sided $\alpha = 5\%$, assuming the actual Hb response rates for epoetin theta and placebo were 50% and 20%, respectively)
Attrition rate (loss to follow-up)?	Yes; placebo $n = 21$ withdrawals ($n = 4$ because of AEs, $n = 12$ patient request, $n = 2$ loss to follow-up, $n = 3$ other); epoetin beta $n = 9$ withdrawals ($n = 1$ because of AE, $n = 7$ patient request, $n = 1$ other); epoetin theta $n = 12$ withdrawals ($n = 2$ because of AEs, $n = 2$ patient request, $n = 1$ because of inclusion/exclusion criteria, $n = 3$ loss to follow-up, $n = 4$ other)
Was attrition rate adequately dealt with?	Unclear
No. (%) followed up from each condition?	NA; no follow-up reported

Baseline characteristics					
Malignancy type (e.g. solid/solid head neck, lung, ovarian, cervical/ haematological/myelodysplastic syndrome/mixed)		Solid tumours			
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Platinum-containing chemotherapy			
Adjuvant anaemia treatment	Iron	Iron substitution was allowed during the study			
	G-CSF				
	Transfusion trigger	Hb ≤ 8.5 g/dl			
	Hb inclusion criterion level	≤ 11.0 g/dl			
		Arm 1 = epoetin theta (*n* = 76)	**Arm 2 = epoetin beta (*n* = 73)**	**Arm 3 = placebo (*n* = 74)**	***p*-value**
Sex, *n* (%)					
Male		30 (39.5)	22 (30.1)	19 (25.7)	
Female		46 (60.5)	51 (69.9)	55 (74.3)	
Age (years), mean ± SD, median (range)		53.7 ± 10.3, 53.5 (19.0–76.0)	57.3 ± 10.5, 57.0 (28.0–83.0)	57.3 ± 11.5, 59.5 (26.0–76.0)	
ECOG performance status, *n* (%)					
0		6 (7.9)	9 (12.3)	5 (6.8)	
1		55 (72.4)	40 (54.8)	48 (64.9)	
2		15 (19.7)	24 (32.9)	20 (27.0)	
3		0	0	1 (1.4)	
Hb (g/dl), mean ± SD		9.6 ± 1.1	9.5 ± 0.8	9.4 ± 1.2	
Iron (U/l), median (range)		NR	NR	NR	
Epoetin (mU/ml)		NR	NR	NR	
Target Hb		NR	NR	NR	
Most common tumour types, *n* (%)					
Ovarian epithelial cancer		14 (18.4)	21 (28.8)	20 (27.0)	
Gastric cancer		6 (7.9)	5 (6.8)	7 (9.5)	
Lung squamous cell carcinoma		4 (5.3)	5 (6.8)	7 (9.5)	
Breast cancer		6 (7.9)	3 (4.1)	6 (8.1)	
Ovarian epithelial cancer metastatic		6 (7.9)	6 (8.2)	3 (4.1)	
Most common on-study treatment					
Cisplatin		55 (72.4)	48 (65.8)	42 (56.8)	
Carboplatin		22 (28.9)	29 (39.7)	24 (32.4)	
Cyclophosphamide		18 (23.7)	17 (23.3)	15 (20.3)	
Etoposide		20 (26.3)	11 (15.1)	14 (18.9)	
Were intervention and control groups comparable?		No *p*-values reported; authors stated that 'no relevant differences between treatment groups with regard to medical history, prior or concomitant medications, ECOG performance status, blood transfusions prior to study entry, concomitant diseases, tumour types and on-study chemotherapies' were found (p. 48)			

Results				
Hb				
Hb at end of study (g/dl), mean (SD)	11.2 (2)	11.4 (2)	9.6 (1.2)	
Change in Hb level (g/dl), mean (SD)[a]	1.6	1.9	0.2	
Complete Hb response without blood transfusion (increase of ≥ 2 g/dl from baseline), *n* (%)	50 (65.8)	52 (71.2)	15 (20.3)	
Epoetin beta vs. placebo	OR 10.25 (95% CI 4.86 to 22.83)			< 0.0001
Epoetin theta vs. placebo	OR 8.06 (95% CI 3.89 to 17.63)			< 0.0001
Epoetin theta vs. epoetin beta	OR 0.79 (95% CI 0.39 to 1.58)			0.5004
Complete Hb response without blood transfusion and dose adjustment, *n* (%)	26 (34.2)	29 (39.7)	8 (10.8)	
Epoetin beta vs. placebo	OR 5.40 (95% CI 2.35 to 13.68)			0.0001
Epoetin theta vs. placebo	OR 4.24 (95% CI 1.84 to 10.76)			0.0012
Epoetin theta vs. epoetin beta	OR 0.79 (95% CI 0.40 to 1.53)			0.4765
Partial Hb response without blood transfusion (increase of ≥ 1 g/dl from baseline), *n* (%)	69 (90.8)	66 (90.4)	37 (50)	
Epoetin beta vs. placebo	OR 9.39 (95% CI 4.01 to 24.93)			< 0.0001
Epoetin theta vs. placebo	OR 9.8 (95% CI 4.19 to 26.00)			< 0.0001
Transfusions				
Received blood transfusion, *n* (%)	8 (10.5)	9 (12.3)	18 (24.3)	
Epoetin beta vs. placebo	NR			0.1042
Epoetin theta vs. placebo	OR 0.38 (95% CI 0.14 to 0.95)			0.0433
Epoetin theta vs. epoetin beta	OR 1.04 (95% CI 0.34 to 3.20)			0.9394
No. of blood units transfused, mean (SD)	3.3 (2.2)	1.8 (0.7)	2.8 (2.9)	
HRQoL				
FACT-An including FACT-F and FACT-G	NR	NR	NR	

Results

Adverse effects of treatment, n *(%)*			
Any TEAE	58 (76.3)	63 (86.3)	63 (85.1)
TEADR	14 (18.4)	16 (21.9)	13 (17.6)
Serious TEAE	9 (11.8)	9 (12.3)	15 (20.3)
Serious TEADR	1 (1.3)	1 (1.4)	0
Death[b]	5 (6.6)	4 (5.5)	12 (16.2)
Discontinuation	4	3	6

a Results for Hb change from baseline presented graphically (figure 3).
b Most frequent reason for death was disease progression ($n = 1$ epoetin beta, $n = 6$ placebo, $n = 3$ epoetin theta).

Notes

Changes in haematocrit values were very similar to the changes in Hb values over time. Absolute reticulocyte values showed a high degree of variability in all three treatment groups and at all time points.
The mean ± SD average weekly dose was higher in the epoetin beta group than in the epoetin theta group (36,973 ± 13,967 IU vs. 26,425 ± 9157 IU). This was to be expected as the weekly starting doses were different.
Baseline Hb levels had no statistically significant effects on the response rates.
Baseline Hb levels had a statistically significant effect on the rate of blood transfusion ($p = 0.0005$), with an OR of 0.53 (95% CI 0.37 to 0.75) per g/dl baseline Hb comparing epoetin theta with placebo.
Tolerability: assessed by the patients was very good or good in 89.3%, 76.4% and 90.3% of patients in the epoetin theta, placebo and epoetin beta groups respectively; assessed by the investigator was very good or good in 93.3%, 88.9% and 93.1% of patients respectively.
No patients in the study developed neutralising anti-epoetin antibodies to epoetin beta or epoetin theta (assessed at the beginning and end of the study and at 60 days after the end of the treatment period).
Overall frequencies of AEs exceeded 10% for nausea (33.2%), neutropenia (22.9%), asthenia (22.4%), vomiting (18.4%), thrombocytopenia (16.6%) and leukopenia (16.1%). The incidence of skin reactions possibly caused by subcutaneous administration was low and comparable across groups ($n = 1$ epoetin theta, $n = 3$ epoetin beta, $n = 1$ placebo). The incidence of hypertension was 2.6% in the epoetin theta group and 2.7% in the epoetin beta and placebo groups, respectively.

Quality appraisal

1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Yes
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	Unclear[a]
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear, no *p*-values reported; similar ECOG scores between groups; other characteristics similar
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes[b]
6. Were the outcome assessors blind to treatment allocation?	Yes
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially (variability can be calculated from data presented in the paper)
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	Yes; quality-of-life data not reported
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes; however four and three participants withdrew for unspecified 'other' reasons in the epoetin and placebo groups respectively

a 'Only the person administering study medication was unblinded' (p. 46), which might imply that the person allocating treatment was unaware of the next allocation, but there is nothing explicitly stated and so this remains unclear.
b e.g. patients randomised to epoetin theta received a starting dose of 20,000 IU of epoetin theta subcutaneously once weekly (e.g. on Mondays) and the same volume of placebo twice weekly (e.g. on Wednesdays and Fridays) for blinding purposes.

Other	
Generalisability	Yes
Author conclusions	No conclusions regarding epoetin beta. Epoetin theta with a weekly starting dose of 20,000 IU is superior to placebo in terms of complete Hb response without blood transfusion. Epoetin theta is a safe and effective treatment for the treatment of anaemia resulting from platinum-based chemotherapy in patients with solid tumours
Reviewer comments	The differences between epoetin beta and placebo and between epoetin beta and epoetin theta were estimated with the same statistical model

ECOG, Eastern Cooperative Oncology Group; NR, not reported; TEAE, treatment-emergent adverse event; TEADR, related treatment-emergent adverse event.

EndNote ref. ID: 436	Malignancy type: solid tumour or non-myeloid haematological tumour Treatment: epoetin theta
Study design	**Participants**
Author, year	Tjulandin 2011[77]
Objective	The objective of this study was to demonstrate the superiority of epoetin theta compared with placebo for efficacy during the treatment period of 12 weeks in patients with solid tumours or non-myeloid haematological malignancies receiving non-platinum-based chemotherapy
No. of centres	72 sites; between November 2005 and May 2007
Other references/aliases	Trial registration: ISRCTN08063129
Geographical setting	International; 10 countries (Argentina, Belarus, Brazil, Bulgaria, Croatia, India, Moldova, Romania, Russia, Ukraine)
Duration of treatment	12 weeks. The mean ± SD treatment duration was comparable in both groups (71.9 ± 6.9 days placebo vs.72.1 ± 15.7 days epoetin theta
Length of follow-up (if different)	NA
Country of corresponding author	Germany
Language of publication	English
Sources of funding	Sponsored by BioGeneriX AG, a company of the ratiopharm Group SA
Randomisation and allocation	A total of 186 patients were randomised using a computer-generated allocation schedule in a 1 : 1 ratio stratified by country to double-blind treatment for 12 weeks with either epoetin theta ($n = 95$) or placebo ($n = 91$). All persons involved in the conduct of the study were blinded with respect to the study medication. The investigator and all other study personnel were kept blinded and performed all assessments of the patient without knowledge of treatment. An unblinded independent data safety monitoring committee closely monitored safety to ensure that patients were not exposed to an unjustifiable risk
	$n = 186$ Inclusion criteria: Age ≥ 18 years; histologically or cytologically proven diagnosis of a solid tumour or non-myeloid haematological tumour; anaemia caused by non-platinum-based chemotherapy defined by a documented Hb concentration of ≤ 11 g/dl after the last chemotherapy cycle prior to inclusion; at least one previous non-platinum-based chemotherapy cycle as treatment for the current malignancy during the last 4 weeks; ECOG performance status = 0, 1, 2 or 3 Exclusion criteria: Any other primary haematological disorder that would cause anaemia; head and neck tumours; uncontrolled severe hypertension; concomitant radiotherapy

Treatment arms		
Arm drug name(s)	Epoetin theta	Placebo
n	95	91
Dose and frequency (once daily, twice daily, etc.)	20,000 IU once per week. The mean ± SD average weekly dose was 25,905 ± 10,956 IU in the epoetin theta group	
Dose adjustment (yes/no)	Yes. After 4 weeks increase to 40,000 IU if Hb increase is < 1 g/dl, with a further increase to 60,000 IU if after the next 4 weeks there is still an insufficient response. Reduce by 50% if Hb increase is > 2 g/dl at 4 weeks. If Hb level is > 13 g/dl, dose interruption or 50% dose reduction	Yes, according to the same schedule as for epoetin theta for blinding purposes
Route of administration	Subcutaneous	Subcutaneous
Duration of epoetin treatment	12 weeks	12 weeks
Adjuvant anaemia treatment	Iron substitution was allowed during the study	Iron substitution was allowed during the study
Transfusion trigger	At the discretion of the investigator but should be avoided if Hb ≥ 8.5 g/dl	At the discretion of the investigator but should be avoided if Hb ≥ 8.5 g/dl
Outcomes		
Primary outcome	Haematological response (increase in Hb of ≥ 2 g/dl from baseline without the benefit of a transfusion within the previous 4 weeks)	
Other outcomes	Haematological response (partial Hb response of ≥ 1 g/dl from baseline; no. of patients having a complete and partial Hb response with the initial dose; time course of Hb, haematocrit and reticulocytes; dose of epoetin theta at the time of Hb response); RBCT (no. of patients requiring a RBCT; no. of blood units transfused); HRQoL [FACT-An (including FACT-G and FACT-F)]; AEs (immunogenicity was assessed by a predefined cascade of antibody assays; this cascade was structured into a sequential scheme comprising screening, confirmation and characterisation of clinical specimens; confirmed positive samples were investigated for neutralising antibodies in a cellular assay using an erythropoietin-dependent UT-7 cell line)	
Analysis		
Statistical technique used	A logistic regression analysis with treatment and type of cancer as explanatory variables and baseline Hb value as a continuous variable was performed to estimate the difference in the proportion of complete Hb responders between the epoetin theta group and the placebo group in the confirmatory analysis of the primary efficacy end point. For the primary efficacy end point a subgroup analysis with type of malignancy (solid, non-myeloid haematological) was performed. For the other binary secondary efficacy end points the same logistic regression model as for the primary end point was estimated. Changes in quality of life from baseline to end of study were compared pairwise with the Wilcoxon–Mann–Whitney test. Other secondary efficacy end points were compared only descriptively. Descriptive *p*-values were calculated with appropriate statistical tests but were regarded as supportive only	
ITT analysis?	Yes. Full analysis set used for efficacy end points; no crossovers and end points reported for full patient numbers	
Does statistical technique adjust for confounding?	NR; however, logistic regression analysis was adjusted for baseline Hb level to estimate the effects of treatment on Hb response	
Power calculation (a priori sample calculation)?	Partial; sample size calculation given for statistical superiority test comparing epoetin theta and placebo but not overall: $n = 80$ patients per treatment group to achieve a power of 90% for the statistical superiority test comparing epoetin theta and placebo assuming a response rate of 45% for epoetin theta and 20% for placebo	

Analysis	
Attrition rate (loss to follow-up)?	Yes; $n = 25$ prematurely discontinued: $n = 15$ in placebo group ($n = 6$ AEs, $n = 4$ patient request, $n = 2$ lack of efficacy, $n = 1$ lost to follow-up and $n = 2$ other) and $n = 10$ in epoetin theta group ($n = 4$ AEs, $n = 5$ patient request, $n = 0$ lack of efficacy, $n = 1$ lost to follow-up and $n = 0$ other)
Was attrition rate adequately dealt with?	Unclear; full analysis set used for efficacy end points
No. (%) followed up from each condition?	NA; no follow-up reported

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		Solid tumour or non-myeloid haematological tumour
Treatment (e.g. chemotherapy platinum/ non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Non-platinum-based chemotherapy
Adjuvant anaemia treatment	Iron	Iron substitution was allowed during the study
	G-CSF	NR
	Transfusion trigger	Hb ≤ 8.5 g/dl at the discretion of the investigator
	Hb inclusion criterion level	≤ 11.0 g/dl

	Arm 1 = epoetin theta ($n = 95$)	Arm 3 = placebo ($n = 91$)	Notes	*p*-value
Sex, *n* (%)				
Male	30 (31.6)	34 (37.4)		
Female	65 (68.4)	57 (62.6)		
Age (years), mean ± SD, median (range)	56.9 ± 14.7, 60 (18.0–83.0)	55.8 ± 14.3, 57.0 (18.0–82.0)		
ECOG performance status, *n* (%)				
0	14 (14.7)	9 (9.9)		
1	53 (55.8)	60 (65.9)		
2	28 (29.5)	21 (23.1)		
3	0	1 (1.1)		
Hb (g/dl), mean ± SD	9.2 ± 1.3	9.1 ± 1.3		
Iron (U/l), median (range)	NR	NR		
Epoetin (mU/ml)	NR	NR		
Target Hb (g/dl)	NR	NR		
Most common malignancies, *n* (%)				
Multiple myeloma	19 (20)	17 (18.7)		
Breast cancer	16 (16.8)	17 (18.7)		
Chronic lymphocytic leukaemia	5 (5.3)	7 (7.7)		
Gastric cancer	6 (6.3)	3 (3.3)		

Baseline characteristics		
Most common on-study chemotherapy, *n* (%)		
Cyclophosphamide	50 (52.6)	47 (51.6)
Doxorubicin	32 (33.7)	29 (31.9)
Vincristine	26 (27.4)	28 (30.8)
Dexamethasone	22 (23.2)	21 (23.1)
Prednisolone	14 (14.7)	26 (28.6)
Were intervention and control groups comparable?	No *p*-values reported; authors stated that 'There were no relevant differences between treatment groups with regard to medical history, prior or concomitant medications, ECOG performance status, previous chemotherapy, concomitant diseases, and primary malignant disease (Table 1). There were no clinically noteworthy differences between the treatment groups with regard to on-study chemotherapies' (p. 35)	

Results			
Hb			
Hb at end of study (g/dl), mean (SD)	11.3 (2)	< 10	
Change in Hb levels (g/dl), mean (SD)	2.1 (NR)		< 0.0001
Results for Hb change from baseline presented graphically (Figure 3)			

	Arm 1 = epoetin theta (*n* = 95)			Arm 3 = placebo (*n* = 91)		
Hb (estimated from Figure 3)	**Mean**	**SEM**	**SD**	**Mean**	**SEM**	**SD**
At the end of study (g/dl)	11.31	0.22	2.14	9.89	0.22	2.10

SEM, standard error of the mean.

Complete Hb response without blood transfusion (increase of ≥ 2 g/dl from baseline), *n* (%)	69 (72.6)	23 (25.3)	
Epoetin beta vs. placebo	Hb-adjusted OR 7.944 (95% CI 4.182 to 15.632)		<0.0001
Complete Hb response without blood transfusion and dose adjustment (increase of ≥ 2 g/dl from baseline), *n* (%)	43 (45.3)	9 (9.9)	
Epoetin beta vs. placebo	OR 7.728 (95% CI 3.59 to 18.285)		< 0.0001
Partial Hb response without blood transfusion (increase of ≥ 1 g/dl from baseline), *n* (%)	78 (82.1)	56 (61.5)	
Epoetin beta vs. placebo	OR 2.841 (95% CI 1.462 to 5.694)		0.0025
Partial Hb response without blood transfusion and dose adjustment, *n* (%)	56 (58.9)	24 (26.4)	
Epoetin beta vs. placebo	OR 4.028 (95% CI 2.179 to 7.632)		< 0.0001
Transfusions			
Patients received blood transfusions, *n* (%)	13 (13.7)	23 (25.3)	
Epoetin beta vs. placebo	OR 0.352 (95% CI 0.133 to 0.868)		0.0277
No. of blood units transfused, mean (SD)	3.5 (3.5)	4.1 (2.8)	

Results			
HRQoL			
FACT-An total, mean (SD)	6.3 (21.7)	0.6 (22)	0.243
FACT-An trial outcome index, mean (SD)	5.6 (17.1)	1.2 (18.8)	0.222
FACT-F, mean (SD)	2.9 (7.9)	0.6 (8.8)	0.142
FACT-G, mean (SD)	3.0 (12.7)	–0.2 (12.4)	0.224
AEs			
Any AE	76 (80.0)	71 (78.0)	
Related AE = ADR	27 (28.4)	18 (19.8)	
Serious AE	11 (11.6)	14 (15.4)	
Serious ADR	0	1 (1.1)	
Death[a]	6 (6.3)	5 (5.5)	
Discontinuation[b]	4 (4.2)	6 (6.6)	
Hypertension	8 (8.4)	1 (1.1)	< 0.05

Notes

a Most frequent reason for death was disease progression ($n = 3$ placebo group, $n = 2$ epoetin theta group).

b One patient in the placebo group discontinued because of thrombophlebitis.

The changes in haematocrit values were very similar to the changes in Hb values over time. Absolute reticulocyte values showed a high degree of variability in both treatment groups and at all time points (results not reported).

Type of cancer and baseline Hb levels had no statistically significant effects on any measure of the response rate and blood transfusion. The mean ± SD weekly dose of epoetin theta at the time of complete Hb response without blood transfusion was 27,681.2 ± 14,260.7 IU (median 20,000 IU) and at the time of partial Hb response was 24,871.8 ± 10,659.3 IU (median 20,000 IU). The mean dose of epoetin theta at the time of complete and partial Hb response was similar for solid tumours and haematological malignancies. A dose of up to 20,000 IU/week was sufficient for a complete Hb response in 66.7% of patients with a complete response in the epoetin theta group. In a further 23.2% of patients with a complete response, a response was achieved with a dose of 40,000 IU/week.

The completion rate of the valid FACT-An questionnaire was high in both treatment groups (89.5–97.9% in the epoetin beta group and 85.7–96.7% in the placebo group), with only small decreases in completion rates observed over the course of the study in both groups.

Adverse drug reactions (ADRs) with a causal relationship to the study medication as assessed by the investigator were reported in 27 (28.4%) patients in the epoetin theta group and 18 (19.8%) patients in the placebo group (Table 4). The most common ADRs were asthenia (7.5%), nausea (5.4%), headache (3.2%), pyrexia (2.7%) and vomiting (2.2%). All of these events commonly occur in cancer patients receiving chemotherapy.

Results for safety laboratory variables, vital signs, body weight, 12-lead ECG, physical examination, tolerability and skin irritation and results of current chemotherapy did not give rise to any safety concerns.

Tolerability as assessed by the patients was very good or good in 89.5% and 89.0% of patients in the epoetin theta and placebo group, respectively. The investigators assessed tolerability as very good or good in 98.9% (epoetin theta group) and 96.7% (placebo group) of patients.

Overall, frequencies of AEs exceeded 10% for asthenia (20.4%), neutropenia (18.8%), nausea (17.2%), leukopenia (15.6%) and pyrexia (12.9%).

Skin reactions that might have been caused by the subcutaneous administration of study medication were reported in 20 patients [($n = 13$ (13.7%) epoetin theta group, $n = 7$ (7.7%) placebo group]. None of the skin reactions was severe or serious.

The incidence of antidrug antibodies to epoetin theta was assessed at the beginning and end of the study. Only one patient treated with placebo developed a single positive result at baseline. A cellular assay to detect neutralisation was negative and a blood sample taken from this placebo-treated patient at the end of the study was also negative. None of the patients in the study developed neutralising anti-epoetin antibodies to epoetin theta.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Yes
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear – no *p*-values reported; authors stated that 'There were no relevant differences between treatment groups with regard to medical history, prior or concomitant medications, ECOG performance status, previous chemotherapy, concomitant diseases, and primary malignant disease (Table 1). There were no clinically noteworthy differences between the treatment groups with regard to on-study chemotherapies' (p. 35)
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes
6. Were the outcome assessors blind to treatment allocation?	Yes. An unblinded independent data safety monitoring committee closely monitored safety to ensure that patients were not exposed to an unjustifiable risk
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partially (variability can be calculated from data presented in the paper)
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes, apart from HRQoL (89.5–97.9% and 85.7–96.7% of participants analysed in the epoetin and placebo groups, respectively)
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Yes

Other	
Generalisability	Yes
Author conclusions	Epoetin theta showed a superior efficacy to placebo in terms of complete Hb response without blood transfusion within the previous 4 weeks. Treatment with epoetin theta resulted in a statistically significant increase in mean Hb level compared with placebo. The overall frequencies of AEs were similar in both treatment groups
Reviewer comments	

ADR, adverse drug reaction; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; NR, not reported.

EndNote ref. ID: 961

Malignancy type: breast cancer

Treatment: darbepoetin alfa

Study design		Participants
Author, year	Untch 2011[78]	*n* = 736 enrolled, with 733 randomly allocated
Objective	Latin square design – in a second randomisation, the short- and long-term effects of primary use of darbepoetin alfa independent from Hb levels on tumour response and safety were investigated. The toxicity and response data are described here and the effect on DFS and OS is reported in Untch and colleagues[80]	Inclusion criteria: Age 18–65 years with histologically confirmed primary breast cancer by core biopsy; the primary tumour had to be 2 cm based on either clinical or ultrasound measurement; inflammatory breast cancer was also included; no systemic metastasis according to chest radiography, sonography or computed tomography scan of upper abdomen and bone scan; ECOG score of < 2; adequate organ function: aspartate aminotransferase and bilirubin = 1.5 × upper limit, white blood cells = 3000/µl, neutrophils = 1000/µl, platelets = 100,000/µl and serum creatinine < 2.0 mg/dl; normal left ventricular ejection fraction Exclusion criteria: NR (but see inclusion criteria above)
No. of centres	78	
Other references/aliases	PREPARE trial, Untch 2011,[80] NCT00544232	
Geographical setting	Germany	
Duration of treatment	26 weeks; there were 24 weeks of chemotherapy – darbepoetin alfa was administered with the first dose of epirubicin (day 1) until 14 days after the last dose of paclitaxel	
Length of follow-up (if different)	Median follow-up 43.5 months	
Country of corresponding author	Germany	
Language of publication	English	
Sources of funding	Amgen Inc. Bristol-Myers Squibb	
Randomisation and allocation	Latin square design – patients were randomised in a 1 : 1 allocation to receive standard dose or dose-intensified preoperative chemotherapy. Patients within each treatment arm were further randomised in a 1 : 1 allocation to receive darbepoetin alfa or no darbepoetin alfa therapy	

Treatment arms		
Arm drug name(s)	Darbepoetin alfa	Control (standard care)
n	356	377
Dose and frequency (once daily, twice daily, etc.)	4.5 µg/kg every two weeks	NA
Dose adjustment (yes/no)	To achieve the target Hb level of 12.5–13 g/dl, the dose was doubled if the Hb increase was < 1 g/dl during the first 4 weeks or discontinued if Hb was > 14 g/dl. Treatment was re-induced at 50% of the dose if Hb was ≤ 13.0 g/dl	NA
Route of administration	NR	
Duration of epoetin treatment	Starting with the first dose of epirubicin (day 1) until 14 days after the last dose of paclitaxel	NA
Adjuvant anaemia treatment	200 mg oral iron daily	NA
Transfusion trigger	NR	None

Note
Of 318 patients receiving darbepoetin alfa, 165 (51.9%) had dose modifications, with any dose withheld (25%), missing doses (3%), a dose decrease (17%), a dose increase (8%) or extra doses > 14 days after chemotherapy (3%).

Outcomes	
Primary outcome	
Other outcomes	RBCT; tumour response [pCR at surgery (defined as regression Grades 4–5 according to the modified regression grading system)]; survival (DFS, OS); AEs (haematological and non-haematological, cardiovascular and thromboembolic)

Note
Other efficacy end points included lymph node status, clinical response at surgery, surgical outcome as well as effects of darbepoetin alfa on DFS, OS, pCR, and anaemia.

Analysis	
Statistical technique used	Comparisons between intensified or standard chemotherapy and between treatments with and without darbepoetin alfa used the chi- squared test. All secondary end point tests were two sided and 95% CIs were provided for relevant estimates. The change in Hb level difference between the treatments with and without darbepoetin alfa used ANCOVA with baseline Hb level as a covariate. Binary logistic regression analysis was employed to adjust for major predictive factors. Kaplan–Meier curves were used to estimate DFS and OS probabilities. DFS was defined as the time from informed consent to first documentation of relapse or death from any cause. OS was the time from the date of informed consent to the date of death from any cause. Local DFS was defined as time in weeks between the date of signing the informed consent and the date of local recurrence. Patients with no local recurrence reported were censored at the date of the last contact
ITT analysis?	Yes. The change in Hb level was analysed on the full analysis set (all patients who met all eligibility criteria and were randomly allocated to the chemotherapy treatment) using the last observation carried forward approach. Patients who did not meet eligibility criteria but who received at least one dose of study treatment were included only in the safety (toxicity) evaluation
Does statistical technique adjust for confounding?	Yes; OS and DFS were analysed adjusted for baseline factors. Binary logistic regression analysis was employed to adjust for major predictive factors. For multivariable analysis, Cox proportional hazards models for adjusting survival end points were used; adjustments were made for age, hormone receptor status, clinical tumour size and nodal status, grade, chemotherapy arm, darbepoetin alfa application and pCR
Power calculation (a priori sample calculation)?	Yes; 720 patients needed to detect an improvement of 10% in PFS with the dose-dense regimen with an expected proportion of relapses of 30% after 5 years in the standard treatment arm. This is equal to a HR of 1.4 with a type 1 error of $\alpha = 5\%$ using a one-sided test
Attrition rate (loss to follow-up)?	Partially – until the point of surgery (as reported in supplemental online materials). In total, 733 participants were randomly allocated and 19 did not receive any study treatment; 318/356 patients randomly allocated to darbepoetin alfa actually received the treatment. Most of the patients had surgery after chemotherapy: $n = 326$ in the darbepoetin group and $n = 343$ in the control group remained at that point
Was attrition rate adequately dealt with?	Partially; the change in Hb level was analysed on the 'full analysis set' using the last observation carried forward approach, but patient flow and numbers used in the analysis were difficult to follow and remain unclear
No. (%) followed up from each condition?	NR

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/ haematological/myelodysplastic syndrome/mixed)		Breast cancer
Treatment (e.g. chemotherapy platinum/non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Preoperative chemotherapy of epirubicin, cyclophosphamide and paclitaxel each 3-weekly ($n = 370$) for four cycles or epirubicin and paclitaxel with pegfilgrastim followed by CMF (combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil) each 2-weekly and for three cycles ($n = 363$). There were eight and nine planned cycles in the standard and intensified regimen respectively
Adjuvant anaemia treatment	Iron	200 mg oral iron in the darbepoetin alfa arm
	G-CSF	Yes, in the intensified regimen chemotherapy only (5 µg/kg/day)
	Transfusion trigger	NR
	Hb inclusion criterion level	NR

	Arm 1 = darbepoetin alfa ($n = 356$)	Arm 2 = control ($n = 377$)	Notes	*p*-value
Sex	NR	NR		
Age (years), median (range)	NR; median age reported separately for the intensified and standard chemotherapy arms only; the median age at randomisation was 48 years (range 23–65 years)			
< 50 years, *n* (%)	183 (51.4)	213 (56.4)		
≥ 50 years, *n* (%)	173 (43.6)	164 (43.6)		
ECOG performance status, *n* (%)				
0	306 (86.0)	323 (85.7)		
1	20 (5.6)	29 (7.7)		
2/3	2 (0.6)	4 (1.1)		
Missing	28 (7.9)	21 (5.6)		
Hb (g/dl), mean (SD)[a]	($n = 333$) 13.64 (1.17)	($n = 360$) 13.61 (1.16)	As reported in supplemental online materials	
Clinical tumour stage				
T1–T3	315 (88.5)	334 (88.6)		
T4	27 (7.6)	31 (8.2)		
Missing	14 (3.9)	12 (3.2)		
Tumour grade				
1–2	118 (33.1)	120 (31.8)		
3	97 (27.3)	117 (31)		
Missing	141 (39.6)	140 (37.2)		
Were intervention and control groups comparable?	No *p*-values are reported; authors stated that 'baseline characteristics were similar in the treatment arms' (p. 1991). It is assumed that this refers to the chemotherapy arms and it is not clear whether it also refers to the epoetin vs. no epoetin arms			

a As reported in supplemental online materials.

Results			
Hb			
Hb at the end of chemotherapy (g/dl), mean (SD)[a]	(*n* = 342) 13.59 (1.7)		(*n* = 368) 12.61 (1.38)
Change in Hb (g/dl), mean (SD) (95% CI)[b]	(*n* = 330) –0.07 (0.11) (–0.28 to 0.14)		(*n* = 359) –0.98 (0.07) (–1.12 to –0.84)
Tumour response, *n* (%)[c]			
pCR	57 (16)	60 (15.9)	0.972 (pCR vs. no pCR)
CR (by most appropriate method)	46 (12.9)	54 (14.3)	0.580
Toxicity (safety analysis set), *n* (%)	(*n* = 318)	(*n* = 396)	
Cardiovascular and thromboembolic events	20 (6.3)	17 (4.3)	0.232
Thromboembolic events: embolism/ thrombosis	18 (5.7)	12 (3)	0.055
Nausea grades 1–4	251 (78.9)	315 (79.5)	
Nausea grades 3–4	19 (6.0)	19 (4.8)	
Anaemia grades 1–4	31 (9.7)	35 (8.8)	
Anaemia grades 3–4	1 (0.3)	1 (0.3)	
Transfusions, *n*	1	0	
Survival[d]			
DFS	(*n* = 345)	(*n* = 369)	
Estimated at 3 years (%)	74.3	78	HR 1.31 (95% CI 0.99 to 1.74); $p = 0.061$
Events, *n*	106	90	
Events adjusted for baseline, *n* (%)[e]	104 (30)	88 (24)	HR 1.23 (95% CI 0.83 to 1.83); $p = 0.296$ in multivariate analyses adjusted for chemotherapy, age, initial tumour size, grading, ER/PgR status
DFS subgroup analyses: no pCR vs. pCR (better outcome observed for patients who achieved a pCR)[e]			With darbepoetin alfa: HR 2.38 (95% CI 1.2 to 4.71); $p = 0.013$; without darbepoetin alfa: HR 2.13 (95% CI 1.03 to 4.41); $p = 0.041$
OS			
Estimated at 3 years (%)	88	91.8	HR 1.33 (95% CI 0.91 to 1.95); $p = 0.139$
Events, *n*	59	48	HR 1.33 (95% CI 0.91 to 1.95); $p = 0.139$ in univariate analysis
Events adjusted for baseline, *n* (%)[e]	59 (17)	48 (13)	HR 1.24 (95% CI 0.71 to 2.19); $p = 0.4502$ in multivariate analyses adjusted for chemotherapy, age, initial tumour size, grading, ER/PgR status

Results

Subgroup analyses: no pCR vs. pCR (better outcome observed for patients who achieved a pCR)[b]	With darbepoetin alfa: HR 4.02 (95% CI 1.26 to 12.85); $p = 0.019$; without darbepoetin alfa: HR 3.08 (95% CI 0.95 to 9.92); $p = 0.060$

a As reported in supplemental online materials.
b The Hb levels in the control group decreased significantly, whereas the levels in the darbepoetin alfa group did not change significantly. It is not clear why the numbers analysed differ from the numbers randomised if LOCF was used. Hb at baseline $n = 360$ darbepoetin alfa, $n = 333$ control; Hb at end of chemotherapy $n = 368$ darbepoetin alfa, $n = 342$ control; change in Hb data from baseline $n = 359$ darbepoetin alfa, $n = 330$ control. Could not find full analysis of the Hb data.
c No difference for clinical response or nodal response.
d At a median follow-up of 43.5 months, as reported in Untch and colleagues[80] (this study reports follow-up DFS and OS data).
e As reported in supplemental online materials.

Notes

A trend (without showing a relevant effect on the clinical and pathohistological response) towards worse DFS in the darbepoetin alfa arm compared with the darbepoetin alfa-free arm was found. The absolute DFS difference in the dose-dense arm between patients treated with and patients treated without darbepoetin alfa is larger than the difference between the two chemotherapy regimens. In unplanned subgroup analysis the study revealed that poor prognostic factors were associated with significantly decreased DFS and OS in patients who received darbepoetin alfa. In unplanned subgroup analysis, the impact of darbepoetin on DFS and OS was investigated. Patients with either a grade 3 tumour or a tumour size ≥ 4 cm had significantly worse DFS when treated with darbepoetin alfa. This effect on OS was significant only for grade 3 tumours.
pCR at surgery, defined as regression grade 4–5 according to the modified regression grading system. Regression grade 5, no microscopic evidence of residual viable tumour cells (invasive or non-invasive) in all breast specimens and lymph nodes; grade 4, no residual tumour in breast specimens but involved lymph nodes; grade 3, only residual non-invasive (in situ) tumour in breast tissue, irrespective of lymph node status; grade 2, extensive tumour sclerosis with focal or multifocal evidence only of minimally invasive residual tumour (< 0.5 cm), frequently extensive ductal carcinoma in situ; grade 1, increased tumour sclerosis with focal resorptive inflammation and/or marked cytopathic effects; grade 0, no effect.
Complete clinical response was defined as no signs or symptoms of disease present in the breast before surgery.
A participant had a complete response if all available examinations showed a complete response.

Quality appraisal

1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	NR
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	NR – *p*-values for baseline comparisons are not reported; authors stated that 'baseline characteristics were similar in the treatment arms' (p. 1991). It is assumed that this refers to the chemotherapy arms and it is not clear whether it also refers to the epoetin vs. no epoetin arms
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	No (open label)
6. Were the outcome assessors blind to treatment allocation?	No (open label)
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Yes
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Partially – only until the point of surgery; $n = 326$ darbepoetin alfa group and $n = 343$ control group

Other	
Generalisability	
Author conclusions	Primary use of darbepoetin alfa did not affect pCR whereas darbepoetin alfa might have detrimental effects on DFS. Patients should not be treated with ESAs in the neoadjuvant setting under the assumption of better tumour oxygenation because a negative influence of darbepoetin alfa on DFS cannot completely be ruled out. The dose-intensified regimen was found to be superior to conventional chemotherapy in terms of pCR, but no difference in DFS or OS was found
Reviewer comments	Patient flow and numbers used in analysis were difficult to follow and remain unclear

ANCOVA, analysis of covariance; CR, complete response; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; ER, restrogen; LOCF, last observation carried forward; NR, not reported; pCR, pathological complete response; PgR, progesterone.

EndNote ref. ID: 2698 (HTA)	Malignancy type: lung cancer Treatment: darbepoetin alfa	
Study design		**Participants**
Author, year	Vansteenkiste 2002[73]	$n = 314$
Objective	The safety and efficacy of darbepoetin alfa compared with placebo in patients with lung cancer receiving chemotherapy	Inclusion criteria: Lung cancer; expected to receive at least 12 additional weeks of platinum-containing chemotherapy; age ≥ 18 years; life expectancy of at least 6 months; ECOG performance status 0 –2; anaemia (i.e. Hb ≤ 11.0 g/dl) primarily because of cancer or chemotherapy; adequate serum folate, vitamin B_{12}, ferritin, and saturated transferrin levels; adequate renal and hepatic function Exclusion criteria: Iron deficiency; primary or metastatic malignancy of the central nervous system; more than two RBCTs within 4 weeks of randomisation or received any RBCT within 2 weeks of randomisation; rHuEPO therapy within 8 weeks of randomisation or any previous treatment with darbepoetin alfa; pregnant, breastfeeding or not using adequate birth control measures; history of seizure disorders, active cardiac disease, uncontrolled hypertension, active infection or inflammation or a primary hematological disorder as the cause of the present anaemia
No. of centres	70	
Other references/aliases	NESP 980297, Tchekmedyian 2003[202] [examined the correlation between psychological distress (anxiety and depression) and fatigue over time], secondary analysis in Vantenkeenste 2004[84] (determined whether the degree of benefit obtained from treatment with darbepoetin alfa is affected by a patient's Hb level at the start of treatment)	
Geographical setting	Australia, Canada, Western Europe and Central and Eastern Europe	
Duration of treatment	12 weeks	
Length of follow-up (if different)	4-week follow-up period after the last dose of study drug and long-term follow-up to determine tumour status and survival (in this paper 6 months after the last patient completed the study; planned for at least 1 year)	
Country of corresponding author	Belgium	
Language of publication	English	
Sources of funding	R Pirker received research and travel grants and consulting fees from Amgen, Inc. and D Tomita holds stock in Amgen, Inc., the maker of darbepoetin alfa and epoetin alfa	
Randomisation and allocation	A double-blind, placebo-controlled, randomised Phase III study; patients were randomly assigned by a central randomisation service for all sites in a 1 : 1 ratio. Randomisation was stratified by tumour type (small-cell lung cancer or non-small-cell lung cancer) and geographical region (Australia, Canada, Western Europe or Central and Eastern Europe)	

Treatment arms		
Arm drug name(s)	Darbepoetin alfa	Placebo
n	156	158
Dose and frequency (once daily, twice daily, etc.)	2.25 µg/kg/week	Volume equivalent to darbepoetin alfa treatment
Dose adjustment (yes/no)	Yes. At week 6 if Hb was ≤ 1.0 g/dl over baseline Hb the dose of the study drug was doubled to 4.5 µg/kg/week, or the volume equivalent, beginning at week 7 (and continuing for the remainder of the study). Treatment was withheld if Hb was > 15.0 g/dl for men or > 14.0 g/dl for women. Once Hb decreased to ≤ 13.0 g/dl, the dose was reinstated at 50%	Yes, same as darbepoetin alfa (see above)
Route of administration	Subcutaneous	Subcutaneous
Duration of epoetin treatment	12 weeks	
Adjuvant anaemia treatment		
Transfusion trigger	Recommended when Hb was ≤ 8.0 g/dl and based on clinical judgement (transfusion policies can vary widely from country to country)	As for darbepoetin alfa
Outcomes		
Primary outcome	RBCT (proportion of participants who received a RBCT during a specific time period – from week 5 until the end of treatment[a])	
Other outcomes	Haematological response (haematopoietic response,[b] Hb collected weekly); RBCT (the incidence of RBCT from week 1 until the end of treatment, the incidence of transfusion or Hb concentration ≤ 8.0 g/dl, number of units of blood transfused); tumour response (tumour status and survival information are being collected during an open-label, long-term follow-up period); survival (disease progression and survival were also assessed quarterly for a minimum of 1 year if applicable); HRQoL (FACT-F, collected every 3–4 weeks on the first day of each cycle of chemotherapy, before any other study procedures); AEs (AE profile; incidence and duration of hospitalisation)	

a The effects on RBCT requirements are not apparent until the second month of treatment; therefore, the proportion of patients receiving a transfusion from week 5 until the end-of-treatment phase was selected as the primary end point.
b Haematopoietic response was defined as an increase in Hb concentration of ≥ 2.0 g/dl or a Hb concentration of ≥ 12.0 g/dl in the absence of a RBCT within the previous 28 days.

Note
Antibody formation to darbepoetin alfa was assessed.

Analysis	
Statistical technique used	Kaplan–Meier estimates were used for the proportion of patients who received at least one transfusion during week 5 until the end of treatment and for secondary transfusion-related end points and OS and PFS. The SE of the Kaplan–Meier proportion was calculated using Greenwood's formula; 95% CIs were also reported. Efficacy end points were analysed with and without adjusting for the two factors used to stratify the randomisation: tumour type and geographical region. Results of both types of analyses were consistent and so only the results of the unstratified analyses are presented. Cox proportional hazards and logistic regression were used to compare treatment groups after adjusting for tumour type, geographical region and other potentially prognostic factors once it had been determined that data complied with assumptions for this method. No adjustments were made for multiple significance tests. The percentage of change from baseline for the FACT–F score was analysed as two dichotomous variables (any improvement and at least a 25% improvement) in patients who had the baseline and at least one post-treatment score using the uncorrected chi-squared test. Safety was evaluated in all patients who received at least one dose of study drug

Analysis	
ITT analysis?	NR. All patients randomly assigned into the study who received at least one dose of study drug were included in the analyses. In total, 314 participants received the study drug and were included in the analysis for all end points (including OS and PFS). However this does not seem to apply to analyses of FACT-F. However, in the analysis of transfusions during week 5 until the end-of-treatment phase, patients who withdrew ($n = 17$) before study day 29 were excluded. In total, 297 participants (93%) completed the first 28 days of the study and were included in the analysis of the primary end point
Does statistical technique adjust for confounding?	NR
Power calculation (a priori sample calculation)?	Yes; 90% power to detect a 50% reduction (from 40% to 20%) in the proportion of participants with at least one transfusion during week 5 until the end of treatment (anticipated that 30% of patients would withdraw)
Attrition rate (loss to follow-up)?	Yes, CONSORT flow diagram provided. A total of 101 participants withdrew from the study (49 in the darbepoetin alfa group and 52 in the placebo group). Reasons for withdrawal included death, tumour progression, chemotherapy delayed or discontinued, AEs, withdrew consent, administrative decision and loss-to-follow-up. The numbers of participants withdrawn before study day 29 were also reported
Was attrition rate adequately dealt with?	NR
No. (%) followed up from each condition?	Partially

Baseline characteristics		
Malignancy type (e.g. solid/solid head, neck, lung, ovarian, cervical/haematological/ myelodysplastic syndrome/mixed)		Lung cancer
Treatment (e.g. chemotherapy platinum/ non-platinum based; chemotherapy + radiotherapy; no specific malignancy treatment; NR)		Platinum-based chemotherapy
Adjuvant anaemia treatment	Iron	NR
	G-CSF	NR
	Transfusion trigger	Recommended when Hb ≤ 8.0 g/dl and based on clinical judgement
	Hb inclusion criterion level	< 11 g/dl

	Arm 1 = darbepoetin alfa ($n = 156$)	Arm 2 = placebo ($n = 158$)	Notes	*p*-value
Sex, *n* (%)				
Male	111 (71)	116 (73)		
Female	45 (29)	42 (27)		
Age (years), mean (SD), median (range)	61.6 (9.2), 62.5 (39–80)	61.3 (8.8), 61 (36–79)		
WHO/ECOG performance status, *n* (%)				
0	22 (14)	23 (15)		
1	109 (70)	98 (62)		
2	24 (15)	37 (23)		
> 2	1 (1)	0		

	Arm 1 = darbepoetin alfa ($n = 156$)	Arm 2 = placebo ($n = 158$)	Notes	*p*-value
Hb (g/dl), mean (SD), median (range)	10.28 (1.08), 10.4 (7.4–13.6)	9.93 (1.01), 10.15 (6.6–12.3)		
Iron (U/l), median (range)				
Epoetin (mU/ml)				
Target Hb				
Ferritin (µg/l), mean (SD), median (range)	552.22 (453.45), 431 (36–3046)	534.5 (528.1), 402 (14–4895)		
Transferrin saturation (%), mean (SD), median (range)	20.98 (13.25), 18 (5–90)	18.95 (12.26), 16 (6–73)		
Data from secondary analyses (Vansteenkiste 2004[84])				
Baseline Hb (g/dl), mean (SD)				
Hb < 10 g/dl	9.1 (0.7) ($n = 51$)	9 (0.7) ($n = 69$)		
Hb ≥ 10 g/dl	10.9 (0.7) ($n = 105$)	10.7 (0.5) ($n = 89$)		
Were intervention and control groups comparable?	No *p*-values are reported; authors stated that 'Baseline demographics and clinical characteristics were similar between the two treatment groups' (p. 1214)			

Results				
Haematological and transfusions				
Transfusions	$n = 148$ and $n = 149$ for darbepoetin alfa and placebo groups respectively			
Participants with RBCTs from week 5 to end of treatment period (%) (95% CI)	27 (20 to 35)	52 (44 to 66)	Difference 25% (95% CI 14% to 36%)	< 0.001
First RBCT or Hb ≤ 8 g/dl (%) (95% CI)	32 (24 to 39)	62 (54 to 71)		< 0.001
RBC units transfused, mean (SD)	0.67 (1.7)	1.92 (3.27)	Difference 1.25 (95% CI 0.65 to 0.84)	< 0.001
Haematopoietic response (%) (95% CI)	66 (58 to 74) (103 participants calculated)	24 (16 to 31) (38 participants calculated)	Difference 42 (31 to 53)	< 0.001
Participants with RBCTs from week 1 to EOTP (%) (95% CI)[a]	28 (21 to 35)	57 (49 to 65)		
Time to disease progression or death (weeks), median (95% CI)[a]	23 (19 to 31)	20 (17 to 23)		
Data from secondary analyses (Vansteenkiste 2004[84])				
Hb < 10 g/dl (%) (95% CI)	($n = 51$) 65 (50 to 80) (33 participants calculated)	($n = 69$) 31 (17 to 45) 21 participants calculated		< 0.002
Hb ≥ 10 g/dl (%) (95% CI)	($n = 105$) 67 (57 to 77) (70 participants calculated)	($n = 89$) 20 (11 to 29) (17 participants calculated)		< 0.001

Results				
HRQoL	$n = 127$ and $n = 128$ in the darbepoetin and placebo groups, respectively, completed the scale through study week 4; also completed baseline and at least one time from week 5 until the end of the treatment phase			
Improvement in FACT-F scale (%) (95% CI)	56 (47 to 65)	44 (35 to 52)		0.052
Patients with at least a 25% improvement from baseline in FACT-F scale (%) (95% CI)	32 (23 to 40)	19 (12 to 26)	Difference 13 (CI 2 to 23)	0.019
Adverse effects of treatment				
Deaths, *n* (%)	22 (14)	19 (12)		
Death because of disease progression (%)	61	58		
Thrombotic events, *n* (%)	7 (5)	5 (3)		
Hypertension, *n* (%)	9 (6)	6 (4)		
Hospitalisations for overnight stays (days), mean (SD)	10.3 (13.7)	13 (17.7)		
Average of 1 year of follow-up after participants' first dose of study drug (n = 156 and n = 158 for darbepoetin and placebo groups, respectively)				
OS (weeks), median (95% CI)	46 (39 to 53)	34 (29 to 39)		
Deaths, *n* (%)	92 (59)	109 (69)		
PFS (weeks), median (95% CI)	22 (18 to 31)	20 (17 to 23)		
Disease progression or died, *n* (%)	129 (83)	141 (89)		

EOTP, end of the treatment period.
a As reported in Vansteenkiste 2004.[84]

Notes

The difference in the mean change in Hb from baseline between patients receiving darbepoetin alfa and those receiving placebo was 1.3 g/dl ($p < 0.001$) for participants with a baseline Hb of < 10 g/dl, and 1.4 g/dl ($p < 0.001$) for participants with a baseline Hb of > 10 g/dl (reported by Hb subgroup < 10 g/dl and > 10 g/dl in Vansteenkiste 2004).[84]
An analysis of the proportion of participants hospitalised was also carried out considering all hospitalisations (i.e. with or without an overnight stay), with similar results.
Changes in laboratory test variables and patient vital signs from baseline and the minimum absolute neutrophil count values on study in both treatment groups were similar.
No anti-darbepoetin antibodies were detected in 1054 serum samples ($n = 531$ darbepoetin, $n = 523$ placebo) and no clinical sequelae indicative of antibody formation have been observed during the follow-up period.

Quality appraisal	
1. Was the method used to generate random allocations adequate? (Yes = random numbers, coin toss, shuffle, etc.; no = patient's number, date of birth, alternate; unclear = method not stated)	Unclear; no randomisation details given
2. Was the treatment allocation adequately concealed? (Yes = central allocation at trial office/pharmacy, sequentially numbered coded vials, other methods in which the triallist allocating treatment could not be aware of treatment allocation; inadequate = allocation alternate or based on information known to the triallist)	Unclear; randomisation was performed using a centralised system, but details on allocation concealment were not reported
3. Were the groups similar at baseline in terms of prognostic factors, e.g. severity of disease?	Unclear – no *p*-values are reported; authors stated that 'Baseline demographics and clinical characteristics were similar between the two treatment groups' (p. 35)
4. Were the eligibility criteria specified?	Yes
5. Were the participants blind to treatment allocation?	Yes
6. Were the outcome assessors blind to treatment allocation?	Yes
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Yes
8. Is there evidence to suggest that the authors collected more outcome data than they reported?	No
9. Did the analyses include an ITT analysis or was < 10% of each study arm excluded?	Yes[a] – not for HRQoL; only 81% of patients analysed in both treatment groups
10. Were withdrawals, dropouts and loss to follow-up in each group stated?	Partially

a < 10% dropout but ITT defined as all randomised participants who received one or more dose of the study drug.

Notes

250 participants were analysed; data are collated (no separate results for darbepoetin alfa and placebo arms). Participants were included in the analysis if they completed at least 4 weeks of treatment and reported a BSI score at baseline and at least once after 4 weeks of treatment. The following were confounding variables for evaluation of the relationship between psychological outcomes and fatigue: age, gender, baseline ECOG performance status, tumour type (small-cell or non-small-cell lung cancer), number of days spent in the hospital during the study period and disease status (complete response, partial response, stable disease or progressive disease) (not Hb).

Authors' results: At baseline, 25% and 35% of 250 patients reported high levels (normed BSI scores ≥ 65) of anxiety and depression, respectively. Correlations of changes in normed BSI anxiety and depression subscale scores with changes in FACT-F scores had coefficients of –0.45 ($p < 0.001$) and –0.44 ($p < 0.001$), respectively. In the multiple regression models, change in the FACT-F score was the only significant explanatory variable ($p < 0.001$). For every unit improvement in FACT-F score there was a corresponding improvement of 0.7 points and 0.8 points in anxiety and depression levels, respectively.

Authors' conclusion: improvements in fatigue were significantly associated with reductions in anxiety and depression. For patients with anaemia, fatigue can be improved or reversed with darbepoetin alfa therapy. Thus, less fatigued patients may also benefit from reduced levels of anxiety and depression.

Other	
Generalisability	The majority of participants were male
Author conclusions	Patients with chemotherapy-associated anaemia can safely and effectively be treated with weekly darbepoetin alfa therapy. Darbepoetin alfa decreased RBCT requirements, increased Hb concentration and decreased fatigue. Although no conclusions can be drawn about survival from this study, the potential salutary effect on disease outcome warrants further investigation in a prospectively designed study
Reviewer comments	

BSI, Brief Symptom Inventory; CONSORT, Consolidated Standards of Reporting Trials; ECOG, Eastern Cooperative Oncology Group; NR, not reported.

Appendix 3 Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment

GRADE table for the use of erythropoiesis-stimulating agents for the treatment of treatment-induced anaemia in cancer patients: anaemia-related outcomes

No. of participants (no. of studies)	Quality assessment						Summary of findings
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	
Hb change (overall) (measured by change in Hb levels (g/dl) from baseline until the end of treatment period; better indicated by higher values)							
3170 (16 trials reported in 26 papers[17,48,50,51,53,58–60,63–67,69–71,74,77–83,85,86]) Meta-analysis: 18 trials[a]	Serious[b]	Serious; significant heterogeneity ($I^2 = 75.9\%$; $p < 0.01$)	No serious indirectness	No serious imprecision	Undetected; funnel plot analysis did not show statistically significant asymmetry ($p = 0.13$)	⊕⊕⊖⊖ LOW because of risk of bias, inconsistency	Sample sizes, *n*: control 1489, ESAs 1681; WMD 1.59 (95% CI 1.33 to 1.84) The random-effects meta-analysis demonstrated a statistically significant difference in Hb change (increase from baseline) in favour of treatment
Haematological response (overall) (assessed by proportion of participants with an increase in Hb level of ≥ 2 g/dl or an increase in haematocrit of ≥ 6 percentage points, unrelated to transfusion)							
2228 (10 trials reported in 19 papers[17,48,50,53,58–60,63,65,66,70,71,77,79,81–83,85,86]) Meta-analysis: 12 trials[a]	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; funnel plot analysis did not show statistically significant asymmetry ($p = 0.28$)	⊕⊕⊕⊖ MODERATE because of risk of bias	Study event rates, *n/N* (%): control 182/1015 (17.9), ESAs 759/1213 (62.6); RR 3.29 (95 CI 2.84 to 3.81) The random-effects meta-analysis demonstrated a statistically significant difference in haematological response in favour of treatment
RBCT requirements (overall) (assessed by proportion of participants requiring RBCT							
4779 (22 trials reported in 33 papers[17,48,50–53,58–60,62,63–71,73–86]) Meta-analysis: 24 trials[a]	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; funnel plot analysis did not show statistically significant asymmetry ($p = 0.23$)	⊕⊕⊕⊖ MODERATE because of risk of bias	Study event rates, *n/N* (%): control 835/2299 (36.3), ESAs 554/2480 (22.3); RR 0.63 (95% CI 0.57 to 0.69) The random-effects meta-analysis demonstrated a statistically significant difference in RBCT requirement in favour of treatment

No. of participants (no. of studies)	Quality assessment					Overall quality of evidence	Summary of findings
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		
RBC units (overall) [assessed by no. of units transfused per average patient (i.e. including participants not requiring transfusion)]							
1920 (10 trials reported in 16 papers[51,52,58,59,63,65,66,69,71,73,74,77,79,84–86]) Meta-analysis: 11 trials[a]	Serious[b]	Serious; significant heterogeneity ($I^2 = 59.3\%$; $p = 0.01$)	No serious indirectness	No serious imprecision	Undetected; funnel plot analysis did not show statistically significant asymmetry ($p = 0.14$)	⊕⊕⊖⊖ LOW because of risk of bias, inconsistency	Sample sizes, *n*: control 947, ESAs 973; WMD –0.87 (95% CI –1.28 to –0.46) The random-effects meta-analysis demonstrated a statistically significant difference in RBC units used in favour of the treatment

a Trials with multiple experimental arms were split into subsets (i.e. Tjulandin and colleagues[48] – epo theta and epo beta; Abels and colleagues[63] – cisplatin and non-cisplatin).
b The majority of trials had one or more limitations with regard to concealment of allocation, blinding or follow-up.

GRADE table for the use of erythropoiesis-stimulating agents for the treatment of treatment-induced anaemia in cancer patients: malignancy-related outcomes

No. of participants (no. of studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Summary of findings
Complete tumour response (overall) (assessed by total disappearance of all known malignant disease)							
1909 (seven trials published in 12 papers[51,60,66,70,71,74,76,78–82]) Meta-analysis: 7 trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected; funnel plot analysis not conducted because of low number of primary studies ($n = 7$)	⊕⊕⊖⊖ LOW because of risk of bias, imprecision	Study event rates, *n/N* (%): control 142/906 (15.7), ESAs 177/1003 (17.6); RR 1.10 (95% CI 0.86 to 1.41) The random-effects meta-analysis demonstrated a statistically non-significant difference in complete tumour response in favour of the treatment

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No. of participants (no. of studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Summary of findings
OS (calculated from the longest follow-up available using HRs)[c]							
4454 (21 trials published in 32 papers[17,48,50–53,58–60,62,63,65–71,73–86]) Meta-analysis: 18 trials[e,f]	Serious[d]	Serious; significant heterogeneity ($I^2 = 42.4\%$; $p = 0.03$)	No serious indirectness	No serious imprecision	Undetected; funnel plot analysis did not suggest asymmetry; the Harbord test could not be performed because raw data were not available	⊕⊕⊖⊖ LOW because of risk of bias, inconsistency	Study event rates, *n/N* (%): control 744/2137 (35), ESAs 818/2317 (35); HR 0.97 (95% CI 0.83 to 1.13) The random-effects meta-analysis demonstrated no statistically significant difference in survival in favour of treatment
Mortality (assessed by deaths occurring up to 30 days after the active study period)							
2967 (21 trials published in 32 papers[17,48,50–53,58–60,62,63,65–71,73–86]) Meta-analysis: 14 trials[e,g]	Serious[d]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected; funnel plot analysis did not suggest asymmetry; the Harbord test could not be performed because raw data were not available	⊕⊕⊖⊖ LOW because of risk of bias, imprecision	Study event rates, *n/N* (%): control 164/1381 (12), ESAs 174/1586 (11); HR 0.86 (95% CI 0.67 to 1.11) The random-effects meta-analysis demonstrated no statistically significant difference in mortality in favour of treatment

a All trials had one or more limitations with regard to concealment of allocation, blinding or follow-up.
b GRADE default thresholds to assess imprecision were used (0.25% RR reduction or RR increase). Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower minimally important difference (MID) or the upper or lower 95% CI crossed the upper MID.
c Some HRs were from IPD and some using other methods.
d The majority of trials had one or more limitations with regard to concealment of allocation, blinding or follow-up.
e Trials with multiple experimental arms were split into subsets (i.e. Tjulandin and colleagues[48] – epo theta and epo beta; Abels and colleagues[63] – cisplatin and non-cisplatin).
f Two studies[53,69] reported zero effects and three studies[50–52] reported events/effect size for the combined treatment arm (studies evaluated different ESA doses).
g Six studies[53,62,67,69,76,78,80] reported zero events and four studies[50–53] reported events/effect size for the combined treatment arm (studies evaluated different ESA doses).

GRADE table for the use of erythropoiesis-stimulating agents for the treatment of treatment-induced anaemia in cancer patients: safety outcomes

No. of participants (no. of studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Summary of findings
Thromboembolic events (overall)							
4013 (14 trials published in 25 papers[17,51,52,58–60,62,63,66,70,71,73–86]) Meta-analysis: 15 trials[b]	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; funnel plot analysis did not show statistically significant asymmetry ($p = 0.63$)	⊕⊕⊕⊖ MODERATE because of risk of bias	Study event rates, *n/N* (%): control 66/1984 (3.3), ESAs 103/2029 (5.1); RR 1.46 (95% CI 1.07 to 1.99) The random-effects meta-analysis demonstrated a statistically significant difference favouring the control
Hypertension (overall)							
2086 (10 trials published in 19 papers[48,51,52,58–60,63,66,70–73,77,79,81,82,84–86]) Meta-analysis: 12 trials[b]	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; funnel plot analysis did not show statistically significant asymmetry ($p = 0.69$)	⊕⊕⊕⊖ MODERATE because of risk of bias	Study event rates, *n/N* (%): control 27/934 (2.9), ESAs 62/1152 (5.4); RR 1.8 (95% CI 1.14 to 2.85) The random-effects meta-analysis demonstrated a statistically significant difference favouring the control
Thrombocytopenia/haemorrhage events (assessed by decrease of platelets in the blood/haemorrhage)							
1715 (seven trials published in 11 papers[52,60,65–67,70,76,78,80–82])	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	Undetected; funnel plot analysis not conducted because of low number of primary studies ($n = 7$)	⊕⊖⊖⊖ VERY LOW because of risk of bias, imprecision	Study event rates, *n/N* (%): control 54/838 (6.4), ESAs 55/877 (6.3); RR 0.93 (95% CI 0.65 to 1.34) The random-effects meta-analysis demonstrated no statistically significant difference in thrombocytopenia/haemorrhage favouring treatment

No. of participants (no. of studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Summary of findings
Seizures (overall)							
289 (one trial published in five papers[58,59,63,85,86]) Meta-analysis: two trials[b]	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	Undetected; funnel plot analysis not conducted because of low number of primary studies ($n = 2$)	⊕⊕⊖⊖ VERY LOW because of risk of bias, imprecision	Study event rates, *n/N* (%): control 4/141 (2.8), ESAs 5/148 (3.4); RR 1.19 (95% CI 0.33 to 4.38) The random-effects meta-analysis demonstrated no statistically significant difference in seizures favouring treatment
Pruritus (overall)							
904 (seven trials published in 12 papers[52,58,59,63,67,69,71,76,77,79,85,86]) Meta-analysis: six trials[d]	Serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; funnel plot analysis not conducted because of low number of primary studies ($n = 6$)	⊕⊕⊕⊖ MODERATE because of risk of bias	Study event rates, *n/N* (%): control 13/454 (2.9), ESAs 30/450 (6.7); RR 2.04 (95% CI 1.11 to 3.75) The random-effects meta-analysis demonstrated a statistically significant difference in pruritus favouring the control

a The majority of trials had one or more limitations with regard to concealment of allocation, blinding or follow-up.
b Trials with multiple experimental arms were split into subsets (i.e. Tjulandin and colleagues[48] – epo theta and epo beta; Abels and colleagues[63] – cisplatin and non-cisplatin).
c GRADE default thresholds to assess imprecision were used (0.25% RR reduction or RR increase). Outcomes were downgraded by two increments if the upper CI simultaneously crossed the upper minimally important difference (MID) and the lower CI crossed the lower MID.
d One study[69] did not report any events of pruritus in the treatment or placebo arms.
e All trials had one or more limitations with respect to concealment of allocation, blinding or follow-up.

Appendix 4 Excluded studies

Clinical effectiveness review: excluded studies

Reason for exclusion: population (n = 7)

Abdelrazik N, Fouda M. Once weekly recombinant human erythropoietin treatment for cancer-induced anemia in children with acute lymphoblastic leukemia receiving maintenance chemotherapy: a randomized case-controlled study. *Hematology* 2007;**12**:533–41.

Agnihotri P, Telfer M, Butt Z, Jella A, Cella D, Kozma CM, *et al.* Chronic anemia and fatigue in elderly patients: results of a randomized, double-blind, placebo-controlled, crossover exploratory study with epoetin alfa. *J Am Geriatr Soc* 2007;**55**:1557–65.

Cella D, Kallich J, McDermott A, Xu X. The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. *Ann Oncol* 2004;**15**:979–86.

Corwin HL, Gettinger A, Fabian TC, May A, Pearl RG, Heard S, *et al.* Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med* 2007;**357**:965–76.

Gordon D, Nichols G, Ben-Jacob A, Tomita D, Lillie T, Miller C. Symptom management and supportive care. 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**:715–24.

Gurion R, Gafter-Gvili A, Paul M, Vidal L, Ben-Bassat I, Yeshurun M, *et al.* Hematopoietic growth factors in aplastic anemia patients treated with immunosuppressive therapy-systematic review and meta-analysis. *Haematologica* 2009;**94**:712–19.

Henke M, Mattern D, Pepe M, Bezay C, Weissenberger C, Werner M, *et al.* Do erythropoietin receptors on cancer cells explain unexpected clinical findings? *J Clin Oncol* 2006;**24**:4708–13.

Reason for exclusion: intervention (n = 4)

Radiation Therapy Oncology Group. Radiation therapy with or without epoetin alfa in treating anemic patients with head and neck cancer. ClinicalTrials.gov identifier: NCT00004917. URL: https://clinicaltrials.gov/ct2/show/NCT00004917 (accessed 17 July 2010).

Krzakowski M. Epoetin delta: efficacy in the treatment of anaemia in cancer patients receiving chemotherapy. *Clin Oncol* 2008;**20**:705–13.

Lindholm E, Daneryd P, Korner U, Hyltander A, Fouladiun M, Lundholm K. Effects of recombinant erythropoietin in palliative treatment of unselected cancer patients. *Clin Cancer Res* 2004;**10**:6855–64.

Macdougall IC. CERA (continuous erythropoietin receptor activator): a new erythropoiesis-stimulating agent for the treatment of anemia. *Curr Hematol Rep* 2005;**4**:436–40.

Reason for exclusion: comparator (n = 3)

Casadevall N, Durieux P, Dubois S, Hemery F, Lepage E, Quarre MC, *et al.* Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. *Blood* 2004;**104**:321–7.

Laurie SA, Ding K, Whitehead M, Feld R, Murray N, Shepherd FA, *et al.* The impact of anemia on outcome of chemoradiation for limited small-cell lung cancer: a combined analysis of studies of the National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol* 2007;**18**:1051–5.

Weigang-Kohler K, Vetter A, Thyroff-Friesinger U. HX575, recombinant human epoetin alfa, for the treatment of chemotherapy-associated symptomatic anaemia in patients with solid tumours. *Onkologie* 2009;**32**:168–74.

Reason for exclusion: outcomes (n = 1)

Littlewood TJ, Schenkel B, Liss M. Effect of patient exclusion criteria on the efficacy of erythropoiesis-stimulating agents in patients with cancer-related anemia. *Oncologist* 2005;**10**:357–60.

Reason for exclusion: study design (n = 140)

Aapro M. Emerging topics in anaemia and cancer. *Ann Oncol* 2012;**23**(Suppl. 10):x289–93.

Aapro M, Coiffier B, Dunst J, Österborg A, Burger HU. Effect of treatment with epoetin beta on short-term tumour progression and survival in anaemic patients with cancer: a meta-analysis. *Br J Cancer* 2006;**95**:1467–73.

Aapro M, Jelkmann W, Constantinescu SN, Leyland-Jones B. Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer. *Br J Cancer* 2012;**106**:1249–58.

Aapro M, Spivak JL. Update on erythropoiesis-stimulating agents and clinical trials in oncology. *Oncologist* 2009;**14**(Suppl. 1):6–15.

Bennett CL. The blue cross blue shield assessment technology review: summary of findings. *Best Pract Res Clin Haematol* 2005;**18**:423–31.

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**:914–24.

Beutel G, Ganser A. Risks and benefits of erythropoiesis-stimulating agents in cancer management. *Semin Hematol* 2007;**44**:157–65.

Bohlius J, Langensiepen S, Schwarzer G, Seidenfeld J, Piper M, Bennett C, *et al.* Recombinant human erythropoietin and overall survival in cancer patients: results of a comprehensive meta-analysis. *J Natl Cancer Inst* 2005;**97**:489–98.

Bohlius J, Tonia T, Schwarzer G. Twist and shout: one decade of meta-analyses of erythropoiesis-stimulating agents in cancer patients. *Acta Haematol* 2011;**125**:55–67.

Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, *et al.* Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2006;**3**:CD003407.

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. *J Natl Cancer Inst* 2006;**98**:708–14.

Bohlius JF, Langensiepen S, Engert A, Schwarzer G, Bennett CL. Effectiveness of erythropoietin in the treatment of patients with malignancies: methods and preliminary results of a Cochrane review. *Best Pract Res Clin Haematol* 2005;**18**:449–54.

Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, A-Sterborg A, *et al.* EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. *Eur J Cancer* 2004;**40**:2201–16.

Boogaerts M, Oberhoff C, ten Bokkel Huinink W, Nowrousian MR, Hayward CRW, Burger HU. Epoetin beta (NeoRecormon) therapy in patients with solid tumours receiving platinum and non-platinum chemotherapy: a meta-analysis. *Anticancer Res* 2006;**26**:479–84.

Booton R, Thatcher N. The value of erythropoietin therapy in cancer patients. *Am J Cancer* 2005;**4**:87–103.

Boulaamane L, Goncalves A, Boutayeb S, Viens P, M'Rabti H, Bertucci F, *et al.* Prognostic impact of the combination of erythropoiesis-stimulating agents to cancer treatment: literature review. *Support Care Cancer* 2013;**21**:2359–69.

Cersosimo RJ, Jacobson DR. Epoetin alfa versus darbepoetin alfa in chemotherapy-related anemia. *Ann Pharmacother* 2006;**40**:58–65

Cheer SM, Wagstaff AJ. Epoetin beta – a review of its clinical use in the treatment of anaemia in patients with cancer. *Drugs* 2004;**64**:323–46.

Coiffier B, Boogaerts M, Aapro M, Hayward C, Burger H-U. Effect of treatment with epoetin beta on thromboembolic events in anemic patients with cancer: a metaanalysis. *Support Cancer Ther* 2006;**4**:49–55.

Cornes P, Coiffier B, Zambrowski JJ. Erythropoietic therapy for the treatment of anemia in patients with cancer: a valuable clinical and economic option. *Curr Med Res Opin* 2007;**23**:357–68.

Cortesi E, Gascon P, Henry D, Littlewood T, Milroy R, Pronzato P, *et al.* Standard of care for cancer-related anemia: improving hemoglobin levels and quality of life. *Oncology* 2005;**68**(Suppl. 1):22–32.

Couture F, Turner AR, Melosky B, Xiu L, Plante RK, Lau CY, *et al.* Prior red blood cell transfusions in cancer patients increase the risk of subsequent transfusions with or without recombinant human erythropoietin management. *Oncologist* 2005;**10**:63–71.

Crawford J. Erythropoiesis-stimulating protein support and survival. *Oncology (Williston Park)* 2006;**20**:39–43.

Crawford J, Robert F, Perry MC, Belani C, Williams D. A randomized trial comparing immediate versus delayed treatment of anemia with once-weekly epoetin alfa in patients with non-small cell lung cancer scheduled to receive first-line chemotherapy. *J Thoracic Oncol* 2007;**2**:210–20.

De Los Santos JF, Thomas GM. Anemia correction in malignancy management: threat or opportunity? *Gynecol Oncol* 2007;**105**:517–29.

Desai J, Demetri GD. Recombinant human erythropoietin in cancer-related anemia: an evidence-based review. *Best Pract Res Clin Haematol* 2005;**18**:389–406.

Donato H. Erythropoietin: an update on the therapeutic use in newborn infants and children. *Exp Opin Pharmacother* 2005;**6**:723–34.

Eton DT, Cella D. Do erythropoietic-stimulating agents relieve fatigue? A review of reviews. *Cancer Treat Res* 2011;**157**:181–94.

Ferrario E, Ferrari L, Bidoli P, De Candis D, Del Vecchio M, De Dosso S, *et al.* Treatment of cancer-related anemia with epoetin alfa: a review. *Cancer Treat Rev* 2004;**30**:563–75.

Feusner J. Guidelines for epo use in children with cancer. *Pediatr Blood Cancer* 2009;**53**:308–9.

Folloder J. Effects of darbepoetin alfa administered every two weeks on hemoglobin and quality of life of patients receiving chemotherapy. *Oncology Nurs Forum* 2005;**32**:81–9.

Gao S, Ma JJ, Lu C. Venous thromboembolism risk and erythropoiesis-stimulating agents for the treatment of cancer-associated anemia: a meta-analysis. *Tumour Biol* 2014;**35**:603–13.

Gascon P. Evaluating erythropoietic agents for the treatment of anaemia in the oncology setting. *Eur J Cancer* 2005;**41**:2601–12.

Glaspy J, Beguin Y. Anaemia management strategies: optimising treatment using epoetin beta (NeoRecormon (R)). *Oncology* 2005;**69**:8–16.

Glaspy J, Crawford J, Vansteenkiste J, Henry D, Rao S, Bowers P, *et al.* Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. *Br J Cancer* 2010;**102**:301–15.

Glaspy J, Rossi G. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease – reply. *Cancer* 2004;**10**:1546.

Glaspy JA. Randomized controlled trials of the erythroid-stimulating agents in cancer patients. *Cancer Treat Res* 2011;**157**:195–215.

Goodnough LT, Shander A. Update on erythropoiesis-stimulating agents. *Best Pract Res Clin Anaesthesiol* 2013;**27**:121–9.

Gosselin A, McKenzie RS, Lefebvre P, Mody SH, Piech CT, Duh MS. Dose-conversion ratio for epoetin alfa and darbepoetin alfa in chemotherapy patients with anemia and cancer. *PT* 2006;**31**(10).

Hedenus M, Österborg A, Tomita D, Bohac C, Coiffier B. Effects of erythropoiesis-stimulating agents on survival and other outcomes in patients with lymphoproliferative malignancies: a study-level meta-analysis. *Leuk Lymphoma* 2012;**53**:2151–8.

Hedenus M, Vansteenkiste J, Kotasek D, Austin M, Amado RG. Darbepoetin alfa for the treatment of chemotherapy-induced anemia: disease progression and survival analysis from four randomized, double-blind, placebo-controlled trials. *J Clin Oncol* 2005;**23**:6941–8.

Henry DH. Epoetin alfa for the treatment of cancer- and chemotherapy-related anaemia: product review and update. *Exp Opin Pharmacother* 2005;**6**:295–310.

Henry DH. Epoetin alfa treatment for patients with chemotherapy-induced anemia. *Support Cancer Ther* 2007;**4**:78–91.

Heuser M, Ganser A. Recombinant human erythropoietin in the treatment of nonrenal anemia. *Ann Hematol* 2006;**85**:69–78.

Jadersten M, Hellstrom-Lindberg E. Myelodysplastic syndromes: biology and treatment. *J Intern Med* 2009;**265**:307–28.

Jadersten M, Malcovati L, Dybedal I, Della Porta MG, Invernizzi R, Montgomery SM, *et al.* Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. *J Clin Oncol* 2008;**26**:3607–13.

Janecka IP. Erythropoletin to treat anaemia in patients with head and neck cancer. *Lancet* 2004;**363**:993–4.

Jones M, Schenkel B, Just J, Fallowfield L. Epoetin alfa improves quality of life in patients with cancer: results of metaanalysis. *Cancer* 2004;**101**:1720–32. [Erratum published in *Cancer* 2005;**103**:1984].

Juneja V, Keegan P, Gootenberg JE, Rothmann MD, Shen YL, Lee KY, *et al.* Continuing reassessment of the risks of erythropoiesis-stimulating agents in patients with cancer. *Clin Cancer Res* 2008;**14**:3242–7.

Kaanders JH, van der Kogel AJ. Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet* 2004;**363**:78–9; author reply 81–2.

Katodritou E, Dimopoulos MA, Zervas K, Terpos E. Update on the use of erythropoiesis-stimulating agents (ESAs) for the management of anemia of multiple myeloma and lymphoma. *Cancer Treat Rev* 2009;**35**:738–43.

Kelaidi C, Fenaux P. Darbepoetin alfa in anemia of myelodysplastic syndromes: present and beyond. *Exp Opin Biol Ther* 2010;**10**:605–14.

Kimel M, Leidy NK, Mannix S, Dixon J. Does epoetin alfa improve health-related quality of life in chronically ill patients with anemia? Summary of trials of cancer, HIV/AIDS, and chronic kidney disease. *Value Health* 2008;**11**:57–75.

Klarenbach S, Manns B, Reiman T, Reaume MN, Lee H, Lloyd A, *et al.* Economic evaluation of erythropoiesis-stimulating agents for anemia related to cancer. *Cancer* 2010;**116**:3224–32.

Kowalczyk M, Banach M, Mikhailidis DP, Rysz J. Erythropoietin update 2011. *Med Sci Monit* 2011;**17**:RA240–7.

Lambin P, Ramaekers BL, van Mastrigt GA, Van den Ende P, de Jong J, De Ruysscher DK, *et al.* Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer. *Cochrane Database Syst Rev* 2009;**3**:CD006158.

Larsson AM, Landberg G, Pahlman S, Albertsson M. Erythropoietin enhances response to treatment in patients with advanced breast cancer. *Acta Oncol* 2004;**43**:594–7.

Leonard RC, Untch M, Von Koch F. Management of anaemia in patients with breast cancer: role of epoetin. *Ann Oncol* 2005;**16**:817–24.

Littlewood T. Epoetin alfa (Eprex) and quality of life. *Curr Med Res Opin* 2005;**21**(Suppl. 2):S1–2.

Littlewood T, Collins G. Epoetin alfa: basic biology and clinical utility in cancer patients. *Exp Rev Anticancer Ther* 2005;**5**:947–56.

Lonnroth C, Svensson M, Wang W, Korner U, Daneryd P, Nilsson O, *et al.* Survival and erythropoietin receptor protein in tumours from patients randomly treated with rhEPO for palliative care. *Med Oncol* 2008;**25**:22–9.

Ludwig H, Crawford J, Österborg A, Vansteenkiste J, Henry DH, Fleishman A, *et al.* Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. *J Clin Oncol* 2009;**27**:2838–47.

Ludwig H, Wedding U, Van Belle S. Anaemia in elderly patients with cancer: focus on chemotherapy-induced anaemia. *J Geriatr Oncol* 2012;**3**:256–64.

Lyman GH, Glaspy J. Are there clinical benefits with early erythropoietic intervention for chemotherapy-induced anemia? A systematic review. *Cancer* 2006;**106**:223–33.

Marec-Berard P, Chastagner P, Kassab-Chahmi D, Casadevall N, Marchal C, Misset JL, *et al.* 2007 standards, options, and recommendations: use of erythropoiesis- stimulating agents (ESA: epoetin alfa, epoetin beta, and darbepoetin) for the management of anemia in children with cancer. *Pediatr Blood Cancer* 2009;**53**:7–12.

McKinney M, Arcasoy MO. Erythropoietin for oncology supportive care. *Exp Cell Res* 2011;**317**:1246–54.

Melosky BL. Erythropoiesis-stimulating agents: benefits and risks in supportive care of cancer. *Curr Oncol* 2008;**15**:S10–15.

Metzger NL, Francis KE, Voils SA. A comparative review of erythropoiesis stimulating agents. *J Pharm Pract* 2008;**21**:424–30.

Milano M, Schneider M. EPO in cancer anemia: benefits and potential risks. *Crit Rev Oncol Hematol* 2007;**62**:119–25.

Miller CP, Lowe KA, Valliant-Saunders K, Kaiser JF, Mattern D, Urban N, *et al.* Evaluating erythropoietin-associated tumor progression using archival tissues from a Phase III clinical trial. *Stem Cells* 2009;**27**:2353–61.

Minisini A, Atalay G, Bottomley A, Puglisi F, Piccart M, Biganzoli L. What is the effect of systemic anticancer treatment on cognitive function? *Lancet Oncol* 2004;**5**:273–82.

Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. *J Natl Cancer Inst* 2008;**100**:1155–66.

Morere J-F. Role of epoetin in the management of anaemia in patients with lung cancer. *Lung Cancer* 2004;**46**:149–56.

Morreale A, Plowman B, DeLattre M, Boggie D, Schaefer M. Clinical and economic comparison of epoetin alfa and darbepoetin alfa. *Curr Med Res Opin* 2004;**20**:381–95.

Moyo V, Lefebvre P, Duh MS, Yektashenas B, Mundle S. Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: a meta-analysis. *Ann Hematol* 2008;**87**:527–36.

Mystakidou K, Potamianou A, Tsilika E. Erythropoietic growth factors for children with cancer: a systematic review of the literature. *Curr Med Res Opin* 2007;**23**:2841–7.

Newland AM, Black CD. Tumor progression associated with erythropoiesis-stimulating agents. *Ann Pharmacother* 2008;**42**:1865–70.

Nowrousian MR. Regarding 'andomized comparison of epoetin alfa and darbepoetin alfa in anemic patients with cancer receiving chemotherapy'. *Oncologist* 2006;**11**:535–6; author reply 536–7.

Nowrousian MR, Dunst J, Vaupel P. Erythropoiesis-stimulating agents: favorable safety profile when used as indicated. *Strahlenther Und Onkol* 2008;**184**:121–36.

Oberhoff C. Speed of haemoglobin response in patients with cancer: a review of the erythropoietic proteins. *Support Care Cancer* 2007;**15**:603–11.

Ohashi Y, Uemura Y, Fujisaka Y, Sugiyama T, Ohmatsu H, Katsumata N, *et al.* Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: individual patient data from Japanese randomized, placebo-controlled trials. *Cancer Sci* 2013;**104**:481–5.

Oster HS, Hoffman M, Prutchi-Sagiv S, Katz O, Neumann D, Mittelman M. Erythropoietin in clinical practice: current use, effect on survival, and future directions. *Isr Med Assoc J* 2006;**8**:703–6.

Oster HS, Neumann D, Hoffman M, Mittelman M. Erythropoietin: the swinging pendulum. *Leuk Res* 2012;**36**:939–44.

Österborg A. New erythropoietic proteins: rationale and clinical data. *Semin Oncol* 2004;**31**:12–18.

Ots PMS, Carrizosa CL, Perez AR, de Dios Saez Garrido J, Perez JMD. Darbepoetin versus epoetin alfa for the correction of anemia in cancer patients receiving radiotherapy or chemoradiotherapy treatment. *Clin Med Oncol* 2008;**2**:393–9.

Parrish C, Owen RG. Waldenstrom macroglobulinemia with a durable clinical response to epoetin beta. *Leuk Lymphoma* 2012;**53**:1811–13.

Pedrazzoli P, Cinieri S, Lorusso V, Gamucci T, Secondino S, Silvestris N. Darbepoetin alpha coming of age. *Anticancer Res* 2007;**27**:4419–24.

Pelegri A. Impact of erythropoietin treatment on the quality of life of oncologic patients. *Clin Transl Oncol* 2007;**9**:645–51.

Petru E, Stummvoll W, Angleitner-Boubenizek L, Scholl T, Sevelda P, Benedicic C, *et al.* A literature review-based clinical guide on the use of erythropoiesis-stimulating agents (ESA) in the treatment of patients with gynaecological malignancies and related anaemia. *Geburtshilfe Frauenheilkd* 2010;**70**:646–57.

Pirker R. Darbepoetin alfa for the treatment of cancer-related anemia: an update. *Exp Rev Anticancer Ther* 2004;**4**:735–44.

Pirker R. Safety considerations for erythropoietin treatment in patients with cancer. *Exp Opin Drug Saf* 2007;**6**:63–9.

Pirker R. Clinical use of erythropoiesis-stimulating agents: defining the benefits. *J Thoracic Oncol* 2009;**4**:S153–5.

Pirker R. Erythropoiesis-stimulating agents in patients with cancer: update on safety issues. *Exp Opin Drug Saf* 2009;**8**:515–22.

Pronzato P, Jassem J, Mayordomo J. Epoetin beta therapy in patients with solid tumours. *Crit Rev Oncol Hematol* 2006;**58**:46–52.

Pujade-Lauraine E, Topham C. Once-weekly treatment of anemia in patients with cancer: a comparative review of epoetins. *Oncology* 2005;**68**:122–9.

Quercia RA, Keating KP, Goldman MC. Management of epoetin alpha use in the intensive care unit: a drug use evaluation. *Formulary* 2006;**41**:442–9.

Quirt I, Kovacs M, Couture F, Turner AR, Noble M, Burkes R, *et al.* Patients previously transfused or treated with epoetin alfa at low baseline hemoglobin are at higher risk for subsequent transfusion: an integrated analysis of the Canadian experience. *Oncologist* 2006;**11**:73–82.

Rades D, Golke H, Schild SE, Kilic E. The impact of tumor expression of erythropoietin receptors and erythropoietin on clinical outcome of esophageal cancer patients treated with chemoradiation. *Int J Radiat Oncol Biol Phys* 2008;**71**:152–9.

Reed SD, Radeva JI, Daniel DB, Mody SH, Forlenza JB, McKenzie RS, *et al.* Economic evaluation of weekly epoetin alfa versus biweekly darbepoetin alfa for chemotherapy-induced anaemia: evidence from a 16-week randomised trial. *Pharmacoeconomics* 2006;**24**:479–94.

Revicki DA, Stull D, Vernon M, Rader M, Tomita D, Viswanathan HN. Assessing the effect of darbepoetin alfa on patient-reported fatigue in chemotherapy-induced anemia in four randomized, placebo-controlled clinical trials. *Qual Life Res* 2012;**21**:311–21.

Rigolin GM, Castoldi G. The role of rHuEpo in low-risk myelodysplastic syndrome patients. *Leuk Lymphoma* 2005;**46**:823–31.

Rizzo JD. Evidence-based medicine: can it be applied to stimulation of erythropoiesis for patients with malignancy? *Best Pract Res Clin Haematol* 2005;**18**:439–48.

Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, *et al.* American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *J Clin Oncol* 2010;**28**:4996–5010.

Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, *et al.* Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol* 2008;**26**:132–49.

Rosberg JH, Ben-Hamadi R, Cremieux PY, Fastenau JM, Piech CT. Dose conversion and cost effectiveness of erythropoietic therapies in chemotherapy-related anaemia: a meta-analysis. *Clin Drug Invest* 2005;**25**:33–48.

Ross SD, Allen IE, Henry DH, Seaman C, Sercus B, Goodnough LT. Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature. *Clin Ther* 2006;**28**:801–31.

Saintigny P, Besse B, Soria LC, Bernaudin JF, Callard P. Does erythropoietin promote tumor growth? Reply. *Clin Cancer Res* 2008;**14**:1920–1.

Santini V. Treatment of low-risk myelodysplastic syndrome: hematopoietic growth factors erythropoietins and thrombopoietins. *Semin Hematol* 2012;**49**:295–303.

Savona MR, Silver SM. Erythropoietin-stimulating agents in oncology. *Cancer J* 2008;**14**:75–84.

Schrijvers D, De Samblanx H, Roila F. Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO clinical practice guidelines for use. *Ann Oncol* 2010;**21**:v244–7.

Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. *Am J Health System Pharm* 2007;**64**:S5–S13.

Siddiqui MAA, Keating GM. Darbepoetin alfa – a review of its use in the treatment of anaemia in patients with cancer receiving chemotherapy. *Drugs* 2006;**66**:997–1012.

Siddiqui MAA, Keating GM. Spotlight on darbepoetin alfa in the treatment of anemia in patients with cancer receiving chemotherapy. *BioDrugs* 2006;**20**:321–3. [Reprint of *Drugs* 2006;**66**:997–1012].

Spaeth D. Epoetin beta once weekly: review of its efficacy and safety in patients with chemotherapy-induced anemia. *Exp Rev Anticancer Ther* 2008;**8**:875–85.

Spano JP, Khayat D. Treatment options for anemia, taking risks into consideration: erythropoiesis-stimulating agents versus transfusions. *Oncologist* 2008;**13**:27–32.

Spivak JL. The anaemia of cancer: death by a thousand cuts. *Nature Rev Cancer* 2005;**5**:543–55.

Stasi R, Amadori S, Littlewood TJ, Terzoli E, Newland AC, Provan D. Management of cancer-related anemia with erythropoietic agents: doubts, certainties, and concerns. *Oncologist* 2005;**10**:539–54.

Steensma DP, Loprinzi CL. Erythropoietin use in cancer patients: a matter of life and death? *J Clin Oncol* 2005;**23**:5865–8.

Steensma DP, Witzig TE. Does treatment with recombinant human erythropoietin affect the survival of anemic patients with cancer? *Nature Clin Pract Oncol* 2005;**2**:444–5.

Straus DJ. Treatment of anemia with erythropoietic agents in patients with hematologic malignancies. *Support Cancer Ther* 2005;**2**:215–24.

Straus DJ. Management of anemia in patients with hematologic malignancies. *Oncology (Williston Park)* 2006;**20**:8–11.

Szenajch J, Wcislo G, Jeong JY, Szczylik C, Feldman L. The role of erythropoietin and its receptor in growth, survival and therapeutic response of human tumor cells. From clinic to bench – a critical review. *Biochim Biophys Acta Rev Cancer* 2010;**1806**:82–95.

Testa U. Erythropoietic stimulating agents. *Exp Opin Emerg Drugs* 2010;**15**:119–38.

Tonia T, Bohlius J. Ten years of meta-analyses on erythropoiesis-stimulating agents in cancer patients. *Cancer Treat Res* 2011;**157**:217–38.

Tonia T, Schwarzer G, Bohlius J. Cancer, meta-analysis and reporting biases: the case of erythropoiesis-stimulating agents. *Swiss Med Wkly* 2013;**143**:w13776.

Tovari J, Pirker R, Timar J, Ostoros G, Kovacs G, Dome B. Erythropoietin in cancer: an update. *Curr Mol Med* 2008;**8**:481–91.

Vansteenkiste J, Glaspy J, Henry D, Ludwig H, Pirker R, Tomita D, *et al.* Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: study-level and patient-level meta-analyses. *Lung Cancer* 2012;**76**:478–85.

Vansteenkiste J, Hedenus M, Gascon P, Bokemeyer C, Ludwig H, Vermorken 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.

Vansteenkiste J, Wauters I. The use of darbepoetin alfa for the treatment of chemotherapy-induced anaemia. *Exp Opin Pharmacother* 2005;**6**:429–40.

Vansteenkiste J, Wauters I, Elliott S, Glaspy J, Hedenus M. Chemotherapy-induced anemia: the story of darbepoetin alfa. *Curr Med Res Opin* 2013;**29**:325–37.

Vaupel P, Dunst J, Engert A, Fandrey J, Feyer P, Freund M, *et al.* Effects of recombinant human erythropoietin (rHuEPO) on tumor control in patients with cancer-induced anemia. *Onkologie* 2005;**28**:216–21.

Vaupel P, Mayer A, Gemici C, Henke M, Pajonk F, Janecka IP. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2004;**363**:992–4.

Volgger B, Petru E, Angleitner-Boubenizek L, Weigert M, Reinthaller A, Lass H, *et al.* Erythropoetin beta twice weekly versus standard therapy in patients with gynaecological malignancies – a randomised Austrian AGO trial. *Anticancer Res* 2008;**28**:3977–84.

Waltzman RJ. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease. *Cancer* 2004;**100**:1545–6; author reply 1546.

Wauters I, Pat K, Vansteenkiste J. Flexible dosing with darbepoetin alfa for the treatment of chemotherapy-induced anemia. *Ther Clin Risk Manag* 2006;**2**:175–86.

Wauters I, Vansteenkiste J. Darbepoetin alfa in the treatment of chemotherapy-induced anaemia. *Exp Opin Biol Ther* 2009;**9**:221–30.

Wauters I, Vansteenkiste J. Erythropoiesis-stimulating agents in cancer patients: reflections on safety. *Exp Rev Clin Pharmacol* 2011;**4**:467–76.

Wauters I, Vansteenkiste J. Darbepoetin alfa in the treatment of anemia in cancer patients undergoing chemotherapy. *Exp Rev Anticancer Ther* 2012;**12**:1383–90.

Wiffen PJ. Evidence-based pain management and palliative care in issue one for 2009 of The Cochrane Library. *J Pain Palliat Care Pharmacother* 2009;**23**:166–8.

Ziegler JA, Herrington JD. Current and future options for the treatment of chemotherapy-induced anaemia. *Exp Opin Invest Drugs* 2006;**15**:1051–65.

Reason for exclusion: study design (systematic reviews of randomised controlled trials that were scrutinised for references) (n = 12)

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, *et al.* Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet* 2009;**373**:1532–42.

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 Syst Rev* 2009;**3**:CD007303.

Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Österborg A, *et al.* EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur J Cancer* 2007;**43**:258–70.

Grant MD, Piper M, Bohlius J, Tonia T, Nadege R, Vikrant V, *et al. Epoetin and Darbepoetin for Managing Anaemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update*. Chicago, IL: Blue Cross and Blue Shield Association Technology Evaluation Center; 2013.

Kvam AK, Fayers P, Hjermstad M, Gulbrandsen N, Wisloff F. Health-related quality of life assessment in randomised controlled trials in multiple myeloma: a critical review of methodology and impact on treatment recommendations. *Eur J Haematol* 2009;**83**:279–89.

Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J Natl Cancer Inst Monogr* 2004;(32):40–50.

Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev* 2010;**7**:CD006704.

Ross SD, Allen IE, Probst CA, Sercus B, Crean SM, Ranganathan G. Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: a systematic review and meta-analysis. *Oncologist* 2007;**12**:1264–73.

Shehata N, Walker I, Meyer R, Haynes AE, Imrie K, Cancer Care Ontario Hematology Disease Site Group. The use of erythropoiesis-stimulating agents in patients with non-myeloid hematological malignancies: a systematic review. *Ann Hematol* 2008;**87**:961–73.

Tonelli M, Hemmelgarn B, Reiman T, Manns B, Reaume MN, Lloyd A, *et al.* Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. *CMAJ* 2009;**180**:E62–71.

Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, *et al.* Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2012;**12**:CD003407.

Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al.* A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007;**11**(13).

Reason for exclusion: duplicate (n = 4)

Bohlius J, Langensiepen S, Schwarzer G, Seidenfeld J, Piper M, Bennet C, *et al.* Erythropoietin for patients with malignant disease. *Cochrane Database Syst Rev* 2004;**3**:CD003407.

Ohashi Y, Uemura Y, Fujisaka Y, Sugiyama T, Ohmatsu H, Katsumata N, *et al.* Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: individual patient data from Japanese randomized, placebo-controlled trials. *Cancer Sci* 2013;**104**:481–5.

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. *J Clin Oncol* 2006;**24**:3583–9.

Schwartzberg LS, Yee LK, Senecal FM, Charu V, Tomita D, Wallace J, *et al.* Symptom management and supportive care. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. *Oncologist* 2004;**9**:696–707.

Reason for exclusion: language (n = 9)

Hernandez MAL, Lopez EU. [Weekly beta erythropoietin high doses in patients with lymphoblastic acute leukemia in remission and under chemotherapy, its effects in transfusion requirements]. *Med Intern Mex* 2008;**24**:375–80.

Liang J, Bi Q, Shen LD, Cheng HY. [The clinical study on recombinant human erythropoietin for chemotherapy-related anemia]. *Tumor* 2009;**29**:58–60.

Meric JB, Morere JF. Anemia in lung cancer patients. *Bull Cancer* 2005;**92**:439–44.

Ray-Coquard I, Kassab-Chahmi D, Casadevall N, Chastagner P, Marchal C, Marec-Berard P, *et al.* Clinical practice guidelines for the use of erythropoiesis-stimulating agents (ESA: epoetin alfa, epoetin beta, darbepoetin) in anaemic patients with cancer: 2007 update (summary report). *Bull Cancer* 2008;**95**:433–41.

Ray-Coquard I, Kassab-Chahmi D, Casadevall N, Chastagner P, Marchal C, Marec-Berard P, *et al.* Standards, options and recommendations for the use of erythropoiesis-stimulating agents (ESA: epoetin alfa, epoetin beta, darbepoetin) in anaemic patients with cancer: 2007 update. *Oncologie* 2008;**10**:160–6.

Sanchez CO, Gonzalez GP, Sanchez LFO. Erythropoietin and cancer-related anaemia. Light and shade. *Med Clin* 2005;**124**:186–95.

Schipper J, Henke M. [Erythropoietin in patients with head and neck carcinomas?]. *Laryngorhinootologie* 2004;**83**:292–7.

Spaeth D, Casadevall N, Daouphars M, Marchal C, Marec-Berard P, Fabre N, *et al.* Summary version of the standards, options and recommendations for the use of recombinant erythropoietin (epoietin-alpha and beta, darbepoietin-alpha, EPO) in the management of anaemia in oncology – update 2003. *Bull Cancer* 2004;**91**:179–88.

Zemelka T, Rolski J, Ziobro M, Michalczyk A. [Opinion on influence of erythropoietin on quality of life and survival in patients with advanced non-small cell lung cancer]. *Wspolczesna Onkol* 2007;**11**:37–40.

Reason for exclusion: unobtainable (n = 5)

Coiffier B, Milpied N, Facon T, Beris P. Epoetin beta (NeoRecormon) once weekly or three-times weekly produces a rapid haemoglobin response in anaemic patients with lymphoproliferative malignancies. 2004. URL: wwwehaweborg.

Costa EC, Martin EG, Vilaplana PG. Current approach in the use of erythropoietin. *Cancer Chemother Rev* 2007;**2**:121–32.

Littlewood T, Zagari M, Schenkel B. Effects of population definitions and study endpoints on efficacy of epoetin alfa vs placebo in anemic patients with hematologic malignancies receiving chemotherapy. 2004. URL: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/246/CN-00525246/frame.html (accessed 9 August 2015).

Vandebroek A, Altintas S, Gaede B, Smith K, Yao B, Schupp M. Darbepoetin alfa administered every 3 weeks with or without parenteral iron in anaemic patients with nonmyeloid malignancies receiving chemotherapy: interim results from a randomised open-label study. *Haematologica* 2006;**91**(Suppl. 1):0029.

Wang R. Safety of erythropoiesis-stimulating agents: lessons and limitations of meta-analyses. 2009 Annual Meeting Student Poster Abstract.

Reason for exclusion: no usable data (n = 2)

Benefits of epoetin alfa for cancer patients' quality of life are confirmed after modelling to account for missing data. *Curr Med Res Opin* 2005;**21**(Suppl. 2):S6–8.

Golshayan AR, Jin T, Maciejewski J, Fu AZ, Bershadsky B, Kattan MW, *et al.* Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes. *Br J Haematol* 2007;**137**:125–32.

Reason for exclusion: abstract only (n = 57)

Alexopoulos CG, Kotsori AA. A randomized comparison of rHuEPO with darbepoetin for cancer related anaemia. *Ann Oncol* 2004;**15**:219.

Canon JL, Vansteenkiste J, Bodoky G, Mateos MV, Bastit L, Ferreira I, *et al.* Final results of a randomized, double-blind, active-controlled trial of darbepoetin alfa administered once every 3 weeks (Q3W) for the treatment of anemia in patients receiving multicycle chemotherapy. *J Clin Oncol* 2005;**23**:799S.

Canon JL, Vansteenkiste J, Bodoky G, Mateos MV, Bastit L, Ferreira I, *et al.* Darbepoetin alfa administered once every 3 weeks (Q3W) is effective for treating anaemia in patients receiving multicycle chemotherapy: results of a randomised, double-blind, active-controlled trial. *EJC Suppl* 2005;**3**:370.

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. *J Clin Oncol* 2004;**22**:749S.

Charu V, Belani CP, Gill AN, Bhatt M, Ben-Jacob A, Tomita D, *et al.* A controlled, randomized, open-label study to evaluate the effects of every-2-week darbepoetin alfa for anemia of cancer. *J Support Oncol* 2005;**3**:12–13.

Charu V, Saidman B, Ben-Jacob A, Justice GR, Maniam AS, Rearden T, *et al.* Improvements in fatigue are associated with early treatment with every 3-week (Q3W) darbepoetin alfa (DA) treatment in anemic patients (pts) receiving chemotherapy. *Blood* 2004;**104**:233.

Crawford J, Glaspy J, Vansteenkiste J, Henry DH, Tomita D, Bridges K, *et al.* Use of erythropoiesis-stimulating agents (ESAs) in lung cancer patients: study-level and patient-level meta-analyses of safety outcomes. *J Thoracic Oncol* 2010;**5**:S552–3.

Delarue R. Survival impact of prophylactic administration of darbepoetin alfa in patients with diffuse large B-cell lymphoma treated with immunochemotherapy: the LNH03-6B study. Educational Cancer Convention Lugano of the European School of Oncology, Lugano, Switzerland, April 2012.

Delarue R, Haioun C, Broussais-Guillaumot F, Sibon D, Fournier M, Mounier N, *et al.* Efficacy and safety of prophylactic use of darbepoetin alfa in patients with diffuse large B-cell lymphoma (DLBCL) treated with immunochemotherapy: results of the interim analysis of the LNH03-6B gela study. *Blood* 2009;**114**:1701.

Freemantle N, Yao B, Calvert M, Lillie T. Impact of darbepoetin alfa on transfusion, hemoglobin response, and survival in cancer patients with chemotherapy-induced anemia: results of a meta-analysis of randomized, placebo-controlled trials. *Blood* 2005;**106**:871A.

Gupta S, Singh PK, Bhatt ML, Pant MC, Sundar S, Verma J, *et al.* Clinical benefits of epoetin beta in patients with advanced stage hormone refractory prostate cancer. *Eur Urol Suppl* 2011;**10**:337.

Hartmann JT, Metzner B, Binder C, Mergenthaler HG, Rick O, Sayer HG, *et al.* Addition of darbepoetin alfa to sequential high-dose VIP chemotherapy for patients with advanced metastatic germ cell cancer. *J Clin Oncol* 2012;**30**(Suppl. 1):e15026.

Heras P, Hatzopoulos A, Karagiannis S. Efficacy and safety of epoetin beta 30,000 IU once weekly in patients with solid tumors and chemotherapy-induced anemia. *J Clin Oncol* 2006;**24**(18S):697.

Heras P, Hatzopoulos A, Karagiannis S, Kritikos K. Epoetin beta (30000) vs. epoetin alfa (40000) for chemotherapy induced anemia in patients with colorectal cancer: a randomized comparative study. *Ann Oncol* 2007;**18**:VII77.

Hernandez E, Di Benedetto J, Kotasek D, Ganly P, Silberstein P, Tomita D, *et al.* Effectiveness of darbepoetin alfa 300 mcg every 3 weeks in patients with chemotherapy-induced anemia. *J Clin Oncol* 2006;**24**:S691.

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. *J Support Oncol* 2005;**3**(Suppl. 4):10–11.

Houben R, Pijls-Johannesma M, Ramaekers B, Van Den Ende P, De Jong J, De Huysscher D, *et al.* Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer: updated systematic review with additional data and new methodology. European Society for Therapeutic Radiology and Oncology (ESTRO) 29 Congress, Barcelona, Spain, September 2010.

Katsumata N, Fujiwara Y, Sugiyama T, Goto I, Ohmatsu H, Okamoto R, *et al.* Erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anemia and mortality: a meta-analysis of individual patient data from Japanese randomized trials. *Eur J Cancer* 2011;**47**:S242.

Kelada OJ, Marignol L. Does the use of erythropoietin-stimulating agents in breast cancer patients with chemotherapy-induced anaemia impact on clinical outcomes? A critical review of the literature. European Society for Therapeutic Radiology and Oncology (ESTRO) 29 Congress, Barcelona, Spain, September 2010.

Kotsori AA, Alexopoulos CG. A randomized comparison of darbepoetin alfa with epoetin for chemotherapy induced anemia in nonhematological tumors. *J Clin Oncol* 2006;**24**:S692.

Langer CJ. Managing anemia in lung cancer. *J Thoracic Oncol* 2009;**4**:S144–5.

Ludwig H, Crawford J, Österborg A, Fleishman A, Lillie T, Sueto T, *et al.* Patient-level integrated analysis of data from 6 randomized, double-blind, placebo-controlled trials of darbepoetin alfa (DA) in patients (pts) with chemotherapy-induced anemia (CIA). *EJC Suppl* 2007;**5**:142–3.

Marangolo M, Lang I, Beato C, Colomer R, Ukarma L. Breast Cancer – Anaemia and the Value of Erythropoietin (BRAVE): preliminary results from a study of the efficacy of epoetin beta 30,000 IU once weekly in patients with metastatic breast cancer receiving chemotherapy. *Eur J Cancer* 2005;**3**:388.

Marangolo M, Malamos N, Pedrini JL, Rotarski, M. Epoetin beta in patients with metastatic breast cancer receiving chemotherapy: results from the Breast Cancer – Anaemia and the Value of Erythropoietin (BRAVE) study. *J Clin Oncol* 2005;**23**(Suppl.):764.

Marinaccio M, Mele E, Poma S, Cantinieri C, Cocca M, Latiano T. Pretreatment normalisation of mild anemia with epoetin alfa predicts long-term outcome for women with epithelail ovarian cancer. *J Clin Oncol* 2004:**22**:S5132.

Markus R, Henry D, Gascon P, Fleishman A, Borenstein J. Design and rationale of a double-blind, randomized, placebo-controlled study to evaluate the long-term safety and efficacy of darbepoetin alfa administered 500 mcg once every three weeks (Q3W) in anemic patients with advanced non-small cell lung cancer (NSCLC) receiving multi-cycle chemotherapy. *J Thoracic Oncol* 2009;**4**:S431.

Mihaylov G, Tsekova V, Koytchev R. Epoetin zeta: safety data from an open-label, Phase III trial in patients with chemotherapyinduced anaemia. *Ann Oncol* 2008;**19**(Suppl. 8):278.

Moehler M, Geissler M, Raedle J, Ebert MD, Flieger D, Seufferlein T, *et al.* Epoetin beta once weekly in anaemic patients with advanced cancer of the stomach or gastroesophageal junction: interim results of a randomized German AIO Phase II trial. *Onkologie* 2007;**30**:140–1.

Nitz U, Oberhoff C, Reimer T, Schumacher C, Hackmann J, Warm M, *et al.* Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: a safety analysis from the Phase III ARA plus trial. *Cancer Res* 2009;**69**(Suppl.):4100.

Norris L, Mattison D, Qureshi ZP, Bennett C. Location, location, location: reassessing erythropoiesis stimulating agents (ESAs) in the United States (US), Canada, and Europe (2007–2011). *Blood* 2011;**118**:4753.

Norris L, Qureshi Z, Barnato S, Lai S, Bennett C. Serious adverse drug reactions (sADRS) associated with hematopoietic growth factors: a systematic review from the Southern Network on Adverse Reactions (SONAR) program. 7th Annual Hematology/Oncology Pharmacy Association (HOPA) Conference, Salt Lake City, UT, USA, March 2011.

Ohmatsu H, Nishiwaki Y, Ichinose Y, Ohe Y, Yamada Y, Takeda K, *et al.* Randomized Phase II study of weekly administration of darbepoetin alfa (DA) in anemic patients with lung cancer and ovarian cancer receiving platinum-based chemotherapy. *Ann Oncol* 2006;**17**:291–2.

Paladini L, Clark O, Clark LG, Engel T, Pegoretti B, Faleiros E. Erythropoiesis stimulating agents (ESA) for the treatment of chemotherapy induced anemia in patients with hemoglobin levels (HB) < 11 g/dl – a systematic review and meta-analysis. ISPOR 12th Annual European Congress, Paris, France, October 2009. *Value Health* 2009;**12**:A493.

Pirker R, Collins H, Legg JC, Vansteenkiste J. F. Rate of hemoglobin (Hb) decline from less than 10 g/dl to less than 9 g/dl in placebo-treated patients (pts) receiving chemotherapy: a pooled analysis of data from six randomized darbepoetin alfa trials. *J Clin Oncol* 2011;**29**(Suppl. 1):e19637.

Pollera CF, Nelli F, Gamucci T, Sperduti I, Giampaolo AM, Moscetti L, *et al.* Prospective evaluation of epoetin-alfa (EA) vs epoetin-beta (EB) vs darbepoetin (DE) in anemic cancer patients (pts) receiving chemotherapy (CT): early results of an independent observational survey by the Italian ReVERTO network. *J Clin Oncol* 2006;**24**:S692.

Rearden TP, Charu V, Saidman B, Ben-Jacob A, Justice GR, Manaim AS, *et al.* Results of a randomized study of every three-week dosing (Q3W) of darbepoetin alfa for chemotherapy-induced anemia (CIA). *J Clin Oncol* 2004;**22**:745S.

Reed N, Chan S, Hayward C, Burger H, Bokkel Huinink W. Impact of epoetin beta on the survival of anemic patients with ovarian cancer receiving platinum-based chemotherapy. *J Clin Oncol* 2005;**23**:S5102.

Rosti G, Secondino S, Giordano L, Garassino I, Gandini C, Auerbach M, *et al.* Intravenous iron supplementation and erythropoiesis stimulating agents (ESAs): meta-analysis of randomized trials in patients with chemotherapy-induced anemia. Joint ECCO 15 – 34th ESMO Multidisciplinary Congress, Berlin, Germany, September 2009. *Eur J Cancer* 2009;**7**:256.

Schwartzberg L, Yee L, Charu V, Tomita D, Rossi G, Senecal F. Comparable efficacy and safety of darbepoetin alfa 200 mug every 2 weeks and epoetin alfa 40,000 U weekly in patients with breast cancer: results of a randomized comparison. *J Support Oncol* 2005;**3**:30–1.

Sevinir B, Durmaz O. Once a week erythropoietin in children with cancer. *Pediatr Blood Cancer* 2004;**43**:491–2.

Shah B. Darbepoetin in cancer related anemia. 54th Annual Conference of the Indian Society of Haematology and Blood Transfusion (Haematacon), Mumbai, India, 2013.

Steensma DP, Dakhil SR, Novotny PJ, Sloan JA, Johnson DB, Anderson DM, *et al.* A randomized comparison of standard weekly epoetin alfa to every-3-week epoetin alfa and every-3-week darbepoetin alfa: a study of the Mayo Clinic Cancer Research Consortium (MCCRC). 51st Annual Meeting of the American Society of Hematology (ASH), New Orleans, LA, USA, December 2009. *Blood* 2009;**114**:abstract 3008.

Strauss H, Haensgen G, Dunst J, Hayward C, Koelbl H. Effects of anaemia correction with epoetin beta in patients with advanced cervical cancer and radiochemotherapy. *J Clin Oncol* 2005;**23**:S5121.

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). 34th Congress of the European Society for Medical Oncology (ESMO), Stockholm, Sweden, 2008. *Ann Oncol* 2008;**19**(Suppl. 8):viii277.

Taylor K, Ganly P, Charu V, Di Benedetto 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. *Blood* 2005;**106**:3556.

Tesch H, Liberati AM, Ifrah N. Assessment of cognitive effects of once-weekly epoetin alfa in anemic patients with hematologic malignancies receiving chemotherapy: results of the EPOLYM trial. *Haematologica* 2006;**91**(Suppl. 1):abstract 022.

Toma A, Chevret S, Kosmider O, Delaunay J, Stamatoullas A, Rose C, *et al.*, editors. 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. 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, USA, June 2013. *J Clin Oncol* 2013;**31**(Suppl.):7002.

Tzekova V, Koytchev R. Efficacy of epoetin zeta in patients with chemotherapy-induced anemia and hematological malignancies: interim results. *Haematologica* 2008;**93**:S444.

Tzekova V, Mihaylov G, Koytchev R. Epoetin zeta: efficacy data from an open-label, Phase III trial in patients with chemotherapyinduced anaemia. *Ann Oncol* 2008;**19**(Suppl. 8):278.

Van Groeningen CJ, Kok TC, Biesma B, Melissant CF, De Klerk G, Brok R, *et al.* Epoetin alfa and darbepoetin alfa in clinical practice in patients with chemotherapy induced anemia in the Netherlands (EVALUATE). *Eur J Cancer* 2011;**47**(Suppl. 1):237.

Vandebroek A, Gaede B, Altintas S, Smith K, Yao B, Schupp M, *et al.* A randomized open-label study of darbepoetin alfa administered every 3 weeks with or without parenteral iron in anemic subjects with nonmyeloid malignancies receiving chemotherapy. *J Clin Oncol* 2006;**24**:S8612.

Vandebroek A, Gaede B, Altintas S, Smith K, Yao B, Schupp M, *et al.* A randomized open-label study of darbepoetin alfa administered every 3 weeks with or without parenteral iron in anemic subjects with nonmyeloid malignancies receiving chemotherapy. *J Support Oncol* 2007;**5**:24–6.

Walter E, Ribnicsek E, Kutikova L. Economic evaluation of darbepoetin alfa (Aranesp) compared to epoetin alfa (Erypo) and epoetin beta (NeoRecormon) in the treatment of chemotherapy-induced anemia (CIA) in Austria. *Value Health* 2010;**13**:A377.

Waltzman RJ, Fesen M, Justice GR, Croot C, Williams D. Epoetin alfa 40,000 U QW vs darbepoetin alfa 200 mcg Q2W in anemic cancer patients receiving chemotherapy: preliminary results of a comparative trial. *J Clin Oncol* 2004;**22**:S8153.

Waltzman R, Williams D. Head-to-head comparison of epoetin alfa (EPO) 40,000 U QW vs. darbepoetin alfa (DARB) 200 µg Q2W in anemic cancer patients receiving chemotherapy (CT): final results of a planned interim analysis (IA). *Blood* 2004;**104**:4233.

Watanbabe 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. *Ann Oncol* 2006;**17**:294.

Youssef LA, Hussien DH, Sulaiman S. The effectiveness of a fixed low dose of erythropoietin (EPO) in anemic solid tumor patients receiving concomitant chemotherapy: a prospective, randomized, controlled study. 53rd Annual Meeting of the American Society of Hematology (ASH), San Diego, CA, USA, December 2011. Abstract 2092.

Quality-of-life review: excluded studies

Reason for exclusion: population (n = 9)

Abdelrazik N, Fouda M. Once weekly recombinant human erythropoietin treatment for cancer-induced anemia in children with acute lymphoblastic leukemia receiving maintenance chemotherapy: a randomized case-controlled study. *Hematology* 2007;**12**:533–41.

Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. *Oncologist* 2007;**12**:43–51.

Casadevall N, Durieux P, Dubois S, Hemery F, Lepage E, Quarre MC, *et al.* Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. *Blood* 2004;**104**:321–7.

Hoskin PJ, Robinson M, Slevin N, Morgan D, Harrington K, Gaffney C. Effect of epoetin alfa on survival and cancer treatment-related anemia and fatigue in patients receiving radical radiotherapy with curative intent for head and neck cancer. *J Clin Oncol* 2009;**27**:5751–6.

Lindholm E, Daneryd P, Korner U, Hyltander A, Fouladiun M, Lundholm K. Effects of recombinant erythropoietin in palliative treatment of unselected cancer patients. *Clin Cancer Res* 2004;**10**:6855–64.

Mystakidou K, Kalaidopoulou C, 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 Res* 2005;**25**:3495–500.

Norager CB, Jensen MB, Madsen MR, Qvist N, Laurberg S. Effect of darbepoetin alfa on physical function in patients undergoing surgery for colorectal cancer – a randomized, double-blind, placebo-controlled study. *Oncology* 2006;**71**:212–20.

Oliansky DM, Antin JH, Bennett JM, Deeg HJ, Engelhardt C, Heptinstall KV, *et al.* The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: an evidence-based review. *Biol Blood Marrow Transplant* 2009;**15**:137–72.

Smith RE, Aapro MS, Ludwig H, Pinter T, Smakal M, Ciuleanu TE, *et al.* Darbepoetin alfa 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. *J Clin Oncol* 2008;**26**:1040–50.

Reason for exclusion: intervention (n = 5)

Berndt E, Kallich J, McDermott A, Xu X, Lee H, Glaspy J. Reductions in anaemia and fatigue are associated with improvements in productivity in cancer patients receiving chemotherapy. *Pharmacoeconomics* 2005;**23**:505–14.

Blair S, Bardwell WA, Podbelewicz-Schuller Y, Mortimer JE. Correlation between hemoglobin and fatigue in women undergoing adjuvant chemotherapy without erythropoietin-stimulating-agent support. *Clin Breast Cancer* 2008;**8**:522–6.

Cheng Z, Wu JL, Chen JF. Clinical observation on the treatment of male neoplastic anemia with Yixuesheng capsule combined with recombination human erythropoietin. *Chin J Integr Med* 2009;**15**:63–5.

Gascon P, Pirker R, Del Mastro L, Durrwell L. Effects of CERA (continuous erythropoietin receptor activator) in patients with advanced non-small-cell lung cancer (NSCLC) receiving chemotherapy: results of a Phase II study. *Ann Oncol* 2010;**21**:2029–39.

Krzakowski M. Epoetin delta: efficacy in the treatment of anaemia in cancer patients receiving chemotherapy. *Clin Oncol* 2008;**20**:705–13.

Reason for exclusion: comparator (n = 11)

Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H, *et al.* Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. *J Clin Oncol* 2004;**22**:1301–7.

Balleari E, Rossi E, Clavio M, Congiu A, Gobbi M, Grosso M, *et al.* Erythropoietin plus granulocyte colony-stimulating factor is better than erythropoietin alone to treat anemia in low-risk myelodysplastic syndromes: results from a randomized single-centre study. *Ann Hematol* 2006;**85**:174–80.

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 alfa administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *J Clin Oncol* 2008;**26**:1611–18.

Canon JL, Vansteenkiste J, Bodoky G, Mateos MV, Bastit L, Ferreira J, *et al.* Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. *J Natl Cancer Inst* 2006;**98**:273–84.

Courneya KS, Jones LW, Peddle CJ, Sellar CM, Reiman T, Joy AA, *et al.* Effects of aerobic exercise training in anemic cancer patients receiving darbepoetin alfa: a randomized controlled trial. *Oncologist* 2008;**13**:1012–20.

Crawford J, Robert F, Perry MC, Belani C, Williams D, Anemia Prevention in NSCLC Group. A randomized trial comparing immediate versus delayed treatment of anemia with once-weekly epoetin alfa in patients with non-small cell lung cancer scheduled to receive first-line chemotherapy. *J Thorac Oncol* 2007;**2**:210–20.

Glaspy J, Henry D, Patel R, Tchekmedyian D, Applebaum S, Berdeaux D, *et al.* Effects of chemotherapy on endogenous erythropoietin levels and the pharmacokinetics and erythropoietic response of darbepoetin alfa: a randomised clinical trial of synchronous versus asynchronous dosing of darbepoetin alfa. *Eur J Cancer* 2005;**41**:1140–9.

Gupta S, Singh PK, Bhatt ML, Pant MC, Sundar S, Verma J, *et al.* Clinical benefits of two different dosing schedules of recombinant human erythropoietin in anemic patients with advanced head and neck cancer. *Biosci Trends* 2010;**4**:267–72.

Justice G, Kessler JF, Jadeja J, Campos L, Weick J, Chen CF, *et al.* A randomized, multicenter study of subcutaneous and intravenous darbepoetin alfa for the treatment of chemotherapy-induced anemia. *Ann Oncol* 2005;**16**:1192–8.

Larsson AM, Landberg G, Pahlman S, Albertsson M. Erythropoietin enhances response to treatment in patients with advanced breast cancer. *Acta Oncol* 2004;**43**:594–7.

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. *J Clin Oncol* 2011;**29**:97–105.

Reason for exclusion: outcomes (n = 20)

Bell D, Grimes D, Gurney H, Dalley D, Blackwell T, Fox R, *et al.* Outcomes and predicting response in anaemic chemotherapy patients treated with epoetin alfa. A multicentre, 4-month, open-label study in Australia and New Zealand. *Intern Med J* 2008;**38**:751–7.

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**:914–24.

Bohlius J, Langensiepen S, Schwarzer G, Seidenfeld J, Piper M, Bennett C, *et al.* Recombinant human erythropoietin and overall survival in cancer patients: results of a comprehensive meta-analysis. *J Natl Cancer Inst* 2005;**97**:489–98.

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, *et al.* Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet* 2009;**373**:1532–42. [Erratum published in *Lancet* 2009;**374**:28].

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 Syst Rev* 2009;**3**:CD007303.

Bohlius J, Trelle S, Weingart O, Schwarzer G, Brillant C, Clarke MJ, *et al.* Erythropoietin or darbepoetin for patients with cancer – meta-analysis based on individual patient data. *Cochrane Database Syst Rev* 2008;**3**:CD007303.

Devon KM, McLeod RS. Pre and peri-operative erythropoietin for reducing allogeneic blood transfusions in colorectal cancer surgery. *Cochrane Database Syst Rev* 2009;**1**:CD007148.

Duh MS, Weiner JR, White LA, Lefebvre P, Dreenberg PE. Management of anaemia – a critical and systematic review of the cost effectiveness of erythropoiesis-stimulating agents. *Pharmacoeconomics* 2008;**26**:99–120.

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**:231–42.

Henry DH, Gordan LN, Charu V, Wilhelm FE, Williams D, Xie J, *et al.* Randomized, open-label comparison of epoetin alfa extended dosing (80000 U Q2W) vs. weekly dosing (40000 U QW) in patients with chemotherapy-induced anemia. *Curr Med Res Opin* 2006;**22**:1403–13.

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). *Int J Radiat Oncol Biol Phys* 2007;**69**:1008–17.

Moyo V, Lefebvre P, Duh MS, Yektashenas B, Mundle S. Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: a meta-analysis. *Ann Hematol* 2008;**87**:527–36.

Reed SD, Radeva JI, Daniel DB, Fastenau JM, Williams D, Schulman KA. Early hemoglobin response and alternative metrics of efficacy with erythropoietic agents for chemotherapy-related anemia. *Curr Med Res Opin* 2005;**21**:1527–33.

Reed SD, Radeva JI, Daniel DB, Mody SH, Forlenza JB, McKenzie RS, *et al.* Economic evaluation of weekly epoetin alfa versus biweekly darbepoetin alfa for chemotherapy-induced anaemia – evidence from a 16-week randomised trial. *Pharmacoeconomics* 2006;**24**:479–94.

Rosenzweig MQ, Bender CM, Lucke JP, Yasko JM, Brufsky AM. The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. *J Pain Symptom Manage* 2004;**27**:185–90.

Schwartzberg L, Yee L, Charu V, Tomita D, Rossi G, Senecal F. Comparable efficacy and safety of darbepoetin alfa 200 mug every 2 weeks and epoetin alfa 40,000 U weekly in patients with breast cancer: results of a randomized comparison. *J Support Oncol* 2005;**3**(Suppl. 1):30–1.

Schwartzberg LS, Yee LK, Senecal FM, Charu V, Tomita D, Wallace J, *et al.* Symptom management and supportive care. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. *Oncologist* 2004;**9**:696–707.

Senecal FM, Yee L, Gabrail N, Charu V, Tomita D, Rossi G, *et al.* Treatment of chemotherapy-induced anemia in breast cancer: results of a randomized controlled trial of darbepoetin alfa 200 microg every 2 weeks versus epoetin alfa 40,000 U weekly. *Clin Breast Cancer* 2005;**6**:446–54.

Strauss HG, Haensgen G, Dunst J, Hayward CRW, Burger HU, Scherhag A, *et al.* Effects of anemia correction with epoetin beta in patients receiving radiochemotherapy for advanced cervical cancer. *Int J Gynecol Cancer* 2008;**18**:515–24.

Tonia T, Bohlius J. Ten years of meta-analyses on erythropoiesis-stimulating agents in cancer patients. *Cancer Treat Res* 2011;**157**:217–38.

Reason for exclusion: study design (n = 64)

Aapro M, Coiffier B, Dunst J, Österborg A, Burger HU. Effect of treatment with epoetin beta on short-term tumour progression and survival in anaemic patients with cancer: a meta-analysis. *Br J Cancer* 2006;**95**:1467–73.

Aapro M, Osterwalder B, Scherhag A, Burger HU. Epoetin-beta treatment in patients with cancer chemotherapy-induced anaemia: the impact of initial haemoglobin and target haemoglobin levels on survival, tumour progression and thromboembolic events. *Br J Cancer* 2009;**101**:1961–71.

Aapro M, Scherhag A, Burger HU. Effect of treatment with epoetin-beta on survival, tumour progression and thromboembolic events in patients with cancer: an updated meta-analysis of 12 randomised controlled studies including 2301 patients. *Br J Cancer* 2008;**99**:14–22.

Aapro MS, Dale DC, Blasi M, Sarokhan B, Ahmed F, Woodman RC. Epoetin alfa increases hemoglobin levels and improves quality of life in anemic geriatric cancer patients receiving chemotherapy. *Support Care Cancer* 2006;**14**:1184–94.

Ariganello O, Mancuso A, Di Molfetta M, Diana F, Beccaglia P, Cortesi E, *et al.* A new induction schedule of epoetin alfa 40.000 IU in anemic patients with advanced lung cancer. *Lung Cancer* 2004;**46**:119–24.

Azzara A, Carulli G, Galimberti S, Barate C, Fazzi R, Cervetti G, *et al.* High-dose (40,000 IU twice/week) alpha recombinant human erythropoietin as single agent in low/intermediate risk myelodysplastic syndromes: a retrospective investigation on 133 patients treated in a single institution. *Am J Hematol* 2011;**86**:762–7.

Badzek S, Curic Z, Krajina Z, Plestina S, Golubic-Cepulic B, Radman I. Treatment of cancer-related anemia. *Coll Antropol* 2008;**32**:615–22.

Beer TM, Bergenstock M, Birt K, Higano CS. Darbepoetin alfa administered every 4 weeks for anemia in patients with advanced prostate cancer. *Clin Genitourin Cancer* 2007;**5**:329–33.

Bennett CL. The blue cross blue shield assessment technology review: summary of findings. *Best Pract Res Clin Haematol* 2005;**18**:423–31.

Boccia R, Lillie T, Tomita D, Balducci L. The effectiveness of darbepoetin alfa administered every 3 weeks on hematologic outcomes and quality of life in older patients with chemotherapy-induced anemia. *Oncologist* 2007;**12**:584–93.

Bogdanos J, Karamanolakis D, Milathianakis K, Repousis P, Chloraki-Bobota A, Majed H, *et al.* Epoetin beta (NeoRecormon) corrects anaemia in patients with hormone-refractory prostate cancer and bone metastases. *Anticancer Res* 2004;**24**:1957–61.

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. *J Natl Cancer Inst* 2006;**98**:708–14.

Boogaerts M, Oberhoff C, Huinink WTB, Nowrousian MR, Hayward CRW, Burger HU. Epoetin beta (NeoRecormon (R)) therapy in patients with solid tumours receiving platinum and non-platinum chemotherapy: a meta-analysis. *Anticancer Res* 2006;**26**:479–84.

Boulaamane L, Goncalves A, Boutayeb S, Viens P, M'Rabti H, Bertucci F, *et al.* Prognostic impact of the combination of erythropoiesis-stimulating agents to cancer treatment: literature review. *Support Care Cancer* 2013;**21**:2359–69.

Burstein HJ, Parker LM, Keshaviah A, Doherty J, Partridge AH, Schapira L, *et al.* Efficacy of pegfilgrastim and darbepoetin alfa as hematopoietic support for dose-dense every-2-week adjuvant breast cancer chemotherapy. *J Clin Oncol* 2005;**23**:8340–7.

Cacic DL, Hervig T, Seghatchian J. Anemia treatment of lymphoproliferative malignancies with erypoiesis: an overview of state of the art. *Transfus Apheresis Sci* 2013;**48**:277–81.

Caocci G, La Nasa G, Efficace F. Health-related quality of life and symptom assessment in patients with myelodysplastic syndromes. *Exp Rev Hematol* 2009;**2**:69–80.

Cella D, Kallich J, McDermott A, Xu X. The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from rive randomized clinical trials. *Ann Oncol* 2004;**15**:979–86.

Cella D, Viswanathan H, Hays RD, Mendoza T, Stein K, Pasta D, *et al.* Development of the Brief Functional Capacity Tool (BFCT): a brief instrument to identify functional capacity deficits in anemic cancer patients. *J Support Oncol* 2007;**5**(Suppl. 2):10–11.

Cersosimo RJ, Jacobson DR. Epoetin alfa versus darbepoetin alfa in chemotherapy-related anemia. *Ann Pharmacother* 2006;**40**:58-65; quiz 169–70.

Chu E, Einhorn LH, Lefebvre P. Clinical benefits of once-weekly epoetin alfa in anemic patients with colorectal cancer receiving chemotherapy. *J Support Oncol* 2006;**4**:243–50.

Corapcioglu F, Aksu G, Basar EZ, Demirel A, Oncel S, Mutlu A. Recombinant human erythropoietin beta therapy: an effective strategy to reduce transfusion requirement in children receiving anticancer treatment. *Pediatr Hematol Oncol* 2008;**25**:509–21.

Cornes P, Coiffier B, Zambrowski J-J. Erythropoietic therapy for the treatment of anemia in patients with cancer: a valuable clinical and economic option. *Curr Med Res Opin* 2007;**23**:357–68.

Couture F, Turner AR, Melosky B, Xiu L, Plante RK, Lau CY, *et al.* Prior red blood cell transfusions in cancer patients increase the risk of subsequent transfusions with or without recombinant human erythropoietin management. *Oncologist* 2005;**10**:63–71.

da Silva Costa MT, Schimassek A, Fontes P, Castro V, Fernandes T, Oliveira A, *et al.* Erythropoiesis-stimulating agents in the treatment of anemia in patients with head and neck tumors ? Analysis of quality of life. *Radiother Oncol* 2006;**81**:S339.

Durmaz O, Demirkaya M, Sevinir B. Recombinant human erythropoietin: the effect of weekly dosing on anemia, quality of life, and long-term outcomes in pediatric cancer patients. *Pediatr Hematol Oncol* 2011;**28**:461–8.

Esquerdo G, Llorca C, Cervera JM, Orts D, Juarez A, Carrato A. Effectiveness of darbepoetin alfa in a cohort of oncology patients with chemotherapy-induced anaemia. Relationship between variation in three fatigue-specific quality of life questionnaire scores and change in haemoglobin level. *Clin Transl Oncol* 2011;**13**:341–7.

Eton DT, Cella D. Do erythropoietic-stimulating agents relieve fatigue? A review of reviews. *Cancer Treat Res* 2011;**157**:181–94.

Fagnoni P, Limat S, Chaigneau L, Briaud S, Schmitt B, Merrouche Y, *et al.* Clinical and economic impact of epoetin in adjuvant-chemotherapy for breast cancer. *Support Care Cancer* 2006;**14**:1030–7.

Folloder J. Effects of darbepoetin alfa administered every two weeks on hemoglobin and quality of life of patients receiving chemotherapy. *Oncol Nurs Forum* 2005;**32**:81–91.

Gascon P. Evaluating erythropoietic agents for the treatment of anaemia in the oncology setting. *Eur J Cancer* 2005;**41**:2601–12.

Gaston KE, Kouba E, Moore DT, Pruthi RS. The use of erythropoietin in patients undergoing radical prostatectomy: effects on hematocrit, transfusion rates and quality of life. *Urol Int* 2006;**77**:211–15.

Glaspy J, Crawford J, Vansteenkiste J, Henry D, Rao S, Bowers P, *et al.* Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. *Br J Cancer* 2010;**102**:301–15.

Glaspy JA. Randomized controlled trials of the erythroid-stimulating agents in cancer patients. *Cancer Treat Res* 2011;**157**:195–215.

Gregory SA. Efficacy of darbepoetin alfa in the treatment of chemotherapy-induced anemia in non-Hodgkin's lymphoma. *Support Cancer Ther* 2006;**3**:232–9.

Jones M, Schenkel B, Just J, Fallowfield L. Epoetin alfa improves quality of life in patients with cancer: results of metaanalysis. *Cancer* 2004;**101**:1720–32. [Erratum published in *Cancer* 2005;**103**:1984].

Kallich J, McDermott A, Xu X, Fayers P, Cella D. The relationship between patient knowledge of hemoglobin levels and health-related quality of life. *Qual Life Res* 2006;**15**:57–68.

Kimel M, Leidy NK, Mannix S, Dixon J. Does epoetin alfa improve health-related quality of life in chronically ill patients with anemia? Summary of trials of cancer, HIV/AIDS, and chronic kidney disease. *Value Health* 2008;**11**:57–75.

Larsson G, Janson ET. Anemia in patients with midgut carcinoid, treated with alpha interferon: effects by erythropoietin treatment on the perceived quality of life. *Eur J Cancer Care* 2008;**17**:200–4.

Latagliata R, Oliva EN, Volpicelli P, Carmosino I, Breccia M, Vincelli I, *et al.* Twice-weekly high-dose rHuEpo for the treatment of anemia in patients with low-risk myelodysplastic syndromes. *Acta Haematol* 2008;**120**:104–7.

Ludwig H, Crawford J, Österborg A, Vansteenkiste J, Henry DH, Fleishman A, *et al.* Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. *J Clin Oncol* 2009;**27**:2838–47.

Lyman GH, Glaspy J. Are there clinical benefits with early erythropoietic intervention for chemotherapy-induced anemia? A systematic review. *Cancer* 2006;**106**:223–33.

Maisnar V, Chroust K. Treatment of associated anemia in different hematological disorders with epoetin alpha. *Neoplasma* 2004;**51**:379–84.

Michallet M, Goldet K, Sobh M, Morisset S, Chelghoum Y, Thomas X, *et al.* Prospective study of erythropoietin use on quality of life and cost effectiveness in acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation patients. *Cancer* 2013;**119**:107–14.

Moul JW, Dawson N. Quality of life associated with treatment of castration-resistant prostate cancer: a review of the literature. *Cancer Invest* 2012;**30**:1–12.

Newland AM, Black CD. Tumor progression associated with erythropoiesis-stimulating agents. *Ann Pharmacother* 2008;**42**:1865–70.

Ohashi Y, Uemura Y, Fujisaka Y, Sugiyama T, Ohmatsu H, Katsumata N, *et al.* Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: individual patient data from Japanese randomized, placebo-controlled trials. *Cancer Sci* 2013;**104**:481–5.

Oliva EN, Nobile F, Alimena G, Specchia G, Danova M, Rovati B, *et al.* Darbepoetin alfa for the treatment of anemia associated with myelodysplastic syndromes: efficacy and quality of life. *Leuk Lymphoma* 2010;**51**:1007–14.

Ots PMS, Carrizosa CL, Perez AR, de Dios Saez Garrido J, Perez JMD. Darbepoetin versus epoetin alfa for the correction of anemia in cancer patients receiving radiotherapy or chemoradiotherapy treatment. *Clin Med Oncol* 2008;**2**:393–9.

Palumbo A, Petrucci MT, Lauta VM, Musto P, Caravita T, Barbui AM, *et al.* Correlation between fatigue and hemoglobin level in multiple myeloma patients: results of a cross-sectional study. *Haematologica* 2005;**90**:858–60.

Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Addition of iron to erythropoiesis-stimulating agents in cancer patients: a meta-analysis of randomized trials. *J Cancer Res Clin Oncol* 2012;**138**:179–87.

Quirt I, Kovacs M, Couture F, Turner AR, Noble M, Burkes R, *et al.* Patients previously transfused or treated with epoetin alfa at low baseline hemoglobin are at higher risk for subsequent transfusion: an integrated analysis of the Canadian experience. *Oncologist* 2006;**11**:73–82.

Reinhardt U, Tulusan A, Angermund R, Lutz H. Increased hemoglobin levels and improved quality-of-life assessments during epoetin alfa treatment in anemic cancer patients: results of a prospective, multicenter German trial. *Oncologist* 2005;**10**:225–37.

Reinhardt U, Tulusan A, Angermund R, Lutz H. Symptom management and supportive care. Increased hemoglobin levels and improved quality-of-life assessments during epoetin alfa treatment in anemic cancer patients: results of a prospective, multicenter German trial. *Oncologist* 2005;**10**:225–37.

Revicki DA, Stull D, Vernon M, Rader M, Tomita D, Viswanathan HN. Assessing the effect of darbepoetin alfa on patient-reported fatigue in chemotherapy-induced anemia in four randomized, placebo-controlled clinical trials. *Qual Life Res* 2012;**21**:311–21.

Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, *et al.* American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood* 2010;**116**:4045–59.

Ross SD, Allen E, Henry DH, Seaman C, Sercus B, Goodnough LT. Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature. *Clin Ther* 2006;**28**:801–31.

Steensma DP, Loprinzi CL. Epoetin alfa and darbepoetin alfa go head to head. *J Clin Oncol* 2006;**24**:2232–6.

Stephens JM, Gramegna P, Laskin B, Botteman MF, Pashos CL. Chronic lymphocytic leukemia: economic burden and quality of life: literature review. *Am J Ther* 2005;**12**:460–6.

Stull DE, Vernon MK, Legg JC, Viswanathan HN, Fairclough D, Revicki DA. Use of latent growth curve models for assessing the effects of darbepoetin alfa on hemoglobin and fatigue. *Contemp Clin Trials* 2010;**31**:172–9.

Tonelli M, Hemmelgarn B, Reiman T, Manns B, Reaume MN, Lloyd A, *et al.* Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. *CMAJ* 2009;**180**:E62–71.

Vansteenkiste J, Glaspy J, Henry D, Ludwig H, Pirker R, Tomita D, *et al.* Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: study-level and patient-level meta-analyses. *Lung Cancer* 2012;**76**:478–85.

Vansteenkiste J, Wauters I, Elliott S, Glaspy J, Hedenus M. Chemotherapy-induced anemia: the story of darbepoetin alfa. *Curr Med Res Opin* 2013;**29**:325–37.

Yang S, Jun M, Hong-Li Z, Jian-Min W, Chun W, Lu-Gui Q, *et al.* A multi-center open-labeled study of recombinant erythropoietin-beta in the treatment of anemic patients with multiple myeloma, low-grade non-Hodgkin's lymphoma, or chronic lymphocytic leukemia in Chinese population. *Int J Hematol* 2008;**88**:139–44.

Reason for exclusion: study design (systematic reviews of randomised controlled trials that were scrutinised for references) (n = 8)

Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Österborg A, *et al.* EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur J Cancer* 2007;**43**:258–70.

Kvam AK, Fayers P, Hjermstad M, Gulbrandsen N, Wisloff F. Health-related quality of life assessment in randomised controlled trials in multiple myeloma: a critical review of methodology and impact on treatment recommendations. *Eur J Haematol* 2009;**83**:279–89.

Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J Natl Cancer Inst Monogr* 2004;(32):40–50.

Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev* 2010;**7**:CD006704.

Ross SD, Allen IE, Probst CA, Sercus B, Crean SM, Ranganathan G. Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: a systematic review and meta-analysis. *Oncologist* 2007;**12**:1264–73.

Shehata N, Walker I, Meyer R, Haynes AE, Imrie K, Cancer Care Ontario Hematology Disease Site Group. The use of erythropoiesis-stimulating agents in patients with non-myeloid hematological malignancies: a systematic review. *Ann Hematol* 2008;**87**:961–73.

Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, *et al.* Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2012;**12**:CD003407.

Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al.* A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007;**11**(13).

Reason for exclusion: abstract only (n = 54)

Benefits of epoetin alfa for cancer patients' quality of life are confirmed after modelling to account for missing data. *Curr Med Res Opin* 2005;**21**(Suppl. 2):S6–8.

Darbepoetin during RT boosts Hb level, with QOL benefit. *Oncol News Int* 2006;**15**:37.

Epoetins and darbepoetin alfa in malignant disease. *Drug Ther Bull* 2004;**42**:21–3.

Meta-analysis of the effects of epoetin alfa treatment on quality of life in anaemic cancer patients. *Curr Med Res Opin* 2005;**21**(Suppl. 2):16–18.

Retacrit (epoetin zeta) is an effective treatment for chemotherapy-induced anaemia. *EJHP Pract* 2009;**15**:38.

Treating anaemia with epoetin alfa is associated with improvements in quality of life in cancer patients receiving chemotherapy. *Curr Med Res Opin* 2005;**21**(Suppl. 2):S9–11.

Aapro M, Scherhag A, Osterwalder B, Ukarma L, Burger HU. Epoetin beta treatment in patients with cancer chemotherapy induced anaemia: the impact of initial haemoglobin and target haemoglobin levels on survival, tumour progression and thromboembolic events. 2009 International MASCC/IS00 Symposium, Rome, Italy, June 2009.

Addeo R, Caraglia M, Frega N, Del Prete S. Two faces for Janus: recombinant human erythropoiesis-stimulating agents and cancer mortality. *Exp Rev Hematol* 2009;**2**:513–15.

Altintas S, Bastit L, Vandebroek A, Mossman T, Suto T, Gaede B. Analysis of quality of life responses by efficacy response status in cancer patients with chemotherapy-induced anaemia who received darbepoetin alfa 500 mcg every 3 weeks and IV iron. *Haematologica* 2007;**92**:286–7.

Anonymous. Highlights. *CMAJ* 2009;**180**:1085.

Antonadou D, Kyprianou C, Apostolou D, Coliarakis N, Athanasiou H, Papadopoulos V, *et al.* A multicenter, open study evaluating the impact of darbepoetin alfa on anaemia and quality of life, in cancer patients undergoing radiotherapy. *EJC Suppl* 2005;**3**:374.

Auerbach M, Silberstein PT, Webb RT, Averyanova S, Ciuleanu TE, Cam L, *et al.* Darbepoetin alfa (DA) 500 mcg or 300 mcg once every three weeks (Q3W) with or without iron in patients (PTS) with chemotherapy-induced anemia (CIA). *Ann Oncol* 2008;**19**(S8):3.

Blumberg N, Heal JM. Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet* 2004;**363**:80–1; author reply 81–2.

Brett AS. An erythropoietin-stimulating agent for cancer-related anemia – no benefit. *J Watch Gen Med* 8 April 2008. URL: www.jwatch.org/jw200804080000003/2008/04/08/erythropoietin-stimulating-agent-cancer-related (accessed 28 September 2015).

Bruun KH, Norgaard A, Johansson P, Daugaard G, Sorensen M. HaemOPtimal: randomized feasibility study of the optimal haemoglobin trigger for red blood cell transfusion (RBC) of anaemic cancer patients (PTS) treated with chemotherapy (CT). 12th Annual NATA Symposium, Dublin, Ireland, April 2011. *Tranfus Altern Transfus Med* 2011;**12**:19–20.

Burton MJ, Deschler DG, Rosenfeld RM. Extracts from The Cochrane Library: erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer. *Otolaryngol Head Neck Surg* 2009;**141**:438–41.

Caravita T, Siniscalchi A, Montanaro M, Niscola P, Stasi R, Amadori S, *et al.* High-dose epoetin alfa as induction treatment for severe anemia in multiple myeloma patients. *Int J Hematol* 2009;**90**:270–2.

Charu V, Belani C, Gill A, Bhatt M, Ben-Jacob A, Tomita D, *et al.* A controlled, randomized, open-label study to evaluate the effects of every-2-week darbepoetin alfa for anemia of cancer. *J Support Oncol* 2005;**3**(Suppl. 1):12–13.

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. *J Support Oncol* 2005;**3**(Suppl. 1):14–15.

Dintinjana RD, Nacinovic AD, Dintinjana M, Petranovic D. Influence of anaemia on clinical symptoms, quality of life and cognitive functions in chemotherapy naive cancer patients. IPOS 12th World Congress of Psycho-Oncology, Quebec City, QC, Canada, May 2010. *Psychooncology* 2010;**19**(Suppl. 2):S234.

Engert M, Haverkamp H, Borchmann P, Josting A, Fuchs M, Diehl V. A prospectively randomized placebo-controlled trial of epoetin-a in patients with advanced-stage Hodgkin lymphoma: final analysis of the GHSG HD15-EPO trial. 14th Congress of the European Hematology Association, Berlin, Germany, June 2009. *Haematologica* 2009;**94**:438.

Fagim M, Dina S, Svetlana D. Anaemic syndrome correction in patients receiving chemoradiation therapy with eprex for uterine cervical cancer. *Radiother Oncol* 2011;**99**:S308.

Gabrilove J, Paquette R, Lyons RM, Mushtaq C, Sekeres MA, Lam H, *et al.* The efficacy and safety of darbepoetin alfa for treating anemia in low-risk myelodysplastic syndrome patients: results after 53/55 weeks. *J Support Oncol* 2007;**5**(Suppl. 2):14–15.

Gascon P. Intravenous iron: supplement or substitute to ESAs? *Tumor Biol* 2012;**33**:S62–3.

Green D. Erythropoietin for myelodysplastic syndromes. *J Watch Oncol Hematol* 20 October 2009. URL: www.jwatch.org/oh200910200000003/2009/10/20/erythropoietin-myelodysplastic-syndromes (accessed 28 September 2015).

Gregory SA, Blayney DW, Vadhan-Raj S, Tomita DK, Rossi G, Mirtsching B. Efficacy of darbepoetin alfa in the treatment of chemotherapy-induced anemia in non-Hodgkin's lymphoma. *J Support Oncol* 2005;**3**(Suppl. 1):24–5.

Gupta S, Singh PK, Bhatt ML, Pant MC, Sundar S, Verma J, *et al.* Clinical benefits of epoetin beta in patients with advanced stage hormone refractory prostate cancer. *Eur Urol Suppl* 2011;**10**:337.

Hassan MA, Sleem MM. Phase II trial comparing darbepoetin alfa every 3-week versus weekly epoetin alfa for the treatment of chemotherapy-induced anemia. *J Clin Oncol* 2009;**27**(Suppl. 1):e20724.

Hellstrm-Lindberg E. Erythropoiesis-stimulating agents in myelodysplastic syndromes. *Leuk Lymphoma* 2010;**51**:1155–6.

Henry DH, Dahl NV, Auerbach MA. Thrombocytosis and venous thromboembolism in cancer patients with chemotherapy induced anemia may be related to ESA induced iron restricted erythropoiesis and reversed by administration of IV iron. *Am J Hematol* 2012;**87**:308–10.

Heras P, Hatzopoulos A, Mitsibounas D. Effectivness of recombinant human erythropoietin (epoetin beta, EPO) in improving hematological parameters and QOL in patients with chemotherapy-induced anemia. A double-blind, parallel-group, dose-finding study. *EJC Suppl* 2005;**3**:373.

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. *J Support Oncol* 2005;**3**(Suppl. 4):10–11.

Kaanders JH, der Kogel V. Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet* 2004;**363**:78–9; author reply 81–2.

Katsumata N, Fujiwara Y, Saijo N, Ohashi Y. Once-weekly epoetin beta improves hemoglobin and quality of life in anemic cancer patients receiving chemotherapy. *EJC Suppl* 2005;**3**:375.

Katsumata N, Fujiwara Y, Sugiyama T, Goto I, Ohmatsu H, Okamoto R, *et al.* Erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anemia and mortality: a meta-analysis of individual patient data from Japanese randomized trials. *Eur J Cancer* 2011;**47**:S242.

Leyland-Jones B, Mahmud S. Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet* 2004;**363**:80–2.

Mel JR, Salar A, Rodriguez CA, Alegre A, Gonzalez A, Cassinello J, *et al.* Weekly fixed dose of darbepoetin alfa (DA) is efficacious and improves health-related quality of life in patients with chemotherapy induced anemia (CIA). On behalf of the AMG-DAR-2002-01 study group. *Ann Oncol* 2006;**17**:292–3.

Mhaskar R, Wao H, Kumar A, Miladinovic B, Djulbegovic B. Role of iron supplementation to erythropoiesis stimulating agents in the management of chemotherapy-induced anemia in cancer patients: a systematic review and meta-analysis. *Blood* 2010;**116**:2055.

Michallet M, Goldet K, Morisset S, Sobh M, Chelghoum Y, Thomas X, *et al.* Erythropoietin use in patients with AML or undergoing allogeneic HSCT significantly improves quality of life and reduces red blood cells and platelets transfusions without any survival effect. *Blood* 2010;**116**:3810.

Michallet M, Goldet K, Morisset S, Sobh M, Ducastelle S, Chelghoum Y, *et al.* Erythropoietin use in patients undergoing allogeneic HSCT does not impact on quality of life, reduces red blood cells transfusions without any survival effect. 37th Annual Congress of the European Group for Blood and Marrow Transplantation (EBMT), Paris, France, April 2011.

Nitz U, Oberhoff C, Reimer T, Schumacher C, Hackmann J, Warm M, *et al.* Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: a safety analysis from the Phase III ARA plus trial. *Cancer Res* 2009;**69**(Suppl.):4100.

Oliva EN, Latagliata R, Danova M, Specchia G, Impera S, Rovati B, *et al.* Darbepoetin for the treatment of anemia of myelodysplastic syndromes: efficacy and quality of life. *Leuk Res* 2007;**31**:S117–18.

Oliva EN, Latagliata R, Danova M, Vincelli I, Rovati B, Ronco F, *et al.* Darbepoetin for the treatment of anemia of myelodysplastic syndromes: efficacy and improvements in quality of life. *Blood* 2006;**108**:754A.

Ordonez A, Gonzalez-Baron M, De Castro J, Isla D, Sanchez A, Arrivi A, *et al.* Epoetin beta (NeoRecormon (R)) prevents anaemia and improves quality of life in lung cancer patients receiving platinum-based chemotherapy. *Lung Cancer* 2005;**49**:S339.

Patrick D, Gagnon DD, Zagari MJ. Improvements in quality of life associated with epoetin alfa treatment are clinically, as well as statistically, significant. *Curr Med Res Opin Suppl* 2005;**21**:S3–5.

Ross SD, Allen IE, Henry D, Seaman C, Sercus B, Goodnough LT. Clinical benefits and risks associated with epoetin (alfa/beta) and darbepoetin alfa in patients with chemotherapy-induced anemia: a systematic review of the literature. *J Support Oncol* 2007;**5**(Suppl. 2):20–1.

Sakai H, Saijo N, Ohashi Y. Once-weekly epoetin beta improves hemoglobin levels and quality of life in patients with chemotherapy-induced anemia: a randomized, double-blind, parallel-group, dose-finding study. *Ann Oncol* 2004;**15**:219.

Steensma DP, Dakhil SR, Novotny PJ, Sloan JA, Johnson DB, Anderson DM, *et al.* A randomized comparison of standard weekly epoetin alfa to every-3-week epoetin alfa and every-3-week darbepoetin alfa: a study of the Mayo Clinic Cancer Research Consortium (MCCRC). 51st Annual Meeting of the American Society of Hematology (ASH), New Orleans, LA, USA, December 2009. *Blood* 2009;**114**:abstract 3008.

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). *Ann Oncol* 2008;**19**:viii277.

Wilkinson PM, Antonopoulos M, Lahousen M, Lind M, Kosmidis P. Epoetin alfa in platinum-treated ovarian cancer patients: results of a multinational, multicentre, randomised trial. *Br J Cancer* 2006;**94**:947–54.

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. *J Clin Oncol* 2009;**27**:644–6.

Witzig TE, Silbertstein PT, Loprinzi CL, Spigel DR. Weekly erythropoietin improves anemia associated with cancer treatment. *J Clin Outcomes Manage* 2004;**11**:751–2.

Yoshizaki A, Kumagai S, Sugiyama T, Goto I, Saito H, Ariyoshi Y, *et al.* A Phase III, randomized double-blind placebocontrolled study of epoetin beta in lung and gynecological cancer receiving platinum-based chemotherapy: Japan erythropoietin study group. 35th ESMO Congress, Milan, Italy, October 2010. *Ann Oncol* 2010;**21**:viii385.

Youssef LA, Hussien DH, Sulaiman S. The effectiveness of a fixed low dose of erythropoietin (EPO) in anemic solid tumor patients receiving concomitant chemotherapy: a prospective, randomized, controlled study. 53rd Annual Meeting of the American Society of Hematology (ASH), San Diego, CA, USA, 2011. *Blood* 2011;**118**:abstract 2092.

Reason for exclusion: duplicate (n = 6)

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. *J Natl Cancer Inst* 2006;**98**:708–14.

Palumbo A, Petrucci MT, Lauta VM, Musto P, Caravita T, Barbui AM, *et al.* Correlation between fatigue and hemoglobin level in multiple myeloma patients: results of a cross-sectional study. *Haematologica* 2005;**90**:858–60.

Schwartzberg LS, Yee LK, Senecal FM, Charu V, Tomita D, Wallace J, *et al.* Symptom management and supportive care. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. *Oncologist* 2004;**9**:696–707.

Steensma DP, Dakhil SR, Dalton R, Kahanic SP, Kugler JW, Stella PJ, *et al.* A 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: a study of the Mayo Clinic Cancer Research Consortium (MCCRC). 51st Annual Meeting of the American Society of Hematology (ASH), New Orleans, LA, USA, December 2009. *Blood* 2009;**114**:abstract 630.

Vansteenkiste J, Wauters I, Elliott S, Glaspy J, Hedenus M. Chemotherapy-induced anemia: the story of darbepoetin alfa. *Curr Med Res Opin* 2013;**29**:325–37.

Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al.* A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007;**11**(13).

Reason for exclusion: language (n = 2)

Ludwig H, Auberger T, Burghuber OC, Gnant M, Hopfinger G, Jager U, et al. Replacement of erythropoese stimulated protein in anemic patients with malignant disease. *Wien Klin Wochenschr* 2008;**120**:507–13.

Zemelka T, Rolski J, Ziobro M, Michalczyk A. Opinion on influence of erythropoietin on quality of life and survival in patients with advanced non-small cell lung cancer. *Contemp Oncol* 2007;**11**:37–40.

Reason for exclusion: no usable data (n = 11)

Earlier initiation of treatment recommended in using erythropoietic agents for chemotherapy-induced anemia. *J Support Oncol* 2004;**2**:319.

Anthony LB, Gabrail NY, Ghazal H, Woytowitz DV, Flam MS, Drelichman A, *et al.* IV iron sucrose for cancer and/or chemotherapy-induced anemia in patients treated with erythropoiesisstimulating agents. *Community Oncol* 2011;**8**:270–8.

Arcasoy MO, Amin K, Chou SC, Haroon ZA, Varia M, Raleigh JA. Erythropoietin and erythropoietin receptor expression in head and neck cancer: relationship to tumor hypoxia. *Clin Cancer Res* 2005;**11**:20–7.

Borg S, Glenngard AH, Österborg A, Persson U. The cost-effectiveness of treatment with erythropoietin compared to red blood cell transfusions for patients with chemotherapy induced anaemia: a Markov model. *Acta Oncol* 2008;**47**:1009–17.

Clark J, Schergen A. Advantages of every-3-week dosing of erythropoietic agents to manage chemotherapy-induced anemia. *Oncology* 2006;**20**:795–800.

Dale DC. The benefits of haematopoietic growth factors in the management of gynaecological oncology. *Eur J Gynaecol Oncol* 2004;**25**:133–44.

Greaves P, Agrawal S. Safe and efficacious use of recombinant human erythropoietin in malignancy. *Clin Med* 2007;**7**:617–20.

Jadersten M, Malcovati L, Dybedal I, Della Porta MG, Invernizzi R, Montgomery SM, *et al.* Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. *J Clin Oncol* 2008;**26**:3607–13.

Jadersten M, Montgomery SM, Dybedal I, Porwit-MacDonald A, Hellstrom-Lindberg E. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. *Blood* 2005;**106**:803–11.

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. *J Natl Cancer Inst* 2013;**105**:1018–26.

Roungrong J, Teerawattananon Y, Chaikledkaew U. Cost–utility analysis of recombinant human erythropoietin in anemic cancer patients induced by chemotherapy in Thailand. *J Med Assoc Thai* 2008;**91**(Suppl. 2):119–25.

Reason for exclusion: unobtainable (n = 1)

Adamson JW. Erythropoietic-stimulating agents: the cancer progression controversy and collateral damage to the blood supply. *Transfusion* 2009;**49**:824–6.

Reason for exclusion: unlicensed dose (n = 36)

Aapro M, Scherhag A, Burger HU. Effect of treatment with epoetin-beta on survival, tumour progression and thromboembolic events in patients with cancer: an updated meta-analysis of 12 randomised controlled studies including 2301 patients. *Br J Cancer* 2008;**99**:14–22.

Aapro M, Scherhag A, Osterwalder B, Ukarma L, Burger HU. Epoetin beta treatment in patients with cancer chemotherapy induced anaemia: the impact of initial haemoglobin and target haemoglobin levels on survival, tumour progression and thromboembolic events. International MASCC/IS00 Symposium, Rome, Italy, June 2009. *Support Care Cancer* 2009;**17**:1036–7.

Berndt E, Kallich J, McDermott A, Xu X, Lee H, Glaspy J. Reductions in anaemia and fatigue are associated with improvements in productivity in cancer patients receiving chemotherapy. *Pharmacoeconomics* 2005;**23**:505–14.

Blohmer JU, Paepke S, Sehouli J, Boehmer D, Kolben M, Wurschmidt 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. *J Clin Oncol* 2011;**29**:3791–7.

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**:848–55.

Chang J, Couture F, Young S, McWatters KL, Lau CY. Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. *J Clin Oncol* 2005;**23**:2597–605.

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. *Support Cancer Ther* 2004;**2**:52–8.

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**:727–37.

Christodoulou C, Dafni U, Aravantinos G, Koutras A, Samantas E, Karina M, *et al.* Effects of epoetin-alpha on quality of life of cancer patients with solid tumors receiving chemotherapy. *Anticancer Res* 2009;**29**:693–702.

Engert A, Josting A, Haverkamp H, Villalobos M, Lohri A, Sokler M, *et al.* Epoetin alfa in patients with advanced-stage Hodgkin's lymphoma: results of the randomized placebo-controlled GHSG HD15EPO trial. *J Clin Oncol* 2010;**28**:2239–45.

Fujisaka Y, Sugiyama T, Saito H, Nagase S, Kudoh S, Endo M, *et al.* Randomised, Phase III trial of epoetin-beta to treat chemotherapy-induced anaemia according to the EU regulation. *Br J Cancer* 2011;**105**:1267–72.

Glaspy J, Vadhan-Raj S, Patel R, Bosserman L, Hu E, Lloyd RE, *et al.* Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia: the 20030125 study group trial. *J Clin Oncol* 2006;**24**:2290–7.

Gupta S, Singh PK, Bisth SS, Bhatt ML, Pant M, *et al.* Role of recombinant human erythropoietin in patients of advanced cervical cancer treated 'by chemoradiotherapy.' *Cancer Biol Ther* 2009;**8**:13–17.

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. *Curr Med Res Opin* 2009;**25**:2109–20.

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. *J Clin Oncol* 2005;**23**:5960–72.

Milroy R, Bajetta E, van den Berg PM, O'Brien MER, 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. *Eur J Clin Med Oncol* 2011;**3**:49–56.

Nagel S, Kellner O, Engel-Riedel W, Guetz S, Schumann C, Gieseler F, *et al.* Addition of darbepoetin alfa to dose-dense chemotherapy: results from a randomized Phase II trial in small-cell lung cancer patients receiving carboplatin plus etoposide. *Clin Lung Cancer* 2011;**12**:62–9.

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. *Clin Breast Cancer* 2005;**5**:439–46.

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. *J Clin Oncol* 2008;**26**:2342–9.

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**:935–43.

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. *J Clin Oncol* 2006;**24**:3583–9.

Reed SD, Radeva JI, Daniel DB, Fastenau JM, Williams D, Schulman KA. Early hemoglobin response and alternative metrics of efficacy with erythropoietic agents for chemotherapy-related anemia. *Curr Med Res Opin* 2005;**21**:1527–33.

Rosenzweig MQ, Bender CM, Lucke JP, Yasko JM, Brufsky AM. The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. *J Pain Symptom Manage* 2004;**27**:185–90.

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**:197–205.

Savonije JH, van Groeningen CJ, van Bochove A, Honkoop AH, van Felius CL, Wormhoudt LW, *et al.* 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. *Eur J Cancer* 2005;**41**:1560–9.

Savonije JH, van Groeningen CJ, Wormhoudt LW, Giaccone G. Early intervention with epoetin alfa during platinum-based chemotherapy: an analysis of the results of a multicenter, randomized, controlled trial based on initial hemoglobin level. *Oncologist* 2006;**11**:206–16.

Schwartzberg LS, Yee LK, Senecal FM, Charu V, Tomita D, Wallace J, *et al.* A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. *Oncologist* 2004;**9**:696–707.

Senecal FM, Yee L, Gabrail N, Charu V, Tomita D, Rossi G, *et al.* Treatment of chemotherapy-induced anemia in breast cancer: results of a randomized controlled trial of darbepoetin alfa 200 microg every 2 weeks versus epoetin alfa 40,000 U weekly. *Clin Breast Cancer* 2005;**6**:446–54.

Thomas G, Ali S, Hoebers FJ, 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. *Gynecol Oncol* 2008;**108**:317–25.

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. *Jpn J Clin Oncol* 2009;**39**:163–8.

Wagner LM, Billups CA, Furman WL, Rao BN, Santana VM. Combined use of erythropoietin and granulocyte colony-stimulating factor does not decrease blood transfusion requirements during induction therapy for high-risk neuroblastoma: a randomized controlled trial. *J Clin Oncol* 2004;**22**:1886–93.

Waltzman R, Croot C, Justice GR, Fesen MR, Charu V, Williams D. Randomized comparison of epoetin alfa (40,000 U weekly) and darbepoetin alfa (200 microg every 2 weeks) in anemic patients with cancer receiving chemotherapy. *Oncologist* 2005;**10**:642–50.

Wilkinson PM, Antonopoulos M, Lahousen M, Lind M, Kosmidis P. Epoetin alfa in platinum-treated ovarian cancer patients: results of a multinational, multicentre, randomised trial. *Br J Cancer* 2006;**94**:947–54.

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. *J Clin Oncol* 2009;**27**:644–6.

Witzig TE, Silberstein PT, Loprinzi CL, Sloan JA, Novotny PJ, Mailliard JA, *et al.* Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. *J Clin Oncol* 2005;**23**:2606–17.

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. *J Clin Oncol* 2007;**25**:1027–32.

Wilson and colleagues[2] excluded studies

Reason for exclusion: population (n = 10)

Blohmer JU, Wurschmidt F, Petry KU, Weise G, Sehouli J, Kimmig R. 6th interim analysis of a prospective, randomised, open and controlled AGO- and NOGGO-intergroup study: sequential adjuvant chemo-radiotherapy with vs without epoetin alfa with patients with high-risk cervival cancer. *Proc Am Soc Clin Oncol* 2003;**22**:447.

Henke M, Guttenberger R, Barke A, Pajonk F, Potter R, Frommhold H. Erythropoietin for patients undergoing radiotherapy: a pilot study. *Radiother Oncol* 1999;**50**:185–90.

Henke M, Laszig R, Rube C, Schafer 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.

Henze G, Michon J, Morland B, Perek D, Rizzari C, Zoubek A. Phase III randomised study: efficacy of epoetin alfa in reducing blood transfusions in newly diagnosed pediatric cancer patients receiving chemotherapy. *Proc Am Soc Clin Oncol* 2002;**21**:387a.

Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes, Ferrini PR, Grossi A, Vannucchi AM, Barosi G, Guarnone R, *et al.* A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. *Br J Haematol* 1998;**103**:1070–4.

Rose E, Rai KR, Revicki DA, Brown R, Rebalndo J. Clinical and health status assessments in anemia chronic lymphocytic leukemia (CLL) patients treated with epoetin alfa (EPO). *Blood* 1994;**84**(Suppl. A):526a.

Smith RE Jr, Tchekmedyian NS, Chan D, Meza LA, Northfelt DW, Patel R, *et al.* A dose- and schedule-finding study of darbepoetin alpha for the treatment of chronic anaemia of cancer. *Br J Cancer* 2003;**88**:1851–8.

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 randomised, open-labelled, Phase II trial. *Br J Cancer* 1998;**77**:1996–2002.

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. GM/EPO MDS Study Group. *Blood* 2000;**95**:1175–9.

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**:155–9.

Reason for exclusion: duplicate (n = 2)

Casadevall N, Durieux P, Dubois S, Hemery F, Lepage E, Quarre MC, *et al.* Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. *Blood* 2004;**104**:321–7.

Rosenzweig MQ, Bender CM, Lucke JP, Yasko JM, Brufsky AM. The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. *J Pain Symptom Manage* 2004;**27**:185–90.

Reason for exclusion: abstract only (n = 5)

Carabantes FJ, Benavides M, Trujillo R, Cobo M, Herbrero ML, Garcia S. Epoetin alfa in the prevention of anaemia in cancer patients undergoing platinum-based chemotherapy (CT). A prospective randomised study. 35th Annual meeting of the American Society of Clinical Oncology, Atlanta, GA, USA, May 1999. Abstract 2303.

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 receivin platinum-based chemotherapy. *Ann Oncol* 2002;**13**:177.

Janinis D, Dafni U, Aravantinos G, Kalofonos HP, Papakostas D, Tsavdaridis D, *et al.* Quality of life (QoL) outcome of epoetin alfa (EPO-A) in anemic cancer patients undergoing platinum or non-platinum-based chemotherapy: a randomised study conducted by the Hellenic Cooperative Oncology Group. *Proc Am Soc Clin Oncol* 2003;**22**:789.

Quirt I, Micucci S, Moran LA, Pater J, Browman J. 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 tumours receiving cytotoxic chemotherapy. Results of a randomized, double-blind, placebo-controlled clinical trial. *Blood* 1996;**88**:347a.

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. *Ann Oncol* 2002;**13**:177.

Reason for exclusion: unlicensed dose (n = 11)

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**:102–10.

Cascinu S, Fedeli A, Del Ferro E, Luzi Fedeli S, Catalano G. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double-blind trial with placebo. *J Clin Oncol* 1994;**12**:1058–62.

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**:4446–53.

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. *J Pain Symptom Manage* 2003;**25**:512–18.

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. *Int J Clin Oncol* 2001;**6**:296–301.

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

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. *Ann Oncol* 1998;**9**:255–60.

Österborg 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. The European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma. *Blood* 1996;**87**:2675–82.

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. *Clin Cancer Res* 2003;**9**:1689–97.

Throuvalas N, Antonadu D, Boufi M, Lavey RS, Malamos N. Erythropoietin decreases transfusion requirements during radiochemotherapy. 36th Annual Meeting of the American Society of Clinical Oncology, New Orleans, LA, USA, May 2000. Abstract 1558.

Welch RS, James RD, Wilkinson PM, Belli F, Cowan RA. Recombinant human erythropoietin and platinum-based chemotherapy in advanced ovarian cancer. *Cancer J Sci Am* 1995;**1**:261–6.

Reason for exclusion: unlicensed arms from four of the included studies (n = 4)

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. *Br J Haematol* 2002;**119**:79–86.

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. *Eur J Cancer* 2003;**39**:2026–34.

ten Bokkel Huinink WW, de Swart CA, van Toorn DW, Morack G, Breed WP, Hillen HF. 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. *Med Oncol* 1998;**15**:174–82.

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. *Br J Cancer* 1999;**80**:396–402.

Appendix 5 Systematic reviews

TABLE 91 Systematic reviews: study characteristics

Author, year	Title (no. of included studies)	Participants	Intervention	Comparator	Outcomes	Design	Results	Comment
Lawrence 2004[90]	Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients (27 studies included)	All cancer patients (or cancer survivors) with, or assessed for, fatigue	Various; one study included on epoetin alfa	Various; PBO used in single epoetin alfa study	Fatigue as determined by haemR and QoL measures	Variety; only RCTs included for treatment of CRF	For the epoetin alfa vs. PBO study there was a strong statistically significant correlation between Hb levels and QoL. The mean increase in Hb level from baseline to last value was significantly greater in the epoetin alfa group than in the PBO group (2.2 g/dl vs. 0.5 g/dl; $p < 0.001$). Significant differences were observed for epoetin alfa for all five cancer- and anaemia-specific primary QoL measures ($p \leq 0.0048$)	Only one relevant study involving epoetin alfa was included in this SR
[a]Bokemeyer 2007[41]	EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update (43 studies included in updated search plus additional 78 relevant abstracts)	All anaemic adults with cancer or lymphoproliferative malignancies	ESAs	Various (few individual study details given)	HaemR, RBCT requirement, QoL, OS	Variety; 19 studies were level 1 standard (meta-analysis of good-quality controlled studies or RCTs)	Level 1 evidence exists for a positive impact of erythropoietin proteins on Hb levels when administered to patients with chemotherapy-induced anaemia or anaemia of chronic disease, when used to prevent cancer anaemia, and in patients undergoing cancer surgery	

Author, year	Title (no. of included studies)	Participants	Intervention	Comparator	Outcomes	Design	Results	Comment
Ross 2007[91]	Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: a systematic review and meta-analysis (59 studies included)	Anaemic adults with MDS	ESAs	SC, PBO	HaemR, QoL	Uncontrolled case studies and controlled trials including RCTs (four RCTs included for epoetin vs. control)	Significant increase in haemR (OR 5.2; 95% CI 2.5 to 10.8) found for patients receiving epoetin compared with control patients. Patients receiving erythropoiesis-stimulating proteins attained a pre–post change (measured using FACT-F) that exceeded minimum clinically important differences	Only four relevant studies (RCTs of epoetin vs. control) were included in this SR
[b]Wilson 2007[2]	A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment (46 studies included)	Anaemic adults with cancer	ESAs plus supportive care for anaemia (including RBCT)	SC for anaemia (including RBCT) alone	HaemR, RBCT, Hb change, HRQoL, TR, OS, AEs	RCTs	Epoetin improves haemR (defined as an improvement in Hb of 2 g/dl) (RR 3.4, 95% CI 3 to 3.8; response rate for epoetin of 53%). Hb change showed a WMD of 1.63 g/dl (95% CI 1.46 to 1.8) in favour of epoetin. The number of CIA patients receiving RBCTs reduced by an estimated 18%. A positive effect was observed in favour of an improved HRQoL for patients receiving epoetin	The incidence of side effects and effects on survival remain highly uncertain. Authors suggest that, if there is no impact on survival, it seems highly unlikely that epoetin would be considered a cost-effective use of health-care resources
Shehata 2008[92]	The use of erythropoiesis-stimulating agents in patients with non-myeloid hematological malignancies: a systematic review [22 studies included (17 published reports and five abstracts)]	Adults with non-myeloid hematological malignancies	ESAs	PBO	RBCT, HRQoL, OS	RCTs	Statistically significant decrease in transfusion requirements. No evidence that the use of ESAs improved survival. Impact on QoL was difficult to assess because of limitations in the available studies	Authors state that more data are required to confirm improvements in QoL and inferior survival associated with ESA use

continued

TABLE 91 Systematic reviews: study characteristics (*continued*)

Author, year	Title (no. of included studies)	Participants	Intervention	Comparator	Outcomes	Design	Results	Comment
Kvam 2009[93]	Health-related quality-of-life assessment in randomised controlled trials in multiple myeloma: a critical review of methodology and impact on treatment recommendations (15 studies included)	Adults with MM receiving chemotherapy (total $n = 2200$; epoetin $n = 1207$)	Epoetin alfa, epoetin beta, darbepoetin alfa	PBO (in relevant studies)	RBCT, Hb change, transfusion-free survival, HRQoL outcomes and HRQoL influence on clinical decision-making (authors' statement)	RCTs	Statistically significant decrease in RBCT and rise in Hb levels in patients receiving ESAs. Improvement in HRQoL for epoetin beta (one study); improvement in HRQoL for darbepoetin alfa (one study); improvement in cancer- and anaemic-specific HRQoL domains for epoetin alfa (one study)	Only four relevant studies were included in this SR. Epoetin alfa was recommended based on better clinical outcomes and improvement in HRQoL (two studies). Epoetin beta was recommended based on improved HRQoL and better clinical outcomes (one study). Darbepoetin alfa was recommended based on better clinical outcomes and less fatigue (one study). However, the average HRQoL benefit of ESAs in these trials appears to be of limited subjective importance, despite HRQoL data being used widely for marketing of ESAs

Author, year	Title (no. of included studies)	Participants	Intervention	Comparator	Outcomes	Design	Results	Comment
Tonelli 2009[88]	Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis (52 trials included)	Anaemic adults with cancer	Epoetin alfa, epoetin beta, darbepoetin alfa	No treatment, PBO	Mortality, CV events, HTN, HRQoL, RBCT, TR	RCTs	Pooled all-cause mortality during treatment was significantly higher in the group receiving erythropoiesis-stimulating therapy than in the control group (RR 1.15, 95% CI 1.03 to 1.29). Compared with no treatment, use of ESAs led to clinically detectable improvements in disease-specific measures of QoL. It also reduced the use of RBCTs (RR 0.64, 95% CI 0.56 to 0.73)	Use of ESAs resulted in increased risk of thromboembolic events (RR 1.69, 95% CI 1.27 to 2.24) and serious AEs (RR 1.16, 95% CI 1.08 to 1.25)
[c]Bohlius 2009[7]	Erythropoietin or Darbepoetin for patients with cancer – meta-analysis based on individual patient data (53 studies included)	Paediatric and adult cancer patients	Epoetin alfa, epoetin beta or darbepoetin alfa plus RBCT (as necessary)	RBCT alone (as necessary)	Mortality during the active study period, OS	RCTs	1530 patients died during the active study period and 4993 overall (out of a total of 13,933 cancer patients). ESAs increased mortality during the active study period (cHR 1.17, 95% CI 1.06 to 1.30) and worsened OS (cHR 1.06, 95% CI 1 to 1.12), with little heterogeneity between trials. The cHR for mortality during the active period for patients on chemotherapy was 1.10 (95% CI 0.98 to 1.24) and for OS was 1.04 (95% CI 0.97 to 1.11). There was little evidence of a difference between trials of patients given different anticancer treatments	Authors conclude that treatment with ESAs in patients with cancer increased mortality during active study periods and worsened OS. They recommend that the increased risk of death associated with treatment with these drugs should be balanced against their benefits

continued

TABLE 91 Systematic reviews: study characteristics (*continued*)

Author, year	Title (no. of included studies)	Participants	Intervention	Comparator	Outcomes	Design	Results	Comment
[d]Minton 2010[94]	Drug therapy for the management of cancer-related fatigue (50 studies included)	Adult cancer patients with CRF	Drug therapy for CRF (haemopoietic growth factors e.g. ESAs)	PBO, usual care or a non-pharmacological intervention for CRF	Hb concentration and subsequent change in fatigue scores	RCTs (11 relevant studies for epoetin; four relevant studies for darbepoetin alfa)	A meta-analysis of studies of ESAs showed an effect of ESAs over SC or PBO for the treatment of CRF. A meta-analysis of darbepoetin studies showed a small but statistically significant difference between darbepoetin and PBO for the treatment of CRF	Authors note increased safety concerns raised regarding ESAs and recommend that they are not used in practice. There was a very high degree of statistical and clinical heterogeneity in the trials
Grant 2013[89]	Epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment: comparative effectiveness update (54 studies included)	Anaemic adults undergoing chemotherapy and/or radiotherapy for malignancy	ESAs	Control (various)	OS (on-study and longest available follow-up), PFS, QoL, haemR, RBCT, TR, thromboembolic complications, AEs	RCTs, observational studies	In 38 trials, ESAs decreased the risk of transfusion (pooled RR 0.58, 95% CI 0.53 to 0.64). In 37 trials, thromboembolic event rates were higher in ESA-treated patients (pooled RR 1.51, 95% CI 1.3 to 1.74). In 14 trials reporting QoL (FACT-F subscale), scores decreased by –0.6 in the control arms (95% CI –6.4 to 5.2) and increased by 2.1 in the ESA arms (95% CI –3.9 to 8.1). In 37 trials, mortality was increased during the on-study period (pooled HR 1.17, 95% CI 1.04 to 1.31)	Authors conclude that ESAs reduce the need for RBCT and increase the risk of thromboembolism. FACT-F scores were better with ESA use but the magnitude was less than the minimal clinically important difference. An increase in mortality accompanied the use of ESAs

Author, year	Title (no. of included studies)	Participants	Intervention	Comparator	Outcomes	Design	Results	Comment
[e]Tonia, 2012[11]	Erythropoietin or darbepoetin for patients with cancer (91 studies included)	Paediatric and adult cancer patients with anaemia with/without chemotherapy, radiotherapy or combination therapy	ESAs ± RBCT	PBO, no treatment, RBCT ± PBO	HaemR, RBCT, changes in QoL, TR, on-study mortality, OS, AEs	RCTs	Use of ESAs significantly reduces the relative risk of RBCT (RR 0.65, 95% CI 0.62 to 0.68). HaemR was observed more often in participants receiving ESAs (RR 3.93, 95% CI 3.10 to 3.71). There was suggestive evidence that ESAs may improve QoL. There was strong evidence that ESAs increase mortality during the active study period (HR 1.17, 95% CI 1.06 to 1.29) and some evidence that ESA decrease OS (HR 1.05, 95% CI 1 to 1.11). Risk of thromboembolic complications was increased in patients receiving ESAs compared with control patients, whereas HTN and thrombocytopenia/ haemorrhage may be increased in patients receiving ESAs compared with control patients	Authors conclude that ESAs reduce the need for RBCTs but increase the risk for thromboembolic events and death. Authors recommend that the increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment

CRF, cancer-related fatigue; CV, cardiovascular; haemR, haematological response; HTN, hypertension; MDS, myelodysplastic syndrome; MM, multiple myeloma; PBO, placebo; QoL, quality of life; SC, standard care; SR, systematic review; TR, tumour response.

a This study is an update of the 2004 guidelines by the same authors.[203]

b This review by Wilson and colleagues[2] informed NICE TA142.[1]

c The results of this Cochrane review are also published in Bohlius and colleagues.[95]

d This study is an update of a 2008 Cochrane review.[204,205]

e This study is an update of a 2006 Cochrane review;[206] the 2006 study was also published in Bohlius and colleagues.[207–209]

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TABLE 92 Systematic reviews: PRISMA quality assessment

Section/topic	Item	Checklist item	Studies										
			A	B[a]	C	D[b]	E	F	G	H[c]	I[d]	J[e]	K
Title													
Title	1	Identify the report as a systematic review, meta-analysis or both	N	N	Y	Y	Y	N	Y	Y	N	N	N
Abstract													
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	N	N	P[f]	P[g]	N	P[h]	P[i]	P[j]	P[k]	P[l]	P[m]
Introduction													
Rationale	3	Describe the rationale for the review in the context of what is already known	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes and study design	P[n]	N	P[o]	Y[p]	P[q]	P[r]	Y[s]	P[t]	P[u]	P[t]	Y
Methods													
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed and, if available, provide registration information including registration number	N	N	N	Y	N	N	N	N	N	N	Y
Eligibility criteria	6	Specify study characteristics and report characteristics used as criteria for eligibility, giving rationale	Y[v]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Information sources	7	Describe all information sources in the search and date last searched	P[w]	Y	Y	Y	Y	Y	Y	Y	P[w]	Y	Y
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	N	N	Y	Y	Y	Y	Y[x]	Y[y]	Y[z]	Y[aa]	Y[ab]
Study selection	9	State the process for selecting studies	N	N	N	Y[ac]	Y	Y	Y	Y	Y	Y	Y
Data collection process	10	Describe method of data extraction from reports and any processes for obtaining and confirming data from investigators	N	N	P[ad]	Y	P[ad]	N	P[ad]	Y[ae]	P[ad]	Y[ad]	P[af]

TABLE 92 Systematic reviews: PRISMA quality assessment (*continued*)

Section/topic	Item	Checklist item	Studies										
			A	B[a]	C	D[b]	E	F	G	H[c]	I[d]	J[e]	K
Data items	11	List and define all variables for which data are sought and any assumptions and simplifications made	Y	N	N	Y	Y	N	N	Y	P[ag]	Y	Y
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies and how this information is to be used in any data synthesis	N	N	Y	Y	Y	P[ah]	Y[ai]	Y	Y	Y	Y
Summary measures	13	State the principal summary measures	N/A	N/A	Y	N	N/A	Y	Y	Y	Y	Y	Y
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if carried out, including measures of consistency for each meta-analysis	N/A	N/A	Y	Y	N/A	N/A	Y	Y	Y	Y	Y
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence	N/A	N/A	N	Y	N/A	Y	N	Y	N	Y	Y
Additional analyses	16	Describe methods of additional analyses, if carried out, indicating which were prespecified	N	N	Y	Y	P[aj]	N	Y	Y	N	Y	Y
Results													
Study selection	17	Give numbers of studies screened, assessed for eligibility and included in the review, with reasons for exclusions at each stage, ideally in a flow diagram	N	N	N	Y	N	P[ak]	Y	Y	Y	Y	Y
Study characteristics	18	For each study, present characteristics for which data were extracted and provide the citations	Y	N	N	Y	Y	Y	Y[al]	Y	Y	Y	Y
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessments	Y	P[am]	N	Y	Y	P[an]	Y[ao]	Y	Y	Y	Y
Results of individual studies	20	For all outcomes considered, present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	N	N	P[ap]	Y	N	N	Y	Y	Y	Y	Y
Synthesis of results	21	Present results of each meta-analysis carried out, including confidence intervals and measure of consistency	N	N	P[aq]	Y	N	N	Y	Y	Y	Y	Y

continued

TABLE 92 Systematic reviews: PRISMA quality assessment (*continued*)

Section/topic	Item	Checklist item	Studies										
			A	B[a]	C	D[b]	E	F	G	H[c]	I[d]	J[e]	K
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies	N	N	N	Y	N	Y	N	Y	N	Y	N
Additional analysis	23	Give results of additional analyses, if carried out	N/A	N/A	Y	Y	Y[ar]	N/A	Y	Y	N/A	Y	Y
Discussion													
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome; consider their relevance for key groups	N	Y	P[as]	Y	Y	Y	P[at]	Y	Y	Y	P[au]
Limitations	25	Discuss limitations at study and outcome level and at review level	N	N	N	P[av]	Y	Y	Y	N	Y	P[aw]	N
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research	Y	Y	Y	Y	Y[ax]	Y	Y	Y	Y	Y	Y
Funding													
Funding	27	Describe sources of funding for the systematic review and other support and role of funders for the systematic review	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

?, unclear; N, absent; P, partially reported; PICOS, participants, interventions, comparators, outcomes and study design; Y, present.

Studies: A, Lawrence 2004;[90] B, Bokemeyer 2007;[41] C, Ross 2007;[91] D, Wilson 2007;[2] E, Shehata 2008;[92] F, Kvam 2009;[93] G, Tonelli 2009;[88] H, Bohlius 2009;[7] I, Minton 2010;[94] J, Tonia 2012;[11] K, Grant 2013.[89]

a This study is an update of the 2004 guidelines by the same author, published as Bokemeyer and colleagues.[203]
b This review by Wilson and colleagues[2] informed NICE TA142.[1]
c The results of this Cochrane review are also published in Bohlius *et al.*[95]
d This study is an update of a 2008 Cochrane review.[204] Also published in Minton and colleagues.[205]
e This study is an update of a 2006 Cochrane review.[206] Also published in Bohlius and colleagues.[207–209]
f No background, databases, inclusion/exclusion criteria, participants, quality appraisal, review implications/limitations or review registration number mentioned in abstract.
g No details of quality assessment, study appraisal and synthesis in abstract, with full details presented in methods section.
h Background detailed in introduction. Objectives specified in abstract but PICOS criteria not appropriate. Data extraction detailed in methods section. Limitations detailed in discussion section. No systematic review registration number.
i Details online; no systematic review registration number.
j Data extraction detailed in methods section. No limitations mentioned in abstract but stated in discussion section. No systematic review registration number.
k Objectives in abstract lacking in detail. Elements of PICOS criteria detailed in methods section. Synthesis methods not described. Limitations not described in abstract but described in methods. Limitations of study detailed in discussion. No systematic review registration number.
l Objectives lacking in detail with respect to comparators and study design; details described in methods section. Data synthesis not detailed in abstract but described in methods. Limitations of study described in discussion. No systematic review registration number.
m Data sources listed in methods section together with details of study selection criteria, data extraction, synthesis methods and outcomes of interest. Outcomes detailed in executive summary. No systematic review registration number provided.
n Research questions defined in methods section; full PICOS criteria not applicable.
o Comparators, main outcome and study design not mentioned in introduction.
p PICOS criteria contained in executive summary.
q Population, intervention and outcome described in abstract and study design in methods section; comparator not defined in either abstract, introduction or methods.
r Patients, outcomes and study design detailed in objectives (intervention and comparator not applicable).
s PICOS criteria covered in abstract and introduction despite being no defined 'objectives' section.
t Population, intervention and outcome covered in objectives; comparator and study details in methods section.
u Population, intervention and comparator covered in objectives. Outcome and study details in methods section.

v Full PICOS criteria not applicable.
w No search start date specified.
x Details in online appendix.
y Online (Appendix A).
z Online appendix.
aa Details in appendix.
ab Appendix.
ac PRISMA flow diagram in appendix.
ad No mention of piloting or processes for obtaining/confirming data.
ae No mention of piloting.
af No mention of processes for obtaining/confirming data.
ag Broad categories described rather than individual data items.
ah Methodological quality was assessed according to a checklist developed for evaluating HRQoL outcomes in clinical trials.
ai Details online (*Appendix 4*).
aj ITT analysis conducted.
ak Minimum detail provided.
al Details online.
am Risk of bias assessed using ASCO levels of evidence and grades of recommendation.
an Summary of checklist given but no detailed breakdown of criteria.
ao Details online.
ap Event rates given as percentages rather than frequencies and only ORs provided.
aq I^2 values not given in results section.
ar Summary of numbers needed to treat.
as Relevance for key groups not addressed.
at No assessment/ranking of evidence robustness.
au No consideration of applicability of review's findings.
av Limitations at review level mentioned.
aw Limitations at review level.
ax Implications for future research not mentioned.

Appendix 6 Study and baseline characteristics of excluded unlicensed studies

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Wilson and colleagues[2]								
Bamias 2003[210] ROL	*n* = 2; age (years): 60 (18–77); male, *n* (%): 35 (49); Hb BL (g/dl): 11.5 (11.1–11.9); epoetin BL (mU/ml): 24.8 (16.6–37)	*n* = 72; age (years): 62 (19–80); male, *n* (%): 39 (54); Hb BL (g/dl): 11.5 (11.2–11.8); epoetin BL (mU/ml): 12.5 (8.7–18)	Brand: epoetin alfa; dose: 30,000 IU QW; dose adjustment: Y, ↓; duration of epoetin tx: 21–24 weeks (duration of chemotherapy); duration of trial: duration of chemotherapy + 3 weeks; follow-up	SC	Iron: NR; G-CSF: NR; RBCT trigger: prn (Hb inclusion criterion level: < 13 g/dl)	Disease: solid; treatment: chemotherapy platinum containing	Hb, RBCT, HRQoL measured in a subset	Y
Cascinu 1994[211] RCT	*n* = 50; age (years): 58 (44–72); male, *n* (%): 24 (48); Hb BL (g/dl): 8.63 ± 0.62; epoetin BL (mU/ml): 67.9 ± 66.6	*n* = 50; age (years): 57 (45–68); male, *n* (%): 29 (58); Hb BL (g/dl): 8.73 ± 0.52; epoetin BL (mU/ml): 49.3 ± 39.9	Brand: epoetin alfa; dose: 300 IU/kg QW; dose adjustment: Y; duration of epoetin tx: 9 weeks; duration of trial: 9 weeks; follow-up: NR	PBO	Iron: Y, oral (as indicated by serum iron, serum ferritin, transferrin saturation); G-CSF: NR; RBCT trigger: < 8 g/dl (Hb inclusion criterion level: < 9 g/dl)	Disease: solid; treatment: chemotherapy, platinum containing	Hb, RBCT, AEs	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Cazzola 1995[212] ROL	Epoetin beta 1000 IU/kg: *n* = 31 (analysed *n* = 31); age (years): 67 (48–82); male, *n* (%): 16 (51.6); Hb BL (g/dl): 9.3 (0.9); epoetin BL (mU/ml): 43 (22–69) Epoetin beta 2000 IU/kg: *n* = 29 (analysed *n* = 29); age (years): 65 (40–82); male, *n* (%): 19 (65.5); Hb BL (g/dl): 9.4 (0.9); epoetin BL (mU/ml): 30 (21–64) Epoetin beta 5000 IU/kg: *n* = 31 (analysed *n* = 31); age (years): 68 (42–85); male, *n* (%): 14 (45.2); Hb BL (g/dl): 9.4 (1.2); epoetin BL (mU/ml): 24 (11–47) Epoetin beta 10,000 IU/kg: *n* = 26 (analysed *n* = 26); age (years): 63 (28–80); male, *n* (%): 16 (61.5); Hb BL (g/dl): 9.4 (1.0); epoetin BL (mU/ml): 38 (18–70)	*n* = 29 (analysed *n* = 29); age (years): 68 (28–82); male, *n* (%): 16 (55.2); Hb BL (g/dl): 9.5 (1.1); epoetin BL (mU/ml): 32 (19–66)	Brand: epoetin beta; dose: 5000 IU/day or 10,000 IU/day; dose adjustment: NR; duration of epoetin tx: NR; duration of trial: NR; follow-up: NR	SC	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: NR)	Disease: haematological; treatment: chemotherapy, non-platinum containing	HaemR, Hb, RBCT, AEs	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
[b]Hedenus 2002[53] RCT, dose–response study; only licensed dose included in current review	Darbepoetin alfa 1.0 µg/kg QW:[b] *n* = 11; age (years): 64 (26–80); male, *n* (%): 7 (64); Hb BL (g/dl): 9.7 (0.8); epoetin BL (mU/ml): 46 (12–208) Darbepoetin alfa 4.5 µg/kg QW:[b] *n* = 22; age (years): 70 (52–84); male, *n* (%): 14 (64); Hb BL (g/dl): 9.7 (0.9); epoetin BL (mU/ml): 57 (12–227)	*n* = 11; age (years): 63 (25–80); male, *n* (%): 2 (18); Hb BL (g/dl): 9.5 (1.0); epoetin BL (mU/ml): 45 (12–132	Brand: darbepoetin alfa; dose: 1.0 and 4.5 µg/kg QW;[b] dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 16 weeks; follow-up: unclear	PBO	Iron: NR; G-CSF: NR; RBCT trigger: Hb ≤ 8 g/dl (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: haematological; treatment: chemotherapy, NR	HaemR, Hb, RBCT, AEs	Y
Iconomou 2003[213] ROL	*n* = 57; age (years): 60.6 (33–85); male, *n* (%): 22 (39); Hb BL (g/dl): 10.1 ± 0.6; epoetin BL (mU/ml): NR	*n* = 55; age (years): 62.6 (34–80); male, *n* (%): 24 (44); Hb BL (g/dl): 10.1 ± 0.6; epoetin BL (mU/ml): NR	Brand: rHuEPO; dose: 30,000 IU QW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: NR	SC	Iron: Y; G-CSF: NR; RBCT trigger: Hb 7.5 g/dl or prn (Hb inclusion criterion level: ≤ 11 g/dl)	Disease: solid; treatment: chemotherapy, mixed	HaemR, HRQoL	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
[b]Kotasek 2003[50] RCT, dose–response study; only licensed dose included in current review	Darbepoetin alfa 1.5 µg/kg QW: *n* = 32; male, *n* (%): 9 (28) Darbepoetin alfa 3.0 µg/kg QW: *n* = 46; male, *n* (%): 13 (28) Darbepoetin alfa 4.0 µg/kg QW: *n* = 28; male, *n* (%): 8 (28) Darbepoetin alfa 4.5 µg/kg QW: *n* = 35; male, *n* (%): 10 (28) Darbepoetin alfa 5.0 µg/kg QW: *n* = 40; male, *n* (%): 11 (28) Age (years): 58.3 (11.9);[c] Hb BL (g/dl): 9.93 (1.0);[c] epoetin BL (mU/ml): 17% patients ≥ 100 mU/ml[c]	*n* = 51; age (years): 56.2 (12.4); male, *n* (%): 16 (31); Hb BL (g/dl): 9.87 (1.12); epoetin BL (mU/ml): NR	Brand: darbepoetin alfa; dose: 1.0, 3.0, 4.0, 4.5 and 5.0 µg/kg QW; dose adjustment: Y, ↓; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: unclear	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: solid (breast, gynaecological, gastrointestinal, lung); treatment: chemotherapy, NR	HaemR, Hb, RBCT, HRQoL,[c] AE[c]	Y
Kunikane 2001[214] RCT	Epoetin beta 300 IU/kg QW *n* = 16; age (years): NR; male, *n* (%): NR; Hb BL (g/dl): > 12; epoetin BL (mU/ml) Epoetin beta 600 IU/kg QW *n* = 18; age (years): male, *n* (%): Hb BL (g/dl): > 12; epoetin BL (mU/ml)	*n* = 38; age (years): NR; male, *n* (%): NR; Hb BL (g/dl): > 12; epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 300 and 600 IU/kg QW; dose adjustment: NR; duration of epoetin tx: 6 weeks; duration of trial: NR; follow-up: NR	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: NR)	Disease: solid (non-small-cell lung cancer); treatment: chemotherapy, platinum containing	Hb, RBCT	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Leyland-Jones 2003[14] RCT	n = NR (total for trial 939); age (years): NR; male, n (%): NR; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	n = NR (total for trial 939); age (years): NR; male, n (%): NR; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: NR; dose adjustment: NR; duration of epoetin tx: NR; duration of trial: 12–19 months; follow-up: NR	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR [Hb inclusion criterion level: 13 g/dl (aim of study to keep Hb > 12 g/dl to < 14 g/dl)]	Disease: solid (metastatic breast); treatment: NR	Survival	Y
Oberhoff 1998[215] ROL	n = 114; age (years): NR; male, n (%): NR; Hb BL (g/dl): ≤ 10; epoetin BL (mU/ml): NR	n = 104; age (years): NR; male, n (%): NR; Hb BL (g/dl): 10; epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 5000 IU/day; dose adjustment: 12 weeks; duration of epoetin tx: NR; duration of trial: NR; follow-up: NR	SC	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: NR)	Disease: solid; treatment: chemotherapy, platinum containing	HaemR, Hb, RBCT, AEs	Y
Österborg 1996[216] ROL	Epoetin beta 10,000 IU/day n = 47; age (years): NR; male, n (%): NR; Hb BL (g/dl): ≤ 10; epoetin BL (mU/ml): NR Epoetin beta 2000 IU/day n = 48; age (years): NR; male, n (%): NR; Hb BL (g/dl): ≤ 10; epoetin BL (mU/ml): NR	n = 49; age (years): NR; male, n (%): NR; Hb BL (g/dl): ≤ 10; epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 2000 and 10,000 IU/day; dose adjustment: NR; duration of epo tx: 24 weeks; duration of trial: NR; follow-up: NR	SC	Iron: NR; G-CSF: Y; RBCT trigger: NR (Hb inclusion criterion level: NR)	Disease: haematological; treatment: chemotherapy, non-platinum containing	HaemR, Hb, RBCT, AEs	Y
Rosen 2003[217] ROL	n = 47; age (years): 56 (35–80); male, n (%): 33 (71); Hb BL (g/dl): < 10; epoetin BL (mU/ml): NR	n = 43; age (years): 56 (35–80); male, n (%): 31 (71); Hb BL (g/dl): < 10; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: NR; duration of epoetin tx: 14 weeks + 4 weeks continuation; duration of trial: 48 months; follow-up: NR	SC	Iron: Y (tx arm only); G-CSF: NR; RBCT trigger: Hb < 10 g/dl (Hb inclusion criterion level: ≤ 16 g/dl)	Disease: solid (head/neck); treatment: chemotherapy + radiotherapy	Hb, RBCT	Y
[b]ten Bokkel Huinink 1998[51] ROL, three-arm study; only comparison with licensed dose included in current review	n = 42 (analysed 42);[b] age (years): 60.97; male, n (%): all female; Hb BL (g/dl): 12.0 (1.3–12.6); epoetin BL (mU/ml): NR	n = 34 (analysed 33); age (years): 58.83; male, n (%): all female; Hb BL (g/dl): 11.8 (10.6–12.5); epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 300 IU/kg TIW;[b] dose adjustment: Y; duration of epoetin tx: 24 weeks; duration of trial: 24 weeks; follow-up: NR	SC	Iron: NR; G-CSF: N; RBCT trigger: Hb < 9.7 g/dl (Hb inclusion criterion level: < 13 g/dl)	Disease: solid (ovary); treatment: chemotherapy, platinum containing	RBCT, AEs	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
[b]Thatcher 1999[52] ROL, three-arm study; only comparison with licensed dose included in current review	$n = 44$;[b] age (years): 58.5 (30–72); male, *n* (%): 29 (66); Hb BL (g/dl): 13.6 (10.9–17.0); epoetin BL (mU/ml): NR	$n = 44$; age (years): 60 (39–74); male, *n* (%): 27 (61.3); Hb BL (g/dl): 13.4 (10.9–16.4); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 300 IU/kg TIW;[b] dose adjustment: Y; duration of epoetin tx: 26 weeks; duration of trial: 26 weeks; follow-up: NR	SC	Iron: N; G-CSF: N; RBCT trigger: prn (Hb inclusion criterion level: ≥ 10.5 g/dl)	Disease: solid (small-cell lung cancer); treatment: chemotherapy, mixed[d]	Hb, RBCT, HRQoL, AEs	Y
Throuvalas 2000[218] ROL	$n = 28$ (analysed 28); age (years): NR; male, *n* (%): NR; Hb BL (g/dl): > 10 to ≤ 12; epoetin BL (mU/ml): NR	$n = 27$ (analysed 26); age (years): NR; male, *n* (%): NR; Hb BL (g/dl): > 10 to ≤ 12; epoetin BL (mU/ml): NR	Brand: rHuEPO; dose: 50,000 IU QW; dose adjustment: unclear; duration of epoetin tx: NR; duration of trial: 6 weeks; follow-up: NR	SC	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: NR)	Disease: solid (cervix, bladder); treatment: chemotherapy (platinum containing) + radiotherapy	RBCT	Y
Welch 1995[219] ROL	$n = 15$; age (years): NR; male, *n* (%): NR; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	$n = 15$; age (years): NR; male, *n* (%): NR; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 300 IU/kg TIW; dose adjustment: NR; duration of epoetin tx: NR; duration of trial: 24 weeks; follow-up: NR	SC	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: NR)	Disease: solid (ovary); treatment: chemotherapy, platinum containing	Hb, RBCT, HRQoL, AEs	Y
PenTAG review: 2004 to current								
Aapro 2008[220] ROL (Breast Cancer – Anemia and the Value of Erythropoietin; BRAVE), supplementary reference Aapro 2009[221]	$n = 231$; age (years): 56 (27–78); male, *n* (%): all female; Hb BL (g/dl): 11.2 ± 1.2; epoetin BL (mU/ml): NR	$n = 232$; age (years): 57.5 (29–83); male, *n* (%): all female; Hb BL (g/dl): 11.5 ± 1.1; epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 450 IU/kg QW; dose adjustment: Y; duration of epoetin tx: 24 weeks; duration of trial: 24 weeks; follow-up: 18 months	SC	Iron: Y, oral or intravenous; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: < 12.9 g/dl)	Disease: solid (breast); treatment: chemotherapy, non-platinum containing	HaemR, Hb, RBCT, HRQoL, AEs, TR, survival	Y
Aapro 2009[221] Subgroup analysis of Aapro 2008[220]	$n = 231$; age (years): 56 (27–78); male, *n* (%): all female; Hb BL (g/dl): 11.2 ± 1.2; epoetin BL (mU/ml): NR	$n = 232$; age (years): 57.5 (29–83); male, *n* (%): all female; Hb BL (g/dl): 11.5 ± 1.1; epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 450 IU/kg QW; dose adjustment: Y; duration of epoetin tx: 24 weeks; duration of trial: 24 weeks; follow-up: 18 months	SC	Iron: Y, oral or intravenously; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: < 12.9 g/dl)	Disease: solid (breast); treatment: chemotherapy, non-platinum containing	AEs (subgroup analysis, TVEs among patients receiving and not receiving antithromboembolic therapy; hypothesis generating)	N

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Berndt 2005[222] ROL, subgroup analysis of Glaspy 2002[122] (not included in previous HTA review[2])	$n = 300$;[e] age (years): 60.8 (12.3) (20–91); male, *n* (%): 91 (30.3); Hb BL (g/dl): 9.9 (0.9) (6.2–12.2); epoetin BL (mU/ml): NR		Brand: darbepoetin alfa; dose: 0.5, 1.0, 1.5, 2.25, 4.5, 6.0 and 8.0 µg QW and 3.0, 5.0, 7.0 and 9.0 µg Q2W; dose adjustment: Y, ↓; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: NR Brand: epoetin alfa; dose: 150 IU/kg TIW and 40,000 IU/kg QW; dose adjustment: Y;[f] duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: NR	Head-to-head	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 11 g/dl)	Disease: solid; treatment: chemotherapy, mixed	Analysis explores the impact of fatigue on productivity and caregiver burden (although includes licensed doses of intervention under review, results reported are based on pooled data)	N
Blohmer 2011[223] ROL [Nordostdeutsche Gesellschaft fur Gynaekologische Onkologie Arbeitsgemeinschaft Gynaekologische Onkologie (NOGGO-AGO)]	$n = 127$; age (years): 41 (24–73); male, *n* (%): all female; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	$n = 129$; age (years): 42 (25–66); male, *n* (%): all female; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: rHuEPO; dose: 10,000 IU TIW; dose adjustment: Y; duration of epoetin tx: unclear; duration of trial: unclear; follow-up: 3 years	No epoetin	Iron: Y, oral; G-CSF: NR; RBCT trigger: Hb < 9 g/dl (Hb inclusion criterion level: NR)	Disease: solid (cervix); treatment: chemotherapy + radiotherapy	Hb, RBCT, HRQoL (ECOG performance status), AEs, survival	Y
Cabanillas 2012[224] ROL	$n = 55$; age (years): 41 ± 16.7; male, *n* (%): 33 (58); Hb BL (g/dl): 9 ± 1.5; epoetin BL (mU/ml): 473 ± 570	$n = 54$; age (years): 42 ± 17.3; male, *n* (%): 24 (42); Hb BL (g/dl): 8.9 ± 1.5; epoetin BL (mU/ml): 326 ± 514	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: unclear; duration of trial: unclear; follow-up: 3 years	No epoetin	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: > 10 g/dl)	Disease: haematological; treatment: chemotherapy, non-platinum containing	RBCT, HRQoL, AEs, TR, survival	N, excluded trials if > 80% of participants were diagnosed with an acute leukaemia
Chang 2005[32] ROL	$n = 175$; age (years): 50.4 (11.1) (27–78); male, *n* (%): all female; Hb BL (g/dl): 11.2 (0.9) (8.15–12.6);[g] epoetin BL (mU/ml): NR	$n = 175$; age (years): 50.1 (10.0) (31–85); male, *n* (%): all female; Hb BL (g/dl): 11.3 (0.8) (7.8–13.4);[g] epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: NR	SC	Iron: Y, oral, daily (as indicated by transferrin saturation); G-CSF: NR; RBCT trigger: Hb < 8 g/dl, prn (Hb inclusion criterion level: ≤ 15 g/dl at screening; ≤ 12 g/dl randomised)	Disease: solid (breast); treatment: chemotherapy, NR	HaemR,[h] Hb, RBCT, HRQoL, AEs	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Chang 2004[225] ROL, subgroup analysis of Chang 2005[32] (published online ahead of print 2004)	$n = 176$; age (years): 50.4 (11.1) (27–78); male, *n* (%): all female; Hb BL (g/dl): 11.2 (0.9) (8.15–12.6); epoetin BL (mU/ml): NR	$n = 178$; age (years): 50.1 (10.0) (31–85); male, *n* (%): all female; Hb BL (g/dl): 11.3 (0.8) (7.8–13.4); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: NR	SC	Iron: Y, oral, daily (as indicated by transferrin saturation); G-CSF: NR; RBCT trigger: Hb < 8 g/dl, prn (Hb inclusion criterion level: ≤ 15 g/dl at screening; ≤ 12 g/dl randomised)	Disease: solid (breast); treatment: chemotherapy, NR	Analysis of the effect of epoetin alfa on changes in quality of life and utility scales at 12 weeks	Y
Charu 2007[226] ROL	$n = 226$; age (years): 71.7 (10.4); male, *n* (%): 95 (42); Hb BL (g/dl): 10.1 (0.9) (for $n = 220$); epoetin BL (mU/ml): NR	$n = 59$; age (years): 67.2 (12.5); male, *n* (%): 23 (39); Hb BL (g/dl): 10.3 (0.9) (for $n = 55$); epoetin BL (mU/ml): NR	Brand: darbepoetin alfa; dose: 3 µg/kg Q2W; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks;[i] follow-up: NR	No epoetin	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 11 g/dl)	Disease: mixed; treatment: chemotherapy, NR	HaemR, Hb, RBCT, HRQoL, AEs, numbert of hospitalisations	Y
Christodoulou 2009[227] ROL	$n = 167$; age (years): 61 (22–82); male, *n* (%): 88 (53); Hb BL (g/dl): 10.15 ± 0.69; epoetin BL (mU/ml): NR	$n = 170$; age (years): 63 (30–89); male, *n* (%): 81 (48); Hb BL (g/dl): 10.30 ± 0.58); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 10,000 IU TIW; dose adjustment: Y; duration of epoetin tx: NR; duration of trial: NR; follow-up: NR	No epoetin	Iron: Y, oral; G-CSF: NR; RBCT trigger: Hb < 8.5 g/dl prn (Hb inclusion criterion level: ≤ 12 g/dl)	Disease: solid; treatment: chemotherapy, mixed	Hb, RBCT, HRQoL, TR, survival	Y
Engert 2010[228] RCT [German Hodgkin Study Group (GHSG)-HD15-EPO]	$n = 648$; age (years): 34 (18–60); male, *n* (%): 402 (62); Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	$n = 685$; age (years): 34 (18–60); male, *n* (%): 406 (62); Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: unclear; duration of trial: unclear; follow-up: unclear	PBO	Iron: Y, oral (as indicated by BL transferrin saturation or serum ferritin level); G-CSF: NR; RBCT trigger: Hb < 8 g/dl (Hb inclusion criterion level: NR)	Disease: haematological; treatment: chemotherapy, non-platinum containing	Hb, RBCT, HRQoL, AEs, survival	Y
Fujisaka 2011[229] RCT	$n = 89$; age (years): 67 (40–79); male, *n* (%): 47 (53); Hb BL (g/dl): 9.4 (8.1–11.4); epoetin BL (mU/ml): 43 (7.78–577)	$n = 92$; age (years): 63.5 (44–79); male, *n* (%): 40 (43); Hb BL (g/dl): 9.3 (7.2–11.4); epoetin BL (mU/ml): 43.6 (10.5–320)	Brand: epoetin beta; dose: 36,000 IU QW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: 12 months	PBO	Iron: Y, oral daily (as indicated by transferrin saturation); G-CSF: NR; RBCT trigger: prn (Hb inclusion criterion level: ≤ 8 g/dl/≤ 10 g/dl)	Disease: solid (lung or gynaecological); treatment: chemotherapy, platinum containing	Hb, RBCT, HRQoL, AEs, survival	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Glaspy 2006[230] ROL, active control	Darbepoetin alfa: $n = 606$; age (years): 63.2 (12.4); male, *n* (%): 191 (32); Hb BL (g/dl): 10.2 (0.9); epoetin BL (mU/ml): NR	Epoetin alfa: $n = 603$; age (years): 63.7 (11.6); male, *n* (%): 222 (37); Hb BL (g/dl): 10.2 (0.9); epoetin BL (mU/ml): NR	Brand: darbepoetin alfa; dose: 200 µg Q2W; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: NR Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: NR	NA (active control; see left)	Iron: NR; G-CSF: NR; RBCT trigger: Hb > 8 g/dl prn (Hb inclusion criterion level: ≤ 11 g/dl)	Disease: solid; treatment: chemotherapy, NR	Hb, RBCT, HRQoL, AEs; haemR measured but defined as achievement of target Hb range 11–13 g/dl)	N; excluded as ESAs were given in context with surgery, stem cell transplantation
Gupta 2009[231] RCT	$n = 60$ (analysed $n = 58$); age (years): 48.27 (18–70); male, *n* (%): NR; Hb BL (g/dl): 10.45 (9.5–11.0); epoetin BL (mU/ml): NR	$n = 60$ (analysed $n = 57$); age (years): 48.18 (20–65); male, *n* (%): NR; Hb BL (g/dl): 10.70 (10.0–12.5); epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 10,000 IU TIW; dose adjustment: NR; duration of epoetin tx: unclear; duration of trial: unclear; follow-up: 24 months	PBO	Iron: Y, oral 10–15 days before chemotherapy + radiotherapy (unclear whether given in control arm); G-CSF: NR; RBCT trigger: Hb ≤ 10 g/dl (Hb inclusion criterion level: 9.5–12.5 g/dl)	Disease: solid (cervix); treatment: chemotherapy (platinum containing) + radiotherapy	Hb, RBCT, HRQoL, AE, TR, survival	Y
Hernandez 2009[232] RCT	$n = 193$; age (years): 64.5 (12.1); male, *n* (%): 76 (39); Hb BL (g/dl): 10.1 (0.9); epoetin BL (mU/ml): 90.3 (96.1) ($n = 186$)	$n = 193$; age (years): 63.6 (12.3); male, *n* (%): 76 (39); Hb BL (g/dl): 10.0 (0.9); epoetin BL (mU/ml): 109.9 (186.4) ($n = 184$)	Brand: darbepoetin alfa; dose: 300 µg Q3W; dose adjustment: Y; duration of epoetin tx: 13 weeks; duration of trial: 16 weeks; follow-up: 29 weeks	PBO	Iron: Y, not specified, although based on serum iron, serum ferritin or transferrin saturation; G-CSF: NR; RBCT trigger: Hb ≤ 8 g/dl or if > 8 g/dl and signs of anaemia present (Hb inclusion criterion level: < 11 g/dl)	Disease: solid and haematological?; treatment: chemotherapy, mixed	Hb, RBCT, HRQoL, AEs, TR, survival	Y
Leyland-Jones 2005[233] RCT (Breast Cancer Erythropoietin Survival Trial; BEST)	$n = 469$; age (years): 55.8 (11.1; 24–83); male, *n* (%): all female; Hb BL (g/dl): 12.5 (1.8); epoetin BL (mU/ml): NR	$n = 470$; age (years): 55.1 (10.5; 30–84); male, *n* (%): all female; Hb BL (g/dl): 12.5 (1.7); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 12 months; duration of trial: 12 months;[j] follow-up: NR	PBO	Iron: Y, oral (as indicated by transferrin saturation); G-CSF: NR; RBCT trigger: prn (Hb inclusion criterion level: NR)	Disease: solid (breast); treatment: chemotherapy, NR	Hb, RBCT, HRQoL, AEs, TR, survival	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Milroy 2011[234] ROL	$n = 214$ (analysed $n = 189$); age (years): 61.6 ± 8.7 (41–82); male, *n* (%): 142 (75.1); Hb BL (g/dl): 12.8 ± 1.4; epoetin BL (mU/ml): NR	$n = 191$ (analysed $n = 191$); age (years): 60.1 ± 9.3 (34–83); male, *n* (%): 148 (77.5); Hb BL (g/dl): 12.6 ± 1.6; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 10,000 IU TIW; dose adjustment: Y; duration of epoetin tx: 22–28 weeks; duration of trial: 22–28 weeks; follow-up: 6 and 12 months	SC	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 15 g/dl men; ≤ 14 g/dl women)	Disease: solid (non-small-cell lung cancer); treatment: chemotherapy, platinum containing	HaemR, Hb, RBCT, HRQoL, AEs, TR, survival	Y
Nagel 2011[235] ROL	$n = 37$; age (years): 61 (41–88); male, *n* (%): 29 (77.8); Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	$n = 37$; age (years): 59 (37–80); male, *n* (%): 24 (63.9); Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: darbepoetin alfa; dose: 300 µg Q2W; dose adjustment: Y; duration of epoetin tx: up to 28 weeks; duration of trial: up to 28 weeks; follow-up: 24 months	SC	Iron: Y, oral; G-CSF: Y, pegfilgastrim D4 each cycle; RBCT trigger: prn (Hb inclusion criterion level: < 12 g/dl; treatment initiated at this point in the intervention group)	Disease: solid (small-cell lung cancer); treatment: chemotherapy, platinum containing	HRQoL, AEs, TR, survival	N; excluded as too many patients in experimental arm did not receive ESAs
O'Shaugnessy 2005[236] RCT	$n = 47$; age (years): 53.3 ± 9.7; male, *n* (%): all female; Hb BL (g/dl): 12.8 ± 1.0; epoetin BL (mU/ml): NR	$n = 47$; age (years): 54.3 ± 12.0; male, *n* (%): all female; Hb BL (g/dl): 13.0 ± 1.0; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 16 weeks; follow-up: 6 months	PBO	Iron: Y, not specified but prn; G-CSF: NR; RBCT trigger: Hb < 8 g/dl (Hb inclusion criterion level: 9–14 g/dl)	Disease: solid (breast); treatment: chemotherapy, platinum containing	Hb, cognitive function and mood [Executive Interview (EXIT25), Clock Drawing task (CLOX) 1 (prompted) and 2 (unprompted), Profile of Mood States (POMS)], HRQoL, AEs	Y
Pirker 2008[237] RCT	$n = 298$; age (years): NR; male, *n* (%): NR; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	$n = 298$; age (years): NR; male, *n* (%): NR; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: darbepoetin alfa; dose: 300 µg QW for 4 weeks then every 3 weeks up to six cycles of chemotherapy; dose adjustment: Y; duration of epoetin tx: 13 weeks?; duration of trial: 24 weeks; follow-up: 12 months	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≥ 9 g/dl and ≤ 13 g/dl)	Disease: solid (small-cell lung cancer); treatment: chemotherapy, platinum containing	Hb, RBCT, HRQoL, AEs, survival, disease progression	Y
Pronzato2010[238] ROL (EPO-INT-47)	$n = 107$; age (years): 58.3 ± 10.3 (29–76); male, *n* (%): all female; Hb BL (g/dl): 10.6; epoetin BL (mU/ml): NR	$n = 109$; age (years): 54.3 ± 11.6 (27–77); male, *n* (%): all female; Hb BL (g/dl): 10.8; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 10,000 IU TIW (5000 IU QW if < 45 kg); dose adjustment: Y; duration of epoetin tx: up to 28 weeks; duration of trial: up to 28 weeks; follow-up: 6 and 12 months	SC	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 12 g/dl)	Disease: solid; treatment: chemotherapy, platinum containing	HaemR, Hb, HRQoL, AEs, TR, survival	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
[k]Razzouk 2006[239] RCT	$n = 111$; age (years): 12.4 (3.6); male, *n* (%): 63 (56.8); Hb BL (g/dl): 9.8 (1.3); epoetin BL (mU/ml): NR	$n = 111$; age (years): 10.8 (4.0); male, *n* (%): 58 (52.3); Hb BL (g/dl): 9.5 (1.0); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 600 IU/kg QW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: NR	PBO	Iron: Y, oral (as indicated by transferrin saturation or ferritin level); G-CSF: NR; RBCT trigger: Hb ≤ 7 g/dl (Hb inclusion criterion level: < 10.5, < 11.0 or < 12.0 g/dl dependent on age)	Disease: haematological; treatment: chemotherapy, NR	Hb, RBCT, HRQoL, AEs	Y
Reed 2005[240] ROL, active control; subgroup analysis of Waltzman 2005[241]	$n = 274$; age (years): 62.4 (11.7); male, *n* (%): 93 (34); Hb BL (g/dl): NR; epoetin BL (mU/ml): NR		Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: NR Brand: darbepoetin alfa; dose: 200 µg Q2W; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: NR	Head-to-head	Iron: Y, oral, daily or intravenously if contraindicated; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 11 g/dl)	Disease: solid; treatment: chemotherapy, mixed	Analysis of patients with a baseline Hb value and at least one post-randomisation Hb value or documentation of RBCT. Patients were dichotomised based on whether they experienced an early Hb response, regardless of treatment assignment	N; compared different ESA products (epoetin vs. darbepoetin)
Rosenzweig 2004[242] Retrospective analysis; original trial unknown	$n = 14$; age (years): 55.9 ± 11.7; male, *n* (%): all female; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	$n = 13$; age (years): 53.9 ± 14.20; male, *n* (%): all female; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: rHuEPO; dose: 40,000 IU QW; dose adjustment: NR; duration of epoetin tx: NR; duration of trial: NR;[l] follow-up: NA	SC	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: < 12 g/dl)	Disease: solid (breast); treatment: chemotherapy, NR	Analysis to determine the efficacy of rHuEPO in reducing cancer-related fatigue and improving quality of life and fatigue in patients with metastatic breast cancer experiencing mild anaemia (retrospective review over an 18-month period)	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Savonije 2006[243] RCT, subgroup analysis of Savonije 2006[244]	$n = 211$; age (years): 57 ± 11 (20–80); male, *n* (%): 117 (55); Hb BL (g/dl): 10.7 ± 1.0 (7.6–13.8); epoetin BL (mU/ml): NR	$n = 104$; age (years): 58 ± 10 (27–78); male, *n* (%): 61 (59); Hb BL (g/dl): 10.8 ± 10 (8.5–12.7); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 10,000 IU TIW; dose adjustment: Y; duration of epoetin tx: NR; duration of trial: 13.9 weeks vs. 14.5 weeks (mean intervention vs. control); follow-up: 12 months	SC	Iron: Y, oral (as indicated by BL transferrin saturation ± serum ferritin level); G-CSF: NR; RBCT trigger: Hb ≥ 9.7 g/dl prn (Hb inclusion criterion level: ≤ 12.1 g/dl)	Disease: solid; treatment: chemotherapy, platinum containing	HRQoL in patients with solid tumours and mild-to-moderate anaemia receiving platinum-containing chemotherapy relative to population norms	Y
Savonije 2006[244] RCT, subgroup analysis of Savonije 2006[244]	$n = 211$; age (years): 57 ± 11 (20–80); male, *n* (%): 117 (55); Hb BL (g/dl): 10.7 ± 1.0 (7.6–13.8); epoetin BL (mU/ml): NR	$n = 104$; age (years): 58 ± 10 (27–78); male, *n* (%): 61 (59); Hb BL (g/dl): 10.8 ± 10 (8.5–12.7); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 10,000 IU TIW; dose adjustment: Y; duration of epoetin tx: NR; duration of trial: 13.9 weeks vs. 14.5 weeks (mean intervention vs. control); follow-up: 12 months	SC	Iron: Y, oral (as indicated by BL transferrin saturation ± serum ferritin level); G-CSF: NR; RBCT trigger: Hb ≥ 9.7 g/dl prn (Hb inclusion criterion level: ≤ 12.1 g/dl)	Disease: solid; treatment: chemotherapy, platinum containing	Analysed the effect of BL Hb level on HaemR, Hb, RBCT, and HRQoL	N
Savonije 2005[245] RCT (NCT00283465)	$n = 211$; age (years): 57 ± 11 (20–80); male, *n* (%): 117 (55); Hb BL (g/dl): 10.7 ± 1.0 (7.6–13.8); epoetin BL (mU/ml): NR	$n = 104$; age (years): 58 ± 10 (27–78); male, *n* (%): 61 (59); Hb BL (g/dl): 10.8 ± 10 (8.5–12.7); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 10,000 IU TIW; dose adjustment: Y; duration of epoetin tx: NR; duration of trial: 13.9 weeks vs. 14.5 weeks (mean intervention vs. control); follow-up: 12 months	SC	Iron: Y, oral (as indicated by BL transferrin saturation ± serum ferritin level); G-CSF: NR; RBCT trigger: Hb ≥ 9.7 g/dl prn (Hb inclusion criterion level: ≤ 12.1 g/dl)	Disease: solid; treatment: chemotherapy, platinum containing	HaemR, Hb, RBCT, HRQoL, AEs, survival (6 and 12 months)	Y
Schwartzberg 2004[246] ROL, active control; integrated analysis of three RCTs including Senecal 2005[247]	Darbepoetin alfa: $n = 157$; age (years): 58.7 (11.5); male, *n* (%): 23 (15); Hb BL (g/dl): 10.4 (0.8); epoetin BL (mU/ml): NR	Epoetin alfa: $n = 155$; age (years): 61.7 (12.1); male, *n* (%): 26 (17); Hb BL (g/dl): 10.4 (0.8); epoetin BL (mU/ml): NR	Brand: darbepoetin alfa; dose: 200 µg Q2W; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 19/20 weeks; follow-up: NR Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 19/20 weeks; follow-up: NR	Head-to-head	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 11 g/dl)	Disease: solid (breast, lung, gynaecological); treatment: chemotherapy, mixed	Hb, RBCT, HRQoL, PSQ, AEs; subgroup analysis by BL Hb category < 10 g/dl and ≥ 10 g/dl)	N; excluded as compared darbepoetin with epoetin

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Senecal 2005[247] RCT, active control; also reported in Schwartzberg 2004[246]	Darbepoetin alfa: $n = 72$; age (years): 53.6 ± 11.4 (35–81); male, *n* (%): all female; Hb BL (g/dl): 10.5 ± 0.8; epoetin BL (mU/ml): NR	Epoetin alfa: $n =$; age (years): 58.4 ± 12.5 (34–81); male, *n* (%): all female; Hb BL (g/dl): 10.6 ± 0.7; epoetin BL (mU/ml): NR	Brand: darbepoetin alfa; dose: 200 µg Q2W; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 19/20 weeks; follow-up: NR Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 19/20 weeks; follow-up: NR	Head-to-head	Iron: Y, not specified, per institution standards; G-CSF: NR; RBCT trigger: Hb < 8 g/dl (Hb inclusion criterion level: ≤ 11 g/dl)	Disease: solid (breast); treatment: chemotherapy, mixed	HaemR, Hb, RBCT, PSQ, AEs; subgroup analysis by BL Hb category < 10 g/dl and ≥ 10 g/dl)	N; excluded as ESAs were given in context with surgery, stem cell transplantation
Thomas 2008[248] ROL (GOG-0191; NCT00017004; CAN-NCIC-CX4)	$n = 57$; age (years): 46 (25–77); male, *n* (%): all female; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	$n = 52$; age (years): 50 (32–78); male, *n* (%): all female; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: rHuEPO; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: unclear; duration of trial: unclear; follow-up: 37 months (9.8–50.4 months)	SC	Iron: NR; G-CSF: NR; RBCT trigger: Hb < 12 g/dl (as a result of vaginal bleeding, intervention arm) (Hb inclusion criterion level: < 12 g/dl for randomisation; < 14 g/dl at study entry)	Disease: solid (cervix); treatment: chemotherapy (platinum containing) + radiotherapy	Hb, RBCT, AEs (TVEs), survival; trial terminated early with < 25% of planned accrual because of concerns over TVEs with rHuEPO	Y
Tsuboi 2009[249] RCT	$n = 61$; age (years): 61.8 ± 11.9; male, *n* (%): 34 (56); Hb BL (g/dl): 10.0 ± 1.0; epoetin BL (mU/ml): 67.3 ± 72.0	$n = 56$; age (years): 62.1 ± 9.6; male, *n* (%): 33 (59); Hb BL (g/dl): 10.4 ± 1.0; epoetin BL (mU/ml): 49.1 ± 33.4	Brand: epoetin beta; dose: 36,000 IU QW; dose adjustment: Y; duration of epoetin tx: 8 weeks; duration of trial: 8 weeks; follow-up: median follow-up 670 days	PBO	Iron: Y, oral, if indicated by serum iron saturation or MCV); G-CSF: NR; RBCT trigger: prn (Hb inclusion criterion level: ≤ 8.0 g/dl and ≤ 11 g/dl)	Disease: solid (lung) and haematological; treatment: chemotherapy, mixed	HaemR, Hb, RBCT, HRQoL, AEs, survival[m]	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Wagner 2004[61] ROL[k]	$n = 18$; age (years): 3.2 (1.2–19.4); male, n (%): NR; Hb BL (g/dl): 8.85 (6.10–11.20); epoetin BL (mU/ml): NR	$n = 20$; age (years): 3.2 (1.1–7.3); male, n (%): NR; Hb BL (g/dl): 9.35 (7.00–15.3); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 200 IU/kg/day; dose adjustment: Y; duration of epoetin tx: day 6 of cycle 1 continuing to 48 hours before start of cycle 2 – in subsequent cycles given 24 hours after completion of chemotherapy; duration of trial: unclear; follow-up: NR	SC	Iron: Y, oral, daily (as indicated by transferrin saturation); G-CSF: 10 µg/kg/day both tx arms; RBCT trigger: Hb ≤ 8 g/dl (Hb inclusion criterion level: NR)	Disease: haematological; treatment: chemotherapy, mixed	Hb, RBCT, survival	N; excluded as no usable data for any outcome
Waltzman 2005[241] ROL, active control	Epoetin alfa: $n = 178$; age (years): 62.1 ± 11.8; male, n (%): 69 (38.8); Hb BL (g/dl): 10.16 ± 0.749; epoetin BL (mU/ml): NR	Darbepoetin alfa: $n = 180$; age (years): 63.4 ± 11.8; male, n (%): 61 (33.9); Hb BL (g/dl): 10.07 ± 0.787; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: NR Brand: darbepoetin alfa; dose: 200 µg Q2W; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: NR	Head-to-head	Iron: Y, oral daily or intravenously if contraindicated; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 11 g/dl)	Disease: solid; treatment: chemotherapy, mixed	HaemR, Hb, RBCT, HRQoL, AEs	N; excluded as ESAs were given in context with surgery, stem cell transplantation
Wilkinson 2006[250] ROL	$n = 114$; age (years): 59.1 ± 10.6 (35–87); male, n (%): all female; Hb BL (g/dl): 10.75 ± 0.94; epoetin BL (mU/ml): NR	$n = 59$; age (years): 60.3 ± 11.2 (30–79); male, n (%): all female; Hb BL (g/dl): 10.66 ± 0.83; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 10,000 IU TIW; dose adjustment: Y; duration of epoetin tx: up to 28 weeks; duration of trial: up to 28 weeks; follow-up: NR	SC	Iron: Y, oral (as indicated by transferrin saturation); G-CSF: Y, not specified; RBCT trigger: Hb < 9 g/dl prn (Hb inclusion criterion level: ≤ 12 g/dl)	Disease: solid (ovary); treatment: chemotherapy, platinum containing	HaemR, Hb, RBCT, HRQoL, AEs, TR	Y
Winquist 2009[251] RCT	$n = 26$; age (years): 71 (53–87); male, n (%): all male; Hb BL (g/dl): 104 (73–120); epoetin BL (mU/ml): NR	$n = 30$; age (years): 71 (50–83); male, n (%): all male; Hb BL (g/dl): 104 (81–120); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU TIW; dose adjustment: Y; duration of epoetin tx: 16 weeks;[n] duration of trial: 16 weeks;[n] follow-up: NA[n]	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 12 g/dl)	Disease: solid (prostate); treatment: unclear, NR	Hb, RBCT, HRQoL, AEs, survival	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Witzig 2005[167] RCT (NCT00003600; CDR0000066673; NCCTG-979253; NCI-P98-0133)	*n* = 174; age (years): 63.6 (11.89); male, *n* (%): 75 (45); Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	*n* = 170; age (years): 63.7 (13.0); male, *n* (%): 71 (43); Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: 16 weeks; follow-up: 12 months	PBO	Iron: Y, oral, daily; G-CSF: NR; RBCT trigger: Hb prn (Hb inclusion criterion level: < 11.5 g/dl men; < 10.5 g/dl women)	Disease: solid and haematological; treatment: chemotherapy, mixed	HaemR, Hb, RBCT, HRQoL, AEs, TR, survival	Y
Wright 2007[19] RCT	*n* = 33; age (years): 68 (47–86); male, *n* (%): 17 (52); Hb BL (g/dl): 103 (72–118); epoetin BL (mU/ml): NR	*n* = 37; age (years): 70 (39–87); male, *n* (%): 20 (54); Hb BL (g/dl): 103 (76–120); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 40,000 IU QW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: 26 weeks+	PBO	Iron: Y, not specified, prn; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: NR)	Disease: solid (non-small-cell lung cancer); treatment: chemotherapy, non-platinum containing[o]	Hb, RBCT, HRQoL, AEs, survival	Y

↓ decrease only; BL, baseline; C, cycles; ECOG, Eastern Cooperative Oncology Group; haemR, haematopoietic response; incl., includ(e/ing); MCV, mean corpuscular volume; N, no; NR, not reported; PBO, placebo; prn, pro re nata (as needed); PSQ, Patient Satisfaction Questionnaire; QW, once weekly; Q2W, once every 2 weeks; Q3W, once every 3 weeks; ROL, randomised open-label study; SC, standard care; TIW, three times a week; TR, tumour response; TVEs, thrombovascular events; tx, treatment; Y, yes.

a Values are mean (SD) or median (range) unless otherwise stated.
b Study includes other doses of intervention under review (either dose–response study[17,53,50] or three-arm trial;[51,52] for licensed dose details see *Appendix 7*).
c BL characteristics and some efficacy outcomes reported for all participants randomised (i.e. for all doses of darbepoetin alfa).
d Majority of participants received platinum-based chemotherapy.
e A total of 389 patients in the original RCT. Patients were included in this retrospective analysis if they were randomised, received at least 4 weeks of study treatment and reported outcomes at BL and at least once after 4 weeks of treatment (*n* = 300). In total, 89 patients did not report outcomes at baseline or at least once after 4 weeks of treatment.
f Because dose increases were allowed with epoetin alfa, the ability to directly compare the dose of darbepoetin alfa with epoetin alfa is confounded, although descriptive comparisons were made.
g Haematology values were protocol entry deviations.
h Definition changed retrospectively to allow comparison with other studies (from maintenance of Hb ≥ 12 g/dl to 2 g/dl increase without transfusion in the previous 4 weeks).
i Randomised comparative phase followed by optional open-label treatment phase (12 weeks).
j Trial was halted early in accordance with a recommendation from the independent Data Monitoring Committee because of higher mortality in the epoetin alfa group.
k Intervention evaluated in a paediatric population.
l Trial was halted early by the Data and Safety Monitoring Board because 28.5% of participants developed thromboembolic events.
m A retrospective analysis was performed for survival.
n Trial terminated early because of low accrual (contributors' emergent widespread availability of epoetin alfa therapy through provincial drug plans and third-party payers and the early closure of a concurrent trial of epoetin alfa in patients with non-small-cell lung cancer). Both trials underwent planned safety analyses because of an increase in thromboembolism reported in other trials.
o Eligibility criteria relaxed to exclude only platinum-based chemotherapy.

Appendix 7 Study and baseline characteristics of included licensed studies

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Wilson and colleagues 2007:[2] primary studies								
Abels 1993[63] RCT; multiple publications: Abels 1996,[59] Henry 1995,[58] Henry 1994,[85] Case 1993[86]	$n = 153/213$ (analysed $n = 143/206$);[b] age (years): 61.2 ± 13.0; male, *n* (%): 102 (47.8); Hb BL (g/dl): NR; epoetin BL (mU/ml): 146 ± 260	$n = 200$ (analysed $n = 135/190$); age (years): 62.5 ± 12.3; male, *n* (%): 95 (47.5); Hb BL (g/dl): NR; epoetin BL (mU/ml): 149 ± 217	Brand: rHuEPO;[c] dose: 150 IU/kg TIW; dose adjustment: NR; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks;[d] follow-up: NR	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 10.5 g/dl)	Disease: haematological and solid; treatment: chemotherapy, mixed	HaemR, haematocrit, RBCT, HRQoL,[b] AEs[b]	Y
Aravantinos 2003[64] ROL	$n = 24$; age (years): 59 (18–76); male, *n* (%): 2 (8); Hb BL (g/dl): 9.8 ± 0.5; epoetin BL (mU/ml): NR	$n = 23$; age (years): 64 (23–75); male, *n* (%): 7 (30%); Hb BL (g/dl): 9.3 ± 0.8; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y, ↓prn; duration of epoetin tx: unclear, median five cycles; duration of trial: NR; follow-up: NR	SC	Iron: Y, oral, fixed; G-CSF: NR; RBCT trigger: Hb < 9 g/dl (Hb inclusion criterion level: < 10.5 g/dl)	Disease: solid (including ovarian); treatment: chemotherapy, platinum-containing	Hb, haematocrit, RBCT	Y
Boogaerts 2003[65] ROL; identified: citation checking (abstract of this paper – Coiffier 2001[87] was included in Wilson and colleagues'[2] review)	$n = 133$; age (years): 62 (24–85); male, *n* (%): 46 (35); Hb BL (g/dl): 9.0 (5–13); epoetin BL (mU/ml): 54 (7–1650)	$n = 129$; age (years): 62 (24–85); male, *n* (%): 52 (40); Hb BL (g/dl): 9.2 (5–12); epoetin BL (mU/ml): 58 (5–4300)	Brand: epoetin beta; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: NR	SC	Iron: Y, oral (as indicated by transferrin saturation level); G-CSF: NR; RBCT trigger: Hb < 8.5 g/dl (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: haematological and solid; treatment: chemotherapy, NR	HaemR, Hb, RBCT, HRQoL, AEs	Y
Dammacco 2001[66] RCT NCT00270101; CR005911	$n = 69$; age (years): 67 (43–80); male, *n* (%): 34 (49); Hb BL (g/dl): 9.3 ± 1.27; epoetin BL (mU/ml): 116 (18–5220)	$n = 76$; age (years): 65 (38–89); male, *n* (%): 31 (41); Hb BL (g/dl): 9.6 ± 0.95; epoetin BL (mU/ml): 93 (10–408)	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks;[d] follow-up: NR	PBO	Iron: NR; G-CSF: NR; RBCT trigger: Hb < 8 g/dl (Hb inclusion criterion level: < 11.0 g/dl)	Disease: haematological; treatment: chemotherapy, mixed[e]	HaemR, Hb, RBCT, HRQoL, AEs	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Del Mastro 1997[67] ROL	$n = 31$; age (years): 54 (31–68); male, *n* (%): NR; Hb BL (g/dl): 13.0 ± 0.7; epoetin BL (mU/ml): 21.0 (0–512)	$n = 31$; age (years): 56 (29–68); male, *n* (%): NR; Hb BL (g/dl): 13.1 ± 0.6; epoetin BL (mU/ml): 25.5 (0–800)	Brand: rHuEPO;[c] dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 14 weeks; duration of trial: 14 weeks; follow-up: 6 months	SC	Iron: Y, oral iron (as indicated by serum iron, ferritin and transferrin saturation levels); G-CSF: Y, 5 µg/kg subcutaneously days 4–11, cycles 1–5; RBCT trigger: Hb < 8 g/dl (Hb inclusion criterion level: ≥ 12.0 g/dl)	Disease: solid (breast); treatment: chemotherapy, non-platinum containing	Hb, RBCT, HRQoL, AEs	Y
Dunphy 1999[68] ROL	$n = 15$ (analysed $n = 13$); age (years): 59 (42–76); male, *n* (%): 12 (92); Hb BL (g/dl): 14.1 ± 2.1; epoetin BL (mU/ml): 8.8 (5.1)	$n = 15$ (analysed $n = 14$); age (years): 67 (32–82); male, *n* (%): 7 (50); Hb BL (g/dl): 14.1 ± 1.6; epoetin BL (mU/ml): 7.3 (4.4)	Brand: rHuEPO;[c] dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: unclear, ≈6 weeks; duration of trial: unclear; follow-up: NR	SC	Iron: Y, oral, dailly; G-CSF: NR; RBCT trigger: Hb < 8 g/dl (Hb inclusion criterion level: NR)	Disease: solid (including head and neck, lung); treatment: chemotherapy, mixed	Hb, RBCT	Y
Hedenus 2002[53] RCT, dose–response study; two unlicensed doses excluded	$n = 22$;[f] age (years): 69 (20–84); male, *n* (%): 14 (64); Hb BL (g/dl): 9.4 (1.3); epoetin BL (mU/ml): 69 (12–1362)	$n = 11$; age (years): 63 (25–80); male, *n* (%): 2 (18); Hb BL (g/dl): 9.5 (1.0); epoetin BL (mU/ml): 45 (12–132)	Brand: darbepoetin alfa; dose: 2.25 µg/kg QW;[f] dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 16 weeks; follow-up: unclear	PBO	Iron: prn; G-CSF: NR; RBCT trigger: Hb ≤ 8 g/dl prn (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: haematological; treatment: chemotherapy, NR	HaemR, Hb, RBCT, AEs	Y
Hedenus 2003[17] RCT; multiple publications: Littlewood 2006[83] (see PenTAG results below)	$n = 176$ (analysed $n = 174$);[f] age (years): 64.8 (13.8); male, *n* (%): 87 (50); Hb BL (g/dl): 9.59 (1.22); epoetin BL (mU/ml): 68.99 (2.3–1522.7)	$n = 173$ (analysed $n = 170$); age (years): 64.6 (12.2); male, *n* (%): 78 (46); Hb BL (g/dl): 9.5 (1.21); epoetin BL (mU/ml): 54.49 (10.9–3169.1)	Brand: darbepoetin alfa; dose: 2.25 µg/kg QW;[f] dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 16 weeks; follow-up: median ≈11 months	PBO	Iron: prn; G-CSF: NR; RBCT trigger: Hb ≤ 8 g/dl prn (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: haematological; treatment: chemotherapy, NR	HaemR, RBCT, HRQoL, AEs	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Kotasek 2003[50] RCT, dose–response study; five unlicensed doses excluded	$n = 17/198$;[b,f] age (years): 58.3 (11.9);[b] male, *n* (%): 56 (28);[b] Hb BL (g/dl): 9.93 (1.00);[b] epoetin BL (mU/ml): NR	$n = 51$; age (years): 56.2 (12.4); male, *n* (%): 16 (31); Hb BL (g/dl): 9.87 (1.12); epoetin BL (mU/ml): NR	Brand: darbepoetin alfa; dose: 2.25 µg/kg QW;[f] dose adjustment: Y, ↓; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks;[d] follow-up: unclear	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: solid (breast, gynaecological, gastrointestinal, lung); treatment: chemotherapy, NR	HaemR, Hb, RBCT, HRQoL,[b] AEs[b]	Y
Kurz 1997[69] RCT	$n = 23$; age (years): 54.4 ± 9.7; male, *n* (%): NR; Hb BL (g/dl): 9.88 ± 0.8; epoetin BL (mU/ml): NR	$n = 12$; age (years): 52.7 ± 7.5; male, *n* (%): NR; Hb BL (g/dl): 9.85 ± 0.60; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: NR	PBO	Iron: Y, intravenous iron; G-CSF: NR; RBCT trigger: Hb < 8 g/dl (Hb inclusion criterion level: < 11.0 g/dl)	Disease: solid (ovary, cervix, uterus); treatment: chemotherapy, mixed[g]	HaemR, RBCT, HRQoL, AEs	Y
Littlewood 2001[70] RCT (EPO-INT-1); multiple publications: Aapro, 2004,[82] Bajetta 2004,[81] Patrick 2003[60] (see PenTAG results below)	$n = 251$ (analysed $n = 244$); age (years): 58.3 ± 14.2; male, *n* (%): 85 (34); Hb BL (g/dl): 9.9 ± 1.1; epoetin BL (mU/ml): NR	$n = 124$ (analysed $n = 115$); age (years): 59.5 ± 13.9; male, *n* (%): 39 (31); Hb BL (g/dl): 9.7 ± 1.1; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: up to 28 weeks; duration of trial: up to 28 weeks; follow-up: 12 months[h]	PBO	Iron: Y, oral (or intravenous as indicated by transferrin saturation level); G-CSF: N; RBCT trigger: Hb < 8 g/dl prn (Hb inclusion criterion level: ≤ 10.5 g/dl or > 10.5 g/dl but ≤ 12.0 g/dl after a ≥ 1.5 g/dl decrease in Hb)	Disease: solid and haematological; treatment: chemotherapy, non-platinum containing	HaemR, Hb, RBCT, HRQoL, AEs, survival (at 12 months' follow-up)	Y
Österborg 2002[71] RCT; multiple publications: Österborg 2005[79] (see PenTAG results below)	$n = 173$ (analysed $n = 170$); age (years): 63 (32–86); male, *n* (%): 91 (54); Hb BL (g/dl): 9.2 ± 1.1; epoetin BL (mU/ml): 38 (20–72)	$n = 176$ (analysed $n = 173$); age (years): 64 (28–83); male, *n* (%): 82 (47); Hb BL (g/dl): 9.3 ± 1.0; epoetin BL (mU/ml): 41 (21–77)	Brand: epoetin beta; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: up to 16 weeks; follow-up: min. 17.5 months both tx groups	PBO	Iron: Y, intravenously (or orally if intravenously precluded); G-CSF: NR; RBCT trigger: Hb < 8.5 g/dl or increase in Hb of < 0.5 g/dl vs. BL (Hb inclusion criterion level: < 10 g/dl[i])	Disease: haematological; treatment: chemotherapy, non-platinum containing	HaemR, Hb, RBCT, HRQoL, AEs, survival, long-term survival	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Silvestris 1995[72] ROL	*n* = 30 (analysed *n* = 27); age (years): NR; male, *n* (%): NR; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	*n* = 24 (analysed *n* = 22); age (years): NR; male, *n* (%): NR; Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: up to 24 weeks; duration of trial: up to 24 weeks; follow-up: NR	SC	Iron: Y, not specified; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 8 g/dl)	Disease: haematological; treatment: chemotherapy, NR	HaemR, Hb, AEs	Y
ten Bokkel Huinink 1998[51] ROL; multiple treatment arms, one unlicensed dose excluded	*n* = 46 (analysed *n* = 45);[f] age (years): 58.81; male, *n* (%): all female; Hb BL (g/dl): 12.0 (1.3–12.6); epoetin BL (mU/ml): NR	*n* = 34 (analysed *n* = 33); age (years): 58.83; male, *n* (%): all female; Hb BL (g/dl): 11.8 (10.6–12.5); epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 24 weeks; duration of trial: 24 weeks; follow-up: NR	SC	Iron: NR; G-CSF: NR; RBCT trigger: Hb < 9.7 g/dl (Hb inclusion criterion level: < 13 g/dl)	Disease: solid (ovary); treatment: chemotherapy, platinum containing	RBCT, AEs	Y
Thatcher 1999[52] ROL; multiple treatment arms, one unlicensed dose excluded	*n* = 42;[f] age (years): 59 (43–72); male, *n* (%): 26 (61.9); Hb BL (g/dl): 13.7 (10.7–16.1); epoetin BL (mU/ml): NR	*n* = 44; age (years): 60 (39–74); male, *n* (%): 27 (61.3); Hb BL (g/dl): 13.4 (10.9–16.4); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 26 weeks; duration of trial: 26 weeks; follow-up: NR	SC	Iron: NR; G-CSF: NR; RBCT trigger: prn (Hb inclusion criterion level: ≥ 10.5 g/dl)	Disease: solid (small-cell lung cancer); treatment: chemotherapy: mixed[g]	Hb, RBCT, HRQoL, AEs	Y
Vansteenkiste 2002[73] RCT; multiple publications: Vansteenkiste 2004[84] (see PenTAG results below)	*n* = 156; age (years): 61.6 (9.2); male, *n* (%): 111 (71); Hb BL (g/dl): 10.28 (1.08); epoetin BL (mU/ml): 53.17 (58.87)[j]	*n* = 158; age (years): 61.3 (8.8); male, *n* (%): 116 (73); Hb BL (g/dl): 9.93 (1.01); epoetin BL (mU/ml): 51.10 (71.72)[j]	Brand: darbepoetin alfa; dose: 2.25 µg/kg QW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: 12 months	PBO	Iron: NR; G-CSF: NR; RBCT trigger: Hb ≤ 8 g/dl (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: solid (lung); treatment: chemotherapy, platinum containing	HaemR, Hb, RBCT (from week 5 and week 1), HRQoL, AEs, disease progression, survival	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Wilson and colleagues 2007:[2] multiple publications								
Abels 1996[59] Double-blind data + unified analysis ; identified: citation checking; primary study: Abels 1993[63]	$n = 153/213$ (analysed $n = 143/206$);[b] age (years): 61.2 ± 13.0; male, *n* (%): 102 (47.8); Hb BL (g/dl): NR; epoetin BL (mU/ml): 146 ± 260	$n = 200$ (analysed $n = 135/190$); age (years): 62.5 ± 12.3; male, *n* (%): 95 (47.5); Hb BL (g/dl): NR; epoetin BL (mU/ml): 149 ± 217	Brand: rHuEPOb; dose: 150 IU/kg TIW; dose adjustment: NR; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks;[d] follow-up: NR	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: ≤ 10.5 g/dl)	Disease: haematological and solid; treatment: chemotherapy, mixed	HaemR, haematocrit, RBCT, HRQoL,[b] AEs[b]	Y
Case 1993[86] RCT; primary study: Abels 1993[63]	$n = 81$ (analysed $n = 79$); age (years): 64 (27–92); male, *n* (%): 33 (40.7); Hb BL (g/dl): NR; epoetin BL (mU/ml): 95.0 (16–1262)	$n = 76$ (analysed $n = 79$); age (years): 64 (30–88); male, *n* (%): 29 (38.1); Hb BL (g/dl): NR; epoetin BL (mU/ml): 93.5 (16–1734)	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y, ↓prn; duration of epoetin tx: NR; duration of trial: NR; follow-up: NR	SC	Iron: Y, oral iron, fixed; G-CSF: N; RBCT trigger: Hb < 9 g/dl (Hb inclusion criterion level: < 10.5 g/dl)	Disease: solid (including ovarian); treatment: chemotherapy, platinum containing	Hb, haematocrit, RBCT	Y
Henry 1995[58] ROL; primary study: Abels 1993[63]	$n = 69$ (analysed $n = 64$); age (years): 58; male, *n* (%): 30 (45); Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	$n = 61$ (analysed $n = 65$); age (years): 59; male, *n* (%): 32 (49); Hb BL (g/dl): NR; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y, ↓prn; duration of epoetin tx: 12 weeks or until haematocrit = 38–40%; duration of trial: 12 weeks; follow-up: NR	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: NR)	Disease: haematological and solid; treatment: chemotherapy, platinum containing	Haematocrit, RBCT, AEs	Y
Henry 1994[85] ROL Double-blind and open-label extension data; identified: citation checking; primary study: Abels 1993[63]	$n = 67$ (analysed $n = 64$); age (years): NR;[k] male, *n* (%): NR;[k] Hb BL (g/dl): NR;[k] epoetin BL (mU/ml): NR[k]	$n = 65$ (analysed $n = 61$); age (years): NR;[k] male, *n* (%): NR;[k] Hb BL (g/dl): NR;[k] epoetin BL (mU/ml): NR[k]	Brand: epoetin alfa; dose: 450 IU/kg QW; dose adjustment: NR; duration of epoetin tx: 12 weeks; duration of trial: NR; follow-up: NR	SC	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: NR)	Disease: solid and haematological; treatment: chemotherapy, platinum containing	HaemR, RBCT, HRQoL, AEs	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
PenTAG review: study characteristics – primary studies 2004 to current								
Grote 2005[74] ROL (N93-004)	*n* = 109; age (years): 64.4 (8.7); male, *n* (%): 59 (54.1); Hb BL (g/dl): 12.8 (1.5); epoetin BL (mU/ml): NR	*n* = 115; age (years): 63.2 (8.9); male, *n* (%): 64 (55.7); Hb BL (g/dl): 13 (1.5); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: unclear; duration of trial: unclear; follow-up: 3 years	PBO	Iron: NR; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: < 14.5 g/dl)	Disease: solid (small-cell lung cancer); treatment: chemotherapy, platinum containing	Hb, RBCT, AEs, TR, survival	Y
Moebus 2013[62] ROL [Arbeitsgemeinschaft für Gynäkologische Onkologie epirubicin, paclitaxel, and cyclophosphamide (AGO ETC) trial]	*n* = 324; age (years): 50 (29–65); male, *n* (%): all female; Hb BL (g/dl): 12.4 (9–16); epoetin BL (mU/ml): NR	*n* = 319; age (years): 52 (28–67); male, *n* (%): all female; Hb BL (g/dl): 12.8 (9–16); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 18 weeks; duration of trial: 18 weeks; follow-up: 10 years (ongoing)	SC	Iron: Y, oral; G-CSF: NR; RBCT trigger: Hb < 9 g/dl and investigator discretion (Hb inclusion criterion level: NR)	Disease: solid (breast); treatment: chemotherapy, non-platinum containing	Hb, RBCT, HRQoL, AEs, survival	N; however, Moebus 2004[192] and 2007[33] included
Ray-Coquard 2009[75] ROL (ELYPSE study)	*n* = 110; age (years): 62.7 (11.6); male, *n* (%): 52 (47.3); Hb BL (g/dl): 10 (1.2); epoetin BL (mU/ml): NR	*n* = 108; age (years): 61.7 (11.6); male, *n* (%): 41 (38); Hb BL (g/dl): 10 (1.2); epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: 12 months (95% CI 12–12.4 months)	SC	Iron: Y, oral; G-CSF: Y; RBCT trigger: NR (Hb inclusion criterion level: ≤ 12.0 g/dl)	Disease: solid and haematological; treatment: chemotherapy, NR	RBCT, OS, HRQoL, AEs	Y
Strauss 2008[76] RCT (NCT00046969; Roche MO16375; Strauss 2005[252])	*n* = 34; age (years): 48.8 ± 10.2; male, *n* (%): all female; Hb BL (g/dl): 11.4 (10.8–12.0); epoetin BL (mU/ml): NR	*n* = 40; age (years): 49.2 ± 12.8); male, *n* (%): all female; Hb BL (g/dl): 11.6 (10.9–12.4); epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: 6 months	PBO	Iron: Y, orally or intravenously; G-CSF: NR; RBCT trigger: ≤ 8.5 g/dl prn (Hb inclusion criterion level: 9–13 g/dl)	Disease: solid (cervix); treatment: chemotherapy + radiotherapy	Hb, RBCT TR, survival, AEs	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Tjulandin 2010[48] RCT (ISRCTN09530309)	Epoetin theta: *n* = 76; age (years): 53.7 ± 10.3; male, *n* (%): 30 (39.5); Hb BL (g/dl): 9.6 ± 1.1; epoetin BL (mU/ml): NR Epoetin beta: *n* = 73; age (years): 57.3 ± 10.5; male, *n* (%): 22 (30.1); Hb BL (g/dl): 9.5 ± 0.8; epoetin BL (mU/ml): NR	*n* = 74; age (years): 57.3 ± 11.5; male, *n* (%): 19 (25.7); Hb BL (g/dl): 9.4 ± 1.2; epoetin BL (mU/ml): NR	Brand: epoetin beta; dose: 150 IU/kg TIW; dose adjustment: Y Brand: epoetin theta; dose: 20,000 IU QW Dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: NR	PBO	Iron: Y, not specified; G-CSF: NR; RBCT trigger: ≤ 8.5 g/dl prn (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: solid; treatment: chemotherapy, platinum containing	HaemR, Hb, RBCT, RBC units, HRQoL, AEs	Y
Tjulandin 2011[77] RCT	*n* = 95; age (years): 56.9 ± 14.7; male, *n* (%): 30 (31.6); Hb BL (g/dl): 9.2 ± 1.3; epoetin BL (mU/ml): NR	*n* = 91; age (years): 55.8 ± 14.3; male, *n* (%): 34 (37.4); Hb BL (g/dl): 9.1 ± 1.3; epoetin BL (mU/ml): NR	Brand: epoetin theta; dose: 20,000 IU QW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: NR	PBO	Iron: Y, not specified; G-CSF: NR; RBCT trigger: ≤ 8.5 g/dl (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: solid and haematological; treatment: chemotherapy, non-platinum containing	HaemR, Hb, RBCT, RBC units, HRQoL, AEs	Y
Untch 2011[78,80] RCT	*n* = 356; age (years): 48 (23–65);[b] male, *n* (%): NR; Hb BL (g/dl): 13.64 ± 1.17; epoetin BL (mU/ml): NR	*n* = 377; age (years): 48 (23–65);[b] male, *n* (%): NR; Hb BL (g/dl): 13.61 ± 1.16; epoetin BL (mU/ml): NR	Brand: darbepoetin alfa; dose: 4.5 mg/kg Q2W;[l] dose adjustment: Y; duration of epoetin tx: NR; duration of trial: NR; follow-up: median 43.5 months	SC	Iron: Y, orally; G-CSF: NR; RBCT trigger: NR (Hb inclusion criterion level: NR	Disease: solid (breast); treatment: chemotherapy, non-platinum containing	Hb, pathological response, disease progression, survival, AEs	Y

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Multiple publications: PenTAG review								
Aapro 2004[82] Primary study: Littlewood 2001[70]	$n = 251$ (analysed $n = 244$); age (years): 58.3 ± 14.2; male, *n* (%): 85 (34); Hb BL (g/dl): 9.9 ± 1.1; epoetin BL (mU/ml): NR	$n = 124$ (analysed $n = 115$); age (years): 59.5 ± 13.9; male, *n* (%): 39 (31); Hb BL (g/dl): 9.7 ± 1.1; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: up to 28 weeks; duration of trial: up to 28 weeks; follow-up: 12 months[h]	PBO	Iron: Y, orally or intravenously; G-CSF: N; RBCT trigger: Hb < 8 g/dl prn (Hb inclusion criterion level: ≤ 10.5 g/dl or > 10.5 g/dl but ≤ 12.0 g/dl after a ≥ 1.5 g/dl decrease in Hb)	Disease: solid + haematological; treatment: chemotherapy, non-platinum containing	HaemR, Hb, RBCT, HRQoL, AEs, survival (at 12 months' follow-up)	N
Bajetta 2004[81] Primary study: Littlewood 2001[70]	Subgroup: breast population: $n = 78$ (analysed $n = 75$); age (years): 54.6; male, *n* (%): 1 (1); Hb BL (g/dl): 10.0 ± 1.6; epoetin BL (mU/ml): NR	Subgroup: breast population: $n = 36$ (analysed $n = 35$); age (years): 52.9; male, *n* (%): all female; Hb BL (g/dl): 9.9 ± 1.01; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: up to 28 weeks; duration of trial: up to 28 weeks; follow-up: 12 months[h]	PBO	Iron: Y, orally (or intravenously as indicated by transferrin saturation level); G-CSF: N; RBCT trigger: Hb < 8 g/dl prn (Hb inclusion criterion level: ≤ 10.5 g/dl or > 10.5 g/dl but ≤ 12.0 g/dl after a ≥ 1.5 g/dl decrease in Hb)	Disease: solid and haematological; treatment: chemotherapy, non-platinum containing	HaemR, Hb, RBCT, HRQoL, AEs (retrospective analysis of breast cancer cohort[70])	N
Littlewood 2006[83] Primary study: Hedenus, 2003[17]	Subgroup: HRQoL sample: $n = 303$;[m] age (years): 64.8 (12.8); male, *n* (%): 146 (48.2); Hb BL (g/dl): 9.6 (1.2); epoetin BL (mU/ml): NR		Brand: darbepoetin alfa; dose: 2.25 µg/kg QW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: median ≈11 months	PBO	Iron: prn; G-CSF: NR; RBCT trigger: Hb ≤ 8 g/dl (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: haematological; treatment: chemotherapy, NR	HRQoL (alleviating fatigue and effect of fatigue on quality of life)	N

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Österborg 2005,[79] survival data from Österborg 2002[71] RCT; primary study: Österborg 2002[71]	$n = 173$ (analysed $n = 170$); age (years): 63 (32–86); male, *n* (%): 91 (54); Hb BL (g/dl): 9.2 ± 1.1; epoetin BL (mU/ml): 38 (20–72)	$n = 176$ (analysed $n = 173$); age (years): 64 (28–83); male, *n* (%): 82 (47); Hb BL (g/dl): 9.3 ± 1.0; epoetin BL (mU/ml): 41 (21–77)	Brand: epoetin beta; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: 16 weeks; duration of trial: up to 16 weeks; follow-up: minimum 17.5 months both tx groups	PBO	Iron: Y, oral iron or intravenous iron if transferrin saturation $\leq 20\%$; G-CSF: N; RBCT trigger: Hb < 8.5 g/dl or increase in Hb of < 0.5 g/dl vs. BL (Hb inclusion criterion level: < 10 g/dl[i])	Disease: haematological; treatment: chemotherapy, non-platinum containing	Long-term survival	Y
Patrick 2003[60] Primary study: Littlewood 2001[70]	$n = 251$ (analysed $n = 244$); age (years): 58.3 ± 14.2; male, *n* (%): 85 (34); Hb BL (g/dl): 9.9 ± 1.1; epoetin BL (mU/ml): NR	$n = 124$ (analysed $n = 115$); age (years): 59.5 ± 13.9; male, *n* (%): 39 (31); Hb BL (g/dl): 9.7 ± 1.1; epoetin BL (mU/ml): NR	Brand: epoetin alfa; dose: 150 IU/kg TIW; dose adjustment: Y; duration of epoetin tx: up to 28 weeks; duration of trial: up to 28 weeks; follow-up: 12 months[h]	PBO	Iron: Y, orally (or intravenously as indicated by transferrin saturation level); G-CSF: N; RBCT trigger: Hb < 8 g/dl prn (Hb inclusion criterion level: ≤ 10.5 g/dl or > 10.5 g/dl but ≤ 12.0 g/dl after a ≥ 1.5 g/dl decrease in Hb)	Disease: solid and haematological; treatment: chemotherapy, non-platinum containing	HRQoL (minimally important difference in HRQoL)	N

Study, year	Intervention group characteristics[a]	Control group characteristics[a]	Study intervention[a]	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Included in Cochrane review 2012,[11] Y/N
Vansteenkiste 2004[84] Primary study: Vansteenkiste, 2002[73]	Subgroup Hb < 10 g/dl: *n* = 51; age (years): 63 (47–76); male, *n* (%): 42 (82); Hb BL (g/dl): 9.2 (7.4–9.9); epoetin BL (mU/ml): 50.3 (13.3–739.8) Subgroup Hb ≥ 10 g/dl *n* = 105; age (years): 62 (39–80); male, *n* (%): 69 (66); Hb BL (g/dl): 10.8 (10.0–13.6); epoetin BL (mU/ml): 28.8 (12.0–106.1)	Subgroup Hb < 10 g/dl: *n* = 69; age (years): 60 (42–78); male, *n* (%): 52 (75); Hb BL (g/dl): 9.2 (6.6–9.9); epoetin BL (mU/ml): 52.2 (14.3–1998.6) Subgroup Hb ≥ 10 g/dl *n* = 89; age (years): 62 (36–76); male, *n* (%): 64 (72); Hb BL (g/dl): 10.6 (10.0–12.3); epoetin BL (mU/ml): 30.2 (12.0–109.8)	Brand: darbepoetin alfa; dose: 2.25 µg/kg QW; dose adjustment: Y; duration of epoetin tx: 12 weeks; duration of trial: 12 weeks; follow-up: 12 months	PBO	Iron: N; G-CSF: N; RBCT trigger: Hb ≤ 8 g/dl and prn (Hb inclusion criterion level: ≤ 11.0 g/dl)	Disease: solid (lung); treatment: chemotherapy, platinum containing	HaemR, Hb, RBCT (from week 5 and week 1), HRQoL, AEs, disease progression, survival	Y

Key: ↓, decrease only; BL, baseline; haemR, haematopoietic response; N, no; NR, not reported; PBO, placebo; prn, pro re nata (as needed); QW, weekly; Q2W, every 2 weeks; ROL, randomised open-label study; SC, standard care; TIW, three times a week; TR, tumour response; tx, treatment; Y, yes.

a Values are mean ± SD or median (range) unless otherwise stated.
b BL characteristics and some efficacy outcomes reported for all participants randomised (i.e. includes participants not receiving chemotherapy;[63] for all doses of darbepoetin alfa;[50] for intervention and control combined at randomisation[78,80]).
c Assumed to be either epoetin alfa or epoetin beta based on date of trial and dose administered in the trial.
d Double-blind phase only; participants given the option to enter the 12-week open-label treatment period.
e Majority of participants received non-platinum-based chemotherapy.
f Study includes other doses of intervention under review (either dose–response study[17,50,53] or three-arm trial[51,52]).
g Majority of participants received platinum-based chemotherapy.
h Survival based on data collected during 12 months after study completed by last participant; reported based on proportion of patients randomised (only available for a proportion of patients randomised: *n* = 151 and *n* = 145 intervention and control groups, respectively).
i Inclusion criteria for Hb further stratified by serum erythropoietin level.
j Serum endogenous erythropoietin (mU/mL) not available for all participants randomised (*n* = 145 and *n* = 151 in intervention and control groups, respectively).
k BL characteristics not reported for treatment or control arms of the study.
l Dose administered in study equates to 2.25 µg/kg QW.
m Patients evaluated for HRQoL from trial sample;[17] not separated by intervention and control group for HRQoL sample.

Appendix 8 Multiple publications in clinical-effectiveness review

Primary study

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. *Br J Haematol* 2003;**122**:394–403.

Secondary publication

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. *J Pain Symptom Manage* 2006;**31**:317–25.

Primary study

Österborg 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. *J Clin Oncol* 2002;**20**:2486–94.

Secondary publication

Österborg A, Brandberg Y, Hedenus M. Impact of epoetin-beta on survival of patients with lymphoproliferative malignancies: long-term follow up of a large randomized study. *Br J Haematol* 2005;**129**:206–9.

Primary study

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. *J Natl Cancer Inst* 2002;**94**:1211–20.

Secondary publication

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. *Support Care Cancer* 2004;**12**:253–62.

Primary study

Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B, Epoetin Alfa Study Group. 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. *J Clin Oncol* 2001;**19**:2865–74.

Secondary publications

Bajetta E, Vercammen E, Reinhardt U, Janmohamed R, da Costa RM, Matulonis U, *et al.* Efficacy of epoetin alfa in a retrospective non-stratified subgroup analysis of a breast cancer cohort receiving non-platinum chemotherapy. *Tumori* 2004;**90**:449–57.

Aapro M, Bajetta E, Freund M, Littlewood TJ, Nortier JWR, Rapoport B. Is there a possible survival benefit to increasing hemoglobin levels with epoetin alfa during chemotherapy? *Eur J Cancer Suppl* 2004;**2**:20–8.

Patrick DL, Gagnon DD, Zagari MJ, Mathijs R, Sweetenham J, Epoetin Alfa Study Group. Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients receiving epoetin alfa. *Eur J Cancer* 2003;**39**:335–45.

Primary study

Abels R. Erythropoietin for anaemia in cancer patients. *Eur J Cancer* 1993;**29A**(Suppl. 2):S2–8.

Secondary publications

Case DC Jr, Bukowski RM, Carey RW, Fishkin EH, Henry DH, Jacobson RJ, *et al.* Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *J Natl Cancer Inst* 1993;**85**:801–6.

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. *Semin Oncol* 1994;**21**:21–8.

Henry DH, Brooks BJ Jr, Case DC Jr, Fishkin E, Jacobson R, Keller AM, *et al.* Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy. *Cancer J Sci Am* 1995;**1**:252–60.

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

Primary study

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 ± darbepoetin alfa in primary breast cancer – results at the time of surgery. *Ann Oncol* 2011;**22**:1988–98.

Secondary publication

Untch M, Minckwitz G, Konecny GE, Conrad U, Fett W, Kurzeder C, *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 with or without darbepoetin alfa in primary breast cancer – outcome on prognosis. *Ann Oncol* 2011;**22**:1999–2006.

Appendix 9 Application of licence in the included studies

Study	*n*	Arms	Malignancy	Treatment	Initial treatment[a]	Start Hb level[a]	Target Hb level[a]	Dose adjustment[a]
Licence details for epoetin alfa and epoetin beta[b]		Initial treatment: 150 IU/kg SC TIW or 450 IU/kg SC QW Start Hb level: ≤ 10 g/dl Target Hb level: 10–12 g/dl Dose adjustment: 4 weeks: Hb increase < 1 g/dl and reticulocyte increase ≥ 40,000 cells/µl: 300 IU/kg Q3W or 900 IU/kg QW; Hb increase ≥ 2 g/dl: reduce dose by 25–50%; Hb ≥ 12 g/dl: reduce dose by 25–50%; Hb ≥ 13 g/dl: stop and reinitiate at Hb 12 g/dl at a 25% lower dose						
Abels 1993[63]	413[c]	Epoetin alfa vs. placebo	Solid and haematological	Chemotherapy: mixed	**150 IU/kg TIW**	≤ 10.5 g/l or haematocrit ≤ 32%	NR	No dose escalation used. Dosing continued for 12 weeks; if haematocrit ≥ 38% withheld until haematocrit fell below 38%
Aravantinos 2003[64]	47	Epoetin alfa vs. standard	Solid	Chemotherapy: mixed	**150 IU/kg TIW**	**< 10.5 g/dl**	NR	No dose escalation used Hb > 14 g/dl: stop and reinitiate at Hb < 12.5 g/dl at 25% lower than the start dose
Boogaerts 2003[65]	262	Epoetin beta vs. standard	Solid and haematological	Chemotherapy: NR	**150 IU/kg TIW**	≤ 11 g/dl	12–14 g/dl	3–4 weeks Hb increase < 0.5 g/dl or 6 weeks Hb increase < 1 g/dl: dose doubled **Hb increase > 2 g/dl: dose reduced by 50%** Hb > 14 g/dl: stop and reinitiate at Hb < 12 g/dl at 50% lower than the start dose
Dammacco 2001[66]	145	Epoetin alfa vs. placebo	Haematological	Chemotherapy: mixed	**150 IU/kg TIW**	< 11 g/dl	12–14 g/dl	**4 weeks Hb increase < 1 g/dl: dose doubled** **4 weeks Hb increase ≥ 2 g/dl: dose reduced by 25%** Hb > 14 g/dl: stop and reinitiate at Hb ≤ 12 g/dl at 25% lower than the start dose

Study	*n*	Arms	Malignancy	Treatment	Initial treatment[a]	Start Hb level[a]	Target Hb level[a]	Dose adjustment[a]
Del Mastro 1997[67]	62	rHuEPO[d] vs. standard	Solid (breast)	Chemotherapy: non-plat	**150 IU/kg TIW**	≤ 12 g/dl	NR	If Hb > 15.0 g/dl in two consecutive weekly assays, treatment stopped until Hb < 13.0 g/dl
Dunphy 1999[68]	30	rHuEPO[d] vs. standard	Solid (head and neck, lung)	Chemotherapy: mixed	**150 IU/kg TIW**	NR; note rHuEPO was initiated if Hb ≤ 16 g/dl	NR	First course of chemotherapy: Hb increase < 1 g/dl: dose doubled Second course of chemotherapy: Hb increase < 1 g/dl: dose increased to 450 IU/kg Hb ≥ 18 g/dl: stop and reinitiate at Hb ≤ 16 g/dl
Grote 2005[74]	224	Epoetin alfa vs. placebo	Solid (SCLC)	Chemotherapy: mixed	**150 IU/kg TIW**	≤ 14.5 g/dl	14–16 g/dl	Dose escalation not permitted Hb > 16 g/dl: stop and reinitiate at Hb < 14 g/dl at a 50% lower dose
Kurz 1997[69]	35	Epoetin alfa vs. placebo	Solid (cervix, ovary, uterus)	Chemotherapy: mixed	**150 IU/kg TIW**	< 11 g/dl	NR	**4 weeks Hb increase < 1 g/dl: dose doubled**
Littlewood 2001[70]	375	Epoetin alfa vs. placebo	Mixed	Chemotherapy: non-plat	**150 IU/kg TIW**	≤ 10.5 g/dl or > 10 and ≤ 12 g/dl with ≥ 1.5 g/dl decrease in Hb per cycle per month	12–15 g/dl	4 weeks Hb increase < 1 g/dl and reticulocyte count increase < 40,000 cells/μl: dose doubled to 300 IU/kg **4 weeks Hb increase ≥ 2 g/dl: reduce dose by 25%** If Hb > 15 g/dl: stop and reinitiate at Hb < 12 g/dl at a 25% lower dose
Moebus 2013[62]	643	Epoetin alfa vs. standard	Solid (breast)	Chemotherapy: non-plat	**150 IU/kg TIW**	NR	12.5–13 g/dl	**4 weeks Hb increase < 2 g/dl: dose doubled** If Hb > 14 g/dl: stop and reinitiate at Hb < 13 g/dl

Study	*n*	Arms	Malignancy	Treatment	Initial treatment[a]	Start Hb level[a]	Target Hb level[a]	Dose adjustment[a]
Österborg 2002,[71] 2005[79]	349	Epoetin beta vs. placebo	Haematological	Chemotherapy: non-plat	**150 IU/kg TIW**	**< 10 g/dl**[e]	13–14 g/dl	4 weeks Hb increase < 0.5 g/dl: dose doubled 4 weeks Hb < 8.5 g/dl or transfusion: dose doubled **4 weeks Hb increase > 2 g/dl: reduce dose by 50%** If Hb > 14 g/dl: stop and reinitiate at Hb ≤ 13 g/dl at 50%
Ray-Coquard 2009[75]	218	Epoetin alfa vs. standard	Mixed	Chemotherapy: NR	**150 IU/kg TIW**	< 12 g/dl	**12–14 g/dl**	4 weeks Hb increase < 1 g/dl and Hb < 10.5 g/dl and reticulocyte count < 40,000 cells/µl: dose increased to 60,000 IU weekly 4 weeks Hb increase ≥ 2 g/dl: reduce dose by 25% If Hb > 12 g/dl: stop and reinitiate at Hb ≤ 12 g/dl
Silvestris 1995[72]	54	Epoetin alfa vs. standard	Haematological	Chemotherapy: NR	**150 IU/kg TIW**	**≤ 8 g/dl**	NR	By sixth week: dose doubled
Strauss 2008[76]	74	Epoetin beta vs. standard	Solid (cervix)	Chemotherapy + radiotherapy	**150 IU/kg TIW**	9–13 g/dl	14–15 g/dl	4 weeks Hb increase < 0.5 g/dl: dose doubled **4 weeks Hb increase > 2 g/dl: reduce dose by 50%** If Hb > 15 g/dl: stop and reinitiate at Hb ≤ 14 g/dl at 50% lower dose If Hb < 8.5 g/dl: dose doubled

Study	*n*	Arms	Malignancy	Treatment	Initial treatment[a]	Start Hb level[a]	Target Hb level[a]	Dose adjustment[a]
ten Bokkel Huinink 1998[51]	122	Epoetin beta vs. standard	Solid (ovary)	Chemotherapy: plat	**150 IU/kg TIW**	< 13 g/dl	14–15 g/dl	**4 weeks Hb increase ≥ 2 g/dl: reduce dose by 50%** Hb > 15 g/dl: stop and reinitiate at Hb ≤ 14 g/dl at 50% lower dose Epoetin withheld while platelet counts < 20,000 µg/l
Thatcher 1999[52]	130	Epoetin alfa vs. standard	Solid (SCLC)	Chemotherapy: plat	**150 IU/kg TIW**	≤ 10.5 g/dl	≥ 10 g/dl	Hb > 15 g/dl: stop and reinitiate at Hb ≤ 13 g/dl at 50% lower dose
Licence details for epoetin theta		Dose: 20,000 IU QW Start Hb level: ≤ 10 g/dl Target HB level: 10–12 g/dl Dose adjustment: 4 weeks Hb increase < 1 g/dl: dose doubled; increase to 60,000 IU if Hb increase insufficient at 8 weeks; Hb > 12 g/dl should be avoided; 12 weeks Hb increase < 1 g/dl: discontinue						
Tjulandin 2010[48]	223	Epoetin theta and epoetin beta vs. placebo	Solid	Chemotherapy: plat	**Epoetin theta: 20,000 IU QW**	≤ 11 g/dl	NR	**4 weeks Hb increase < 1 g/dl: dose doubled; further increase to 60,000 IU if no response at 8 weeks** 4 weeks Hb increase > 2 g/dl: reduce dose by 50% Hb > 13 g/dl: stop or reduce dose by 50%
					Epoetin beta: 150 IU/kg Q3W	≤ 11 g/dl	NR	**4 weeks Hb increase < 1 g/dl: dose doubled**; no further increase allowed 4 weeks Hb increase > 2 g/dl: dose reduced by 50% Hb > 13 g/dl: stop or reduce dose by 50%

Study	*n*	Arms	Malignancy	Treatment	Initial treatment[a]	Start Hb level[a]	Target Hb level[a]	Dose adjustment[a]
Tjulandin 2011[77]	186	Epoetin theta vs. placebo	Mixed	Chemotherapy: non-plat	**20,000 IU QW**	≤ 11 g/dl	NR	**4 weeks Hb increase < 1 g/dl: dose doubled; further increase to 60,000 IU if no response at 8 weeks** 4 weeks Hb increase > 2 g/dl: reduce dose by 50% Hb > 13 g/dl: stop or reduce dose by 50%
Licence details for darbepoetin alfa		Dose: 2.25 µg/kg SC QW; 500 µg (6.75 µg/kg) SC Q3W Start Hb level: ≤ 10 g/dl Target HB level: 10–12 g/dl Dose adjustment: 4 weeks Hb increase < 1 g/dl: dose doubled; 4 weeks Hb increase ≥ 2 g/dl: reduce dose by 25–50%; Hb ≥ 12 g/dl: reduce dose by 25–50%; Hb ≥ 13 g/dl: stop and reinitiate at Hb 12 g/dl at a 25% lower dose						
Hedenus 2002[53]	33[f]	Darbepoetin alfa vs. placebo	Haematological	Chemotherapy: NR	**2.25 µg/kg QW**	≤ 11 g/dl	NR	**4 weeks Hb increase ≥ 2 g/dl: 50% dose reduction** If Hb > 15.0 g/dl (men) or > 14.0 g/dl (women): stop and reinitiate at Hb ≤ 13.0 g/dl at 50% lower dose
Hedenus 2003[17]	349	Darbepoetin alfa vs. placebo	Haematological	Chemotherapy: NR	**2.25 µg/kg QW**	≤ 11 g/dl	13–14 g/dl	**4 weeks Hb increase ≤ 1 g/dl: dose doubled** If Hb > 15.0 g/dl (men) or > 14.0 g/dl (women): stop and reinitiate at Hb ≤ 13.0 g/dl at a 50% lower dose
Kotasek 2003[50]	249	Darbepoetin alfa vs. placebo	Solid	Chemotherapy: NR	**6.75 µg/kg Q3W**	≤ 11 g/dl	13–14 g/dl (women), 13–15 g/dl (men)	Dose increase not allowed If Hb > 15.0 g/dl (men) or > 14.0 g/dl (women): stop and reinitiate at Hb ≤ 13.0 g/dl at a 50% lower dose

Study	*n*	Arms	Malignancy	Treatment	Initial treatment[a]	Start Hb level[a]	Target Hb level[a]	Dose adjustment[a]
Untch 2011[78,80]	733	Darbepoetin alfa vs. standard	Solid (breast)	Chemotherapy: non-plat	4.5 µg/kg (every 2 weeks)[g]	NR	12.5–13 g/dl	**4 weeks Hb increase < 1 g/dl: dose doubled** If Hb > 14.0 g/dl: stop and reinitiate at Hb ≤ 13.0 g/dl at a 50% lower dose
Vansteenkiste 2002[73]	314	Darbepoetin alfa vs. placebo	Solid (lung)	Chemotherapy: plat	**2.25 µg/kg QW**	≤ 11 g/dl	13–14 g/dl (women), 13–15 g/dl (men)	6 weeks Hb increase < 1 g/dl: dose doubled If Hb > 15.0 g/dl (men) or > 14.0 g/dl (women): stop and reinitiate at Hb ≤ 13.0 g/dl at a 50% lower dose

non-plat, non-platinum-based chemotherapy; NR, not reported; QW, once weekly; Q3W, once every 3 weeks; plat, platinum-based chemotherapy; SC, subcutaneous; SCLC, small-cell lung cancer; TIW, three times a week.

a Bold text indicates the elements of administration that were within licence (unclear whether dose reduced).

b Dose increase to 300 IU/kg SC TIW.

c Study population included patients not receiving chemotherapy ($n = 124$); beyond the scope of the current review.

d Assumed to be epoetin alfa or epoetin beta based on the date of the study and the dose administered.

f Hedenus and colleagues[53] evaluated three doses of darbepoetin alfa: 1.0 µg/kg, 2.25 µg/kg and 4.5 µg/kg; only the licensed dose of 2.25 µg/kg ($n = 22$) was considered eligible for inclusion in this review, compared with placebo ($n = 11$).

e > 9 g/dl to < 10 g/dl if serum erythropoietin ≤ 100 IU/l; > 8 g/dl to ≤ 9 g/dl if serum erythropoietin ≤ 180 IU/l or ≤ 8 g/dl if serum erythropoietin 300 IU/l.

g Dose given was within licence but the frequency with which it was given was not.

Appendix 10 Comparison of search results with the manufacturer submissions

TABLE 93 Sandoz UK Ltd's submission

Citation	Reason for exclusion from the PenTAG review
Haag-Weber M, Eckardt KU, Hörl WH, Roger SD, Vetter A, Roth K. Safety, immunogenicity and efficacy of subcutaneous biosimilar epoetin-alpha (HX575) in non-dialysis patients with renal anemia: a multi-center, randomized, double-blind study. *Clinical Nephrol* 2012;**77**:8–17	Comparator (epoetin alfa vs. epoetin alfa); no control
Weigang-Köhler K, Vetter A, Thyroff-Friesinger U. HX575, recombinant human epoetin alfa, for the treatment of chemotherapy-associated symptomatic anaemia in patients with solid tumours. *Onkologie* 2009;**32**:168–74	Comparator (epoetin alfa vs. epoetin alfa); no control
Desrame J, Stamerra O, Labourey JL, Toeldano A, Dauriac C, Ianotto JC, *et al.* Haemoglobin outcomes with biosimilar epoetin alfa in the management of chemotherapy-induced anaemia in cancer patients: first results from the French OncoBOS observational study. Poster presented at the European Cancer Congress, Amsterdam, the Netherlands, 27 September–1 October 2013	Abstract only; observational study
Kerkhofs L, Boschetti G, Lughini A, Stanculeanu DL, Palomo AG. Use of biosimilar epoetin to increase haemoglobin levels in patients with chemotherapy-induced anaemia: real-life clinical experience. *Future Oncol* 2012;**8**:751–6	Abstract only; retrospective analysis
Lorenz A, Heine O. First comparison of biosimilar epoetin alfa and darbepoetin alfa for the treatment of chemotherapy-induced anaemia. Poster presented at the European Cancer Congress, Amsterdam, the Netherlands, 27 September–1 October 2013	Abstract only; retrospective, matched-cohort analysis
Rodriguez Garzotto A, Cortijo Cascajares S, Pernaut Sanchez C, Otero Blas I, Ruiz Ares G, Rebollo Laserna FJ, *et al.* Use of erythropoiesis-stimulating agents and comparison of different products for the treatment of chemotherapy-induced anaemia. Poster presented at the European Cancer Congress, Amsterdam, the Netherlands, 27 September–1 October 2013	Abstract only; study design single centre audit

TABLE 94 Amgen Inc.'s submission

Citation	Reason for exclusion from the PenTAG review
Delarue R. Survival impact of prophylactic administration of darbepoetin alfa in patients with diffuse large B-cell lymphoma treated with immunochemotherapy: the LNH03-6B study. Educational Cancer Convention Lugano of the European School of Oncology, Lugano, Switzerland, April 2012. *Crit Rev Oncol Haematol* 2012;**82**(Suppl. 1):12–13	Abstract only; included in *Appendix 11* (current trial status unknown)
Hartmann JT, Metzner B, Binder C, Mergenthaler HG, Rick O, Sayer HG, *et al.* Addition of darbepoetin alfa to sequential high-dose VIP chemotherapy for patients with advanced metastatic germ cell cancer. *J Clin Oncol* 2012;**30**(Suppl. 1):e15026	Abstract only
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. 20th Regional Congress of the International Society of Blood Transfusion, Nagoya, Japan, November 2009	Abstract only
Nitz U, Oberhoff C, Reimer T, Schumacher C, Hackmann J, Warm M, *et al.* Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: a safety analysis from the Phase III ARA plus trial. *Cancer Res* 2009;**69**(Suppl.):4100	Abstract only; included in *Appendix 11* (current trial status unknown)
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). *Ann Oncol* 2008;**19**:viii277	Abstract only

Appendix 11 Ongoing studies

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
Active not recruiting								
NCT00482716/ CDR0000549549/ BARTS-06/Q0605/93/ ISRCTN11830961/ EU-20731	St Bartholomew's Hospital, London	Epoetin alfa or epoetin beta with or without iron infusion in treating anemia in patients with cancer	Samir G Agrawal (St Bartholomew's Hospital)	UK	80	Phase III	Active, not recruiting	NA
NCT01444456/ 20101123	Amgen Inc.	Assessment of quality of life in patients with symptomatic chemotherapy-induced anaemia	MD, Amgen Inc.	Austria, Belgium, France, Germany, Greece, Italy, Netherlands, Poland, Romania	1264	?	Ongoing, not recruiting	NA
Recruiting								
NCT00875004/ CDR0000633325/ CLCC-PLATON/CLCC-VA-2007/21/CLCC-AFSSAPS-A70755–52/ INCA-RECF0639/ EUDRACT-2007–003615–31/ ROCHE-CLCC-PLATON	Centre Val d'Aurelle – Paul Lamarque, Montpelier	Epoetin beta in patients undergoing chemotherapy for solid tumors	Damien Pouessel and Paul Lamarque (Centre Val d'Aurelle)	France	300	?	Recruiting	NA
NCT00338286/ CR005143/ EPOANE3010/ CR005143/ 2005–001817–17	Janssen Research & Development, LLC	A Study of epoetin alfa plus standard supportive care versus standard supportive care only in anemic patients with metastatic breast cancer receiving standard chemotherapy	Janssen Research & Development, LLC	USA, Argentina, Australia, Brazil, Bulgaria, Chile, Colombia, Ecuador, Georgia, Hong Kong, India, Indonesia, Macedonia, Malaysia, Mexico, Philippines, Poland, Romania, Russian Federation, South Africa, Taiwan, Ukraine	2100	Phase III	Recruiting	NA

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00858364/ 20070782	Amgen Inc.	Anemia treatment for advanced non-small cell lung cancer (NSCLC) patients receiving chemotherapy	MD, Amgen Inc.	USA, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Croatia, Czech Republic, Germany, Greece, Hong Kong, India, Ireland, Israel, Italy, Korea, Luxembourg, Malaysia, Mexico, Netherlands, Philippines, Poland, Puerto Rico, Romania, Russian Federation, Serbia, Slovenia, South Africa, Spain, Switzerland, Taiwan, Ukraine, UK	3000	Phase III	Recruiting	NA
NCT01374373/ BIOS-012010	Bio Sidus SA	Epoetin alfa (Hemax®) Phase IV study in chemotherapy induced anemia	Roberto Diez, MD (Bio Sidus SA)	Argentina	30	Phase IV	Recruiting	NA
NCT01795690/ iOMTAn	iOMEDICO AG	Clinical registry on anemia therapy (TAn-Registry)	?	Germany	1000	?	Recruiting	NA

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
Status unknown								
NCT00381836/ 2005–005658–37/LM: 2612–3148/Ethical: 20060074/Data Protection: 2005–41–6015	University of Aarhus, Denmark, and Amgen Inc.	Effect of darbepoetin alfa (Aranesp) on anemia in patients with advanced hormone independent prostate cancer	Michael Borre (Department of Urology, Aarhus University Hospital, Aarhus)	Denmark	140	Phase III (anaemia)	Unknown	NA
NCT00400686/ CASE-CCF-5497/ P30CA043703/ CASE-CCF-5497/ ORTHO-CASE-CCF-5497	Cleveland Clinic	Epoetin alfa in treating anemia in patients undergoing chemotherapy for multiple myeloma	Ronald M Sobecks (Case Comprehensive Cancer Center, Cleveland, OH)	USA	50	?	Unknown	NA
NCT00144755	Lymphoma Study Association	R-CHOP-14 versus R-CHOP-21 and darbepoetin alpha in patients aged 60–80 years with diffuse large B-cell lymphoma	Richard Delarue (Lymphoma Study Association)	Belgium, France, Switzerland	600	Phase III	Unknown (some results published Delarue and colleagues[253])	NA
NCT00039884/01/ 155A	Ramin Mirhashemi, MD	Will radiation/ chemotherapy treatment of cervical cancer work better with medication that may improve anemia?	Ramin Mirhashemi	USA	64	Phase II	Unknown	NA
NCT00309920/ CDR0000458037/ WGSG-ARA-PLUS/ AVENTIS-WGSG-ARA-PLUS/SANOFI-WGSF-ARA-PLUS/EU-205108	Heinrich-Heine University, Dusseldorf	Combination chemotherapy with or without darbepoetin alfa in treating women with stage III breast cancer	Ulrike Nitz (Heinrich-Heine University, Dusseldorf)	Germany	1234	?	Unknown (some results published Nitz and colleagues[102])	NA

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00281892/	German CLL Study Group	Fludarabine and darbepoetin alfa in treating older patients with chronic lymphocytic leukemia	Michael Hallek, MD (Medizinische Universitaetsklinik I, University of Cologne)	Germany	348	Phase III	Unknown	–
Terminated								
NCT00386152/ CR012985/ EPOANE2007	Johnson & Johnson Pharmaceutical Research & Development, LLC	A study comparing two different PROCRIT doses to a dose of ARANESP in anemic cancer patients receiving chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, LLC	USA	235	Phase II	Terminated, has results	–
NCT01736215/ CR016558/ EPOCAN4028	Janssen-Cilag Ltd, Thailand	An observational study to predict the response of erythropoietin treatment in participants with cancer related anemia receiving chemotherapy	Janssen-Cilag Ltd, Thailand	Thailand	33	Phase IV	Terminated, has results	–
NCT00258440/ CDR0000445450/ OHSU-ONC-03017-LP/ OHSU-1616/ OHSU-7754/ORTHO-ONC-03017-L	Oregon Health & Science University Knight Cancer Institute, Portland, OR	Epoetin alfa in treating patients with anemia who are undergoing chemotherapy for cancer	Joseph Bubalo (Oregon Health & Science University Knight Cancer Institute)	USA	7	?	Terminated, has results	–
NCT00989092/ 20000219	Amgen Inc.	Darbepoetin alfa and anemia of cancer	Amgen Inc.	?	287	Phase II	Terminated (slow enrolment and change in product development strategy)	–

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00254436/ ID00–264	MD Anderson Cancer Center, Houston, TX	A double-blind, randomized, placebo-controlled study of the efficacy and safety of weekly Procrit given to gastric or rectal patients	Saroj Vadhan-Raj, MD (MD Anderson Cancer Center)	USA	50	Phase III	Terminated	–
NCT00246597/ CR002305	Ortho Biotech Products, LP	A Phase III clinical trial of PROCRIT (epoetin alfa) versus placebo in women undergoing adjuvant chemotherapy for stage I, II or III breast cancer	Ortho Biotech Products, LP	?	37	Phase III	Terminated	–
NCT00189371/ AGO-OVAR 2.7	Christian Jackisch MD (AGO Study Group)	Reinduction chemotherapy containing carboplatin and paclitaxel with or without epoetin alpha in recurrent platinum sensitive ovarian cancer, cancer of the fallopian tube or peritoneum	AGO Study Group	Germany	300	Phase III	Terminated	–
NCT00306267/ CR10540	Johnson & Johnson Pharmaceutical Research & Development, LLC	A study of PROCRIT (epoetin alfa) 80,000 units (U) once every four weeks (Q4W) vs. 40,000 U once every two weeks (Q2W) in cancer patients not receiving chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	61	Phase II	Terminated	–; unlicensed/fixed dose or both[a]

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00310232/CTA-Control-076080/HC File 9427-J0921–22C	Ontario Clinical Oncology Group (OCOG)	Epoetin alfa in advanced non-small cell lung cancer (EPO-CAN-20)	Ontario Clinical Oncology Group (OCOG)	Canada	70	Phase III	Terminated	–
NCT00495378/ CR005128	Ortho Biotech Products, LP	RAPID-2. A study to evaluate the effectiveness of alternate dosing of PROCRIT (epoetin alfa) in maintaining hemoglobin levels in patients with chemotherapy related anemia	Ortho Biotech Products, LP	?	25	Phase IV	Terminated (25/200 patients enrolled)	–; non-randomised study[a]
Completed								
NCT00117039/ 20030206	Amgen Inc.	A study to evaluate the effectiveness of Aranesp for cancer patients with anaemia	MD, Amgen Inc.	?	1500	Phase IV	Completed (results published Boccia and colleagues[254,255])	Identified but excluded as studies non-randomised
NCT00272662/ AFX01–05, 2005–003354–10	Affymax, Inc.	Study of subcutaneously administered peginesatide in anemic cancer patients receiving chemotherapy	Study director, Affymax, Inc.	Czech Republic, Poland, UK	60	Phase II	Completed	–; non-randomised, dose finding, new ESA[a]
NCT00210600/ CR003196	Johnson & Johnson Pharmaceutical Research & Development, LLC	Early and standard intervention with 120,000 units of PROCRIT (epoetin alfa) every three weeks in patients receiving chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	186	Phase II	Completed (results published Glaspy[256])	–; unlicensed/fixed dose or both[a]

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00117117/ 20020132	Amgen Inc.	A study to assess symptom burden in subjects with nonmyeloid malignancies receiving chemotherapy and Aranesp	MD, Amgen Inc.	?	2423	Phase IV	Completed (results published Gregory[257] and Gabrilove and colleagues[258])	Identified Gabrilove and colleagues[258] but not Gregory;[257] however, both non-randomised, single-arm studies
NCT00072059/ROCHE-NA17101/UCLA-0303085/ CDR0000335429	Jonsson Comprehensive Cancer Center, Los Angeles, CA	Ro 50–3821[Mircera® epoetin beta] in treating anemia in patients receiving antineoplastic therapy for stage IIIB or stage IV non-small cell lung cancer	John Glaspy, MD (Jonsson Comprehensive Cancer Center)	USA	210	Phase II	Completed	–
NCT00212862/ CR004561/ ABT-OP-03–02	Ortho Biotech Products, LP	Dosing and outcomes study of erythropoietic stimulating therapies in patients with chemotherapy induced anemia (DOSE)	Ortho Biotech Products, LP	?	2130	Phase IV	Completed (results published Larholt and colleagues[259])	Not identified as beyond scope of review – observational cohort study
NCT00270101/ CR005911	Johnson & Johnson Pharmaceutical Research & Development, LLC	The effect of epoetin alfa on the anemia of patients with multiple myeloma	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	156	Phase III	Completed (results published Dammacco and colleagues[260–262])	Not identified as pre-2004 (PenTAG searches 2004–13)
NCT00158379/ 3002000	North-Eastern German Society of Gynaecologic Oncology	Taxol carboplatin and erythropoietin	Jalid Sehouli, Charité Campus Virchow-Klinikum, Berlin	?	105	Phase II	Completed	–; non-randomised study[a]

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00315484/ CR004609	Ortho Biotech Products, LP	Hematologic response of epoetin alfa (PROCRIT) versus darbepoetin alfa (ARANESP) in chemotherapy induced anemia	Ortho Biotech Products, LP	?	358	Phase IV	Completed (results published Waltzman and colleagues[241])	Identified; excluded as unlicensed/fixed dose or both
NCT00540384/980291	Amgen Inc.	Dose-finding study of novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia in subjects with solid tumours receiving multicycle chemotherapy	MD, Amgen Inc.	?	405	Phase II	Completed (results published Kotasek and colleagues[50])	Identified; included treatment arm evaluating a licensed dosage
NCT00344409/ KRN321-SC/05-A54	Kyowa Hakko Kirin Company, Ltd	A double-blind study of KRN321 for the treatment of anemia in cancer patients	Nagahiro Saijo, MD (National Cancer Center Hospital East)	Japan	200	Phase III	Completed	–
NCT00144482/ EPO307JP	Chugai Pharmaceutical Company Ltd	A study of recombinant human erythropoietin in anemic cancer patients undergoing chemotherapy	Yoshiharu Ishikura (Chugai Pharmaceutical Company, Ltd)	?	122	Phase III	Completed	–; unlicensed/fixed dose or both[a]
NCT00628043/ EPO316JP	Chugai Pharmaceutical Company Ltd	Clinical study of epoetin beta to chemotherapy-induced anaemia (CIA) patients	Yoshito Suzuki (Chugai Pharmaceutical Company, Ltd)	Japan	160	Phase III	Completed	–; unlicensed/fixed dose or both[a]

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00338299/ CR005098	Johnson & Johnson Pharmaceutical Research & Development, LLC	Alternate dosing of PROCRIT (epoetin alfa) in patients with cancer and chemotherapy induced anemia	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	51	Phase III	Completed (results published Reddy and colleagues[263])	Not identified; study was a non-randomised, single-arm study
NCT00144495/ EPO308JP	Chugai Pharmaceutical Company Ltd	A study of recombinant human erythropoietin in anemic cancer patients undergoing chemotherapy	Yoshiharu Ishikura (Chugai Pharmaceutical Company, Ltd)	?	104	Phase III	Completed	–; non-randomised, unlicensed/fixed dose or both[a]
NCT00776425/ ML20197	Hoffmann-La Roche	A study of the quality of life and treatment response to once weekly NeoRecormon (epoetin beta) treatment in anemic patients with solid and lymphoid malignancies	Clinical Trials, Hoffman-La Roche	Russian Federation	125	Phase IV	Completed	–; non-randomised, single arm, unlicensed/fixed dose[a]
NCT00035607/ 20010199	Amgen Inc.	Chemotherapy related anemia	MD, Amgen Inc.	?	120	Phase III	Completed (results published Justice and colleagues[264])	Identified; excluded as comparison of darbepoetin alfa vs. darbepoetin alfa – beyond scope
NCT00711958/ 2003–31-INJ-11	Novartis	Study to assess the efficacy and safety of HX575 in the treatment of chemotherapy associated anemia in cancer patients	Andrea Vetter, MD (Hexal AG)	Germany, Romania	105	Phase III	Completed	–; unlicensed/fixed dose or both, bioequivalence study[a]

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00117624/ 20020118	Amgen Inc.	A study of darbepoetin alfa for the treatment of anemia in subjects with a non-myeloid malignancy	MD, Amgen Inc.	?	?	Phase III	Completed (results published Kotasek and colleagues[265])	Identified; excluded as comparison of darbepoetin alfa vs. darbepoetin alfa – beyond scope
NCT00046969/ AGOSG-OVAR-MO16375-MARCH/ CDR0000257189, EU-20217/ROCHE-MO16375 ROCHE-RO2053859	AGO Study Group	Epoetin beta in treating anemia in patients with cervical cancer	Heinz Koelbl, MD (Martin-Luther-Universität of Halle-Wittenberg)	Germany	450	Phase IV	Completed	–
NCT00261313/ 20040137	Amgen Inc.	ACCELERATE: doxorubicin and cyclophosphamide followed by paclitaxel with pegfilgrastim and darbepoetin alfa support for the treatment of women with breast cancer	MD, Amgen Inc.	?	80	Phase II	Completed	–; appears G-CSF not given in both treatment arms[a]
NCT00148421/ 20030125	Amgen Inc.	Study for the treatment of anemia in patients with non-myeloid malignancies receiving multicycle chemotherapy	MD, Amgen Inc.	?	?	Phase III	Completed (results published Glaspy and colleagues[266])	Identified; excluded as unlicensed/fixed dose or both
NCT00401544/ 20060103	Amgen Inc.	Darbepoetin alfa with or without IV iron	MD, Amgen Inc.	?	?	Phase III	Completed	–

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00338416/ CR004612	Johnson & Johnson Pharmaceutical Research & Development, LLC	An efficacy and safety study of PROCRIT (epoetin alfa) in cancer patients receiving chemotherapy every three weeks	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	115	Phase II	Completed (results published Montoya and colleagues[267])	Not identified; study non-randomised, single arm
NCT00269984/ CR005833	Johnson & Johnson Pharmaceutical Research & Development, LLC	A study to determine the safety and effectiveness of epoetin alfa versus placebo in patients with persistent anemia caused by advanced cancer	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	56	Phase II	Completed	–; non-randomised, unlicensed/fixed dose or both[a]
NCT00559195/ CDR0000574173/ CHUL-NEOPALIA/ RECF0359	Centre Hospital Regional Universitaire de Limoges	Epoetin beta in treating fatigue and anemia in patients receiving palliative care for malignant solid tumors	Jean-Luc Labourey (Centre Hospital Regional Universitaire de Limoges)	France	40	Phase II	Completed	–; non-randomised study[a]
NCT00120705/ 20020167	Amgen Inc.	Treatment for anemic subjects with non-myeloid malignancies receiving chemotherapy	MD, Amgen Inc.	?	204	Phase II	Completed (results published Charu and colleagues[268])	Identified; excluded – unlicensed/fixed dose or both
NCT00364455	Janssen-Ortho Inc., Canada, and Ontario Clinical Oncology Group	Impact of erythropoietin treatment versus placebo on quality-of-life in patients with advanced prostate cancer	?	?	56	Phase III	Completed	–

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00135317/	Amgen Inc.	AIM 3: anemia and iron management with every 3 week dosing in anemic subjects with nonmyeloid malignancies	MD, Amgen Inc.	?	?	Phase III	Completed (results published Bastit and colleagues[269])	Identified; excluded – unlicensed/fixed dose or both
NCT00269997/ CR005839	Johnson & Johnson Pharmaceutical Research & Development, LLC	A study to evaluate the safety and effectiveness of epoetin alfa versus placebo in patients with persistent anemia as a result of cancer treatment with cisplatin, a platinum-containing chemotherapy drug	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	72	Phase II	Completed	–
NCT00266617/ CR005845	Johnson & Johnson Pharmaceutical Research & Development, LLC	A study to evaluate the safety and effectiveness of epoetin alfa in patients with anemia as a result of advanced cancer and treatment with aggressive chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	86	Phase II	Completed	–
NCT00110955/ 20030232	Amgen Inc.	Treatment of anemia in subjects with non-myeloid malignancy receiving multicycle chemotherapy	MD, Amgen Inc.	?	391	Phase III	Completed (results published Hernandez and colleagues[232])	Identified; excluded – unlicensed/fixed dose or both

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00337948/ CR004615	Johnson & Johnson Pharmaceutical Research & Development, LLC	An efficacy and safety study of PROCRIT (epoetin alfa) in cancer patients receiving chemotherapy every week or every four weeks	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	129	Phase II	Completed (results published Gregory and Williams,[270] Baltz and colleagues[271] and Gregory and colleagues[272,273])	Not identified; non-randomised, single-arm study
NCT00255749/ CDR0000449950/ UCLA-0504038/ ORTHO-PR04–27–018	Jonsson Comprehensive Cancer Center, Los Angeles, CA	Epoetin alfa in treating patients with anemia who are undergoing chemotherapy for cancer	John A Glaspy, MD (Jonsson Comprehensive Cancer Center)	USA	89	Phase II	Completed (results published Glaspy and colleagues[274])	Identified; excluded – includes randomised and non-randomised studies, unlicensed/ fixed dose used
NCT00058331/ CDR0000288821/ NCCTG-N02C2	North Central Cancer Treatment Group	Epoetin alfa in treating anemia in patients with solid tumors	David P Steensma, MD (Mayo Clinic)	USA	?	Phase II	Completed (results published Steensma and colleagues[275,276])	Identified; excluded – unlicensed/fixed dose or both
NCT00003600/ CDR0000066673, NCCTG-979253, NCI-P98–0133	North Central Cancer Treatment Group	Epoetin alfa in treating anemia in patients who are receiving chemotherapy	Thomas E Witzig, MD (Mayo Clinic)	USA	?	Phase III	Completed	–
NCT00524407/ CR005125	Ortho Biotech Products, LP	Effect of epoetin alfa on hemoglobin, symptom distress, and quality of life in patients receiving chemotherapy	Ortho Biotech Products, LP	?	273	Phase IV	Completed (result published Straus and colleagues[277])	Identified; excluded – unlicensed/fixed dose or both

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00261677/ CR002296	Ortho Biotech Products, LP	A study to evaluate the effect of weekly PROCRIT (epoetin alfa) or placebo on anemia and quality of life in children with cancer undergoing chemotherapy	Ortho Biotech Products, LP	?	224	Phase III	Completed (results published Razzouk and colleagues[239])	Identified; excluded – unlicensed/fixed dose or both (paediatric population)
NCT00036023/ NCT00039247 (obsolete)/20010162	Amgen Inc.	Chemotherapy related anemia in patients with non-myeloid malignancies	MD, Amgen Inc.	?	?	Phase II	Completed (results published Glaspy and colleagues[278])	
NCT00145652	Sundsvall Hospital, Sweden	Adjuvant IV iron therapy during erythropoietin treatment of anemic patients with lymphoproliferative disorders	?	?	66	?	Completed	–
NCT00270166/ CR005923	Johnson & Johnson Pharmaceutical Research & Development, LLC	The effect of epoetin alfa on the anemia of patients with selected cancers receiving chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	201	Phase III	Completed	–
NCT01626547/ORHEO	Hospira, Inc.	Biosimilar Retacrită (epoetin zeta) in the treatment of chemotherapy-induced symptomatic anaemia in haematology and oncology	?	Germany	240	?	Completed	–; non-randomised study[a]

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00121030/ 20020166	Amgen Inc.	Treatment for patients with gynecological malignancies who suffer from anemia due to chemotherapy	MD, Amgen Inc.	?	?	Phase II	Completed (results published Schwartzberg and colleagues[246])	Identified; excluded – unlicensed/fixed dose or both
NCT00038064/ NCT00046982 [obsolete], 20010101	Amgen Inc.	Anemia in patients with a non-myeloid malignancy	MD, Amgen Inc.	?	707	Phase III	Completed	–; unlicensed/fixed dose or both[a]
NCT00120679/ 20020165	Amgen Inc.	Treatment for patients with non-small cell lung cancer who developed anemia due to chemotherapy	MD, Amgen Inc.	?	?	Phase II	Completed (results published Schwartzberg and colleagues[246])	
NCT00264108/ CR002455/ EPOCAN4015	Janssen-Cilag BV	Cost-effectiveness study of epoetin alfa and darbepoetin alfa in adult patients with cancer who have anemia	Clinical Trials Janssen-Cilag BV	?	492	Phase IV	Completed	–; non-randomised, unlicensed/fixed dose or both[a]
NCT00239239/ 20040232	Amgen Inc.	Fractionated dosing study: study to evaluate darbepoetin alfa for the treatment of anemia in subjects with non-myeloid malignancies	MD, Amgen Inc.	?	44	Phase III	Completed	–; non-randomised, pharmacokinetic study[a]

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00146562/03–154	Harold J Burstein, MD, PhD, and Dana-Farber Cancer Institute; Massachusetts General Hospital; Beth Israel Deaconess Medical Center; Lowell General Hospital; Brigham and Women's Hospital; North Shore Medical Center	Pegfilgrastim and darbepoetin alfa in support of adjuvant chemotherapy for breast cancer	Harold Burstein, MD, PhD (Dana-Farber Cancer Institute, Boston, MA)	USA	109	Phase II	Completed	–; non-randomised[a]
NCT00120692/ 20020152	Amgen Inc.	Treatment for patients suffering from anemia due to chemotherapy	MD, Amgen Inc.	?	?	Phase II	Completed (results published Senecal and colleagues[247])	Identified; excluded – unlicensed/fixed dose or both
NCT00119613/ 20010145	Amgen Inc.	A study of subjects with previously untreated extensive-stage small-cell lung cancer (SCLC) treated with platinum plus etoposide chemotherapy with or without darbepoetin alfa	MD, Amgen Inc.	?	600	Phase II	Completed (results published Pirker and colleagues[266])	Identified; excluded – unlicensed/fixed dose or both
NCT00028938/ CDR0000069148/ CCWFU-62299/ CCCWFU-BG01–193/ NCI-P01–0200	Wake Forest Baptist Health/National Cancer Institute	Chemotherapy and radiation therapy with or without epoetin alfa in treating patients with stage IIIA or stage IIIB non-small cell lung cancer	Arthur William Blackstock, MD (Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC)	USA	202–232	Phase III	Completed	–

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00111137/ 20020139	Amgen Inc.	Treatment for patients with non-myeloid malignancies receiving chemotherapy	MD, Amgen Inc.	?	718	Phase III	Completed	–; unlicensed/fixed dose or both[a]
NCT00022386/ ORTHO-PR-00–27–012/ UCLA-0011004/ CDR0000068811/ ORTHO-PR-01–27–003, NCI-G01–2002	Jonsson Comprehensive Cancer Center,, Los Angeles, CA, and National Cancer Institute	Epoetin alfa in treating chemotherapy-related anemia in women with stage I, stage II, or stage III breast cancer	John A Glaspy, MD (Jonsson Comprehensive Cancer Center)	?	2500	Phase IV	Completed	–; non-randomised study[a]
NCT00017004/ CDR0000068641/ GOG-0191/CAN-NCIC-CX4	Gynecologic Oncology Group/National Cancer Institute and NCIC Clinical Trials Group	Radiation therapy and cisplatin with or without epoetin alfa in treating patients with cervical cancer and anemia	Gillian M Thomas (Odette Cancer Center at Sunnybrook, Toronto) and Peter S Craighead (Tom Baker Cancer Center, Calgary)	USA, Canada, Norway, UK	460	Phase III	Completed	–
NCT00270127/ CR005917/EPO-C111–457/EPO-INT-10	Johnson & Johnson Pharmaceutical Research & Development, LLC	Epoetin alfa for anemia in patients with cancer receiving non-platinum chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	375	Phase III	Completed	–
NCT00211133/ CR004414	Johnson & Johnson Pharmaceutical Research & Development, LLC	A study to evaluate the impact of maintaining hemoglobin levels using epoetin alfa in patients with metastatic breast cancer receiving chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	939	Phase III	Completed (results published Leyland-Jones and colleagues[233])	Identified; excluded – unlicensed/fixed dose or both

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00283465/ CR002047	Janssen-Cilag BV	A study of the effectiveness and safety of treatment with epoetin alfa on hemoglobin levels, red blood cell transfusions, and quality of life in patients with cancer receiving platinum-containing chemotherapy	Clinical Trials Janssen-Cilag BV	?	316	Phase IV	Completed (results published Savonije and colleagues[245])	Identified; excluded – unlicensed/fixed dose or both
NCT00095277/ 20030204	Amgen Inc.	Darbepoetin alfa administered once every 4 weeks in the treatment of subjects with anemia of cancer	MD, Amgen Inc.	?	220	Phase II	Completed (results published Gordon and colleagues[279])	Identified; excluded as patients did not receive chemotherapy
NCT00118638/ 20030231	Amgen Inc.	A study of darbepoetin alfa for the treatment of anemia in subjects with non-myeloid malignancy receiving multicycle chemotherapy	MD, Amgen Inc.	?	705	Phase III	Completed (results published Canon and colleagues[280,281] and Vansteenkiste and colleagues[282])	All identified; excluded Canon and colleagues[280] as comparison of darbepoetin alfa vs. of darbepoetin alfa and beyond scope and excluded Canon and colleagues[281] and Vansteenkiste and colleagues[282] as retrospective analyses

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00144131/ 20040262	Amgen Inc.	Flexibility: a study to assess the impact of darbepoetin alfa in subjects with non-myeloid malignancies with anemia due to chemotherapy	MD, Amgen Inc.	?	750	Phase II	Completed (results published Schwartzberg and colleagues[283])	Identified; excluded as comparison of darbepoetin alfa vs. of darbepoetin alfa and beyond scope
NCT00091858/ NCT00098696 (obsolete)/20010103	Amgen Inc.	Study of darbepoetin alfa for the treatment of anemia of cancer	MD, Amgen Inc.	?	1000	Phase III	Completed (results published Smith and colleagues[16])	Identified; excluded as patients not receiving chemotherapy
NCT00216541/ CR003541	Janssen-Cilag BV	A study of the safety and effectiveness of epoetin alfa on hemoglobin levels and blood transfusions in cancer patients receiving chemotherapy	Clinical Trials Janssen-Cilag BV	?	110	Phase IV	Completed (results published Schouwink and colleagues[284])	Identified; excluded as comparison of epoetin alfa vs. epoetin alfa and beyond scope and unlicensed/fixed dose or both
NCT00245895/ 03–6503-A	University of Washington, Seattle/ Amgen	Study of Aranesp to treat anemia in prostate cancer patients	Celestia S Higano, MD (University of Washington) and Tomasz M Beer, MD (Oregon Health & Science University)	USA	20	Phase II	Completed	–; non-randomised study[a]
NCT00039247/ 20010162	Amgen Inc.	Chemotherapy related anemia in patients with non-myeloid malignancies	MD, Amgen Inc.	?		Phase II	Completed (results published Glaspy and colleagues[278])	Identified; excluded as comparison of darbepoetin alfa vs. darbepoetin alfa

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT01099202	MD Anderson Cancer Center, Houston, TX	Procrit versus no Procrit in acute lymphocytic leukemia, lymphoblastic lymphoma, or Burkitt's undergoing induction/ consolidation chemotherapy	Jorge Cortes, (University of Texas, MD, Anderson Cancer Center)	USA	109	Not provided	Completed	–
NCT00661999	National Cancer Institute	Darbepoetin alfa with or without iron in treating anemia caused by chemotherapy in patients with cancer	Charles L Loprinzi (Mayo Clinic)	USA	502	Phase III	Completed	–
NCT01394991/ CR010543/ EPOANE4008	Johnson & Johnson Pharmaceutical Research & Development, LLC	A safety study of epoetin alfa in patients with cancer who have chemotherapy-related anemia	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	504	Phase IV	Completed	–
NCT00236951	Luitpold Pharmaceuticals, Inc.	Intravenous (IV) iron vs. no iron as the treatment of anemia in cancer patients undergoing chemotherapy and erythropoietin therapy	Marc Tokars (Senior Director of Clinical Operations, Luitpold Pharmaceuticals, Inc.)	?	224	Phase III	Completed	–
NCT00270049/ CR005905	Johnson & Johnson Pharmaceutical Research & Development, LLC	Epoetin alfa for the treatment of anemia resulting from chronic lymphocytic leukemia	Johnson & Johnson Pharmaceutical Research & Development, LLC	?	195	Phase II	Completed	–

Register/identifier number (if not available study ID cited)	Sponsor/collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Included in PenTAG Review
NCT00003341/ 97–125/MSKCC-97125/ORTHO-PR-96–27–031/RPCI-DS-97–38/NCI-G98–1436	Memorial Sloan Kettering Cancer Center, New York	Epoetin alfa in treating anemia in patients with lymphoma, chronic lymphocytic leukemia, or multiple myeloma and anemia caused by chemotherapy	David J Straus (Memorial Sloan Kettering Cancer Center)	USA	275	Phase III	Completed	–
NCT00070382/ CDR0000333213/ P30CA016042/UCLA-0306021/AMGEN-20030125	Jonsson Comprehensive Cancer Center, Los Angeles, CA, and National Cancer Institute	Darbepoetin alfa compared with epoetin alfa in treating anemia in patients receiving chemotherapy for cancer	John A Glaspy, MPH (Jonsson Comprehensive Cancer Center)	?	14	Phase III	Completed (published Glaspy and colleagues[266])	Identified; excluded – unlicensed/fixed dose or both. Possibly duplicate of NCT00148421
NCT00416624/ CDR0000522677/ P30CA015083/ RC05CB/06–002991/ EPOANE3015	Mayo Clinic	Epoetin alfa or darbepoetin alfa in treating patients with anemia caused by chemotherapy	Charles L Loprinzi (Mayo Clinic)	USA	320	?	Completed	–

?, not reported/unclear; –, unable to match to a publication text; AGO, Arbeitsgemeinschaft für Gynäkologische Onkologie.
a Indicates possible reasons for exclusion based on the information provided in the ClinicalTrials or Controlled Trials databases.

Appendix 12 Supplementary analyses

Anaemia-related outcomes

Haemoglobin change

Publication bias

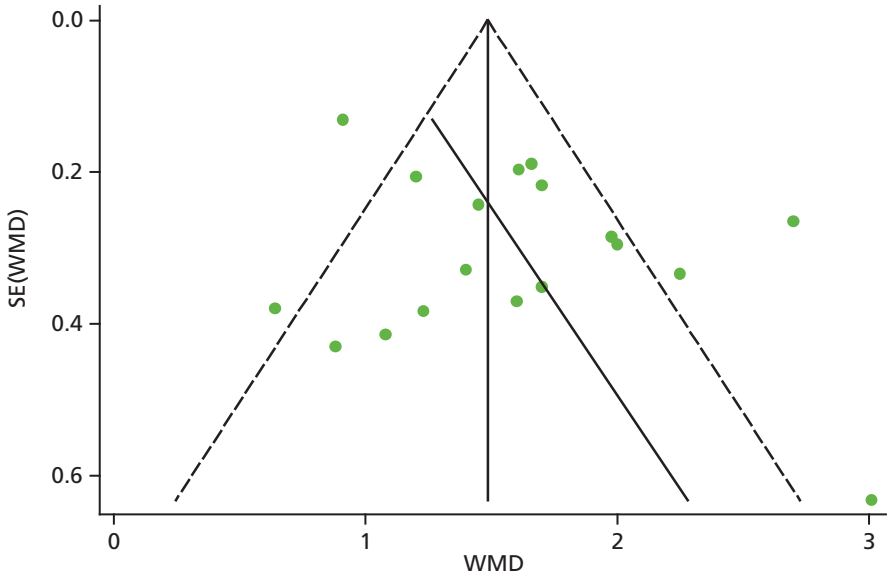

FIGURE 72 Haemoglobin change: publication bias – funnel plot with pseudo 95% confidence limits.

TABLE 95 Haemoglobin change: Egger's test for small study effects

Study effect	Coefficient	SE	*t*	$p > \|t\|$	95% CI
Slope	1.002	0.33	3.06	< 0.01	0.31 to 1.70
Bias	2.020	1.28	–1.16	0.13	–0.69 to 4.73
Test of H_0 no small study effects $p = 0.133$					

MSE, mean squared error.
Notes
No. of studies 18.
Root MSE 1.952.

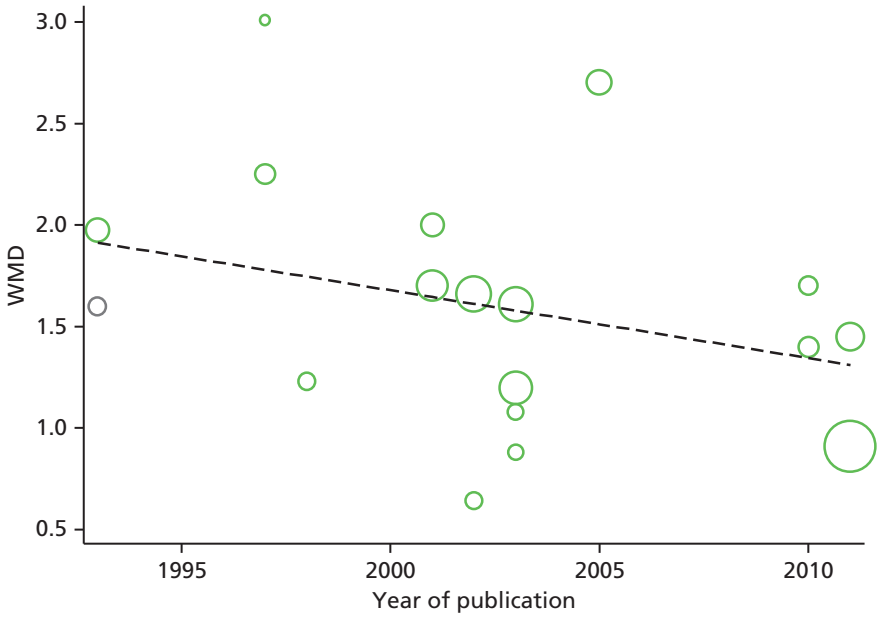

FIGURE 73 Haemoglobin change: publication bias – meta-regression plot with year of publication as a covariate.

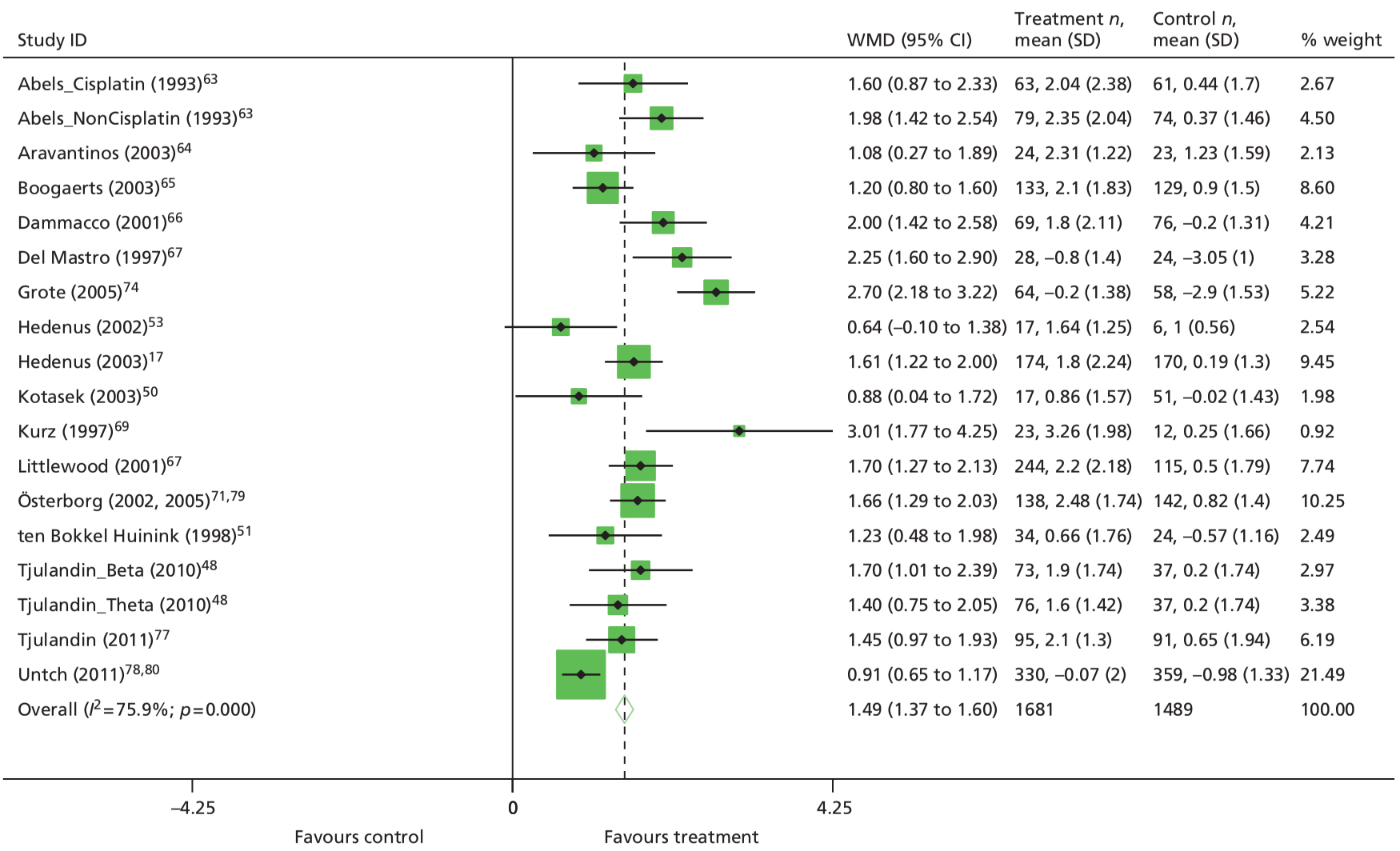

FIGURE 74 Forest plot: haemoglobin change. Fixed-effects meta-analysis (Mantel–Haenszel); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy.

Meta-regression

TABLE 96 Haemoglobin change (g/dl): results of meta-regression analysis

Variable	Mean difference	SE	*p*-value
Intercept (other chemotherapy and erythropoietin)	1.576	0.115	< 0.001
Darbepoetin	–0.491	0.212	0.035
Mixed chemotherapy	0.879	0.006	0.018

Haematological response

Publication bias

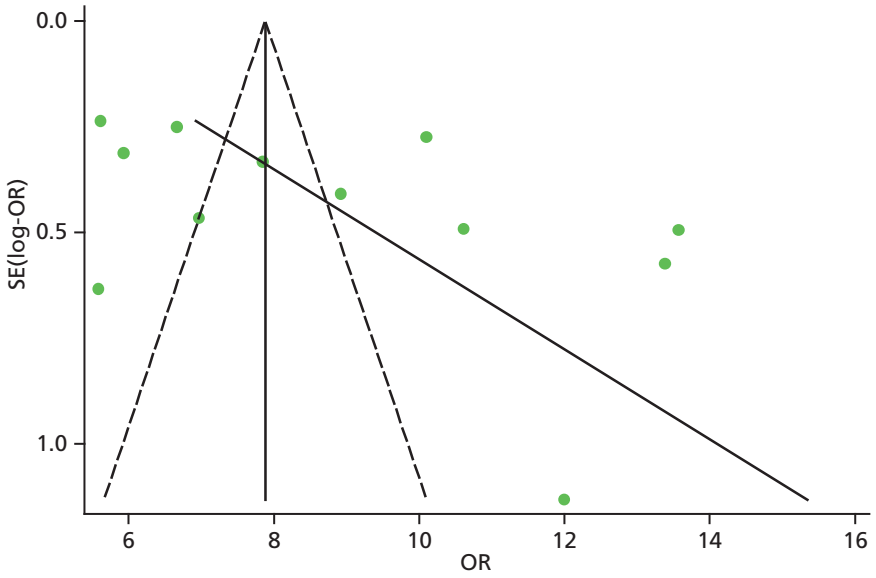

FIGURE 75 Haematological response: publication bias – funnel plot with pseudo 95% confidence limits.

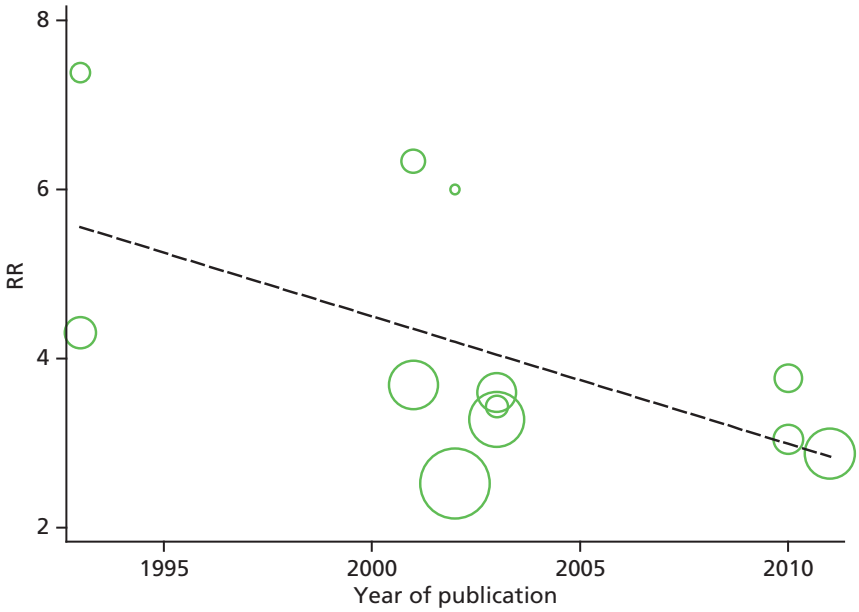

FIGURE 76 Haematological response: publication bias – meta-regression plot with year of publication as a covariate.

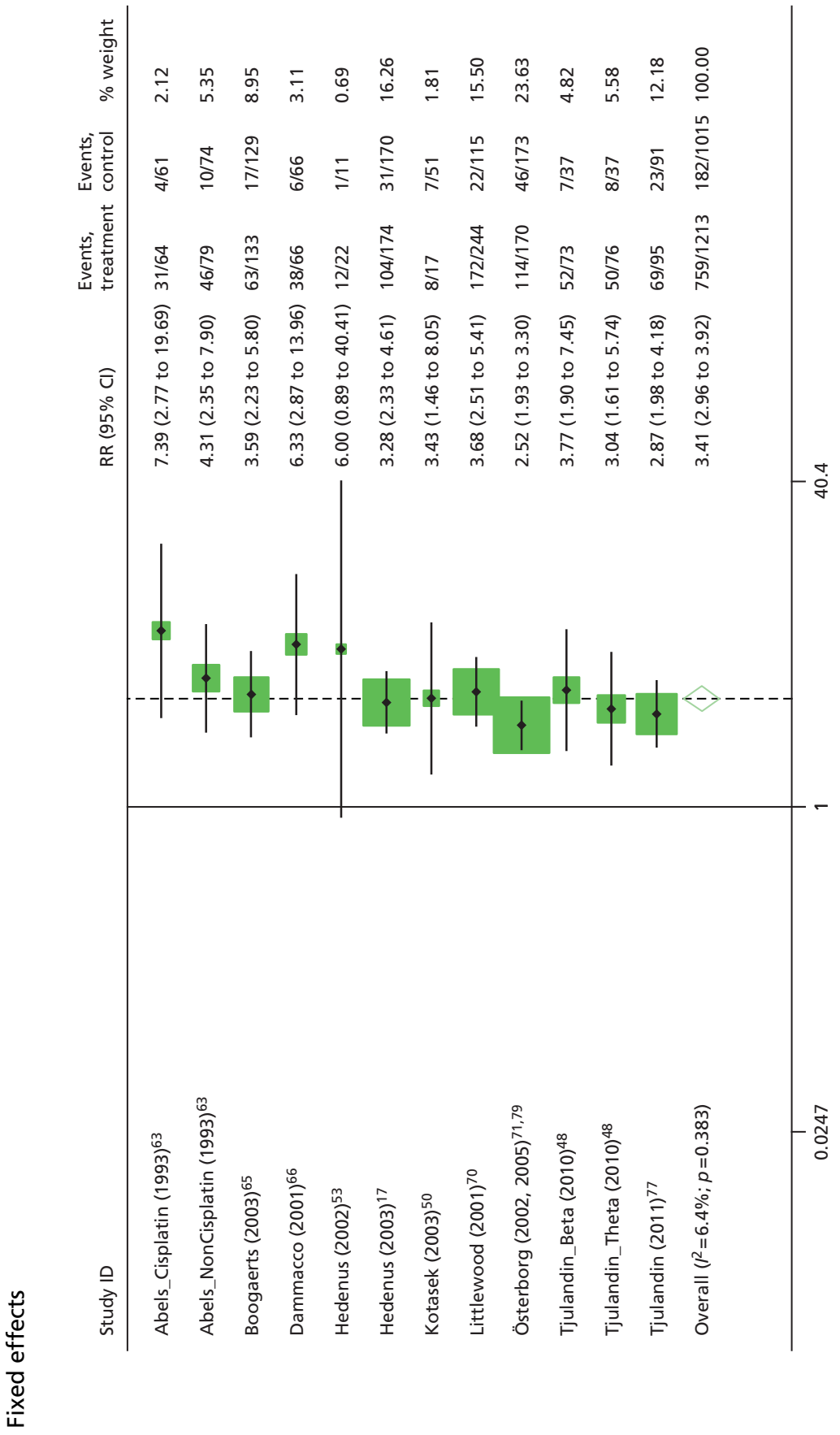

FIGURE 77 Forest plot: haematological response. Fixed-effects meta-analysis (Mantel–Haenszel); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/number of participants in treatment group; events, control = number of events/number of participants in control group.

Additional analyses

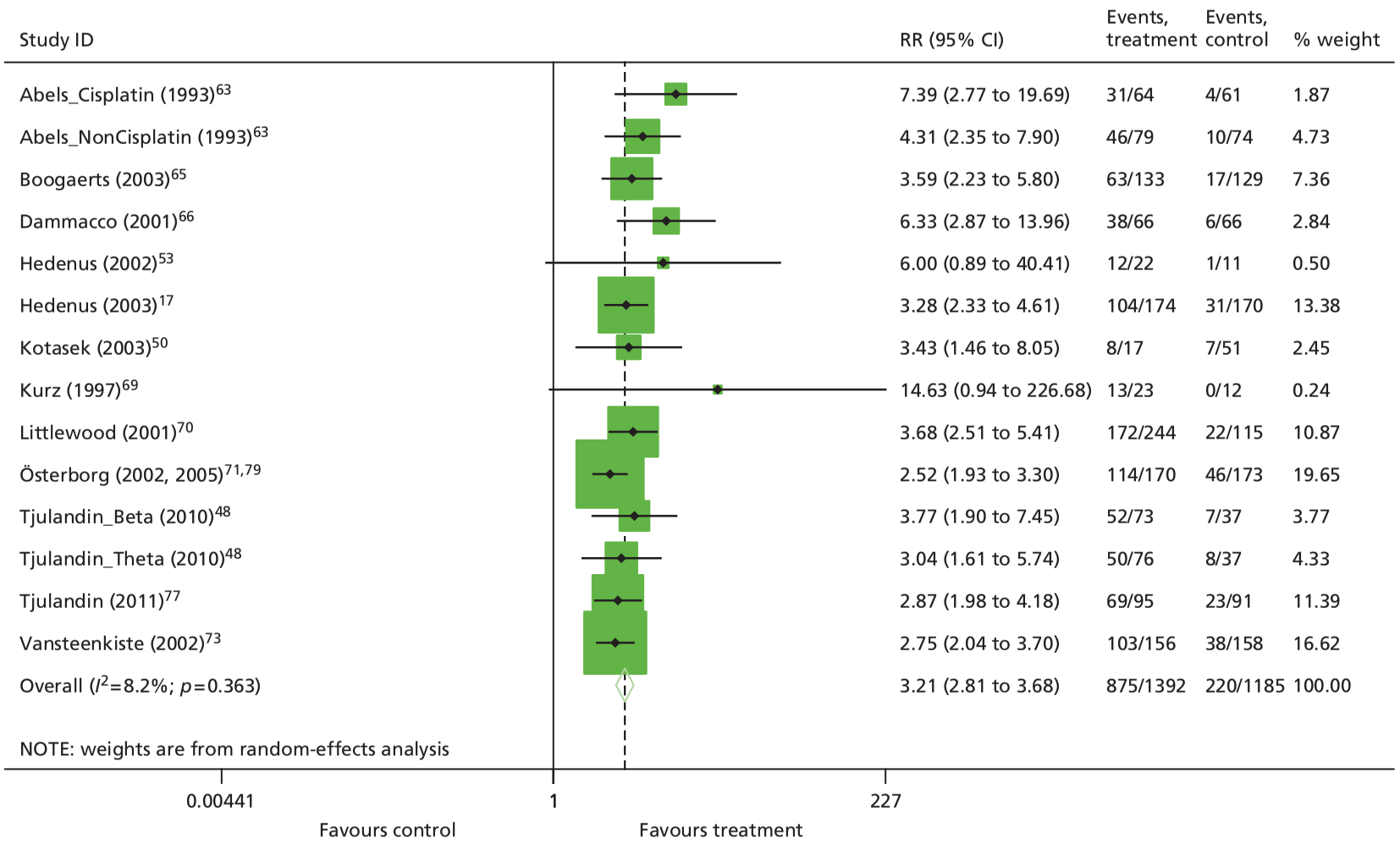

FIGURE 78 Forest plot: haematological response (including Kurz and colleagues[69] and Vansteenkiste and colleagues[73]). Random-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/number of participants in treatment group; events, control = number of events/number of participants in control group.

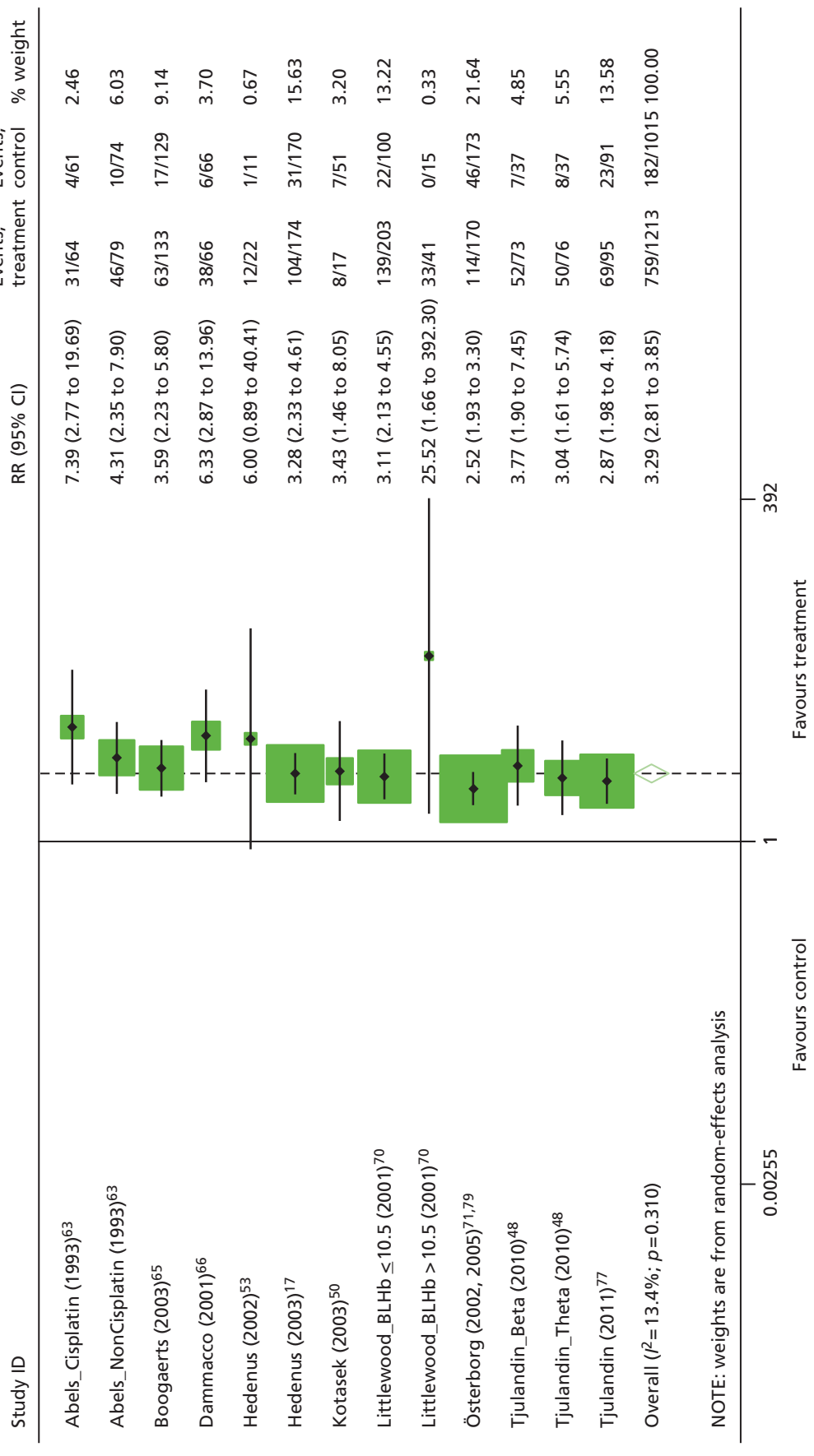

FIGURE 79 Forest plot: haematological response using Hb subgroups.[65] Random-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta, Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy; and Littlewood and colleagues[70] reported data by baseline Hb ≤ 10.5 g/dl and > 10.5 g/dl. Events, treatment = number of events/number of participants in treatment group; events, control = number of events/number of participants in control group.

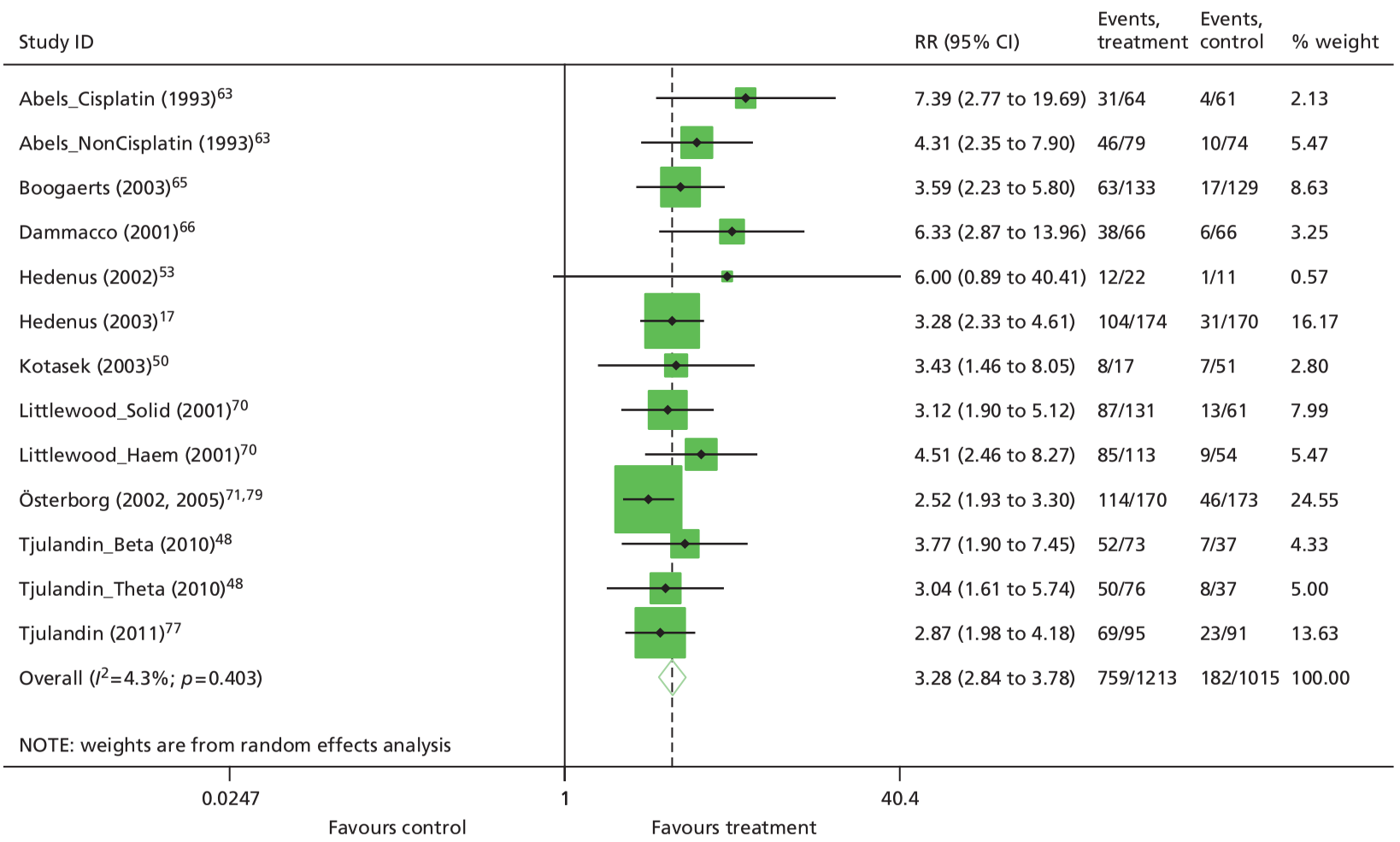

FIGURE 80 Forest plot: haematological response using malignancy subgroups.[65] Random-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta, Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy; and Littlewood and colleagues[70] reported data by malignancy type (solid and haematological tumours). Events, treatment = number of events/number of participants in treatment group; events, control = number of events/number of participants in control group.

Meta-regression

TABLE 97 Haematological response: results of meta-regression analysis with iron subgroup as a covariate

Variable	RR	SE	*p*-value
Intercept (NR)	5.163	0.497	< 0.001
Iron	–2.163	0.626	0.006

NR, not reported.

TABLE 98 Haematological response: results of meta-regression analysis with Hb baseline level as a covariate (using Hb subgroup data[65])

Variable	RR	SE	*p*-value
Intercept (Hb < 12 g/dl)	25.524	2.108	< 0.001
Hb < 11 g/dl	–21.480	2.642	< 0.001
Hb < 10 g/dl	–21.215	2.163	< 0.001

Red blood cell transfusion

Publication bias

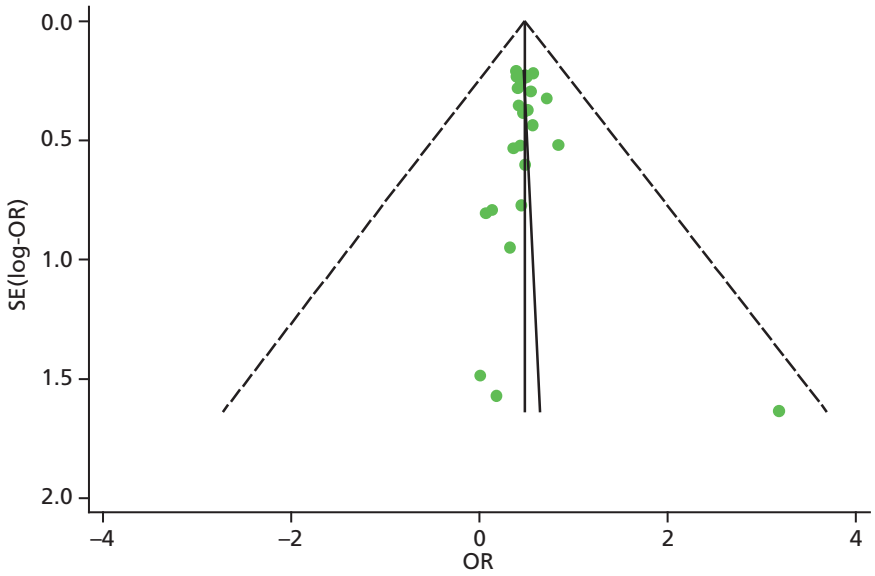

FIGURE 81 Red blood cell transfusion: publication bias – funnel plot with pseudo 95% confidence limits.

TABLE 99 Red blood cell transfusion: Harbord's modified test for small study effects

Z/sqrt(*V*)	Coefficient	SE	*t*	*p* > |t|	95% CI
sqrt(*V*)	–0.60	0.17	–3.44	0.002	–0.96 to –0.24
Bias	–0.62	0.51	–1.22	0.234	–1.68 to 0.43
Test of H_0 no small-study effects $p = 0.234$					

MSE, mean squared error.
Notes
Regress *Z*/sqrt(*V*) on sqrt(*V*) where *Z* is efficient score and *V* is score variance.
Number of studies 24.
Root MSE –1.108.

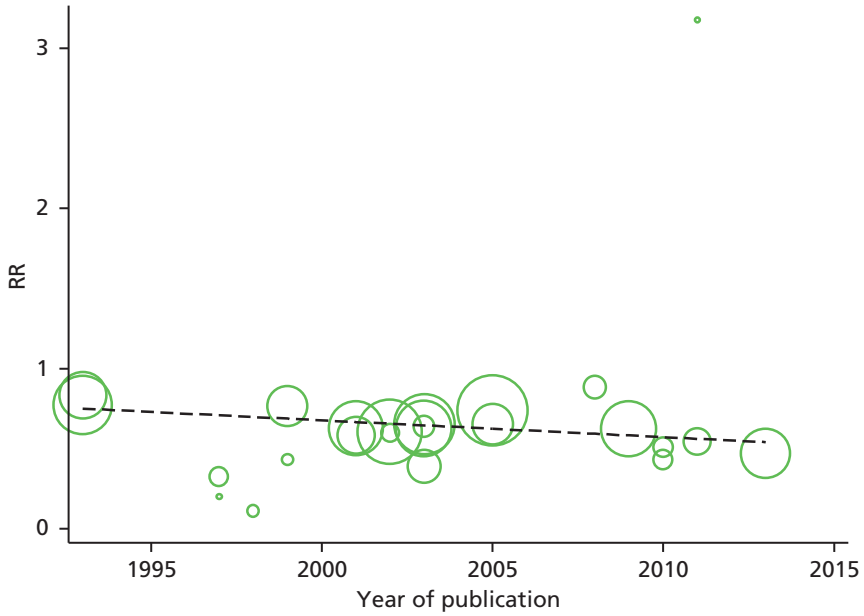

FIGURE 82 Red blood cell transfusion: publication bias – analysis of year of publication. pubyear, publication year.

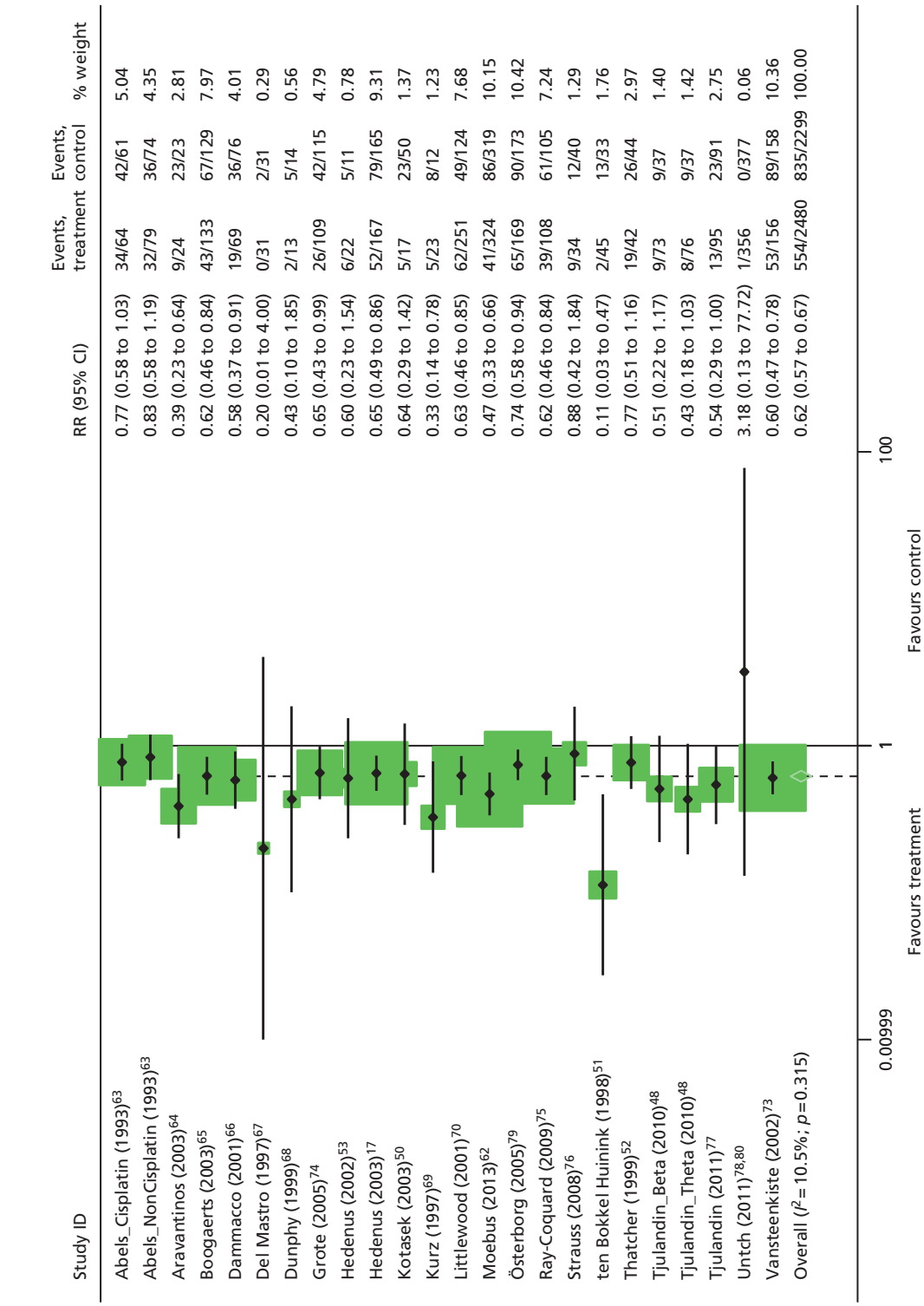

FIGURE 83 Forest plot: red blood cell transfusion. Fixed-effects meta-analysis (Mantel–Haenszel); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/number of participants in treatment group; events, control = number of events/number of participants in control group.

Additional analyses

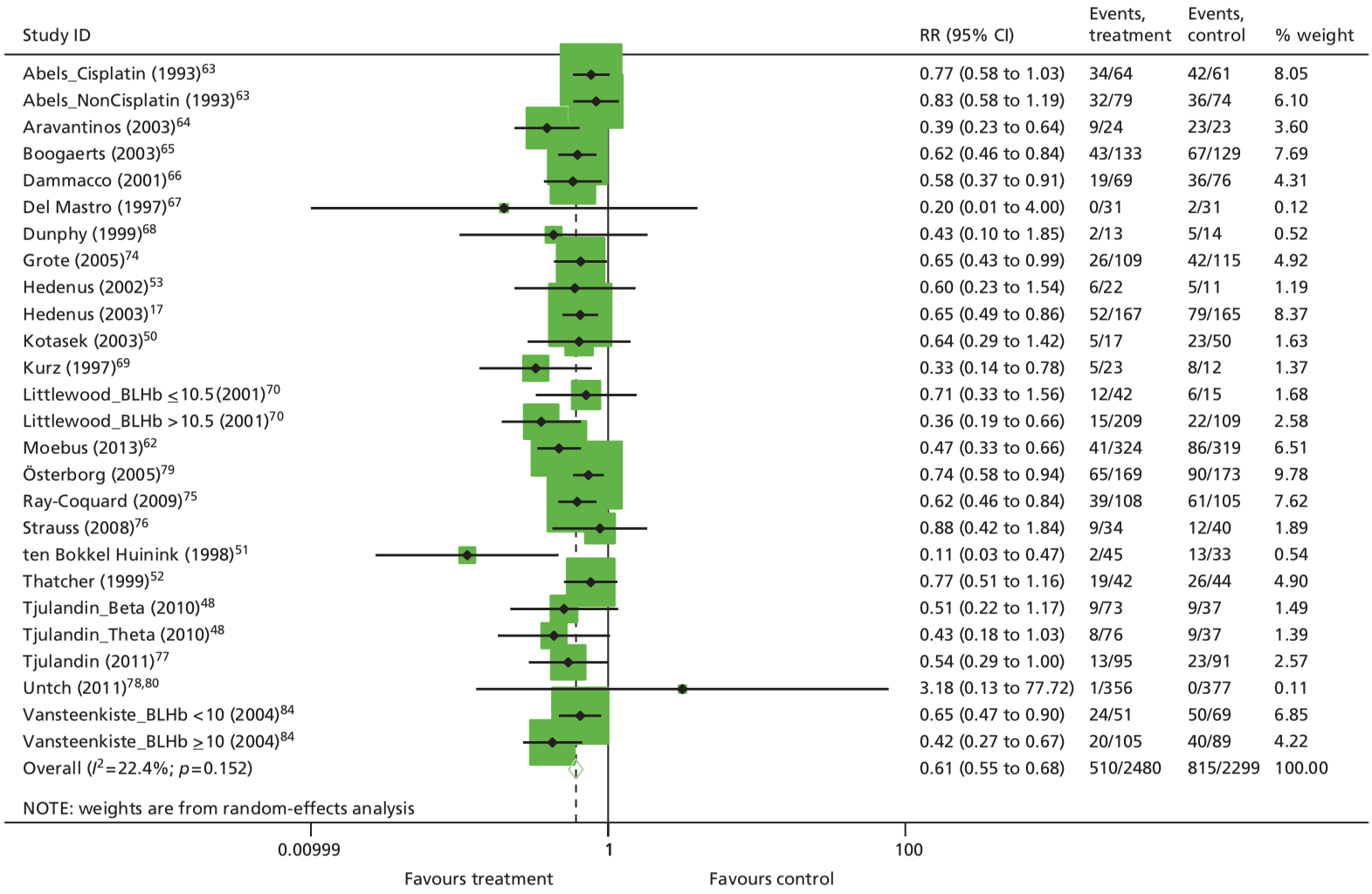

FIGURE 84 Forest plot: red blood cell transfusion using Hb subgroups.[65,73] Random-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/number of participants in treatment group; events, control = number of events/number of participants in control group.

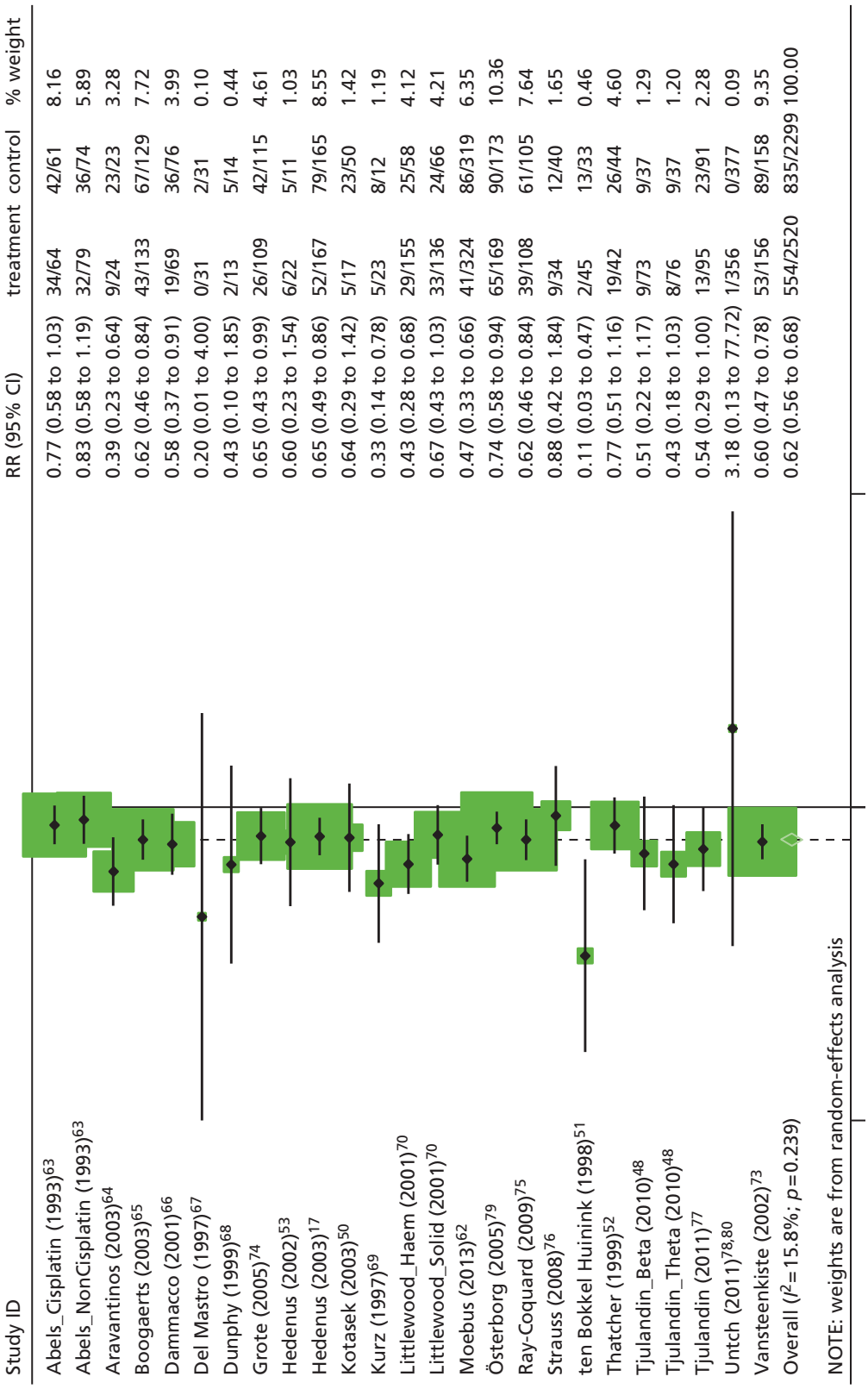

FIGURE 85 Forest plot: red blood cell transfusion using malignancy subgroups.[65] Random-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/number of participants in treatment group; events, control = number of events/number of participants in control group.

Red blood cell units transfused

Publication bias

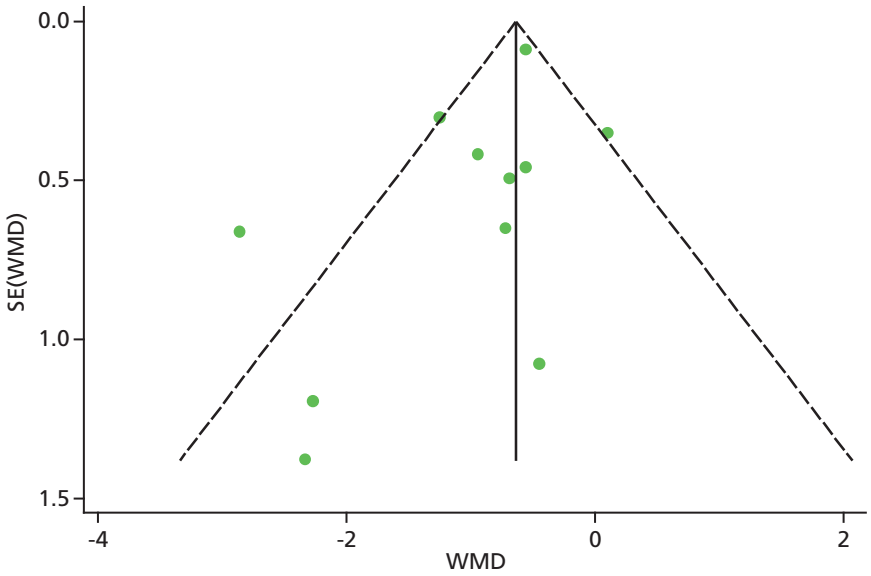

FIGURE 86 Red blood cell units transfused: publication bias – Egger's test; funnel plot with pseudo 95% confidence limits.

TABLE 100 Red blood cell units transfused: Egger's test for small study effects

Study effect	Coefficient	SE	*t*	$p > \|t\|$	95% CI
Slope	–0.4604	0.16	–2.96	0.02	–0.81 to –0.11
Bias	–1.986	0.60	–1.63	0.14	–2.35 to 0.38
Test of H_0 no small study effects $p = 0.137$					

MSE, mean squared error.
Notes
No. of studies 11.
Root MSE –1.455.

Additional analyses

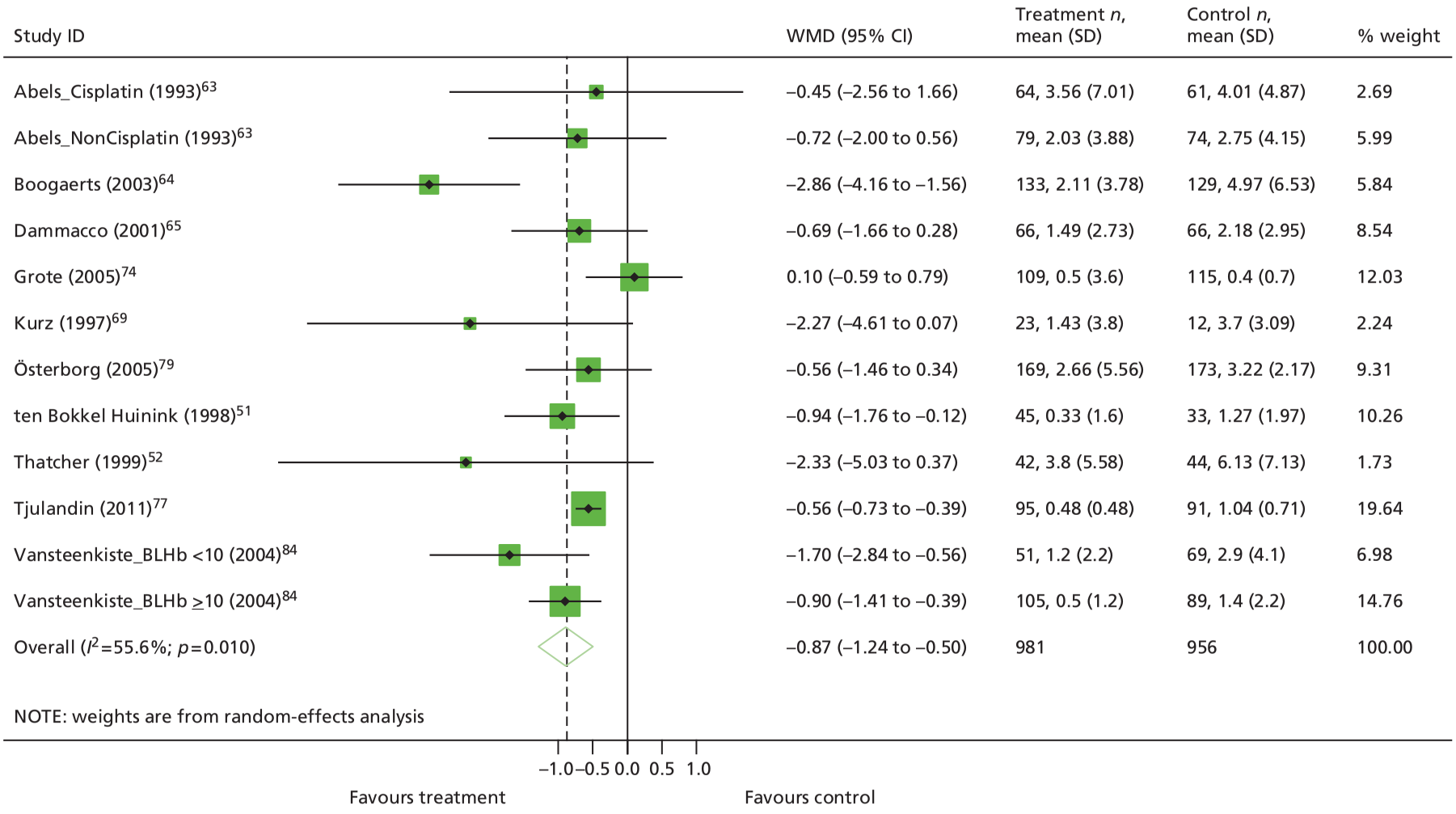

FIGURE 87 Forest plot: red blood cell units transfused using Hb subgroups.[73] Random-effects meta-analysis (DerSimonian–Laird); trial with multiple experimental arm split into subsets in the analysis: Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy.

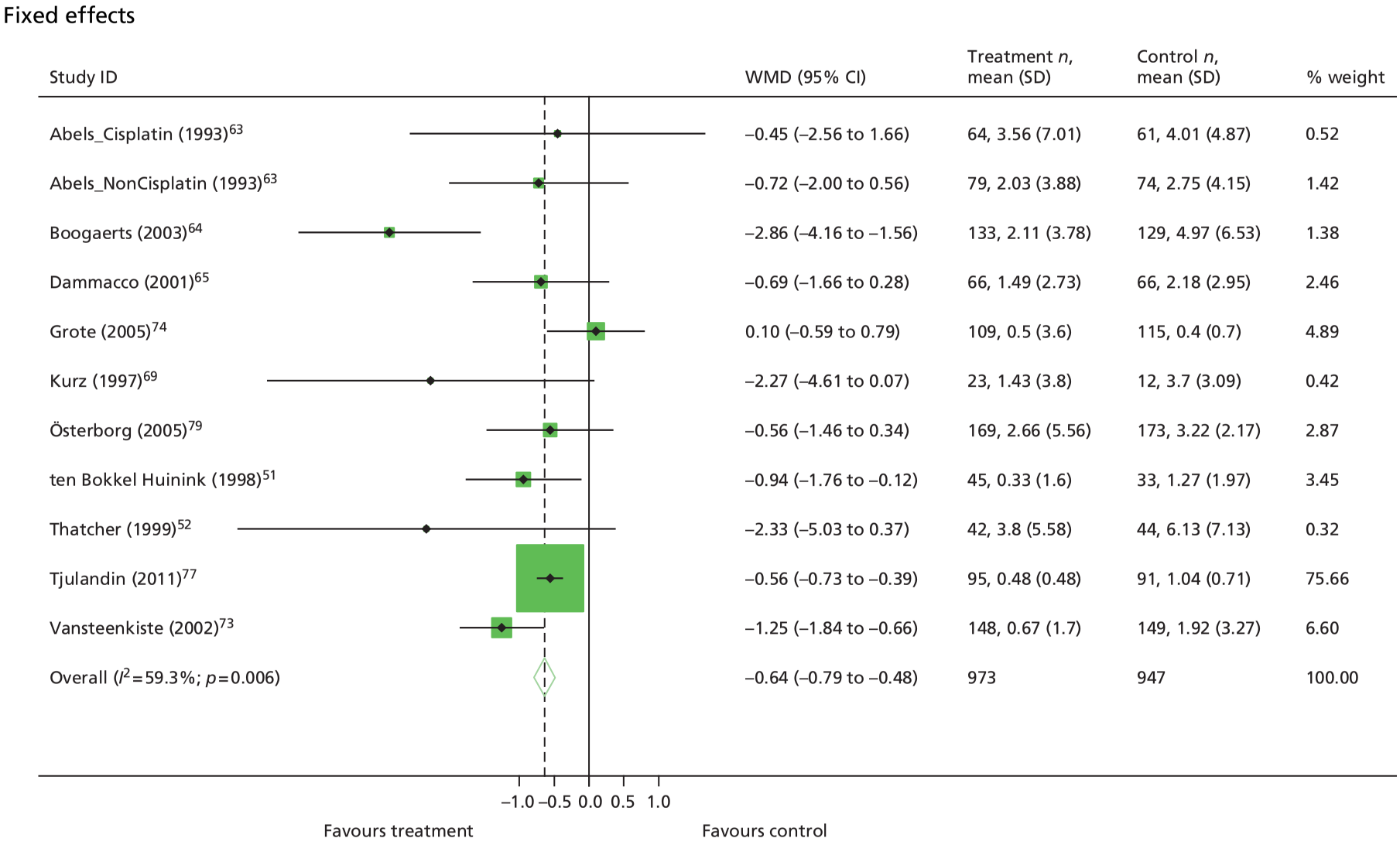

FIGURE 88 Forest plot: red blood cell units transfused. Fixed-effects meta-analysis (Mantel–Haenszel); trial with multiple experimental arm split into subsets in the analysis: Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy.

Malignancy-related outcomes

Tumour response

Fixed effects

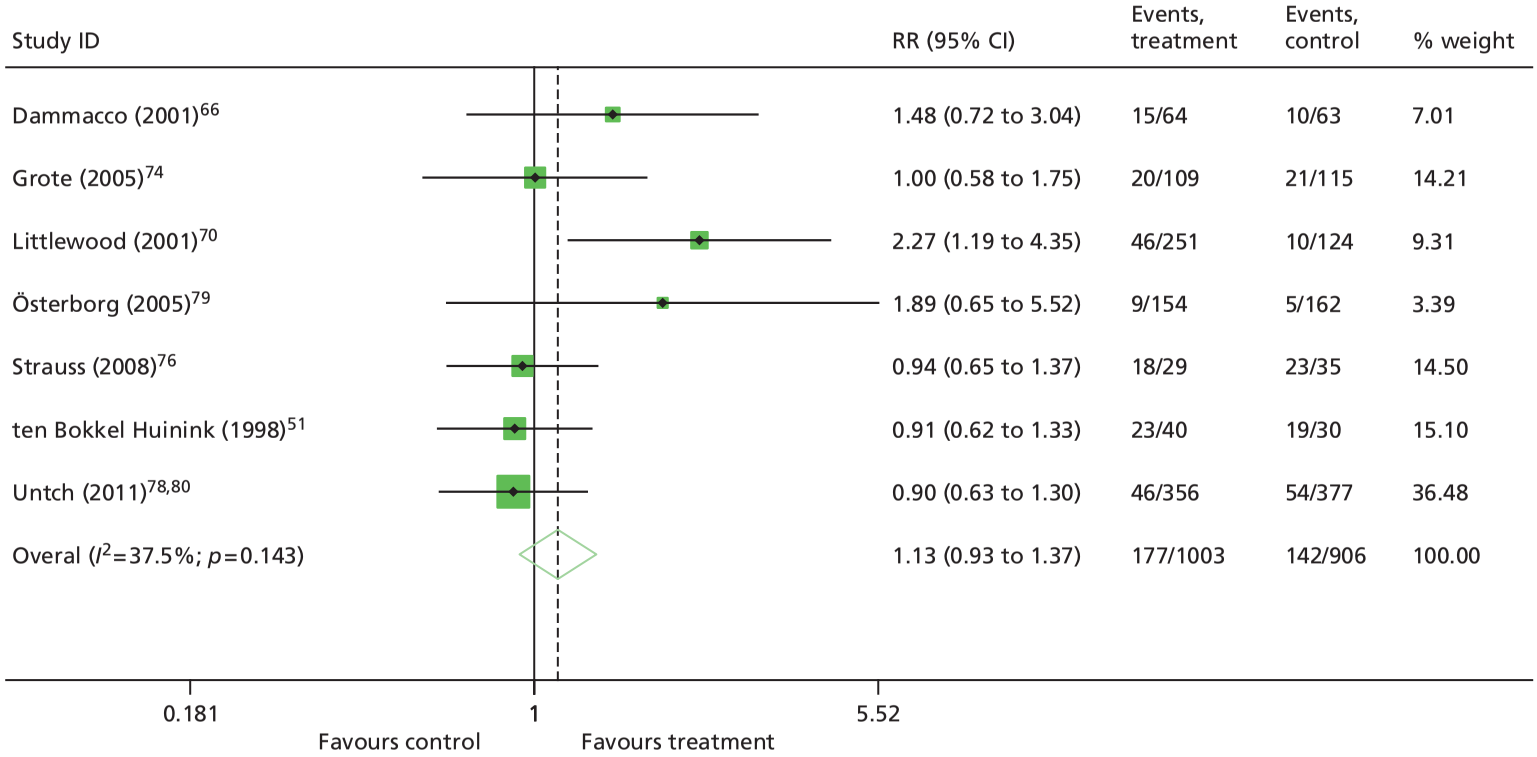

FIGURE 89 Forest plot: tumour response. Fixed-effects meta-analysis (Mantel–Haenszel). Events, treatment = number of events/number of participants in treatment group; events, control = number of events/number of participants in control group.

Overall survival

Publication bias

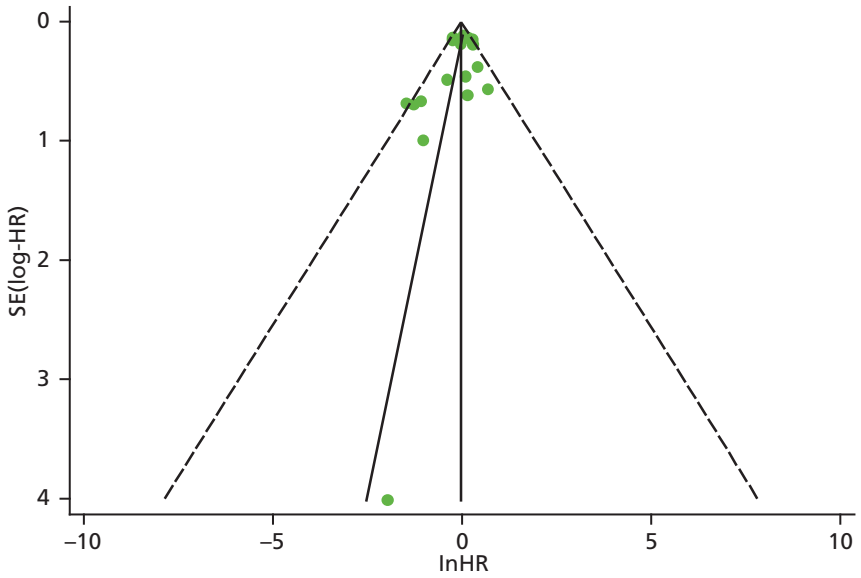

FIGURE 90 Funnel plot with pseudo 95% confidence limits: OS.

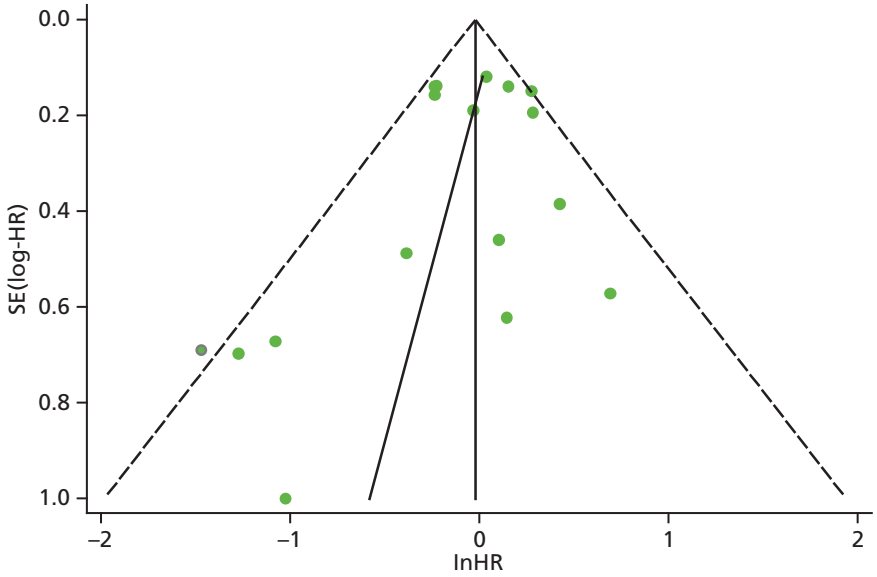

FIGURE 91 Funnel plot with pseudo 95% confidence limits: OS excluding Dunphy and colleagues.[68]

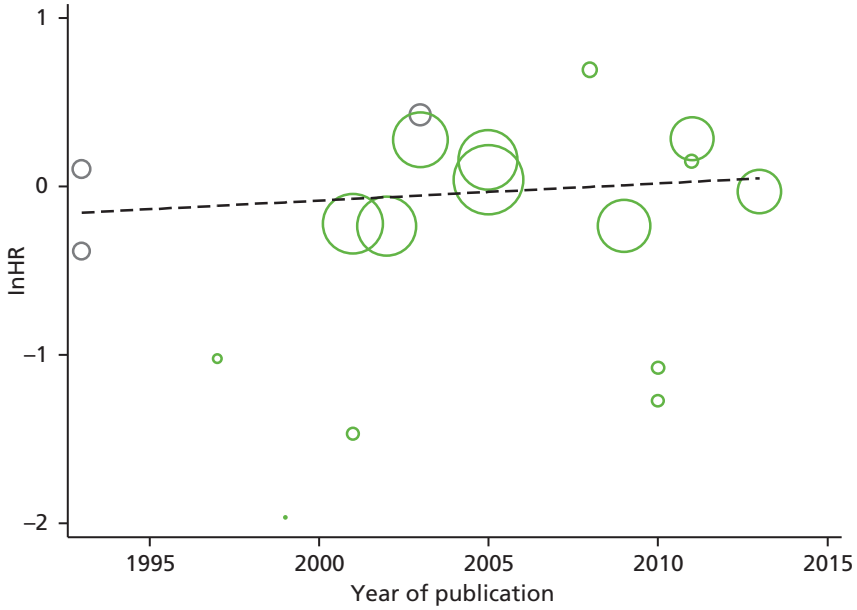

FIGURE 92 Overall survival: publication bias – meta-analysis using year of publication as covariate. pubyear, publication year.

Fixed effects

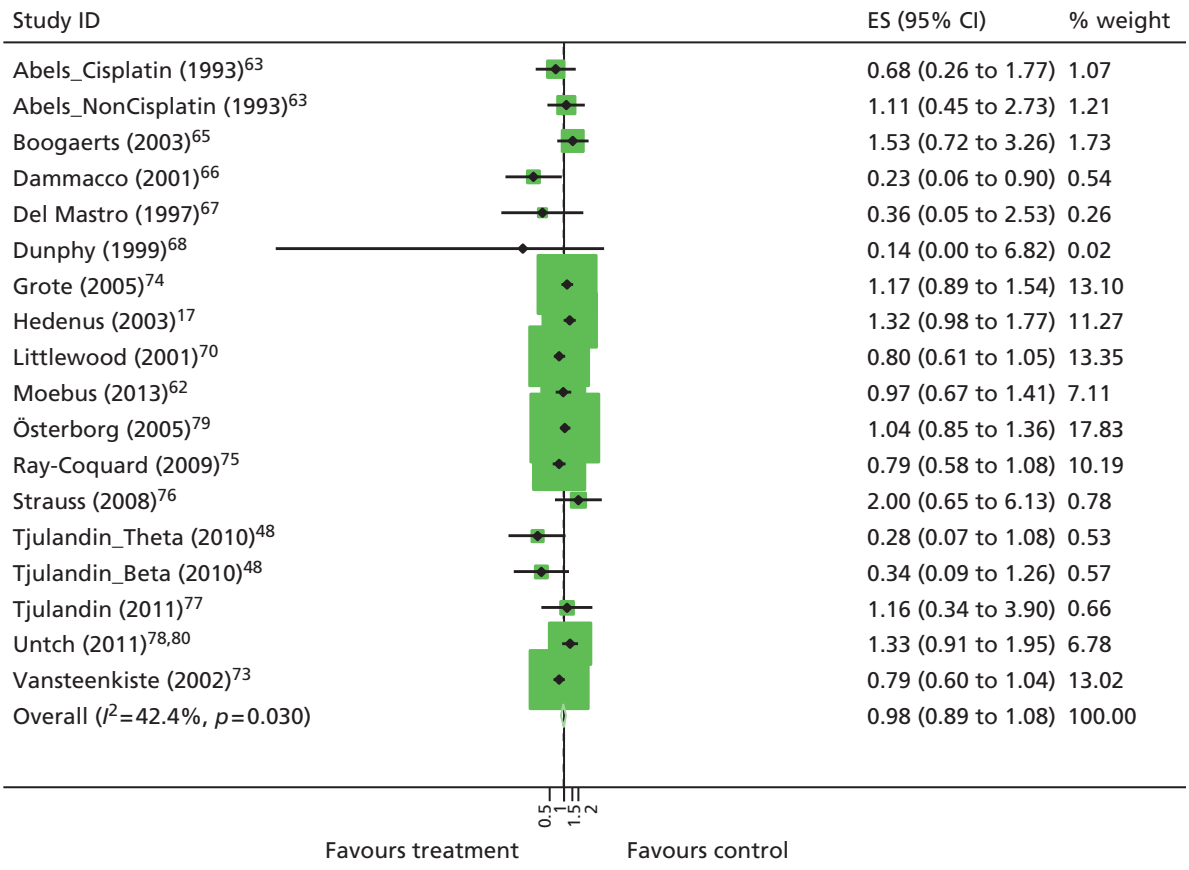

FIGURE 93 Forest plot: overall survival. Fixed-effects meta-analysis; trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy; effect sizes reported are HRs; IPD data as reported in Tonia and colleagues[11] (Cochrane review) for Abels and colleagues,[63] Boogaerts and colleagues,[65] Dammacco and colleagues,[66] Grote and colleagues,[74] Hedenus and colleagues,[17] Littlewood and colleagues,[70] Österborg and colleagues,[71] Ray-Coquard and colleagues,[75] Strauss and colleagues[76] and Vansteenkiste and colleagues.[73] HRs reported for other trials calculated using other accepted methods. ES, effect size.

On-study mortality

Publication bias

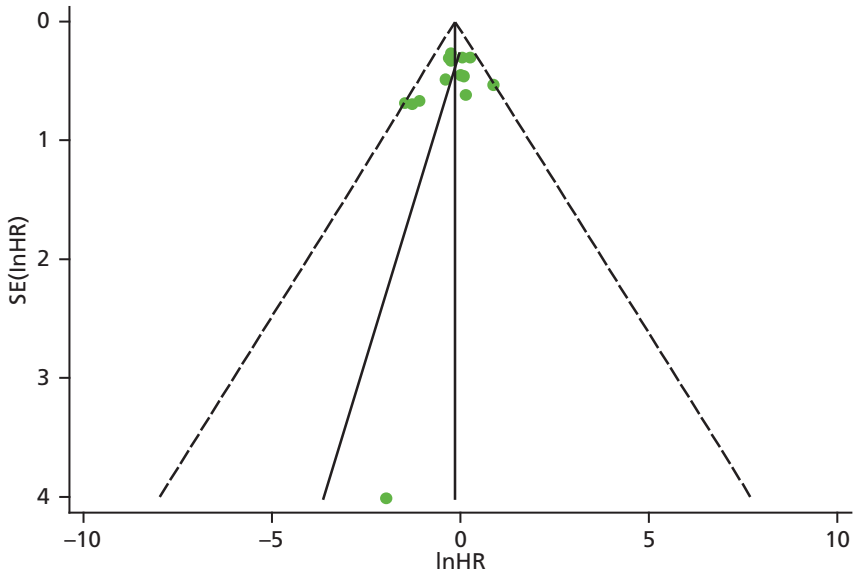

FIGURE 94 Funnel plot with pseudo 95% confidence limits: mortality.

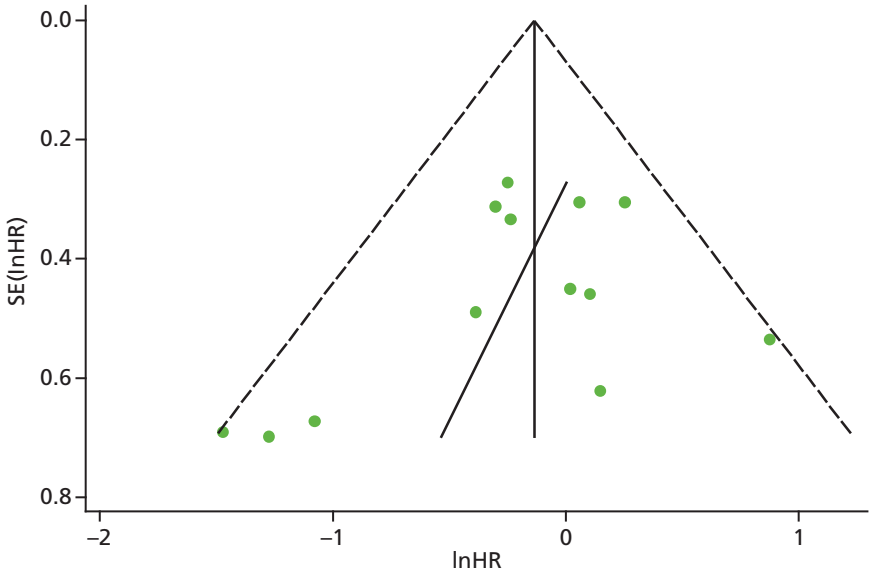

FIGURE 95 Funnel plot with pseudo 95% confidence limits: mortality excluding Dunphy and colleagues.[68]

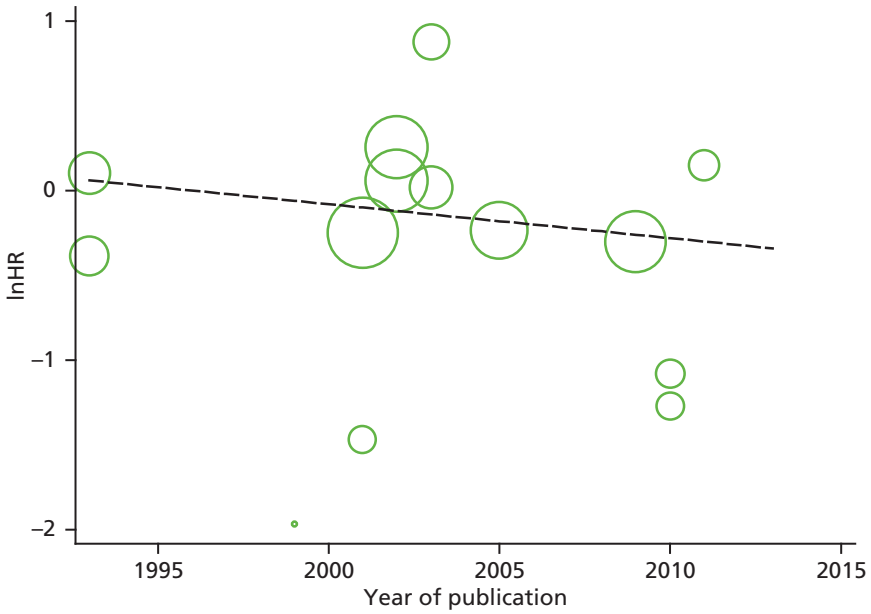

FIGURE 96 Meta-regression plot: mortality.

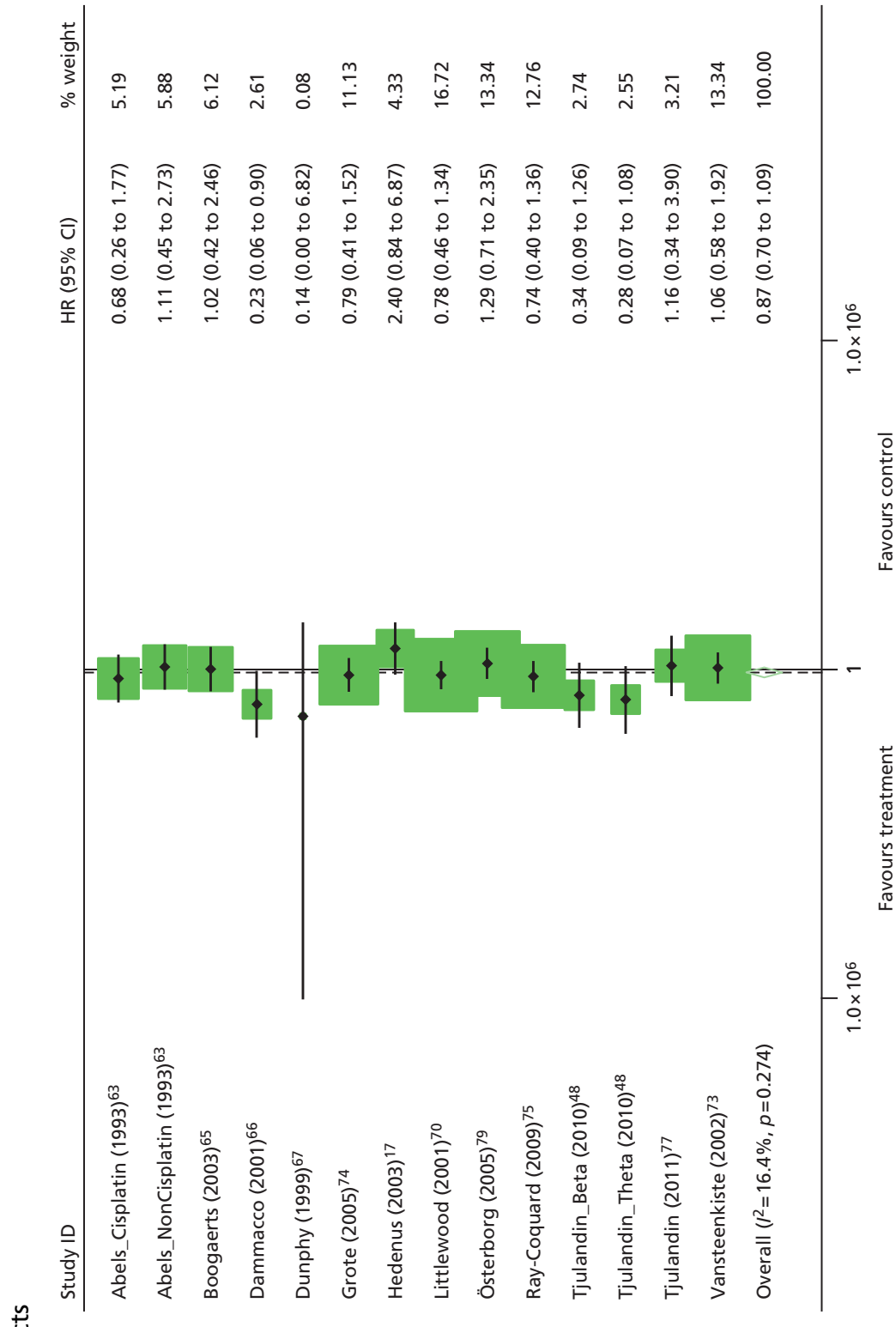

FIGURE 97 Forest plot: mortality. Fixed-effects meta-analysis (DerSimonian–Laird); trials with multiple experimental arms split into subsets in the analysis: Tjulandin and colleagues[48] reported data for epoetin theta and epoetin beta and Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy; IPD data as reported in Tonia and colleagues[11] (Cochrane review) for Abels and colleagues,[63] Boogaerts and colleagues,[65] Dammacco and colleagues,[66] Grote and colleagues,[74] Hedenus and colleagues,[17] Littlewood and colleagues,[70] Österborg and colleagues,[71] Ray-Coquard and colleagues[75] and Vansteenkiste and colleagues.[73] HRs reported for other trials calculated using other accepted methods.

Safety-related outcomes

Thromboembolic events

Publication bias

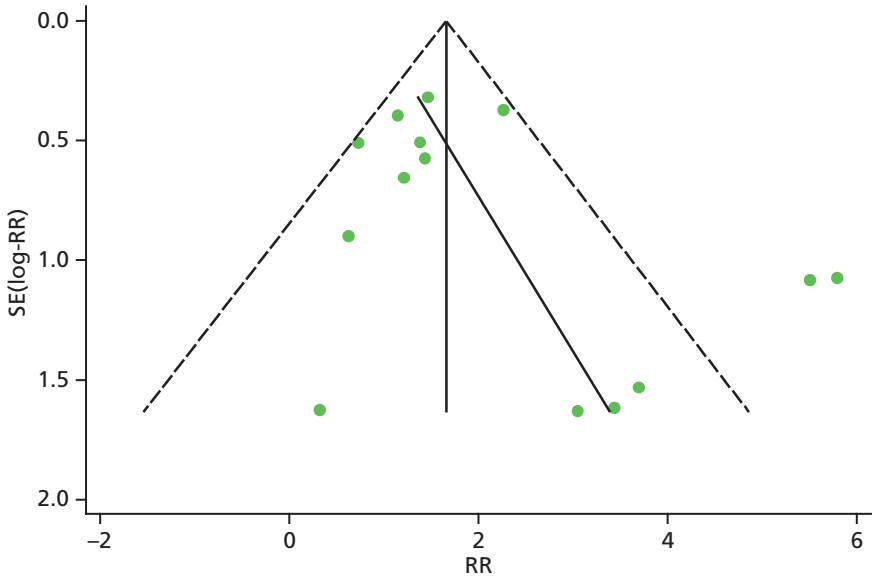

FIGURE 98 Thromboembolic events: publication bias – funnel plot with pseudo 95% confidence limits.

TABLE 101 Thromboembolic events: Harbord's modified test for small study effects

Z/sqrt(*V*)	Coefficient	SE	*t*	*p* > |t|	95% CI
sqrt(*V*)	0.30	0.33	0.91	0.38	–0.42 to 1.03
Bias	0.28	0.56	0.63	0.63	–0.94 to 1.50
Test of H_0 no small study effects $p = 0.627$					

MSE, mean squared error.
Notes
Regress *Z*/sqrt(*V*) on sqrt(*V*) where *Z* is efficient score and *V* is score variance.
No. of studies 14.
Root MSE 0.9755.

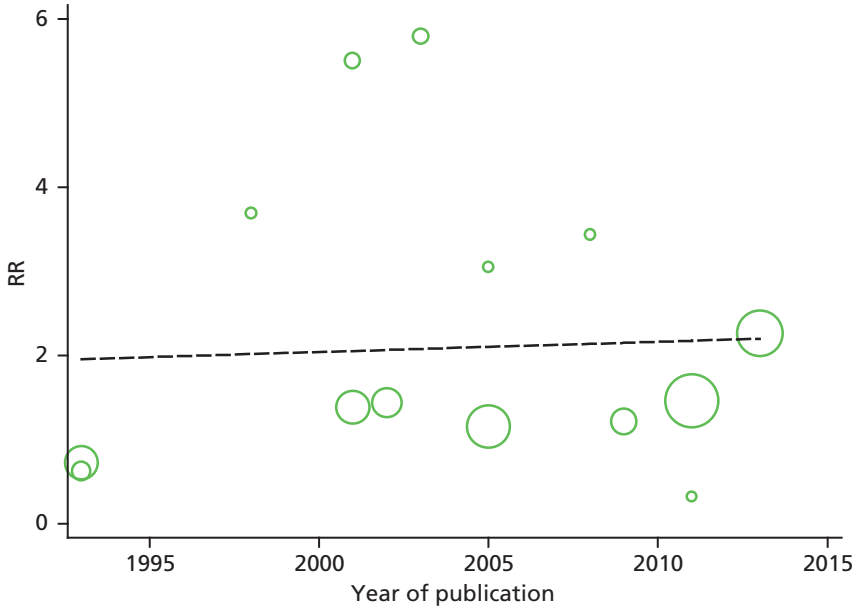

FIGURE 99 Thromboembolic events: publication bias – meta-regression plot with year of publication as a covariate.

Fixed effects

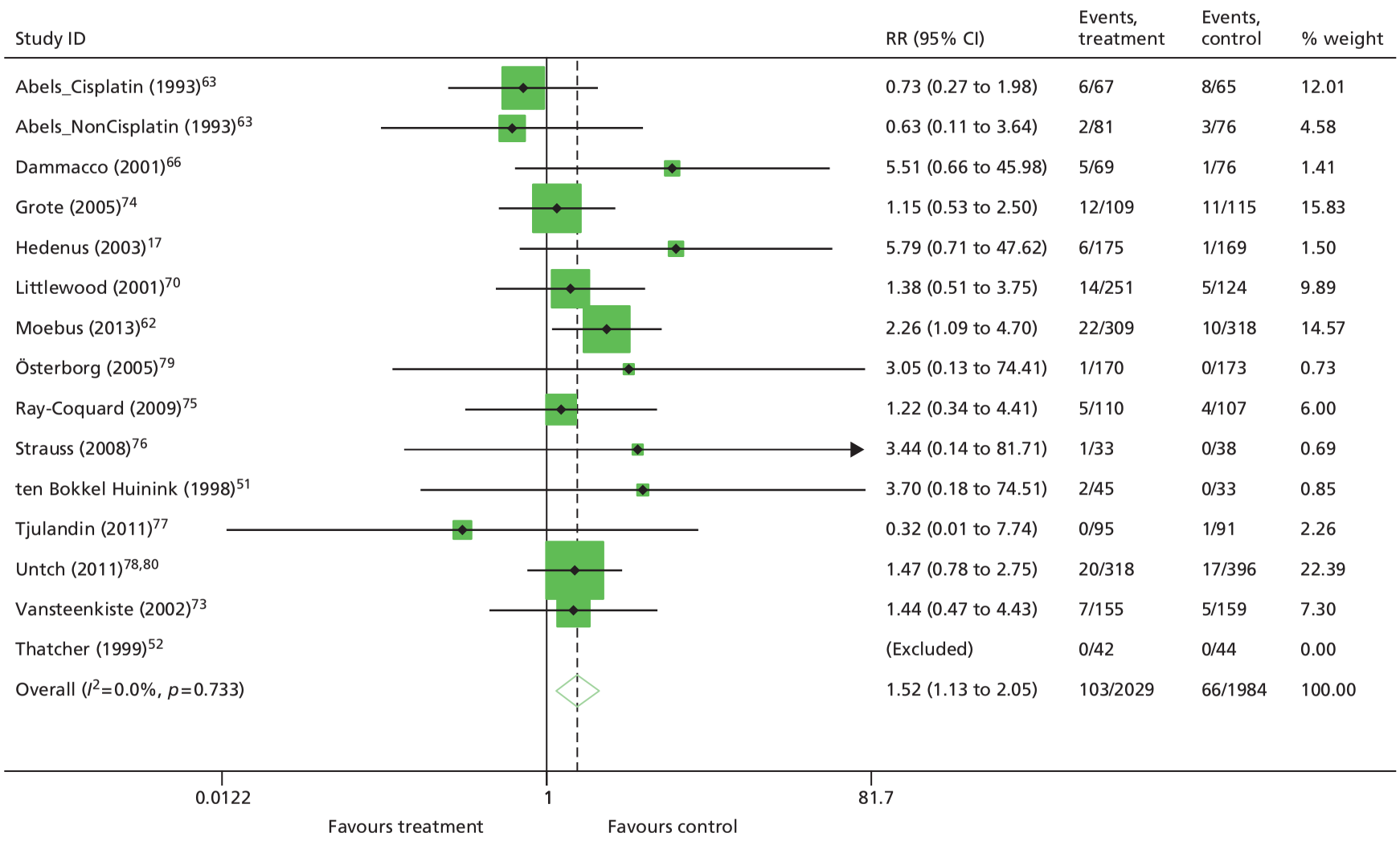

FIGURE 100 Forest plot: thromboembolic events. Fixed-effects meta-analysis (Mantel–Haenszel); trial with multiple experimental arms split into subsets in the analysis: Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/participants in the treatment group; events, control = number of events/participants in the control group.

Hypertension

Publication bias

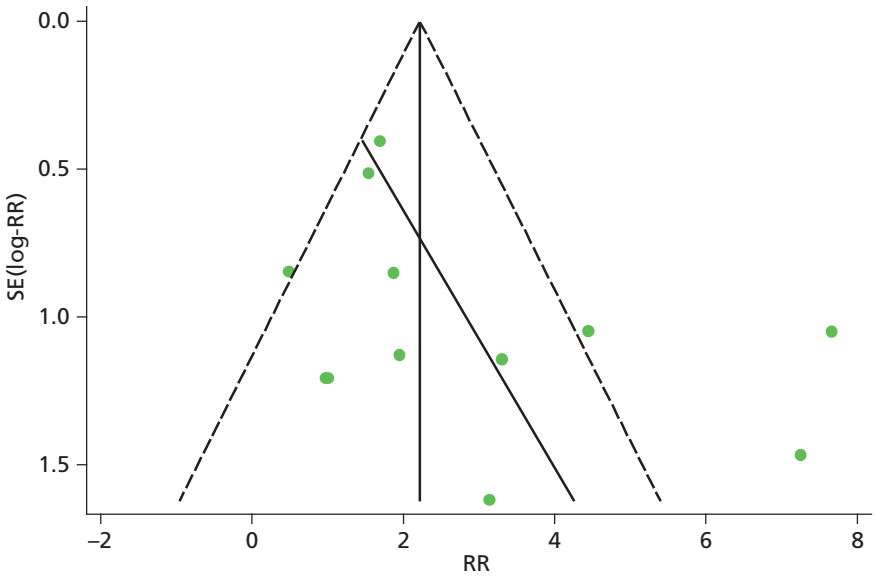

FIGURE 101 Hypertension: publication bias – funnel plot with pseudo 95% confidence limits (fixed effects).

TABLE 102 Hypertension: Harbord's modified test for small study effects

Z/sqrt(*V*)	Coefficient	SE	*t*	$p > \|t\|$	95% CI
sqrt(*V*)	0.49	0.51	0.95	0.364	–0.66 to 1.63
Bias	0.28	0.68	0.41	0.689	–1.22 to 1.79
Test of H_0 no small study effects $p = 0.689$					

MSE, mean squared error.
Notes
Regress *Z*/sqrt(*V*) on sqrt(*V*) where *Z* is efficient score and *V* is score variance.
No. of studies 12.
Root MSE 0.8809.

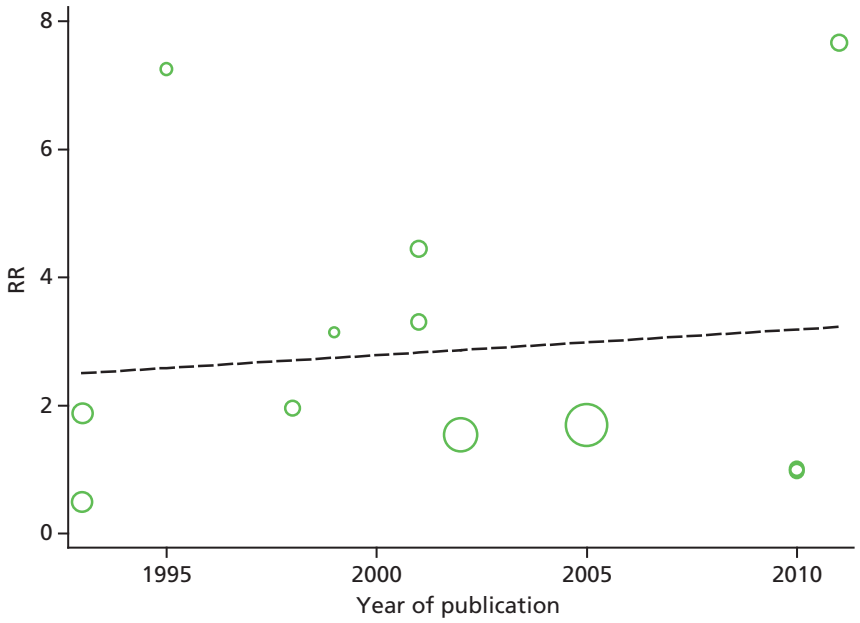

FIGURE 102 Hypertension: publication bias – meta-regression plot with year of publication as a covariate.

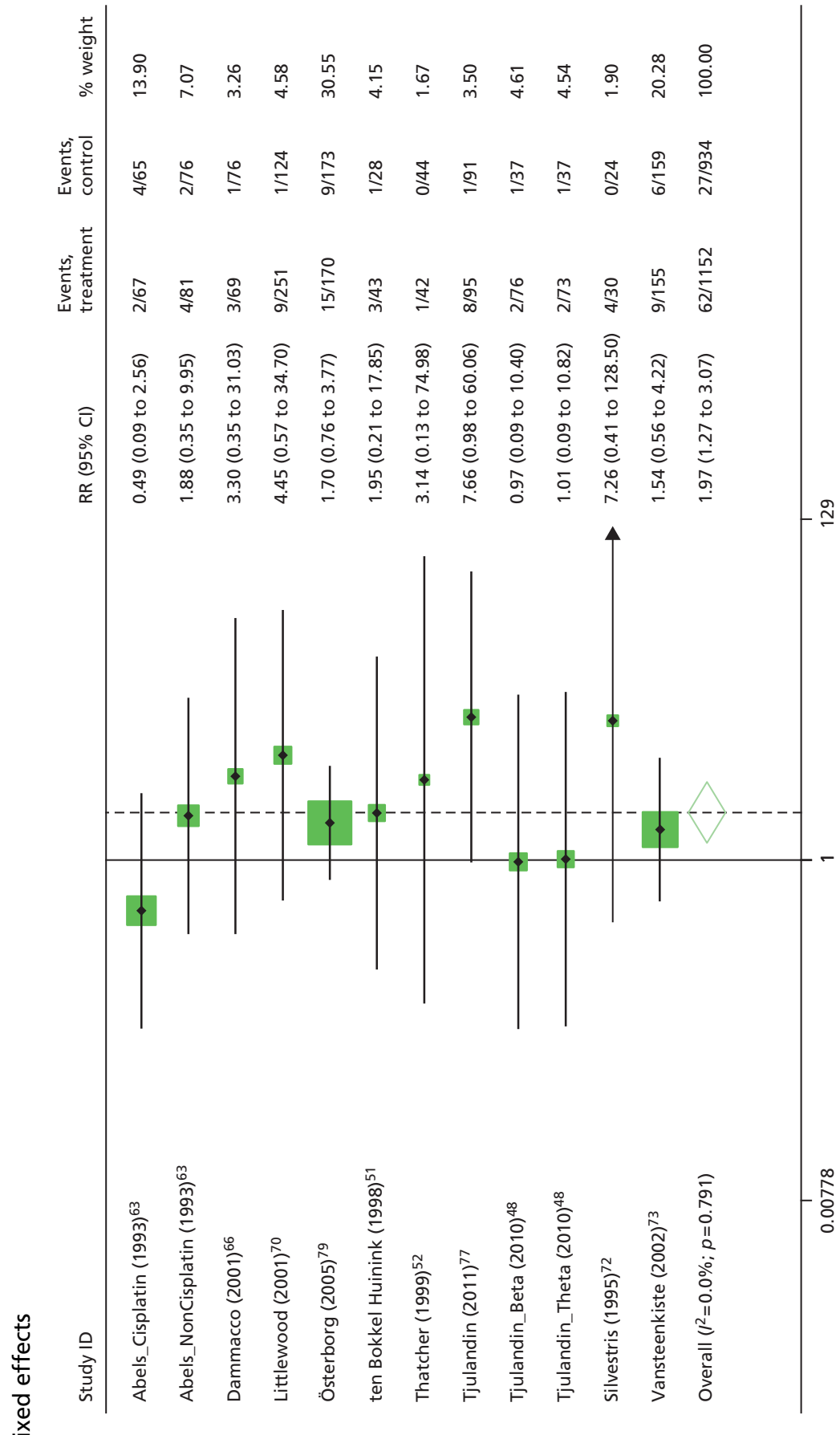

FIGURE 103 Forest plot: hypertension. Fixed-effects meta-analysis (Mantel–Haenszel); trial with multiple experimental arms split into subsets in the analysis: Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/participants in the treatment group; events, control = number of events/participants in the control group.

Thrombocytopenia/haemorrhage

Fixed effects

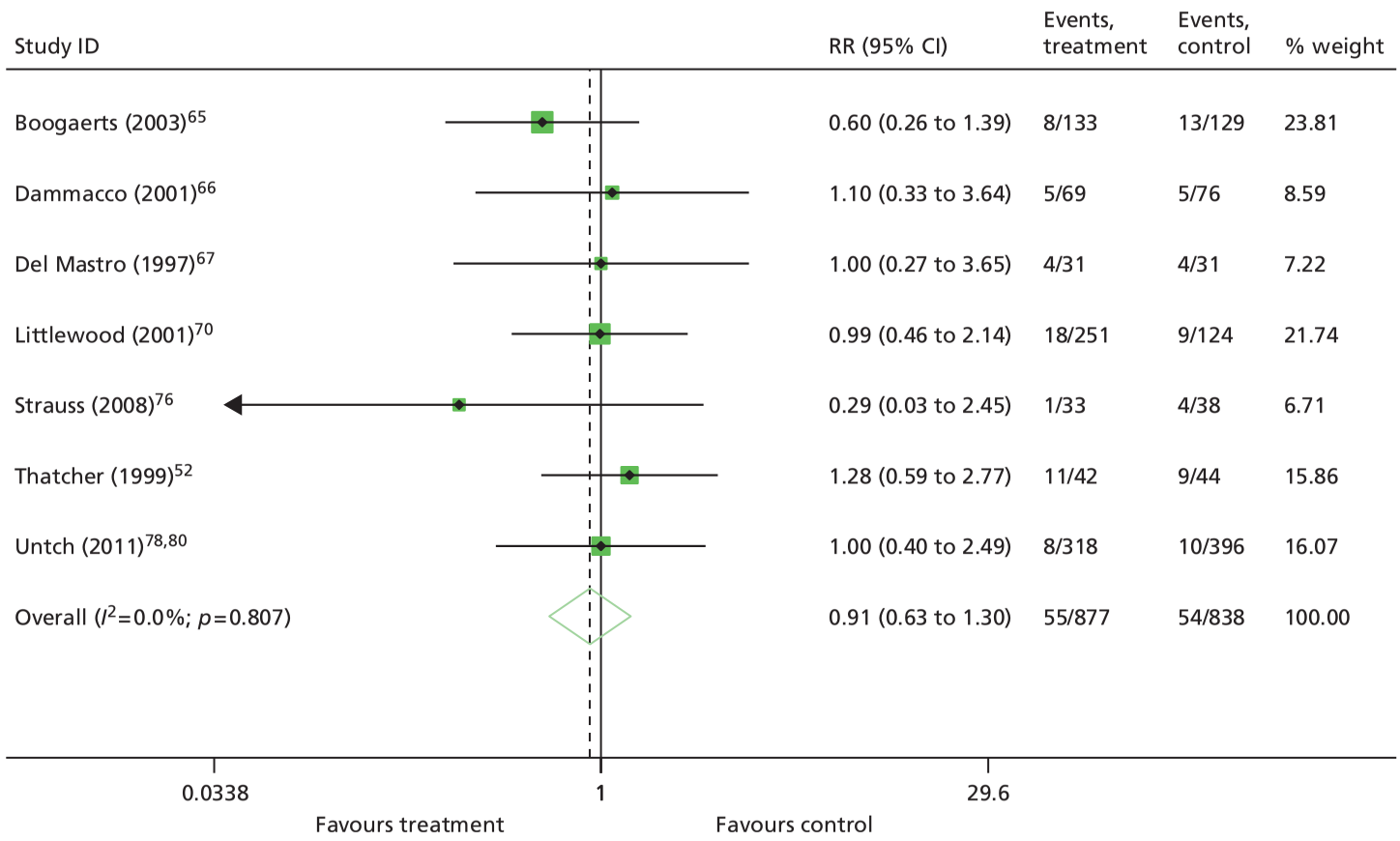

FIGURE 104 Forest plot: thrombocytopenia/haemorrhage. Fixed-effects meta-analysis (Mantel–Haenszel). Events, treatment = number of events/participants in the treatment group; events, control = number of events/participants in the control group.

Seizure

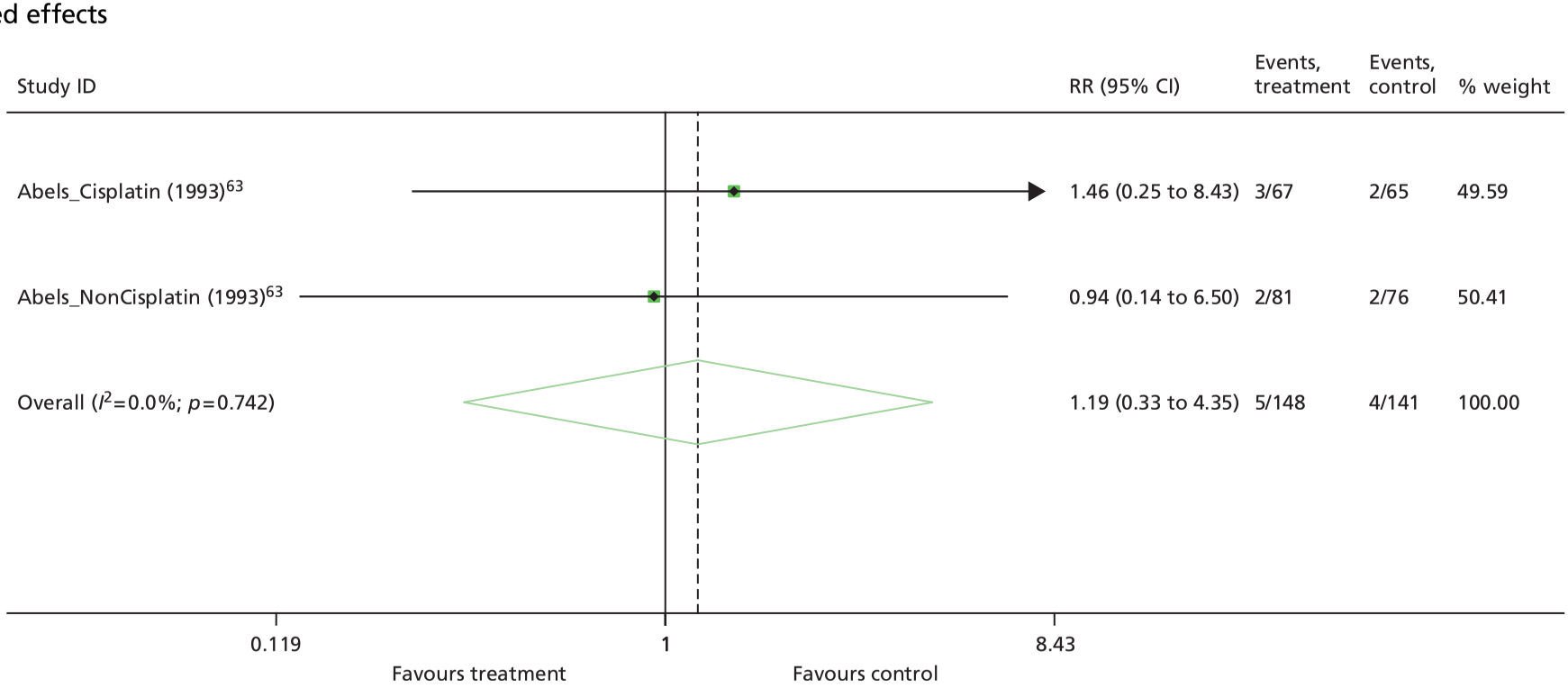

FIGURE 105 Forest plot: seizure. Fixed-effects meta-analysis (Mantel–Haenszel); trial with multiple experimental arms split into subsets in the analysis: Abels and colleagues[63] reported data for participants on platinum-based chemotherapy and non-platinum-based chemotherapy. Events, treatment = number of events/participants in the treatment group; events, control = number of events/participants in the control group.

Pruritus

Fixed effects

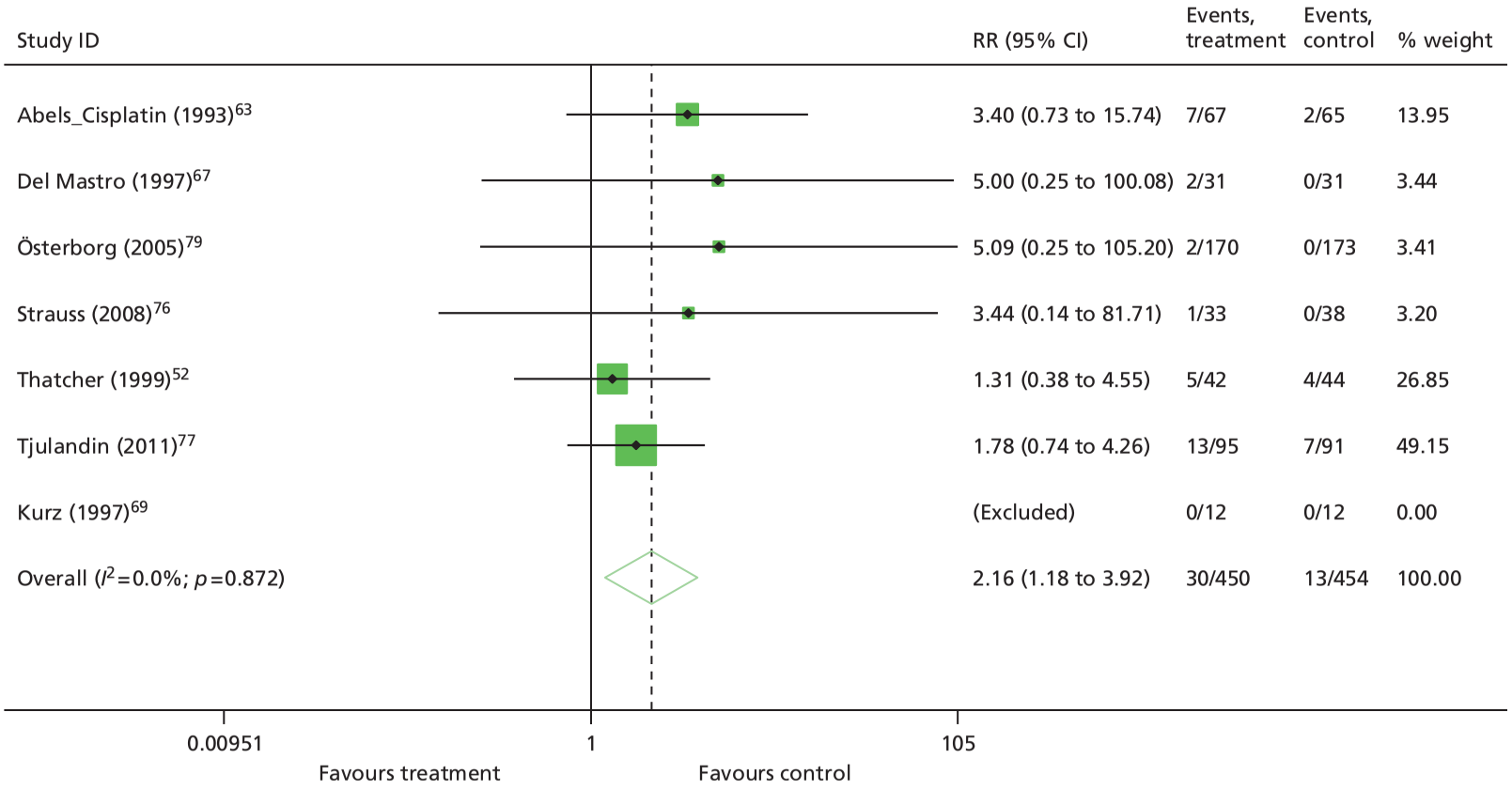

FIGURE 106 Forest plot: pruritus. Fixed-effects meta-analysis (Mantel–Haenszel). Events, treatment = number of events/participants in the treatment group; events, control = number of events/participants in the control group.

Sensitivity 'close to licence' analyses

TABLE 103 Close to licence subgroup analyses using Hb subgroup results from Littlewood and colleagues[70] and Vansteenkiste and colleagues[73]

Licence	Outcome	Trials	ES (95% CI)	I^2
Starting dose criteria met	Hb change[a,b]	18	WMD 1.59 (1.33 to 1.84)	75.9%; $p < 0.01$
	HaemR[a,b,c]	13	RR 3.29 (2.81 to 3.85)	13.4%; $p = 0.31$
	RBCT[a,b,d]	26	RR 0.61 (0.55 to 0.68)	22.4%; $p = 0.15$
	Units[a,e]	12	WMD –0.87 (–1.24 to –0.50)	55.6%; $p = 0.01$
	Tumour response	7	RR 1.10 (0.86 to 1.41)	37.5%; $p = 0.14$
	OS[a,b]	18	HR 0.97 (0.83 to 1.13)	42.4%; $p = 0.03$
	On-study mortality[a,b]	14	HR 0.86 (0.67 to 1.11)	16.4%; $p = 0.27$
	Thromboembolic events[a]	14	RR 1.46 (1.07 to 1.99)	0%; $p = 0.73$
	Hypertension[a,b]	12	RR 1.80 (1.14 to 2.85)	0%; $p = 0.79$
	Thrombocytopenia/ haemorrhage	7	RR 0.93 (0.65 to 1.34)	0%; $p = 0.81$
	Seizures[a]	2	RR 1.19 (0.33 to 4.38)	0%; $p = 0.74$
	Pruritus	6	RR 2.04 (1.11 to 3.75)	0%; $p = 0.87$
Starting dose criteria met and inclusion Hb ≤ 11 g/dl	Hb change[a,b]	13	WMD 1.52 (1.30 to 1.75)	48.1%; $p = 0.03$
	HaemR[a,b,c]	12	RR 3.20 (2.78 to 3.68)	2.0%; $p = 0.43$
	RBCT[a,b,d]	16	RR 0.64 (0.57 to 0.71)	7.3%; $p = 0.37$
	Units[a,e]	9	WMD –0.99 (–1.41 to –0.56)	56.2%; $p = 0.02$
	Tumour response	2	RR 1.60 (0.88 to 2.90)	0%; $p = 0.70$
	OS[a,b]	10	HR 0.91 (0.70 to 1.20)	51.7%; $p = 0.03$
	On-study mortality[a,b]	10	HR 0.89 (0.61 to 1.30)	37.7%; $p = 0.11$
	Thromboembolic events[a]	7	RR 1.29 (0.66 to 2.54)	12.2%; $p = 0.34$
	Hypertension[a,b]	9	RR 1.68 (1.03 to 2.74)	0%; $p = 0.64$
	Thrombocytopenia/ haemorrhage	2	RR 0.73 (0.37 to 1.46)	0%; $p = 0.41$
	Seizures[a]	2	RR 1.19 (0.33 to 4.38)	0%; $p = 0.74$
	Pruritus	3	RR 2.20 (1.05 to 4.58)	0%; $p = 0.66$

continued

TABLE 103 Close to licence subgroup analyses using Hb subgroup results from Littlewood and colleagues[70] and Vansteenkiste and colleagues[73] (*continued*)

Licence	Outcome	Trials	ES (95% CI)	I^2
Starting dose criteria met and target Hb ≤ 13 g/dl	Hb change[b]	4	WMD 1.29 (0.90 to 1.67)	61.9%; $p = 0.05$
	HaemR[b]	3	RR 3.06 (2.28 to 4.09)	0%; $p = 0.79$
	RBCT[b]	4	RR 0.52 (0.34 to 0.80)	48.4%; $p = 0.14$
	Units[e]	1	WMD –0.56 (–0.74 to 0.39)	NA
	Tumour response	1	RR 0.90 (0.63 to 1.3)	NA
	OS[b]	4	HR 0.73 (0.32 to 1.64)	61.8%; $p = 0.05$
	On-study mortality[b]	3	HR 0.50 (0.20 to 1.23)	29.7%; $p = 0.24$
	Thromboembolic events	2	RR 1.38 (0.75 to 2.57)	0%; $p = 0.36$
	Hypertension[b]	3	RR 2.19 (0.53 to 9.12)	16.8%; $p = 0.30$
	Thrombocytopenia/ haemorrhage	1	RR 1.00 (0.40 to 2.50)	NA
	Seizures	0	NA	NA
	Pruritus	1	RR 1.78 (0.74 to 4.26)	NA
Starting dose criteria met, inclusion Hb ≤ 11 g/dl and target Hb ≤ 13 g/dl	Hb change[b]	3	WMD 1.50 (1.16 to 1.83)	0%; $p = 0.80$
	HaemR[b]	3	RR 3.06 (2.28 to 4.09)	0%; $p = 0.79$
	RBCT[b]	3	RR 0.50 (0.33 to 0.77)	0%; $p = 0.92$
	Units[e]	1	WMD –0.56 (–0.74 to 0.39)	NA
	Tumour response	0	NA	NA
	OS[b]	3	HR 0.50 (0.20 to 1.23)	29.7%; $p = 0.24$
	On-study mortality[b]	3	HR 0.50 (0.20 to 1.23)	29.7%; $p = 0.24$
	Thromboembolic events	1	RR 0.32 (0.01 to 7.74)	NA
	Hypertension[b]	3	RR 2.19 (0.53 to 9.12)	16.8%; $p = 0.30$
	Thrombocytopenia/ haemorrhage	0	NA	NA
	Seizures	0	NA	NA
	Pruritus	1	RR 1.78 (0.74 to 4.26)	NA

ES, effect size; haemR, haematological response; units, units transfused per participant.
a Abels and colleagues[63] reported data for participants on platinum-based and non-platinum-based chemotherapy, which were combined.
b Tjulandin and colleagues[48] reported data for epoetin beta and epoetin theta, which were combined.
c Using Hb subgroups from Littlewood and colleagues.[70]
d Using Hb subgroups from Littlewood and colleagues[70] and Vansteenkinste and colleagues.[73]
e Using Hb subgroups from Vansteenkinste and colleagues.[73]

Appendix 13 Supplementary material: health-related quality-of-life review

Health-related quality-of-life review: methods

The search strategy was based on the strategy used in the previous MTA on this topic by Wilson and colleagues,[2] with additional search terms for epoetin theta, epoetin zeta and corresponding drug brand names. It combined free-text and MeSH terms for epoetin (generic and brand names), cancer and anaemia. A search filter was developed by an information scientist to retrieve HRQoL studies, ensuring an appropriate balance of sensitivity and specificity (see *Chapter 3*, *Studies identified*, and *Appendix 1* for further details).

The database search results were exported to EndNote (X5) and deduplicated using the software and manual checking. The search strategies and the numbers retrieved for each database are detailed in *Appendix 1*. After the reviewers completed the screening process, the bibliographies of included papers were scrutinised for further potentially includable studies.

Inclusion criteria were the same as for the main review (see *Chapter 3*, *Eligibility criteria*). Data were tabulated and analysed by meta-analysis to provide an overview with an estimate of overall effect.

Health-related quality-of-life review: results

Studies identified

We screened the titles and abstracts of 1268 unique references identified by the PenTAG searches and additional sources and retrieved 224 papers for detailed consideration. Of these, 191 were excluded (a list of these items with reasons for their exclusion can be found in *Appendix 4*). Update searches conducted on 2 December 2013 yielded 61 titles and abstracts, none of which was considered eligible for inclusion. Thirty-three studies met the prespecified criteria set out in the protocol and were considered eligible for inclusion in the HRQoL review. Fifteen studies were considered eligible from the previous HTA review.[2] At both stages, initial disagreements were easily resolved by consensus.

A total of 48 publications were considered eligible for inclusion. As for the clinical effectiveness review, we further specified that eligible interventions should be assessed as administered in accordance with their licensed indications. This criterion was applied after the first round of full-paper screening to make sure that we captured all relevant evidence (see *Chapter 3*, *Methods*, *Selection of studies* for details). In applying this criterion, a further 25 studies were excluded, as they evaluated an unlicensed dose. In total, 13 studies reported in 23 publications[17,50,52,58–60,63,65–67,69–71,73,76,77,79,81–86] were considered eligible for inclusion in the HRQoL review. This process is illustrated in detail in *Figure 107*.

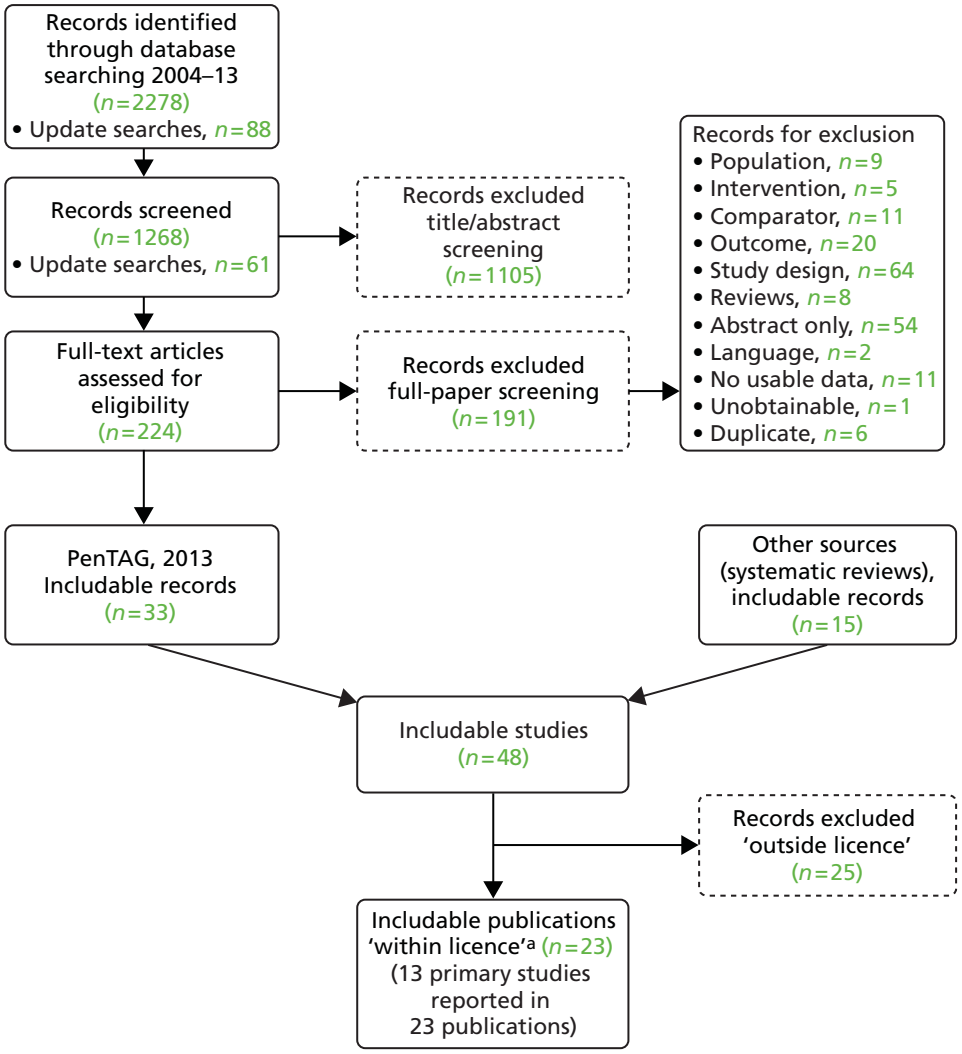

FIGURE 107 Quality-of-life review: PRISMA flow diagram. SR, systematic review. a, 'within licence', based on the administration of ESAs at the licensed weight-based start dose.

Health-related quality-of-life measures

TABLE 104 Summary of scales included in this review

Scale	Type of HRQoL instrument	Domains	Items	Implication of value
FACT-G[284]	Specific for use with patients of any tumour type	• Physical well-being • Social/family well-being • Emotional well-being • Functional well-being	27 items – response between 0 and 4 for each question with a maximum score of 108	Higher score indicates improved HRQoL
FACT-F[284]	Symptom specific (fatigue)	Fatigue-related questions often used in isolation or as a component of other FACT questionnaires	13 items – response between 0 and 4 for each question with a maximum score of 52	Higher score indicates improved HRQoL
FACT-An[284]	Symptom specific (fatigue or anaemia)	Composed of FACT-G, FACT-F and FACT-An-An	47 items – response between 0 and 4 for each question with a maximum score 188	Higher score indicates improved HRQoL

TABLE 104 Summary of scales included in this review (*continued*)

Scale	Type of HRQoL instrument	Domains	Items	Implication of value
FACT-An-An[285]	Symptom specific (additional concerns for anaemia)	Anaemia-related questions that do not include fatigue	Seven items – response between 0 and 4 for each question with a maximum score of 28	Higher score indicates improved HRQoL
SF-36[286]	Generic	• Physical functioning • Role physical • Bodily pain • General health • Vitality • Social functioning • Role emotional • Mental health Questions compare experiences to a time in the past, e.g. 4 weeks ago	36 items – each scale is directly transformed into a 0–100 scale	The lower the score, the greater the disability
NHP[287]	Generic	• Sleep • Energy level • Physical mobility • Pain • Emotional reactions • Social isolation	38 items – scores on the first component are weighted to give a score between 0 and 100	The higher the score, the lower the HRQoL; however, it should be noted the NHP was not originally intended to measure HRQoL and is not considered highly sensitive[2,288]
Cancer Linear Analog Scale or LASA[289,290]	Specific for cancer patients to indicate feelings	• Symptoms and effects of disease and treatment • Psychological consequences • Physical indices • Personal relationships	25 items – 100 mm lines	Higher score indicates improved HRQoL
Brief Symptom Inventory[291]	Generic psychiatry/ psychology	• Somatisation • Obsessive–compulsive • Interpersonal sensitivity • Depression • Anxiety • Hostility • Phobic anxiety • Paranoid ideation • Psychoticism • Global severity index • Positive symptom distress index • Positive symptom total	53 items – scores between 0 and 4 with a maximum score of 212	The higher the score the greater the distress
Psychological Distress Inventory[292]	Specific for cancer patients	• Reactive anxiety to cancer and its therapies • Reactive depression • Emotional reactions	13 items – scores between 0 and 5	A higher score indicates a higher level of distress
EORTC-QLQ-C30[293]	Specific for cancer patients	A range of questions including on daily activities, sleep, pain, mobility, emotions and health	30 items – 28 items with a score between 0 and 4 and two items with a score between 0 and 7 with a maximum score of 126	The higher the score, the higher the level of functioning

NHP, Nottingham Health Profile.

Meta-analysis: health-related quality of life

FACT-F: fixed effects

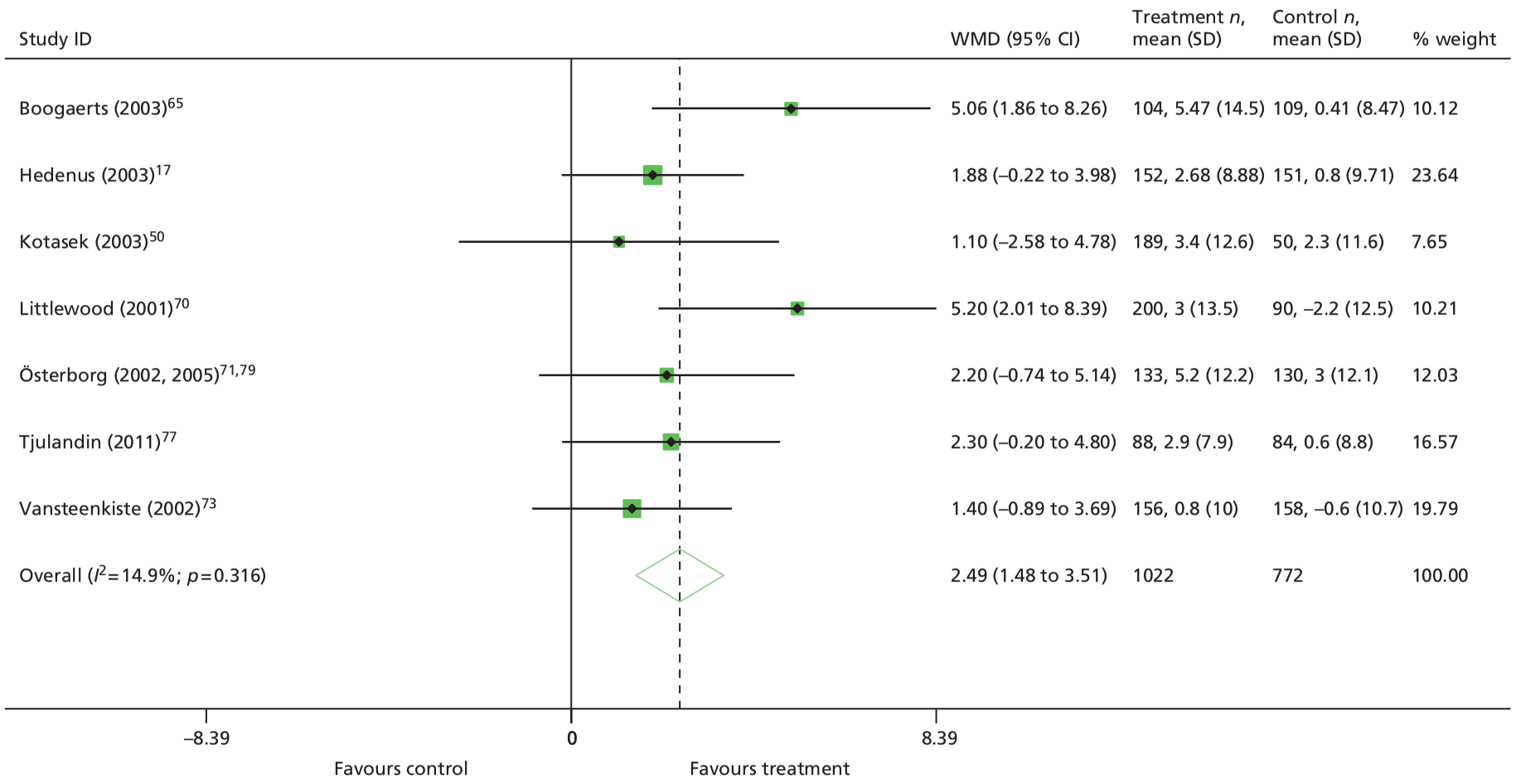

FIGURE 108 Forest plot: HRQoL [change in FACT-F score – overall (fixed effects – Mantel–Haenszel pooled WMD)].

FACT-F: subgroup analyses (random effects)

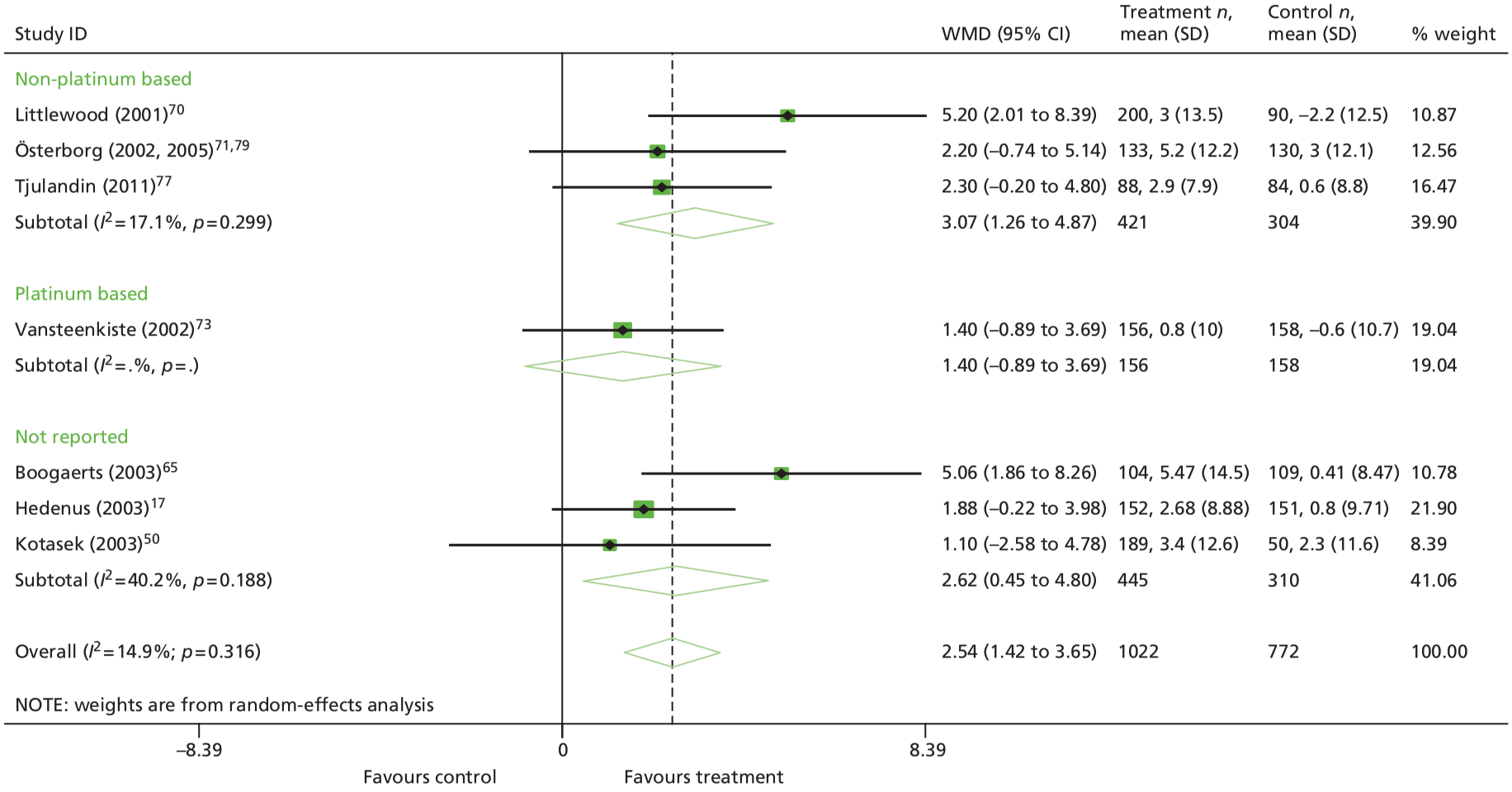

FIGURE 109 Forest plot: HRQoL [change in FACT-F score by chemotherapy type (random effects – DerSimonian–Laird pooled WMD)].

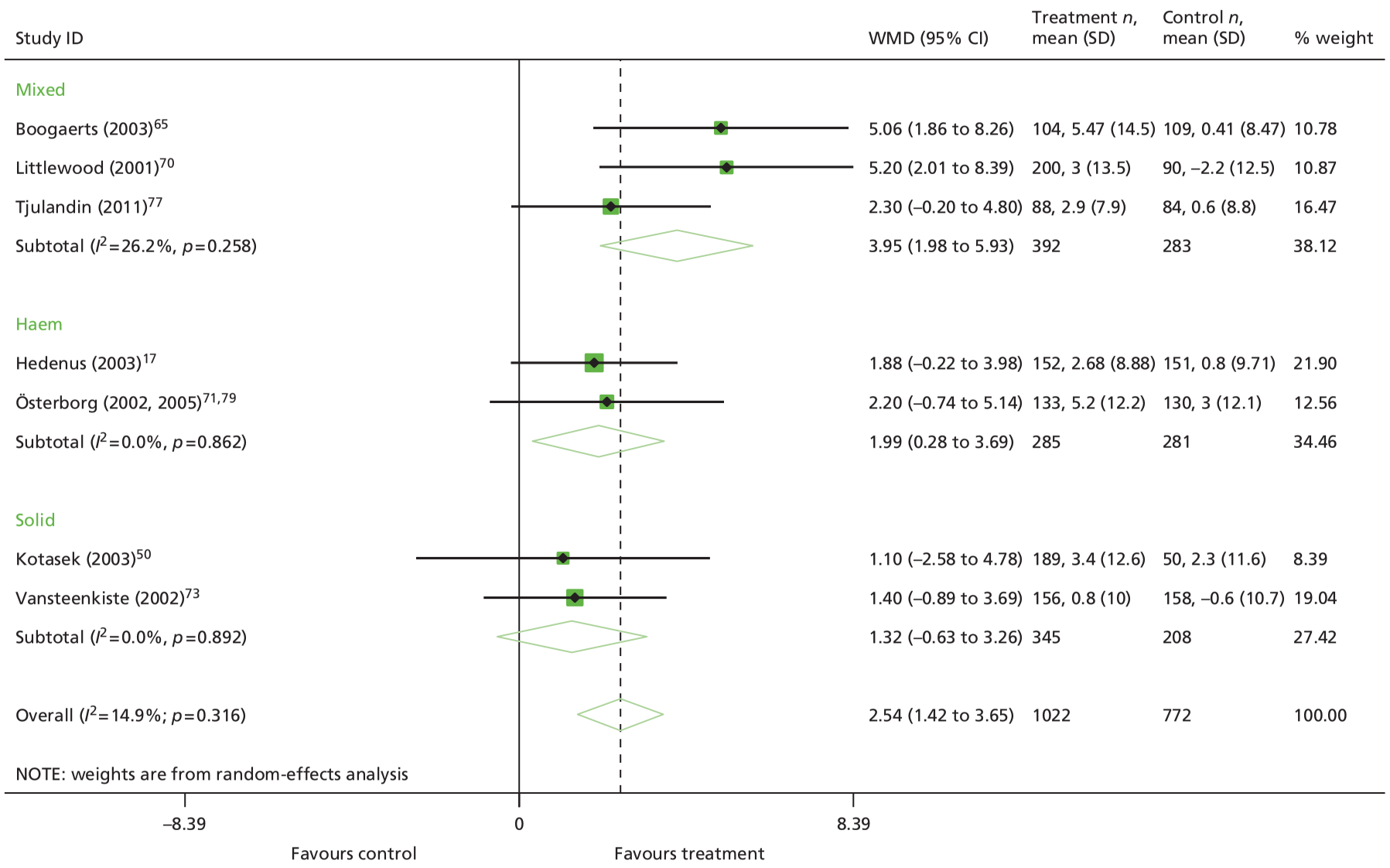

FIGURE 110 Forest plot: HRQoL [change in FACT-F score by malignancy (random effects – DerSimonian–Laird pooled WMD)].

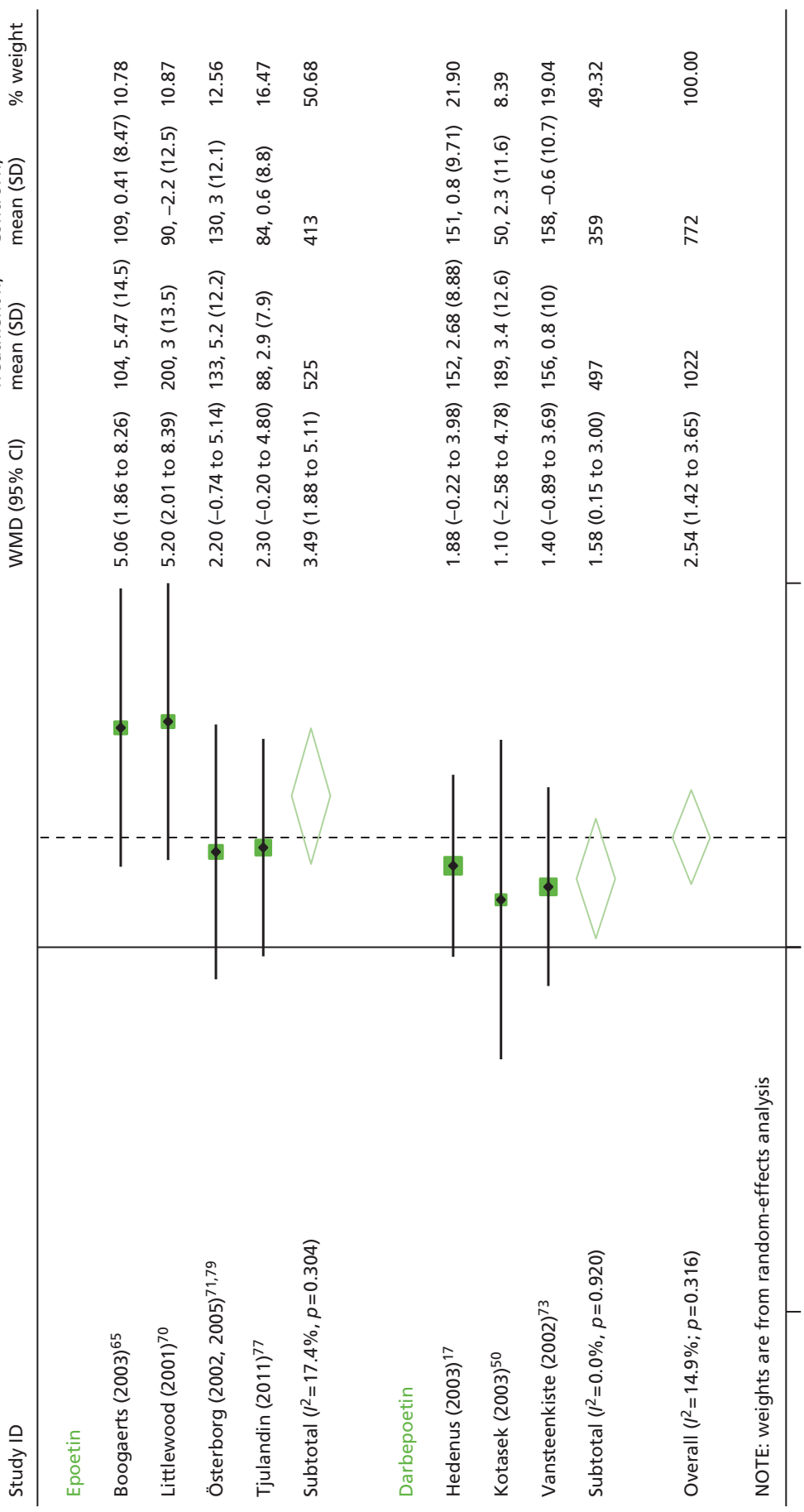

FIGURE 111 Forest plot: HRQoL [change in FACT-F score by intervention (random effects – DerSimonian–Laird pooled WMD)].

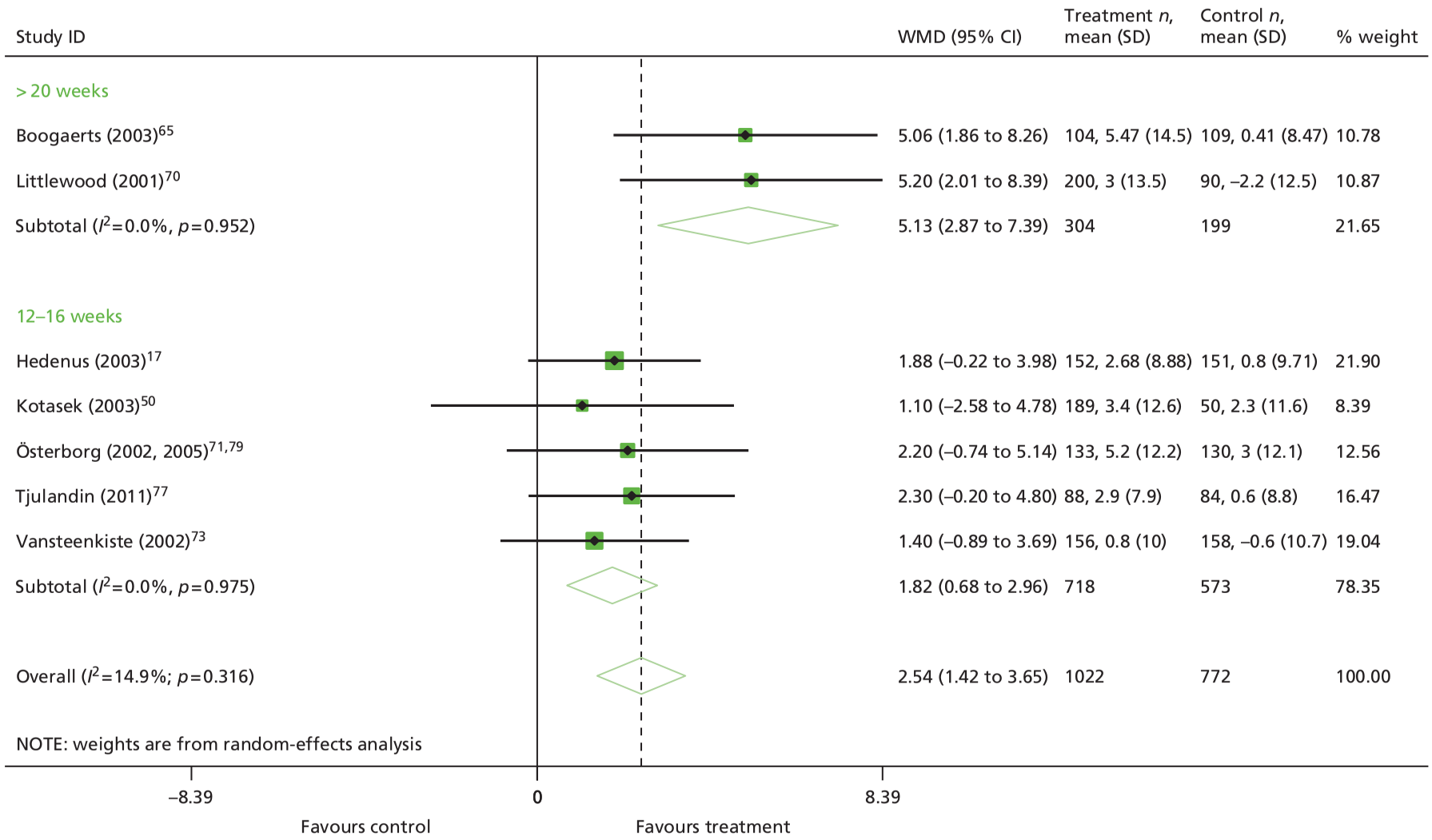

FIGURE 112 Forest plot: HRQoL [change in FACT-F score by study duration (random effects – DerSimonian–Laird pooled WMD)].

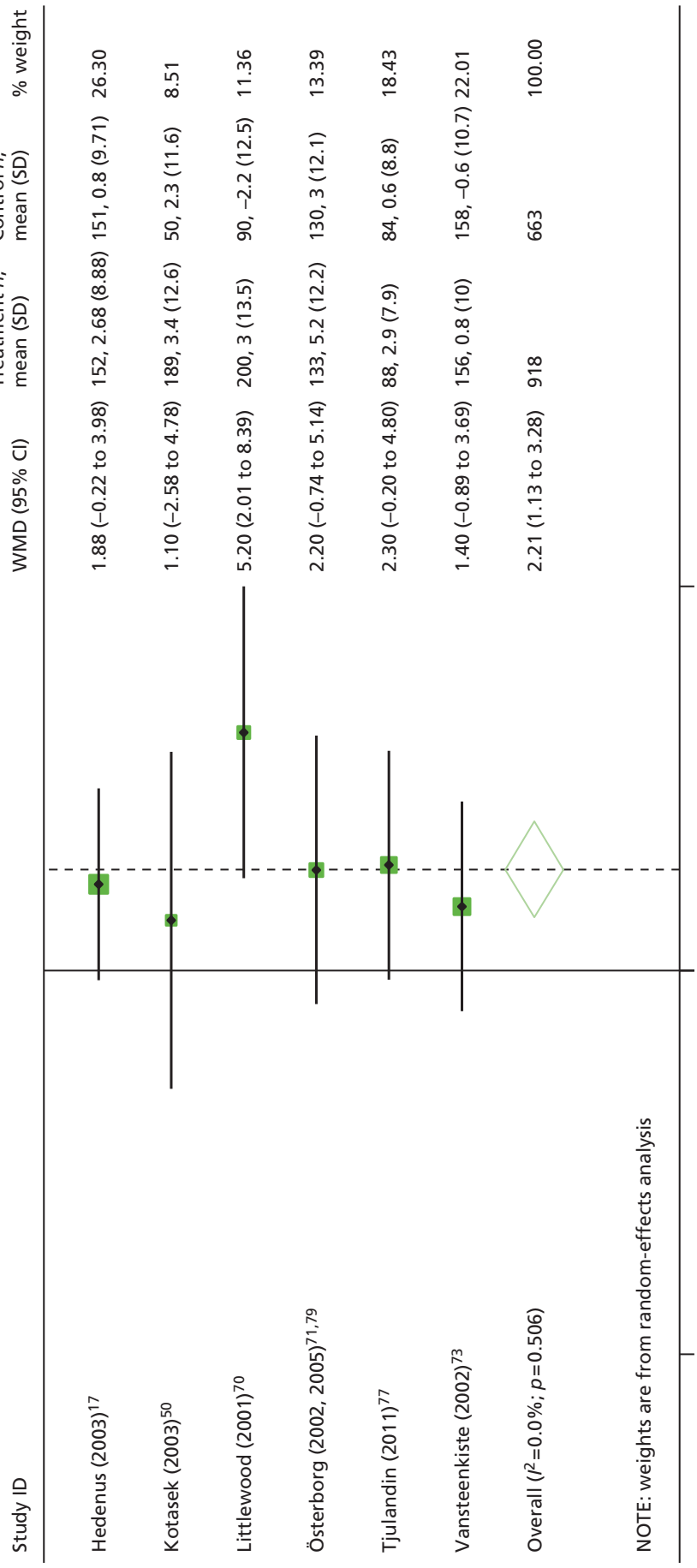

FIGURE 113 Forest plot: HRQoL [change in FACT-F score with data from Boogaerts and colleagues[65] removed (random effects – DerSimonian–Laird pooled WMD)].

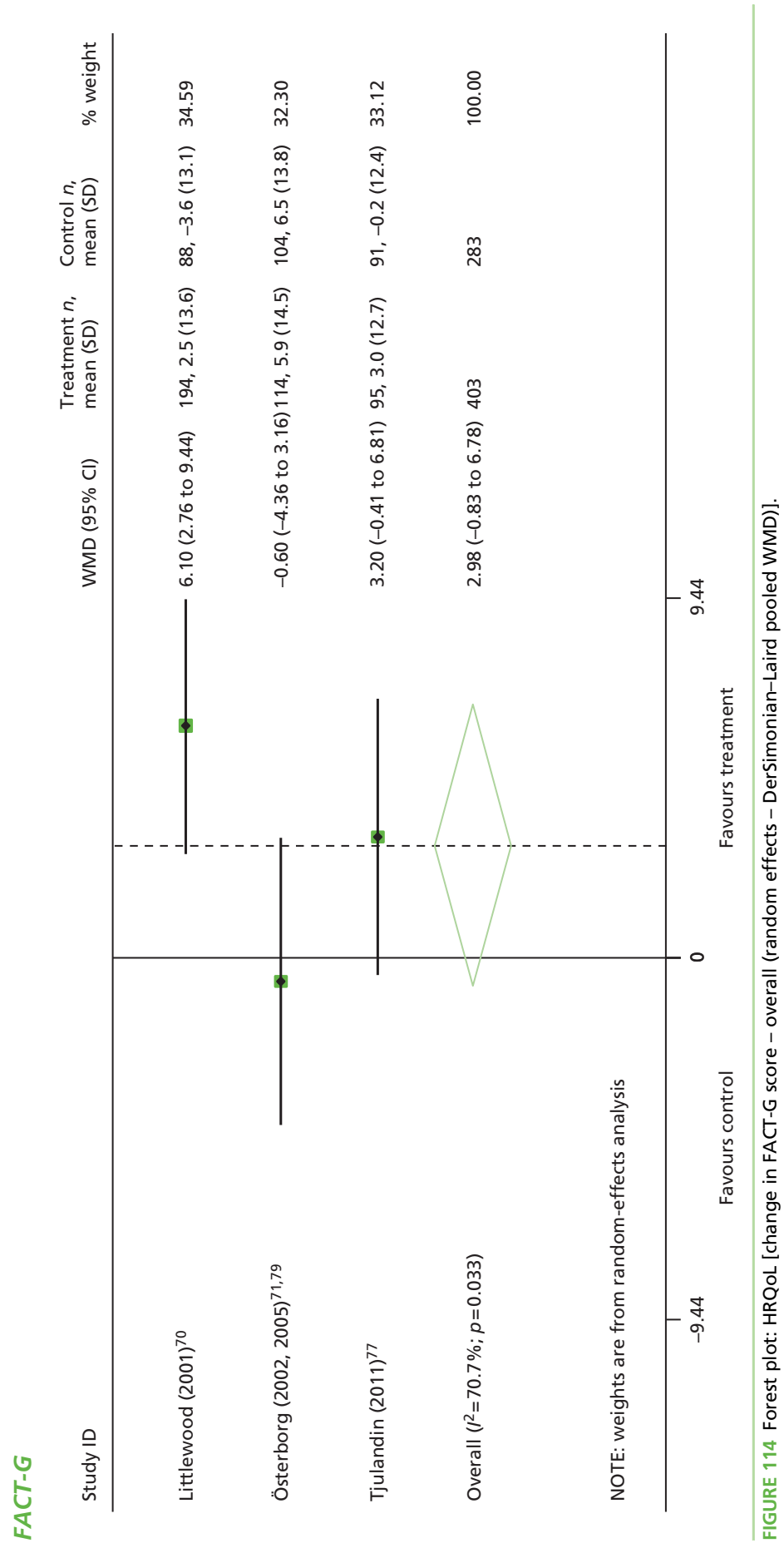

FIGURE 114 Forest plot: HRQoL [change in FACT-G score – overall (random effects – DerSimonian–Laird pooled WMD)].

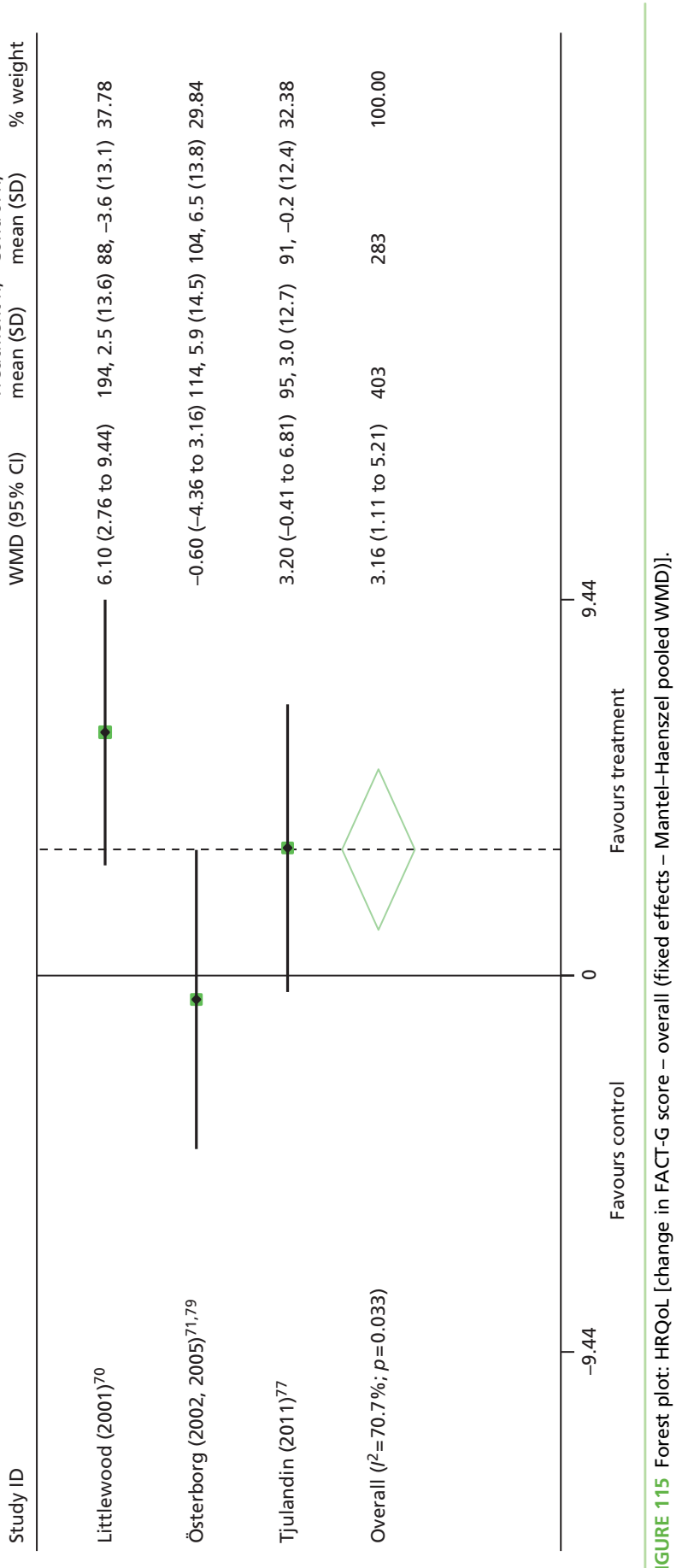

FIGURE 115 Forest plot: HRQoL [change in FACT-G score – overall (fixed effects – Mantel–Haenszel pooled WMD)].

FACT-An

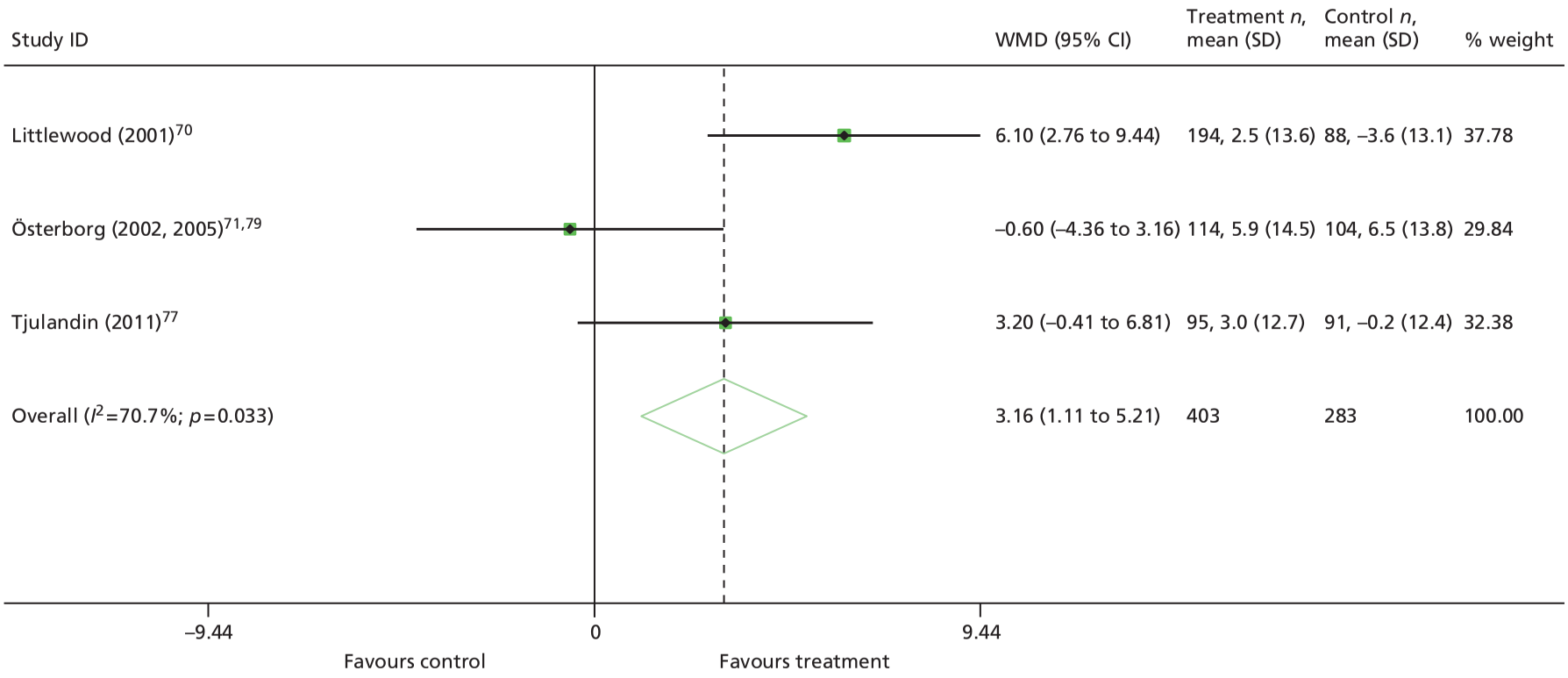

FIGURE 116 Forest plot: HRQoL [change in FACT-An score – overall (fixed effects – Mantel–Haenszel pooled WMD)].

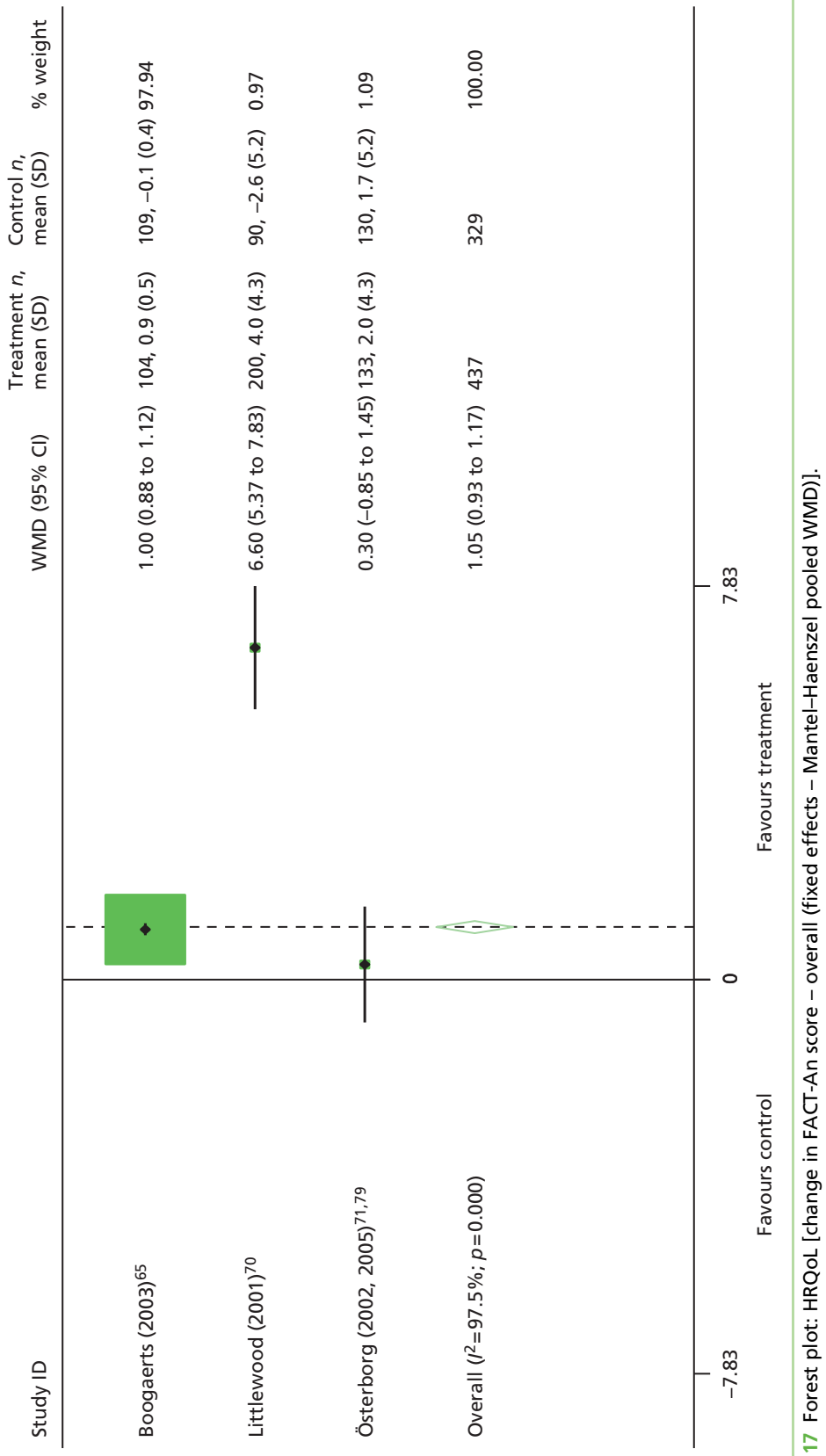

FIGURE 117 Forest plot: HRQoL [change in FACT-An score – overall (fixed effects – Mantel–Haenszel pooled WMD)].

Appendix 14 Study characteristics, key parameters and results of conference abstracts identified in the cost-effectiveness review

Parameter	Szucs and colleagues[132]	Cremieux and colleagues[133]	Mark and colleagues[135]	van Hout and Gagnon[136]
Evaluation type	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost–consequences analysis	Cost-effectiveness analysis
Modelling used	No	No	No	Yes
Nature of modelling	NA	NA	NA	'Bayesian simulation model'
Perspective	Societal	Societal	Drug cost only	Health care[a]
Country (setting)	Multiple (France, Germany, Italy, Sweden and UK)	Not stated (probably USA)	Not stated (probably USA)	UK[a]
Intervention/ comparator	Epoetin beta TIW: 150 IU/kg; standard care	Epoetin alfa QW: 40,000 IU; darbepoetin alfa QW: 2.25 µg/kg	Epoetin alfa; darbepoetin alfa	Epoetin alfa QW: 150 IU/kg;[b] darbepoetin alfa QW: 2.25 µg/kg[c]
Population	Patients with solid or lymphoid tumours	Patients with lung cancer receiving chemotherapy	Non-myeloid cancer patients with chemotherapy-related anaemia	Anaemic cancer patients receiving chemotherapy
Outcomes considered	SF-36 PCS, FACIT-F, FACT-An	Cumulative change in Hb (AUC), change in FACIT-F	Proportion of patients requiring transfusion, change in Hb from baseline, Hb AUC	Hb response (≥ 2 g/dl change or Hb ≥ 12 g/dl unrelated to transfusion), dose escalation, avoidance of transfusion
Time frame	12 weeks	12 weeks	12 weeks	12 weeks
Discounting	Not stated	Not stated	Not stated	Not stated
Funding	Not stated	Ortho Biotec (manufacturer of epoetin alfa)	Ortho Biotec (manufacturer of epoetin alfa)	Johnson & Johnson (manufacturer of epoetin alfa)

AUC, area under the curve; PCS, physical component summary; QW, once weekly; TIW, three times weekly.
a Separate analyses were conducted for the UK (health care), France (health care) and the USA (private health insurance); only UK results were abstracted.
b Dose doubled if Hb not increased by > 1 g/dl by week 4.
c Dose doubled if Hb not increased by > 1 g/dl by week 6.

Parameter	Ben-Hamadi and colleagues[137]	Van Bellinghen and colleagues[138]	Esposito and colleagues[139]	Van Bellinghen and colleagues[140]
Evaluation type	Cost-effectiveness	Cost–consequences analysis	Cost–consequences analysis	Cost–consequences analysis
Modelling used	Minimal	Yes	Yes	Yes
Nature of modelling	Integration of costs with Hb levels from separate placebo-controlled RCTs	Decision tree	Decision tree	Decision tree
Perspective	Societal	Societal	Health care	Societal
Country (setting)	Not stated (probably USA)	France	Italy	Germany
Intervention/ comparator	Epoetin alfa QW: 40,000 IU; darbepoetin alfa QW: 2.25 µg/kg	Darbepoetin alfa Q3W: 500 µg; epoetin alfa QW: European label dose; epoetin beta QW: European label dose	Darbepoetin alfa Q3W: 500 µg; epoetin alfa QW: European label dose; epoetin beta QW: European label dose	Darbepoetin alfa Q3W: 500 µg; epoetin alfa QW: European label dose; epoetin beta QW: European label dose
Population	Patients with chemotherapy-induced anaemia	Patients with chemotherapy-induced anaemia	Patients with chemotherapy-induced anaemia	Patients with chemotherapy-induced anaemia
Outcomes considered	Area under the Hb change curve over 12 weeks	Hb levels	Hb levels	Hb levels
Time frame	12 weeks	16 weeks (assumed based on trial length)	16 weeks (assumed based on trial length)	16 weeks (assumed based on trial length)
Discounting	Not stated	Not stated	Not stated	Not stated
Funding	Ortho Biotec (manufacturer of epoetin alfa)	Amgen Inc. (manufacturer of darbepoetin alfa)	Amgen Inc. (manufacturer of darbepoetin alfa)	Amgen Inc. (manufacturer of darbepoetin alfa)

Q3W, once every 3 weeks; QW, once weekly.

Parameter	Finek and colleagues[141]	Liwing and colleagues[142]	Walter and colleagues[143]	Fragoulakis and Maniadakis[134]
Evaluation type	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost-effectiveness analysis[a]
Modelling used	Minimal	Yes	Yes	Yes
Nature of modelling	Integration of drug acquisition costs with retrospective, single-centre analysis	Simulation model	Decision tree	Decision tree
Perspective	Not stated	Not stated (probably health care)	Health care	Health care (plus patient transportation)
Country (setting)	Czech Republic (not explicitly stated)	Sweden	Austria	Greece
Intervention/ comparator	Epoetin alfa QW: 40,000 IU; darbepoetin alfa Q3 W: 500 µg	Epoetin alfa; darbepoetin alfa	Darbepoetin alfa Q3W: 500 µg; darbepoetin alfa QW: 150 µg; epoetin alfa QW: 40,000 IU; epoetin beta QW: 30,000 IU; epoetin beta TIW: 30,000 IU (per week)	Darbepoetin alfa Q3W: 500 µg; darbepoetin alfa QW: 150 µg; epoetin alfa QW: 40,000 IU; epoetin beta QW: 30,000 IU; epoetin beta TIW: 30,000 IU (per week)
Population	Patients with chemotherapy-induced anaemia	Patients with chemotherapy-related anaemia	Patients with chemotherapy-induced anaemia	Patients with chemotherapy-induced anaemia
Outcomes considered	Clinical response (Hb ≥ 11 g/dl)	Haematopoietic response rates, dose escalation rates, mean number of RBCTs required	Hb response rate	Hb response (≥ 2 g/dl)
Time frame	Not stated	12 weeks	12 weeks	Not stated
Discounting	Not stated	Not stated	Not stated	Not stated
Funding	None	Johnson & Johnson Pharmaceutical Service (parent company of Janssen-Cilag, manufacturers of epoetin alfa)	Amgen Inc. (manufacturers of darbepoetin alfa)	Genesis Pharma (distributor of darbepoetin alfa)

QW, once weekly; Q3W, once every 3 weeks; TIW, three times weekly.

Note

Although study is described as cost-minimisation analysis, with similar efficacy for all treatments, in fact treatment responses when calculated are different.

Appendix 15 Excluded studies: cost-effectiveness review

Study	Notes
Could not be obtained	
Sheffield R, Sullivan S, Saltiel E, Nishimura L. Cost comparison of recombinant human erythropoietin and blood transfusion in cancer chemotherapy-induced anemia. *Ann Pharmacother* 1997;**31**:15–22	Published pre 2004
Roungrong J, Teerawattananon Y, Chaikledkaew IU. Cost utility analysis of recombinant human erythropoietin in anemic cancer patients induced by chemotherapy in Thailand. *J Med Assoc Thai* 2008;**91**(Suppl. 2):119–25	
Griggs JJ, Sorbero MES. Cost–utility of erythropoietin in the treatment of cancer-related anemia. *Med Decis Making* 1997;**17**:529	Published pre 2004
Griggs JJ, Blumberg N. Recombinant erythropoietin and blood transfusions in cancer chemotherapy-induced anemia. *Anticancer Drugs* 1998;**9**:925–32	Published pre 2004
Malonne H, editor. Cost evaluation of erythropoiesis stimulating agents in the treatment of platinum chemotherapy induced anaemia. 20th Annual Meeting of the Belgian Haematology Society, Genval, Belgium, January 2005	
Study design	
Reeder CE. Anemia in cancer and critical care patients: pharmacoeconomic considerations. *Am J Health System Pharm* 2007;**64**:S22–7	Not a systematic review
Dale DC. The benefits of haematopoietic growth factors in the management of gynaecological oncology. *Eur J Gynaecol Oncol* 2004;**25**:133–44	Expert commentary
Marchetti M, Barosi G. Clinical and economic impact of epoetins in cancer care. *Pharmacoeconomics* 2004;**22**:1029–45	Not a systematic review
Scarpace SL, Miller K, Elefante A, Czuczman MS, McCarthy P, Chanan-Khan A. Cost–utility of darbepoetin alfa (DARBE) on an every-2 week (QOW) schedule in anemic non-myeloid hematologic malignancies: a positive overall impact on the healthcare system (HCS). *J Clin Oncol* 2004;**22**:797S	Cost study, not UK
Steensma DP, Loprinzi CL. Epoetin alfa and darbepoetin alfa go head to head. *J Clin Oncol* 2006;**24**:2232–6	Review/commentary
Cornes P, Coiffier B, Zambrowski J-J. Erythropoietic therapy for the treatment of anemia in patients with cancer: a valuable clinical and economic option. *Curr Med Res Opin* 2007;**23**:357–68	Not a systematic review
Herrmann R. Erythropoietin therapy in cancer-related anaemia, yes or no? *Intern Med J* 2008;**38**:749–50	Not a systematic review
Repetto L, Moeremans K, Annemans L. European guidelines for the management of chemotherapy-induced anaemia and health economic aspects of treatment. *Cancer Treat Rev* 2006;**32**:S5–9	Not a systematic review
Stasi R, Amadori S, Littlewood TJ, Terzoli E, Newland AC, Provan D. Management of cancer-related anemia with erythropoietic agents: doubts, certainties, and concerns. *Oncologist* 2005;**10**:539–54	Not a systematic review
Reichardt B. Evidence-based, novel comparison between epoetin alfa, epoetin beta, and darbepoetin alfa based on drug use, efficacy and treatment costs in daily oncological clinical practice. *Hematol J* 2004;**5**(Suppl. 2):177	Cost study, not UK

Study	Notes
Population	
Wadelin FR, Myers B. Darbepoetin is more cost-effective than regular transfusion: a review of the use of erythropoietin in haematology patients. 49th Annual Scientific Meeting of the British Society for Haematology, Brighton, April 2009. *Br J Haematol* 2009;**145**(Suppl. S1):58	Results not presented separately for malignancy subgroup
Intervention	
Glaspy J, Tchekmedyian N, Gupta S. PCN17 comparing the cost-effectiveness of 3 mcg/kg Q2W darbepoetin alfa with standard dose epoetin alfa for anemia management in chemotherapy-treated cancer patients in united states. *Value Health* 2002;**5**:543	Abstract; uses unlicensed dosing (once every 2 weeks) for darbepoetin alfa; published pre 2004
Outcome	
Ben-Hamadi R, Duh MS, Aggarwal J, Henckler A, McKenzie S, Fastenau J, *et al.* Cost-effectiveness of once weekly epoetin alfa and darbepoetin alfa in treating chemotherapy-induced anemia. *Value Health* 2005;**8**:238	Abstract; cannot calculate ICERs from reported data
Gozzo M, Lucioni C, Mazzi S. Economics evaluation of erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anaemia in Italy. *Eur J Hosp Pharm* 2012;**19**:202	Abstract; cannot calculate ICERs from reported data
No usable data	
Coiffier B, Schlag R, Velasco A, Yao B, Schupp M, Demarteau N, *et al.* Cost and effectiveness of darbepoetin alfa administered every 3 weeks (Q3W DA) compared with weekly epoetin alfa (QW EA) or epoetin beta (QW EB) in patients (PTS) with chemotherapy-induced anaemia (CIA): a retrospective study. *Ann Oncol* 2006;**17**:293	Abstract
Grocott R, Metcalfe S, Moodie P. PHARMAC and erythropoietin for cancer patients. *N Z Med J* 2006;**119**:U2039	Study not complete at time of publication
Published pre 2004	
Cremieux P-Y, Finkelstein SN, Berndt ER, Crawford J, Slavin MB. Cost-effectiveness, quality-adjusted life-years and supportive care: recombinant human erythropoietin as a treatment of cancer-associated anaemia. *Pharmacoeconomics* 1999;**16**:459–72	Included in Wilson and colleagues[2]
Barosi G, Marchetti M, Liberato NL. Cost-effectiveness of recombinant human erythropoietin in the prevention of chemotherapy-induced anaemia. *Br J Cancer* 1998;**78**:781–7	Included in Wilson and colleagues[2]
Language (not English)	
Borget I, Chouaid C, Demarteau N, Annemans L, Pujol JL. Cost-effectiveness of darbepoetin alpha in an every-3-weeks schedule. *Bull Cancer* 2008;**95**:465–73	French language
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA). *Epoetin (EPO) for Anaemic Cancer Patients*. Copenhagen: DACEHTA; 2004. URL: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32005000197/frame.html (accessed 19 August)	Danish language

Appendix 16 Multiple publications in cost-effectiveness review

Primary study

Borget I, Tilleul P, Baud M, Joly AC, Daguenel A, Chouaid C. Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. *Lung Cancer* 2006;**51**:369–76.

Secondary publications

Chouaid C, Borget I, Baud M, Joly AC, Daguenel A, Tilleul P. Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. *Lung Cancer* 2003;**49**:S23.

Borget I, Tilleul P, Joly AC, Chouaid C. Incremental cost-effectiveness ratio of darbepoetin alfa (Aranesp (R)) in the treatment of chemotherapy-induced anemia in lung cancer patients. *Value Health* 2006;**9**:A278–9.

Borget I, Tilleul P, Baud M, Joly AC, Chouaid C. Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. *Pharm World Sci* 2007;**29**:454.

Primary study

Finek J, Holubec L, Wiesnerova A, Pav Z, Dusek L. Darbepoetin alfa versus epoetin alfa for treatment of chemotherapy-induced anemia: a health economic evaluation. *Value Health* 2010;**13**:A465.

Secondary publication

Finek J, Holubec L, Wiesnerova A, Pav Z, Dusek L. Darbepoetin alfa versus epoetin alfa for treatment of chemotherapy-induced anemia: a health economic evaluation. *Ann Oncol* 2010;**21**(Suppl. 8):344.

Primary study

Tonelli M, Lloyd A, Weibe N, Hemmelgarn B, Reiman T, Manns B, *et al.* Erythropoiesis-stimulating agents for anemia of cancer or of chemotherapy: systematic review and economic evaluation. HTA issue 119. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2009.

Secondary publication

Klarenbach S, Manns B, Reiman T, Reaume MN, Lee H, Lloyd A, *et al.* Economic evaluation of erythropoiesis-stimulating agents for anemia related to cancer. *Cancer* 2010;**116**:3224–32.

Appendix 17 Update of cost-effectiveness review

All searches were updated on 2 December 2013 and date limited from 1 January 2013 to 2 December 2013. Seventy-three records were obtained from the main database searches, resulting in 51 records following deduplication. Two additional records were obtained from DARE, resulting in a total of 53 records identified for title/abstract screening.

Independent, blinded screening was performed by two reviewers (TS and LC) and both reviewers included exactly one (and the same) study. The full text of this study was retrieved and assessed for eligibility by two reviewers (TS and NH), who both judged it to be eligible.

Data extraction was conducted by TS.

The included study by Michallet and colleagues[294] describes itself as including a cost-effectiveness analysis, although on inspection it is a combined assessment of various effectiveness outcomes, as well as a cost analysis. As such, it would normally be considered a cost–consequences analysis.

The study by Michallet and colleagues[294] is a historically controlled study matching patients receiving ESA therapy with those in the past known not to have received ESA therapy. Not all outcomes were recorded for the control group and so only transfusion requirement and survival (overall and event-free) are evaluated comparatively.

The study found that patients receiving ESA therapy experienced an improvement in HRQoL compared with baseline, but patients receiving ESA therapy were not compared with patients not receiving ESA therapy. The study found that patients receiving ESA therapy had a lower transfusion need; in addition, no statistically significant difference was found in OS or event-free survival between patients receiving ESA therapy and control patients. RBCT costs were lower for patients receiving ESA therapy, but these did not sufficiently offset the increased cost of ESA acquisition/administration.

The tables below show the characteristics, key parameters and results of the study.

TABLE 105 Study characteristics

Parameter	Michallet and colleagues[294]
Evaluation type	Cost–consequences analysis
Modelling used	No
Nature of modelling	NA
Perspective	Health care
Country (setting)	France
Intervention/comparator	Darbepoetin alfa QW: 150 µg; no treatment
Population	Patients with anaemia following consolidation chemotherapy for AML
Outcomes considered	HRQoL (FACT-G, FACT-F, FACT-An), Hb response (CR = Hb ≥ 12 g/dl; PR = Hb increase ≥ 2 g/dl), AEs, costs, Hb levels, transfusion need, survival (overall and event-free)
Time-frame	NA
Discounting	Not stated
Funding	Not disclosed

AML, acute myeloid leukaemia; CR, complete response; PR, partial response; QW, once weekly.
Note
All data presented are for group 1 (patients with AML treated with chemotherapy); group 2 (patients having received allogeneic haematopoietic stem cell transplant for any haematological disease) data are excluded.

TABLE 106 Key parameters

Parameter	Michallet and colleagues[294]
Effectiveness (source): transfusion, response rate, survival, QALYs	Historically controlled study (this study)
Effectiveness (data): transfusion, response rate	Transfusion requirement – median reduction RBC units: 3.9 ($p = 0.0002$); median reduction platelet units: 1.7 ($p = 0.029$)
Effectiveness (data): survival	Not statistically significant (OS, $p = 0.77$; event-free survival, $p = 0.57$)
Effectiveness (data): QALYs	NA
QoL/utility (source)	This study
QoL/utility (data)	NA (not evaluated for control group)
Costs (source)	This study
Cost year	Not stated

QoL, quality of life.
Note
The following outcomes were not evaluated for the control group and hence are not shown here: Hb response rate, Hb level, AEs and HRQoL.

TABLE 107 Results

Parameter	Michallet and colleagues[294]
Measure	Costs, transfusion requirement, survival
Cost year; currency	NR; euros
Base case	ESA cost: darbepoetin alfa €3904, no treatment €0; RBCT cost: darbepoetin alfa €2568, no treatment €4280; total cost: darbepoetin alfa €6472, no treatment €4280
Probabilistic results	NA
Sensitivity analyses	NA

NR, not reported.
Note
Costs presented are median costs. Consequences as shown in *Table 106*.

Appendix 18 Use of MathMap to construct cumulative hazard and Weibull plots

MathMap [freely available from www.complang.tuwien.ac.at/schani/mathmap/ (accessed 20 August 2015)] is a flexible tool and programming language for constructing and manipulating raster graphics with support for general mathematical transformations.

To construct cumulative hazard and Weibull plots we made use of functionality in which the result image, B, can be based on the input image, A, using an arbitrary mathematical backward mapping; that is, expressions of the form $B(x, y) = A(f(x, y), g(x, y))$.

The cumulative hazard graph plots $\ln(-S(t))$ versus t and therefore the backward mapping functions are $f(x, y) = x$ and $g(x, y) = \exp(-y)$.

The Weibull graph plots $\ln(-n(-S(t)))$ versus $\ln(t)$ and therefore the backward mapping functions are $f(x, y) = \exp(x)$ and $g(x, y) = \exp(-\exp(y))$.

The code for performing these mappings additionally must account for the dimensions of B and the location of the survival graph in A.

We show example code for transforming the survival plot from Littlewood and colleagues.[70] Note that '#' is used to create a comment (non-functioning line) and has been used to 'comment out' a number of statements that would otherwise create different plots. The code as presented constructs the Weibull plot (time plotted from 1 to 40 and cumulative hazard plotted from 0.1 to 1.2).

```
filter littlewood (image in)
  plotOrigin=[-0.75, -0.37];
  plotTopRight=[0.86, 0.953];

  # CHECK PLOT BOUNDS
  #if x < plotOrigin[0] || x > plotTopRight[0] || y < plotOrigin[1] || y >
plotTopRight[1] then
  #  rgbColor(0,0,0);
  #else
  #  in(xy);
  #end

  # CUMULATIVE HAZARD
  #in(xy:[(x+1)/2*(plotTopRight[0]-plotOrigin[0])+plotOrigin[0],
  #     exp(-(y+1))*(plotTopRight[1]-plotOrigin[1]) + plotOrigin[1]])

  # WEIBULL PLOT
  A = 0.5*(log(40)-log(1));
  B = 0.5*(log(40)+log(1));
  C = 0.5*(log(1.2)-log(0.1));
  D = 0.5*(log(1.2)+log(0.1));
  in(xy:[exp(A*x + B)*(plotTopRight[0]-plotOrigin[0])/40 + plotOrigin[0],
       exp(-exp(C*y + D))*(plotTopRight[1]-plotOrigin[1]) + plotOrigin[1]])
end
```

Appendix 19 Summary of parameters used in the Peninsula Technology Assessment Group cost-effectiveness model

Parameter	Base case (SE)	Subgroup inclusion Hb level ≤ 11.0 g/dl (SE)	Location in report	Wilson and colleagues[r2] value
OS ESA vs. control (HR, SE in log scale)	0.967 (0.079)	0.914 (0.137)	*Chapter 3*, *Assessment of clinical effectiveness*, *Results*, *Effectiveness*, *Overall survival* (*Table 23*)	1
OS (control arm)	2.670 (1.335)	1.447 (0.723)	*Chapter 5*, *Clinical effectiveness parameters*, *Overall survival*	1.54
Change in Hb from baseline to end of ESA treatment: difference between ESA arm and control arm	1.59 (0.130)	1.52 (0.115)	*Chapter 3*, *Assessment of clinical effectiveness*, *Results*, *Effectiveness*, *Anaemia-related outcomes*, *Anaemia-related outcomes: overall summary* (*Table 20*)	1.63 (clinical effectiveness review)
Mean no. of units transfused in control arm	2.09	2.30	*Chapter 5*, *Clinical effectiveness parameters*, *Number of red blood cell transfusions*	2
Mean difference in no. of units of RBCs transfused between the ESA arm and the control arm	−0.87 (0.21)	−0.99 (0.22)	*Chapter 3*, *Assessment of clinical effectiveness*, *Results*, *Effectiveness*, *Anaemia-related outcomes*, *Anaemia-related outcomes: overall summary* (*Table 20*)	−1.05
Relative risk of AEs in the ESA arm vs. the control arm (reported on natural log scale)				
Thromboembolic events	ln(1.46) = 0.378 (0.158)	ln(1.29) = 0.255 (0.344)	*Chapter 3*, *Assessment of clinical effectiveness*, *Results*, *Effectiveness*, *Safety*, *Thromboembolic events*	
Hypertension	ln(1.80) = 0.588 (0.234)	ln(1.68) = 0.519 (0.250)	*Chapter 3*, *Assessment of clinical effectiveness*, *Results*, *Effectiveness*, *Safety*, *Hypertension*	
Thrombocytopenia	ln(0.93) = −0.073 (0.185)	ln(0.73) = −0.315 (0.350)	*Chapter 3*, *Assessment of clinical effectiveness*, *Results*, *Effectiveness*, *Safety*, *Thrombocytopenia/ haemorrhage*	
Probability of AEs in the control arm				0%, but 5% for SAEs on epoetin
Thrombotic events	3.3 (0.4)	3.7 (0.8)	*Chapter 5*, *Clinical effectiveness parameters* (*Table 49*)	
Hypertension	2.9 (0.5)	1.8 (1.0)		
Thrombocytopenia	6.4 (0.8)	2.5 (0.8)		

Parameter	Base case (SE)	Subgroup inclusion Hb level ≤ 11.0 g/dl (SE)	Location in report	Wilson and colleagues'[2] value
Baseline Hb level (g/dl)	10.38 (1.59)	9.40 (0.22)	*Chapter 5, Clinical effectiveness parameters, Initial (baseline) haemoglobin level*	9.9 (calculated using reported figures at baseline)
Change in Hb level (no ESA) (g/dl)	–0.155 (1.25)	0.469 (0.41)	*Chapter 5, Clinical effectiveness parameters, Change in haemoglobin level for patients not receiving erythropoiesis-stimulating agent therapy*	
Mean difference in Hb levels between treatment arms over the trial duration as a proportion of the difference at the end of the trial (%)	80.6 (55.0)	55.5 (12.0)	*Chapter 5, Clinical effectiveness parameters, Mean difference in haemoglobin levels between treatment arms as a proportion of the difference at the end of the trial*	
Mean age (years)	59.1 (5.3)	60.8 (4.2)	*Chapter 5, Patient characteristics*	Not used
Mean weight (kg)	66.6 (3.3)	66.1 (3.6)		Not used
Probability patient is male	0.46			
Mean OS (no ESA) (years)	2.670 (1.335)	1.447 (0.724)	*Chapter 5, Clinical effectiveness parameters, Overall survival*	1.54
Mean weekly ESA dose				
Epoetin alfa (IU)	24,721 (4944)	24,947 (4989)	*Chapter 5, Clinical effectiveness parameters, erythropoiesis-stimulating agent withdrawal rate and mean weekly dose*	
Epoetin beta (IU)	31,138 (6228)	30,997 (6199)		
Epoetin theta (IU)	22,859 (4572)	22,810 (4562)		
Epoetin zeta (IU)	24,721 (4944)	24,947 (4989)		
Darbepoetin alfa (μg)	141.1 (28.2)	141.2 (28.2)		
No. of RBC units per transfusion	2.7 (0.54)		*Chapter 5, Clinical effectiveness parameters, Number of red blood cell transfusions*	
Duration of ESA treatment (weeks)	12			
Normalised Hb level (g/dl)	12[a] (0.51)		*Chapter 5, Clinical effectiveness parameters, Normalisation of haemoglobin levels following chemotherapy cessation*	24
Normalisation rate (g/dl/week)	0.2 (0.051)			13
Utility increase per Hb level increase (1g/dl)	0.028 (0.006)		*Chapter 5, Peninsula Technology Assessment Groupbase-case utilities by haemoglobin level*	0.2 (approx.)

Parameter		Base case (SE)	Subgroup inclusion Hb level ≤ 11.0 g/dl (SE)	Location in report	Wilson and colleagues[72] value
Long-term utility		0.763 (0.183)	0.756 (0.151)	*Chapter 5, Peninsula Technology Assessment Groupbase-case utilities after erythropoiesis-stimulating agent discontinuation*	0.06
ESA acquisition cost (£)					276.70/week (including SAEs)
Epoetin alfa (per 1000 IU)	Eprex	5.53		*Chapter 5, Erythropoietin-stimulating agent prices*	
	Binocrit	5.09			
Epoetin beta (per 1000 IU)	Neo Recormon	7.01			
Epoetin theta (per 1000 IU)	Eporatio	5.99			
Epoetin zeta (per 1000 IU)	Retacrit	5.66			
Darbepoetin alfa (per µg)	Aranesp	1.47			
Dosing schedule of ESA		Once weekly		*Chapter 5, Cost of administering erythropoiesis-stimulating agents*	Three times per week
Average cost per ESA administration (£)		9.13			8.01
Additional blood tests for ESA		4		*Chapter 5, Additional blood tests for erythropoiesis-stimulating agents*	
Cost of blood test (£)		15.14			
Cost of AEs (£)					101
Thrombotic events		1243 (249)		*Chapter 5, Adverse event costs*	
Hypertension		826 (165)			
Thrombocytopenia		744 (149)			
Cost per unit cost of RBCs transfused (£)		127 (25)		*Chapter 5, Red blood cell acquisition costs*	
Cost of transfusion appointment (£)		688		*Chapter 5, Cost of transfusion appointment*	
Time frame		Lifetime			
Cycle length		NA			
HaemR RR (ESA vs. control)		NA		*Chapter 5, Clinical effectiveness parameters*	

HaemR, haematological response; SAE, serious adverse event.
a Normalised Hb level equals 12 g/dl or the final Hb level in the ESA arm, whichever is higher.

Appendix 20 Mean difference in haemoglobin level as a proportion of the final difference in haemoglobin level

The PenTAG economic model uses a parameter corresponding to the mean difference in Hb level as a proportion of the final difference in Hb level. The final difference in Hb level is a commonly reported outcome, but cumulative differences (which incorporate information about Hb levels over time between measurement of baseline and final Hb levels) are not generally reported succinctly. In some studies figures are presented showing the trajectory of Hb levels.

When this parameter is set to 100%, the average difference in Hb level between the intervention arm and the control arm over time is the same as the final difference in Hb level (adjusting for any differences at baseline).

Two calculation methods were applied to estimate this parameter, with the easiest method to apply being used for each figure.

Method 1

Measuring tools of Adobe Acrobat X Pro (Adobe Systems, Inc., San Jose, CA, USA) were used to estimate:

- the area bounded above by the intervention arm Hb level curve and below by the control arm Hb level curve (denoted by A)
- the (vertical) distance between the intervention arm Hb level curve and the control arm Hb level curve at baseline (denoted by L_0; positive if baseline Hb is higher in the intervention arm)
- the (vertical) distance between the intervention arm Hb level curve and the control arm Hb level curve at the final Hb level measurement (denoted by L_1; positive if final Hb is higher in the intervention arm)
- the (horizontal) distance between the times of the baseline and final Hb level measurements (denoted by W).

The required parameter is then calculated as $(A - L_0 \times W)/[W \times (L_1 - L_0)]$.

Method 2

An appropriate tool was used to estimate the mean Hb level at each measurement for both the intervention arm and the control arm.

The area under each Hb level curve was calculated by summing the areas of trapezoids (denoted by $AUC_{Intervention}$ and $AUC_{Control}$). These were adjusted to become area under Hb change curves by subtracting the hypothetical area under the curve if the Hb level did not change (denoted $\Delta AUC_{Intervention}$ and $\Delta AUC_{Control}$).

The hypothetical area under the curve if the Hb level instantaneously jumped to the final Hb level difference was calculated (denoted $\Delta AUC_{Instantaneous}$).

The required parameter is then calculated as $(\Delta AUC_{Intervention} - \Delta AUC_{Control})/\Delta AUC_{Instantaneous}$.

Results

Study	Calculation steps				Result (%)
	A	L_0	L_1	*W*	
Method 1					
Littlewood 2011[70]	1.00	0.05	0.38	2.42	110
Grote 2005[74]	2.39	–0.09	0.24	3.53	232
Tjulandin 2010[48]	ET 1.66	ET 0.00	ET 0.69	ET 3.85	ET 62
	EB 1.79	EB 0.00	EB 0.78	EB 3.85	EB 60
Tjulandin 2011[77]	2.11	0.11	1.10	3.47	50
Moebus 2013[62]	0.69	0.00	0.39	2.29	77
	$\Delta AUC_{Intervention}$	$\Delta AUC_{Control}$	$\Delta AUC_{Instantaneous}$		
Method 2					
Silvestris 1995[72]	46.15	3.04	51.08		84
Del Mastro 1997[67]	0.70	–9.35	13.80		73
Kurz 1997[69]	20.32	2.26	36.12		50
Dunphy 1999[68]	–5.35	–13.00	9.92		77
Thatcher 1999[52]	–6.37	–11.03	5.04		92
Dammacco 2001[66]	12.37	–0.04	22.15		56
Hedenus 2002[53]	9.43	4.11	9.04		59
Aravantinos 2003[64]	4.245	3.235	4.32		23
Boogaerts 2003[65]	15.98	7.02	13.12		68
Strauss 2008[76]	11.80	–6.40	24.00		76

AUC, area under the curve; EB, epoetin beta; ET, epoetin theta.

EME
HS&DR
HTA
PGfAR
PHR

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