NICE National Institute for Health and Care Excellence

Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142)

Assessment Report

Commercial in Confidence stripped version for consultation

Produced by: Peninsula Technology Assessment Group

NB: the Assessment report was update in September 2014 to correct the details of some of the authors

The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model

Produced by: Peninsula Technology Assessment Group, University of Exeter Medical School

Authors:

Louise Crathorne, Research Fellow in HTA, PenTAG, University of Exeter Medical School

Nicola Huxley, Associate Research Fellow in Modelling, PenTAG, University of Exeter Medical School

Marcela Haasova, Associate Research Fellow in HTA, PenTAG, University of Exeter Medical School

Tristan Snowsill, Research Fellow in Modelling, PenTAG, University of Exeter Medical School

Tracey Jones-Hughes, Research Fellow in HTA, PenTAG, University of Exeter Medical School

Martin Hoyle, Senior Research Fellow in Modelling, PenTAG, University of Exeter Medical School

Simon Briscoe, Information Specialist, PenTAG, University of Exeter Medical School

Helen Coelho, Research Fellow in HTA, PenTAG, University of Exeter Medical School

Linda Long, Associate Research Fellow, PenTAG, University of Exeter Medical School

Antonieta Medina-Lara, Senior Lecturer in Health Economics, University of Exeter Medical School

Ruben Mujica-Mota, Senior Lecturer in Health Economics, PenTAG, University of Exeter Medical School

Mark Napier, Royal Devon and Exeter Hospital, Exeter, UK

Chris Hyde, Professor of Public Health & Clinical Epidemiology, PenTAG, University of Exeter Medical School

Simon Briscoe, Information Specialist, PenTAG, University of Exeter Medical School

Helen Coelho, Research Fellow in HTA, PenTAG, University of Exeter Medical School

Correspondence to:
Louise Crathorne
PenTAG
University of Exeter Medical School
Veysey Building
Salmon Pool Lane
Exeter EX2 4SG
L.Crathorne@exeter.ac.uk

Date completed: 21 January 2014

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 12/42/01

Declared competing interests of authors: None

About PenTAG

The Peninsula Technology Assessment Group is part of the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme, systematic reviews and economic analyses for the NICE Centre for Public Health Excellence, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Institute of Health Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

Health technology assessment projects include:

- A systematic review and economic evaluation of diagnostic strategies for Lynch Syndrome
- Bosutinib for previously treated chronic myeloid leukaemia a single technology appraisal
- What is the effectiveness and cost-effectiveness of conservative interventions for tendinopathy: an overview of systematic reviews of clinical effectiveness and systematic review of economic evaluations
- A systematic review and economic evaluation of intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer
- Dasatinib and Nilotinib for the 1st line treatment of chronic phase chronic myeloid Leukaemia (CML): a systematic review and economic model
- Bevacizumab, Cetuximab, and Panitumumab in colorectal cancer (metastatic) after failure of 1st line chemotherapy: a systematic review and economic model
- The psychological consequences of false positive mammograms: a systematic review
- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp
- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK
- Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: a critique of the submission from Novartis
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer

Acknowledgements

We would like to acknowledge the help of: Professor Nicholas Reed (Consultant Clinical Oncologist, Beatson Oncology Centre, Gartnavel General Hospital, Glasgow) for clinical input into the design of the model; Dr Claudius Rudin and Dr Kate Scatchard for clinical input into the systematic review, and the design of the model; and Paul Foster (Clinical Director – Pharmacy and Prescribing, South Devon Healthcare NHS Foundation Trust), Chris Roome (Head of Clinical Effectiveness, Clinical Effectiveness and Medicines Optimisation Team, Northern, Eastern and Western Devon Clinical Commissioning Group), Clint Botha (Technical Pharmacist, Commercial Medicines Unit), and Kevan Wind (Medicines Procurement Specialist, South East England Specialist Pharmacy Services), for information relating to the current use of ESAs in the indication under review and acquisition costs.

We would like to thank: Dr Obi Ukoumunne and Dr Jaime Peters for providing statistical advice on the clinical effectiveness meta-analysis; Dr Will Stahl-Timmins for summary graphics; Mrs Mary Bond and Dr Emily Youngman for reviewing and commenting on the draft report; Dr Rob Anderson for reviewing and commenting on the draft report; Mrs Sue Whiffin and Ms Jenny Lowe for administrative support (organisation and recording of meetings, collation of the report for review, and liaison with external experts), throughout the project; and, to Mrs Sue Whiffin for proofreading the draft report.

Declared competing interests of authors

None.

Rider on responsibility of the report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

Crathorne L, Huxley N, Haasova M, Snowsill T, Jones-Hughes T, Hoyle M, Briscoe S, Coelho H, Long L, Medina-Lara A, Mujica-Mota R, Napier M, Rudin C, Scatchard K, Hyde C. The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model. (2014) PenTAG, University of Exeter Medical School (Report for NICE).

Contributions of authors

Louise Crathorne	Provided overall project management and led the systematic review of clinical effectiveness, including assessment of all abstracts and titles for possible inclusion and meta-analysis for clinical effectiveness outcomes. Drafted and/or edited all sections of the report.
Nicola Huxley	Led the design, development and execution of the economic model and wrote the sections on the design and results of the economic model. Assessed titles and abstracts for inclusion in the cost-effectiveness review.
Marcela Haasova	Assessed abstracts and titles for inclusion, 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. 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 assessment of all abstracts and titles for possible inclusion. 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 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. Contributed 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 (PRISMA) of included systematic reviews, and compiled the summary table of review characteristics. Contributed to the editing of the report.
Antonieta Medina-Lara	Provided advice on the cost-effectiveness (utilities), and quality of life systematic review. 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 section. 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.
Claudius Rudin	Provided clinical input into the design of the model, and advised on clinical matters.
Kate Scatchard	Provided clinical input into the design of the model, and advised on clinical matters.
Chris Hyde	Contributed to the clinical, quality of life and cost-effectiveness review, design of the model, contributed to the writing and editing of the report and was overall Director of the project and Guarantor of the report.

Contents

Contents: Tables

Contents: Figures

List of abbreviations

AEs	adverse events
ASCO	American Society of Clinical Oncology
ASH	American Society of Haematology
BNF	British National Formulary
BSC	best supportive care
BSI	Brief Symptom Inventory
CADTH	Canadian Agency for Drugs and Technologies in Health
cHR	combined hazard ratio
CI	confidence interval
CLAS	Cancer Linear Analogue Scale
CR	complete response
CRF	cancer-related fatigue
Darb A	darbepoetin alfa
DARE	Database of abstracts of reviews of effects
DL	Der-Simonian–Laird
EHA	European Haematology Association
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
Epo A	epoetin alfa
Epo B	epoetin beta
EQ-5D	Euro-Qol 5D
ESAs	erythropoietin stimulating agents
ESMO	European Society for Medical Oncology
FACT	Functional Assessment of Cancer Therapy
FACT-An	Functional Assessment of Cancer Therapy – Anaemia
FACT-F	Functional Assessment of Cancer Therapy – Fatigue
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	Food & Drug Administration
G-CSF	granulocyte colony stimulating factor
HaemR	haematological response
Hb	haemoglobin
Hct	haematocrit
HMIC	Health Management Information Consortium
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology appraisal
HUI	health utilities index
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IPD	individual patient data
ISRCTN	International Standard Randomised Controlled Trial Number

ITT	intention-to-treat
i.v.	intravenous
IV	inverse variance
LASA	Linear Analogue Scale Assessment
MD	mean difference
MH	Mantel–Haenszel
MID	minimally important difference
MTA	multiple technology appraisal
NA	not applicable
NHP	Nottingham Health Profile
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	not reported
OHE EED	Office for Health Economic Economic Evaluation Database
OS	overall survival
OR	odds ratio
ORR	overall response rate
PAS	patient access scheme
PDI	Psychological Distress Inventory
PR	partial response
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
QW	once weekly
Q3W	once every three weeks
RBC	red blood cell
RBCT	red blood cell transfusion
RCT	randomised controlled trial
ROL	randomised open label
RR	risk ratio
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SF-36	Short-Form 36 item
SPC	Summary of Product Characteristics
SR	systematic review
SMC	summary of product characteristics
STA	single technology appraisal
TIW	thrice weekly
VAS	visual analogue scale
WHO	World Health Organisation
wk(s)	week(s)
WMD	weighted mean difference
yr(s)	year(s)

Executive summary

1.1. Background

Anaemia is defined as a deficiency in red blood cells. It is the most frequent haematological manifestation in patients with cancer; more than 50% of all cancer patients will be anaemic regardless of the treatment received, and approximately 20% of all patients undergoing chemotherapy will require red blood cell transfusion (RBCT). The cause is multifactorial: 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; e.g. 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 two to four 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 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, there is a small proportion of people unable to receive RBCT (Jehovah's Witnesses and people with multiple antibodies to RBCs as they have required regular RBCT in the past).

1.1.1. Treatment landscape, 10 years on

Erythropoietin is a glycoprotein hormone, which is produced mainly in the kidney and is responsible for regulating red blood cell production. Erythropoietin for clinical use is produced by recombinant DNA technology. Erythropoiesis stimulating agents (ESAs) are

used as an addition to, rather than a replacement for, existing approaches to the management of anaemia induced by cancer treatment. RBCT, in particular, may still be needed in people treated with ESAs.

Previous National Institute for Health and Care Excellence (NICE) guidance (TA142) in 2007 recommended ESAs: 'in combination with intravenous iron as an option for the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin level of 8 g/100 ml or lower. The use of ESAs does not preclude the use of existing approaches to the management of anaemia, including blood transfusion where necessary. ESAs in combination with intravenous iron may be considered for people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.'

While evidence at the time documented a clear improvement in haematological response and a reduction in the need for red blood cell transfusions 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 as to 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 level ≤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 request. These changes came into effect in 2008 – after the previous guidance was issued – and included: a decrease in the haemoglobin value for treatment initiation to Hb ≤10 g/dl (to either increase haemoglobin by <2 g/dl or to prevent further decline); to amend haemoglobin target values to 10–12 g/dl and haemoglobin 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 increased risk of deaths when ESAs are administered to a target of 12–14 g/dl; and, in people treated with curative intent, ESAs should be used with caution.

1.1.2. Current evidence

Previous guidance (TA142) was based on evidence presented as part of the HTA process by **Wilson and colleagues (2007)**. 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 caused by cancer treatment.

Scoping searches identified two relevant recent Cochrane reviews (**Tonia and colleagues, 2012**; and **Bohlius and colleagues, 2009**). As in **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 caused by cancer treatment.

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

1.2. Objective

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

The review was based on a pre-defined scope issued by NICE, and conducted in accordance with a pre-defined protocol. Given the publication of the 2012 Cochrane review (**Tonia and colleagues, 2012**), and the fact that no studies were completely aligned with the 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 are: epoetin alfa (Eprex®, [Janssen-Cilag] and Binocrit® [Sandoz]); epoetin beta (NeoRecormon®, Roche Products); epoetin theta (Eporatio® [Teva UK]); epoetin zeta (Retacrit® [Hospira UK]) Darbepoietin alfa (Aranesp® [Amgen]). All interventions will only be considered according to their UK marketing authorisation. The key assumption maintained throughout this report is that all ESAs are equally effective.

1.3. Methods

1.3.1. Clinical effectiveness and health-related quality of life:

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, Embase, Web of Science; CINAHL; British Nursing Index; HMIC; Current Controlled Trials; Clinical trials.gov; FDA website; and, EMA website. 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 scrutinized for further potentially includable studies. The reference lists of the industry submissions were also scrutinised for additional studies. Due to resource limitations the search was restricted to English language papers only. All references were managed using Endnote (X5; Thomson ISI ResearchSoft) and Microsoft Excel 2010 software.

Titles and abstracts returned by the search strategy were examined independently by four researchers (LC and MH [clinical] and TJH and LL [health-related quality of life]) and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Four researchers (LC and MH [clinical], and TJH and LL [health-related quality of life]) examined these 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 (LC and MH).

Dosing strategies vary considerably in the literature in terms of: start dose (fixed or weight-based); trigger haemoglobin level, target haemoglobin level; dose escalation; stopping rules for non-responders; and, duration of use. These aspects will have an impact on effect estimates. Given the publication of the 2012 Cochrane review (**Tonia and colleagues, 2012**), this HTA review focused on the administration of ESAs in accordance with UK marketing authorisations. However, as none of the trials completely met the current licence recommendations, they were considered eligible for inclusion if they used a licensed starting dose irrespective of how they dealt with other criteria stipulated by the licence; e.g. inclusion or target Hb levels. Thus, ESAs administered weekly, for epoetin alfa and epoetin zeta, three-times weekly, for epoetin beta; and, every three weeks for darbepoetin alfa were considered eligible for inclusion. Fixed (epoetin theta) and weight-based (epoetin alfa, epoetin beta, epoetin zeta, and darbepoetin alfa) dosages were allowed. 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 closer to licence ≤13g/dl and >13 g/dl.

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

Subgroup analyses were conducted: mean Hb at baseline (<10 g /dl versus <11 g/dl versus <12 g/dl versus <14.5 g/dl versus 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 wks, 12–16 wks, 17–20 wks, >20 wks); and, study design (blinded [RCT], unblinded [randomized open label [ROL]]).

1.3.2. Cost effectiveness

1.3.2.1. Review of past economic evaluations

The previous NICE appraisal (TA142), published in **Wilson and colleagues (2007)**, included a systematic review of published evidence of the cost-effectiveness of ESAs for cancer treatment-induced anaemia. 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 QALYs of interventions).

We undertook to update the systematic review to identify any evidence regarding the cost-utility of ESAs, particularly as relevant to the NHS. ESA administration was considered

within licence for inclusion in this review based on dose frequency but not dose quantity (i.e., QW for any ESA, TIW for epoetin alfa and epoetin zeta, Q3W for darbepoetin alfa and 3–7 times weekly for epoetin beta). Fixed and weight-based dosages were allowed.

Searches were conducted in several databases (including MEDLINE and EMBASE), with results limited to studies published since 2004 where possible, resulting in 1,163 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 24 studies were included.

1.3.2.2. PenTAG cost-utility model

1.3.2.2.1. Model structure

In the PenTAG assessment, the model takes the form of a simple, empirical model, informed directly by the systematic review of clinical effectiveness. The model compares patients receiving ESA therapy to patients not receiving ESA therapy 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, red blood cell transfusion costs and costs of adverse events. Cancer costs are assumed equal for all patients. No difference in survival time in the short term is modelled between arms. Long term costs are not modelled due to 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 are taken directly from clinical trials and this approach attempts to bolt-on an economic evaluation to the RCTs of ESAs. The short term QALY gain includes time receiving ESA therapy and a time post-ESA therapy called normalisation where patients return to their ‘normal’ Hb level (in the base case this is set to 12 g/dL).

Long-term QALYs are accrued due to potential differences in overall survival between the two arms. These are calculated by estimating overall survival in each arm and applying a long-term utility common to both arms, i.e., it is assumed long-term QALY differences only

come about through a difference in survival due to ESA therapy, not through any enduring impact on health-related quality of life.

An exponential distribution is assumed for overall survival of patients not receiving ESA therapy in the base case as this is consistent with results from a number of trials. A hazard ratio is applied to overall survival for lifetime for patients receiving ESA therapy. Alternative modelling assumptions are explored through scenario analyses.

1.3.2.2.2. 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, are varied between ESAs.

In order to ensure consistency between costs and benefits, all parameters are estimated on the basis of intention-to-treat. For example, we use 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.

1.3.2.2.3. 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 normalization of Hb levels following chemotherapy cessation, so this part of the model had to be parameterised on the basis of clinical expert opinion.

1.3.2.2.4. Utilities

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

A review was conducted of studies for (1) and a single study chosen from which the PenTAG base case was calculated (**Harrow and colleagues, 2011**) and scaled to the EQ-5D, giving a 0.028 increase in utility per unit increase in Hb. The long term utility of (2) is calculated using an estimate for cancer utility from **Tengs and Wallace (2000)** and applying the age related utility calculated from **Ara and Brazier (2010)**. This gives a utility of 0.76.

The model does not explicitly model disutility from adverse events, due to lack of data.

1.3.2.2.5. Costs

In this analysis we model the following costs: blood tests, ESA prices, red blood cell transfusion (RBCT) cost (unit cost of blood and cost of transfusion appointment) and costs of adverse events. 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. We assume that the cost of intravenous iron supplementation can be ignored as it will be very similar for all arms. Costs are adjusted to 2014/15 prices where appropriate.

Base case ESA costs are taken from the *British National Formulary* 2013. Wholesale acquisition costs for ESAs have also been obtained and are used in a scenario analysis. ESAs are assumed to be administered once weekly in the base case, by a mixture of GP, district, hospital staff nurse and self- administration. ESAs are also assumed to incur costs for four additional blood tests compared to 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 we account for in this cost-effectiveness analysis are identified through the clinical effectiveness review. In particular we account 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 are identified through NHS Reference Costs 2012-13.

Unit costs for the supply of red blood cells (RBCs) are taken directly from NHSBT 2012/13 costs (£122 per unit) and unit costs of a transfusion appointment are calculated using figures reported in Varney and Guest 2003.

1.3.2.2.6. Other model characteristics

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

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

1.4. Results

1.4.1. Clinical effectiveness

1.4.1.1. Number and quality of effectiveness studies

From 1,458 titles and abstracts screened 11 systematic reviews (reported in 14 publications), and 23 RCTs (reported in 35 publications), were found that matched the inclusion criteria for this review. Update searches yielded 70 unique titles and abstracts; however, none were considered to meet the criteria for 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 and colleagues, 2013**) reporting a study for which only an earlier abstract (**Moebus and colleagues, 2007**) 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, ten 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 haemoglobin levels, and stopping rules were all generally higher than specified in the license.

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 due to reporting omissions. Most notably, all trials lacked clarity in the reporting of allocation methods (the procedure for randomisation and/or allocation concealment).

1.4.1.2. Assessment of effectiveness

Overall the analysis of haematological response (defined as an improvement of 2 g/dl or a 6% increase in haematocrit level) included 10 studies with 2,228 participants. Meta-analysis showed a statistically significant difference in Hb response in favour of treatment (RR 3.29, 95% CI 2.84–3.81). Sixty-three per cent (n/N=759/1,213) of participants who received ESAs achieved a haematological response compared with 18% (n/N=182/1,015). Subgroup analyses were inconclusive. Treatment with ESAs reduces the number of patients receiving RBCTs by an estimated 37%. These estimates are consistent with previously reported estimates.

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 23 studies including 5,064 participants. The HR for survival was 0.97 (95% CI 0.83, 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, 1.11), and 1.03 (95% CI 0.83, 1.13) respectively, there was considerable uncertainty around this estimate and statistically significant heterogeneity was identified(I^2 42.4%; X^2=29.5, df=17, p=0.03). In addition subgroup analyses did not identify groups at lower or higher risk.

On-study mortality was defined as deaths 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 5,085 participants. Analyses suggest that treatment with ESA in patients with CIA did not have a statistically significant effect on mortality (HR 0.86, 95% CI 0.67 to 1.11). Eleven per cent (174/1,586) participants who received ESA had died within 30 days of the active study period, compared to 12% (164/1,381) of patients in control groups.

All AEs were relatively rare compared to the other outcomes considered in this report. The AE with the highest rate was thrombocytopenia/haemorrhage; 6% (55/877) in ESA treatment groups, and 6% (54/838) in control groups. The summary estimate for thrombocytopenia/haemorrhage in the PenTAG review was RR 0.93 (95% CI 0.65, 1.34) compared with RR 1.21 (95% CI 1.04, 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, data suggest increased risk for thromboembolic events, hypertension, seizures and pruritus (skin rash, irritation and pruritus were combined in the analyses) consistent with previous estimates. Analyses suggest that treatment with ESA 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) and suggests a non-significant increase in the number of seizures (RR of 1.19; 95% CI 0.33 to 4.38).

1.4.1.2.1. 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 blood transfusion.

One trial (**Ten Bokkel and colleagues, 1998**) evaluated the use of ESAs in women with ovarian cancer. Data confirm results from prior analyses with respect to anaemia-related outcomes; i.e. improvements in haematological response and reduction in RBCT requirement, but increased risk for thromboembolic events. Overall survival was not measured. No trials were identified that evaluated people unable to receive blood transfusions. However, it is reasonable to assume that ESAs are likely to be effective in improving 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.

1.4.1.2.2. 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 this we also considered this in combination with other licence criteria; i.e. inclusion Hb criteria (closer to the licence ≤11 g/dl and >11 g/dl), and target Hb (closer to the licence ≤13 g/dl and >13 g/dl) in post hoc 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 licenced indications; e.g. 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 prior analyses. The effectiveness on 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 prior analyses. Importantly, although the results for thromboembolic events from the PenTAG review agree with the Cochrane review (**Tonia and colleagues, 2012**), suggesting an increase in thromboembolic events in patients with ESA compared to controls, the closer the studies were to the licence

recommendations, the smaller the point estimates (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 confidence intervals remain wide. The analyses may not have statistical power to detect the effects of license application on the effectiveness of outcomes, if such effects exist. Furthermore, we have not sought to address multiple testing issues which arise when considering subgroups and so the statistical significance of results may appear overstated.

1.4.2. 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 due to 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 of 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 FACT-F 13 item (score 0–52), data 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, conclusions from the PenTAG review are in agreement with the Cochrane review (**Tonia and colleagues, 2012**) in that there is a statistically significant difference between patients treated with ESAs and controls when combining HRQoL parameters. However, the pooled mean difference between the treatment and control arms is <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 results between intervention and control.

Meta-analysis was performed on FACT-G and FACT-An (7 items), however, only three studies were suitable for inclusion for each scale, and their results displayed high levels of

heterogeneity. The results of no statistical difference between intervention and control must therefore be treated with caution.

Overall, conclusions from the PenTAG review are in agreement with 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 only able to use a vote counting method to estimate the positive direction of effect, results from the PenTAG review have been quantified and pooled to enable a more direct comparison between treatments.

1.4.3. Cost-effectiveness

1.4.3.1. 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 and colleagues, 2006**; **Borg and colleagues, 2008**; **Tonelli and colleagues, 2009**). Two were or included new systematic reviews (**Duh and colleagues, 2008**; **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 (Evers and Philips checklists 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 ESA therapy would lead to 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 health-related quality of life, though 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), whilst 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 ESA therapy cost 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 which still remains.

1.4.3.2. Appraisal of industry submissions

Six manufacturer submissions were potentially available for this MTA. However, no manufacturers' submitted an economic evaluation.

1.4.3.3. PenTAG model

1.4.3.3.1. Base case

We find that the deterministic base case has incremental cost-effectiveness ratios (ICERs) for ESA treatment versus no ESA treatment range from £19,429–£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 analyses (PSA).

1.4.3.3.2. Sensitivity analyses

The expected mean results from the PSA gave ICERs that were lower than the deterministic base case (£14,724–£27,226 per QALY gained). The QALYs gained for ESA treatment compared to no ESA treatment had an average of 0.092 with a confidence interval of (-0.264 – 0.447). The incremental costs for the most-cost-effective ESA (Binocrit® [epoetin alfa]) were £1,349 (£710-£1,987, 95% CI). The ICER for Binocrit had a 95% credible interval (CrI) that was dominated by no ESA use (had fewer QALYs and higher costs) at its upper end,

with a lower value of £2,350 per QALY gained (rounded to the nearest £50). In 36% of simulations there was an overall survival loss, with 31.4% of simulations having an overall QALY loss. Given this was the most cost-effective ESA treatment, it is unsurprising that the rest of the ESAs were also dominated at their upper credible interval limit. These results suggest that ESAs may be cost-effective at a threshold of £20,000 per QALY, but also suggest that there is also a potential QALY loss from ESA use. These results suggest that ESAs could 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.

1.4.3.3.3. Scenario analyses

Scenario analyses were conducted to investigate what was driving the wide range of values in the ICERs credible intervals. The three considered most important are:

(1) Setting the overall survival hazard ratio to exactly 1, such 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
(3) Setting the overall survival hazard ratio to exactly 1 and the ESA costs to wholesale acquisition costs.

In the first of these scenarios, where survival is assumed equal for both treatment arms, we find that the QALY gain has greatly reduced (as well as the confidence interval: 0.014 (0.001–0.027), suggesting that much of the variability in the base case QALYs came from the QALYs accrued in 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 over £300,000 per QALY gained) in the PSA. None of the credible intervals for the ICERs fall below £30,000 per QALY gained, suggesting in this scenario that ESAs are unlikely to be cost-effective.

In the second scenario, where wholesale acquisition costs were implemented, [redacted] (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) at one end, to being dominated by the no ESA arm at the other end.

In the third scenario, where survival is assumed equal for both treatment arms and wholesale acquisition costs are used [redacted]

We also conducted scenario analyses on a subgroup of studies where initial Hb level for participants was ≤11 g/dl, and to investigate the assumptions around overall survival. Univariate sensitivity analyses were also conducted. All these analyses resulted in less significant areas of uncertainty than those identified by the results presented in this section.

1.5. Discussion

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

The overview of clinical effectiveness systematic reviews were conducted by an independent, experienced research team using the latest evidence and working to a pre-specified 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 the fact that no studies were completely aligned with the current UK authorization, we identified studies which were closest to the current marketing UK authorization, focusing initially on the starting dose. It is important to note that beyond the start dose there was still a significant differences from the current licence recommendations of the included studies. Also we did not pre-specify the criteria used to define closest to the current UK authorization, 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 done 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 topicwas greatly assisted by the recent Cochrane review (**Tonia and colleagues, 2012).** The authors had gathered further information from Investigators and manufacturers, which were used in the meta-analysis for the current review.

- **Heterogeneity:** There is considerable considerable unexplained statistical heterogeneity for a number of outcomes, particularly survival .

- **Publication bias:** There was some evidence in both the previous review and the Cochrane review 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 ie HRQoL this could not be further investigated because of the small number of included studies, in 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 close as possible to current UK authorization. 95% confidence intervals were in consequence often wide and include values indicating no difference in effect. The problem was compounded by the fact that total number of patients in the trials included were insufficient to establish the true presence of or absence of an effect, either because events are uncommon ie adverse events, or because the effect size which 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 sub-groups analyses done, we did not formally make adjustments for this

The limitations identified above impact on the key outcomes as follows:

- Haematological response and numbers transfused seem 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
- 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 confidence intervals.
- Survival is also subject to all 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 availableans as result there was a mix of short- and long-term studies.

1.5.2. Strengths and limitations: cost-effectiveness

1.5.2.1. 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 pre-specified protocol. Two new systematic reviews were identified, neither of which identified studies which would have been eligible for this review but were not included.
- Limitations were identified as follows:
- The searches were limited to English language due to 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 in **Wilson and colleagues (2007)**;Studies using darbepoetin alfa once every two weeks were excluded as out of licence although these could have usefully contributed to the review.

1.5.2.2. PenTAG model

The main limitations for viewing the updated model and its outputs with such caution are:

- Despite being highly influential on the model results, the marginally beneficial overall survival hazard ratio 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 survival observed in individual ESA RCTs, most of these results can be explained by chance alone.

- The overall survival hazard ratio is applied assuming proportional hazards applying for lifetime after ESA therapy, although to our knowledge the proportional hazards assumption has not been tested. Most included studies had limited follow-up so the long-term impact on survival is not well known. Limiting the effect of ESA therapy on survival to three years results in a significant worsening of cost-effectiveness for ESAs.

- The mapping of Hb to utility is a surrogate outcome with the problems 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 relation between utility and Hb level may be biased due to unmeasured confounding variables, and it is likely that this would bias the results in favour of ESAs versus controls.

- Furthermore, evidence is lacking for the process of normalisation and this was entirely informed by clinical expert opinion.

- We also assumed constant cancer costs between ESA and no ESA arms, where this may not be the case.

- The model also assumes that there is no long term cost difference between arms, but does assume a long term survival benefit. As previous models indicated, this long term aspect of the model is an area which has not been assessed in great detail before, as such this is an area where there need 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 in to the cost-effectiveness

results. Furthermore the inherent uncertainty in the estimates from the clinical-effectiveness meta-analysis and its associated limitations are a main source of uncertainty that occurs within the model. This also means that the effectiveness of ESAs are assumed equal, as this follows from the clinical effectiveness review.

1.6. Conclusions

The previous HTA review (**Wilson and colleagues, 2007**) concluded: "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."

Additional clinical effectiveness evidence identified in this update systematic review continues to suggest that there is clinical benefit from ESAs with respect to anaemia-related outcomes; i.e. improvements in haematological response and reduction in RBCT requirement. Data also suggest an improvement in HRQoL and this is better quantified compared with 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% confidence intervals are wide.

Conclusions concerning cost-effectiveness are also no clearer. Base case ICERs for ESA treatment versus no ESA treatment ranged from £19,429–£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, survival was an influential parameter. If the survival benefit reported in the clinical effectiveness review (0.97 [95% CI 0.83–1.13]) 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 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 1 in 5 simulations give an ICER over £30,000 per QALY and approximately 1 in 3 simulations give an ICER over £20,000 per QALY.

In summary, ESAs could be cost-effective but there is considerable uncertainty mainly due to unknown impacts on overall survival.

1.6.1. 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 due to concerns about safety and effectiveness (overall survival) as well as restriction from previous NICE guidance (TA142).

- **Current usage:** It is difficult to assess how frequently ESA therapy is used within the indication of cancer treatment-induced anaemia 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 cancer treatment-induced anaemia 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 experience that many clinicians do not use ESAs due to safety concerns and current NICE guidance (TA142), although data quality is low and interpretation challenging.

- **Acquisition costs:** The cost at which hospitals acquire ESAs may be significantly lower than the list price for the 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 disturbed if there were developments in the management of CKD or if demand for ESAs increased for patients with cancer treatment-induced anaemia (as might be expected following positive NICE guidance).

1.6.2. Suggested research priorities

- If ESAs are thought to have major potential in 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 haemoglobin 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 re-visit Cochrane IPD meta-analysis 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 i.e. do ESAs allow better compliance with chemotherapy

Background

2.1. Aim of the review

The aim of this assessment is to review and update research evidence as necessary, to inform National Institute for Health and Care Excellence (NICE) guidance to the National Health Service (NHS) in England and Wales on the clinical and cost-effectiveness of erythropoiesis-stimulating agents (ESAs) for the treatment of cancer treatment-induced anaemia (see Section 2.4.2.2, page 44).

This previous guidance (TA142) was primarily based on evidence presented to NICE in the assessment report by **Wilson and colleagues, 2007**.[1] We will incorporate relevant evidence presented in this previous report and report new evidence since 2004.

2.2. 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".[2] A commonly used classification of anaemia according to Hb levels is shown in Table 1.[2]

Table 1. Classification of anaemia (from Wilson and collegues, 2007)[1]

Severity	WHO	NCI
Grade 0 (WNL)	≥11 g/dl	WNL
Grade 1 (mild)	9.5–10.9 g/dl	>10 g/dl WNL
Grade 2 (moderate)	8.0–9.4 g/dl	8–10 g/dl
Grade 3 (serious/adverse)	6.5–7.9 g/dl	6.5–7.9 g/dl
Grade 4 (life threatening)	<6.5 g/dl	<6.5 g/dl
Key: NCI, National Cancer Institute; WHO, World Health Organisation; WNL, within normal limits		

It is the most frequent haematological manifestation in patients with cancer; more than 50% of all cancer patients will be anaemic regardless of the treatment received, and approximately 20% of all patients undergoing chemotherapy will require red blood cell transfusion (RBCT).[3]

The cause of anaemia is usually multifactorial and may be patient-, disease-, or treatment-related.[3] 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, deficiency in folic acid and vitamin B12, can be acute or chronic. In the advanced stages of haematological malignancies, 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 utilization.

Chemotherapy may cause both transient and sustained anaemia.[3] 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, immune-mediated haematopoietic cell destruction etc.[3] Patients treated with platinum-based regimens develop anaemia most often and frequently need transfusions.[3] As a consequence, dose-intensified regimens or shortened treatment intervals, as well as multimodal therapies, are associated with a higher degree of anaemia.[3] 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.[3]

Among 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.[3,4] 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; e.g. age, disease stage and pre-treatment Hb level. In haematological cancers, anaemia is an almost invariable feature of the disease.[3] In addition, some of the newer chemotherapeutic agents such as taxanes or vinorelbine are strongly myelosuppressive and frequently cause anaemia.[5]

The clinical manifestation and severity of anaemia can vary considerably among individual patients.[3] Mild-to-moderate anaemia can typically cause signs and symptoms such as headache, palpitations, tachycardia and shortness of breath.[3] Chronic anaemia can result in severe organ damage affecting the cardiovascular system, immune system, lungs, kidneys, and the central nervous system.[3] In addition to physical symptoms, the subjective impact of

cancer-related anaemia on quality of life (QoL), mental health and social activities may be substantial.[3] A common anaemia-related problem is fatigue, which impairs the patient's ability to perform normal daily activities.[3]

2.3. 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, 2009**,[6] one explanation may be that, as a result of a low Hb, the tumour cells become hypoxic and are subsequently less sensitive to cytotoxic drugs, in particular oxygen-dependent chemotherapies.[7-9] Evidence for this, as reported in **Tonia and colleagues (2012)**,[10] exists in studies where tumour control and overall survival are improved in solid tumour patients with better tumour oxygenation.[9,11] 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 overall survival.[6] 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.[12]

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.[13-19] This effect is postulated to be due to the presence of erythropoietin receptors on various cancers,[20-24] whereby the endogenously produced or exogenously administered erythropoietin promotes the proliferation and survival of erythropoietin receptor expressing cancer cells.[6]**.** However, controversy about the functionality of these receptors remains[25-29] and there are several studies which show no effect on tumour progression for patients receiving ESAs.[16,30-32]

It should be noted that the majority of studies examined in the systematic reviews by **Bohlius and colleagues (2009)[6]** and **Tonia and colleagues (2012)**,[10] have used a wide range of administration frequencies and dosage of ESAs (generally exceeding the license), which may cause a rise in adverse events and mortality. This knowledge, along with the generally poor reporting and data omission on factors such as tumour stage and method of assessment, have lead to the conclusion by **Tonia and colleagues (2012)**,[10] that no clear evidence was found to either exclude or prove a tumour promoting effect of ESAs.

2.4. Current management

2.4.1. Red blood cell transfusions

Anaemia in cancer patients can be treated with red blood cell transfusions (RBCTs), and 15% of people with solid tumours are treated with RBCT.[33]

Different cut-off values are used for transfusions, depending on clinical symptoms and patient characteristics, with a haemoglobin of <9 g/dl commonly used.[33] After administration of one unit of RBCs, Hb rises by 1 g /dl and the life span of transfused RBC is 100–110 days. Complications related to RBCT are procedural problems, iron overload, viral and bacterial infections, and immune injury.[33]

2.4.2. Erythropoetin stimulating agents

Erythropoietin is an acidic glycoprotein hormone. Approximately 90% of the hormone is synthesised in the kidney and 10% in the liver and is responsible for regulating red blood cell production. Erythropoietin for clinical use is produced by recombinant DNA technology.[34]

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 a complete replacement of the existing treatments. Blood transfusion, in particular, may still be needed.[34]

2.4.2.1. Marketing authorisations: Hb levels

Initially all ESAs were recommended for use at Hb level ≤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 cancer treatment-induced anaemia was conducted by the Pharmacovigilance Working Party at the request of the Committee for Medicinal Products for Human Use (CHMP) in 2008. As a result of this safety review, the European Medicines Agency (EMA) requested that the Summary of Product Characteristics (SmPCs) for all ESAs were changed to highlight that ESAs should only be used 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 haemoglobin 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 Hb ≤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 an Hb level of ≤10 g/dl, treatment with ESAs might be considered to increase Hb to <2 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 increased risk of deaths when ESAs are administered to a target Hb of 12–14 g/dl.
- In patients with curative intent, ESAs should be used with caution.

Table 2. Changes to marketing authorisations

Pre-2008	2008 onwards
• An Hb level of ≤11 g/dl, administered to a target Hb level <13 g/dl	• In patients treated with chemotherapy and an Hb level of ≤10 g/dl, treatment with ESAs might be considered to increase Hb to <2 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 increased risk of deaths when ESAs are administered to a target Hb of 12–14 g/dl. • In patients with curative intent, ESAs should be used with caution.
Key: ESAs, erythropoiesis stimulating agents; Hb, haemoglobin	

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

Details of current licence recommendations are summarised in Table 3.

Table 3.Treatment recommendations according to licence

	Epoetin alfa **Epoetin zeta**	**Epoetin beta**	**Epoetin theta**	**Darbepoetin alfa**
Manufacturer (Product)	Janssen-Cilag (Eprex®)[35] Sandoz Ltd (Binocrit®)[36] Hospira UK (Retacrit®)[37]	Roche Products (Neorecormon®)[38]	Teva UK (Eporatio®)[39]	Amgen Ltd (Aranesp®)[40]
Marketing authorisation	Treatment of anaemia 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	
Start 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** **450 IU/kg SC QW**	**150 IU/kg SC TIW** **450 IU/kg SC QW**	**20,000 IU/QW**	**2.25 µg/kg SC QW** **500 µg (6.75 µg/kg) SC Q3W**
Dose increase	4 wks Hb increase <1 g/dl & reticulocyte increase ≥ 40 000 cells/µl dose is doubled 300 IU/kg TIW or 900 IU/kg QW	300 IU/kg SC TIW	4 wks Hb increase <1 g/dl dose is doubled 40,000 IU/QW; if Hb increase insufficient at 8 wks increase to 60,000 IU/QW	4 wks Hb increase <1 g/dl dose is doubled 4.5 µg/kg SC QW
Dose reduction	If Hb increase ≥2 g/dl: 25–50% If Hb >12 g/dl: 25–50%			If Hb increase ≥2 g/dl: 25–50% If Hb ≥12 g/dl: 25–50%
Dose withholding	If Hb >13 g/dl until 12g/dl reinitiate at 25% lower dose		Hb >12 g/dl: should be avoided; 12 wks Hb increase <1 g/dl: discontinue	If Hb >13 g/dl until 12g/dl reinitiate at 25% lower dose

Key: Hb, haemoglobin; IU, international units; QW, once weekly; Q3W, once every three weeks; RBCT, red blood cell transfusion; SC, subcutaneous; TIW, thrice weekly; UK, United Kingdom; wks, weeks

2.4.2.2. Current service provision

NICE guidance (Technology Appraisal [TA] 142)[34] currently recommends ESAs in combination with intravenous iron as an option for:

- the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin level of 8 g/dl or lower. The use of ESAs does not preclude the use of existing approaches to the management of anaemia, including blood transfusion where necessary.[34]
- people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.[34]
- Where indicated the ESA used should be the one with the lowest acquisition cost.[34]

2.5. Description of technology under assessment

Several short- and long-acting erythropoiesis stimulating agents (ESAs) are available including epoetin alfa, epoetin beta and darbepoetin beta. Since the last appraisal (2004), an additional two ESAs have become available: epoetin theta and epoetin zeta; the latter is referenced to epoetin alfa. All are administered by subcutaneous injection. This technology assessment report (TAR) will consider six pharmaceutical interventions: epoetin alfa (Eprex® [Janssen-Cilag], Binocrit® [Sandoz]), epoetin beta (NeoRecormon® [Roche Products]), epoetin theta (Eporatio® [Teva UK]), epoetin zeta (Retacrit® [Hospira UK]), and darbepoetin alfa (Aranesp® [Amgen]).[34] Treatment recommendations according to licence are summarised for each in Table 3.

This NICE appraisal focuses on the treatment of cancer treatment-induced anaemia. 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 due to chronic renal failure.

2.6. Clinical guidelines

2.6.1. EORTC

In Europe, treatment guidelines for cancer treatment induced anaemia have been formulated by the European Organisation for Research and Treatment of Cancer (EORTC), which most recently updated their 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 Hb <10 g/dl, depending on the severity of the anaemia or clinical circumstances, and may also be warranted by clinical conditions in patients with Hb ≥10 g/dl but <12 g/dl.[42]

Recommendations for ESA therapy for CIA are broadly similar between the EORTC guidelines and those of the 2010 joint American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) guidelines, with small differences in the threshold for initiation of ESA therapy and variation in the wording related to Hb levels.[41-43]

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

2.6.2. British Columbia Cancer Agency

The British Columbia Cancer Agency (BCCA) guidelines recommend treatment with ESAs for the treatment of CIA when Hb level is 10 g/dl and there is a minimum of two months planned chemotherapy.[41]

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, ESAs 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.[41]

2.7. Existing evidence

2.7.1. 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 pre-specified in the protocol; a summary of eligible systematic reviews and a quality assessment (versus PRISMA statement) are in Appendix I.

2.7.1.1. Cochrane review (Tonia and colleagus, 2012)

The Cochrane review by **Tonia and colleagues (2012**) was the most recent and authoritative. The Cochrane review's conclusions were: "*ESAs reduce the need for RBCTs but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve QoL. Whether and how ESAs affect tumour control remains uncertain. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient's clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumour progression. 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.*" (**Tonia and colleagues, 2012**; page 2).

This was an update of a Cochrane review first published in 2004 (**Bohlius and colleagues, 2004**). Searches were conducted in CENTRAL, EMBASE, MEDLINE and other databases. Searches were done for the periods January 1985 to December 2001 for the first review, January 2002 to April 2005 for the first update, and to November 2011 for the most recent update. The authors of the review also contacted experts in the field and pharmaceutical companies (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 the PenTAG review in Table 4. The Cochrane review differed from the PenTAG review in respect of population (cancer related anaemia vs chemotherapy induced

anaemia), and intervention (all ESAs irrespective of licence vs ESAs within licence (defined based on start dose).

Table 4. Differences between Tonia and colleagues (2012) and PenTAG systematic reviews

	Tonia and colleagues, 2012	Current systematic review, 2013
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). Excluded trials where >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 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 indication, defined by start dose even if they 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]

Key: AEs, adverse events; CR, complete response; ESAs, erythropoiesis stimulating agents; Hb, haemoglobin; OS, overall survival; RBC, red blood cell; RBCT red blood cell transfusion; RCTs, randomized controlled trials; SRs, systematic review
Notes: (a) Specifically epoetin alfa, beta, theta, zeta; darbepoetin alfa; **(b)** Defined as an increase in Hb level of ≥2 g/dL, or an increase in haematocrit of ≥6% points; **(c)** Used for scrutinisation of bibliographies and comparison of results

A total of 91 studies with 20,102 participants were included in this review. Results from the Cochrane review are summarised in Table 5 and compared with the results of the PenTAG HTA review throughout Section 0 (page 56).

Table 5. Results: Cochrane review (Tonia and colleagues, 2012)

Anaemia-related outcomes			
Hb change[a]	**HaemR[b]**	**RBCT**	**Units transfused**
WMD 1.57	RR 3.39	RR 0.65	WMD -0.98

95% CI 1.51−1.62 $X^2_{(het)}$; 564.37; df 74 (p<0.001) 75 trials, n=11,609	95% CI 3.10−3.71 $X^2_{(het)}$; 95.56; df 45 (p<0.001) 46 trials, n=6,413	95% CI 0.62−0.68 $X^2_{(het)}$ 217.08; df 87 (p<0.001) 88 trials, n=16,093	95% CI -1.17−-0.78 $X^2_{(het)}$ 34.52; df 24 (p=0.080) 25 trials, n=4,715
Malignancy-related outcomes			
Tumour response	**Overall survival**	**Mortality**	
RR 1.02 95% CI 0.98−1.06 $X^2_{(het)}$ 16.10; df 18 (p=0.59) 19 trials, n=5,012	HR 1.05 95% CI 1.00−1.11 $X^2_{(het)}$ 95.40; df 75 (p=0.060) 80 trials, n=19,003		
Safety-related outcomes			
Thromboembolic events	**Hypertension**	**Thrombocytopenia/haemoorhage**	**Seizures**	**Pruritus**
RR 1.52 95% CI 1.34−1.74 $X^2_{(het)}$ 34.99; df 55 (p=0.980) 60 trials, n=15,498	RR 1.30 95% CI 1.08−1.56 $X^2_{(het)}$ 26.87; df 34 (p=0.800) 35 trials, n=7,006	RR 1.21 95% CI 1.04−1.42 $X^2_{(het)}$ 14.50; df 20 (p=0.800) 21 trials, n=4,220	RR 0.77 95% CI 0.42−1.41 $X^2_{(het)}$ 6.19; df 6 (p=0.400) 7 trials, n=2,790	RR 1.49 95% CI 0.99−2.24 $X^2_{(het)}$ 13.18; df 15 (p=0.590) 16 trials, n=4,346
FACT-F 13 item (score 0-52)	**Any subgroup effect**			
Health related quality of life related outcomes				
MD 2.08 95% CI 1.43, 2.72 $X^2_{(het)}$36.48; df 17 (p=0.004) 18 trials, n=4,965	Yes: imputed vs. non-imputed data, baseline Hb level, type of anti-cancer therapy, duration of ESA treatment and ITT analysis.			

Key: CI, confidence interval; df, degrees of freedom; haemR, haematological response; het, heterogeneity; RBCT, red blood cell transfusion; RR, relative risk; WMD, weighted mean difference
Notes: fixed effects (Mantel-Haenzel) **a** change from baseline to end of study; **b** haematological response was defined as the proportion of participants with an increase in Hb level of two g/dl or more, or as an increase in haematocrit of six percentage points or more.

2.7.1.2. Cochrane review: meta-analysis based on IPD data (Bohlius and colleagues, 2009)

Another Cochrane review (**Bohlius and colleagues, 2009**) examined the effect of ESAs and identified factors that modify the effects of ESAs on overall survival, progression free survival, thromboembolic and cardiovascular events as well as the need for transfusions and other important safety and efficacy outcomes in cancer patients. It concluded: '*ESA treatment in cancer patients increased on study mortality and worsened overall survival. For patients undergoing chemotherapy the increase was less pronounced, but an adverse effect could not be excluded.*' (**Bohlius and colleagues, 2009**).

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 comparing ESAs plus RBCT (as necessary) versus RBCT (as necessary) alone, to prevent or treat anaemia in adult or pediatric 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.

A total of 13,933 cancer patients from 53 trials were analysed, 1,530 patients died on-study and 4,993 overall. ESAs increased on-study mortality (combined hazard ratio [cHR] 1.17; 95% CI 1.06-1.30) and worsened overall survival (cHR 1.06; 95% CI 1.00-1.12), with little heterogeneity between trials (I2 0%, p=0.87 and I2 7.1%, p=0.33, respectively). Thirty-eight trials enrolled 10,441 patients receiving chemotherapy. The cHR for on-study mortality was 1.10 (95% CI 0.98-1.24) and 1.04; 95% CI 0.97-1.11) for overall survival. There was little evidence for a difference between trials of patients receiving different cancer treatments (p for interaction=0.42).

Table 6. Results: Cochrane review (Bohlius and colleagues, 2009)

Malignancy-related outcomes			
Overall survival	**On-study mortality**		
cHR 1.04 95% CI 0.97–1.11 38 trials; n=10,441	cHR 1.10 95% CI 0.98–1.24 38 trials; n=10,441		
Key: cHR, combined hazard ratio; CI, confidence interval			

2.7.1.3. Previous HTA review (Wilson and colleagues, 2007)

The previous HTA (**Wilson and colleagues, 2007**) informed National Institute for Health and Care Excellence (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: "*Epo is effective in improving haematological response and RBCT requirements, and appears to have a positive effect on health-related quality of life (HRQoL). The incidence of side-effects and effects on survival remains highly uncertain. If there is no impact on survival, it seems highly unlikely that epo would be considered a cost-effective use of healthcare resources.*" (**Wilson and colleagues, 2007**; page x).

Using the Cochrane review published in 2004 as the start point **Wilson and colleagues (2007)** conducted a systematic review of randomised controlled trials (RCTs) comparing ESAs with standard care was conducted. 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 the PenTAG review in Table 7. Where 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 Section 6.1.1., page 203).

Table 7. Differences between Wilson and colleagues (2007) and PenTAG systematic reviews

	Wilson and colleagues, 2007	Current systematic review, 2013
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 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 indication, defined by start dose even if they 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]

Key: AEs, adverse events; CR, complete response; ESAs, erythropoiesis stimulating agents; Hb, haemoglobin; OS, overall survival; RBC, red blood cell; RBCT red blood cell transfusion; RCTs, randomized controlled trials; SRs, systematic review
Notes: (a) Specifically epoetin alfa, beta; darbepoetin alfa; **(b)** Defined as an increase in Hb level of ≥2 g/dL, or an increase in haematocrit of ≥6% points; **(c)** Used for scrutinisation of bibliographies and comparison of results

A total of 46 RCTs were included in the previous HTA review (**Wilson and colleagues, 2007**), 27 of which had been included in the Cochrane review (**Bohlius and colleagues,**

2004). All 46 studies compared ESA plus supportive care for anaemia (including transfusions) with supportive care for anaemia (including transfusions alone). Outcomes assessed with anaemia-related outcomes (haematological response [haemR], haemoglobin (Hb) change, RBCT requirements, malignancy –related outcomes (tumour response and overall survival [OS]), health-related quality of life (HRQoL), and adverse events (AEs).

Results from the previous HTA review (**Wilson and colleagues, 2007**) are compared with the results of the PenTAG HTA throughout Section 0 (page 56).

Table 8. Results: Wilson and colleagues, 2007[1]

Hb change[a]	**HaemR[b]**	**RBCT**	**Units transfused**
Anaemia-related outcomes			
WMD 1.63 95% CI 1.46−1.80 $X^2_{(het)}$ 23.74; df 19 (p=0.21) 10 trials, n=1,620	RR 3.40 95% CI 3.01−3.83 $X^2_{(het)}$ 23.60; df 32 (p=0.86) 21 trials, n=3,740	RR 0.63 95% CI 0.58−0.67 $X^2_{(het)}$ 94.75; df 48 (p=0.001) 35 trials, n=5,564	WMD -1.05 95% CI -1.32−-0.78 $X^2_{(het)}$ 8.96; df 16 (p=0.91) 14 trials, n=2,353
Tumour response	**Overall survival**	**Mortality**	
Malignancy-related outcomes			
RR 1.31 95% CI 1.08−1.60 $X^2_{(het)}$ NR; df NR (p=NR) 9 trials, n=1,260	HR 1.03 95% CI 0.92−1.16 $X^2_{(het)}$ 37.74; df 27 (p=0.08) 28 trials, n=5,308	NR	
Safety-related outcomes			
No safety related meta-analysis			
FACT-F 13 item (score 0-52)	**Any subgroup effect**		
Health related quality of life related outcomes			
No HRQoL meta-analyses			

Key: CI, confidence interval; df, degrees of freedom; haemR, haematological response; het, heterogeneity; RBCT, red blood cell transfusion; RR, relative risk; WMD, weighted mean difference
Notes: fixed effects (Mantel-Haenzel) **a** change from baseline to end of study; **b** haematological response was defined as the proportion of participants with an increase in Hb level of two g/dl or more, or as an increase in haematocrit of six percentage points or more.

KEY POINTS

- Anaemia is defined as a deficiency in red blood cells. It is the most frequent haematological manifestation in patients with cancer; more than 50% of all cancer patients will be anaemic regardless of the treatment received, and approximately 20% of all patients undergoing chemotherapy will require red blood cell transfusion. 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; e.g. 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 may return to pretreatment levels.
- Options available for the management of cancer treatment-induced anaemia 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 red blood cell transfusion include procedural problems, iron overload, viral and bacterial infectios, and immune injury.
- Current evidence suggests that ESAs reduce the need for RBCT but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve quality of life. Whether and how ESAs affect tumour control remains uncertain.
- Current NICE guidance (TA142) recommends: the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin level of 8 g/dl or lower. The use of ESAs does not preclude the use of existing approaches to the management of anaemia, including blood transfusion where necessary; and, in people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

Definition of the decision problem

3.1. Decision problem

The purpose of this assessment is to review and update as necessary guidance to the NHS in England and Wales on the clinical and cost-effectiveness of erythropoiesis-stimulating agents: epoetin alfa (Eprex® [Janssen-Cilag], Binocrit® [Sandoz]), epoetin beta (NeoRecormon® [Roche Products]), epoetin theta (Eporatio® [Teva UK]), epoetin zeta (Retacrit® [Hospira UK]), and darbepoetin alfa (Aranesp® [Amgen]), within their licensed indications for the treatment of cancer-treatment induced anaemia.

The project was undertaken based on a published scope,[42] and in accordance with a predefined protocol (see Appendix A). 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 were completely aligned with current licences we applied a definition of 'within licence' which was not pre-defined. Given the recent publication of the 2012 Cochrane review (**Tonia and colleagues, 2012**) which considered all ESAs irrespective of licence, 'within licence' was therefore defined as a licensed starting dose irrespective of how other licence criteria were dealt with.

3.2. Population

The population will be people receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and people with non-myeloid malignancies at risk of transfusion as assessed by 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).

3.3. Interventions

The interventions considered are erythropoiesis-stimulating agents: epoetin alfa (Eprex®, [Janssen-Cilag] and Binocrit® [Sandoz]); epoetin beta (NeoRecormon®, Roche Products); epoetin theta (Eporatio® [Teva UK]); epoetin zeta (Retacrit® [Hospira UK]) Darbepoietin alfa

(Aranesp® [Amgen]). All interventions will only be considered according to their UK marketing authorisation (Section 4.1.2.3, page 59).

3.4. Comparators

The following comparators will be considered:

- Best supportive care (including adjustment to the cancer treatment regimen, blood transfusion and iron supplementation)
- One of the other interventions under consideration; provided in line with their marketing authorisations

3.5. Outcomes

Evidence in relation to the following kinds of outcomes will be considered:

- haematological response to treatment: defined as a transfusion free increase of Hb of ≥2 g dl-1 or a haematocrit increase of 6%
- need for blood transfusion after treatment: number of patients transfused, number of units transfused per patient, and number of patients transfused per patient per four weeks
- tumour response: time to cancer progression
- overall survival
- adverse effects of treatment: hypertension, rash/irritation, pruritus, mortality, thromboembolic events, seizure, haemorrhage / thrombocytopenia, fatigue, pure red cell aplasia. A note will be made of other adverse events described within the trial reports
- health-related quality of life: validated quality of life measures; e.g. FACT (FACT-General, FACT-Fatigue, FACT-Anaemia), EQ-5D, SF-36

3.6. Research question

This assessment will address the question: “What is the effectiveness and cost-effectiveness of ESAs (epoetin alfa, beta, theta and zeta; and, darbepoetin alfa) for treating cancer-treatment induced anaemia (including review of TA142)?”

Assessment of clinical effectiveness

The review commissioned by the National Institute for Health and Care Excellence (NICE) was to update the previous guidance (TA142)[34] based on the health technology assessment (HTA) review conducted by **Wilson and colleagues (2007)**.[1] The differences between the remit of the previous review and the current one are discussed in Section 2.7.1.2 (page 48). The project was undertaken in accordance with a predefined protocol (see Appendix A). 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 were completely aligned with current licences we applied a definition of 'within licence' which was not pre-defined. Given the recent publication of the 2012 Cochrane review (**Tonia and colleagues, 2012**) which considered all ESAs irrespective of licence, 'within licence' was therefore 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 (**Bohlius and colleagues, 2009** and **Tonia and colleagues, 2012**),[10,43] which assessed the effectiveness of erythropoiesis stimulating agents up to 2010 and 2012 respectively.

The aim was to systematically review the effectiveness of ESAs, with regard to treating cancer treatment-related anaemia, its effects on the patient regarding underlying malignancy and survival, its effectiveness in improving quality of life and the impact of adverse events. Given the recent publication of the Cochrane review (**Tonia and colleagues, 2012**), the focus for this review was to identify and consider trials where ESAs have been used in a manner consistent with or closest to their respective marketing authorisations (see Section 4.1.2.3.1, page 60).

4.1. Methods

4.1.1. Identification of studies

The search strategy is based on the strategy used in the previous MTA on this topic by **Wilson and colleagues (2007)**.[1] It combines free-text and MeSH terms for epoetin (generic and brand names), cancer and anaemia using the AND Boolean operator. Search filters are applied to retrieve RCTs, cost effectiveness studies and quality of life studies. The search terms and structure of the search is mainly the same as in **Wilson and colleagues (2007)**,[1]

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 (QoL) studies are different to those used in **Wilson and colleagues (2007)**.[1] 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 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 (**Wilson and colleagues [2007]**,[1] search end-date: 2004). Although epoetin alfa (Binocrit® [Sandoz]), 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 prior to this date, given that the drugs were launched in 2007 (epoetin alfa [Binocrit®, Sandoz]) 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 (Ovid); EMBASE (Ovid); the Cochrane Library including CENTRAL, the Cochrane Database of Systematic Reviews, DARE, HTA, NHS EED and HEED; Web of Science (Thomson Reuters); CINAHL (EBSCO); British Nursing Index (ProQuest); HMIC (Ovid); Current Controlled Trials; Clinical Trials.gov; FDA website; EMA website.

In addition, the following websites were searched for background information:

Medical societies

British Society for Haematology	http://www.b-s-h.org.uk/
The Association of Cancer Physicians	http://www.cancerphysicians.org.uk/
American Society of Hematology	http://www.hematology.org/
American Society of Clinical Oncology	http://www.asco.org/
The Canadian Oncology Societies	http://www.cos.ca/
Haematology Society of Australia and New Zealand	http://www.hsanz.org.au/
Clinical Oncology Society of Australia	http://www.cosa.org.au/
New Zealand Society for Oncology	http://www.nzsoncology.org.nz/

UK charities

Cancer Research UK	http://www.cancerresearchuk.org/home/
Macmillan	http://www.macmillan.org.uk/

Marie Curie	http://www.mariecurie.org.uk/
Non-UK charities	
American Cancer Society	http://www.cancer.org/
Canadian Cancer Society	http://www.cancer.ca/
Cancer Council Australia	http://www.cancer.org.au/
Cancer Society of New Zealand	http://www.cancernz.org.nz/
World Cancer Research Fund	http://www.wcrf-uk.org/

The database search results were exported to, and de-duplicated using Endnote (X5).De-duplication was also performed using manual checking. The search strategies and the numbers retrieved for each database are detailed in Appendix B. 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 so the search strategy was limited to MEDLINE. These searches are detailed in Appendix B.

4.1.1.1. Wilson and colleagues, 2007

Studies included in the previous HTA review (**Wilson and colleagues, 2007**)[1] were screened versus the inclusion criteria for the PenTAG review for includable studies.

4.1.1.2. Reference lists

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

4.1.1.3. 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 following trial registers: ClinicalTrials.gov and Controlled Trials (ISRCTN) for ongoing trials. Trials that did not relate to cancer-induced or chemotherapy-related anaemia were removed by hand-sorting. Finally, duplicates, identified via their study

identification numbers where possible, were removed. Searches were carried out on 28 August 2013.

4.1.2. Eligibility criteria

4.1.2.1. Study design

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

4.1.2.2. Population

People had to be receiving chemotherapy for solid tumours, malignant lymphoma, or multiple myeloma (and people with non-myeloid malignancies), at risk of transfusion as assessed by general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy), and non-myeloid malignancies. There were no age restrictions; however, it is recognised that the licenses for all the interventions of interest do not cover erythropoietin use in children for this indication. Studies where erythropoietin was 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.

4.1.2.3. Interventions

Studies evaluating the use of erythropoiesis stimulating agents (ESAs) were included if given to treat cancer treatment-induced anaemia. The ESAs of interest for this appraisal were: epoetin alfa (Eprex®, Janssen-Cilag; Binocrit®, Sandoz), epoetin beta (NeoRecormen®, Roche Products), Epoetin theta (Eporatio®, Teva UK), epoetin zeta (Retacrit®, Hospira UK), or darbepoetin alfa (Aranesp®, Amgen).

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

4.1.2.3.1. Dose

ESA administration varied considerably among the published literature. Variation with respect to: Hb levels (trigger [the point below which ESAs should be administered, ≤10.0 g/dl]; and, targeted [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); abandonment for persistent non-responders; and, duration of use following each chemotherapy session. The majority (82%) of studies were initiated before the 2008 update of the Summary of Products Characteristics (SPCs) and no studies were completely aligned with the UK marketing authorisation for these drugs in respect of these criteria (see Appendix C).

For the main analysis for this systematic review, studies were considered eligible for inclusion if they used a licensed start dose regardless of how they dealt with other criteria stipulated by the license. Thus, ESAs administered weekly, for epoetin alfa and epoetin zeta to be administered three-times weekly, for epoetin beta to be administered three to seven times per week; and, for darbepoetin alfa to be administered every three weeks. Fixed (epoetin theta) and weight-based (epoetin alfa, epoetin beta, epoetin zeta, and darbepoetin alfa) dosages were allowed.

In addition we also considered inclusion Hb criteria as closer to licence ≤11 g/dl and >11 g/dl; and target Hb as closer to licence ≤13 g/dl and >13 g/dl.

4.1.2.4. Comparator

The main comparators of interest were: placebo, 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 it was administered in line with the relevant marketing authorisations.

4.1.2.5. Outcomes

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

- **Anaemia-related outcomes:** haematological response to treatment (defined as a transfusion free increase of haemoglobin (Hb) of ≥2 g/dL or a haematocrit increase

(Hct) 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).

- **Malignancy-related outcomes:** tumour response, and overall survival (OS)
- **Adverse events (AEs):** hypertension, rash/irritation, pruritus, mortality, thromboembolic events, seizure, haemorrhage/thrombocytopenia, fatigue, and pure red cell aplasia. A note was made of other adverse events described within the trial.
- **Health-related quality of life (HRQoL):** data on validated quality of life (QoL) measures was sought, anticipated quality of life measures would include FACT (including FACT-General (G), FACT-Fatigue (F), and FACT-Anaemia (A)). A note was made of any other HRQL measure reported.

4.1.3. Selection of studies

Studies retrieved from the update searches were selected for inclusion according to the inclusion/exclusion criteria specified in Section 4.1.2. First, titles and abstracts returned by the search strategy were screened for inclusion independently by two researchers (LC and MH). Disagreements were resolved by discussion, with involvement of a third reviewer (TJ-H or HC). Full texts of identified studies were obtained and screened in the same way. Abstract only studies were included provided sufficient methodological details were reported to allow critical appraisal of study quality.

In addition, studies included in the review conducted by **Wilson and colleagues (2007)**[1] were screened for inclusion against the eligibility criteria for this review.

Eligible studies were then re-screened to apply the inclusion criteria 'intervention administered in accordance with their licensed indications'. For this systematic review, this was defined as a licensed start dose irrespective of how the study dealt with other criteria stipulated by the license. Thus, ESAs administered weekly, for epoetin alfa and epoetin zeta to be administered three-times weekly, for epoetin beta to be administered three to seven times per week; and, for darbepoetin alfa to be administered every three weeks. Fixed (epoetin theta) and weight-based (epoetin alfa, epoetin beta, epoetin zeta, and darbepoetin alfa) dosages were allowed.

4.1.4. Data extraction and management

Included full papers were split between four reviewers (LC, MH, TJ-H, HC) for the purposes of data extraction using a standardised data extraction form, and checked independently by another reviewer. Discrepancies were resolved by discussion with the involvement of an additional review team member (CH) if necessary. Information extracted and tabulated included details of the study's design and methodology, baseline characteristics of participants, and results including HRQL and any AEs if reported (see Appendix D).

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

For studies comparing more than one experimental arm to one control arm, we assigned a separate reference for each study arm with the author and publication year of the main publication and added the suffixes a; b. For example, the study by **Tjulandin and colleagues 2010** compared two different experimental study arms with one control group. The two different study arms are listed separately in the included studies (Table 10) and Section 0, page 649). Due to this referencing system a study may appear more than twice in the list of included studies.

Where there was incomplete information on key data, we referred to the 2012 Cochrane Review. For the update of the Cochrane Review the authors evaluated documents presented at the Oncology Drug Advisory Committee (ODAC) hearing at the USA Food and Drug Administration (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.

4.1.5. Critical appraisal

Four reviewers (LC, MH, TJ-H, HC) independently assessed quality for the newly identified studies (2004 onwards) based on the criteria in **Error! Reference source not found.** (used for the assessment in the previous HTA [**Wilson and colleagues, 2007**] and Cochrane [**Tonia and colleagues, 2012**] reports).[1,10]

Table 9. Quality assessment

Table 9. Quality assessment

Treatment allocation	1. Was allocation truly random? Yes: random numbers, coin toss, shuffle, etc No: for patients 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 where the trialist allocating treatment could not be aware Inadequate: allocation was alternate, or based on information known to the trialist 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 lost to follow-up in each group stated? 7. Did the analysis include an ITT or were less than 10% of study arm excluded?
Key: ITT, intention-to-treat	

4.1.6. Methods of data analysis/synthesis

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

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, mean differences were calculated if the outcome was measured on the same scale in all trials. For QoL only identical scales and sub-scales were combined in a given meta-analysis. For time-to-event data; i.e. OS, data were extracted from the Cochrane review (**Tonia and colleagues, 2012**).[10] In the Cochrane review hazard ratios (HRs) were based on individual patient data (IPD) data; where IPD were not available, the HR was calculated from published reports including secondary analyses, using methods reported in Parmar and colleagues (1998),[44] or binary mortality data.[10] Similarly, data from the Cochrane review (**Tonia and colleagues, 2012**)[10] were used for mean Hb change, transfusion requirement, mean units of blood transfused, complete tumour response, QoL, and AEs, if this information was not available in the published trials' reports.

One study (**Tjulandin and colleagues, 2010**)[45] 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 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 (**Ten Bokkel and colleagues, 1998; Thatcher and colleagues,1999; Hedenus and colleagues, 2002**; **Kotasek and colleagues, 2003**),[46-49] all participants assigned to the control arm were included.

The following pre-specified subgroup analyses were conducted, if appropriate:

- **Hb level at study entry** (<10 g /dl versus <11 g/dl versus <12 g/dl versus <14.5 g/dl versus not reported)
- **Hb inclusion criteria** (≤11 g/dl versus <11 g/dl versus)
- **Target Hb** (≤12 g/dl and >12 g/dl)
- **Solid tumours versus haematological malignancies** (solid versus haematological versus mixed versus not reported)
- **Ovarian cancer** (ovarian cancer versus other cancers)
- **Type of chemotherapy treatment** (platinum chemotherapy versus non-platinum chemotherapy versus chemotherapy+radiotherapy versus mixed chemotherapy versus not reported)
- **Short-lasting ESA versus long-lasting ESA** (epoetins versus darbepoetin)
- **Iron supplementation** (iron supplementation given versus no iron supplementation versus iron handled differently in study arm versus not reported)
- **Duration of ESA medication** (six to nine weeks versus 12–16 weeks versus 17–20 weeks versus >20 weeks)
- **Study design** (placebo versus standard care)

In addition based on subgroup analyses, meta-regression models were conducted including random effect and a subgroup as a covariate to assess the effects of subgroups on the outcomes. These analyses were conducted if there was sufficient number of studies in each subgroup. The Der Simonian-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 have to be interpreted with caution as they can only be exploratory, and should be considered as hypothesis generating rather than hypothesis testing analyses.[50,51]

In addition, we stated in the protocol that we would consider: the use of iron supplementation + 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 v.12.

4.1.6.1. Sensitivity analysis

To allow comparison with the Cochrane review (**Tonia and colleagues, 2012**)[10] and with the previous HTA review (**Wilson and colleagues, 2007**),[1] fixed-effects meta-analyses for the main analysis were also conducted.

4.1.6.2. 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 was used for continuous outcomes (mean difference; SE), and the Harbord test was used for binary outcomes (OR, logSE). 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 effect and using publication year as a covariate to assess the effect of publication year on the considered outcome were conducted.

4.1.7. 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 the PenTAG Health Technology Assessment group 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.

4.2. Results

4.2.1. Studies identified

We screened the titles and abstracts of 1,458 unique references identified by the PenTAG searches and additional sources, and retrieved 293 papers for detailed consideration. Of these, 232 were excluded, five because they were unobtainable and 227 for other reasons (a list of these items with reasons for their exclusion can be found in Appendix E). Sixty one studies met the pre-specified criteria set out in the protocol and were considered eligible for inclusion. In assessing titles and abstracts, agreement between the two reviewers was good (κ=0.693 [95% CI 0.648–0.738]). At the full-text stage, agreement was substantial (κ=0.792 [95% CI 0.705–0.879]). At both stages, initial disagreements were easily resolved by consensus.

We then re-assessed included studies (n=46) from the review conducted by **Wilson and colleagues (2007).**[1] Of these, 29 studies were considered eligible for inclusion in the update review. The scope for **Wilson and colleagues (2007)**[1] differed from the current scope; the population of interest was not defined by treatment type compared with the current scope which specifies patients on chemotherapy (see Section 2.7.1.2, page 48). Reasons for exclusion included: data only available in abstract format, population (either participants not receiving chemotherapy or receiving radiotherapy only), or duplicate (studies also retrieved in the PenTAG update searches).

We identified and included one full paper (**Boogaerts and colleagues, 2003)**[52] of an abstract (**Coiffier and colleagues, 2001)**[53] included in the review by **Wilson and colleagues (2007)**.[1] In addition, one study (**Abels and colleagues, 1993)**[54] included in the previous HTA review Wilson and colleagues, 2007) was published in five papers; three were included in the Wilson and colleagues review (**Abels and colleagues, 1993;**[54] **Case and colleagues, 1993**;[55] and, **Henry and colleagues, 1994**[56]), and an additional two were identified when scrutinising the bibliographies of included studies (**Henry and colleagues, 1995;**[57] and, **Abels and colleagues, 1996**[58]).

Citations of the includable studies (including the 2012 Cochrane Review **[Tonia and colleagues, 2012[10]]**) were also searched by two reviewers (LC, MH). This process revealed an additional six papers:

- Systematic reviews (n=1): **Grant and colleagues, 2013**[59]
- Primary studies (n=5): **Henry and colleagues (1995)**;[57] **Abels and colleagues (1996)**;[58] **Patrick and colleagues (2003);**[60] **Wagner and colleagues (2004)**;[61] **Moebus and colleagues (2013)**[62]

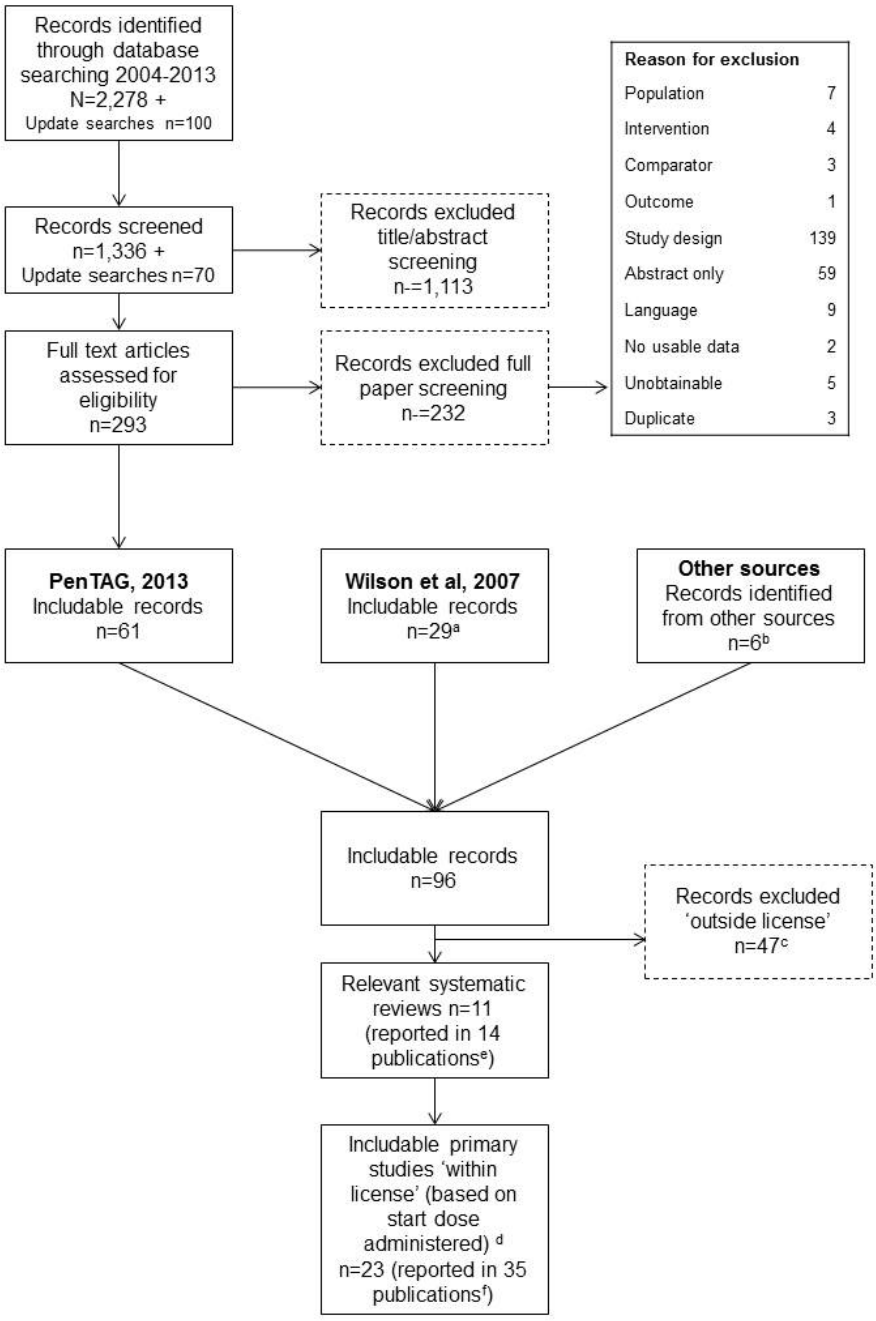
For this review we further specified that eligible interventions should be assessed as administered in accordance with their licensed indications. This criterion was applied after the first-round of full-paper screening in order to make sure that we captured all relevant evidence. As the majority of trials were initiated before the 2008 update of the SmPCs the inclusion criteria for these studies did not reflect the revised ESA license with regards to the treatment initiation threshold of Hb ≤10 g/dl or Hb treatment target levels of 10–12 g/dl. As a result none of the included studies were completely in line with the current UK marketing authorisation. We therefore considered studies eligible for inclusion if they used a licensed, weight-based starting dose, regardless of other criteria stipulated by the license; e.g. Hb levels.

In applying this eligibility criterion, 47 were considered to have evaluated the interventions outside of the licensed indication (a list of these studies together with study characteristics can be found in Appendix F). In total, 23 primary studies reported in 35 publications were judged to meet the inclusion criteria for the review (Table 10); study characteristics are summarised in Appendix G. Primary studies are linked to multiple publications in Appendix H. Eleven systematic reviews reported in 14 publications (see Appendix I) were also identified; these were used to identify other studies and to compare results.

Update searches were conducted on 2nd December using the same methodology as described earlier. Seventy 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 by LC and MH. A list of these items with reasons for their exclusion can be found in Appendix E.

The process is illustrated in detail in Figure 1.

Figure 1. PRISMA flowchart: clinical effectiveness review



Key: DX, data extraction; SRs, systematic reviews; RCTs, randomised controlled trials
Notes: **(a)** Studies excluded (reasons for exclusion): **abstract:** Quirt (1996), Carabantes (1999), Huddart (2002), Thomas (2002), Janinis (2003); **population (receiving radiotherapy only or not receiving chemotherapy):** Rose (1994), Wurnig (1996), Sweeney (1998), Italian Coop Study Group (1998), Henke (1999), Thompson (2000), Henze (2002), Blohmer (2003), Henke (2003), Smith (2003); **duplicates (studies also returned in the update searches):** Casadevall 92004), Rosenzweig (2004); (**b) Systematic reviews:** Grant et al; **primary studies:** Abels (1996), Henry (1994), Patrick (2003), Wagner (2004), Moebus (2013); **(c)** Four studies (Ten Bokkel [1998], Thatcher [1999], Hedenus [2002], Kotasek [2003]) evaluated different ESA doses only the within license doses were included in the PenTAG review; details of the excluded treatment arms documented in Section 0, page 637; **(d)** 'within licence', based on the administration of ESAs at the licensed weight-based start dose; **(e)** Systematic reviews not formally included; used as a reference with which to compare results and identify other citations; **(f)** A list of primary publications and multiple publications is available in Appendix I

Table 10. Study characteristics

Study, year	n	Agent	Control	Malignancy	Treatment	Outcomes	Multiple publications identified
Wilson and colleagues (2004 [HTA]) included studies meeting inclusion criteria for the PenTAG review							
Abels, 1993[54]	413[a]	Epoetin alfa	Placebo	Haem[e]	Chemo: mixed	HaemR, Hct, RBCT, HRQoL[b], AE[b]	Abels, 1996; Case, 1993; Henry 1994, Henry, 1995
Aravantinos, 2003[63]	47	Epoetin alfa	Standard	Solid	Chemo: plat	Hb, HCT, patients' RBCT	NA
Boogaerts, 2003[52]	262	Epoetin beta	Standard	Solid & haem[e]	Chemo: NR	HaemR, Hb, RBCT, HRQoL	Coiffier, 1999 (abstract)
Dammacco, 2001[64]	145	Epoetin alfa	Placebo	Haem[e]	Chemo: mixed[d]	HaemR, Hb, RBCT, HRQoL, AE	NA
Del Mastro, 1999[65]	62	rHuEPO[b]	Standard	Solid (breast)	Chemo: non-plat	Hb, RBCT, HRQoL, AE	NA
Dunphy, 1999[66]	30	rHuEPO[b]	Standard	Solid (head & neck, lung)	Chemo: mixed	Hb, RBCT	NA
Hedenus, 2002[49]	33[e]	Darb alfa	Placebo	Haem[e]	Chemo: NR	HaemR, Hb, RBCT, AE	NA
Hedenus, 2003[16]	349	Darb alfa	Placebo	Haem[e]	Chemo: NR	HaemR, RBCT, AE, HRQoL	Littlewood, 2006
Kotasek, 2003[46]	249	Darb alfa	Placebo	Solid	Chemo: NR	HaemR, Hb, RBCT, HRQoL	NA
Kurz, 1997[67]	35	Epoetin alfa	Placebo	Solid (cervix, ovary, uterus)	Chemo: mixed	HaemR, RBCT, HRQoL, AE	NA
Littlewood, 2001[68]	375	Epoetin alfa	Placebo	Mixed	Chemo: non-plat	HaemR, Hb, RBCT, HRQoL, AE	Aapro, 2004; Bajetta, 2004; Patrick 2003
Osterborg, 2002, 2005[69,70]	349	Epoetin beta	Placebo	Haem[e]	Chemo: non-plat	HaemR, Hb, RBCT, HRQoL, AE	Osterborg, 2005 (long-term follow-up)
Silvestris, 1995[71]	54	Epoetin alfa	Standard	Haem[e]	Chemo: NR	HaemR, Hb, AE	NA
Ten Bokkel, 1998[47]	122	Epoetin beta	Standard	Solid (ovary)	Chemo: plat	Patients' RBCT, AE	NA

Study, year	n	Agent	Control	Malignancy	Treatment	Outcomes	Multiple publications identified
Thatcher, 1999[48]	130	Epoetin alfa	Standard	Solid (SCLC)	Chemo: mixed	Hb, Patients' RBCT, HRQoL, AE	NA
Vansteenkiste, 2002[72]	314	Darb alfa	Placebo	Solid (lung)	Chemo: plat	HaemR, Hb, RBCT, HRQoL, AE, disease progression, survival	Vansteenkiste, 2004
Study characteristics: PenTAG review update 2004 to July 2007							
Grote, 2005[73]	224	Epoetin alfa	Placebo	Solid (SCLC)	Chemo: mixed	Hb, RBCT, TR; survival; AE	NA
Moebus, 2013[62]	643	Epoetin alfa	Standard	Solid (breast)	Chemo: non-plat	Hb, RBCT, HRQoL, survival, AE	NA
Ray-Coquard, 2009[74]	218	Epoetin alfa	Standard	Mixed	Chemo: NR	RBCT, OS, HRQoL, AE	NA
Strauss, 2008[75]	74	Epoetin beta	Standard	Solid (cervix)	Chemo + Radio	Hb RBCT, TR, survival, AE	NA
Tjulandin, 2010[45]	223	Epetin theta Epoetin beta	Placebo	Solid	Chemo: plat	HaemR, Patients' RBCT, HRQoL, AE	NA
Tjulandin, 2011[76]	186	Epoetin theta	Placebo	Mixed	Chemo: non-plat	HaemR, Patients' RBCT, HRQoL, AE	NA
Untch, 2011a, b[77,78]	733	Darb alfa	Standard	Solid (breast)	Chemo: non-plat	Hb, pathological response, disease progression, survival, AE	NA

Key: AE, adverse event; Darb, darbepoetin; HaemR, haematopoietic response; Hb, haemoglobin; HRQoL, health-related quality of life; NR, not reported; OS, overall survival; plat, platinum-based chemotherapy; RBCT, red blood cell transfusion; refs, references; rHuEPO, recombinant human erythropoietin; SCLC, small-cell lung cancer; TR, tumour response
Notes: (a) Study population included patients not receiving chemotherapy (n=124); beyond the scope for the current review; **(b)** Outcomes reported for all participants (i.e. includes patients not receiving chemotherapy); **(c)** Assumed to epoetin alfa or epoetin beta based on date of study and dose administered; **(d)** majority of participants reported to be on non-platinum chemotherapy; **e** Dose-response study other doses of darbepoetin alfa included; **(e)** specifically haematological non-myeloid malignancies (chronic lymphocytic leukaemia; non Hodgkin's lymphoma; Hodgkin's disease and multiple myeloma within these studies)

4.2.2. Study characteristics

4.2.2.1. Study design

ESAs plus standard care vs placebo plus standard care

The 2004 review identified nine RCTs investigating the effectiveness of ESAs plus standard care compared with placebo plus standard care, those reported by **Abels and colleagues (1993)**,[54] **Dammacco and colleagues (2001)**,[64] **Hedenus and colleagues (2002 and 2003)**,[16,49] **Kotasek and colleagues (2003)**,[46] **Kurz and colleagues (1997)**,[67] **Littlewood and colleagues (2001)**,[68] **Osterborg and colleagues (2002 and 2005)**,[69,70] and **Vanseteenkiste and colleagues (2002)**[72]. Three of these evaluated epoetin alfa, one epoetin beta, and four darbepoetin alfa. In one study it was uncertain which brand of erythropoietin was used (although it was assumed to be either epoetin alfa or epoetin beta [based on the study date and dose administered]).

PenTAG searches identified an additional four RCTs. These are: **Grote and colleagues (2005)**,[73] **Strauss and colleagues (2008)**,[75] **Tjulandin and colleagues (2010 and 2011)**.[45,76] One of these evaluated epoetin alfa, two epoetin beta, and two epoetin theta (one was a three-arm study comparing epoetin beta vs epoetin theta vs placebo (**Tjulandin and colleagues, 2010**)). We also identified one paper (**Osterborg and colleagues [2005]**[70]) evaluating long-term survival for epoetin beta compared with placebo from the earlier 2002 RCT (**Osterborg and colleague [2002]**[69]) identified in the 2004 review. We also identified five retrospective analyses based on three primary studies identified in the 2004 review (**Patrick and colleagues, 2003**;[60] **Bajetta and colleagues, 2004**;[79] **Aapro and colleagues, 2004**;[80] **Vansteenkiste and colleagues, 2004**;[81] **Littlewood and colleagues, 2006**).[82]

ESAs plus standard care vs standard care alone

The 2004 review identified seven RCTs investigating the effectiveness of ESAs plus standard care compared with standard care alone, those reported by: **Aravantinos and colleagues (2003)**,[63] **Boogaerts and colleagues (2003)**,[52] **Del Mastro and colleagues (1999)**,[65] **Dunphy and colleagues (1999)**,[66] **Silvestris and colleagues (1995)**,[71] **Ten Bokkel and colleagues (1998)**,[47] and **Thatcher and colleagues (1999)**.[48] Three of these evaluated epoetin alfa, two epoetin beta, and in two studies it was uncertain which brand of erythropoietin was used (although it was assumed to be either epoetin alfa or epoetin beta,based on the study date and dose administered).

PenTAG searches identified an additional three RCTs (reported in four publications). These are: **Moebus and colleagues (2013)**,[62] **Ray Coquard and colleagues (2009)**,[74] **Untch and colleagues (2011a,b)**.[77,78] Two studies reported evaluations of epoetin alfa and one study (two publications) darbepoetin alfa.

Head-to-head

No head-to-head studies were identified in the 2004 review.

PenTAG searches identified one three-arm study comparing epoetin beta and epoetin theta vs placebo (**Tjulandin and colleagues, 2010**).[45] No head-to-head comparison was made.

4.2.2.2. Dose

Dosing strategies varied considerably in the literature in terms of: start dose (fixed or weight-based); trigger haemoglobin level, target haemoglobin level; dose escalation; stopping rules for non-responders; and, duration of use. These aspects will have an impact on the clinical effectiveness. Given the publication of the 2012 Cochrane review (**Tonia and colleagues, 2012**) this review focused on the administration of ESA in accordance with their UK marketing authorisation. Studies were considered eligible for inclusion if they used a licensed starting dose irrespective of how they dealt with other criteria stipulated by the licence. Thus, ESAs administered weekly, for epoetin alfa and epoetin zeta to be administered three-times weekly, for epoetin beta to be administered three to seven times per week; and, for darbepoetin alfa to be administered every three weeks. Fixed (epoetin theta) and weight-based (epoetin alfa, epoetin beta, epoetin zeta, and darbepoetin alfa) dosages were allowed.

The current licensed weight-based, starting dose for epoetin alfa is 450 IU/kg per week (given as either three divided doses or as a once-weekly dose); for epoetin beta the licensed dose is 450 IU/kg per week (given in three to seven divided doses). The maximum licensed dose for both epoetin alfa and beta is 900 IU/kg per week. For epoetin theta the licensed dose is 20,000 IU per week independent of body weight. The maximum licensed dose per week is 60,000 IU per week independent of body weight. For darbepoetin alfa the licensed weight-based, starting dose is 2.25 μg/kg in a once-weekly dose or 6.75 μg/kg once every three weeks. The maximum dose is 4.5 μg/kg per week.

This review focuses only on those studies evaluating the interventions at their licensed starting dose (as detailed in the previous paragraph), irrespective of other aspects of the license (e.g. Hb levels). For darbepoetin alfa, two studies were dose-response studies and therefore evaluated doses under and over the current licence recommendation (**Hedenus and colleagues, 2002**;[49] and **Kotasek and colleagues, 2003**[46]); and, two included studies included a second intervention group evaluating epoetin alfa at a start dose of 300 IU/kg (**Ten Bokkel and colleagues, 1998**;[47] and, **Thatcher and colleagues, 1999**[48]). Only the licensed start doses from these studies were included in the PenTAG review). In addition, one study (**Untch and colleagues, 2011a,b**[77,78]) evaluated darbepoetin alfa at a dose of 4.5 μg/kg once every two weeks this was considered 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 start and target haemoglobin levels, and stopping rules all of which were generally higher than specified in the license. A table summarising the administration of ESAs in relation to their respective licenses within the included studies is given in Appendix C. Two additional definitions of 'within licence' were considered in retrospective sensitivity analyses: (1) licensed start dose plus inclusion Hb ≤11 g/dl plus target Hb ≤13 g/dl; and, (2) licensed start dose plus inclusion Hb ≤11 g/dl.

4.2.2.3. Duration of ESA treatment and duration of study

The majority of the trials gave erythropoietin therapy over the course of the chemotherapy, with many continuing with erythropoietin therapy for four 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 (**Osterborg and colleagues, 2005**[70]).

4.2.2.4. Concomitant treatments

There were several possible concomitant treatments: granulocyte colony-stimulating factor (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 G.

Two studies were identified that gave G-CSF. In one study (**Del Mastro and colleagues, 1997**[65]) 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 (**Ray-Coquard and colleagues, 2009**[74]) stated that G-CSF could be used in primary or secondary prophylaxis as recommended by the American Society of Clinical Oncology (ASCO) and French Federation of Cancer Center 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=16) 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 allowing daily oral iron supplementation if transferrin saturation fell to ≤20% i.v. iron was recommended. In two studies (**Osterborg and colleagues 2002, 2005**;[69,70] and, **Strauss and colleagues, 2008**[75]) enrolled patients with a baseline of <25% and <20% (respectively) participants were given i.v. iron supplementation at a dose of 100 mg per week before the start of study treatment. In cases where patients were contraindicated or the drug was not available oral iron supplementation was administered. In one study (**Kurz and colleagues, 1997**[67]) i.v. 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 (**Untch and colleagues, 2011a,b**[77,78]). Several studies reported that iron supplementation was allowed during the study without specifying details, or that supplementation was given at the investigators' discretion. Nine studies do not report concomitant treatment, and in two studies (**Thatcher and colleagues, 1999**;[48] and **Vansteenkiste and colleagues, 2002**[72]) iron supplementation during the study period was not permitted.

4.2.2.5. Population characteristics

Population characteristics of the included trials are summarised in Table 11 and Table 12; characteristics are described in more detail in Appendix G.

Trials had an age range of 18–92. 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 one patient was male [**Littlewood and colleagues, 2001**][68]). However, in one study (**Dunphy and colleagues, 1999**;[66] 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).

There was a variety of malignancies (see Table 11): five trials had patients with a mix of solid tumours; one of the retrospective analyses identified (**Bajetta and colleagues, 2004**)[79] was a subgroup analysis of a breast cancer cohort enrolled in the study conducted by **Littlewood and colleagues, 2001**;[68] 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; ovary n=1; cervix n=1; lung n=3). There were four studies with a mix of haematological malignancies (specifically haematological non-myeloid malignancies [chronic lymphocytic leukaemia; non Hodgkin's lymphoma; Hodgkin's disease and multiple myeloma within these studies]); of these, one study was reported in two papers; **Osterborg and colleagues (2005)** reported long-term survival data from an earlier study (**Osterborg and colleagues, 2002**).[69,70] One study concentrated on multiple myeloma (MM) (**Silvestris and colleagues, 1995**). Five studies included participants with a mix of solid and haematological malignancies.

Table 11. Malignancies included in the trials

Malignancy	Mixed types	Specific malignancies
Solid tumours	Tjulandin, 2010; Aravantinos, 2003; Kotasek 2003; Dunphy, 1999; Kurz 1997	Moebus, 2013 (breast); Untch, 2011 a,b (breast); Strauss, 2008 (cervix); Grote, 2005 (SCLC); Vansteenkiste, 2002 (lung); Thatcher, 1999 (SCLC); Ten Bokkel, 1998 (ovary); Del Mastro, 1997 (breast)
Haematological[c]	Hedenus, 2003; Osterborg, 2002 & 2005[a]; Hedenus 2002; Dammacco, 2001	Silvestris, 1995 (MM)
Mixed solid & haematological[c] malignancies	Tjulandin, 2011; Ray-Coquard, 2009; Boogaerts, 2003; Littlewood, 2001; Abels, 1993[b]	

Key: ALL, acute lymphoblastic leukaemia; met, metastatic; MM, multiple myeloma; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer
Notes: (a) Follow-up of Osterborg 2002 study; **(b)** Population includes patients receiving plat and non-plat chemotherapy; and, patients receiving no treatment; **(c)** specifically haematological non-myeloid malignancies (chronic lymphocytic leukaemia; non Hodgkin's lymphoma; Hodgkin's disease and multiple myeloma within these studies)

Malignancy treatments consisted of chemotherapy (platinum-based and non-platinum based), and chemotherapy plus radiotherapy. In four studies participants received platinum-based chemotherapy, in six studies participants were on non-platinum chemotherapy, in six studies participants were receiving chemotherapy but the type was unknown, five studies

included participants on mixed chemotherapy treatment. Of the latter group, in two of the studies the majority of patients received platinum-based chemotherapy (proportion not reported); and, in one of the studies the majority of participants received non-platinum based chemotherapy (proportion not reported). One trial involved participants on chemotherapy plus radiotherapy.

Table 12. Malignancy treatments

Malignancy	Trials
Chemo: plat based	Tjulandin, 2010; Vansteenkiste, 2002; Aravantinos, 2003; Ten Bokkel, 1998; Abels, 1993[b]
Chemo: non-plat based	Moebus, 2013; Tjulandin, 2011; Untch, 2011a, b; Osterborg, 2002, 2005;[a] Littlewood, 2001; Del Mastro, 1997; Abels, 1993[b]
Chemo: type unknown	Ray-Coquard, 2009; Boogaerts, 2003; Hedenus, 2003; Kotasek, 2003; Hedenus 2002; Silvestris, 1995
Mixed chemo	Grote, 2005; Dammacco, 2001; Dunphy, 1999; Thatcher, 1999; Kurz, 1997
Chemo + Radio	Strauss, 2008

Key: chemo, chemotherapy; plat, platinum; radio, radiotherapy
Notes: (a) Follow-up of Osterborg 2002 study; **(c)** Population includes participants receiving plat and non-plat chemotherapy; and, patients receiving no treatment but data are reported separately for each group

The majority of included studies specified the required baseline degree of anaemia in the eligibility criteria; in three studies this baseline degree of anaemia was not specified in the eligibility criteria reported. The highest was ≤14.5 g/dl (**Grote and colleagues, 2005**),[73] and the lowest was ≤8 g/dl (**Silvestris and colleagues, 1995**).[71] Despite this, mean/median Hb level at baseline ranged from 9.2 to 14.1 g/dl in the intervention group and from 9.1 to 14.1 g/dl in the control group.

4.2.3. Quality of included studies

Quality assessment criteria are presented in **Error! Reference source not found.** (page 63), and study appraisal is presented in Table 13. All trials were assessed using the same quality assessment tool as the previous HTA (**Wilson and colleagues, 2007)**.[1] However, there is some variation in the method of quality assessment between the previous 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 (Issue 3). Cochrane review authors contacted the trials 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. Secondary analyses of previously published data were not assessed. Similarly, if a trial was reported in multiple publications, only one quality assessment of the trial was conducted. In total, 24 trials were assessed, including eight trials not included in the previous HTA review.

4.2.3.1. Overall assessment

The 23 included RCTs were of variable quality, but all are flawed, some due to reporting issues, but others more substantially. For most of the trials it was difficult to make a general assessment about study quality due to reporting omissions. In fact, 10 of the 23 trials either did not report, or lacked clarity on, at least three of the seven items constituting the Cochrane risk of bias tool. 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 (**Kurz and colleagues, 1997**,[67] **Tjulandin and colleagues, 2011**,[76] **Tjulandin and colleagues 2010**),[45] with each of these satisfactorily addressing five of the seven items of the Cochrane risk of bias tool. However, even the reports of these three studies omitted important information relating to study quality. The study by **Dunphy and colleagues (1999)**[66] has the poorest quality profile, followed by **Boogaerts and colleagues (2003)**,[52] **Ray-Coquard and colleagues (2009)**,[74] and **Silvestris and colleagues (1995)**.[71] Further details of the quality of included studies, according to individual items on the Cochrane risk of bias tool are described as follows.

4.2.3.2. Treatment allocation

Random allocation: The method of random allocation was clearly stated and sufficient in nine trials while 14 trials did not specify the method used.

Concealment of allocation: The method of concealment of allocation was not clearly reported in any of the included trials. Fifteen trials did not report any information on allocation concealment, while eight trials provided some information. A centralised system for randomisation was reported in seven trials, and, authors of one trial stated that only the person administering study medication was unblinded. So it is possible that the allocation sequence was concealed in these eight trials. However, as no specific details on allocation concealment were reported, this remains unclear.

4.2.3.3. Similarity of groups

Baseline characteristics: Only three trials fully reported baseline characteristics including p-values for baseline group comparisons. Authors of 14 trials stated “similarity between groups”; however no statistical information was reported to support this. Another four studies reported some baseline difference for one or more outcomes. Whereas no baseline characteristics were reported for two trials; one of these two studies used a Latin square design, and baseline characteristics are reported for groups randomised by chemotherapy, but not for the erythropoietin randomisation.

4.2.3.4. Implementation of masking

Treatment allocation masked from participants: Participants were blinded to treatment allocation in 12 trials. Ten trials did not blind participants from treatment allocation and one trial did not report any information about blinding participants to treatment allocation.

Treatment allocation masked from clinicians: The 12 trials which blinded participants to treatment allocation also masked treatment allocation from clinicians. Eight trials did not blind clinicians to treatment allocation. Whereas three trials did not report any information about clinicians’ blinding to treatment allocation; these three trials compared erythropoietin groups with standard care.

4.2.3.5. Completeness of trial

Reporting of loss to follow-up, withdrawals and dropouts: loss to follow-up, withdrawals and dropouts were fully reported in nine trials and partially reported in 12 trials. In the 12 trials where this information was partially reported, five trials reported withdrawals and dropouts until the end of trials, but did not provide any data on the follow up period. Two trials did not report any information on loss to follow-up, withdrawals and dropouts.

ITT analysis or less than 10% lost: ITT analyses or less than 10% participants lost were reported in 14 studies for all measured outcomes. ITT analyses or less than 10% participants lost were reported in seven studies for the primary outcome and most of the secondary outcomes. Only two trials did not use ITT or reported 10% and more participants’ loss.

Table 13. Study quality (Cochrane Risk of Bias tool)

Study, year	Random	Concealment allocation	Baseline similarity	Patients blinded	Physicians blinded	Losses	ITTor <10%dropout
Abels, 1993[54]	Unclear[a]	NR	Unclear[b]	Yes	Yes	Partially	Yes
Aravantinos, 2003[63]	Unclear[a]	NR	Unclear[b]	No	No	NR	Yes
Boogaerts, 2003[52]	Unclear[a]	NR	No: prior chemotherapy, FACT-F	No	No	Partially	Yes
Dammacco, 2001[64]	Unclear[a]	Unclear[d]	Unclear[b]	Yes	Yes	Yes	Yes, primary endpoint and HRQoL only
Del Mastro, 1999[65]	Yes	NR	Unclear[b]	No	NR	Partially	Yes, apart from HRQoL (87% and 84% participants were analysed in treatment and control groups respectively).
Dunphy, 1999[66]	Unclear[a]	NR	No: gender	No	No	Yes	No
Grote, 2005[73]	Yes	NR	Unclear[b]	Yes	Yes	Partially[c]	Yes
Hedenus, 2002[49]	Yes	Unclear[d]	No: gender, platelet and neutrophil counts	Yes	Yes	Partially	Yes[g]
Hedenus, 2003[16]	Yes	NR	Unclear	Yes	Yes	Partially[c]	Yes[g]
Kotasek, 2003[46]	Unclear[a]	NR	Yes[e]	Yes	Yes	Partially[c]	Yes[g]
Kurz, 1997[67]	Yes	Unclear[d]	Yes	Yes	Yes	NR	Yes, results report response for all participants; assumed ITT.
Littlewood, 2001[68]	Unclear[a]	NR	Unclear[b]	Yes	Yes	Yes	Yes, apart from HRQoL (80% and 73% participants were analysed in treatment and control groups respectively).
Moebus, 2013[62]	Yes	Unclear[d]	Unclear[b]	NR	NR	Yes	Yes
Osterborg, 2002[69]	Unclear[a]	NR	Unclear[b]	Yes	Yes	Partially[c]	Yes
Ray-Coquard, 2009[74]	Unclear[a]	Unclear[d]	No: HRQoLb	No	No	Partially	Yes, apart from HRQoL (54% and 57% participants were analysed in

Study, year	Random	Concealment allocation	Baseline similarity	Patients blinded	Physicians blinded	Losses	ITTor <10%dropout
							treatment and control groups respectively.
Silvestris, 1995[71]	Yes	NR	NR	No	No	Yes	No
Strauss, 2008[75]	Unclear[a]	Unclear[d]	Yes	No	No	Yes	Yes
Ten Bokkel, 1998[47]	Unclear[a]	NR	Unclear[b]	No	No	Partially	Yes, but two participants were excluded from ITT analyses.
Thatcher, 1999[48]	Unclear[a]	NR	Unclear[b]	No	NR	Yes	Yes, apart from HRQoL (75% and 61% participants were analysed in treatment and control groups respectively).
Tjulandin, 2011[76]	Yes	NR	Unclear[b]	Yes	Yes	Yes	Yes, apart from HRQoL (89.5-97.9% and 85.7-96.7% participants were analysed in treatment and control groups respectively).
Tjulandin, 2010[45]	Yes	Unclear[h]	Unclear[b]	Yes	Yes	Yes	Yes
Untch, 2011a, b[77,78]	Unclear[a]	NR	NR[f]	No	No	Partially[c]	Yes
Vansteenkiste, 2002[72]	Unclear[a]	Unclear[d]	Unclear[b]	Yes	Yes	Partially	Yes[g], apart from HRQoL (81% participants were analysed in both, treatment and control groups).

Key: HRQoL, health-related quality of life; ITT, intention-to-treat; NR not reported.
Notes: **(a)** Randomisation details are not reported; **(b)** P-values for baseline comparisons are not reported, although authors report "similarity between groups"; **(c)** Losses reported for the treatment period only, data for the follow up period are not reported. **(d)** Randomisation was performed using a centralised system, but no details on allocation concealment were not reported; **(e)** 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 higher proportion of patients had breast cancer the mean baseline Hb concentration was higher; **(f)** Authors stated that "baseline characteristics were similar in the treatment arms". It is assumed that this refers to the chemo arms, thus a baseline comparison is not reported for the epo vs no epo arms. **(g)** Less than 10% dropout, but ITT was defined as all randomised participants who received at least 1 dose of study drug; **(h)** 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 so concealment of allocation remains unclear.

4.2.4. Manufacturers' reviews of clinical effectiveness

Two submissions were presented summarising evidence on the effectiveness of darbepoetin alfa (Aranesp®) and epoetin alfa (Binocrit®, Sandoz UK Ltd).

One systematic review was presented summarising evidence of the effectiveness of darbepoetin alfa (Aranesp®). One manufacturer (Sandoz Ltd) submitted an evidence summary; summarising trials from their clinical development programme and post-approval trials (biosimilar epoetin alfa [Binocrit®]). Although neither are part of the PenTAG systematic review it is presented here for convenience and because the results are compared. Each submission is briefly discussed in the sections below.

4.2.4.1. Epoetin alfa (Binocrit®, Sandoz UK Ltd)

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

The evidence summary comprised:

- details of the clinical development programme for Binocrit®
  - **three Phase I studies:** multiple intravenous (i.v.) doses Binocrit® vs epoetin alfa 100 IU.kg thrice weekly (TIW) (**Sorgel and colleagues, 2009a**);[83] multiple subcutaneous (s.c.) doses Binocrit® vs epoetin alfa 100 IU.kg TIW (**Sorgel and colleagues, 2009b**);[84] multiple sc. doses Binocrit® vs epoetin beta 100 IU.kg TIW (**Sorgel and colleagues, 2009c**).[85] All studies were four weeks in duration.
  - **pivotal data:** two Phase III studies (**Weigang-Kohler and colleagues, 2009** and **Haag-Weber and colleagues, 2009**).[86,87] Both of the Phase III studies were identified in the PenTAG review; one was excluded on population (chronic renal failure [**Haag-Weber and colleagues, 2009**]), and the other excluded on comparator (epoetin alfa assessed by class [**Weigang-Kohler and colleagues, 2009**]).
- **post-approval data**: four retrospective studies were identified: three were abstracts (**Desrame and colleagues, 2013** [observational study];[88] **Rodriguez-Garzotto and**

colleagues, 2013 [single-centre audit];[89] **Lorenz and colleagues, 2013** [retrospective, matched-cohort analysis]);[90] And one, **Kerkhofs and colleagues, 2012** [retrospective study]), was fully published. These were not included in the PenTAG review as they were non-randomised studies.

Results from the identified studies were reported narratively. One Phase 3 trial 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®, Janssen–Cilag). The primary endpoint was haemR (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 four weeks). HaemR (as defined) was reported in 62% (n=37/60) (95% CI, 48.2%, 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 as expected for the therapeutic area.

Results from non-RCT and observational data were presented to support the application with regards to the effectiveness of ESAs with regards to HaemR; Hb change; RBCT requirement. 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; e.g. syringes have an innovative safety needle protector; extended shelf-life of 24 months.

4.2.4.2. Darbepoetin alfa (Aranesp®, Amgen Ltd)

Amgen Ltd presented a meta-analysis of pivotal trials as part of their submission. Searches for the systematic review were based on the previous HTA appraisal (**Wilson and colleagues, 2007**[1]), 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 which used a licensed starting dose (500 μg, 6.75 μg/kg Q3W or 2.25 μg/kg QW were considered eligible for inclusion.

A total of nine studies were identified evaluating darbepoetin alfa compared with BSC (placebo, no treatment, usual care) for the treatment of CIA in cancer patients. Four were included in the PenTAG review (**Hedenus and colleagues, 2002**; **Hedenus and colleagues, 2003**; **Kotasek and colleagues, 2003**; and **Vansteenkiste and colleagues, 2002**).[16,46,49,72] Five studies were abstracts (**Suzuki and colleagues, 2008; Katsumata and colleagues, 2009; Nitz and colleagues, 2009; Delarue and colleagues, 2012; Hartmann and colleagues, 2012**),[91-95] and as such were not appraised in the PenTAG systematic review; they are described in Appendix J.

The pooled summary estimates presented for the effect of darbepoetin alfa on chemotherapy induced anaemia in cancer patients are given in Table 14.

Table 14. Summary of results from meta-analyses: Amgen Ltd

	Amgen Ltd[b]
Anaemia-related outcomes	
Hb change	WMD 1.06 95% CI 0.86, 1.26, p<0.00001 $X^2_{(het)}$ 10.79; df 2 (p=0.005); I^2 81% 3 trials, n=1,645
HaemR[a]	RR 3.67 95% CI 2.73, 4.94, p<0.00001 $X^2_{(het)}$ 1.77; df 3 (p=0.62); I^2=0% 4 trials, n=528
RBCT	RR 0.56 95% CI 0.49, 0.64; p<0.00001 $X^2_{(het)}$ 4.43; df 6 (p=0.62); I^2=0% 7 trials, n=1,744
Units transfused	WMD -1.25 95% CI -1.84−-0.66; p<0.00001 Heterogeneity, NA 1 trial, n=298
Malignancy-related outcomes	
Tumour response	RR 0.99 95% CI 0.89, 1.09, p=0.84 Heterogeneity NA 1 trial, n=599
OS	HR 0.88 95% CI 0.72, 1.06, p=0.18 $X^2_{(het)}$ 4.74; df 3 (p=0.19); I^2=37% 4 trials
HRQoL	
FACT-F	3 trials: Results indicated darbe alfa and PBO have a similar effect on HRQoL; 1 study reported a difference in favour of darbe alfa vs PBO but NSD

FACT-An	1 trial: Results indicated darbe alfa and PBO have a similar effect on HRQoL (NSD between studies) 1 trial: 1 study reported a difference in favour of darbe alfa vs PBO but NSD
FACT-G	1 trial: Results indicated darbe alfa and PBO have a similar effect on HRQoL (NSD between studies)
Safety-related outcomes	
No. of AEs[d]	RR 1.03 95% CI 0.94, 1.12, p=0.51 $X^2_{(het)}$ 0.02; df 1 (p=0.90); I^2=0% 1 trial, n=665
No. of SAEs[e]	RR 1.13 95% CI 0.99, 1.29, p=0.08 $X^2_{(het)}$ 0.03; df 1 (p=0.86); I^2=0% 2 trials, n=1,798
Thromboembolic events[f]	RR 2.15 95% CI 1.41, 3.28, p=0.0004 $X^2_{(het)}$ 0.88; df 2 (p=0.64); I^2=0% 3 trials, n=2,112

Key: AEs, adverse events; CI, confidence interval; darbe alfa, darbepoetin alfa; df, degrees of freedom; FACT, Fucntional Assessment of Cancer Therapy (F, Fatigue; G, General; An, Anaemia subscales); haemR, haematological response; Hb, haemoglobin; het, heterogeneity; HRQoL, health-related quality of life; NA, not applicable; NSD, no significant difference; PBO, placebo; RBCT, red blood cell transfusion; RR, relative risk; SAEs, serious adverse events; WMD, weighted mean difference

Notes: (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 two g/dl or more, or as an increase in haematocrit of six percentage points or more with a mean/median baseline of ≤12 g/dl at study entry; **(d)** Incidence of any AE; **(e)** Defined as fatal, life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect or is an 'other significant medical hazard' that does not meet any of the other criteria; **(f)** Includes DVT, pulmonary embolism, myocardial infarction and stroke

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 for haemR and reduction in RBCT requirement. No significant difference was observed for the outcome Hb change. Estimates for the malignancy-related outcomes – tumour response and survival - suggested a benefit with treatment compared with control; however, the data 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, 3.28) were worse than estimated in the PenTAG review.

4.2.5. Ongoing studies

Searches of ClinicalTrials.gov and Controlled Trials yielded a total of 218 trials (see Section 4.1.1.3, page 58). Of these, 94 trials were considered as 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 five trials the current status was recorded as 'unknown'. Ten trials had terminated; of these, three had results available. And, 72 studies were completed. An overview of these trials is provided in Appendix K.

4.2.6. Effectiveness

4.2.6.1. Anaemia-related outcomes

Anaemia-related outcomes: mean Hb change (measured as a change in Hb levels (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 two g/dl or more, or as an increase in haematocrit of six percentage points or more, 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).

4.2.6.1.1. Haemoglobin change

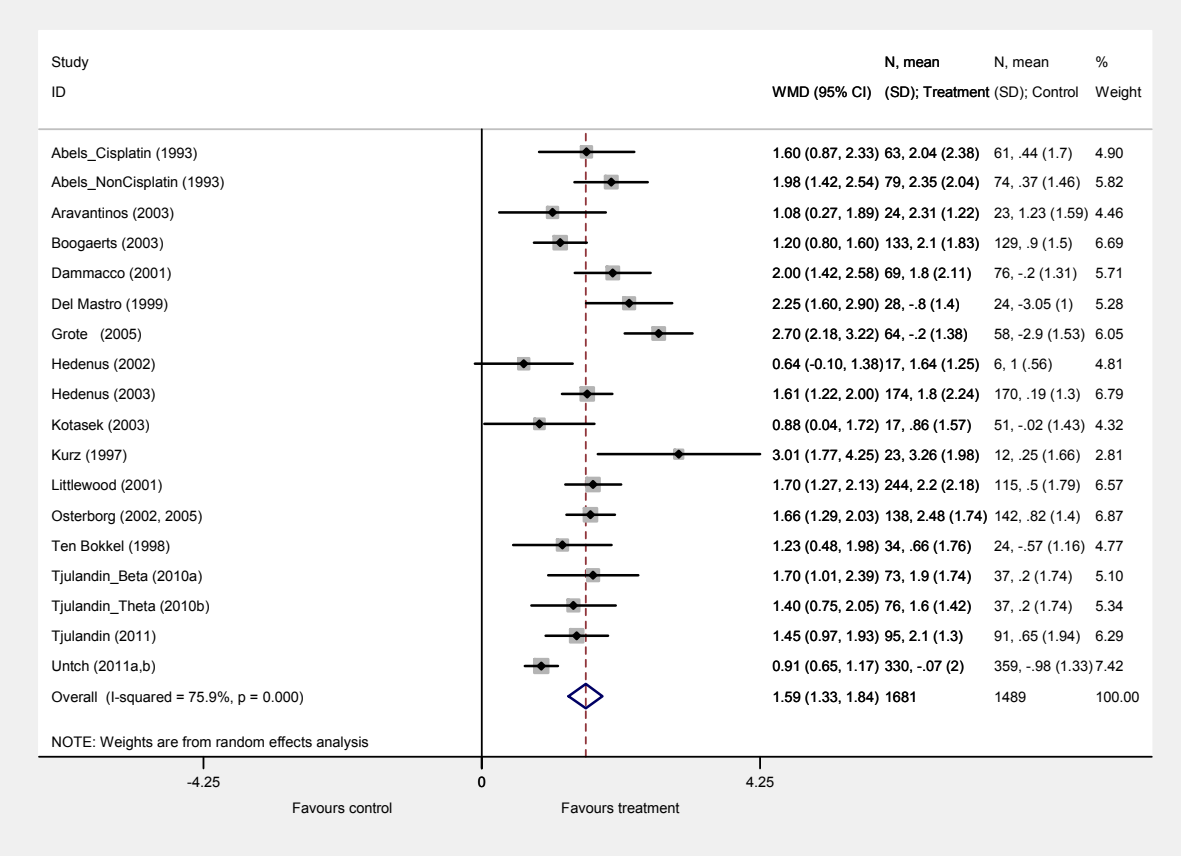
The mean Hb change was measured as a change in Hb levels (g/dl) from baseline until the end of the treatment period. Two studies, **Moebus and colleagues (2013)**[62] (included as an abstract Moebus and colleagues, 2007, in the Cochrane review by **Tonia and colleagues, (2012)**,[10] and **Strauss and colleagues (2008)**,[75] only reported median change in Hb (g/dl) without any measure of variance so they were excluded from the analyses.

Overall, the analysis included 16 trials with 3,170 participants. Four trials were newly identified in the update searches (**Grote and colleagues, 2005; Tjulandin and colleagues, 2010; Tjulandin and colleagues, 2011; Untch and colleagues, 2011a,b;**).[45,73,76-78] As some trials with multiple experimental arms were split into subsets (**Tjulandin and colleagues, 2010**; **Abels and colleagues, 1993**)[45,54] the number of trials displayed is 18.

The random effects meta-analysis demostrated statistically significant difference in Hb change in favour of treatment (WMD 1.59, 95% CI 1.33 to 1.84; Figure 2). Although all

individual studies indicated a beneficial effect of ESA 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; X^2=70.52, df=17, p<0.01). To assess whether publication bias was likely, a funnel plot was constructed (Appendix L). 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 from any effect of publication year (p=0.206); the meta-regression plot is presented in Appendix L. The fixed effects meta-analysis undertaken as a sensitivity analysis also showed statistically significant difference in Hb change in favour of treatment (WMD 1.49, 95% CI 1.37 to 1.60; I^2=75.9%, p<0.001); the forest plot of this analysis is included in Appendix L.

Figure 2. Forest plot: Hb change overall (random effects)



Key: CI: confidence Intervals; ID: identification; N: number of participants; SD; standard deviation; WMD: weighted mean difference
Notes: Random effects meta-analysis (Der-Simonian–Laird)

To identify sources of heterogeneity, subgroup analyses were conducted (Table 15). 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 15. All covariates showing a significant effect (p<0.05) in a univariate analysis were further considered in a model selection.

Table 15. Subgroup analysis: Hb change

	Trials	WMD	CI	I^2	Tau^2
Overall	**18**	**1.59**	**1.33 − 1.84**	**75.9%; p<0.01**	**0.22**
Inclusion Hb					
≤11.0 g/dl	13	1.52	1.30 − 1.75	48.1%; p=0.03	0.08
>11.0 g/dl	5	1.75	1.03 − 2.47	91.4%; p<0.01	0.60
F (between:within)				$F_{(1,16)}$ =0.47; p=0.50	
Baseline Hb					
≤10.0 g/dl	13	1.51	1.29 − 1.72	43.6%; p=0.05	0.06
≤11.0 g/dl	1	1.98	1.42 − 2.54	NA	0
≤12.0 g/dl	1	1.23	0.48 − 1.98	NA	0
≤14.5 g/dl	3	1.94	0.68 − 3.19	95.5%; p<0.01	1.17
F (between:within)				$F_{(3,14)}$ =0.60; p=0.63	
Target Hb					
≤13.0 g/dl	4	1.29	0.90 − 1.67	61.9%; p=0.05	0.10
>13.0 g/dl	11	1.59	1.27 – 1.91	74.0%; p<0.01	0.21
NR	3	2.03	1.42 − 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 − 2.18	85.2%; p<0.01	0.53
Haematological tumours	6	1.63	1.33 − 1.93	49.2%; p=0.08	0.07
Mixed	3	1.44	1.15 − 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 − 1.98	NA	0
Other cancers	17	1.60	1.34 − 1.87	77.2%; p<0.01	0.23
F (between:within)				$F_{(1,16)}$ =0.34; p=0.57	
Chemotherapy treatment					
Platinum-containing	5	1.42	1.10 − 1.75	0%; p=0.77	0
Non-platinum-containing	6	1.62	1.20 − 2.03	82.4%; p<0.01	0.21
NR	4	1.18	0.78 − 1.59	55.0%; p=0.08	0.09

Mixed	3	2.47	1.90−3.04	50.0%; p=0.14	0.12
F (between:within)				$F_{(3,14)}$ =4.61; p=0.02	
Iron supplementation					
Iron in both arms	10	1.60	1.38 − 1.82	40.7%; p=0.09	0.0476
Iron in an intervention arm	1	0.91	0.65 − 1.17	NA	0
NR	7	1.62	1.07 − 2.16	79.2%; p<0.01	0.42
F (between:within)				$F_{(2,15)}$ =1.07; p=0.37	
Study design					
RCT	13	1.70	1.43 − 1.97	64.9%; p<0.01	0.15
ROL	5	1.30	0.86 − 1.73	72.0%; p<0.01	0.16
F (between:within)				$F_{(1,16)}$ =1.97; p=0.18	
Study duration					
12–16 wks	12	1.65	1.40 − 1.89	50.4%; p=0.02	0.09
17–20 wks	2	1.92	0.34 − 3.51	90.8%; p<0.01	1.19
>20 wks	4	1.24	0.86 − 1.62	69.6%; p=0.02	0.10
F (between:within)				$F_{(2,15)}$ =1.67; p=0.22	
ESA					
Erythropoetin	14	1.74	1.49 − 2.00	62.7%; p<0.01	0.14
Darbepoetin	4	1.07	0.61 − 1.52	71.4%; p=0.02	0.14
F (between:within)				$F_{(1,16)}$ =6.32; p=0.02	

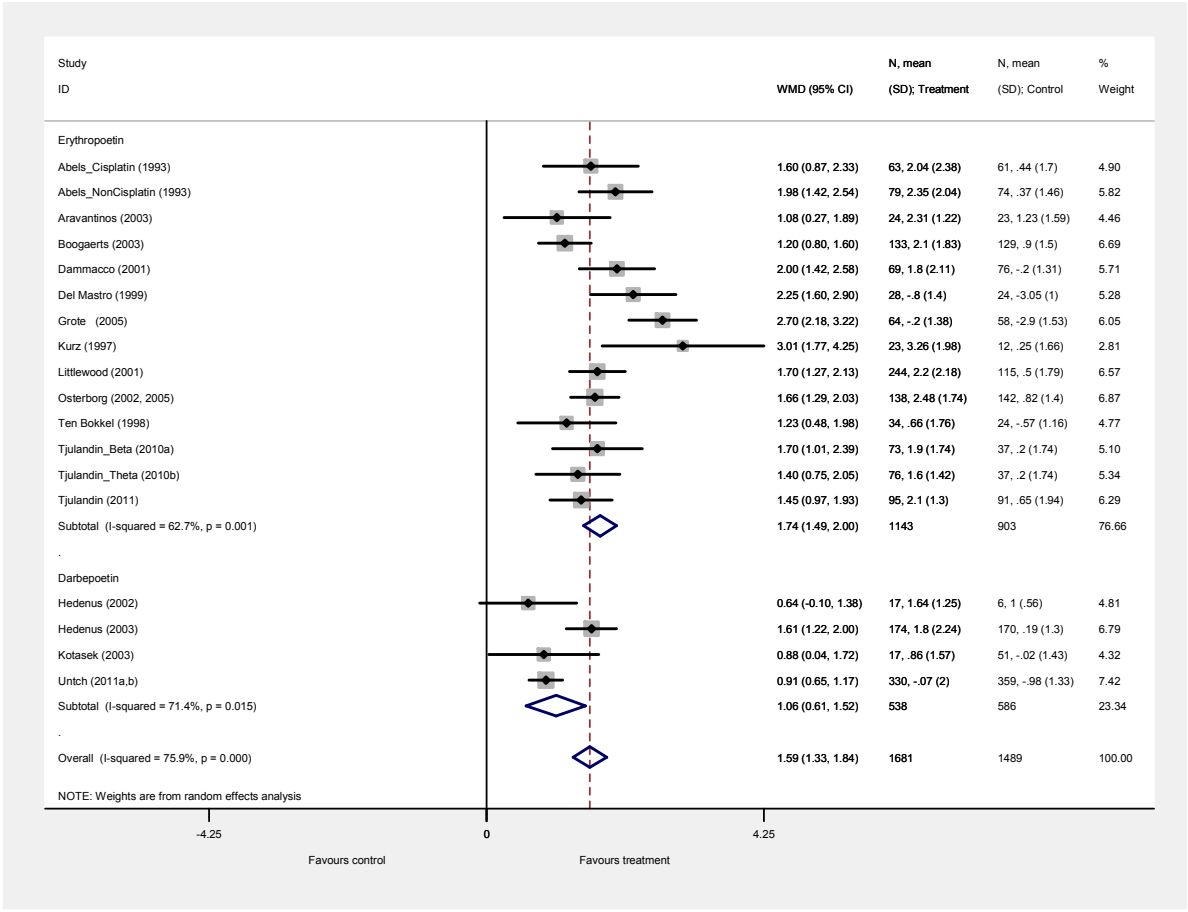
Key: ESA, erythropoiesis stimulating agents; Hb, haemoglobin; NA, not applicable; NR, not reported; RCT, randomised controlled trial; ROL, randomised open label (standard care); wks, weeks.

Univariate analyses identified significant differences between short versus long lasting ESA therapy (p=0.023; Figure 3) and between chemotherapy treatments (p=0.019). Trials with mixed chemotherapy treatments were significantly different from those using platinum based chemotherapy, from those using non-platinum based chemotherapy, and from those not reporting what type of chemotherapy was used (Figure 4). The erythropoietin treatment (WMD 1.74, 95% CI 1.49 to 2.00; I^2=62.7%, p=0.001) seemed to offer greater benefit compared to the longer lasting darbepoetin treatment (WMD 1.06, 95% CI 0.61 to 1.52; I^2=71.4%, p=0.015). Similarly, the mixed chemotherapy treatment (WMD 2.47, 95% CI 1.90 to 3.04; I^2=50.0%, p=0.135) appeared to offer greater benefits compared to the platinum based therapy (WMD 1.42, 95% CI 1.10 to 1.74; I^2=0.0%, p=0.774), the non-platinum based therapy (WMD 1.62, 95% CI 1.20 to 2.03; I^2=82.4%, p<0.001), and compared to studies that did not report what type of chemotherapy treatment was used (WMD 1.18, 95% CI 0.78 to 1.59; I^2=55.0%, p=0.084).

Because of the small number of studies included in the analyses, studies using platinum based chemotherapy, non-platinum based chemotherapy and studies not reporting what chemotherapy was used, were combined into an “other treatments” group to allow further analyses. ESA subgroup (erythropoietin versus darbepoetin) and the new chemotherapy subgroup (mixed therapy versus other treatments) were included in the same model to explore the effects of the individually significant subgroups on Hb change in one analysis. The model including the ESA subgroup and the new chemotherapy subgroup remained significant (p=0.002) and is presented in Appendix J (Table 109). However, as stated in Section 4.1.6 (page 63) these analyses have to be interpreted with caution. The number of studies per subgroup is small (3-6;Table 15). In addition, the heterogeneity between studies within the chemotherapy subgroups does not appear to reduce compared to the overall analysis (Figure 4).

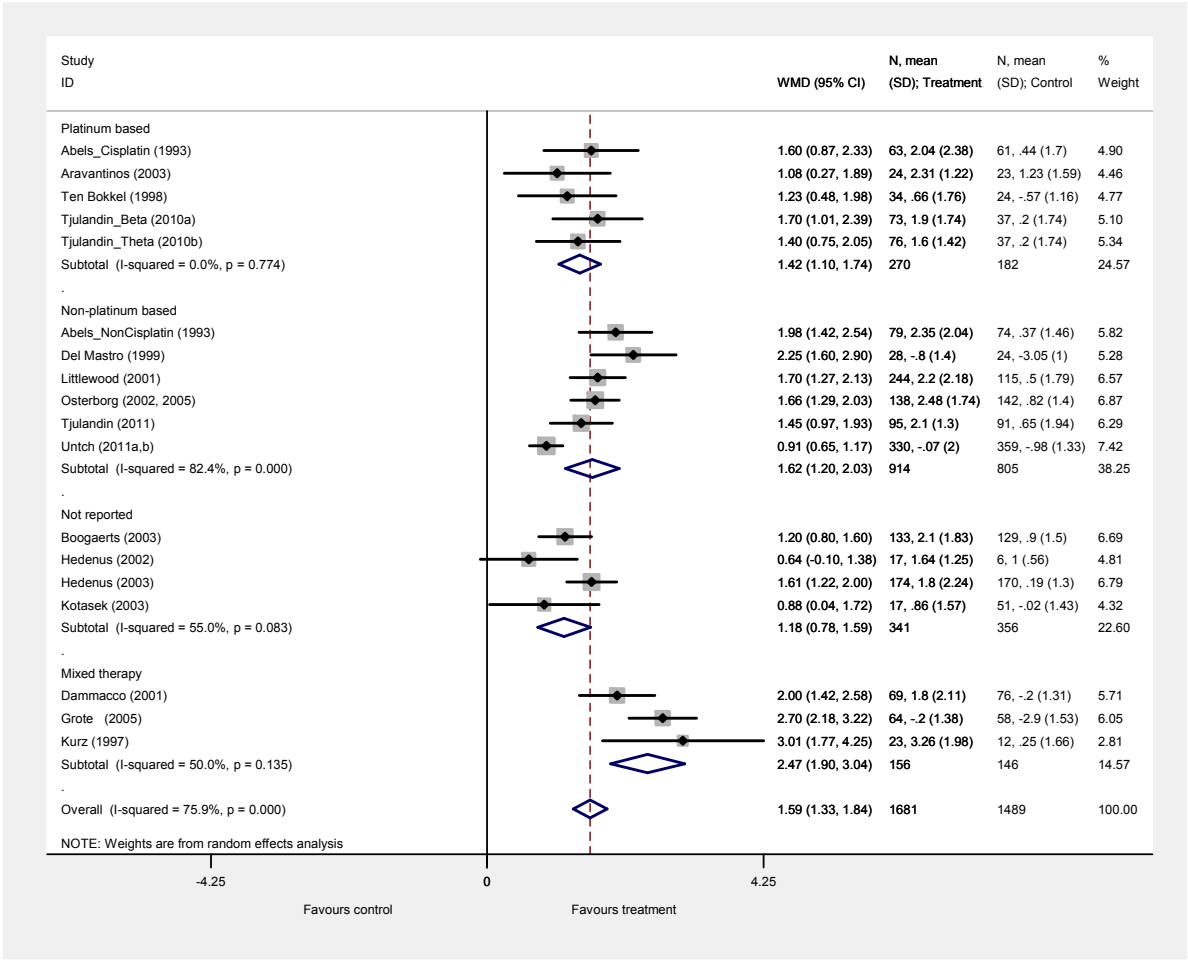
The results were also investigated visually. One small study (**Kurz and colleagues, 1997**;[67] n=35) appeared to differ from most of the other included trials; this study reported the highest mean difference between the ESA and control groups. Excluding this study from the meta-analysis did not change the overall conclusions (data not reported); we therefore included all 18 trials in the analyses of Hb change.

Figure 3. Forest plot: Hb change by treatment drug (random effects)



Key: CI: confidence Intervals; ID: identification; N: number of participants; SD; standard deviation; WMD: weighted mean difference.
Notes: Random effects meta-analysis (Der-Simonian–Laird)

Figure 4. Forest plot: Hb change by chemotherapy treatment (random effects)



Key: CI: confidence Intervals; ID: identification; N: number of participants; SD; standard deviation; WMD: weighted mean difference.
Notes: Random effects meta-analysis (Der-Simonian–Laird)

Summary: Overall, there is a statistically significant effect of ESA on Hb change. Compared to controls, patients receiving ESA achieve a weighted mean Hb level increase of 1.59 g/dl from baseline to the end of treatment (CI 1.33−1.84). We identified statistically significant heterogeneity between the trials (I^2=75.9%, p<0.001), however all individual studies indicated a beneficial effect of ESA with regard to Hb change. Subgroup analyses suggested that Erythropoietin may offer greater benefits compared to Darbepoetin, and that mixed chemotherapy treatment may offer greater benefits compared to other chemotherapy treatments, and to studies that did not report what chemotherapy treatment was used. However, as the number of studies in the subgroups was very small, these analyses may not have a statistical power to detect the effects of chemotherapy treatment and ESA on Hb

change, if such effects exist. Overall, the data confirm results from prior analyses; compared to controls, patients receiving ESA improved their Hb levels.

4.2.6.1.2. Haematological response

This binary outcome was defined as the proportion of participants with an increase in Hb level of two g/dl or more, or as an increase in haematocrit of six percentage points or more, unrelated to transfusion. Eight trials defined haemR as the proportion of participants with an increase in Hb level of two g/dl or more (**Boogaerts and colleagues, 2003**; **Dammaco and colleagues, 2001**; **Hedenus and colleagues, 2003**; **Kotasek and colleagues, 2003**; **Littlewood and colleagues, 2001**; **Osterborg and colleagues, 2002, 2005**; **Tjulandin and colleagues, 2010**; **Tjulandin and colleagues, 2011**).[16,45,46,52,64,68-70,76] One study defined haemR as an increase in haematocrit of six percentage points or more (**Abels and colleagues, 1993**).[54] One trial reported haemR using both definitions (**Hedenus and colleagues, 2002**);[49] for consistency, haemR as defined by an increase in Hb level was used in the analyses. Two studies (**Kurz and colleagues, 1997** and **Vansteenkiste and colleagues, 2002**),[67,72] described haemR as an increase in Hb level of two g/dl or more, or as a Hb level greater than 12 g/dl, and were therefore excluded from the analyses.

Although both the previous HTA review (**Wilson and colleagues, 2007**)[1] and **Tonia and colleagues, 2012**,[10] used the same definition of haematological response, only **Tonia and colleagues, 2012**[10] excluded both **Kurz and colleagues,1997**[67] and **Vansteenkiste and colleagues, 2002**[72] trials from the analyses. The previous HTA review (**Wilson and colleagues, 2007**)[1] argued that most of the data in the **Vansteenkiste and colleagues, 2002**[72] trial 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, 2002**[72] reported a mean baseline Hb of 10.28 g/dl (SD=1.08) and a mean baseline Hb of 9.93 g/dl (SD=1.01) in the treatment and control groups respectively. **Kurz and colleagues, 1997**[67] reported a mean baseline Hb of 9.88 g/dl (SD=0.89) and a mean baseline Hb of 9.85 g/dl (SD=0.60) in the treatment and control groups respectively. For consistency with the previous HTA, sensitivity analyses including the **Vansteenkinste and colleagues, 2002** and **Kurz and colleagues, 1997** trials were performed.[67,72]

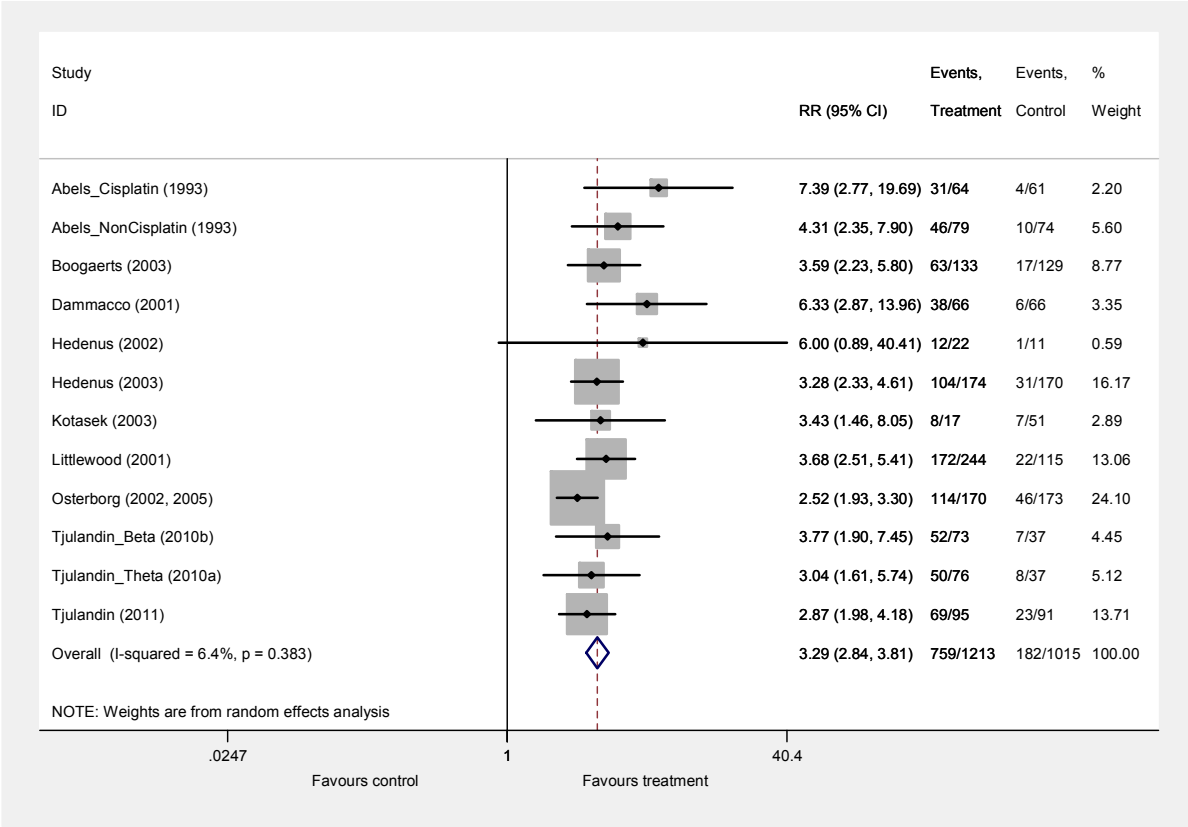
Overall, the analysis of haemR included 10 trials with 2,228 participants. Two trials were newly identified in the update searches (**Tjulandin and colleagues, 2010; Tjulandin and colleagues, 2011**).[45,76] As some trials with multiple experimental arms were split into

subsets (**Tjulandin and colleagues, 2010**; **Abels and colleagues, 1993**)[45,54] the number of trials displayed is 12.

HaemR was observed in 759 out of 1,213 participants in the ESA-treated groups, compared to 182 out of 1,015 in the control groups. The random effects meta-analysis showed statistically significant difference in HaemR in favour of treatment (RR 3.29, 95% CI 2.84 to 3.81; Figure 5). Heterogeneity between the trials was not significant (I^2=6.4%, p=0.383; X^2=11.75, df=11, p=0.383), with all individual studies indicating a beneficial effect of ESAs with regard to HaemR. To test whether publication bias was present in the meta-analysis, funnel plot asymmetry was investigated (Appendix L). 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 L).

The fixed effects meta-analysis undertaken as a sensitivity analysis, also showed statistically significant difference in HaemR 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 included in Appendix L. Similarly including the **Kurz and colleagues,1997**[67] and **Vansteenkiste, 2002**[72] trials in the meta-analyses 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 included in Appendix L). Similar to the Hb change outcome, **Kurz and colleagues, 1997** (N=35), appeared to differ from most of the other included trials. This study reported the highest RR for HaemR with wide CI (RR 14.63, 95% CI 0.94−226.68).[67]

Figure 5. Forest plot: HaemR overall (random effects)



Key: CI: confidence intervals; Events, Treatment: number of events/ number of participants in treatment group; Events, Control: number of events/ number of participants in control group; ID: identification; RR, risk ratio
Notes: Random effects meta-analysis (Der-Simonian–Laird)

Pre-specified subgroup analyses were performed (Table 16). None of the studies with available HaemR 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 16. All covariates showing a significant effect ($p<0.05$) in a univariate analysis were further considered in a model selection.

One study (**Littlewood and colleagues, 2001**)[68] provided separate results for solid and haematological malignancy, and for participants with less or equal to 10.5 g/dl, and more than 10.5 g/dl inclusion Hb levels (but ≤ 12 g/dl). Meta-analyses including the subgroup results were conducted for the haemoglobin subgroups (RR 3.29, 95% CI 2.81 to 3.85; I^2=13.4%, p=0.310; Appendix L), and for the malignancy subgroups (RR 3.28, 95% CI 2.84 to 3.78; I^2=13.4%, p=0.403; Appendix L). The results of these analyses were similar to the

main analysis and were used in the subgroup analyses if appropriate (Table 16). In addition, the **Vansteenkiste and colleagues, 2002**[72] trial provided separate results for participants with baseline Hb levels less than 10.0 g/dl, and for participants with baseline Hb levels equal to or more than 10.0 g/dl (but ≤11 g/dl). Including **Kurz and colleagues, 1997** and **Vansteenkiste and colleagues, 2002** in the meta-analyses with subgroup results had no impact on the overall conclusions.[67]

Table 16.Subgroup analysis: HaemR

	Trials	RR	CI	I^2	Tau^2
Analyses using all main trials:					
Overall	**12**	**3.29**	**2.84 − 3.81**	**6.4%; p=0.383**	**<0.01[a]**
Chemotherapy treatment					
Platinum-containing	3	3.93	2.50 − 6.17	11.9%; p=0.32	0.02
Non-platinum-containing	4	3.05	2.43 − 3.82	29.9%; p=0.23	0.02
NR	4	3.42	2.64 − 4.44	0%; p=0.93	0
Mixed	1	6.33	2.87 − 13.96	NA	0
F (between:within)				$F_{(3,8)}$ =1.38; p=0.32	
Iron supplementation					
Iron in both arms	7	3.05	2.63 − 3.54	0%; p=0.67	0
NR	5	4.94	3.38 − 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 − 3.90	13.8%; p=0.32	0.01
ROL	1	3.59	2.23 − 5.80	NA	0
F (between:within)				$F_{(1,10)}$ =0.12; p=0.73	
Study duration					
12–16 wks	10	3.29	2.73 − 3.97	18.6%; p=0.27	0.02
>20 wks	2	3.65	2.71 − 4.92	0%; p=0.94	0
F (between:within)				$F_{(1,10)}$ =0.23; p=0.64	
ESA					
Erythropoetin	9	3.41	2.80 − 4.16	29.7%; p=0.18	0.03
Darbepoetin	3	3.35	2.45 − 4.58	0%; p=0.83	0
F (between:within)				$F_{(1,10)}$ =0; p=0.96	
	Trials	**RR**	**CI**	**I^2**	**Tau^2**
Analyses using results for Hb inclusion subgroups (Littlewood 2001):					
Overall	**13**	**3.29**	**2.81 − 3.85**	**13.4%; p=0.31**	**0.01**
Inclusion Hb					
≤11.0 g/dl	12	3.20	2.78 − 3.68	2.0%; p=0.43	<0.01
>11.0 g/dl	1	25.52	1.66 − 392.30	NA	0

F (between:within)				$F_{(1,11)}$ =104.53; p<0.01	
Baseline Hb					
≤10.0 g/dl	11	3.15	2.72 − 3.63	1.9%; p=0.42	<0.01
≤11.0 g/dl	1	4.31	2.35 − 7.90	NA	0
≤12.0 g/dl	1	25.52	1.66 − 392.30	NA	0
F (between:within)				$F_{(2,10)}$ =49.43; p<0.01	
Target Hb					
≤13.0 g/dl	3	3.06	2.28 – 4.09	0%; p=0.79	0
>13.0 g/dl	8	3.25	2.63 – 4.01	24.5%; p=0.23	0.02
NR	2	5.00	2.99 – 8.37	0%; p=0.35	0
F (between:within)				$F_{(2,10)}$ =0.31; p=0.74	
	Trials	**RR**	**CI**	**I^2**	**Tau^2**
Analyses using results for malignancy subgroups (Littlewood 2001):					
Overall	**13**	**3.28**	**2.84−3.79**	**4.3%; p=0.40**	**<0.01[b]**
Malignancy type					
Solid tumours	4	3.70	2.63 − 5.18	0%; p=0.844	0
Haematological tumours	7	3.55	2.70 − 4.67	43%; p=0.10	0.05
Mixed	2	3.13	2.33 − 4.20	0%; p=0.47	0
F (between:within)				$F_{(2,10)}$ =0.89; p=0.44	

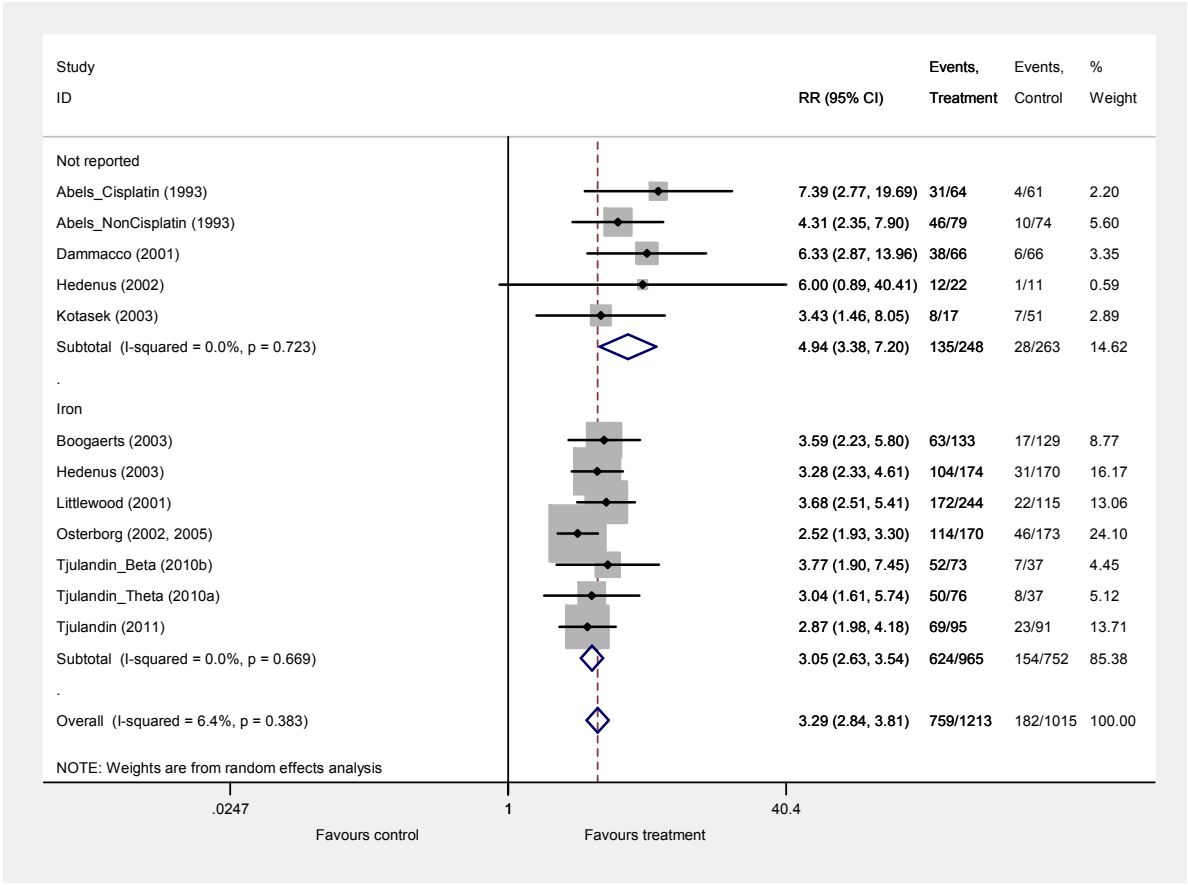
Key: ESA, erythropoiesis stimulating agents; Hb, haemoglobin; NA, not applicable; NR, not reported; RCT, randomised controlled trial; ROL, randomised open label (standard care); wks, weeks.
Notes: (a)Tau^2 =0.0044 **(b)** Tau^2 =0.0031

Univariate analyses identified significant differences between trials using iron supplementation compared to trials not reporting iron supplementation use (p=0.006; Figure 6). Trials, that did not report whether they used iron, appeared to offer greater benefits (RR 4.94, 95% CI 3.38 to 7.20; I^2=0%, p=0.752), compared to 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 L. However, including **Kurz and colleagues (1997)**[67] and **Vansteenkiste and colleagues (2002)**[72] in the meta-regression model with iron supplementation as a covariate provided different results; the difference between trials using iron supplementation compared to trials not reporting iron supplementation was no longer significant (p=0.735). As noted above, the **Kurz and colleagues (1997)**[67] trial appeared to differ from the included studies. A sensitivity analysis including **Vansteenkiste and colleagues (2002)**,[72] but excluding **Kurz and colleagues (1997)**[67] trials, again suggested that trials not reporting iron supplementation offer greater benefits (p=0.037). The studies not reporting whether they used iron tended to be smaller (Figure 6).[67] Univariate analyses using the Hb subgroups results identified significant differences based on baseline and inclusion Hb levels (Table 16). However, these results seemed to be driven mainly by

Littlewood and colleagues (2001)[68] study (Hb subgroup <12; R 25.52, 95% CI 1.66 to 392.3; I^2=NA; Figure 7) for both, the baseline and inclusion Hb levels. Because of collinearity we did not combine the baseline and inclusion Hb levels subgroups in the same model. A model using the Hb baseline subgroup as a covariate suggests that participants with 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), compared to trials with Hb baseline values <11 g/dl (RR 3.76, 95% CI 2.62 to 5.39; I2=0%, p=0.583), and compared to trials with Hb baseline values <10 g/dl (RR 3.10, 95% CI 2.64 to 3.64; I^2=19.7%, p=0.244; Figure 7). The meta-regression with baseline Hb subgroup as a covariate is presented in Appendix L. Including the **Kurz and colleagues (1997)**[67] and **Vansteenkiste and colleagues (2002)**[72] trials 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 <12 g/dl.

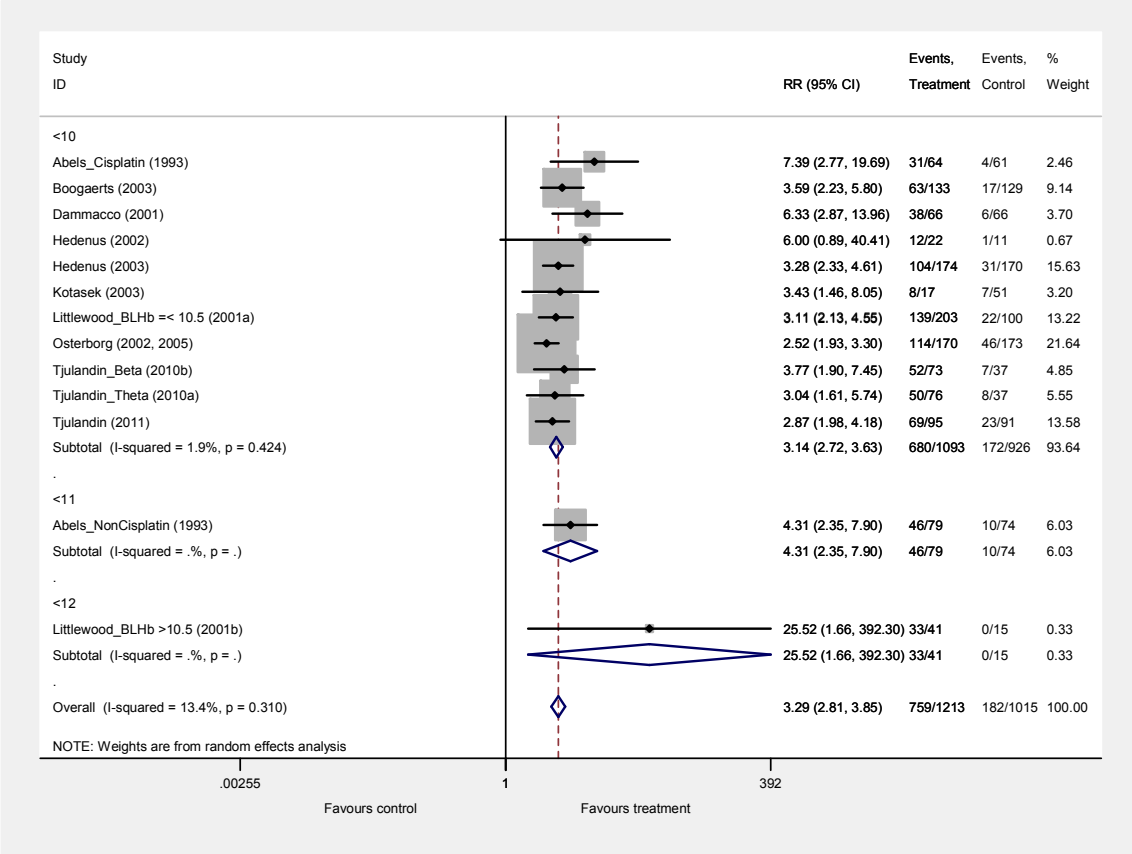
Due to the small number of studies in the meta-analysis, these meta-regressions and subgroups analyses have to be interpreted with caution (Section 4.1.6, page 63), the Cohrane handbook recommends at least 10 studies per subgroup.[50] In addition, sensitivity analyses (e.g. including data from **Kurz and colleagues (1997)**[67] and **Vansteenkiste and colleagues (2002)**[72]) suggest differences on the impact of covariates.

Figure 6. Forest plot: HaemR by iron supplementation (random effects)



Key: CI: confidence intervals; Events, Treatment: number of events/ number of participants in treatment group; Events, Control: number of events/ number of participants in control group; ID: identification; RR, risk ratio
Notes: Random effects meta-analysis (Der-Simonian–Laird)

Figure 7. Forest plot: HaemR using Hb subgroups by Hb baseline (random effects)



Key: CI: confidence intervals; Events, Treatment: number of events/ number of participants in treatment group; Events, Control: number of events/ number of participants in control group; ID: identification; RR, risk ratio
Notes: Random effects meta-analysis (Der-Simonian–Laird)

Summary: Analyses suggests that ESA treatment in CIA is effective in producing a haemR as defined as an increase in Hb level of 2 g/dL or more, or increase in haematocrit of six percentage points or more. Sixty-three per cent (759/1,213) of participants who received ESA treatment had a haemR, in contrast to 18% (182/1,015) 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 subgroups analyses were non-conclusive suggesting that analyses may not have a statistical power to detect effects of subgroups on haemR, if such an effect did exist. Overall the results support previous analyses.

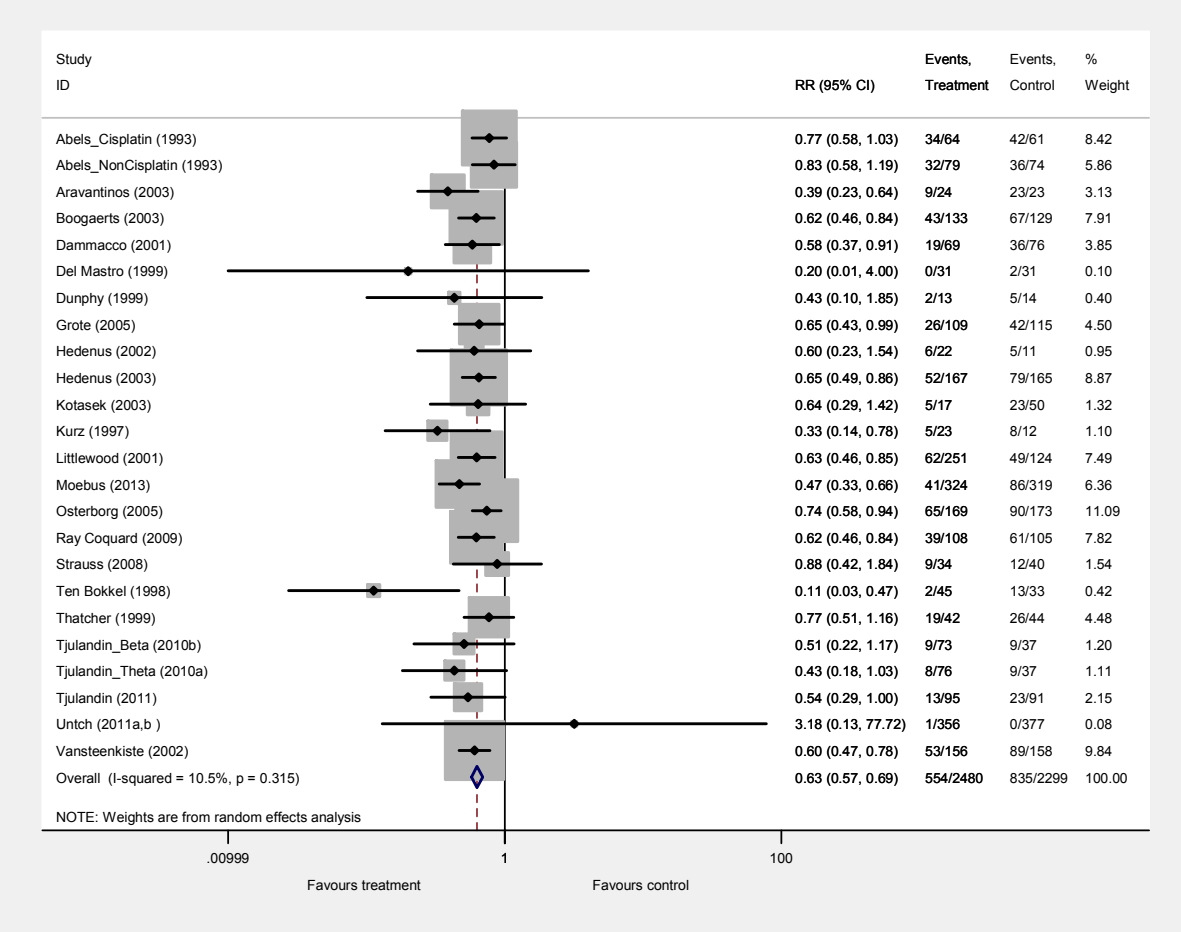
4.2.6.1.3. RBCT requirement

This binary outcome was defined as the proportion of participants requiring blood transfusion. Overall, the analysis of RBCT requirement included 22 studies with 4,779

participants. Seven studies were newly identified in the update searches (**Grote and colleagues, 2005; Strauss and colleagues, 2008; Ray-Coquard and colleagues, 2009; Tjulandin and colleagues, 2010; Tjulandin and colleagues, 2011; Untch and colleagues, 2011a,b; Moebus and colleagues, 2013**).[45,62,73-78] As some trials with multiple experimental arms were split into subsets (**Abels and colleagues, 1993**; **Tjulandin and colleagues, 2010**)[45,54] the number of studies displayed is 24.

RBCT was required by 554 of 2,480 participants treated with ESAs compared to 835 of 2,299 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, 0.69; Figure 8). The heterogeneity between the trials was not significant (I^2=10.5%, p=0.315; X^2=25.71, df =23, p=0.315). All but one individual study **(Untch and colleagues, 2011a,b)**[77,78] 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 (Appendix L). 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=0.207; see meta-regression plots Appendix L).

Figure 8. Forest plot: RBCT (random effects)



Key: CI, confidence interval; events treatment, control, number of events/participants in treatment/control arms ID, identification; RR, risk ratio
Notes: (a) Der-Simonian Laird pooled RR; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Tjulandin and colleagues, 2010a, b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

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

Pre-specified subgroup analyses were performed (Table 17). 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 17. All covariates showing a significant effect ($p<0.05$) in a univariate analysis were further considered in model selection.

One study (**Littlewood and colleagues, 2001**)[68] provided separate results for solid and haematological malignancy, and for participants with inclusion Hb levels ≤10.5 g/dl and >10.5 g/dl (but ≤12 g/dl). In addition, **Vansteenkiste and colleagues (2002)**[72] provided separate results for participants with baseline Hb levels <10.0 g/dl, and ≥10.0 g/dl (but ≤11 g/dl). Meta-analyses including these subgroup results were conducted for Hb subgroups (RR 0.61, 95% CI 0.55, 0.68; I^2= 22.4%, p=0.015), and for the malignancy subgroups (RR 0.62, 95% CI 0.56, 0.68; I^2=15.8%, p=0.239; see Appendix L). The results of these analyses were similar to the main analysis and were used in the subgroup analyses if appropriate (Table 17).

Table 17. RBCT: Subgroup analyses

	Trials	RR	CI	I^2	Tau^2
Analyses using all main trials:					
Overall	**24**	**0.63**	**0.57 − 0.69**	**10.5%; p=0.32**	**0.01**
Chemotherapy treatment					
Platinum-containing	6	0.52	0.37 − 0.72	60.0%; p=0.03	0.08
Non-platinum-containing	7	0.65	0.53 − 0.79	31.1%; p=0.19	0.02
NR	5	0.63	0.54 − 0.74	0%; p=1	0
Mixed	5	0.63	0.50 − 0.79	0%; p=0.48	0
Chemo+radio	1	0.88	0.42 − 1.84	NA	0
F (between:within)				$F_{(4,19)}$ 0.16; p=0.96	
Iron supplementation					
Iron in both arms	14	0.61	0.54 − 0.68	0%; p=0.460	0
Iron in an intervention arm	1	3.18	0.13 − 77.7	NA	0
Iron not used	1	0.77	0.50 − 1.16	NA	0
NR	8	0.66	0.55 −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 − 0.73	0%; p=0.78	0
ROL	10	0.56	0.45 − 0.71	37.7%; p=0.11	0.04
F (between:within)				$F_{(1,22)}$ 0.61; p=0.44	
Study duration					
6–9 wks	2	0.76	0.40 − 1.47	0%; p=0.39	0
12–16 wks	14	0.66	0.60 − 0.74	0%; p=0.73	0
17–20 wks	3	0.50	0.38 − 0.66	26.5%; p=0.26	0.02
>20 wks	5	0.62	0.45 − 0.85	48.0%; p= 0.10	0.05
F (between:within)				$F_{(3, 20)}$ 0.57; p=0.64	

	Trials	RR	CI	I^2	Tau^2
Analyses using all main trials:					
ESA					
Erythropoetin	19	0.62	0.55 −0.70	27.1%; p=0.13	0.02
Darbepoetin	5	0.63	0.52 −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 Littlewood and colleagues, 2001 and Vansteenkiste and colleagues, 2002					
Overall	**26**	**0.61**	**0.55−0.68**	**22.4%; p=0.15**	**0.02**
Inclusion HB					
≤11.0 g/dl	16	0.64	0.57 − 0.71	7.3%; p=0.37	<0.01
>11.0 g/dl	10	0.56	0.44 − 0.72	39.1%; p=0.10	0.05
F (between:within)				$F_{(1.24)}$ 0.72; p=0.40	
Baseline Hb					
≤10.0 g/dl	15	0.64	0.58 − 0.71	0%; p=0.69	0
≤11.0 g/dl	2	0.60	0.31 − 1.18	81.4%; p=0.02	0.19
≤12.0 g/dl	3	0.38	0.14 − 1.00	74.1%; p=0.02	0.52
≤14.5 g/dl	5	0.69	0.52 − 0.92	0%; p=0.69	0
NR	1	0.47	0.34 − 0.66	NA	NA
F (between:within)				$F_{(1.24)}$ 0.28; p=0.60	
Target HB					
≤13.0 g/dl	4	0.52	0.34 − 0.80	48.4%; p=0.14	0.04
>13.0 g/dl	19	0.60	0.53 − 0.67	0%; p=0.70	0
NR	3	0.71	0.51 – 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 Littlewood and colleagues, 2001					
Overall	**25**	**0.62**	**0.56−0.68**	**15.8%; p=0.24**	**0.01**
Malignancy type					
Solid tumours	15	0.56	0.48 − 0.66	17.2%; p=0.26	0.01
Haematological tumours	7	0.68	0.59 − 0.79	15.3%; p=0.31	0.02
Mixed	3	0.61	0.50 − 0.75	0%; p=0.92	0
F (between:within)				$F_{(2, 22)}$ 0.70; p=0.51	

Key: CI, confidence interval; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; NA, not applicable; NR, not reported; RCT, randomised controlled trial; ROL, randomised open label (standard care); wks, weeks.

Univariate analyses did not identify any significant differences based on the pre-defined subgroups (Table 17).

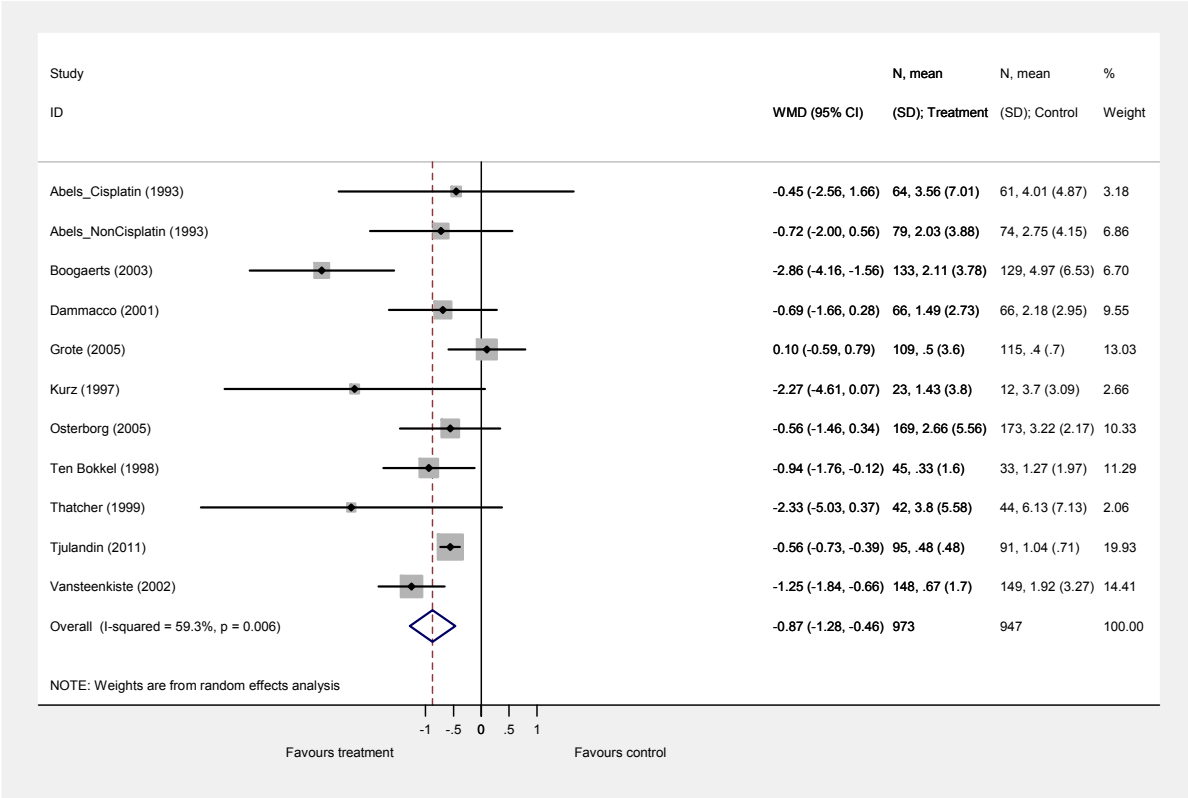
Summary: The RR to receive RBCT was statistically significantly reduced in the study groups receiving ESAs by 37% (RR 0.63, 95% CI 0.57, 0.69). The heterogeneity between the studies was non significant (I^2=10.5%, P=0.315). Overall, the data confirm results from prior analyses that ESAs reduce the RR to receive RBCT in patients with cancer-treatment induced anaemia.

4.2.6.1.4. RBC units transfused

Overall, 10 studies evaluating a total of 1,920 participants are included. As one study (**Abels and colleagues, 1993**)[54] was split into subsets the number of studies displayed is 11. Two studies were newly identified (**Grote and colleagues, 2005** and **Tjulandin and colleagues, 2011**);[73,76] neither were included in the Cochrane review (**Tonia and colleagues, 2012**[10])for the analysis of this outcome. All except one study (**Tjulandin and colleagues, 2011**[76]) reported mean units transfused per average participant (i.e. regardless of whether participants had received RBCT). For **Tjulandin and colleagues (2011)** this was calculated from the data presented in the published paper.[76]

The overall mean difference showed a statistically significant benefit for participants receiving ESAs (WMD -0.87, 95% CI -1.28, -0.46; Figure 9); 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 to controls. A funnel plot analysis did not suggest statistically significant asymmetry (p=0.137; see Appendix L).

Figure 9. Forest plot: RBCT mean RBC units transfused (random effects)



Key: CI, confidence interval; ID, identification; N, number of events/participants in treatment/control arms; WMD, weighted mean difference
Notes: (a) Random effects (Der-Simonian Laird pooled RR); **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy; **(c)** Mean units transfused per average participant (i.e. regardless of whether participants had received RBCT)

One study (**Vansteenkiste and colleagues, 2002**)[72] provided separate results for participants with baseline Hb levels <10.0 g/dl, and ≥10.0 g/dl (but≤ 11 g/dl). Meta-analysis including these subgroup results were conducted (WMD -0.87, 95% CI -1.24, -0.50; see Appendix L). 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, -0.48); the forest plot of this analysis is included in (Appendix L).

To identify sources of heterogeneity, subgroup analyses were conducted (Table 18). 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 18. All covariates showing a significant effect (p<0.05) in a univariate analysis were further considered in a model selection.

Table 18. RBC units: Subgroup analyses

	Trials	WMD	CI	I^2	Tau^2
Overall	**11**	**-0.87**	**-1.28 − -0.46**	**59.3%; p=0.02**	**0.21**
Chemotherapy treatment					
Platinum-containing	3	-1.11	-1.58 − -0.64	0%; p=0.69	0
Non-platinum-containing	3	-0.56	-0.73 − -0.40	0%; p=0.97	0
NR	1	-2.86	-4.16 − -1.56	NA	0
Mixed	4	-0.76	-1.77 − 0.25	55.7%; p=0.08	0.52
F (between:within)				$F_{(3,7)}$ 5.22; p=0.03	
Iron supplementation					
Iron in both arms	4	-1.30	-2.31 − -0.29	78.3%; p=<0.01	0.73
Iron not used	1	-2.30	-5.03 − -0.37	NA	0
NR	6	-0.70	-1.19 − -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 − -0.30	35.4%; p=0.15	0.07
ROL	3	-1.91	-3.37 − -0.44	68.6%; p=0.04	1.10
F (between:within)				$F_{(1,9)}$ 4.25; p=0.07	
Study duration					
12–16 wks	7	-0.70	-0.96 − -0.44	11.7%; p=0.34	0.02
17–20 wks	1	0.10	-0.59 − 0.79	NA	0
>20 wks	3	-1.91	-3.37 − -0.44	68.6%; p= 0.04	1.08
F (between:within)				$F_{(2,8)}$ 3.72; p=0.07	
ESA					
Erythropoetin	10	-0.89	-1.43 − -0.35	53.8%; p=0.02	0.36
Darbepoetin	1	-1.25	-1.84 − -0.66	NA	0
F (between:within)				$F_{(1,9)}$ 0.27; p=0.61	
Malignancy type					
Solid tumours	5	-0.95	-1.73− -0.17	65.7%; p=0.02	0.44
Haematological tumours	4	-0.63	-1.19 − -0.06	0%; p=0.99	0
Mixed	2	-1.62	-3.86 − -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− -0.12	NA	0
Other cancers	10	-0.88	-1.34 − -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 Vansteenkiste and colleagues, 2002					

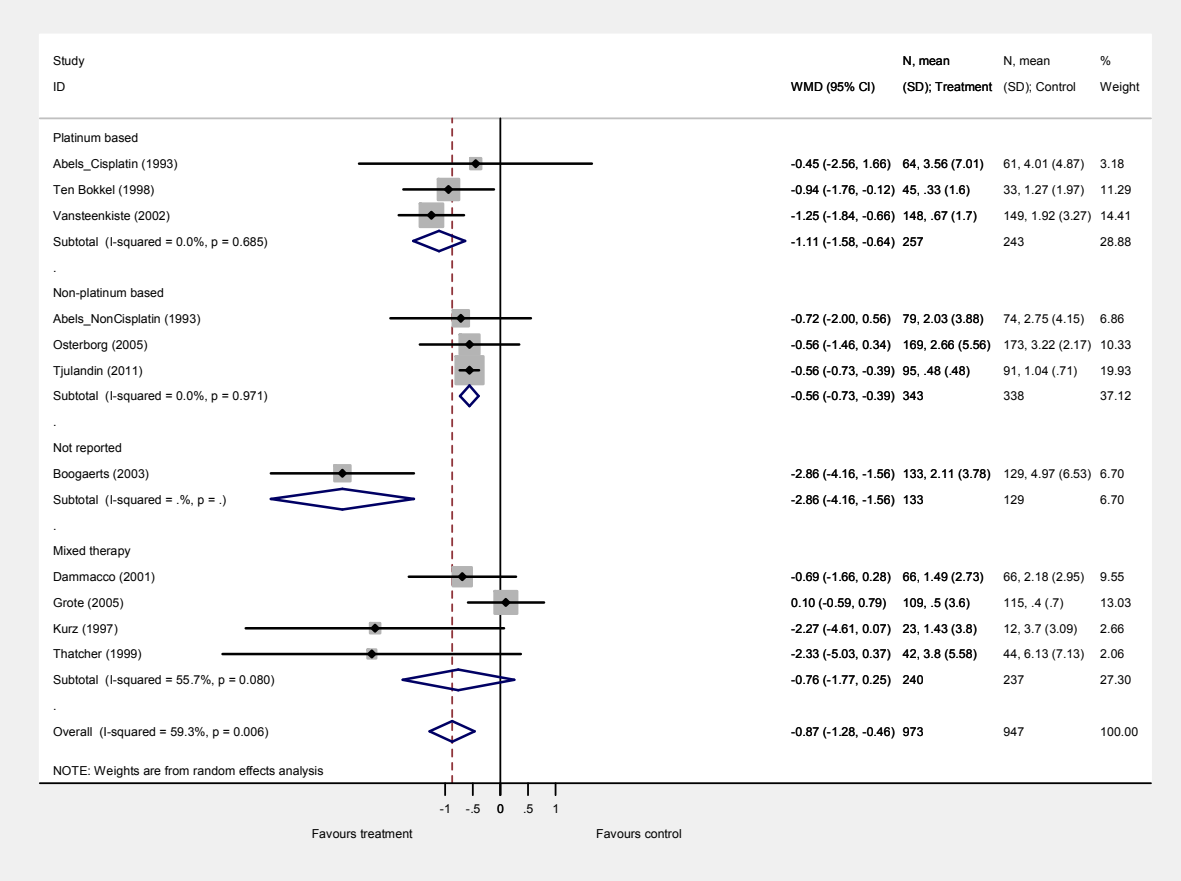
	Trials	WMD	CI	I^2	Tau^2
Overall	**12**	**-0.87**	**-1.24 − -0.50**	**55.6%; p=0.01**	**0.17**
Inclusion Hb					
≤11.0 g/dl	9	-0.99	-1.41 − -0.56	56.2%; p=0.02	0.18
>11.0 g/dl	3	-0.63	-1.67 – 0.41	64.7%; p=0.06	0.49
F (between:within)				$F_{(1,10)}$ 0.76; p=0.41	
Baseline Hb					
≤10.0 g/dl	7	-1.13	-1.76 − -0.49	65.3%; p=0.01	0.39
≤11.0 g/dl	2	-0.88	-1.35 − -0.40	0%; p=0.80	0
≤12.0 g/dl	1	-0.94	-1.76 − -0.12	NA	0
≤14.5 g/dl	2	-0.75	-3.02 − -1.52	65.8%; p=0.09	1.94
F (between:within)				$F_{(3,8)}$ 0.36; p=0.79	
Target Hb					
≤13.0 g/dl	1	-0.56	-0.74 − -0.39	NA	0
>13.0 g/dl	8	-1.01	-1.57 − -0.45	65.7%; p<0.01	0.39
NR	3	-0.94	-1.93 − -0.05	0%; p=0.46	0
F (between:within)				$F_{(2,9)}$ 0.20; p=0.82	

Key: CI, confidence interval; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; NA, not applicable; NR, not reported; RCT, randomised controlled trial; ROL, randomised open label (standard care); wks, weeks.

Univariate analyses identified significant differences in the chemotherapy treatments subgroup (p=0.033). A study not reporting what chemotherapy was used was significantly different from trials with mixed chemotherapy treatments, studies using platinum and studies with non-platinum based chemotherapy (Figure 10). The study that did not report what type of chemotherapy treatment was used (WMD -2.86, 95% CI -4.16 to -1.56; I^2=NA) appeared to offer greater benefits compared to the platinum based therapy (WMD -1.11, 95% CI -1.58 to 0.64; I^2=0%, p=0.685), the non-platinum based therapy (WMD -0.56, 95% CI -0.73 to -0.40; I^2=0%, p=0.971) and mixed chemotherapy treatment (WMD -0.76, 95% CI -1.77 to 0.25; I^2=55.7%, p=0.080).

As stated in Section 4.1.6 (page 63) these analyses have to be interpreted with caution. There is only one study in the subgroup not reporting what chemotherapy was used; in addition the number of studies per subgroup is small (1-4; Figure 10). Thus the analyses may not have statistical power to detect the effects of chemotherapy treatment and ESA on RBC units transfused, if such effects exist.

Figure 10. Forest plot: RBC units transfused by chemotherapy treatment (random effects)



Key: CI, confidence interval; ID, identification; N, number of events/participants in treatment/control arms; WMD, weighted mean difference

Summary: Overall, there is a statistically significant effect of ESA on RBC units transfused. The weighted mean difference in RBC units was -0.87 (95% CI -1.28− -0.46), suggesting that fewer units per participant were used in the treatment arm compared to controls. 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 ESA with regard to RBC units transfused. Overall, the data confirm results from prior analyses, there is only a slight difference between the number of RBC units that intervention and control participants receive.

4.2.6.1.5. Anaemia-related outcomes: overall summary

Table 19. Anaemia-related outcomes results comparison: Wilson, 2007 vs Tonia, 2012 vs PenTAG 2013[1,10]

	Wilson, 2007[b]	Tonia, 2012[b]	PenTAG, 2013[b]	PenTAG, 2013[c]
Anaemia-related outcomes				
Hb change[a]	WMD 1.63 95% CI 1.46−1.80 $X^2_{(het)}$ 23.74; df 19 (p=0.21) 10 trials, n=1,620	WMD 1.57 95% CI 1.51−1.62 $X^2_{(het)}$; 564.37; df 74 (p<0.001) 75 trials, n=11,609	WMD 1.49 95% CI 1.37−1.60 $X^2_{(het)}$70.52; df 17 (p<0.001) 18 trials, n=3,170	WMD 1.59 95% CI 1.33−1.84 $X^2_{(het)}$70.52; df 17 (p<0.001) 18 trials, n=3,170
HaemR	RR 3.40 95% CI 3.01−3.83 $X^2_{(het)}$ 23.60; df 32 (p=0.86) 21 trials, n=3,740	RR 3.39 95% CI 3.10−3.71 $X^2_{(het)}$; 95.56; df 45 (p<0.001) 46 trials, n=6,413	RR 3.41 95% CI 2.96−3.92 $X^2_{(het)}$ 11.75; df 11 (p=0.383) 12 trials, n=2,228	RR 3.29 95% CI 2.84−3.81 $X^2_{(het)}$ 11.75; df 11 (p=0.383) 12 trials, n=2,228
RBCT	RR 0.63 95% CI 0.58−0.67 $X^2_{(het)}$ 94.75; df 48 (p=0.001) 35 trials, n=5,564	RR 0.65 95% CI 0.62−0.68 $X^2_{(het)}$ 217.08; df 87 (p<0.001) 88 trials, n=16,093	RR 0.62 95% CI 0.58−0.67 $X^2_{(het)}$ 25.71; df 23 (p=0.315) 24 trials, n=4,799	RR 0.63 95% CI 0.57−0.69 $X^2_{(het)}$ 25.71; df 23 (p=0.315) 22 trials, n=4,799
Units transfused	WMD -1.05 95% CI -1.32−-0.78 $X^2_{(het)}$ 8.96; df 16 (p=0.91) 14 trials, n=2,353	WMD -0.98 95% CI -1.17−-0.78 $X^2_{(het)}$ 34.52; df 24 (p=0.080) 25 trials, n=4,715	WMD -0.64 95% CI -0.79−-0.48 $X^2_{(het)}$ 24.55; df 10 (p=0.006) 11 trials, n=1,920	WMD -0.87 95% CI -1.28−-0.46 $X^2_{(het)}$ 24.55; df 10 (p=0.006) 11 trials, n=1,920

Key: CI, confidence interval; df, degrees of freedom; haemR, haematological response; het, heterogeneity; RBCT, red blood cell transfusion; RR, relative risk; WMD, weighted mean difference
Notes: (a) change from baseline to end of study; **(b)** fixed effects (Mantel-Haenzel); **(c)** random effects (Der-Simonian Laird);), haematological response was defined as the proportion of participants with an increase in Hb level of two g/dl or more, or as an increase in haematocrit of six percentage points or more; **(d)** the number of trials includes multiple experimental arms for some studies.

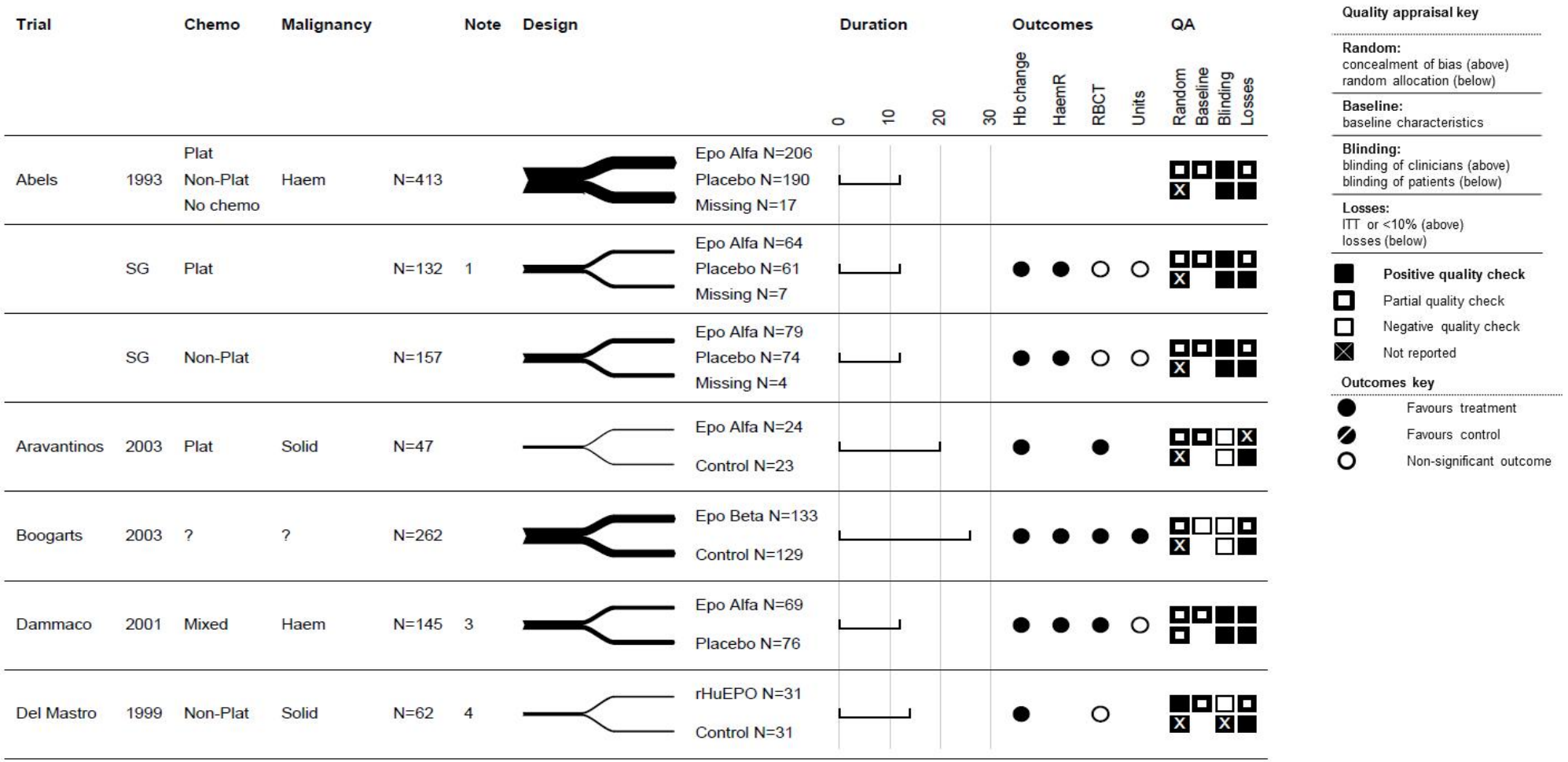
Hb change was reported in 16 studies; all the studies indicated a beneficial effect of ESA with regard to Hb change and varied only in magnitude. The overall EMD Hb increase was 1.59 g/dl. Hb change was not restricted to patients who were transfusion-free, therefore the results may have been confounded by transfusion in some of the patients. HaemR was defined as the proportion of participants with an increase in Hb level of two g/dl or more, or as an increase in haematocrit of six percentage points or more, unrelated to transfusion. Ten studies reported this outcome. This 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. Sixty-three per cent (759/1,213) of participants who received ESAs had a haemR, compared to 18% (182/1,015) of control patients.

The number of patients receiving RBCTs was the third outcome assessed to investigate the effects of ESAs on cancer-treatment induced anaemia (including data from 22 trials). 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 in comparison to 33% in the control groups. The number of transfusions per patient was also investigated. Only 10 studies reported this outcome, and many of these data were received by the Cochrane review through further questions to the trial authors. There was little difference between ESA and control groups regarding the amount of blood transfused.

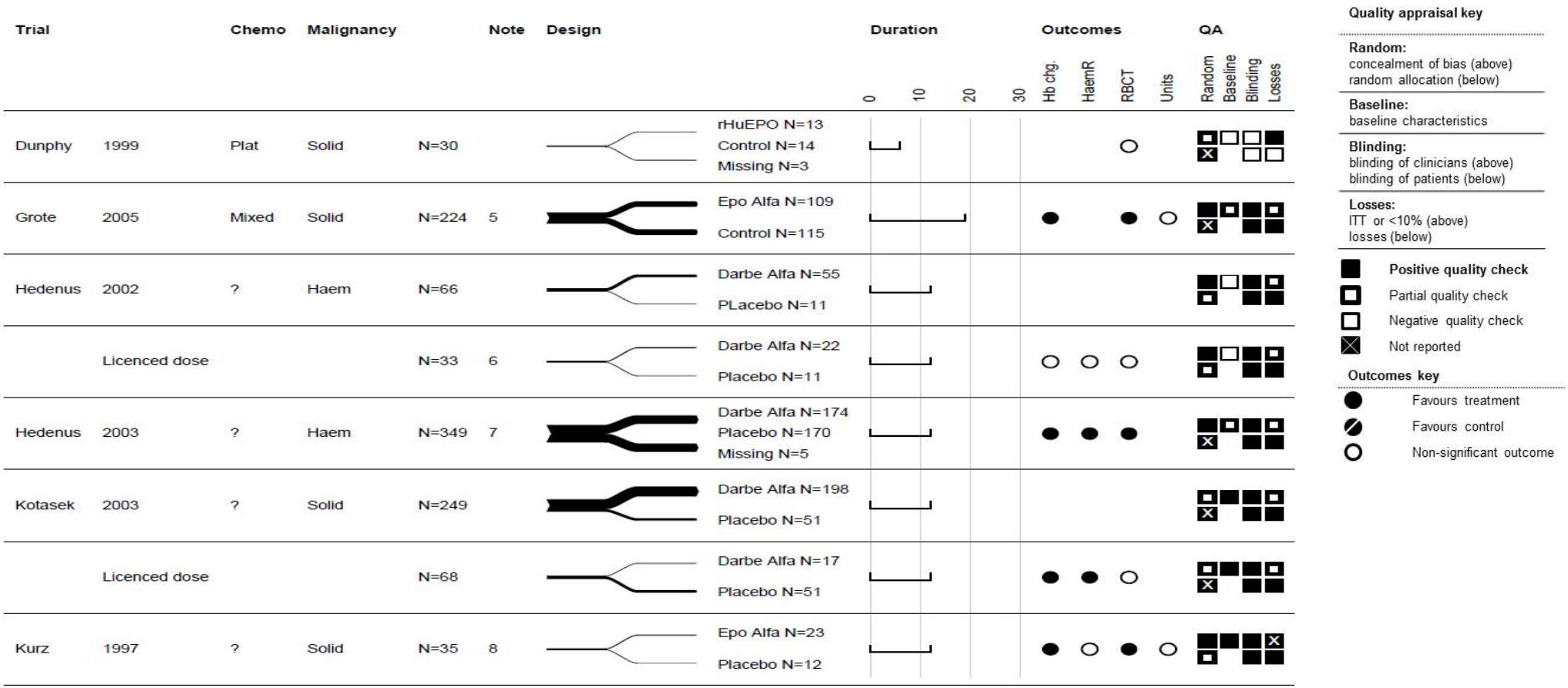
Effectiveness estimates were consistent with previously reported estimates for the anaemia-related outcomes; Table 19. A graphical summary of study characteristics and results for these outcomes is presented in Figure 11.

Figure 11. Anaemia-related outcomes: Graphical summary



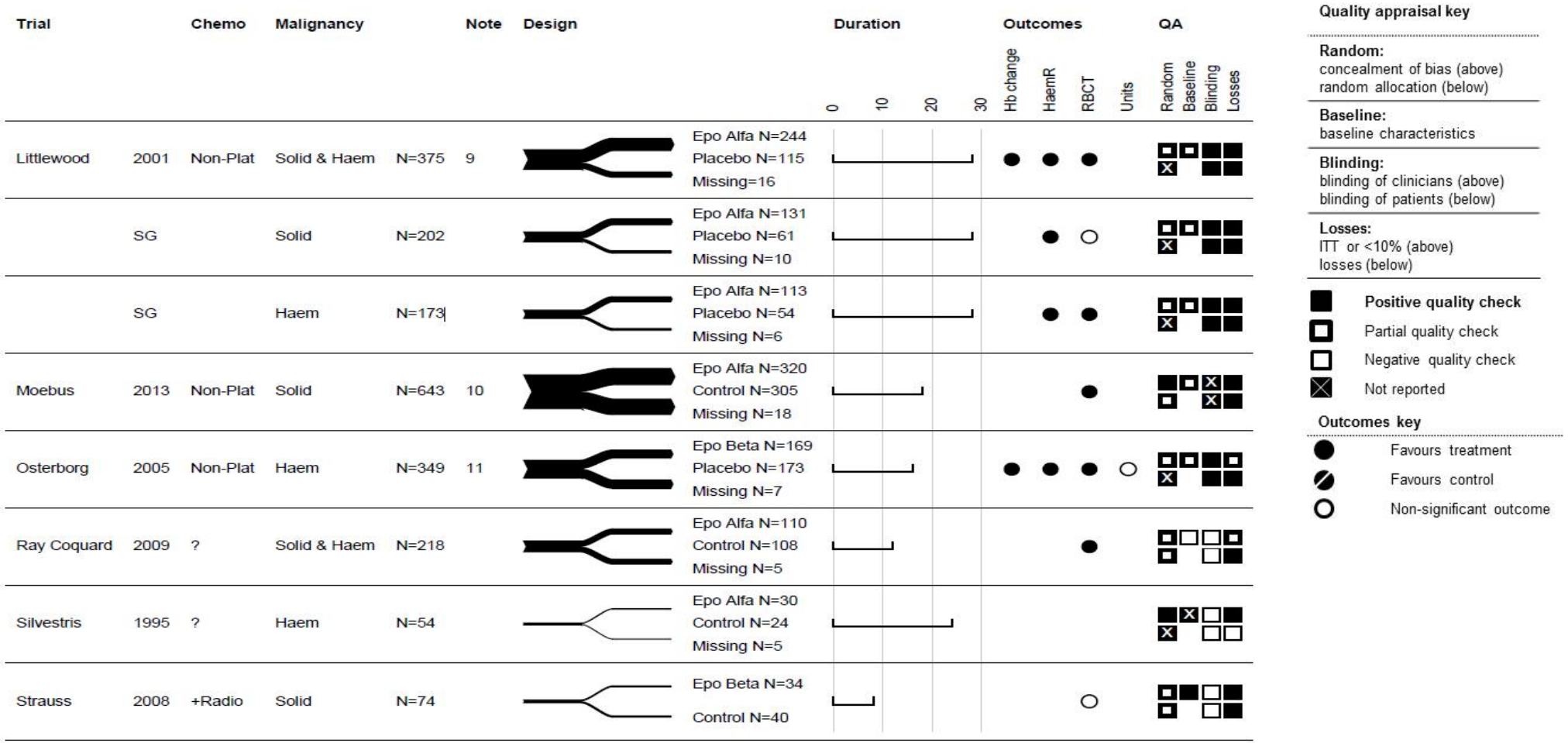
Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Hb chg., Haemoglobin change; HaemR, haematological response ; RBCT, red blood cell transfusion ; units, units transfused; Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

Figure 11. Anaemia-related outcomes: Graphical summary (continued)



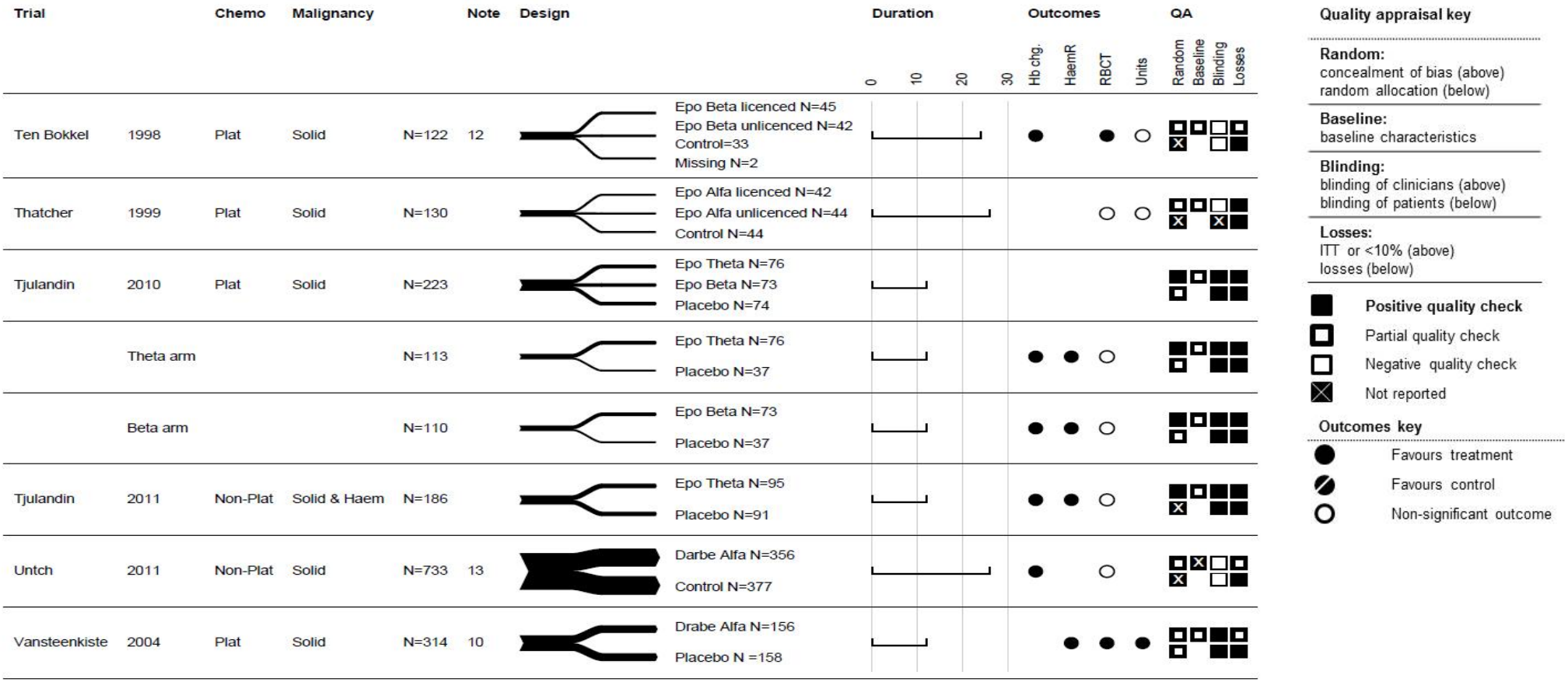
Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Hb chg., Haemoglobin change; HaemR, haematological response ; RBCT, red blood cell transfusion ; units, units transfused; Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

Figure 11. Anaemia-related outcomes: Graphical summary (continued)



Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Hb chg., Haemoglobin change; HaemR, haematological response ; RBCT, red blood cell transfusion ; units, units transfused; Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

Figure 11. Anaemia-related outcomes: Graphical summary (continued)



Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Hb chg., Haemoglobin change; HaemR, haematological response ; RBCT, red blood cell transfusion ; units, units transfused; Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

4.2.6.2. Malignancy-related outcomes

Malignancy-related outcomes: complete tumour response and overall survival. In addition on study mortality was considered in this section.

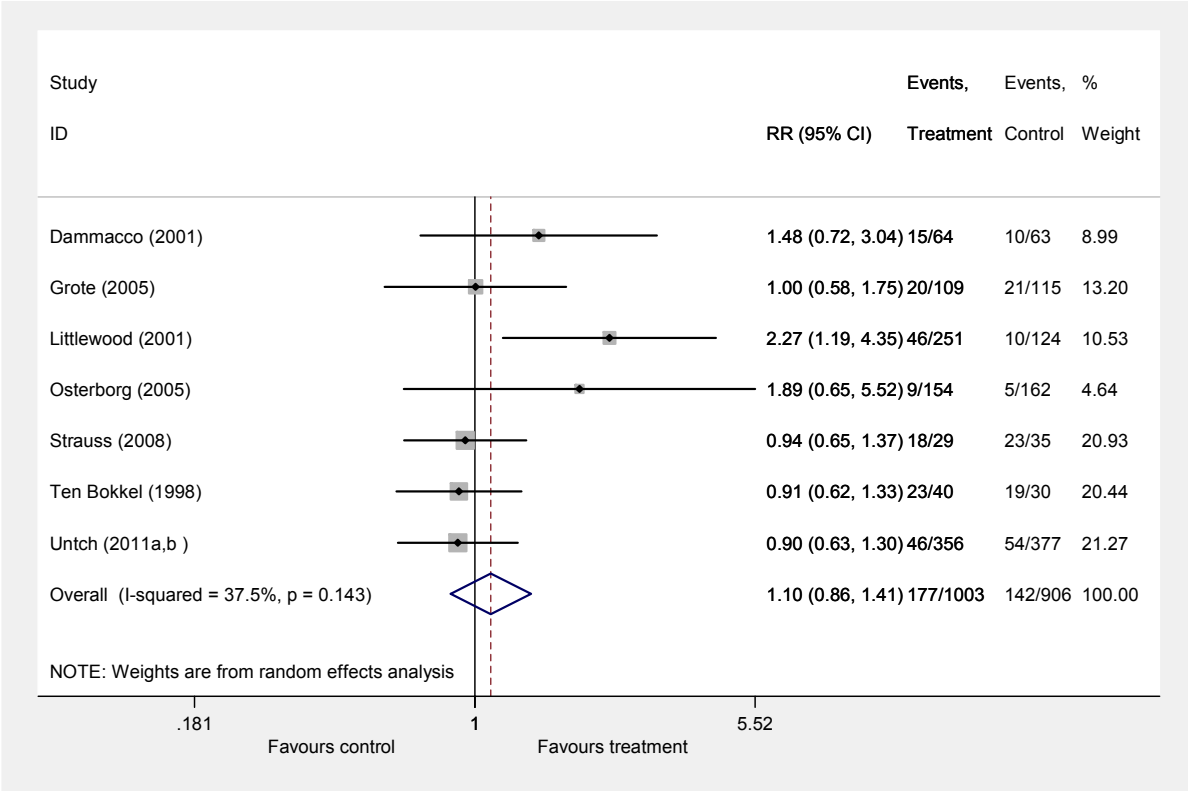
4.2.6.2.1. Tumour response

We identified seven studies that measured a complete tumour response. Overall, the analysis included seven trials with 1,909 participants. Two trials were newly identified in the update searches (**Strauss and colleagues, 2008**; **Untch and colleagues, 2011a,b**).[75,77,78]

A complete tumour response was reported in 177 out of 1,003 participants in the ESA-treated groups compared to 142 out of 906 in the control groups. The random effects meta-analysis showed a RR of 1.10 (RR 1.10; 95% CI 0.86 to 1.41; see Figure 12) that was not statistically significant. There was non significant heterogeneity between the trials (I^2=37.5%, p=0.143; X^2=9.59, df =6, p=0.143); however the direction of effects of the individual studies varied (Figure 12). Because there were only seven primary studies included in the meta-analysis, the funnel plot analysis to assess whether publication bias was likely was not conducted.[50] 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 L.

The previous HTA review (**Wilson and colleagues, 2007;**[1] using a fixed effects model) suggested that ESAs have detrimental effects with regards to tumour response (RR 1.31; 95% CI 1.08, 1.60). However, the Cochrane review (**Tonia and colleagues, 2012**[10]) did not find any differences between controls and treatments with regards to tumour response (RR 1.02; 95% CI 0.98, 1.06). It must be emphasised that the current analysis included only studies complying with the licenced ESA dose, while the HTA review and the Cochrane review did not apply any restrictions regarding the ESA posology. The HTA meta-analyses included nine trials with 1,200 participants, and the Cochrane review included 19 trials with 5,002 participants.

Figure 12. Forest plot: Tumour response (random effects)



Key: CI: confidence intervals; Events, Treatment: number of events/ number of participants in treatment group; Events, Control: number of events/ number of participants in control group; ID: identification; RR, risk ratio
Notes: Random effects meta-analysis (Der-Simonian–Laird)

Pre-specified 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 (2012)**[10] used additional quality criteria to assess the quality of trials reporting data on tumour control. The study's population had to be homogenous (i.e. all participants had to have the same tumour type/stage), all participants had to receive a predefined, identical anti-cancer 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 the study was stratified by treatment and /or by tumour type (tumour stage). Only two studies included in the current review met the **Tonia and colleagues (2012)**[10] additional criteria, **Strauss and colleagues (2008)**[75] and **Untch and colleagues (2011a,b)**.[77,78]

Summary: Analyses suggest that treatment with ESA in patients with cancer-induced anaemia did not have a significant effect on complete tumour response (RR of 1.10; 95% CI

0.86 to 1.41). Fourteen per cent (177/1003) of participants who received ESA had a complete tumour response, compared to 16% (142/906) of patients in control groups. There was non significant heterogeneity between the trials (I^2=37.5%, p=0.143), however the direction of the effects of ESA with regard to tumour response varied across the individual trials. The data from seven trials suggest no difference between patients treated with ESA and patients in control groups with regard to tumour response. Overall, the data confirm results from prior analyses.

4.2.6.2.2. Overall survival

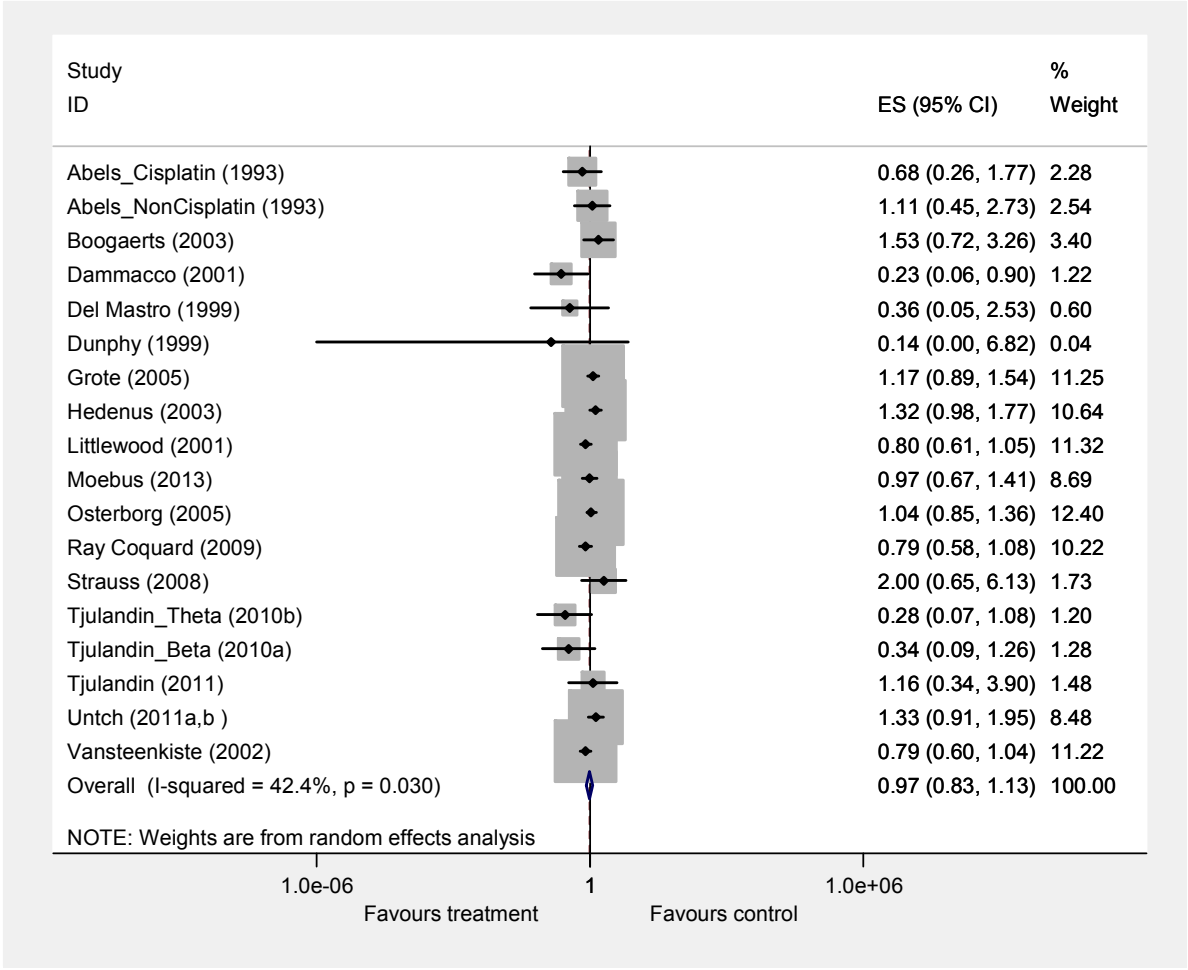
For OS, data were extracted from the Cochrane review (**Tonia and colleagues, 2012**).[10] In the Cochrane review reported hazard ratios (HRs) were based on individual patient data (IPD). Where IPD were not available, the authors extracted HRs from the published study, or calculated them from published reports including secondary analyses, using methods reported in Parmar and colleagues (1998),[44] or from binary mortality data. OS was calculated from the longest follow-up available and varied between studies.

OS data were available from 23 studies including 5,064 participants. Seven studies (**Grote and colleagues, 2005**; **Strauss and colleagues, 2008**; **Ray-Coquard and colleagues, 2009**; **Tjulandin and colleagues, 2010**; **Tjulandin and colleagues, 2011**; **Untch and colleagues, 2011a,b**; **Moebus and colleagues, 2013**)[45,62,73-78] were newly identified. Two studies (**Abels and colleagues, 1993** and **Tjulandin and colleagues, 2010**)[45,54] were split into subsets, two studies (**Kurz and colleagues, 1997** and **Hedenus and colleagues, 2002**)[49,67] reported zero events, and three studies (**Ten Bokkel and colleagues, 1998**; **Thatcher and colleagues, 1999**; and **Kotasek and colleagues, 2003**)[46-48] reported events/effect size for combined treatment arm (studies evaluated different ESA doses) and as such included unlicensed doses; as a result the number of included in the meta-analysis is 18.

The overall survival estimate is provided in Figure 13 (HR 0.97, 95% CI 0.83, 1.13). The heterogeneity between trials was significant with an I^2 of 42.4%; p=0.030 (X^2=29.5, df=17, p=0.030); the forest plot suggested that there was a tendency for smaller studies to favour treatment (Figure 13). Funnel plot analysis Appendix L) identified one outlier (Dunphy and colleagues, 1999)[66] and also suggested that smaller studies had a tendency to favour treatment; a funnel plot without the outlier is presented in Appendix L. The Harbord test was not performed, because raw data were not available.

A meta-regression using publication year as a covariate (to assess the effect of publication year on OS) showed that the effects of ESA on OS were independent from any effect of publication year (p=0.60; the meta-regression plot is presented in Appendix L).

Figure 13. Forest plot: Overall survival (random effects)



Key: CI, confidence interval; ES effect size; ID, identification
Notes: (a) Der-Simonian Laird pooled RR; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Tjulandin and colleagues, 2010a,b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy; **(c)** Effect sizes reported are hazard ratios; **(d)** IPD data as reported in Tonia and colleagues, 2012 (Cochrane review): Abels and colleagues, 1993; Boogaerts and colleagues, 2003; Dammacco and colleagues, 2001; Grote and colleagues, 2005; Hedenus and colleagues, 2003; Littlewood and colleagues, 2001; Osterborg and colleagues, 2002; Ray-Coquard and colleagues, 2009; Strauss and colleagues, 2008; Vansteenkiste and colleagues, 2002. HRs reported for other trials calculated using other accepted methods.

To identify sources of heterogeneity, we performed subgroup analyses (Table 20). 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 20. All covariates showing a significant effect (p<0.05) in a univariate analysis were further considered in model selection.

Table 20. Overall survival: Subgroup analyses

	Trials	HR	CI	I^2	Tau^2
Overall	**18**	**0.97**	**0.83 − 1.13**	**42.4%; p=0.03**	**0.04**
Inclusion Hb					
≤11.0 g/dl	10	0.91	0.70 − 1.20	51.7%; p=0.03	0.07
>11.0 g/dl	8	0.99	0.81 − 1.20	35.5%; p=0.15	0.02
F (between:within)				$F_{(1,16)}$ 0.09; p=0.77	
Baseline Hb					
≤10.0 g/dl	11	0.88	0.71 − 1.08	53.0%; p=0.02	0.05
≤11.0 g/dl	1	1.11	0.45 − 2.73	NA	NA
≤12.0 g/dl	1	2.00	0.65 − 1.13	NA	NA
≤14.5 g/dl	4	1.20	0.96− 1.50	0%; p=0.56	0
NR	1	0.97	0.67 − 1.41	NA	NA
F (between:within)				$F_{(4,13)}$ 0.78; p=0.56	
Target Hb					
≤13.0 g/dl	4	0.73	0.32 − 1.64	61.8%; p=0.05	0.41
>13.0 g/dl	12	0.97	0.82 − 1.14	46.6%; p=0.04	0.03
NR	2	0.88	0.46 − 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 − 1.25	46.3%; p=0.06	0.06
Haematological tumours	5	1.01	0.73 − 1.40	48.5%; p=0.10	0.05
Mixed	4	0.84	0.69 − 1.02	0%; p=0.40	0
F (between:within)				$F_{(2,15)}$ 0.40; p=0.68	
Chemotherapy treatment					
Platinum-containing	4	0.67	0.46 − 0.98	14.5%; p=0.32	0.03
Non-platinum-containing	7	0.99	0.86 − 1.14	0%; p= 0.42	0
NR	3	1.11	0.73 − 1.68	69%; p=0.04	0.09
Mixed	3	0.59	0.14 − 2.40	64.2%; 0.06	0.87
Chemo + Radio	1	2.00	0.65 − 6.14	NA	0
F (between:within)				$F_{(4,13)}$ 1.33; p=0.31	
Iron supplementation					
No iron	12	0.96	0.79 − 1.17	38.9%; p= 0.08	0.03
Iron in an intervention arm	1	1.33	0.91 − 1.95	NA	0
NR	5	0.87	0.61 − 1.23	54.0%; p= 0.07	0.07

	Trials	HR	CI	I^2	Tau^2
F (between:within)				$F_{(2,15)}$ 0.72; p=0.50	
Study design					
RCT	11	0.92	0.75 − 1.13	52.4%; p=0.02	0.05
ROL	7	1.05	0.81 − 1.36	28.1%; p=0.21	0.03
F (between:within)				$F_{(1,16)}$ 0.50; p=0.49	
Study duration					
6–9 wks	2	1.90	0.63 − 5.76	0%; p=0.51	0
12–16 wks	11	0.86	0.68 − 1.08	48.8%; p=0.03	0.05
17–20 wks	2	1.10	0.88 − 1.37	0%; p=0.43	0
>20 wks	3	1.10	0.72 − 1.67	66.4%; p=0.05	0.09
F (between:within)				$F_{(3,14)}$ 0.87; p=0.48	
ESA					
Erythropoetin	15	0.92	0.77 − 1.10	31.2%; p=0.12	0.03
Darbepoetin	3	1.10	0.77 − 1.58	74.6%; p=0.03	0.08
F (between:within)				$F_{(1,16)}$ 0.92; p=0.35	

Key: CI, confidence interval; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; NA, not applicable; NR, not reported; RCT, randomised controlled trial; ROL, randomised open label (standard care); wks, weeks.

Univariate analyses did not identify any significant differences based on the pre-defined subgroups (Table 20). The fixed effects meta-analysis undertaken as a sensitivity analysis, showed similar results (HR 0.98, 95% CI 0.89, 1.08); the forest plot of this analysis is included in Appendix L. Both fixed and random effects estimates suggested no difference in OS between the control and treatment arms. Interestingly, the fixed effects estimate reported in the recent Cochrane review (**Tonia and colleagues, 2012**)[10] favoured controls, suggesting that higher mortality occurred in patients treated with ESA; HR 1.05 (95% CI 1.00, 1.11). The previous HTA review (**Wilson and colleagues, 2007**) did not find a significant difference between controls and treatments with regards to survival (HR 1.03; 95% CI 0.92, 1.16).[1] It must be emphasised that the current analysis only included studies complying with the licenced ESA dose, while the Cochrane review did not apply any restrictions regarding the ESA posology. The Cochrane review included 76 studies in the on overall survival meta-analysis; however subgroup analyses comparing studies using licenced and unlicensed dose ESA dose were not conducted.

Summary: Analyses suggest that treatment with ESAs in patients with CIA did not have a significant effect on overall survival. Thirty five per cent (818/2,317) participants who received ESA had died, and 35% (744/2,137) of patients died in control groups. The risk of death was 0.97 (HR 0.97, 95% CI 0.83, 1.13). However, there was significant heterogeneity

between the trials (I^2=42.4%, p=0.030). In addition, OS was calculated from the longest follow-up available (no mnimum was required),as such, there was variation between the studies (short- and long-term) and this should be considered when interpreting the results. Overall, the data appear different to previous analyses. It appears that if the licenced ESA dosage is followed, there are no detrimental effects of ESA on overall survival. However, these results should be interpreted with caution, see Section 4.2.7 (page 149) for more details.

4.2.6.2.3. On-study mortality

For on-study mortality, data were extracted from the Cochrane review (**Tonia and colleagues, 2012**).[10] In the Cochrane review reported HRs were based on IPD. Where IPD were not available, the authors extracted HR's from the published study, or calculated them from data published in reports, including secondary analyses, using the methods reported in Parmar and colleagues (1998)[44]. On-study mortality was defined as deaths occurring up to 30 days after the active study period.

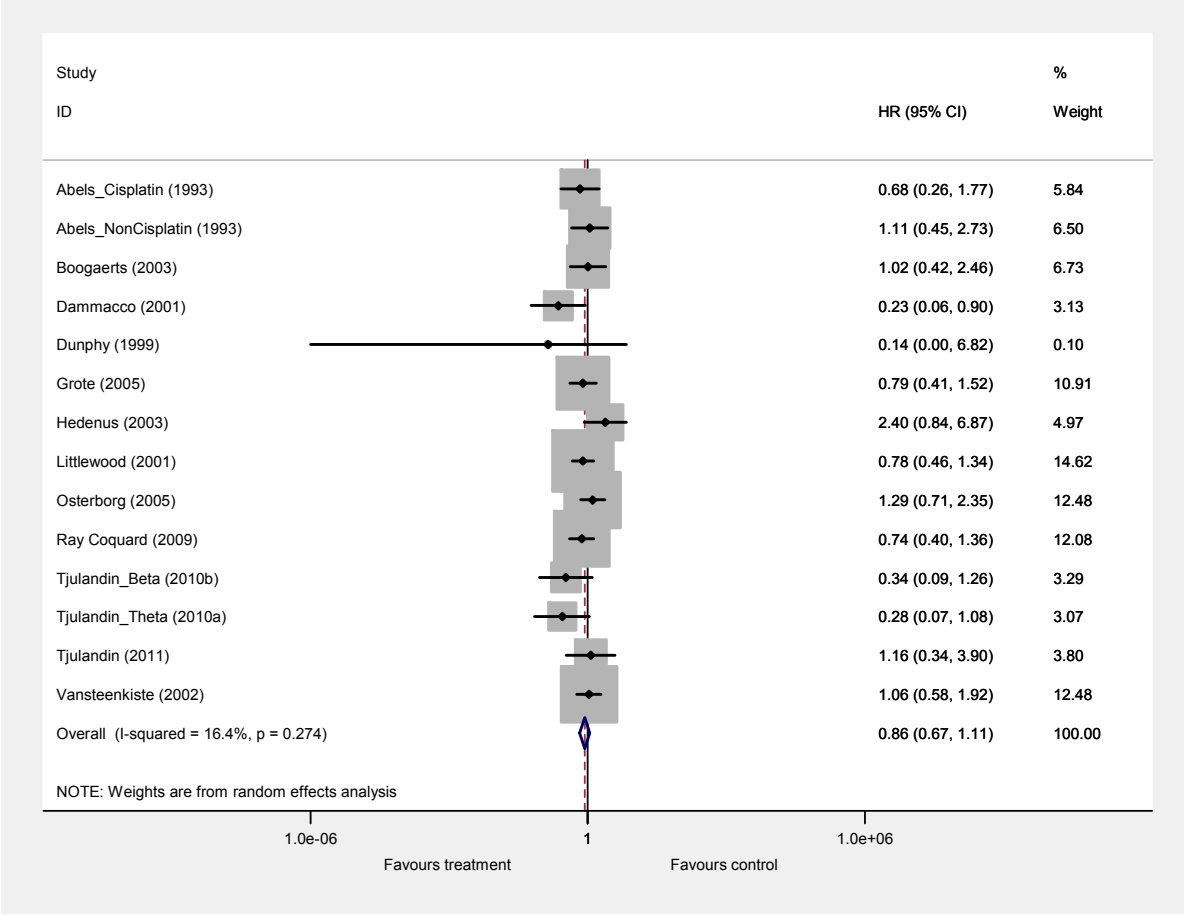
Mortality data were available from 21 studies including 5,085 participants. Seven studies (**Grote and colleagues, 2005**; **Strauss and colleagues, 2008**; **Ray-Coquard and colleagues, 2009**; **Tjulandin and colleagues, 2010**; **Tjulandin and colleagues, 2011**; **Untch and colleagues, 2011**; **Moebus and colleagues, 2013**)[45,62,73-78] were newly identified. Two studies (**Abels and colleagues, 1993** and **Tjulandin and colleagues, 2010**)[45,54] were split into subsets, six studies **(Del Mastro and colleagues, 1999**; **Hedenus and colleagues, 2002; Kurz and colleagues, 1997**; **Moebus and colleagues, 2013**; **Strauss and colleagues, 2008** and **Untch and colleagues, 2011a,b**[75,77,78])[49,62,65,67] reported zero events, and four studies (**Hedenus and colleagues, 2002**; **Kotasek and colleagues, 2003; Ten Bokkel and colleagues, 1998**; **Thatcher and colleagues, 1999**)[46-49] 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 2,967 participants). One study (**Dunphy and colleagues, 1999**) reported mortality events in the control arm, while there were no deaths recorded in the treatment arm; HR 0.14 (95% CI 0.00, 6.82).[66]

The results from the on-study mortality meta-anlysis are provided below (Figure 14; HR 0.86, 95% CI 0.67, 1.11). Heterogeneity between trials was not significant (I^2=16.4%, p=0.274; X^2=15.55, df=13, p=0.274); however the forest plot may suggest a tendency for smaller studies to favour treatment (Figure 14). Similarly to overall survival data, funnel plot analysis

(Appendix L) identified one outlier (**Dunphy and colleagues, 1999**)[66] and was also suggestive of a tendency for smaller studies to favour treatment; a funnel plot without the outlier is presented in Appendix L. The Harbord test was not performed, because raw data were not available.

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

Figure 14. Forest plot: Mortality (random effects)



Key: CI, confidence interval; ID, identification; HR, Hazard ratio
Notes: **(a)** Der-Simonian Laird pooled HR; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Tjulandin and colleagues, 2010a,b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy; **(c)** IPD data as reported in Tonia and colleagues, 2012 (Cochrane review): Abels and colleagues, 1993; Boogaerts and colleagues, 2003; Dammacco and colleagues, 2001; Grote and colleagues, 2005; Hedenus and colleagues, 2003; Littlewood and colleagues, 2001; Osterborg and colleagues, 2002; Ray-Coquard and colleagues, 2009; Vansteenkiste and colleagues, 2002. HRs reported for other trials calculated using other accepted methods.

The fixed effects meta-analysis undertaken as a sensitivity analysis showed similar results (HR 0.87, 95% CI 0.70, 1.09); the forest plot of this analysis is included in (Appendix L). Both fixed and random effects estimates suggested no difference in on-study mortality between the control and treatment arms. Interestingly, the fixed effects estimate reported in the recent Cochrane review (**Tonia and colleagues, 2012**)[10] favoured controls, suggesting that higher mortality occurred in patients treated with ESA (HR=1.17; 95% CI 1.03, 1.29). Again it must be emphasised that the current analysis included only studies complying with the licenced ESA dose, while 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 licenced and unlicensed ESA dose were not conducted.

Pre-defined subgroup analyses were performed (Table 21). 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 peformed which includedrandom effect and subgroups as covariates; the F statistics from these analyses are reported in Table 21. All covariates showing a significant effect ($p<0.05$) in a univariate analysis were further considered in model selection.

Table 21. Mortality: Subgroup analyses

	Trials	HR	CI	I^2	Tau^2
Overall	**14**	**0.86**	**0.67 − 1.11**	**16.4%; p=0.27**	**0.04**
Inclusion Hb					
≤11.0 g/dl	10	0.89	0.61 − 1.30	37.7%; p=0.11	0.13
>11.0 g/dl	4	0.77	0.55 − 1.08	0%; p=0.98	0
F (between:within)				$F_{(1,12)}$ 0.74; p=0.41	
Baseline Hb					
≤10.0 g/dl	11	0.84	0.62 − 1.15	33.2%; p=0.13	0.09
≤11.0 g/dl	1	1.11	0.45 − 2.73	NA	0
≤14.5 g/dl	2	0.78	0.41 − 1.50	0%; p=0.67	0
F (between:within)				$F_{(2,11)}$ 0.14; p=0.87	
Target Hb					
≤13.0 g/dl	3	0.50	0.20 − 1.22	29.7%; p=0.24	0.19
>13.0 g/dl	9	0.92	0.70 − 1.22	20.0%; p=0.27	0.04
NR	2	0.88	0.46 − 1.70	0%; p=0.47	0
F (between:within)				$F_{(2,11)}$ 0.89; p=0.44	

	Trials	HR	CI	I^2	Tau^2
Malignancy type					
Solid tumours	5	0.71	0.44 − 1.15	17.6%; p=0.30	0.06
Haematological tumours	5	0.98	0.54 − 1.79	52.7%; p=0.08	0.24
Mixed	4	0.83	0.58 − 1.17	0%; p=0.88	0
F (between:within)				$F_{(2,11)}$ 0.61; p=0.56	
Chemotherapy treatment					
Platinum-containing	4	0.64	0.34 − 1.18	36.0%; p=0.20	0.14
Non-platinum-containing	4	1.01	0.71 − 1.43	0%; p= 0.65	0
NR	3	1.09	0.58 − 2.08	44.4%; p=0.17	0.14
Mixed	3	0.53	0.21 − 1.30	26.6%; p=0.26	0.21
F (between:within)				$F_{(3,10)}$ 1.06; p=0.41	
Iron supplementation					
Iron in both arms	9	0.89	0.63 − 1.26	25.6%; p= 0.22	0.07
NR	5	0.82	0.55 − 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 − 1.17	33.0%; p=0.14	0.09
Unblinded (ROL)	3	0.82	0.49 − 1.35	0.0%; p=0.77	0
F (between:within)				$F_{(1,12)}$ 0.07; p=0.80	
Study duration					
6–9 wks	1	0.14	0 − 365.61	NA	0
12–16 wks	10	0.85	0.59 − 1.23	39.6%; p=0.09	0.13
17–20 wks	1	0.79	0.41 − 1.52	NA	0
>20 wks	2	0.84	0.53 − 1.32	0.0%; p=0.61	0
F (between:within)				$F_{(3.10)}$ 0.070; p=0.97	
ESA					
Erythropoetin	12	0.80	0.63 − 1.02	1.0%; p=0.43	<0.01
Darbepoetin	2	1.42	0.66 − 3.05	43.0%; p=0.19	0.14
F (between:within)				$F_{(1.12)}$ 2.51; p=0.14	

Key: CI, confidence interval; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; NA, not applicable; NR, not reported; RCT, randomised controlled trial; ROL, randomised open label (standard care); wks, weeks.

Univariate analyses did not identify any significant differences based on the pre-defined subgroups (Table 21).

Summary: Analyses suggest that treatment with ESA in patients with CIA did not have a significant effect on mortality. Eleven per cent (174/1586) of participants who received ESA had died within 30 days of the active study period, compared to 12% (164/1381) of patients

in control groups. The risk of death was 0.86 (HR 0.86, 95% CI 0.67, 1.1). There was no significant heterogeneity between the trials (I^2=16.4%, p=0.274). Overall, the data appear different to previous analyses. It appears that if the licenced ESA dosage is followed, there are no detrimental effects of ESA on overall survival. However, these results should be interpreted with caution, see Section 4.2.7 (page 149) for more details.

4.2.6.2.4. Malignancy-related outcomes: overall summary

Table 22. Malignancy-related outcomes results comparison: Wilson and colleagues, 2007 vs Tonia and colleagues, 2012 vs PenTAG 2013[1,10]

	Wilson, 2007[a]	Tonia, 2012[a]	PenTAG, 2013[a]	PenTAG, 2013[b]
Malignancy-related outcomes				
Tumour response	RR 1.31 95% CI 1.08−1.60 $X^2_{(het)}$ NR; df NR (p=NR) 9 trials, n=1,260	RR 1.02 95% CI 0.98−1.06 $X^2_{(het)}$ 16.10; df 18 (p=0.59) 19 trials, n=5,012	RR 1.20 95% CI 0.85−1.71 $X^2_{(het)}$ 9.59; df 6 (p=0.14) 7 trials, n=1,909	RR 1.10 95% CI 0.86−1.41 $X^2_{(het)}$ 9.59; df 6 (p=0.14) 7 trials, n=1,909
Overall survival	HR 1.03 95% CI 0.92−1.16 $X^2_{(het)}$ 37.74; df 27 (p=0.08) 28 trials, n=5,308	HR 1.05 95% CI 1.00−1.11 $X^2_{(het)}$ 95.40; df 75 (p=0.060) 76 trials, n=18.754	HR 0.98 95% CI 0.89−1.08 $X^2_{(het)}$ 29.50; df 17 (p=0.03) 18[c] trials, n=4,399	HR 0.97 95% CI 0.83−1.13 $X^2_{(het)}$ 29.50; df 17 (p=0.03) 18[c] trials, n=4,399
Mortality	NR	HR 1.17 95% CI 1.03−1.29 $X^2_{(het)}$ 59.49; df=63 (p=0.600) 64 trials, n=14,179	HR 0.87 95% CI 0.70−1.09 $X^2_{(het)}$ 15.55; df=13 (p=0.274) 14 trials. n=2,967	HR 0.86 95% CI 0.67−1.11 $X^2_{(het)}$ 15.55; df=13 (p=0.274) 14 trials. n=2,967

Key: CI, confidence interval; df, degrees of freedom; het, heterogeneity; RR, relative risk
Notes: The number of trials includes multiple experimental arms for some studies **(a)** fixed effects (Mantel-Haenzel); **(b)** random effects (Der-Simonian Laird);), haematological response was defined as the proportion of participants with an increase in Hb level of two g/dl or more, or as an increase in haematocrit of six percentage points or more; **(c)** 16 studies; however, two studies split into subsets thus 18 trials included in meta-analysis

Effectiveness estimates are compared with previously reported estimates for the malignancy-related outcomes; see Table 22. A graphical summary of study characteristics and results for these outcomes is presented in Figure 15**.**

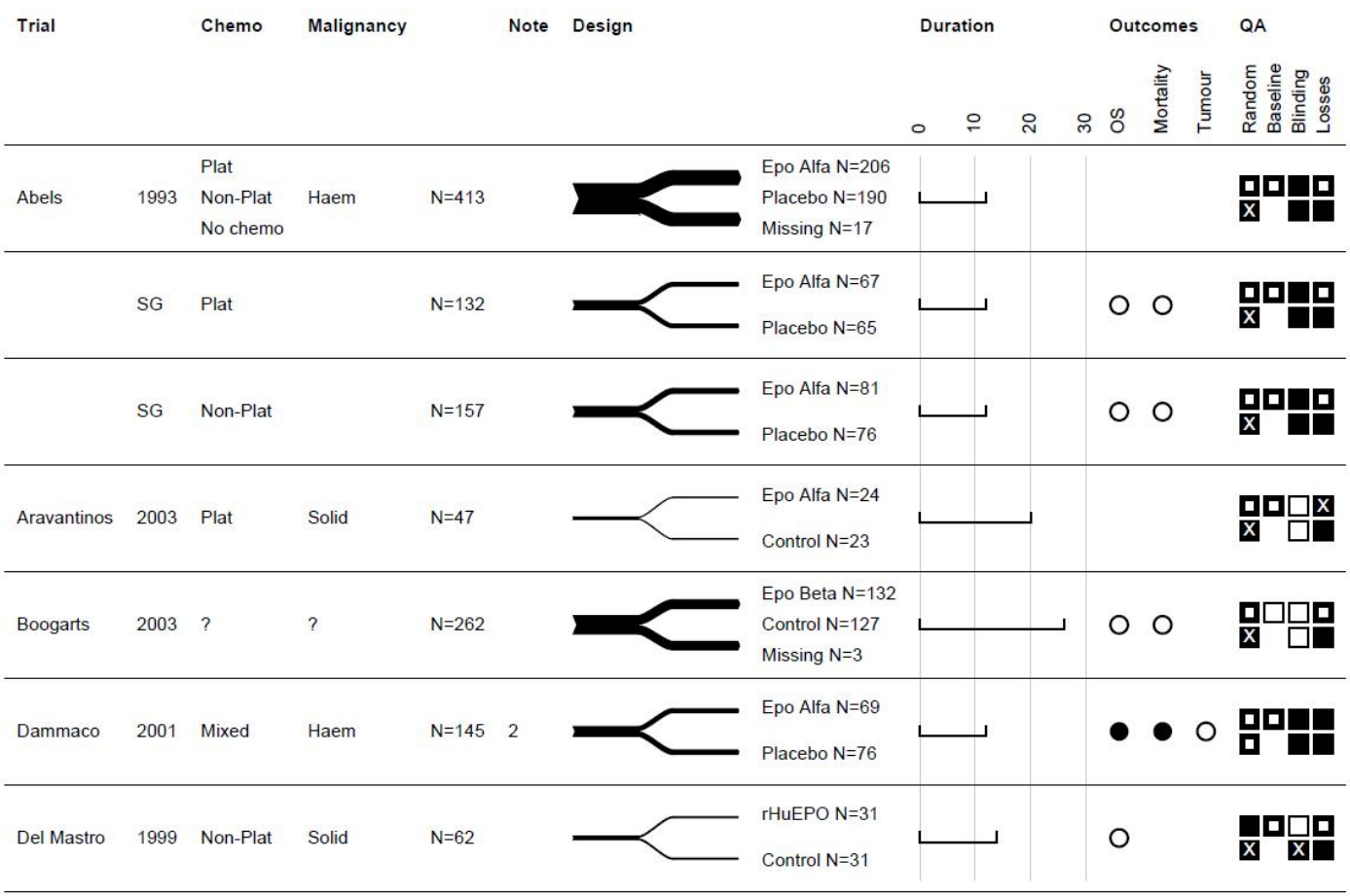
Seven studies reported tumour response (complete response). Data available suggest that ESAs do not have a beneficial effect on tumour control; however, the data are insufficient to exclude detrimental effects. It should also be noted that this is a difficult area of assessment, especially in a heterogenous mix of tumour types, and results should be treated with caution.

Survival estimates (HR) were available for 16 of the included studies; the HR (HR 0.98, 95% CI 0.89, 1.08) differed from those previously reported (Table 22). In addition, statistically

significant heterogeneity was identified (I^2 42.4%; p=0.03), which adds uncertainty to this estimate. It was not possible to identify subgroups that were at higher or lower risk. In addition, OS was calculated from the longest follow-up available (no mnimum was required),as such, there was variation between the studies (short- and long-term) and this should be considered when interpreting the results. On-study mortality was assessed in 12 studies. The risk of death was 0.86 (HR 0.86, 95% CI 0.67, 1.1); with no significant heterogeneity between the trials (I^2=16.4%, p=0.274).

Overall the results for malignancy-related outcomes seem to be different to previous analyses. It appears that if the licenced ESA dosage is followed, there are no detrimental effects of ESA on-study mortality or on overall mortality. However, these results should be interpreted with caution. However, these results should be interpreted with caution, see Section 4.2.7 (page 149) for more details.

Figure 15. Malignancy-related outcomes: Graphical summary



Quality appraisal key

Random:
concealment of bias (above)
random allocation (below)

Baseline:
baseline characteristics

Blinding:
blinding of clinicians (above)
blinding of patients (below)

Losses:
ITT or <10% (above)
losses (below)

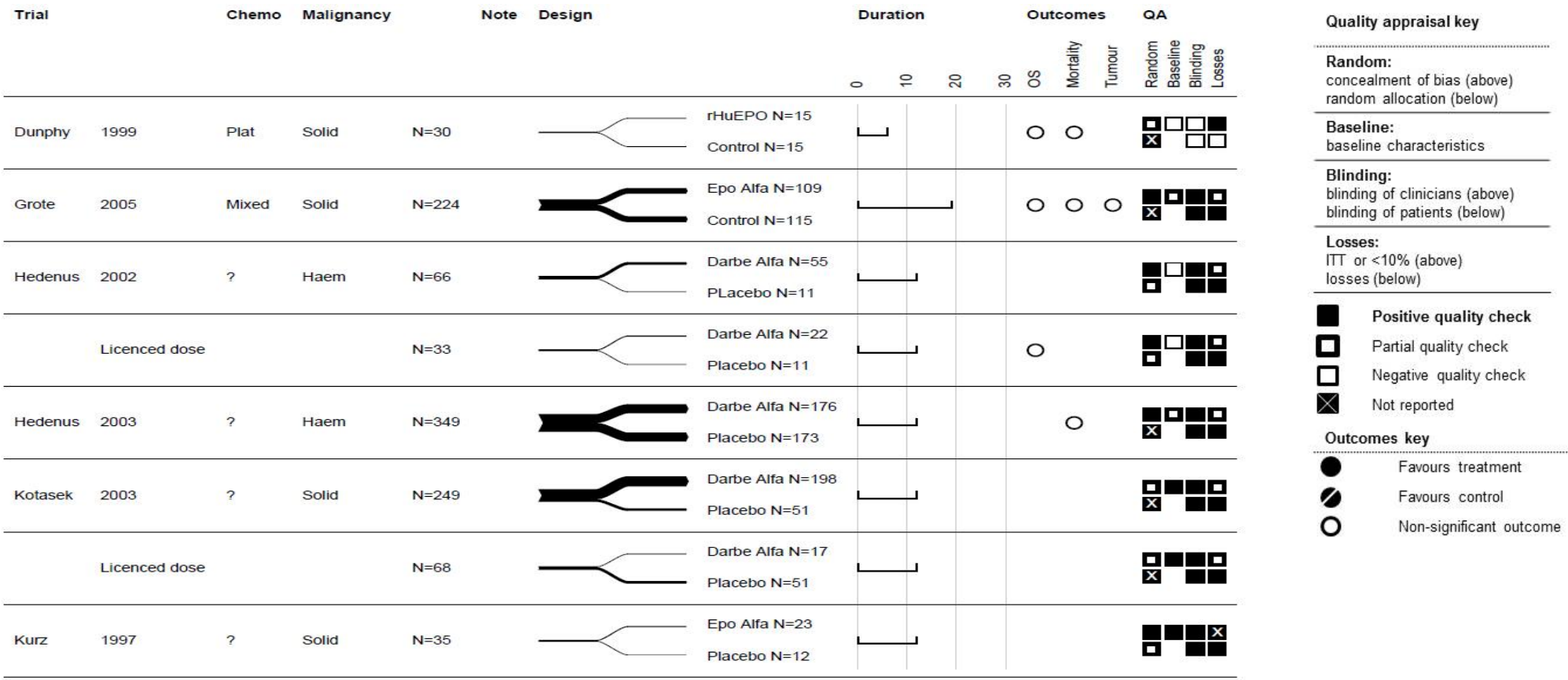
Positive quality check
Partial quality check
Negative quality check
Not reported

Outcomes key

Favours treatment
Favours control
Non-significant outcome

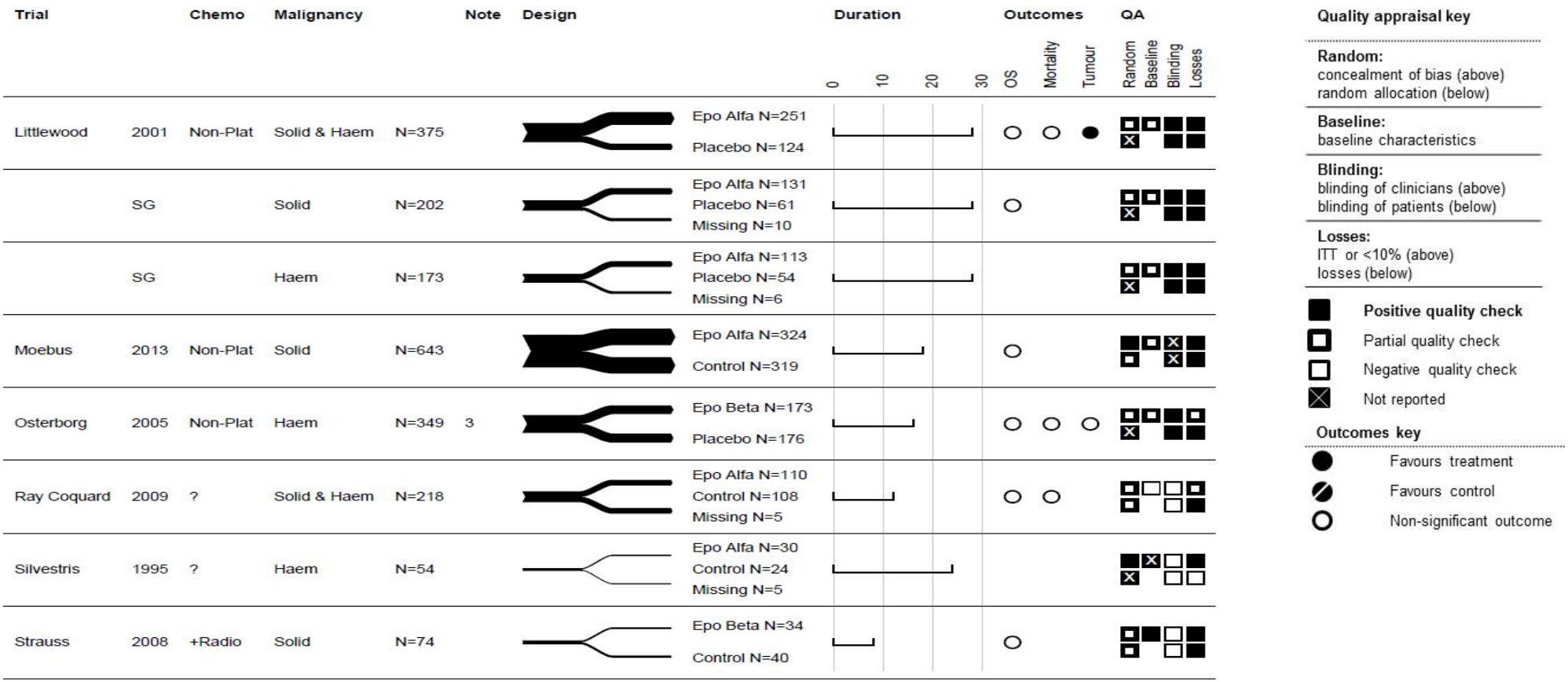
Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; OS, overall survival; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

Figure 15. Malignancy-related outcomes: Graphical summary



Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; OS, overall survival; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

Figure 15. Malignancy-related outcomes: Graphical summary



Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; OS, overall survival; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 23: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

Figure 15. Malignancy-related outcomes: Graphical summary

Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; OS, overall survival; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

4.2.6.3. Safety

Adverse events, as included in the Cochrane review (**Tonia and colleagues, 2012**[10]) thromboembolic events, hypertension, thrombocytopenia/haemorrhage, seizures and pruritus (pruritus, rash and irritation were considered as defined in **Tonia and colleagues, 2012**[10]), and red cell aplasia

There was considerable variability in the reporting of AEs among the included studies; e.g. some reported adverse events (AEs) in >5% of patients; some in >10% of patients; and some 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 than that reported in the primary papers, data from the Cochrane review (**Tonia and colleagues, 2012**),[10] were used to conduct meta-analyses for the following adverse events: 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 was safety outcome was not analysed in the Cochrane review.

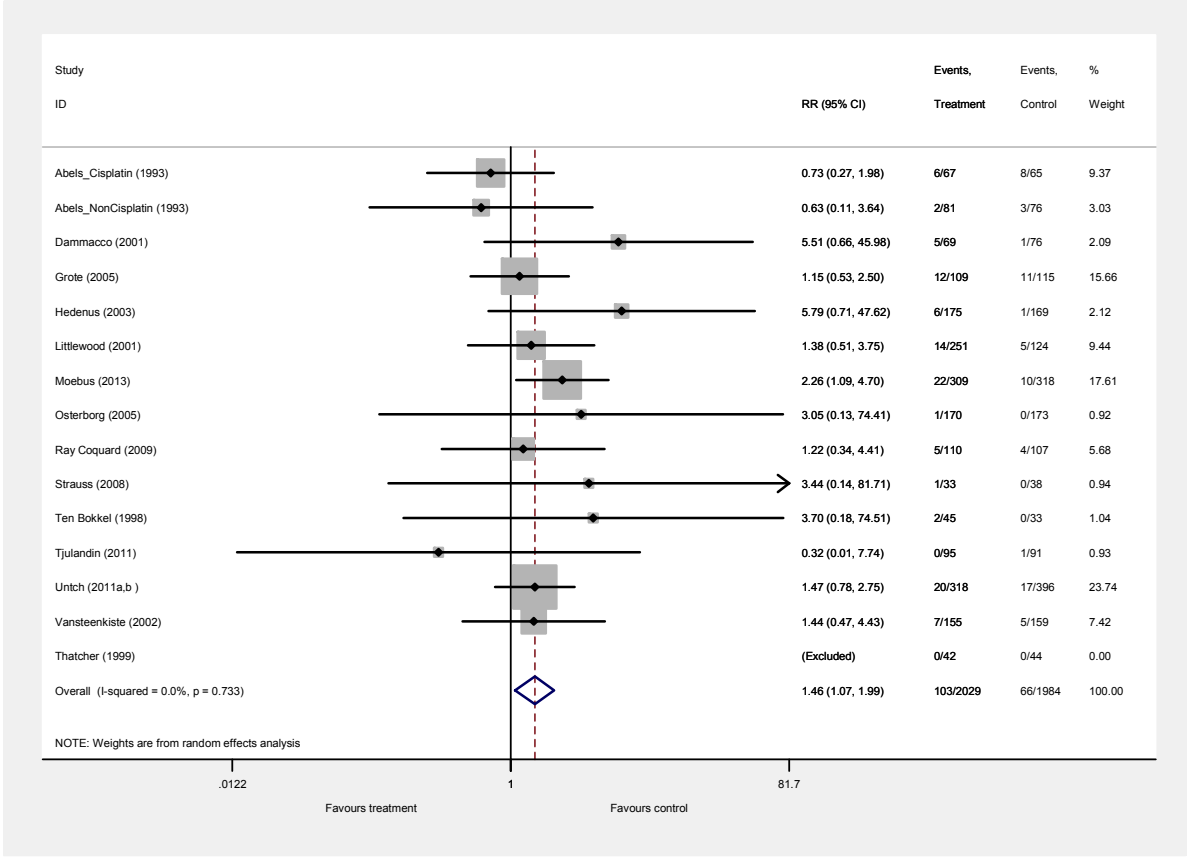
4.2.6.3.1. Thromboembolic events

We identified 14 studies that measured thromboembolic events, including 4,013 participants. Of these, 2,029 participants were treated with ESAs. As one multi-arm study (**Abels and colleagues, 1993**)[54] was split into subsets the number of studies displayed is 15. Five included studies were newly identified in the update searches (**Strauss and colleagues, 2008**; **Ray-Coquard and colleagues, 2009**; **Tjulandin and colleagues, 2011**; **Untch and colleagues, 2011a,b**; and **Moebus and colleagues, 2013**).[62,74-78] If thromboembolic events were not reported, we used data from the Cochrane review by **Tonia and Colleagues (2012)**[10] in the PenTAG analyses. One study (**Thatcher and colleagues 1999**),[48] did not report any thromboembolic events in the treatment or placebo arms, therefore the number of trials included in the meta-analysis is 14.

Moebus and colleagues (2013)[62] replaced **Moebus and colleagues (2007)**[32] (used in **Tonia and colleagues, 2012**[10]), different number of thromboembolic events were used in the PenTAG meta-analyses compared to the analysis in Tonia 2012. The **Moebus and colleagues (2013)**[62] trial showed an increased risk for patients treated with ESA compared to controls (RR 2.26 CI 1.09−4.70), while no difference between treatment and controls was reported in **Moebus and colleagues (2007)**.[32]

Thromboembolic events were reported in 103 out of 2,029 participants treated with ESAs compared to 66 out of 1,984 participants in the control group. The random effects meta-analysis showed a RR of 1.46 favouring controls (RR 1.46 95% CI 1.07 to 1.99; see Figure 16). There was no heterogeneity between the trials (I^2=0%, p=0.733; X^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 (Appendix L). 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 suggests that the effects of ESA on thromboembolic events were independent from when the trial results were published (p=0.871); the meta-regression plot is presented in Appendix L.

Figure 16. Thromboembolic events: overall (random effects)



Key: CI, confidence interval; events, treatment, control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: (a) Random effects (Der-Simonian Laird pooled RR); **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

The fixed effects meta-analysis undertaken as a sensitivity analysis showed similar results favouring controls compared to ESA (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 L.

Pre-specified subgroup analyses were conducted (Table 23). 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 inTable 23. All covariates showing a significant effect (p<0.05) in a univariate analysis were further considered in a model selection.

Table 23.Thromboembolic events: Subgroup analyses

	Trials	RR	CI	I^2	Tau^2
Overall	**14**	**1.46**	**1.08 − 1.99**	**0%; p=0.73**	**0**
Inclusion Hb					
≤11.0 g/dl	7	1.29	0.66 – 2.54	12.2%; p=0.34	0.10
>11.0 g/dl	7	1.55	1.08 − 2.21	0%; p=0.88	0
F (between:within)			$F_{(1,12)}$ =0.35; p=0.57		
Baseline Hb					
≤10.0 g/dl	8	1.34	0.82 − 2.21	0%; p=0.52	0
≤11.0 g/dl	1	0.63	0.11 − 3.64	NA	0
≤12.0 g/dl	2	3.58	0.40 − 31.59	0%; p=0.97	0
≤14.5 g/dl	2	1.33	0.82 − 2.17	0%; p=0.64	0
NR	1	2.26	1.09 − 4.70	NA	0
F (between:within)			$F_{(4,9)}$ =0.53; p=0.72		
Target Hb					
≤13.0 g/dl	**2**	1.38	0.75 – 2.57	0%; p=0.36	0
>13.0 g/dl	**10**	1.73	1.72 − 2.54	0%; p=0.82	0
NR	**2**	0.70	0.29 – 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 − 2.32	0%; p=0.82	0
Haematological tumours	5	1.57	0.57 − 4.34	35.1%; p=0.19	0.46
Mixed	3	1.21	0.57 − 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 − 74.51	NA	0
Other cancers	13	1.45	1.06 − 1.97	0%; p=0.69	0
F (between:within)			$F_{(1,12)}$ =0.61; p=0.45		
Chemotherapy treatment					
Platinum-containing	3	1.06	0.51 − 2.20	0%; p=0.47	0
Non-platinum-containing	6	1.57	1.04 − 2.37	0%; p=0.66	0

Mixed	2	1.84	0.44 − 7.63	47.3%; p=0.17	0.60
+Radiotherapy	1	3.44	0.15 − 81.71	NA	0
NR	2	2.12	0.48 − 9.47	37.4%; p=0.21	0.47
F (between:within)			$F_{(4,9)}$ =0.63; p=0.65		
Iron supplementation					
Iron in both arms	7	1.86	1.13 − 3.07	0%; p=0.73	0
Iron in an intervention arm	1	1.47	0.78 − 2.75	NA	0
NR	6	1.15	0.70 − 1.89	0%; p=0.53	0
F (between:within)			$F_{(2,11)}$ =0.21; p=0.82		
Study design					
RCT	9	1.24	0.81 − 1.90	0%; p=0.55	0
ROL	5	1.74	1.12 − 2.69	0%; p=0.83	0
F (between:within)			$F_{(1,12)}$ =0.01; p=0.94		
Study duration					
6–9 wks	1	3.44	0.15 − 81.71	NA	0
12–16 wks	8	1.24	0.72 − 2.13	0%; p=0.45	0
17–20 wks	2	1.64	0.84 − 3.18	35.7%; p=0.21	0.08
>20 wks	3	1.48	0.88 − 2.51	0%; p=0.83	0
F (between:within)			$F_{(3,10)}$ =0.17; p=0.91		
ESA					
Erythropoetin	11	1.40	0.96 − 2.04	0%; p=0.65	0
Darbepoetin	3	1.60	0.94 − 2.71	0%; p=0.46	0
F (between:within)			$F_{(1,12)}$ =037; p=0.56		

Key: ESA, erythropoiesis stimulating agents; Hb, haemoglobin; NA, not applicable; NR, not reported; RCT, randomised controlled trial; ROL, randomised open label (standard care); wks, weeks.

Univariate analyses did not identify any significant differences based on the pre-defined subgroups (Table 23).

Summary: Analyses suggest that treatment with ESA in patients with CIA increases the risk for thromboembolic events (RR 1.46; 95% CI 1.08 to 1.99). Five per cent (103/2,029) participants who received ESA reported thromboembolic events, compared to 3% (66/1,984) of patients in control groups. There was no heterogeneity between the trials (I^2=0%, p=0.733). Overall, the data confirm results from prior analyses; an increased risk of thromboembolic events in patients with ESA compared to controls.

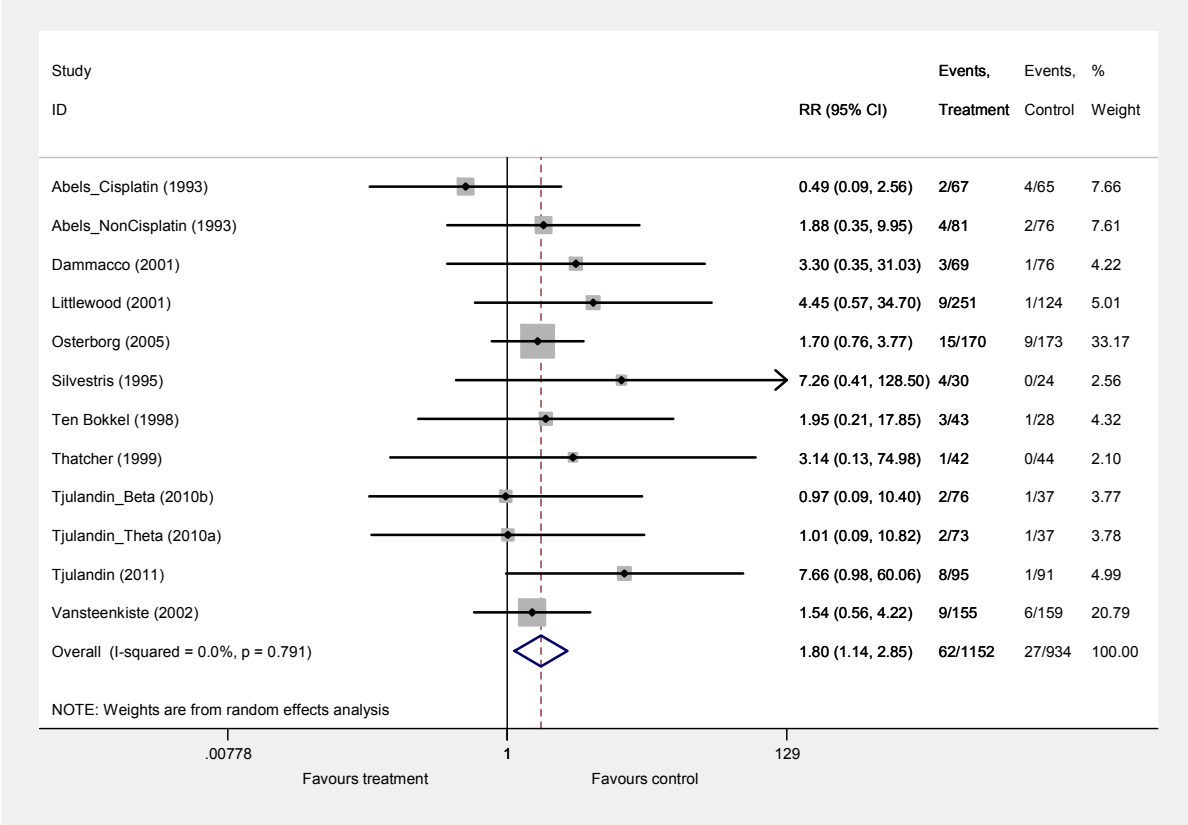
4.2.6.3.2. Hypertension

We identified ten studies that measured hypertension. Overall, the analysis included nine studies with 2,032 participants; of these, 1,122 participants were treated with ESAs. As two multi-arm studies (**Abels and colleagues, 1993** and **Tjulandin and colleagues, 2010**)[45,54]

were split into subsets the number of studies displayed is 12. Two included studies were newly identified in the update searches (**Tjulandin and colleagues, 2010** and **Tjulandin and colleagues, 2011**).[45,76] If hypertension was not reported, we used data from the Cochrane review by **Tonia and Colleagues (2012)**[10] in the PenTAG analyses.

Hypertension was reported in 62 out of 1,152 participants (5%) treated with ESAs compared to 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; see **Figure 17**) favouring controls. There was no statistical heterogeneity between the trials (I^2=0%; X^2=7.10, df=11, p=0.791); however the direction of the effects of ESA with regard to hypertension varied across the individual trials (Figure 17). To test whether publication bias was present in the sample included in the meta-analysis, a funnel plot was constructed (Appendix L). 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 ESA on hypertension were independent from when the trial results were published (p=0.735); the meta-regression plot is presented in Appendix L.

Figure 17. Hypertension: overall (random effects)



Key: CI, confidence interval; events, treatment, control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: (a) Random effects (Der-Simonian Laird pooled RR); (b) Trial with multiple experimental arm split into subsets in the analysis: Tjulandin and colleagues, 2010a, b reports data for epoetin theta (2010a) and epoetin beta (2010b) and Abels and colleagues 1993 reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

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 L.

Pre-specified subgroup analyses were conducted (Table 24). 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 24. All covariates showing a significant effect (p<0.05) in a univariate analysis were further considered in a model selection.

Table 24. Hypertension: subgroup analyses

	Trials	RR	CI	I^2	Tau^2
Overall	**12**	**1.80**	**1.14 − 2.85**	**0%; p=0.79**	**0**
Inclusion Hb					

≤11.0 g/dl	9	1.68	1.03 – 2.74	0%; p=0.64	0
>11.0 g/dl	3	3.06	0.78− 11.91	0%; p=0.86	0
F (between:within)			$F_{(1,10)}$ =0.07; p=0.79		
Baseline Hb					
≤10.0 g/dl	9	1.76	1.07 − 2.89	0%; p=0.54	0
≤11.0 g/dl	1	1.88	0.35 − 9.95	NA	0
≤12.0 g/dl	1	1.95	0.21 − 17.85	NA	0
≤14.5 g/dl	1	3.14	0.13 − 74.98	NA	0
F (between:within)			$F_{(3,8)}$ =0.10; p=0.96		
Target Hb					
≤13.0 g/dl	3	2.19	0.53 – 9.12	16.8%; p=0.30	0.27
>13.0 g/dl	6	1.89	1.09 − 3.28	0%; p=0.94	0
NR	3	1.39	0.35 – 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 − 3.28	0%; p=0.97	0
Haematological tumours	5	1.63	0.88 − 3.02	0%; p=0.48	0
Mixed	2	5.83	1.36 − 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 − 17.85	NA	0
Other cancers	11	1.79	1.12 − 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 − 2.41	0%; p=0.81	0
Non-platinum-containing	4	2.20	1.15 − 4.19	0%; p=0.49	0
NR	1	7.26	0.41 − 128.50	NA	0
Mixed	2	3.25	0.52 − 20.25	0%; p=0.99	0
F (between:within)			$F_{(3,8)}$ =3.07; p=0.09		
Iron supplementation					
Iron in both arms	6	2.13	1.13 − 3.99	0%; p=0.55	0
No iron supplementation	1	3.14	0.13 − 74.98	NA	0
NR	5	1.44	0.72 − 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 − 2.76	0%; p=0.65	0
ROL	3	3.17	0.68 − 14.72	0%; p=0.77	0
F (between:within)			$F_{(1,10)}$ =0.84; p=0.38		
Study duration					
12–16 wks	8	1.61	0.98 − 2.64	0%; p=0.66	0
>20 wks	4	3.58	1.05 − 12.24	0%; p=0.90	0
F (between:within)			$F_{(1,10)}$ =1.69; p=0.22		

ESA					
Erythropoetin	11	1.88	1.12 − 3.15	0%; p=0.73	0
Darbepoetin	1	1.54	0.56 − 4.22	NA	0
F (between:within)			$F_{(1,10)}$ =0.38; p=0.55		

Key: ESA, erythropoiesis stimulating agents; Hb, haemoglobin; NA, not applicable; NR, not reported; RCT, randomised controlled trial; ROL, randomised open label (standard care); wks, weeks.

Univariate analyses did not identify any significant differences based on the pre-defined subgroups (Table 24).

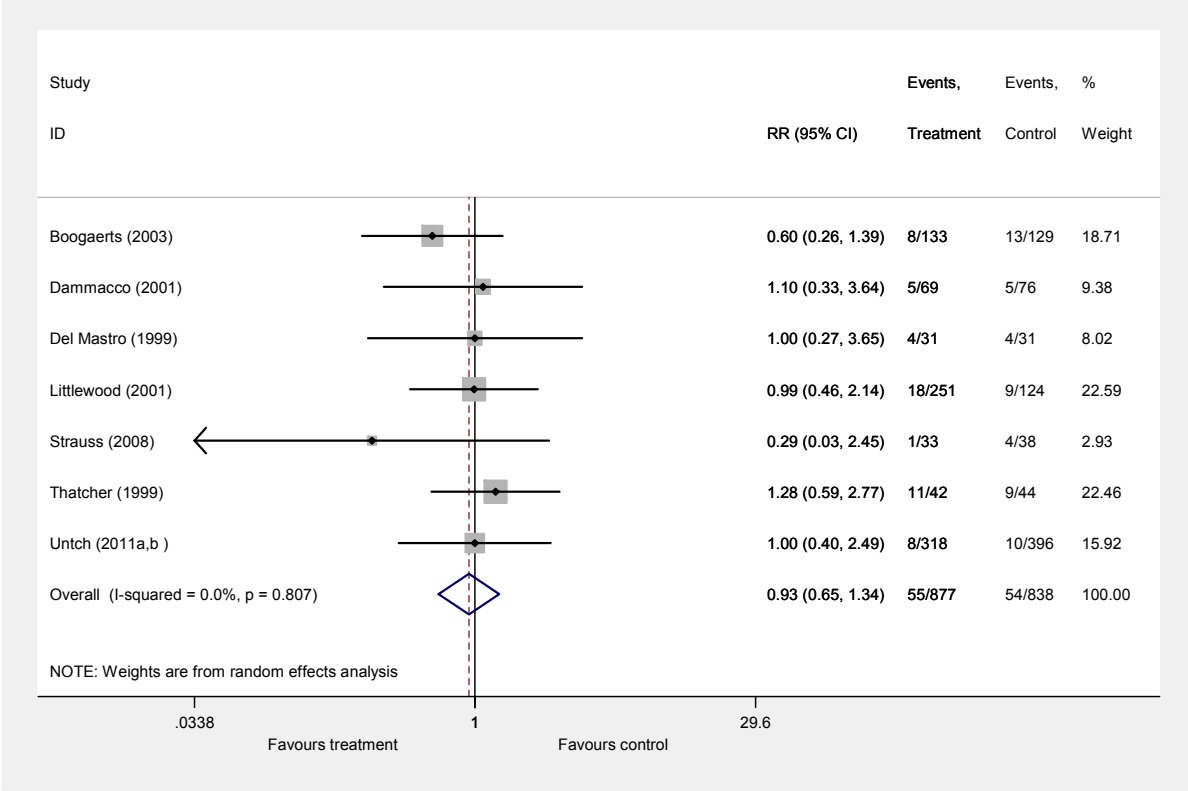
Summary: Analyses suggest that treatment with ESAs in patients with CIA increases the number of hypertension events (RR 1.80 95% CI 1.14 to 2.85). Five per cent (62/1,152) of participants who received ESA reported hypertension, compared to 3% (27/934) of participants in control groups. There was no heterogeneity between the trials (I^2=0%, p=0.791). Overall, the data confirm results from prior analyses; an increased risk of hypertension in patiens with ESA compared to controls.

4.2.6.3.3. Thrombocytopenia/haemorrhage

Data for thrombocytopenia (decrease of platelets in the blood)/haemorrhage were available from seven studies. Overall, the analysis included seven studies with 1,715 participants. If thrombocytopenia/haemorrhage was not reported, data were obtained from the Cochrane review by **Tonia and Colleagues (2012)**.[10]

Thrombocytopenia/haemorrhage was reported in 55 out of 877 participants treated with ESAs compared to 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; see Figure 18) that was not statistically significant. There was no statistical heterogeneity between the trials (I^2=0%; X^2=3.02, df=6, p=0.807); however the direction of the effects of ESA 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.[50]

Figure 18. Thrombocytopenia/haemorrhage: overall (random effects)



Key: CI, confidence interval; events treatment control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: (a) Random effects (Der-Simonian Laird pooled RR)

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

Pre-specified subgroup analyses and meta-regressions 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 patients with cancer indused anaemia did not have an effect on thrombocytopenia/haemorrhage (RR 0.93 95% CI 0.65 to 1.34). Six per cent (55/877) of participants who received ESA reported thrombocytopenia/haemorrhage, and 6% (54/838) of participants in 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 to previous analyses. Data suggest that ESAs do not have a detrimental effect on thrombocytopenia/haemorrhage. However, these results should be interpreted with caution, see Section 4.2.7 (page 149**)** for more details.

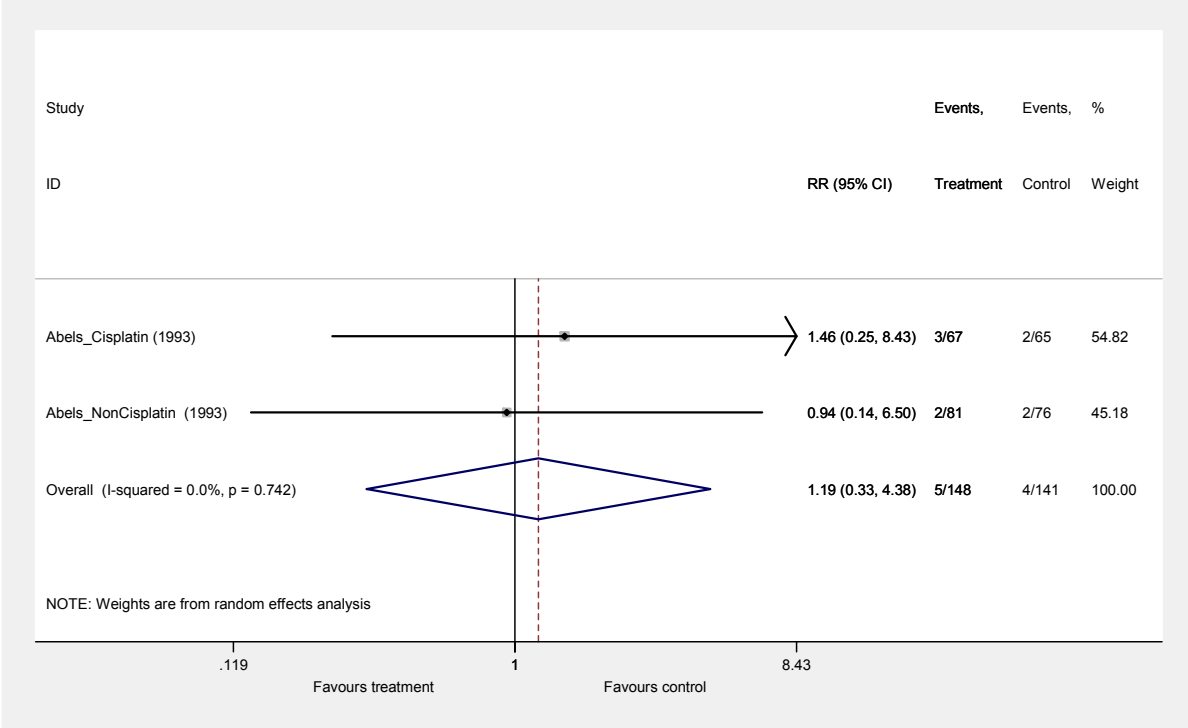
4.2.6.3.4. Seizures

Data on seizures were available from one study (**Abels and colleagues, 1993**)[54] including 289 participants. As this trial was split into subsets the number of studies in the Forest plot is two. If seizure was not reported, we used data from the Cochrane review by **Tonia and Colleagues (2012)**[10] in the PenTAG analyses.

Overall, five events of seizure were reported in the ESA-treated group (n=148) and four events in the control group (n=141), resulting in a RR of 1.19 (RR 1.19; 95% CI 0.33 to 4.38; see Figure 19**)**. There was no heterogeneity between the trials (I^2=0%, p=0.742; X^2=0.11, df=5, p=0.742); although the two included trials indicated effects in opposite directions. Because there were only two primary studies included in the meta-analysis, the funnel plot analysis to test whether publication bias was present was not conducted.[50] The fixed effects meta-analysis undertaken as a sensitivity analysis showed similar non-significant results (RR 1.19, 95% CI 0.33, 4.35; I^2=0%, p=0.742; Appendix L).

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

Figure 19. Seizures: overall (random effects)



Key: CI, confidence interval; events, treatment, control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: (a) Der-Simonian Laird pooled RR; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Abels and colleagues 1993** reported data for participants on plat-based and non-plat based chemo

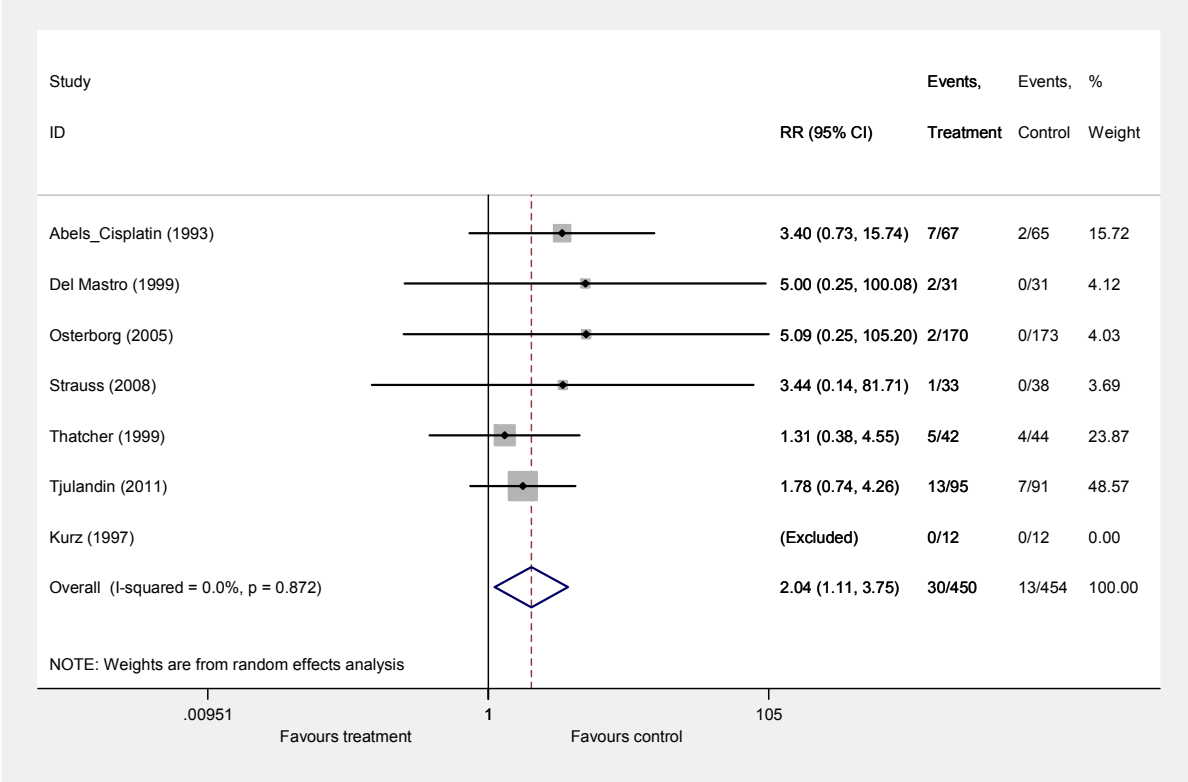
Summary: Analyses suggest that treatment with ESAs in patients with CIA did not have a significant effect on seizures (RR of 1.19; 95% CI 0.33 to 4.38). Less than 1% (5/148) of participants who received ESAs had a seizure, similarly less than 1% (4/141) of participants in control groups had a seizure. There was no heterogeneity between the trials (I^2=0%, p=0.742). While 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, can not be excluded. Overall, the data confirm results from prior analyses.

4.2.6.3.5. Pruritus (pruritus, rash and irritation)

We identified seven studies that measured pruritus (pruritus, rash and irritation were considered; **Tonia and colleagues, 2012**[10]) including 904 participants. Of these, 450 participants were treated with ESA. Two included studies were newly identified in the update searches (**Strauss and colleagues, 2008**; **Tjulandin and colleagues, 2011**).[75,76] If pruritus events were not reported, we used data from the Cochrane review by **Tonia and Colleagues (2012)**[10] in the PenTAG analyses. One study (**Kurz and colleagues 1997**),[67] did not report any events of pruritus in the treatment and placebo arms, therefore the number of trials included in the meta-analysis is six.

The random effects meta-analysis showed a risk ratio of 2.04 (RR 2.04; 95% CI 1.11 to 3.75; see Figure 20) favouring controls. There was no heterogeneity between the trials (I^2=0%, p=0.872; X^2=1.83, df=5, p=0.872); with all of the individual studies indicating a detrimental effect of treatment with ESA with regard to the number of pruritus. Because there were only six primary studies included in the meta-analysis, the funnel plot analysis to test whether publication bias was present was not conducted.[50] 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 L.

Figure 20. Pruritus: overall (random effects)



Key: CI, confidence interval; events, treatment, control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: (a) Random effects (Der-Simonian Laird pooled RR)

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

Summary: Analyses suggest that treatment with ESA in patients with cancer treatment induced anaemia increases the number of cases of pruritus (RR 2.04; 95% CI 1.11 to 3.75). Seven per cent (30/450) participants who received ESA reported pruritus, compared to 3% (13/454) of patients in 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 to previous analyses. Data suggest that ESAs increase the number of cases of pruritus in patients with chemotherapy induced anaemia. The definition of pruritus considered pruritus, rash and irritation (as defined in the Cochrane review [**Tonia and colleagues, 2012**[10]]). The marked variation in event rates may be due to the definition of pruritus. However, these results should be interpreted with caution, see Section 4.2.7 (page 149) for more details.

4.2.6.3.6. Safety-related outcomes: summary

Table 25. Safety-related outcomes results comparison: Wilson, 2007 vs Tonia, 2012 vs PenTAG 2013[1,10]

	Wilson, 2007[b]	Tonia, 2012[b]	PenTAG, 2013[b]	PenTAG, 2013[c]
Safety-related outcome				
Thromboembolic events	NR	RR 1.52 95% CI 1.34−1.74 $X^2_{(het)}$ 34.99; df 55 (p=0.980) 60 trials, n=15,498	RR 1.52 95% CI 1.13−2.05 $X^2_{(het)}$ 9.52; df 14 (p=0.872) 15[d] trials, n=1,984	RR 1.46 95% CI 1.07−1.99 $X^2_{(het)}$ 9.52; df 14 (p=0.872) 15[d] trials, n=1,984
Hypertension	NR	RR 1.30 95% CI 1.08−1.56 $X^2_{(het)}$ 26.87; df 34 (p=0.800) 35 trials, n=7,006	RR 1.97 95% CI 1.27−3.07 $X^2_{(het)}$ 7.10; df 11 (p=0.791) 10 trials, n=2,032	RR 1.80 95% CI 1.14−2.85 $X^2_{(het)}$ 7.10; df 11 (p=0.791) 10 trials, n=2,032
Thromobocytopenia/ haemorrhage	NR	RR 1.21 95% CI 1.04−1.42 $X^2_{(het)}$ 14.50; df 20 (p=0.800) 21 trials, n=4,220	RR 0.91 95% CI 0.63−1.30 $X^2_{(het)}$ 3.02; df 11 (p=0.807) 7 trials, n=1,715	RR 0.93 95% CI 0.65−1.34 $X^2_{(het)}$ 3.02; df 11 (p=0.807) 7 trials, n=1,715
Seizure	NR	RR 0.77 95% CI 0.42−1.41 $X^2_{(het)}$ 6.19; df 6 (p=0.400) 7 trials, n=2,790	RR 1.19 95% CI 0.33−4.35 $X^2_{(het)}$ 0.11; df 1 (p=0.742) 2 trials, n=289	RR 1.19 95% CI 0.33−4.38 $X^2_{(het)}$ 0.11; df 1 (p=0.742) 2 trials, n=289
Pruritus	NR	RR 1.49 95% CI 0.99−2.24 $X^2_{(het)}$ 13.18; df 15 (p=0.590) 16 trials, n=4,346	RR 2.16 95% CI 1.18−3.92 $X^2_{(het)}$ 1.83; df 5 (p=0.872) 7[d] trials, n=904	RR 2.04 95% CI 1.11−3.75 $X^2_{(het)}$ 1.83; df 5 (p=0.872) 7[d] trials, n=904

Key: CI, confidence interval; df, degrees of freedom; het, heterogeneity; HR, hazard ratio; RR, relative risk
Notes: (a) change from baseline to end of study; **(b)** fixed effects (Mantel-Haenzel); **(c)** random effects (Der-Simonian Laird); **(d)** one study was excluded as no events were reported in treatment and placebo arms; **(e)** the number of trials includes multiple experimental arms for some studies

Overall, data suggest increased risk for thromboembolic events and hypertension consistent with previous estimates (Table 25). Data for seizures are also consistent with previous meta-analyses, showing no effects of ESA on seizures (Table 25). Of note is that all adverse effects are relatively rare compared to other outcomes considered in this report (eg. RBCT, Hb change and mortality).

The PenTAG analyses suggest an increased risk of pruritus; a significant diffrence between patients treated with ESA compared to participants in control arms was found (RR 2.04; 95% CI 1.11 to 3.75). In comparision, the Cochrane review (**Tonia and colleagues, 2012**)[10] did not find significant diffrences between patients treated with ESA and in control arms (RR 1.49; 95% CI 0.99 to 2.24). It must be highlighted, that both the current review and the

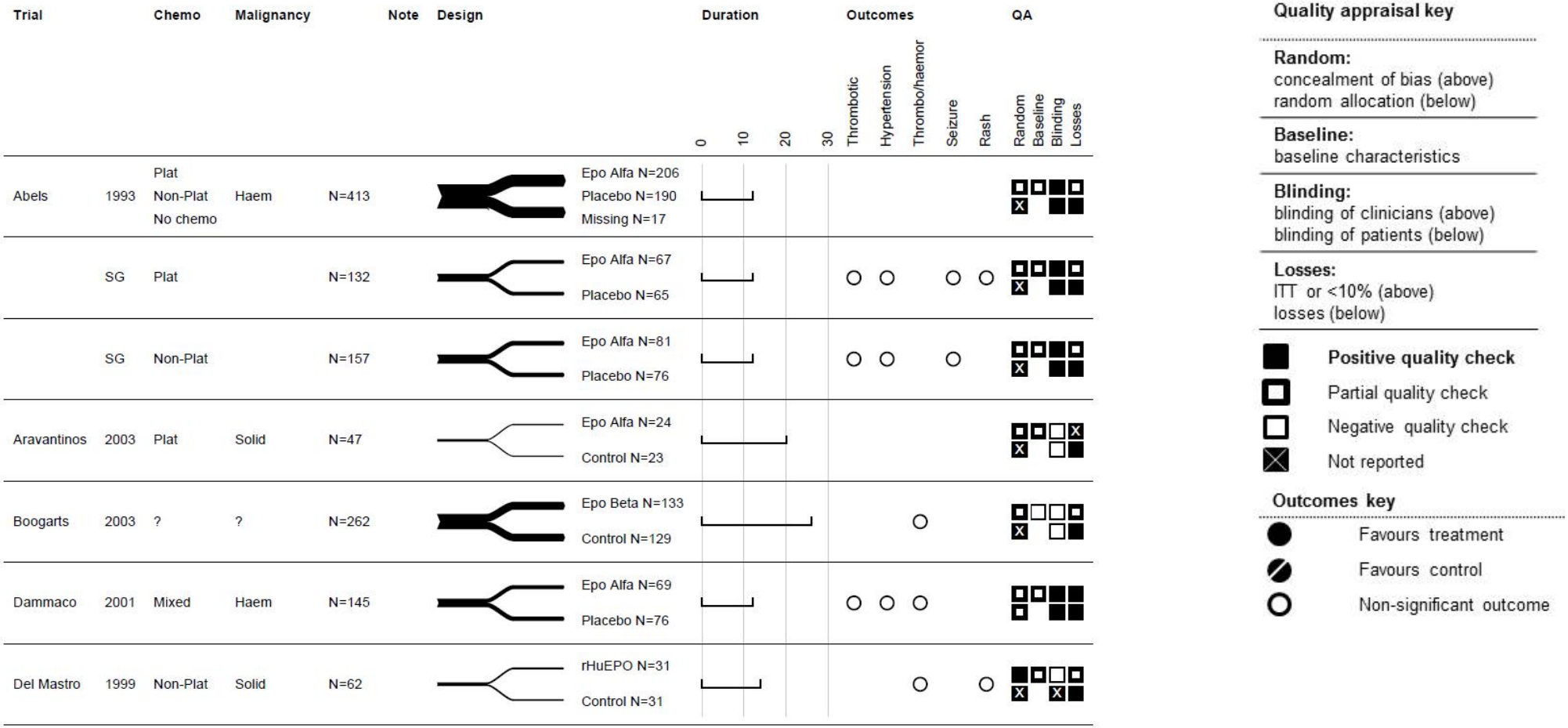
Cochrane review (**Tonia and colleagues, 2012**)[10] combined events of skin rash, irritation and pruritus, in the meta-analyses. However, the rates of skin rash, irritation and pruritus may differ and the way this outcome has been defined may be the cause of the marked variation in event rates..

Also the summary estimate for risk of thrombocytopenia/haemorrhage associated with ESA treatment found in the PenTAG review was RR of 0.93 (RR 0.93; 95% CI 0.65 to 1.34) suggesting that treatment with ESAs in patients with cancer indused anaemia did not have an effect on thrombocytopenia/haemorrhage. However the Cochrane review (**Tonia and colleagues, 2012**)[10] found RR of 1.21 (RR 1.21; 95% CI 1.04 to 1.42) suggesting detrimental effects of ESA on thrombocytopenia/haemorrhage.

It must be emphasised that the current analyses included only studies complying with the licenced ESA dose, while the Cochrane review did not apply any restrictions regarding the ESA posology. However, these results should be interpreted with caution, see Section 4.2.7) for more details.

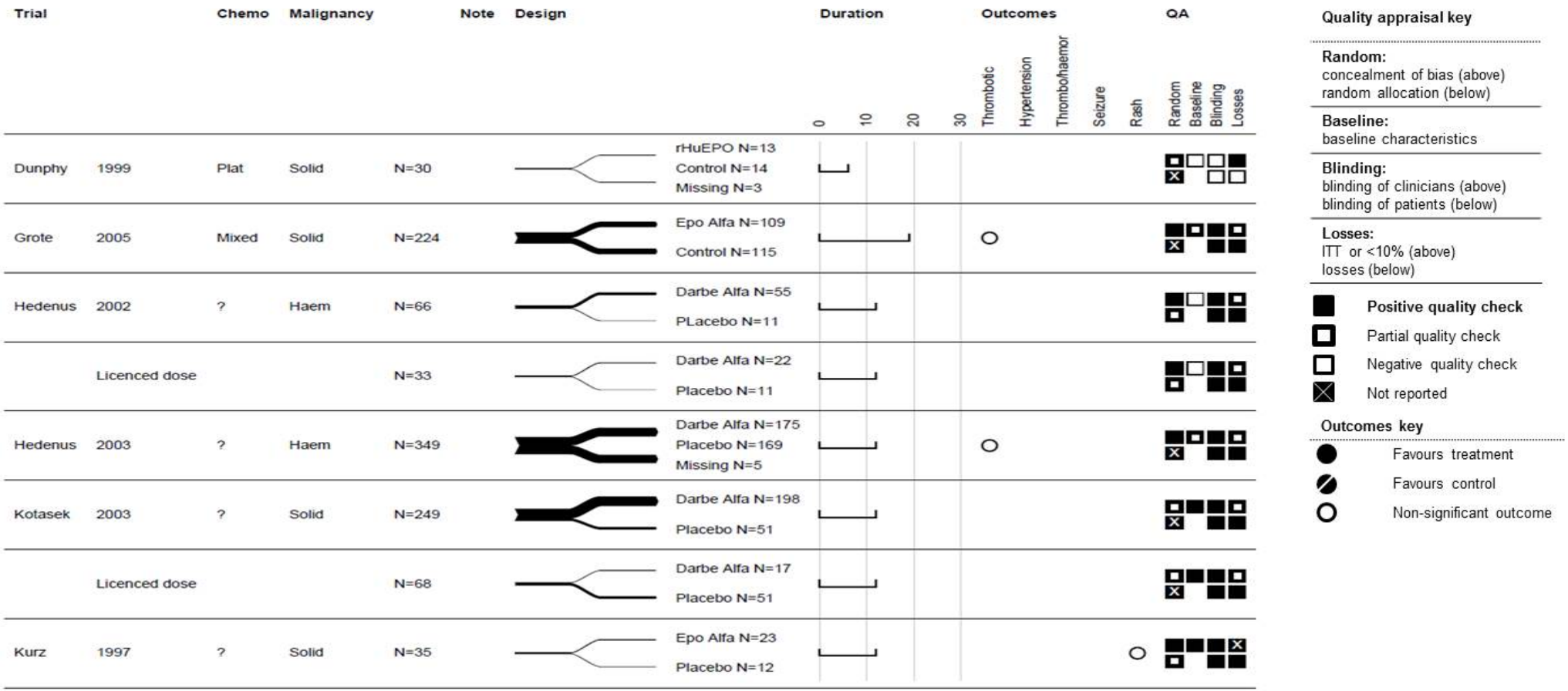
A graphical summary of study characteristics and results for the safety outcomes is presented in Figure 21.

Figure 21. Safety-related outcomes: Graphical summary



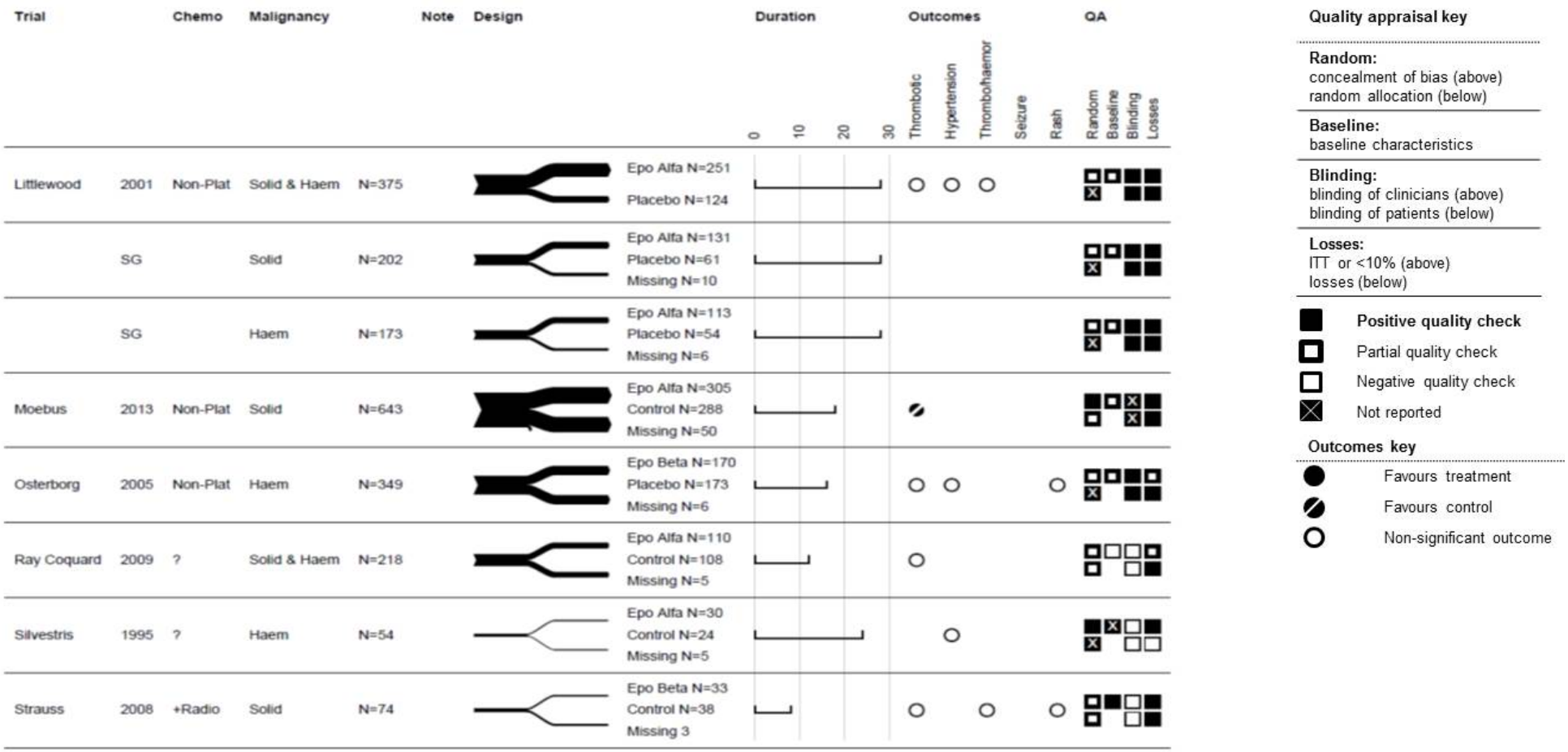
Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

Figure 21. Safety-related outcomes: Graphical summary (continued)



Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; Plat, platinum.
Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

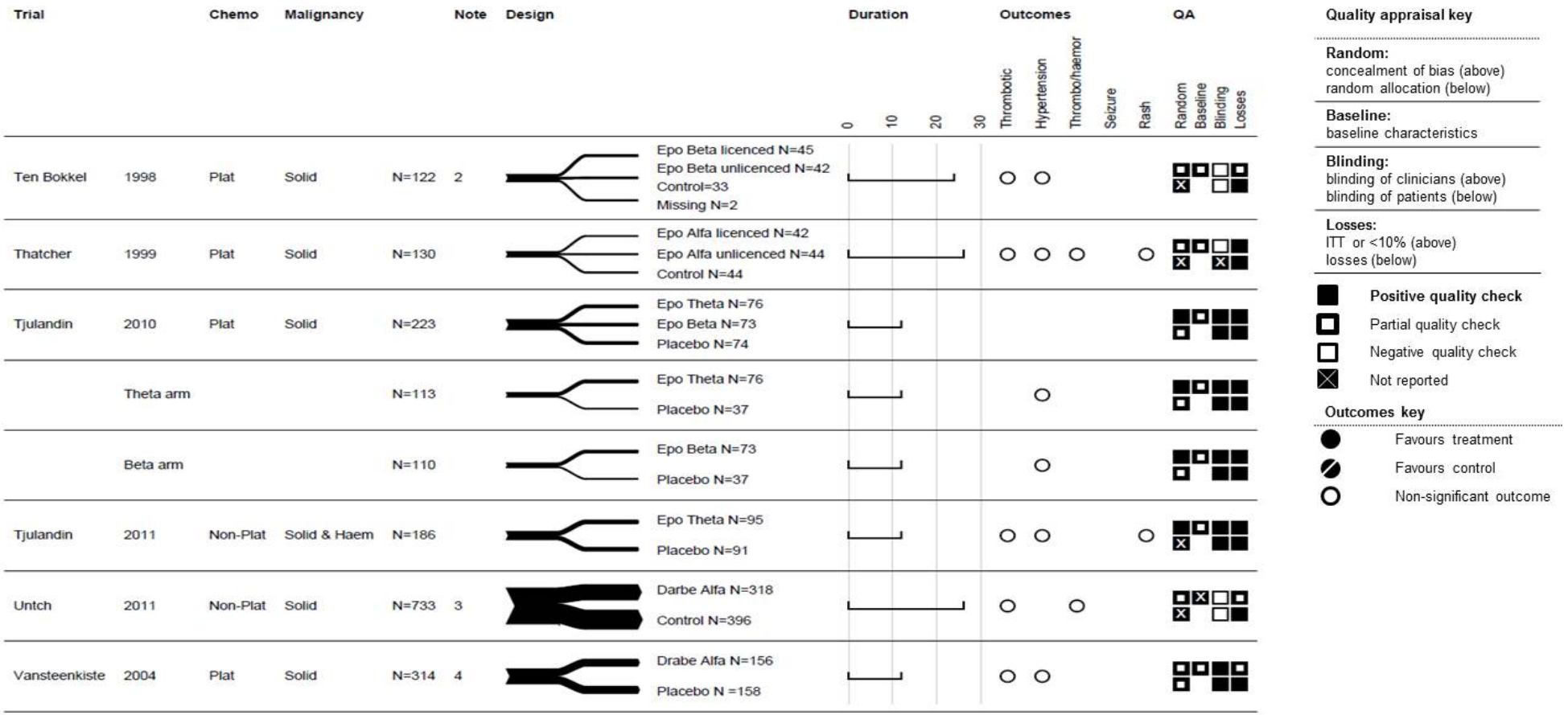
Figure 21. Safety-related outcomes: Graphical summary (continued)



Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; Plat, platinum.

Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

Figure 21. Safety-related outcomes: Graphical summary (continued)



Key: Chemo, chemotherapy: ?: unknown. Duration, recorded in weeks; Outcomes: Darbe, darbepoetin; Epo, epoetin; Haem, haematological; N: Number of participants; Non-plat, non-platinum; Plat, platinum.

Notes: 1: Hb chg.: Epo Alfa N=63; 3: HaemR & units: Epo Alfa N=66 & PBO N=66; 4: Hb chg.: rHuEPO N=28 & Control N=24; 5: Hb chg.: Epo Alfa N=64 & Control N=58; 6 : Hb chg.: Darbe Alfa N=17 & PBO N=6; 7: RBCT: Darbe Alfa N=167 & PBO N=165; 8: HaemR = participants with inc. ≥2 g/dl and/or Hb>12 g/dl; 9: RBCT: Epo Alfa N=251 & PBO N=124; 10: Latin sq. des.; 11: Hb chg.: Epo Beta N=138 & PBO N=142; 12: Hb chg.: licenced Epo Alfa N=34 & Control N=24; 13: Hb chg.: Darbe Alfa N=330 & PBO N=359.

4.2.7. Specific subgroup analyses

Iron supplementation + erythropoiesis-stimulating agents

In 16 of the included trials participants received iron supplementation. Usage varied among the studies; e.g. oral iron supplementation given as needed (dosage and trigger level differed between studies) or as standard, and/or i.v. iron supplementation (see Section 4.2.2.4, page 73). In addition, limited detail from the publications hinders the interpretation of this outcome. Subgroup analyses did not identify any significant differences between groups.

People with any type of cancer receiving platinum-based chemotherapy

Five studies (**Abels, 1993**;[54] **Aravantinos, 2003**;[63] **Ten Bokkel, 1998**;[47] **Tjulandin, 2010**;[45] **Vansteenkiste, 2002**[72]) 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 26.

Table 26. People with any type of cancer receiving platinum-based chemotherapy; outcomes summary

Anaemia-related outcomes[a]			
Hb change	**HaemR**	**RBCT**	**RBC units**
WMD 1.42 95% CI 1.10 –1.75 I^2=0%; p=0.774 Trials: 5	RR 3.93 95% CI 2.50–6.17 I^2=11.9%; p=0.321 Trials: 3	RR 0.52 95% CI 0.37–0.72 I^2=60.0%; p=0.029 Trials: 6	WMD -1.11 95% CI -1.58 – -0.64 I^2=0%; p=0.685 Trials: 3
Malignancy-related outcomes			
Tumour response	**Overall survival**	**On-study mortality**	
RR 0.91 95% CI 0.62–1.33 I^2=NA Trials: 1	HR 0.67 95% CI 0.46 − 0.98 I^2=14.5%; p=0.319 Trials: 4	HR 0.63 95% CI 0.34 – 1.18 I^2=36.0%; p=0.196 Trials: 4	
Safety-related outcomes			
Thromboembolic events	**Hypertension**	**Seizures**	**Pruritus**
RR 1.06 95% CI 0.51 – 2.20 I^2=0%; p=0.473 Trials: 3	RR 1.17 95% CI 0.57–2.41 I^2=0%; p=0.808 Trials: 5	RR 1.19 95% CI 0.33–4.38 I^2=0%; p=0.742 Trials: 2	RR 3.40 95% CI 0.73–15.74 I^2=NA Trials: 1

Key: CI, confidence intervals; Hb, haemoglobin; HR, hazard ratio; RBC, red blood cell; RBCT, red blood cell transfusion; RR, risk ratio; WMD, weighted mean difference.
(**a**) the number of trials includes multiple experimental arms for some studies.

Results from this subgroup analysis are consistent with

	findings from the overall analysis for the anaemia-related outcomes; i.e. improved haemR and reduction in RBCT requirements and are different compared to the results erported in the Cochrane review (**Tonia and colleagues, 2012**)[10]. Similar to the overall analysis, results for the malignancy-related outcomes (overall survival and on-study mortality) suggest 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 confidence intervals remain wide. It is also important to remember that multiple testing issues arise when subgroups are tested and that confidence intervals presented here have not been adjusted for multiple testing.
People with head and neck malignancies receiving platinum-based chemotherapy	No studies were identified that evaluated people with head and neck malignancies receiving platinum-based chemotherapy.
Women with ovarian cancer and women with ovarian cancer receiving platinum-based chemotherapy	Only one included study evaluated participants with ovarian cancer (**Ten Bokkel, 1998**[47]); all participants (n=122) received platinum-chemotherapy. The outcomes measured were: Hb change, RBCT, RBC units transfused, and safety. The point estimates for these outcomes are reported in Table 27. Other included studies may have included a proportion of ovarian cancer patients; however, results are reported for the whole study population and not by malignancy type.

Table 27. Women with ovarian cancer and women with ovarian cancer receiving platinum-based chemotherapy; outcomes summary

Anaemia-related outcomes			
HaemR	**Hb change**	**RBCT**	**RBC units**
NR	WMD 1.23 95% CI 0.48–1.98 Trials: 1	RR 0.11 95% CI 0.03–0.47 Trials: 1	WMD -0.94 95% CI -1.76 – -0.12 Trials: 1
Malignancy-related outcomes			
Tumour response	**Overall survival**	**On-study mortality**	
RR 0.91 95% CI 0.62–1.33 Trials: 1	NR	NR	
Safety-related outcomes			
Thromboembolic events		**Hypertension**	
RR 3.70 95% CI 0.18–74.51 Trials: 1		RR 0.11 95% CI 0.03–0.47 Trials: 1	
Key: Hb, haemoglobin; NR, not reported; RBC, red blood cell; RBCT, red blood cell transfusion; RR, risk ratio; WMD, weighted mean difference			

Data confirm results from prior analyses that ESAs reduce the risk of RBCT (RR 0.11 [95% CI 0.03–0.47), improve physiologic parameters such as Hb level (Hb change WMD 1.23 (95% CI 0.48–1.98), but increase the risk for thromboembolic events (RR 3.70 (95% CI 0.18–74.51). Overall survival was not measured in this study.

People unable to receive blood transfusions

No trials were identified that evaluated people unable to receive blood transfusions. However, it is reasonable to assume that ESAs are likely to work in improving Hb in this sub-population. 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. Fortunately this is a small group (Jehovah's Witnesses and people who have multiple antibodies to red cells because they have required regular transfusions in the past).

4.2.8. 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 this we also retrospectively considered this criteria in combination with

inclusion Hb criteria (closer to the licence ≤11 g/dl and >11 g/dl), and target Hb (closer to the licence ≤13 g/dl and >13 g/dl).

Compared to the Cochrane review (**Tonia and colleagues, 2012**)[2] and the previous HTA review (**Wilson and colleagues, 2007**)[1] a trend associated with the administration of ESAs according to licence recommendations was noticed. It appeared that the effectiveness of some outcomes was improved when ESAs were evaluated closer to their licenced indications; e.g. dose, inclusion Hb level (≤11 g/dl), and/or target Hb leve l (≤13 g/dl). The results for all outcomes as defined by these aspects are summarised in Table 28, and the effectiveness estimates were consistent with previously reported estimates for the anaemia-related outcomes (Table 19).

The effectiveness of malignancy-related outcomes did appear to be affected by the licence application and point estimates were notably different to those reported in previous analyses (Table 22 and Table 28). Compared to the Cochrane review (**Tonia and colleagues, 2012**)[10] which reported a detrimental effect of ESAs on survival and on-study mortality, the PenTAG review did not identify any significant differences between the ESA and control groups. In addition, in studies evaluating ESAs closest to their licenced indications the point estimate decreased (suggesting lower mortality in patients taking ESA) (Table 28). However, these results should be interpreted with caution, as the point estimates are not statistically significant and the confidence intervals around the estimate remain wide.

Similarly, although results for tumour response from the PenTAG review agree with the Cochrane review (**Tonia and colleagues, 2012**),[10] the closer the studies complied with the licenced administration of ESAs, the larger the point estimate (suggesting better tumour response in patients taking ESA) (Table 28). Again, this estimate should be interpreted with caution as they are not statistically significant and the confidence intervals around the estimate are very wide.

Safety outcomes were also affected by the application of the licence (Table 25 and Table 28). The point estimates of pruritus and hypertension did not appear to be affected by the licence application and are consistent across the subgroup analyses (Table 28), suggesting increase in pruritus and hypertension events in participants taking ESA compared to controls. Of note though is that the increase in pruritus was not found significant by the Cochrane review (**Tonia and colleagues, 2012**).[10]

In addition, the Cochrane review (**Tonia and colleagues, 2012**)[10] found a significant increase in thromobocytopenia/haemorrhage events, while the PenTAG review did not

identify any significant differences between the ESA and control groups (Table 28). Overall, the effectiveness of thromobocytopenia/haemorrhage and seizures does not appear to be affected by the application of licence (Table 28).

Importantly, although results from the PenTAG review for thromboembolic events agree with the Cochrane review (**Tonia and colleagues, 2012**),[10] suggesting an increase in thromboembolic events in patients with ESA compared to controls, the closer the studies were to the licence recommendations, the smaller the point estimates (suggesting fewer detrimental effects of ESA) (Table 28). Interestingly, the increase in thromboembolic events in patients taking ESA compared to controls is no longer significant (Table 28). The confidence intervals around the estimate are wide.

In summary, there appears to be some limited evidence to suggest that if the licenced recommendations for ESA administration are followed, there are no detrimental effects of ESA on-study mortality or on 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 changes are not statistically significant and the confidence intervals remain wide. The analyses may not have statistical power to detect the effects of license application on the effectiveness of outcomes, if such effects exist. It should also be noted that this is a difficult area of assessment, especially in a heterogenous mix of tumour types. Furthermore, we have not sought to address multiple testing issues which arise when considering subgroups and so inference is not straightforward.

Table 28. Effectiveness as per licence recommendations; subgroup analyses using Hb subgroups results from Littlewood and colleagues, 2001 and Vansteenkiste and colleagues, 2002

	Starting dose criteria met			Starting dose criteria met and double blind RCT			Starting dose criteria met and inclusion Hb ≤11 g/dl			Starting dose criteria met, inclusion Hb ≤11 g/dl and double blind RCT			Starting dose criteria met, inclusion Hb ≤11 g/dl and target Hb ≤13 g/dl		
Outcome	**N**	**ES (95% CI)**	**I^2; p**	**N**	**ES (95% CI)**	**I^2; p**	**N**	**ES (95% CI)**	**I^2; p**	**N**	**ES (95% CI)**	**I^2; p**	**N**	**ES (95% CI)**	**I^2; p**
Hb change[d,e]	18	**WMD 1.59 (1.33−1.84)**	75.9%; p<0.01	13	**WMD 1.70 (1.43–1.97)**	64.9%; p<0.01	13	**WMD 1.52 (1.30–1.75)**	48.1%; p=0.03	11	**WMD 1.59 (1.35–1.84)**	46.4%; p=0.05	3	**WMD 1.50 (1.16–1.83)**	0%; p=0.80
HaemR [a,d,e]	13	**RR 3.29 (2.81–3.85)**	13.4%; p=0.31	12	**RR 3.30 (2.77–3.93)**	19.5%; p=0.25	12	**RR 3.20 (2.78–3.68)**	2.0%; p=0.43	11	**RR 3.20 (2.74–3.75)**	8.9%; p=0.36	3	**RR 3.06 (2.28–4.09)**	0%; p=0.79
RBCT[b,d,e]	26	**RR 0.61 (0.55−0.68)**	22.4%; p=0.15	16	**RR 0.64 (0.58−0.72)**	6.4%; p=0.38	16	**RR 0.64 (0.57–0.71)**	7.3%; p=0.37	14	**RR 0.66 (0.59–0.74)**	0%; p=0.52	3	**RR 0.50 (0.33–0.77)**	0%; p=0.92
Units[c,d]	12	**WMD -0.87 (-1.24–-0.50)**	55.6%; p=0.01	9	**WMD -0.9 (-0.93–-0.36)**	28.0%; p=0.20	9	**WMD -0.99 (-1.41–-0.56)**	56.2%; p=0.01	8	**WMD -0.63 (-0.79–-0.47)**	0.6%; p=0.43	1	**WMD -0.56 (-0.74–-0.39)**	NA
Tumour response	7	RR 1.10 (0.86–1.41)	37.5%; p=0.14	4	**RR 1.50 (1.01–2.23)**	21.5%; p=0.28	2	RR 1.60 (0.88–2.90)	0%; p=0.70	2	RR 1.60 (0.88–2.90)	0%; p=0.70	0	NA	NA
Overall survival[d,e]	18	HR 0.97 (0.83–1.13)	42.4%; p=0.03	11	HR 0.92 (0.75–1.13)	52.4%; p=0.02	10	HR 0.91 (0.70–1.20)	51.7%; p=0.03	9	HR 0.87 (0.65–1.15)	53.7%; p=0.03	3	HR 0.50 (0.20–1.23)	29.7%; p=0.24
On study mortality[d,e]	14	HR 0.86 (0.67–1.11)	16.4%; p=0.27	11	HR 0.86 (0.63–1.17)	33.0%; p=0.14	10	HR 0.89 (0.61–1.30)	37.7%; p=0.11	9	HR 0.86 (0.56–1.32)	44.5%; p=0.07	3	HR 0.50 (0.20–1.23)	29.7%; p=0.24
T'embolic events[d]	14	**RR 1.46 (1.07–1.99)**	0%; p=0.73	9	RR 1.24 (0.81–1.90)	0%; p=0.55	7	RR 1.29 (0.66–2.54)	12.2%; p=0.34	7	RR 1.29 (0.66–2.54)	12.2%; p=0.34	1	RR 0.32 (0.01–7.74)	NA
HTN[d,e]	12	**RR 1.80 (1.14–2.85)**	0%; p=0.79	9	**RR 1.70 (1.05–2.76)**	0%; p=0.65	9	**RR 1.68 (1.03–2.74)**	0%; p=0.64	8	RR 1.61 (0.98–2.64)	0%; p=0.66	3	RR 2.19 (0.53–9.12)	16.8%; p=0.30
T'cytopenia/haemor	7	RR 0.93 (0.65–1.34)	0%; p=0.81	5	RR 0.89 (0.57–1.39)	0%; p=0.58	2	RR 0.73 (0.37–1.46)	0%; p=0.41	1	RR 1.10 (0.33–3.64)	NA	0	NA	NA
Seizures[d]	2	RR 1.19 (0.33–4.38)	0%; p=0.74	2	RR 1.19 (0.33–4.38)	0%; p=0.74	2	RR 1.19 (0.33–4.38)	0%; p=0.74	2	RR 1.19 (0.33–4.38)	0%; p=0.74	0	NA	NA
Pruritus	6	**RR 2.04 (1.11–3.75)**	0%; p=0.87	3	**RR 2.20 (1.05–4.58)**	0%; p=0.66	3	**RR 2.20 (1.05–4.58)**	0%; p=0.66	3	**RR 2.20 (1.05–4.58)**	0%; p=0.66	1	RR 1.78 (0.74–4.26)	NA

Key: HaemR, haematological response; Haemor, haemorrhage; Hb, haemoglobin; HTn, hypertension; NA, not applicable; RBCT, red blood cell transfusion; Units, units transfused per participant; RR, risk ratio; HR, hazard ratio; T'cytopenia, thrombocytopenia; T'embolic, thromboembolic; WMD, weighted mean difference.
Notes: (a) Using **Littlewood and colleagues, 2001** Hb subgroups; **(b)** Using **Littlewood and colleagues, 2001** and **Vansteenkinste and colleagues, 2002** Hb subgroups; **(c)** Using **Vansteenkinste and colleagues, 2002** Hb subgroups; **(d) Abels and colleagues, 1993** reported data for participants on plat-based and non-plat based chemotherapy which were combined; **(e) Tjulandin and colleagues, 2010** reported data for erythropoietin beta and theta which were combined.

4.3. Summary

KEY POINTS

- From a total of 1,458 titles and abstracts screened 11 systematic reviews (reported in 14 publications), and 23 RCTs (reported in 35 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 start and target haemoglobin levels, and stopping rules were all generally higher than specified in the licence. This could be due to the fact that the majority of studies (82%) were initiated before the changes to the licence in 2008
- Overall the included trials were of moderate-to-poor quality. All are flawed due to reporting issues but others more substantially. For most of the studies it was difficult to make a general assessment about quality due to reporting omissions. Most notably, all trials lacked clarity in the reporting of allocation methods (the procedure for randomisation and/or allocation concealment).
- Pooled estimates for anaemia-related outcomes were consistent with previous estimates in terms of both haematological response and requirement for RBCT in favour of ESA treatment
- The HR for survival was 0.97 (95% CI 0.83, 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 from this
- The HR for on-study mortality (deaths occurring up to 30 days after the active study period) was 0.86 (95% CI 0.67, 1.11).
- Overall, pooled data suggest 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 the data were insufficient to rule out detrimental effects
- 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 for a slight benefit associated with ESA treatment and on-study mortality or overall survival in patients with chemotherapy-induced anaemia. However, these results should be treated with caution due to the small number of studies included in the analysis.
- No studies were identified that considered the use of ESAs among people unable to receive RBCT. However, it is reasonable to assume that ESAs are likely to work in improving Hb in this sub-population. It is also reasonable to believe that if the 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.

- A trend based on adhering to the conditions of licence was noticed; i.e. start dose + include Hb level and start dose + include Hb level + target Hb level. There appears to be some limited evidence to suggest that if the licenced recommendations for ESA administration are followed, there are no detrimental effects of ESA on-study mortality or on overall mortality in patients with chemotherapy induced anaemia. These effects are consistent with improved tumour response and a decrease in the number of thromboembolic events. However, these results should be interpreted with caution, as the point estimates are not statistically significant and the confidence intervals around the estimate remain wide. Furthermore, we have not sought to address multiple testing issues which arise when considering subgroups and so inference is not straightforward.

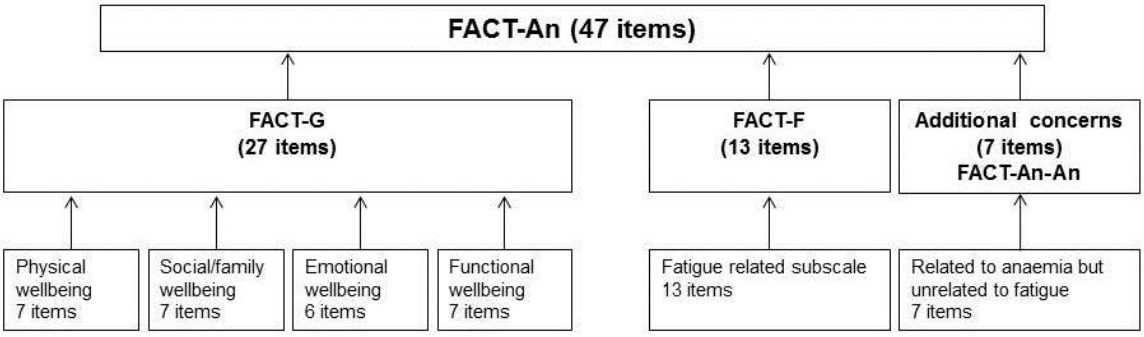
Assessment of quality of life

Anaemia is often associated with cancer, either due to the disease itself or the subsequent treatment. Therefore, the patient may experience exhaustion, fatigue, weakness, impaired concentration, respiratory distress, and chest pain which will in turn, significantly impact HRQoL.[68] Since ESAs may relieve CIA by increasing Hb levels, HRQoL is a particular outcome of interest for the interventions under review.

5.1. Tools to Measure HRQoL

A range of questionnaires are used to measure HRQoL and subsequent changes according to treatment. The scales are summarised in Table 29 (page 158), however, this review focuses on the Functional Assessment of Cancer Therapy (FACT) tool, since it is the most widely used, validated scale employed to measure cancer related fatigue (CRF) and anaemia. This tool, which asks patients to focus on HRQoL issues over the previous seven days, is part of a collection of HRQOL questionnaires beginning with a generic questionnaire called the Functional Assessment of Cancer Therapy-General (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 highlighted in Figure 22 and included in Appendix M. It should be noted that since 1997, the scale has been known as FACIT (Functional Assessment of Chronic Illness Therapy).

Figure 22. Overview FACT scales used in this review



Key: FACT, Functional Assessment Cancer Therapy (-An, Anaemia; -F, Fatigue; -G, General)

Using both anchor-based and distribution-based methods to analyse FACT-F, FACT-G, and FACT-An data on three samples of patients (n=50, n=131 and n=2,402),[96] determined the clinically important difference to be FACT-F = 3.0, FACT-G =4.0 and FACT-An = 7.0.

Table 29. Summary of scales included in this review

Scale	Type of HRQoL instrument	Domains	Items	Implication of value
FACT-General (FACT-G)[97]	Specific for use with patients of any tumour type	Physical wellbeing Social/family wellbeing Emotional wellbeing Functional wellbeing	27 Items Response between 0 and 4 for each question Maximum score 108	Increased score indicates improved HRQoL
FACT-Fatigue (FACT-F)[97]	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 Maximum score 52	Increased score indicates improved HRQoL
FACT-Anaemia (FACT-An)[97]	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 Maximum score 188	Increased score indicates improved HRQoL
FACT-An-An[97]	Symptom specific (additional concerns for anaemia)	Anaemia related questions which do not include fatigue	7 Items Response between 0 and 4 for each question Maximum score 0 to 28	Increased score indicates improved HRQoL
SF-36[98]	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.; four weeks ago.	36 Items Each scale is directly transformed into a 0–100 scale	The lower the score, the greater the disability
Nottingham Health Profile (NHP)[99]	Generic	Sleep Energy level	38 Items Scores on first component are	The higher the score, the lower the HRQoL, however, it should be noted

		Physical mobility Pain Emotional reactions Social isolation	weighted to give a score between 0 and 100.	the NHP was not originally intended to measure HRQoL and is not considered highly sensitive.[1,100]
Cancer Linear Analogue Scale or Linear Analogue Self Assessment (CLAS/LASA)[101,102]	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	Increased score indicates improved HRQoL
Brief Symptom Inventory (BSI)[103]	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 Maximum score 212	The higher the score the greater the distress
Psychological Distress Inventory (PDI)[104]	Specific for cancer patients	Reactive anxiety to cancer and its therapies Reactive depression Emotional reactions	13 Items Score between 0 and 5	A higher score indicates a higher level of distress
The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)[105]	Specific for cancer patients	A range of questions including daily activities, sleep, pain, mobility, emotions and health.	30 Item 28 items score between 0 and 4 ans 2 items between 0 and 7 Maximum score of 126	The higher the score, the higher the level of functioning

5.2. Methods

The search strategy was based on the strategy used in the previous MTA on this topic by **Wilson and colleagues (2007)**[1] 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 using the AND Boolean operator. A search filter was developed by an information scientist to retrieve HRQoL studies, ensuring an appropriate balance of sensitivity and specificity (see Section 4.2.1, page 66; and, Appendix B for further details).

The database search results were exported to Endnote (X5) and de-duplicated using the software and manual checking. The search strategies and the numbers retrieved for each database are detailed in Appendix B. After the reviewers (TJH and LL) completed the screening process, the bibliographies of included papers were scrutinised for further potentially includable studies.

Inclusion criteria were the same as the main review (see Section 4.1.2, page 59). Data were tabulated and analysed by meta-analysis to provide an overview with an estimate of overall effect.

5.3. Results

5.3.1. Studies identified

We screened the titles and abstracts of 1,268 unique references identified by the PenTAG searches and additional sources, and retrieved 221 papers for detailed consideration. Of these, 183 were excluded (a list of these items with reasons for their exclusion can be found in Appendix E). Update searches conducted on 2nd December 2013 yielded 61 titles and abstracts, none were considered eligible for inclusion. Forty one studies met the pre-specified criteria set out in the protocol and were considered eligible for inclusion in the HRQoL review. At both stages, initial disagreements were easily resolved by consensus.

We then re-assessed included studies (n=42) from the review conducted by **Wilson and colleagues (2007)**.[1] Of these, 11 primary studies reported in 15 publications were considered eligible for inclusion in the update of the HRQoL review (see Section 5.3.3.3, page 175). We identified one full paper (**Boogaerts and colleagues, 2003**) [52]of an abstract (**Coiffier and colleagues, 2001**)[53] included in the review by **Wilson and colleagues**

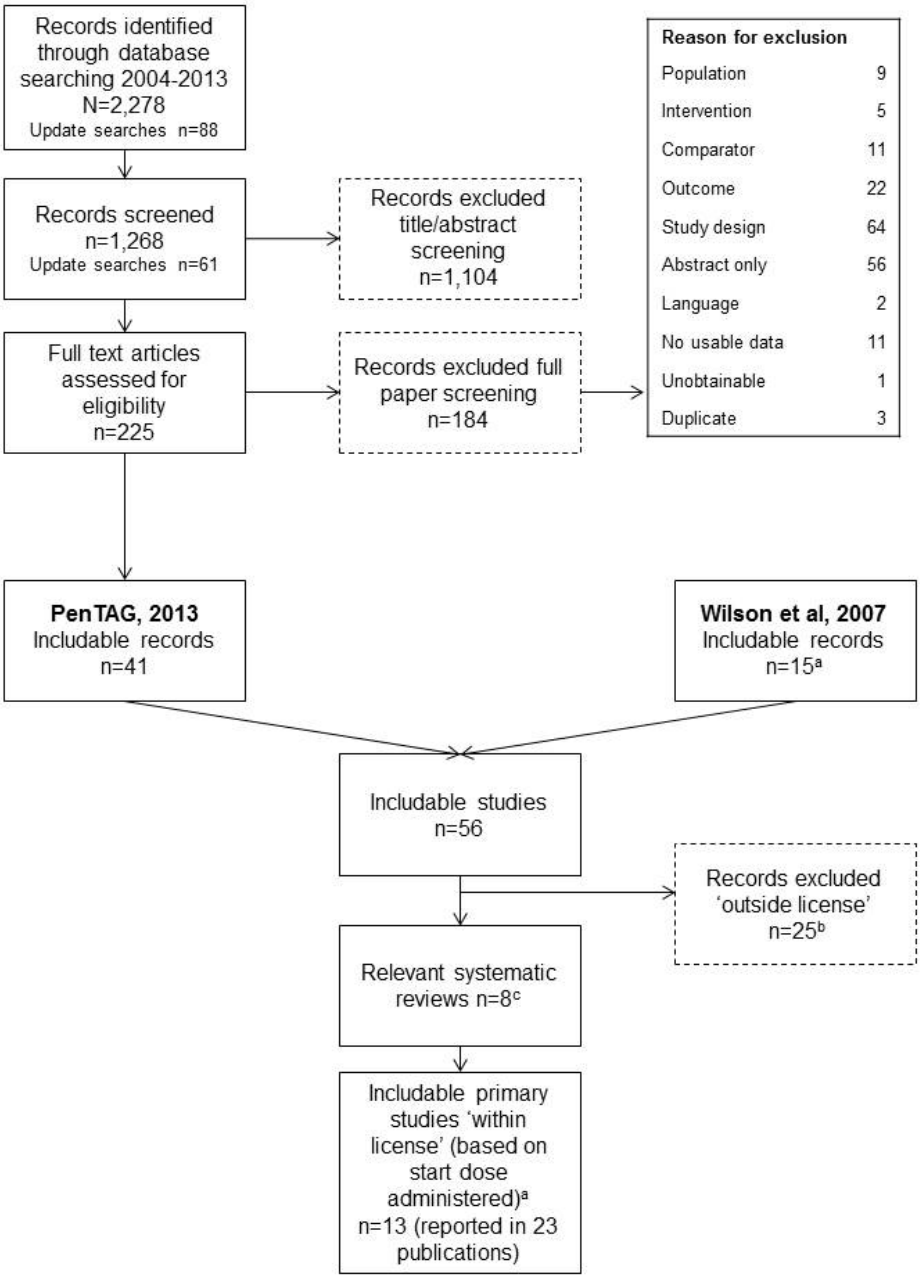
(2007).[1] In addition, one study (**Abels and colleagues, 1993**)[54] included in the previous HTA review was published in five papers; three were included in the previous review (**Abels and colleagues, 1993**;[54] **Case and colleagues, 1993**;[55] and, **Henry and colleagues, 1994**[56]), and an additional two were identified when scrutinising the bibliographies of included studies (**Henry and colleagues 1995**[57]; and, **Abels and colleagues, 1996**[58]).

Citations of the includable studies (including the 2012 Cochrane Review **[Tonia and colleagues, 2012]**[10]) were also searched and this process revealed one additional study: **Patrick and colleagues (2003)**[60] relevant to the HRQoL review (see Section 5.3.3.5, page 190).

In total, 13 studies reported in 23 publications, and eight systematic reviews were included in the review. Of these studies six retrospective analyses and eight systematic reviews were identified in the updated searches.

This process is illustrated in detail in Figure 23.

Figure 23. PRISMA flowchart: quality of life review



Key: RCTs, randomised controlled trials; SRs, systematic reviews
Notes: (a) 'within licence', based on the administration of ESAs at the licensed weight-based start dose

5.3.2. Systematic reviews

The update searches identified eight systematic reviews relevant to the review of HRQoL (**Lawrence and colleagues, 2004**[106]; **Bokemeyer and colleagues, 2007**[107]; **Ross and colleagues, 2007**[108]; **Shehata and colleagues, 2008**[109]; **Wilson and colleagues, 2007**[1];

Kvam and colleagues, 2009[110]; **Minton and colleagues, 2010**[111]; **Tonia and colleagues, 2012**[10]). Characteristics of the identified systematic reviews and quality appraisal are detailed in Appendix I.

5.3.2.1. Previous HTA review (Wilson and colleagues, 2007)[1]

The HRQoL search undertaken by **Wilson and colleagues (2007)**, identified 20 trials and used a vote counting method to summarise the data.[1] It should be noted that a slightly broader population was investigated with any type of malignant disease included, irrespective of stage or previous therapy, whereas this review only included people receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (see Section 2.7.1, page 46; and Section 3.2, page 53).

All of the trials published before 2000 (n=9) had a sample size of less than 100 and used unvalidated HRQoL instruments. Of the remaining trials, ten used FACT, five used LASA and two used SF-36. A total of 3,185 patients were evaluated.

Over half of the studies did not blind patients or physicians to treatment and over half did not include an ITT analysis or lost more than 10% of patient final evaluations. **Wilson and colleagues (2007)** consider blinding the most likely quality parameter to affect HRQoL scores, as patients may be prone to placebo effect.[1]

Although overall, the vote-counting analysis showed a positive direction of effect in favour of ESAs on HRQoL, there was considered to be potential for a variety of within-study methodological problems due to missing data and shifts in patient responses over time due to repeat questionnaires.

5.3.2.2. Cochrane Review (Tonia and colleagues, 2012)[10]

The Cochrane review undertaken by **Tonia and colleagues (2012),** also investigated the effect of ESAs on HRQoL in patients with cancer (see also Section 2.7.1.1, page 46).[10] Again, this was a slightly different population to the current review since it included participants diagnosed with malignant disease, using clinical and histological/cytological criteria, regardless of type or stage of the disease or previous therapy. Radiotherapy was also included in the current review only as an adjacent treatment to chemotherapy.

Tonia and colleagues (2012) focused on the FACT scales for measurement of HRQoL, since they considered this instrument and its subscales to have been widely used in ESA trials, have good responsiveness to change and good convergent and discriminant validity.[10] Twenty-three studies including 5,584 patients reported results on HRQoL, as measured with FACT-F, FACT-An 20 or FACT-An 47. In order to perform a meta-analysis for the FACT measures, means and SDs were extracted. Where no numerical data were given, attempts were made to either calculate or obtain the missing values. Table 30 lists the methods for those studies included in the current review.

Table 30. Methods for obtaining unreported data by Tonia and colleagues (2012), in studies used for current review[10]

Study	Method of obtaining unreported data
Boogaerts, 2003;[52] Hedenus, 2003[16]	No numerical data given, therefore means and/or SDs determined via graphs or figures.
Littlewood 2001[68]	No SDs provided, therefore previously published SDs by **Tonelli and colleagues (2009)**,[112] were used.
Kotasek, 2003,[46] Vansteenkiste, 2002[72]	The mean and SDs reported in a meta-analysis by (**Minton and colleagues, 2008**[111]), were used. These data were not available in the publications and were obtained by the authors of the meta-analysis from the authors of the original studies or the pharmaceutical companies.
Key: SD, standard deviation	

5.3.2.2.1. FACT-F 13 subscale

A total of 18 studies (4,695 patients) reported data for this outcome. The mean difference (MD) was 2.08 (95% CI 1.43 to 2.72). Heterogeneity between the included studies was moderate (I^2=53%). A funnel plot showed significant asymmetry (p=0.02772) with over reporting of studies that showed beneficial effects of ESAs (note not performed in current review as <10 studies). (Other effects found, but in populations not relevant to current review - only studies relevant to current review are included here). The observed effect was larger in unblinded trials (MD 3.76, 95% CI 2.60 to 4.92) compared with double blind trials (MD 1.33, 95% CI 0.56 to 2.10, p=0.0006).

Overall, it appears that there is an effect on fatigue-related symptoms for patients with erythropoietin or darbepoietin compared with controls; this effect, however, did not reach the threshold for a clinically important difference defined as 3.0.[96]

5.3.2.2.2. FACT-An 20

This scale is the anaemia subscale with 13 questions from FACT-F, plus seven anaemia specific questions. Six studies were included to give an estimated MD of 6.14 (95% CI 4.55 to 7.73, n=1,085). There was no evidence for statistical heterogeneity between the studies (I^2 = 0%). ESAs were found to be beneficial reaching both clinical and statistical significance.

5.3.2.2.3. FACT-An 47

Using 20 questions from the FACT-An subscale with 27 from the FACT-General scale. Nine included studies gave an estimated MD of 6.92 (95% CI 4.59 to 9.25, n=1815). Heterogeneity was high with I^2 of 85%. Since one study reported an exceptionally high change for the treatment group, a sensitivity analysis was conducted where this study was excluded. The MD became 3.46 (95% CI 0.96 to 5.96, n=1715) with I^2 of 0%. The result was still statistically significant (p=0.007) in favour of treatment; however, this was not considered likely to be clinically significant.

5.3.2.3. Cochrane Review (Minton and colleagues) (2010)[113]

The objective of this update review was to assess the efficacy of drugs for the management of cancer related fatigue.[111] ESAs were one of the interventions under investigation. Participants at any point of the cancer treatment spectrum were included. Eleven erythropoietin studies and four darbapoetin studies were included (n=2,801). Treatment was favoured with a small MD of -0.23 (95% CI 0.32 to -0.14). For studies using the FACT-F tool combined in a random effects model, a MD of -4.29 was estimated (95% CI-5.04 to -2.60).

5.3.2.4. Other systematic reviews

A further five systematic reviews appraised HRQoL evidence for ESAs in patients with CRF. Additional details can be found in Appendix I.

5.3.3. Primary and retrospective studies

Thirteen trials measuring HRQoL were reported in 23 publications (study and baseline characteristics for these studies is detailed in Appendix G).

Of these publications, 11 primary studies were included in the review by **Wilson and colleagues (2007)**[1] (**Abels and colleagues, 1993**[54]; **Kurz and colleagues, 1997**[67]; **Del**

Mastro and colleagues, 1999[65]; **Thatcher and colleagues, 1999**[48]; **Dammacco and colleagues, 2001**[64]; **Littlewood and colleagues, 2001**[68]; **Osterborg and colleagues 2002**[69]; **Vansteenkiste and colleagues, 2002**[72]; **Boogaerts and colleagues, 2003**[52]; **Hedenus and colleagues, 2003**[16]; **Kotasek and colleagues, 2003**[46]).

Abels and colleagues (1993)[54] was reported in five publications the primary publication (also in Case and colleagues, 1993[55]; Henry and colleagues, 1994[56]; Henry and colleagues, 1995[57]; and Abels and colleagues, 1996[58]) (see Section 5.3.1, page 160).

Two new primary studies were identified in the update searches (**Ray-Coquard and colleagues, 2009**; **Tjulandin and colleagues, 2011**). Six retrospective studies were identified (**Aapro and colleagues, 2004; Bajetta and colleagues, 2004; Patrick and colleagues, 2003; Osterborg and colleagues (2005) Littlewood and colleagues (2006)**; **Vansteenkiste and colleagues (2004).** (primary and multiple publications also detailed in Appendix H)

5.3.3.1. General description

The summary characteristics for included studies in the HRQoL review can be found in Figure 25, page 197 and Appendix G. As mentioned in **Wilson and colleagues (2007)**[1], all the trials published before 2000 had small sample sizes of less than 100 and used unvalidated questionnaires, such as VAS or NHP. The remaining trials, other than **Dammacco and colleagues (2001)**[64] use one of the FACT scales. HRQoL instruments used in the studies are detailed in Table 32.

Table 31. Study characteristics for HRQoL

Study year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	HRQoL measures sought	Incl. in Cochrane 2012, Y/N
WILSON AND COLLEAGUES, 2007: PRIMARY STUDIES								
Abels 1993 RCT Multiple pubs.: *Abels 1996, Henry, 1995; Henry, 1994; Case, 1993*	n = 153/213 (analysed 143/206)[a] Age, yrs: 61.2 ± 13.0 n (%) Male: 102 (47.8) Hb BL g/dl: NR Epo mU/ml BL: 146 ± 260	n = 200 (analysed 135/190) Age, yrs: 62.5 ± 12.3 n (%) Male: 95 (47.5) Hb BL g/dl: NR Epo mU/ml BL: 149 ± 217	Brand: rHuEPO[b] Dose: 150 IU/kg/TIW Dose adj.: NR Dur. of epo tx: 12 wks Dur. of trial: 12 wks[c] Follow-up: NR	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤10.5 g/dl)	Disease: haem & solid Treatment: chemo, mixed	VAS	Y
Boogaerts, 2003 ROL *(Abstract – Coiffier, 2001 included in Wilson and colleagues review)*	n = 133 Age, yrs: 62 (24–85)* n (%) Male: 46 (35) Hb BL g/dl: 9.0 (5–13)* Epo mU/ml BL: 54 (7–1,650)*	n = 129 Age, yrs: 62 (24–85)* n (%) Male: 52 (40) Hb BL g/dl: 9.2 (5–12)* Epo mU/ml BL: 58 (5–4,300)*	Brand: Epoetin beta Dose: 150 IU/kg/TIW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: NR	SC	Iron: Y, oral (as indicated by transferrin sat. level) G-CSF: NR RBCT trigger: Hb <8.5 g/dl (Hb incl. criteria level: ≤11.0 g/dl)	Disease: haem & solid Treatment: chemo, NR	VAS, SF-36, FACT-F, FACT-An-An	Y
Dammacco 2001 RCT NCT00270101; CR005911	n = 69 Age, yrs: 67 (43–80)* n (%) Male: 34 (49) Hb BL g/dl: 9.3 ± 1.27 Epo mU/ml BL: 116 (18–5,220)*	n = 76 Age, yrs: 65 (38–89)* n (%) Male: 31 (41) Hb BL g/dl: 9.6 ± 0.95 Epo mU/ml BL: 93 (10–408)*	Brand: Epoetin alfa Dose: 150 IU/kg/TIW Dose adj.: Y Dur. of epo tx: 12 Dur. of trial: 12 wks[c] Follow-up:	PBO	Iron: NR G-CSF: NR RBCT trigger: Hb <8 g/dl (Hb incl. criteria level: <11.0 g/dl)	Disease: haem Treatment: chemo, mixed[d]	CLAS, NHP	Y
Del Mastro 1997 ROL	n = 31 Age, yrs: 54 (31–68)* n (%) Male: NR Hb BL g/dl: 13.0 ± 0.7 Epo mU/ml BL: 21.0 (0–512)*	n = 31 Age, yrs: 56 (29–68)* n (%) Male: NR Hb BL g/dl: 13.1 ± 0.6 Epo mU/ml BL: 25.5 (0–800)*	Brand:rHuEPO[b] Dose: 150 IU/kg/TIW Dose adj.: Y Dur. of epo tx: 14 wks Dur. of trial: 14 wks Follow-up: 6 mths	SC	Iron: Y, oral iron (as indicated by serum iron, ferritin, & transferrin sat. levels) G-CSF: Y, 5 mcg/kg SC D4-11; C1-5 RBCT trigger: Hb <8 g/dl (Hb incl. criteria level: ≥12.0 g/dl)	Disease: solid (breast) Treatment: chemo, non-plat	PDI	Y
Hedenus 2003 RCT Multiple pubs.: *Littlewood, 2006*	n = 176 (analysed 174)[e] Age, yrs: 64.8 (13.8) n (%) Male: 87 (50) Hb BL g/dl: 9.59 (1.22) Epo mU/ml BL: 68.99 (2.3–1,522.7)*	n = 173 (analysed 170) Age, yrs: 64.6 (12.2) n (%) Male:78 (46) Hb BL g/dl: 9.5 (1.21) Epo mU/ml BL: 54.49 (10.9–3,169.1)*	Brand: Darbepoetin alfa Dose: 2.25 µg/kg/QW[e] Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 16 wks Follow-up: median ~11 mths	PBO	Iron: prn G-CSF: NR RBCT trigger: Hb ≤8 g/dl prn (Hb incl. criteria level: ≤11.0 g/dl)	Disease: haem Treatment: chemo, NR	FACT-F	Y

Kotasek **2003** **RCT** Dose response study, 5 unlicensed doses excluded	n = 17/198[a,e] Age, yrs: 58.3 (11.9)[a] n (%) Male: 56 (28)[a] Hb BL g/dl: 9.93 (1.00)[a] Epo mU/ml BL: NR	n = 51 Age, yrs: 56.2 (12.4) n (%) Male:16 (31) Hb BL g/dl: 9.87 (1.12) Epo mU/ml BL: NR	Brand: Darbepoetin alfa Dose: 2.25 µg/kg/QW[e] Dose adj.: Y, ↓ Dur. of epo tx: 12 wks Dur. of trial: 12 wks[c] Follow-up: Unclear	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤11.0 g/dl)	Disease: solid (breast, gynae, GI, lung) Treatment: chemo, NR	FACT-F	Y
Kurz **1997** **RCT**	n = 23 Age, yrs: 54.4 ± 9.7 n (%) Male: NR Hb BL g/dl: 9.88 ± 0.8 Epo mU/ml BL: NR	n = 12 Age, yrs: 52.7 ± 7.5 n (%) Male: NR Hb BL g/dl: 9.85 ± 0.60 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 U/kg/TIW Dose adj.: Y, Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: NR	PBO	Iron: Y, i.v. iron G-CSF: NR RBCT trigger: Hb <8 g/dl (Hb incl. criteria level: <11.0 g/dl)	Disease: solid (overy, cervix, uterus) Treatment: chemo, mixed[h]	VAS	Y
Littlewood **2001** **RCT** EPO-INT-1 Multiple pubs.: *Aapro, 2004; Bajetta, 2004; Patrick, 2003*	n = 251 (analysed 244) Age, yrs: 58.3 ± 14.2 n (%) Male: 85 (34) Hb BL g/dl: 9.9 ± 1.1 Epo mU/ml BL: NR	n = 124 (analysed 115) Age, yrs: 59.5 ± 13.9 n (%) Male: 39 (31) Hb BL g/dl: 9.7 ± 1.1 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 U/kg/TIW Dose adj.: Y Dur. of epo tx: up to 28 wks Dur. of trial: up to 28 wks Follow-up: 12-mth[f]	PBO	Iron: Y, oral (or i.v. as indicated by transferrin sat. level) G-CSF: No RBCT trigger: Hb <8 g/dl prn (Hb incl. criteria level: ≤10.5 g/dL or >10.5 but ≤12.0 g/dl after a ≥1.5 g/dl decrease in Hb)	Disease: solid + haem Treatment: chemo, non-plat	FACT-F, FACT-G, FACT-An-An, CLAS	Y
Osterborg **2002** **2005, follow-up** **RCT**	n = 173 (analysed 170) Age, yrs: 63 (32–86)* n (%) Male: 91 (54) Hb BL g/dl: 9.2 ± 1.1 Epo U/L BL: 38 (20–72)*	n = 176 (analysed 173) Age, yrs: 64 (28–83)* n (%) Male: 82 (47) Hb BL g/dl: 9.3 ± 1.0 Epo U/L BL: 41 (21–77)*	Brand: Epoetin beta Dose: 150 U/kg/TIW Dose adj.: Y Dur. of epo tx: 16 wks Dur. of trial: up to 16 wks Follow-up: min 17.5 mths both tx grps	PBO	Iron: Y, i.v. (or oral if i.v. precluded) G-CSF: NR RBCT trigger: Hb <8.5 g/dl or inc.in Hb <0.5 g/dl vs BL (Hb incl. criteria level: <10 g/dl[g])	Disease: haem Treatment: chemo, non-plat	FACT-F, FACT-G, FACT-An, FACT-An-An	Y
Thatcher **1999** **ROL** Multiple treatment arms, 1 unlicensed dose excluded	n = 42[e] Age, yrs: 59 (43–72)* n (%) Male: 26 (61.9) Hb BL g/dl: 13.7 (10.7–16.1) Epo mU/ml BL: NR	n = 44 Age, yrs: 60 (39–74)* n (%) Male: 27 (61.3) Hb BL g/dl: 13.4 (10.9–16.4) Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 U/kg/TIW Dose adj.: Y Dur. of epo tx: 26 wks Dur. of trial: 26 wks Follow-up: NR	SC	Iron: NR G-CSF: NR RBCT trigger: prn (Hb incl. criteria level: ≥10.5 g/dl)	Disease: solid (SCLC) Treatment: chemo: mixed[h]	EORTC-QLQ-C30	Y
Vansteenkiste **2002** **RCT** Multiple pubs.: *Vansteenkiste, 2004*	n = 156 Age, yrs: 61.6 (9.2) n (%) Male: 111 (71) Hb BL g/dl: 10.28 (1.08) Epo mU/ml BL: 53.17 (58.87)[i]	n = 158 Age, yrs: 61.3 (8.8) n (%) Male: 116 (73) Hb BL g/dl: 9.93 (1.01) Epo mU/ml BL: 51.10 (71.72)[i]	Brand: Darbepoetin alfa Dose: 2.25 µg/kg/QW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: 12 mths	PBO	Iron: NR G-CSF: NR RBCT trigger: Hb ≤8 g/dl (Hb incl. criteria level: ≤11.0 g/dl)	Disease: solid (lung) Treatment: chemo: plat	FACT-F	Y

PENTAG REVIEW: STUDY CHARACTERISTICS: PRIMARY STUDIES 2004 to CURRENT								
Ray-Coquard 2009 ROL ELYPSE study	n = 110 Age, yrs: 62.7 (11.6) n (%) Male: 52 (47.3) Hb BL g/dl: 10 (1.2) Epo mU/ml BL: NR	n = 108 Age, yrs: 61.7 (11.6) n (%) Male: 41 (38) Hb BL g/dl: 10 (1.2) Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 U/kg/TIW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: 12 mths (95% CI 12–12.4)*	SC	Iron: Y, oral G-CSF: Y RBCT trigger: NR (Hb incl. criteria level: ≤12.0 g/dl)	Disease: solid & haem Treatment: chemo: NR	EPRTC-QLQ-C30	Y
Tjulandin 2011 RCT	n = 95 Age, yrs: 56.9 ± 14.7 n (%) Male: 30 (31.6) Hb BL g/dl: 9.2 ± 1.3 Epo mU/ml BL: NR	n = 91 Age, yrs: 55.8 ± 14.3 n (%) Male: 34 (37.4) Hb BL g/dl: 9.1 ± 1.3 Epo mU/ml BL: NR	Brand: Epoetin theta Dose: 20,000 U/QW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: NR	PBO	Iron: Y, not specified G-CSF: NR RBCT trigger: ≤8.5 g/dL (Hb incl. criteria level: ≤11.0 g/dl)	Disease: solid & haem Treatment: chemo: non-plat	FACT-G, FACT-F, FACT-An	Y
MULTIPLE PUBLICATIONS: PENTAG REVIEW								
Aapro 2004 Primary study: *Littlewood, 2001*	n = 251 (analysed 244) Age, yrs: 58.3 ± 14.2 n (%) Male: 85 (34) Hb BL g/dl: 9.9 ± 1.1 Epo mU/ml BL: NR	n = 124 (analysed 115) Age, yrs: 59.5 ± 13.9 n (%) Male: 39 (31) Hb BL g/dl: 9.7 ± 1.1 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 U/kg/TIW Dose adj.: Y Dur. of epo tx: up to 28 wks Dur. of trial: up to 28 wks Follow-up: 12-mth[f]	PBO	Iron: Y, oral or i.v. G-CSF: No RBCT trigger: Hb <8 g/dl prn (Hb incl. criteria level: ≤10.5 g/dL or >10.5 but ≤12.0 g/dl after a ≥1.5 g/dl decrease in Hb)	Disease: solid + haem Treatment: chemo, non-plat	FACT-G, FACT-F, FACT-An-An	N
Bajetta 2004 Primary study: *Littlewood, 2001*	SUBGROUP: BREAST POP n = 78 (analysed 75) Age, yrs: 54.6 n (%) Male: 1 (1) Hb BL g/dl: 10.0 ± 1.6 Epo mU/ml BL: NR	SUBGROUP: BREAST POP n = 36 (analysed 35) Age, yrs: 52.9 n (%) Male: all female Hb BL g/dl: 9.9 ± 1.01 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 U/kg/TIW Dose adj.: Y Dur. of epo tx: up to 28 wks Dur. of trial: up to 28 wks Follow-up: 12-mth[f]	PBO	Iron: Y, oral (or i.v. as indicated by transferrin sat. level) G-CSF: No RBCT trigger: Hb <8 g/dl prn (Hb incl. criteria level: ≤10.5 g/dL or >10.5 but ≤12.0 g/dl after a ≥1.5 g/dl decrease in Hb)	Disease: solid + haem Treatment: chemo, non-plat	FACT-F, FACT-G, CLAS	N
Littlewood 2006 Primary study: *Hedenus, 2003*	SUBGROUP: HRQoL SAMPLE n = 303[l] Age, yrs: 64.8 (12.8) n (%) Male: 146 (48.2) Hb BL g/dl: 9.6 (1.2) Epo mU/ml BL: NR		Brand: Darbepoetin alfa Dose: 2.25 µg/kg/QW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: median ~11 mths	PBO	Iron: prn G-CSF: NR RBCT trigger: Hb ≤8 g/dl (Hb incl. criteria level: ≤11.0 g/dl)	Disease: haem Treatment: chemo, NR	FACT-F, D&A (from BSI)	N
Osterborg 2005, follow-up of Osterborg 2002 RCT Primary study:	n = 173 (analysed 170) Age, yrs: 63 (32–86)* n (%) Male: 91 (54) Hb BL g/dl: 9.2 ± 1.1 Epo U/L BL: 38 (20–72)*	n = 176 (analysed 173) Age, yrs: 64 (28–83)* n (%) Male: 82 (47) Hb BL g/dl: 9.3 ± 1.0 Epo U/L BL: 41 (21–77)*	Brand: Epoetin beta Dose: 150 U/kg/TIW Dose adj.: Y Dur. of epo tx: 16 wks Dur. of trial: up to 16 wks Follow-up: min 17.5	PBO	Iron: Y, oral iron, or i.v. iron if transferrin saturation ≤20% G-CSF: No RBCT trigger: Hb <8.5 g/dl or inc.in Hb <0.5 g/dl vs BL (Hb incl. criteria level: <10 g/dl[g])	Disease: haem Treatment: chemo, non-plat	FACT-F, FACT-G, FACT-An, FACT-An-An	Y

Osterborg, 2002			mths both tx grps					
Patrick 2003 Primary study: *Littlewood, 2001*	n = 251 (analysed 244) Age, yrs: 58.3 ± 14.2 n (%) Male: 85 (34) Hb BL g/dl: 9.9 ± 1.1 Epo mU/ml BL: NR	n = 124 (analysed 115) Age, yrs: 59.5 ± 13.9 n (%) Male: 39 (31) Hb BL g/dl: 9.7 ± 1.1 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 U/kg/TIW Dose adj.: Y Dur. of epo tx: up to 28 wks Dur. of trial: up to 28 wks Follow-up: 12-mth[f]	PBO	Iron: Y, oral (or i.v. as indicated by transferrin sat. level) G-CSF: No RBCT trigger: Hb <8 g/dl prn (Hb incl. criteria level: ≤10.5 g/dL or >10.5 but ≤12.0 g/dl after a ≥1.5 g/dl decrease in Hb)	Disease: solid + haem Treatment: chemo, non-plat	SF-36, FACT-F, FACT-G, CLAS	N
Vansteenkiste 2004 Primary study: *Vansteenkiste, 2002*	SUBGROUP <10 g/dl n = 51 Age, yrs: 63 (47–76) n (%) Male: 42 (82) Hb BL g/dl: 9.2 (7.4–9.9) Epo mU/ml BL: 50.3 (13.3–739.8) SUBGROUP ≥10 g/dl n = 105 Age, yrs: 62 (39–80) n (%) Male: 69 (66) Hb BL g/dl: 10.8 (10.0–13.6) Epo mU/ml BL: 28.8 (12.0–106.1)	SUBGROUP <10 g/dl n = 69 Age, yrs: 60 (42–78) n (%) Male: 52 (75) Hb BL g/dl: 9.2 (6.6–9.9) Epo mU/ml BL: 52.2 (14.3–1,998.6) SUBGROUP ≥10 g/dl n = 89 Age, yrs: 62 (36–76) n (%) Male: 64 (72) Hb BL g/dl: 10.6 (10.0–12.3) Epo mU/ml BL: 30.2 (12.0–109.8)	Brand: Darbepoetin alfa Dose: 2.25 µg/kg/QW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: 12 mths	PBO	Iron: No G-CSF: No RBCT trigger: Hb ≤8 g/dl & prn (Hb incl. criteria level: ≤11.0 g/dl)	Disease: solid (lung) Treatment: chemo: plat	FACT-F	Y

Key: ~, approximately; ↓, decrease only; AE, adverse event; BSI, Brief Symptom Inventory ; BL, baseline; CLAS, Cancer Linear Analogue Score; C, cycles; chemo, chemotherapy; D, days; D&A, Depression and Anxiety subscale ; EORTC QLQ C-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -F, Fatigue; G, General); G-CSF, granulocyte colony stimulating factor; GI, gastrointestinal; grps., groups; gynae, gynaecological; HaemR, haematopoietic response; Hb, haemoglobin; HRQoL, health-related quality of life; inc., increase; incl., includ(e/ing); med., median; min., minimum; mths., months; NHP, Nottingham Health Profile; NR, not reported; OS, overall survival; PBO, placebo; plat, platinum-based chemotherapy; prn, pro re nata (as needed); PDI, Psychological Distress Inventory; QoL, quality of life; QW, once weekly; RBCT, red blood cell transfusion; rHuEPO, recombinant human erythropoietin; SC, standard care; SCLC, small-cell lung cancer; SF-36, Short Form 36; TIW, three times weekly; TR, tumour response; TVEs, thrombovascular events; tx, treatment; VAS, Visual Analogue Scale; wks., weeks; yrs., years

Notes: * indicates median (range) **(a)** BL characteristics /and some efficacy outcomes reported for all participants randomised (i.e. includes participants not receiving chemotherapy [Abels, 1993]); for all doses of Darbepoetin alfa [Kotasek 2003]); for intervention and control combined at randomisation [Untch 2011a,b]); **(b)** Assumed to be either Epoetin alfa or Epoetin beta based on date of trial and dose administered in the trial; **(c)** Double-blind phase only; participants given the option to enter 12-week open-label treatment period; **(d)** Majority of participants received non-platinum chemotherapy; **(e)** Study includes other doses of intervention under review (either dose-response study Hedenus,2002, 2003; Kotasek, 2003; or three-arm trial Ten-Bokkel, 1998; Thatcher, 1999); **(f)** Survival based on data collected during 12-mth after study completed by last participant; Reported based on proportion of patients randomised (only available for a proportion of patients randomised; 151 and 145 intervention and control groups respectively); **(g)** Inclusion criteria for Hb further stratified by serum epo level; **(h)** Majority of participants received platinum-based chemotherapy; **(i)** Serum endogenous epo (mU/mL not available for all participants randomised; n= 145 and n= 151 in intervention and control group respectively; **(j)** Patients evaluated for HRQoL from trial sample (Hedenus 2003), not separated by intervention and control for HRQoL sample

Table 32. HRQoL intruments included in the studies

HRQoL measure	Study (year)
FACT-G	Osterborg, 2002[69]; Littlewood, 2001[68]; Aapro, 2004[80]; Bajetta, 2004[79]; Patrick, 2003[60]; Tjulandin, 2011[76]
FACT-An	Osterborg, 2002[69]; Tjulandin, 2011[76]
FACT-F	Osterborg, 2002[69]; Littlewood, 2001[68]; Boogaerts, 2003[52]; Hedenus, 2003[16]; Vansteenkiste, 2002[72]; Aapro, 2004[80]; Bajetta, 2004[79]; Kotasek, 2003[46]; Littlewood, 2006[82]; Patrick, 2003[60]; Tjulandin, 2011[76]
FACT-An-An	Aapro, 2004[80]; Boogaerts, 2003[52]; Littlewood, 2001[68]; Osterborg, 2002[69]
SF-36	Boogaerts 2003[52]; Patrick 2003[60]
CLAS/LASA	Dammacco, 2001[64]; Littlewood, 2001[68], Aapro, 2004[80], Bajetta, 2004[79], Patrick, 2003[60]
PDI	Del Mastro, 1999[65]
EORTC-QLQ-C30	Ray-Coquard, 2009[74]
BSI	Littlewood, 2006[82]
NHP	Dammacco, 2001[64]
VAS	Abels, 1993[54]; Boogaerts, 2003[52], Kurz, 1997[67], Thatcher, 1999[48]

Key: BSI, Brief Symptom Inventory; CLAS< Cancer Linear Analogue Score; EORTC QLQ C-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -F, Fatigue; G, General); HRQoL, health-related quality of life; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; PDI, Psychological Distress Inventory; SF-36, Short Form 36; D&A, Depression and anxiety subscale; VAS, visual analogue scale

5.3.3.2. Quality of included studies

The quality of the included studies was assessed according to the criteria presented in Table 9 (page 63). Twenty three primary studies were evaluated in the clinical effectiveness section (Section 4.2.3; **Error! Reference source not found.**, page 63). As six secondary analyses are discussed in the HRQoL review, and only 13 primary studies were included in the HRQoL review; quality appraisal for these 19 studies is presented in Table 33, page 173.

The method of randomisation was unclear in 12 studies with all reports having unclear allocation concealment. Only two trials fully reported baseline similarity. Baseline similarity was unclear in 15 publications with two trials unbalanced; in **Boogaerts and colleagues (2003)**[52] a higher proportion of participants in the control group had prior chemotherapy (80 vs. 68%; p=0.025), and patients randomised to epoetin beta had lower FACT scores (p=0.02); and, in **Ray-Coquard and colleagues (2009)**[74] participants had EORTC QLQ-C30 scores which were significantly different.

Patients were reported as blinded in 15 trials, which has been reported to have a particularly significant impact on HRQoL results.[1] Physicians were also blinded in all trials which blinded participnts; only four trials were unmasked or unclear. Although many trials included an ITT analysis or had less than 10% exclusions for primary outcomes, HRQoL suffered significant losses for at least six trials.[48,65,68,72,74]

A graphical summary of study quality is presented in Figure 25, page 197.

Table 33. Study quality (Cochrane Risk of Bias tool): Retrospective analyses

Study, year	Random	Concealment allocation	Baseline similarity	Patients blinded	Physicians blinded	Losses	ITTor <10%dropout
Aapro, 2004[80] Primary study: Littlewood, 2001[68]	Yes	NR	Unclear[a]	Yes	Yes	Partially[b]	Yes
Abels, 1993[54]	Unclear[c]	NR	Unclear[a]	Yes	Yes	Partially	Yes
Bajetta, 2004[79] Primary study: Littlewood, 2001[68]	Yes	NR	Unclear[a]	Yes	Yes	Partially	NA
Boogaerts, 2003[52]	Unclear[c]	NR	No: prior chemotherapy, FACT-F	No	No	Partially	Yes
Dammacco, 2001[64]	Unclear[c]	Unclear[d]	Unclear[a]	Yes	Yes	Yes	Yes, primary endpoint and HRQoL only
Del Mastro, 1999[65]	Yes	NR	Unclear[a]	No	NR	Partially	Yes, apart from HRQoL (87% and 84% participants were analysed in treatment and control groups respectively).
Hedenus, 2003[16]	Yes	NR	Unclear	Yes	Yes	Partially[e]	Yes[f]
Kotasek, 2003[46]	Unclear[c]	NR	Yes[8]	Yes	Yes	Partially[e]	Yes[f]
Kurz, 1997[67]	Yes	Unclear[d]	Yes	Yes	Yes	NR	Yes, results report response for all participants; assumed ITT.
Littlewood, 2001[68]	Unclear[c]	NR	Unclear[a]	Yes	Yes	Yes	Yes, apart from HRQoL (80% and 73% participants were analysed in treatment and control groups respectively).
Littlewood, 2006[82] Primary study: Hedenus, 2003[16]	Unclear	NR	Unclear[a]	Yes	Yes	Yes	Unclear[g]
Osterborg, 2002[69]	Unclear[c]	NR	Unclear[a]	Yes	Yes	Partially[e]	Yes

Study, year	Random	Concealment allocation	Baseline similarity	Patients blinded	Physicians blinded	Losses	ITTor <10%dropout
Osterborg, 2005[70] Primary study: Osterborg, 2002[69]	NR	NR	Unclear[a]	Yes	Yes	Yes	Yes
Patrick, 2003[60] Primary study: Littlewood, 2001[68]	Yes	NR	NR	Yes	Yes	NR	NR
Ray-Coquard, 2009[74]	Unclear[c]	Unclear[d]	No: HRQoLb	No	No	Partially	Yes, apart from HRQoL (54% and 57% participants were analysed in treatment and control groups respectively.
Thatcher, 1999[48]	Unclear[c]	NR	Unclear[a]	No	NR	Yes	Yes, apart from HRQoL (75% and 61% participants were analysed in treatment and control groups respectively).
Tjulandin, 2011[76]	Yes	NR	Unclear[a]	Yes	Yes	Yes	Yes, apart from HRQoL (89.5-97.9% and 85.7-96.7% participants were analysed in treatment and control groups respectively).
Vansteenkiste, 2002[72]	Unclear[c]	Unclear[d]	Unclear[a]	Yes	Yes	Partially	Yes[e], apart from HRQoL (81% participants were analysed in both, treatment and control groups).
Vansteenkiste, 2004[81] Primary study: Vansteenkiste, 2002[72]	NR	NR	Unclear[a]	Yes	Yes	No	Unclear[h]

Key: HRQoL, health-related quality of life; ITT, intention-to-treat; NR not reported.
Notes: (a) p-values for baseline similarities not reported; (**b)** Loss discussed for treatment period only; (**c)** Randomisation details are not reported; **(d)** Randomisation was performed using a centralised system, but details on allocation concealment were not reported; **(e)** Losses reported for the treatment period only, data for the follow up period are not reported; **(f)** Less than 10% dropout, but ITT was defined as all randomised participants who received at least 1 dose of study drug; **(g)** Data for arms pooled as trial not powered for FACT-F analysis; **(h)** FACT outcomes not imputed

5.3.3.3. Trials identified in previous HTA (Wilson and colleagues, 2007)[1]

5.3.3.3.1. Abels and colleages (1993)[54]

Trial/population characteristics.

The safety of epoetin alfa, its impact on haematocrit, transfusion requirements and quality of life were investigated in the trial reported by **Abels and colleagues (1993),** which is the primary study. It should be noted that this study is reported in a further five papers, by Case and colleagues (1993), Henry and colleagues (1994), Henry and colleagues (1995) and Abels and colleagues (1996) as retrospective studies.

The intervention arm of this trial included 413 patients from three populations: cyclic non-cisplatin chemotherapy (n=157), cyclic cisplatin-chemotherapy (n= 132) and no chemotherapy (n=124), to be compared against placebo (n=200). All patients recruited had anaemic cancers.

Results

The rHuEPO-treated population as a whole had a statistically significant (p≤0.05) increase in baseline-to-final evaluation for overall quality of life (Table 34). When comparing responders to placebo, a significant improvement was seen for all three parameters (p≤0.05).

Summary

A statistically significant increase measured by VAS was found in favour of epoetin alfa.

Table 34. HRQoL: Results for Abels and colleagues (1993)[54]

	Baseline	Week 4 Mean change	Week 8 Mean change	≥ Week 12 Mean change [a]	Difference between ESA and control[c]
Change in VAS (100 mm) from baseline; a higher score indicates a higher HRQoL[b]					
Energy level					
Intervention (n=59)	NR	NR	NR	7.2	2.9 in favour of ESA
Control (n=143)	NR	NR	NR	4.3	
ESA responders (n=83)	NR	NR	NR	13[c]	
Daily activity					
Intervention (n=59)	NR	NR	NR	5.8	4.8 in favour of ESA
Control (n=143)	NR	NR	NR	1	
ESA responders (n=83)	NR	NR	NR	11.5[3]	

Overall HRQoL					
Intervention (n=59)	50.0±24.0	NR	NR	5[c]	7.1 in favour of ESA
Control (n=143)	50.4±26.0	NR	NR	-2.1	
ESA responders (n=83)	NR	NR	NR	9.5[c]	

Key: ESA, erythropoiesis stimulating agent; NR, not reported;
Notes: a Assessment performed after study period **; b** Data taken from **Wilson and colleagues (2007)** as results only presented by **Abels and colleagues (1993) graphically**; **c** Calculated by PenTAG, **d** Statistically significant ($p<0.05$).

5.3.3.3.2. Boogaerts and colleagues (2003)[52]

Trial/population characteristics

This trial investigated the impact of epoetin beta on HRQoL in anaemic patients with lymphoid or solid tumour malignancies receiving myelosuppressive chemotherapy (n=133 for intervention; n=129 for standard care). Change in HRQoL was measured from baseline to week 12 in SF-36, FACT-An, FACT-F and VAS. The method of randomisation was not reported and neither assessors nor patients were blinded. An ITT analysis was performed.

Results

The data are presented in Table 35 with and without LOCF. Compared with transfusion therapy, epoetin beta produces a clinically significant improvement in HRQoL in patients with anaemia associated with malignancy. Epoetin beta improved physical function and well-being as measured by the FACT-An and FACT-F questionnaires. The internal consistency reliability was also estimated for each scale, using Crohnbach α, with the FACT-An and FACT-F subscale showing high consistency (>0.9). 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 showed a significant improvement in favour of epoetin beta, unlike FACT-An (p=0.068).

Summary

Epoetin beta improved physical function and well-being as measured by the FACT-An and FACT-F questionnaires.

Table 35. HRQoL: Results for Boogaerts and colleagues (2003)[52]

	Baseline Mean score (SD)	Week 4 Mean change[a] Mean change from BL w/o LOCF (SD)	Week 8 Mean change[a] Mean change from BL w/o LOCF (SD)	Week 12 Mean change[a] Mean change from BL w/o LOCF (SD)	Difference between ESA and control[c]
SF-36 PCS (0–100%); the higher the score, the lower the disability					
Intervention (n=133)	35 (8.4)	2.0 (1.0)	3.3 (1.0)	3.5 (1.5)	4.2
Control (n=129)	38 (9.5)	1.0 (0.5)	-0.5 (0.5)	-0.7 (0.8)	
FACT-F (13 items: score 0–52); the higher the score, the higher the HRQoL					
Intervention (n=133)	27 (12)	3.5 (1.25)	4.5 (1.5)	5.5 (1.5)	5.0
Control (n=129)	31 (11)[b]	1.3 (1.0)	0.7 (1.5)	0.5 (1.5)	
FACT-An (7 items: 0–28); the higher the score, the higher the HRQoL					
Intervention (n=133)	20 (3.8)	0.8 (0.3)	1.0 (0.4)	0.9 (0.5	1.0
Control (n=129)	21 (4.4)	0.4 (0.5)	0.0 (0.3)	-0.1 (0.4)	
VAS (100 mm); the higher the score, the higher the HRQoL					
Intervention (n=133)	56 (17)	5.0 (2.0)	7.0 (2.0)	11.0 (2)	11.3
Control (n=129)	62 (17)	-0.5 (0.75)	0.5 (1.0)	-0.5 (-2.0)	

Key: ESA, erythropoiesis stimulating agent FACT, Functional Assessment of Cancer Therapy –F, Fatigue; -An, Anaemia); LOCF, last observation carried forward; PCS=Short form 36, physical component summary; VAS, visual analogue score
Notes: a Data taken from **Wilson and colleagues (2007)** as results only presented by Boogaerts and colleagues (2003) graphically **b** p=0.02; **c** Calculated by PenTAG

Table 36. HRQoL: Results for Boogaerts and colleagues (2003)[52] according to median change score

	Baseline Median (range)	Week 4 Median change score	Week 8 Median change score	Week 12 Median change score (LOCF)[a]	Week 12 Median change score (w/o LOCF)[a]	Difference between ESA and control[b]
SF-36 PCS (0–100%) [n]; the higher the score, the lower the disability						
Intervention	35 (17-60)	NR	NR	3.1 [104]	3.3 [77]	NR
Control	38 (15-60)	NR	NR	NR [109]	NR	
p value				<0.05	0.01	
FACT-F (13 items: score 0–52) [n]; the higher the score, the higher the HRQoL						
Intervention	28 (1-49)	NR	NR	3.0 [104]	4.0 [90]	NR
Control	33 (2-51)	NR	NR	NR [109]	NR	
p value				<0.05	0.001	
FACT-An (7 items: 0–28) [n]; the higher the score, the higher the HRQoL						
Intervention	21 (6-27)	NR	NR	1.0 [104]	1.0 [89]	NR

Control	22 (2-28)	NR	NR	NR [109]	NR	
p value				0.08	0.068	
VAS (100 mm); the higher the score, the higher the HRQoL						
Intervention	53 (11-96)	NR	NR	10 [111]	10 [89]	9.0
Control	60 (18-96)	NR	NR	1.0 [112]	3.0 [98]	
p value				0.004	0.001	

Key: ESA, erythropoiesis stimulating agent; FACT, Functional Assessment of Cancer Therapy (–F, Fatigue; -An, Anaemia); LOCF, last observation carried forward; NR, not reported; PCS=Short form 36, physical component summary; VAS, visual analogue score
Notes: (a) p value refers to invervention versus control; **(b)** Calculated by PenTAG

5.3.3.3.3. Dammacco and colleagues (2001)[64]

Trial/population characteristics

This was a trial involving 145 patients with multiple myeloma who had received chemotherapy for at least six months. The intervention arm received epoetin alfa and the control arm received a placebo over 12 weeks. The scales used were the Nottingham Health Profile (NHP) and the CLAS/LASA. Both patients and assessors were blinded. HRQoL analyses were performed for the ITT population minus patients who died during the double-blind phase of the study for whom HRQoL data were incomplete.

Results

HRQoL assessed for 138 patients (66 epoetin alfa and 72 placebo). Data were not reported, however, authors state that both treatment groups showed some improvement in HRQoL 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. Univariate analyses of within-group mean changes from baseline to Week 12 indicated significant improvement in four HRQoL scales for the epoetin alfa group (NHP scale emotional reaction $p<0.001$ & social isolation $p=0.05$; and for the CLAS energy level ($p=0.01$) and ability to do daily activities ($p<0.001$)) and one HRQoL scale for the placebo group (NHP scale sleep $p=0.03$). A trend towards improvement was also noted for CLAS, Overall HRQoL for the epoetin alfa treated group whereas for the placebo group scores were virtually unchanged since baseline.

HRQoL during the open-label phase was also evaluated for 78 patients, using within group analysis. A consistent trend towards improved HRQoL in three out of six NHP scales (energy, sleep, physical mobility) and all three CLAS items was observed for patients in the placebo to epoetin alfa group at Week 24.

Summary

The scales used to measure HRHRQoL in this trial found epoetin alfa is an effective and well tolerated agent for the management of myeloma-associated anaemia, although it should be noted that one is not validated.

5.3.3.3.4. Del Mastro and colleagues (1999)[65]

Trial/population characteristics

The trial reported by **Del Mastro and colleagues (1999)** evaluated the ability of rHuEPO (assumed to be epoetin alfa) in preventing the development of clinically significant anaemia in patients with Stage II breast cancer being treated with chemotherapy (n=62). The duration of treatment was 12 weeks, with the control arm being best supportive care. HRQoL was measured by Psychological Distress Inventory (PDI) with data only available for 85.5% of patients. Patients were not blind to treatment.

Results

Only 87% and 84% of participants were analysed in the intervention and control groups for HRQoL, respectively (Table 37). Psychological distress increased during treatment and decreased at first follow-up visit (p=0.03). Treatment groups did not significantly differ in terms of psychological distress.

Summary

Epoetin alfa was not effective over best supportive care in improving psychological distress.

Table 37. HRQoL: Results for Del Mastro and colleagues (1999)[65]

	Baseline (mean ± SD)	During treatment (mean ± SD)	Follow-up (mean ± SD)	Mean pre/post change[a]	Mean difference between ESA and control [a,b]
PDI score (13-items, score 0 to 65); the higher the score, the higher the level of distress					
Control (n=26)	27.1±7.3	28.3±8.0	26.3±9.8	-0.8	2.3 in favour of control
Intervention (n=27)	27.5±8.6	30.6±10.4	27.4±11.2	-0.1	

Key: ESA, erythropoiesis stimulating agent; No., number; PDI, psychological distress inventory
Notes: a Calculated by PenTAG, **b** During treatment

5.3.3.3.5. Hedenus and colleagues (2003)[16]

Trial/population characteristics

The objective of this trial was to evaluate the efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies (n=349). The study included patients with myeloma and lymphoma, and was stratified to enable a comparison of darbepoetin alfa and placebo within each malignancy type. All patients were scheduled to receive cytotoxic chemotherapy, along with the intervention, for 12 weeks. The HRQoL scale used was FACT-F and the analysis was intention to treat.

Results

Only 84% of patients had completed the FACT-Fatigue subscale at Week 13 (Table 38). Improvement in their score compared with placebo, regardless of their level of fatigue at baseline. However, those patients with the lowest baseline FACT-Fatigue subscale scores reported the largest improvement at the end of treatment. After adjusting for the effect of baseline score, increases in FACT-Fatigue subscale scores with darbepoetin alfa treatment were significantly greater than those observed with placebo (p=0.032).

Summary

Statistically significant improvements in HRQoL were observed with darbepoetin alfa relative to placebo.

Table 38. HRQoL: Results for Hedenus and colleagues (2003)[16]

	Baseline Score	Week 4 Mean change	Week 8 Mean change	Week ≥12[a] Mean change	Pre/post change	Difference between ESA and control[b]
FACT-F (13 items: score 0-52); the higher the score the higher the HRQoL						
For patients with baseline score <24						
Intervention (n=38)	<24	NR	NR	8	8	2 in favour of ESA
Control (n=42)	<24	NR	NR	6	6	
For patients with baseline score 25-36						
Intervention (n=64)	25-36	NR	NR	NR	5	6 in favour of ESA
Control (n=63)	25-36	NR	NR	NR	-1	
For patients with baseline score >36						
Intervention (n=50)	>36	NR	NR	NR	-3	3 in favour of ESA
Control (n=46)	>36	NR	NR	NR	-6	

Key: ESA, erythropoiesis stimulating agent; NR, not reported
Notes: a Data taken from **Wilson and colleagues (2007)** as results only presented by Hedenus and colleagues (2003) graphically , **b** Calculated by PenTAG

5.3.3.3.6. Kotasek and colleagues (2003)[46]

Trial/population characteristics

The safety of darbepoetin alfa in patients with solid cancers receiving cyclic chemotherapy (n=249) and the feasibility of administering darbepoetin alfa three weekly was assessed in the trial reported by **Kotasek and colleagues (2003)**. This was a 12-week, double blinded study where the intervention was compared to placebo. The scales used to measure HRQoL were FACT-G and FACT-F, with analysis performed on patients randomised to study drug who received at least one dose.

Results

Although no data were reported for baseline characteristics between the intervention and control arms, the authors state that a slightly higher proportion of patients in the 12.0 mg/kg group had breast cancer (61%) and a higher mean baseline Hb concentration (104 g/l) compared with the other groups. All randomised patients who received ≥1 dose of study drug were analysed (100% and 95% participants in the darbepoetin arm and placebo arm, respectively). The 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 approximately 5-point improvements 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.

Summary

There appears to be no data in this report comparing placebo with darbepoetin alfa for HRQoL. However, authors report a statistically significant improvement in FACT-F with increase in Hb.

5.3.3.3.7. Kurz and colleagues (1997)[67]

Trial/population characteristics

This small trial was intended to evaluate the effectiveness of rHuEPO with respect to increasing Hb levels and decreasing RBCT requirements and to assess the influence on HRQoL parameters. Participants all had solid malignancies and were receiving platinum and non-platinum based chemotherapy (n=35). Treatment was either intervention or placebo for 12 weeks with iron saccharate substitution following each dose of chemotherapy beginning with the next cycle. It is unclear whether treatment allocation was concealed, but both

patients and assessors were blinded. A self-administered visual analogue scale was employed to measure HRQoL, which had not been validated. ITT analysis appears to have been performed, but not explicitly expressed.

Results

Baseline characteristics were similar for placebo and darbepoetin groups (Table 39). Using an unvalidated assessment tool (Health State Utility Scale), there was no significant difference between treatment arms within each activity or across the ten different scores.

Summary

No statistically significant difference in HRQoL was seen between darbepoetin alfa and placebo.

Table 39. HRQoL: Results for Kurz and colleagues (1997)[67]

	Baseline Score	Interim time points[a]	Pre/post change	Mean change difference between ESA and control[b, c, d]
Health State Utility scale (VAS of 1 to 5) *unclear whether higher or lower scores indicate higher HRQoL*				
Feeling of well being				
Intervention (n=23)	NR	NR	0.004	-0.16
Control (n=12)	NR	NR	-0.16	p=0.77
Pts achieving response under intervention (SD) (n=13)	NR	NR	-0.25 (0.76)	p=0.26
Mood				
Intervention (n=23)	NR	NR	-0.21	-0.03
Control (n=12)	NR	NR	-0.18	p=0.94
Level of activity				
Intervention (n=23)	NR	NR	0.26	0.32
Control (n=12)	NR	NR	0.58	p=0.71
Pts achieving response under intervention (SD) (n=13)	NR	NR	-0.36 (1.14)	p=0.27
Pain				
Intervention (n=23)	NR	NR	0.37	0.11
Control (n=12)	NR	NR	-0.26	p=0.32
Nausea				
Intervention (n=23)	NR	NR	-0.11	-0.32
Control (n=12)	NR	NR	-0.43	p=0.17
Appetite				
Intervention (n=23)	NR	NR	-0.32	-0.25
Control (n=12)	NR	NR	-0.07	p=0.61
Physical ability				

Intervention (n=23)	NR	NR	-0.33	-0.01
Control (n=12)	NR	NR	-0.32	p=0.53
Pts achieving response under intervention (SD) (n=13)	NR	NR	-0.62 (0.87)	p= 0.02
Social activities				
Intervention (n=23)	NR	NR	-0.04	-0.47
Control (n=12)	NR	NR	-0.51	p=0.89
Pts achieving response under intervention (SD) (n=13)	NR	NR	-0.20 (0.99)	p=0.48
Anxiety				
Intervention (n=23)	NR	NR	1.92	0.53
Control (n=12)	NR	NR	2.45	p=0.38
Treatment is helping				
Intervention (n=23)	NR	NR	1.76	0.58
Control (n=12)	NR	NR	2.34	p=0.11

Key:; ESA, erythropoiesis stimulating agent; NR, not reported
Notes: a Questionnaires administered at beginning of treatment and then every 4 weeks before receiving chemotherapy. It is unclear which timepoint the results refer to, **b** Calculated by PenTAG, **c** Multivariate Hotelling's T2 for responders: p=0.21, **d** Multivariate Hotelling's T2: p=0.34

5.3.3.3.8. Littlewood and colleagues (2001)[68]

Trial/population characteristics

Littlewood and colleagues (2001) report on a trial evaluating the effects of epoetin alfa on RBCT requirements, haematopoetic parameters, HRQoL, and safety in patients receiving non-platinum based chemotherapy. Participants had solid or non-myeloid haematologic malignancies and were scheduled to receive non-platinum chemotherapy (n=375). HRQoL was measured via change from baseline to last value on 5 cancer specific scales (FACT-An, FACT-G, FACT-An Fatigue, CLAS/LASA) with both patients and assessors blinded. Treatment duration was 28 weeks.

Results

Only 80% and 73% participants were analysed in the epoetin alfa and placebo groups, respectively. The mean change score for FACT-An:fatigue, FACT-An:anaemia, FACT-G, CLAS-Energy, CLAS-Daily Active and CLAS-Overall displayed a statistically significant difference in favour of epoetin alfa over placebo (Table 40).

Summary

Epoetin alfa significantly improves HRQoL in cancer patients receiving non-platinum chemotherapy.

Table 40. HRQoL: Results for Littlewood and colleagues (2001)[68]

	Baseline Score	Interim time points	Pre/post mean change	Difference between ESA and control[a]
FACT-G (27 items: score 0-108); the higher the score, the higher the HRQoL				
Intervention (n=194)	NR	NR	2.5	6.1 in favour of ESA
Control (n=88)	NR	NR	-3.6	
p value			0.004	
FACT-An-Fatigue (13 items: score 0-52); the higher the score, the higher the HRQoL				
Intervention (n=200)	NR	NR	3.0	5.2 in favour of ESA
Control (n=90)	NR	NR	-2.2	
p value			0.004	
FACT-An-Anaemia (7 items: score 0-28) the higher the score, the higher the HRQoL				
Intervention (n=200)	NR	NR	4.0	6.6 in favour of ESA
Control (n=90)	NR	NR	-2.6	
p value			0.001[b]	
CLAS Energy level (100 mm); the higher the score, the higher the HRQoL				
Intervention (n=228)	NR	NR	8.1	13.9 in favour of ESA
Control (n=108)	NR	NR	-5.8	
			0.001	
CLAS Daily activities (100 mm); the higher the score, the higher the HRQoL				
Intervention (n=228)	NR	NR	7.5	13.5 in favour of ESA
Control (n=108)	NR	NR	-6.0	
p value			0.002	
CLAS Overall HRQoL(100mm) the higher the score, the higher the HRQoL;				
Intervention (n=228)	NR	NR	4.8	10.8 in favour of ESA
Control (n=107)	NR	NR	-6.0	
p value			0.005	

Key: CLAS, Cancer Linear Analogue Scale; ESA, erythropoiesis stimulating agent; FACT, Functional Assessment of Cancer Therapy; NR, not reported; (-An, Anaemia; -G, General)
Notes: a Calculated by PenTAG, **b** p value for the Anaemia subscale (secondary measure) is unadjusted. All other p values, which correspond to primary measures, are adjusted for multiple comparisons (sequentially rejective Bonferroni procedure).

5.3.3.3.9. Osterborg and colleagues (2002)[69]

Trial/participant characteristics

The effect of epoetin beta on HRQOL, as compared to placebo, was assessed in this trial using the FACT scale in patients with lymphoproliferative malignancies (advanced MM, low grade NHL and CLL). All patients (n=349) were scheduled to receive anti-tumour therapy for the following 4 months. Treatment duration was 16 week and both patients and assessors were blinded. The results were ITT.

Results

After 12 and 16 weeks, the improvement in FACT-An and FACT-G score was greater in the epoetin beta arm (p<0.5) (Table 41 and Table 42). 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 wellbeing and emotional wellbeing, respectively. Overall, the improvement in HRQoL was particularly apparent in patients with Hb increases of ≥2 g/dl.

Summary

Two of the scales used to measure HRQoL found a statistically significant increase in favour of epoetin beta.

Table 41. HRQoL: Results according to treatment, Osterborg and colleagues (2002)[69]

	Baseline Mean score±SD (n)	Week 4 Mean change±SD (n)	Week 8 Mean change±SD (n)	Week 12 Mean change±SD (n)	Week 16 Mean change±SD (n)	Mean change difference between ESA and control[a]
FACT-An (49 items, score 0-196) the higher the score, the higher the HRQoL;						
Intervention	115.2±28.0 (128)	4.9±21.4 (127)	7.9±25.7 (118)	13.1±27.6* (114)	14.8±28.0* (105)	6.1 in favour of ESA
Control	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, score 0-116); the higher the score, the higher the HRQoL						
Intervention	69.1±14.4 (129)	1.7±11.8 (128)	3.7±13.0 (118)	5.9±14.5* (114)	6.5±13.8* (106)	3.4 in favour of ESA
Control	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, score 0-52); the higher the score, the higher the HRQoL						
Intervention	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)	2.2 in favour of ESA
Control	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 (7 items, score 0-28) the higher the score, the higher the HRQoL;						
Intervention	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)	0.3 in favour of ESA
Control	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)	

Key: Epo beta, epoetin beta; ESA, erythropoiesis stimulating agent; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -F, Fatigue; -G, General); PBO, placebo; SD, standard deviation;
Notes: a Calculated by PenTAG, **b**Statistically significant difference with placebo (p<0.05)

Table 42. HRQoL: Results according to response, Osterborg and colleagues (2002)[69]

	Baseline	Week 4	Week 8	Week 12	Week 16
	Mean score ± SD (n)	Mean score ± SD (n)	Mean score ± SD (n)	Mean score ± SD (n)	Mean score ± SD (n)
FACT-An (49 items, score 0-196); the higher the score, the higher the HRQoL					
R	118.9±25.1 (92)	5.1±21.6 (91)	9.7±25.2* (87)	15.2±26.3* (88)	17.4±25.9* (82)
NR	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, score 0-116); the higher the score, the higher the HRQoL					
R	70.6±12.9 (92)	1.5±12.2 (91)	4.9±12.4* (87)	6.9±14.3* (88)	7.8±13.4* (83)
NR	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 (13 items, score 0-52); the higher the score, the higher the HRQoL					
R	30.4±10.1 (114)	2.5±8.3* (112)	3.8±10.5* (108)	5.3±10.5* (110)	6.3±10.5* (102)
NR	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-An (7 items, score 0-28); the higher the score, the higher the HRQoL					
R	17.8±4.4 (114)	1.0±3.2 (112)	1.3±4.3 (108)	2.1±3.9* (110)	2.2±4.0 (102)
NR	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)

Key: ESA, erythropoiesis stimulating agent; NR-, non-responder; R-, responder, SD, standard deviation
Notes: *Statistically significant difference with placebo (p<0.05)

5.3.3.3.10.Thatcher and colleagues (1999)[48]

Trial/participant characteristics

This trial involved 130 patients with small cell lung cancer undergoing cyclic chemotherapy, although only 86 patients were relevant to this review since the third arm dose was outside of licence. The treatment duration was a maximum of 26 weeks. To assess HRQoL, patients responses to a questionnaire containing three levels (energy level, daily activity and overall HRQoL) were scored on a 100mm VAS and WHO performance score. The analysis was ITT, however, there was no placebo, therefore patients were not blinded.

Results

Only the overall HRQoL level revealed a statistically significant improvement favouring epoetin alfa (p<0.05) (Table 43). 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 scores revealed similar findings, with no significant between- or within-group differences.

Summary

This trial found a statistically significant increase in favour of epoetin alfa for one of three levels within an unvalidated scale.

Table 43. HRQoL: Results for Thatcher and colleagues (1999)[48]

	Baseline Mean score ± SD (n)	Interim time points	Pre/post change	Mean change difference between ESA and control[a]
CLAS Energy level (100 mm); the higher the score, the higher the HRQoL				
Intervention	53.6±27.7 (n=37)	NR	-2.3±31.9 (n=33)	3.9 in favour of control
Control	48.4±23.6 (n=37)	NR	1.6±23.9 (n=27)	
CLAS Daily activities (100 mm); the higher the score, the higher the HRQoL				
Intervention	50.8±29.3 (n=37)	NR	3.0±31.7 (n=33)	7.8 in favour of control
Control	41.7±28.1 (n=37)	NR	10.8±35.6 (n=27)	
CLAS Overall HRQoL (100 mm); the higher the score, the higher the HRQoL				
Intervention	49.0±28.1 (n=37)	NR	11.7±30.6[b] (n=33)	4.2 in favour of ESA
Control	47.9±26.7 (n=37)	NR	7.5±29.1 (n-27)	

Key: CLAS, Cancer Linear Analogue Scale; ESA, erythropoiesis stimulating agent; NR, not reported; SD, standard deviation
Notes: a Calculated by PenTAG, **b** p<0.05 vs baseline

5.3.3.3.11. Vansteenkiste and colleagues (2002)[72]

Trial/patient characteristics

The trial compared the effect of darbepoetin alfa with placebo for 314 patients with lung cancer receiving platinum chemotherapy. Treatment duration was 12 weeks with HRQoL assessed by FACT-Fatigue. Both patients and assessors were blinded.

Results

The patient compliance rates for patients completing the FACT–Fatigue scale at least once during the treatment phase was 91.2% (95% CI; 87.4% to 94.2%). Fatigue was evaluated for 255 (127 darbepoetin alfa, 128 placebo) patients who received a study drug, who completed the FACT–Fatigue scale through study week 4, and who completed the scale at baseline and at least one time from week 5 until the end-of-treatment phase. Fifty-six percent (95% CI; 47% to 65%) of the patients in the darbepoetin alfa group and 44% (95% CI; 35% to 52%) of patients in the placebo group had an improvement in the FACT– Fatigue scale score (P =0 .052). Thirty-two percent (95% CI; 23% to 40%) of patients in the darbepoetin alfa group

showed at least a 25% improvement, whereas only 19% (95% CI; 12% to 26%) of patients in the placebo group showed at least a 25% improvement (mean difference = 13%; 95% CI ; 2% to 23%; P =0 .019).

Summary

There is a trend towards improved HRQoL for darbepoetin alfa as compared to placebo.

5.3.3.4. Trials identified 2004 to current

5.3.3.4.1. Ray-Coquard and colleagues (2009)[74]

Trial/patient characteristics

The effect of epoetin alfa on HRQoL, as compared to no treatment, was assessed in this trial, using the EORTC QLQ-C30 scale. Patients with solid and haematological tumours receiving their first or second course of chemotherapy were recruited (n=218). The trial was open label with treatment was administered for 12 weeks. Only 54% and 57% participants for the intervention and control groups, respectively, were analysed.

Results

Authors state that no statistically detectable differences were noted during the study period, whatever the date of evaluation (at one, two, three or four months or at the end of the study, all p>0.2), although none of this data was reported. Furthermore, there was a significant difference between groups at baseline for the EORTC QLQ-C30 measurement (p=0.048)

Summary

No statistically significant difference in HRQoL was detected between epoetin alfa and no treatment.

5.3.3.4.2. Tjulandin and colleagues (2011)[76]

Trial/patient characteristics

This trial compared the effectiveness of epoetin theta to placebo for patients with a solid or non-myeloid haematological malignancies and receiving non-platinum based chemotherapy. The duration of treatment was 12 weeks and both patients and assessors were blinded. The scale used to measure HRQoL was FACT-An, FACT-G and FACT-F.

Results

ITT analysis was not undertaken for HRQoL with 89.5–97.9% and 85.7–96.7% of participants analysed in the epoetin theta and placebo groups, respectively (Table 44). No significant difference was evident between trial arms.

Summary

No statistically significant difference was detected between epoetin theta and placebo.

Table 44. Results for Tjulandin and colleagues (2011)[76]

	Baseline Mean score±SD (n)	Interim time points Mean change±SD (n)	Pre/post Mean change±SD (n)	Mean change difference between ESA and control[a]
FACT-An (49 items, score 0-196); the higher the score, the higher the HRQoL				
Intervention (n=88)	NR	NR	6.3 ± 21.7	5.7 in favour of ESA
Control (n=84)	NR	NR	0.6 ± 22.0	
p value	NR	NR	0.243	
FACT-G (29 items, score 0-116); the higher the score, the higher the HRQoL				
Intervention (n=88)	NR	NR	3.0 ± 12.7	3.2 in favour of ESA
Control (n=84)	NR	NR	-0.2 ± 12.4	
p value	NR	NR	0.224	
FACT-F subscale (13 items, score 0-52); the higher the score, the higher the HRQoL				
Intervention (n=88)	NR	NR	2.9 ± 7.9	2.3 in favour of ESA
Control (n=84)	NR	NR	0.6 ± 8.8	
p value	NR	NR	0.142	
FACT-An trial outcome index[b]; the higher the score, the higher the HRQoL				
Intervention (n=88)	NR	NR	1.2 ± 18.8	4.4 in favour of control
Control (n=84)	NR	NR	5.6 ± 17.1	
p value	NR	NR	0.222	

Key: ESA, erythropoiesis stimulating agent; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -F, Fatigue; -G, General); SD, standard deviation
Notes: a Calculated by PenTAG, **b** unclear number of items or score

5.3.3.5. Post hoc studies identified, 2004 to current

5.3.3.5.1. Aapro and colleagues (2004)[80]

Trial/patient characteristics

Secondary analysis of the trial reported by Littlewood and colleagues (2001)[68] which includes further HRQoL data. The scales employed were Cancer Linear Analog Scale (CLAS) and FACT-G; FACT-An-Fatigue and FACT-An-anaemia.

Results

Of the 375 participants, 349 were evaluated for changes in HRQoL (n=200–228 for intervention; n=90–108 for control). All scales showed a statistically significant improvement in favour of epoetin alfa (results are presented graphically, however, they appear to comply with the data for Littlewood and colleages (2001).[68]

Summary

This trial found a statistically significant increase in favour of epoetin alfa.

5.3.3.5.2. Bajetta and colleagues (2004)[79]

Trial/patient characteristics

Further secondary analysis of the trial reported by Littlewood and colleagues (2001)[68], looking at 114 participants with breast cancers from a total of 375 participants. The scales employed were as for Aapro and colleagues (2004)[80] above.

Results

Statistical significance was not assessed, however, change in mean HRQoL score appears to favour epoetin alfa.

Summary

There is a trend towards improved HRQoL for epoetin alfa as compared to placebo.

5.3.3.5.3. Littlewood and colleagues (2006)[82]

Trial/patient characteristics

Secondary analysis of the trial reported by Hedenus and colleagues (2003),[16] aiming to investigate the effects of Hb on patients' fatigue, subsequent to treatment with darbepoetin alfa, and to examine the relationship between improvements in fatigue and HRQoL. The tools used were FACT, Brief Symptom Inventory (BSI) Depression and Anxiety Subscales, numeric rating scales (NRS) of Energy Activity and Overall Health. Of the 344 patients, 303 patients completed the FACT-F subscale at baseline and at least once after receiving four weeks of treatment.

Results

Mean change in FACT-F subscale in score from baseline to end of treatment indicates an improvement for darbepoetin alfa, but this is not analysed statistically, since the trial is underpowered. Data for the other scales are not presented.

Summary

There is a trend towards improved HRQoL for epoetin alfa as compared to placebo.

5.3.3.5.4. Osterborg and colleagues (2005)[70]

Trial/patient characteristics

Analysis of follow-up data from the original trial reported by Osterborg and colleagues (2002).[69] The minimum length of follow up was approximately 17.5 months in both treatment groups, with only four patients in each group receiving less (n=349). FACT-An questionnaires were completed at baseline and every four weeks during the study.

Results

For HRQoL, reported results are given up to Week 16 as for Osterborg and colleagues (2002).[69]

Summary

Two of the scales used to measure HRQoL found a statistically significant increase in favour of epoetin beta, however, the variability between patients was considerable.

5.3.3.5.5. Patrick and colleagues (2003)[60]

Trial/participant characteristics

Additional secondary analysis of the trial reported by **Littlewood and colleagues (2001)**,[68] investigating the observed effects of increased Hb on HRQOL. The scales used were FACT-G, FACT-An Fatigue, CLAS (energy level, daily activities and overall HRQoL), SF-36 Physical and SF-36 Mental.

Results

Patients were pooled across treatment groups and then most patients were assigned to 'Improved' patients (defined as those who experienced an increase in Hb of at least 1 g/dL) and 'stable, or unchanged', patients (change in Hb of less than 1 g/dL to a lower limit of -1g/dL) (Table 45).The difference in the mean HRQoL change score between the improved and stable groups is minimally important difference (MID). If the observed difference between treatment groups is greater than or equal to the MID, then that difference was considered clinically important. The actual difference in mean Hb change between the improved and stable groups in the clinical trial was approximately 2.8 g/dL.

Summary

This trial found a statistically significant increase in favour of epoetin alfa.

Table 45. HRQoL: Results for Patrick and colleagues (2003)[60]

	Baseline Score	Interim time points	Pre/post change	Difference between ESA and control[a]	Minimally important difference
FACT-G (27 items: score 0-108); the higher the score, the higher the HRQoL					
Intervention (n=200)	NR	NR	2.49	6.06 in favour of ESA	2.54
Control (n=90)	NR	NR	-3.57		
p value			0.004		
FACT-An-Fatigue (13 items: score 0-52); the higher the score, the higher the HRQoL					
Intervention (n=200)	NR	NR	2.97	5.15 in favour of ESA	4.24
Control (n=90)	NR	NR	-2.18		
p value			0.004		
CLAS Energy level (100 mm); the higher the score, the higher the HRQoL					
Intervention (n=228)	NR	NR	8.06	13.87 in favour of ESA	9.61
Control (n=108)	NR	NR	-5.8		
p value			0.001		
CLAS Daily activities (100 mm); the higher the score, the higher the HRQoL					
Intervention (n=228)	NR	NR	7.51	13.5 in favour of	8.74
Control (n=108)	NR	NR	-5.99		

p value			0.002	ESA	
CLAS Overall HRQoL (100 mm); the higher the score, the higher the HRQoL					
Intervention (n=228)	NR	NR	4.79	10.76 in favour of ESA	9.81
Control (n=107)	NR	NR	-5.97		
p value			0.005		
SF-36 Physical (0–100%); the higher the score, the lower the disability					
Intervention (n=NR)	NR	NR	1.77	2.3 in favour of ESA	NR
Control (n=NR)	NR	NR	-0.53		
p value			NR		
SF-36 Mental (0–100%) [n]; the higher the score, the lower the disability					
Intervention (n=NR)	NR	NR	2.14	2.39 in favour of ESA	NR
Control (n=NR)	NR	NR	-0.25		
p value			NR		

Key: CLAS, Cancer Linear Analogue Scale; ESA, erythropoiesis stimulating agent; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -G, General); NR, not reported;
Notes: a Calculated by PenTAG, **b** p value for the Anaemia subscale (secondary measure) is unadjusted. All other p values, which correspond to primary measures, are adjusted for multiple comparisons (sequentially rejective Bonferroni procedure).

5.3.3.5.6. Vansteenkiste and colleagues (2004)[81]

Trial/participant characteristics

Secondary analysis of the trial reported by **Vansteenkiste and colleagues (2004)** to determine if the degree of benefit obtained from treatment with darbepoetin alfa is affected by patient's Hb level at the start of treatment. The FACT-F scale was used for assessment of HRQoL.

Results

As per the primary study, results were reported as percentages. Additional results in this report indicate a significant difference (p=0.0147) between darbepoetin alfa and placebo with a baseline Hb of <10 g/dl. In contrast, no difference was apparent between groups with a baseline Hb ≥10 g/dl.

Summary

The trial found a statistically significant improvement in HRQoL for participants with a baseline Hb <10 g/dl at baseline.

5.3.4. Meta-analysis: FACT-F score (random effects)

Given the variability of reporting in the published papers FACT-F 13 item (score 0–52), data were extracted from the Cochrane review by **Tonia and Colleagues (2012)**[10] for use in the PenTAG analyses.

FACT-F scores were available from seven studies (**Littlewood and colleagues, 2001[68]**; **Osterborg and colleagues, 2002, 2005[69,70]; Vansteenkiste and colleagues, 2002[72]; Boogaerts and colleagues, 2003[52];Hedenus and colleagues, 2003[16]; Kotasek and colleagues, 2003[46]; Tjulandin and colleagues, 2011[76])** including 1,794 participants. One new primary study was identified (**Tjuandin and colleagues, 2011**).

The WMD was 2.54 (95% CI 1.42, 3.65; Figure 24). There was low heterogeneity between the trials (I^2=14.9%, p=0.32) (Table 46, page 194). 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.[50] The fixed effects meta-analysis undertaken as a sensitivity analysis showed similar significant results (Appendix M). In terms of quality, all the studies were at a similar level, however, the trial reported by **Boogaerts and colleagues (2003)** did not employ blinding for participants (Figure 26). Removing this study from the meta-analysis had a minimal impact on results with a WMD of 2.21 (95% CI 1.131, 3.280; Appendix M) but did improve heterogeneity (I2=0%, p=0.51). Meta-analysis was performed on FACT-G and FACT-An (7 items), however, only three studies were suitable for inclusion for each scale with high levels of heterogeneity (Table 46, page 194; Appendix M). The results of no statistical difference between intervention and 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, showed significant results, however, the number of studies included was small (Table 46, page 194, Appendix M).

5.3.5. HRQoL outcomes: overall summary

Effectiveness estimates are compared with previously reported estimates for HRQoL; see Table 46. A graphical summary of study characteristics and results for these outcomes is presented in Figure 25, page 197.

Table 46. HRQoL: results comparison for FACT: Wilson and colleagues, 2007 vs Tonia and colleagues, 2012 vs PenTAG 2013[1,10]

	Wilson, 2007[b]	Tonia, 2012[b]	PenTAG, 2013[b]	PenTAG, 2013[c]
HRQoL				
FACT-F 13 item (score 0-52)	NR	MD 2.08 95% CI 1.43, 2.72 $X^2_{(het)}$36.48; df 17 (p=0.004) 18 trials, n=4,965	MD 2.49 95% CI 1.48,3.51 $X^2_{(het)}$7.05; df 6 (p=0.000) 7 trials, n=1,794	MD 2.54 95% CI 1.42, 3.65 $X^2_{(het)}$7.05; df 6 (p=0.000) 7 trials, n= 1,794

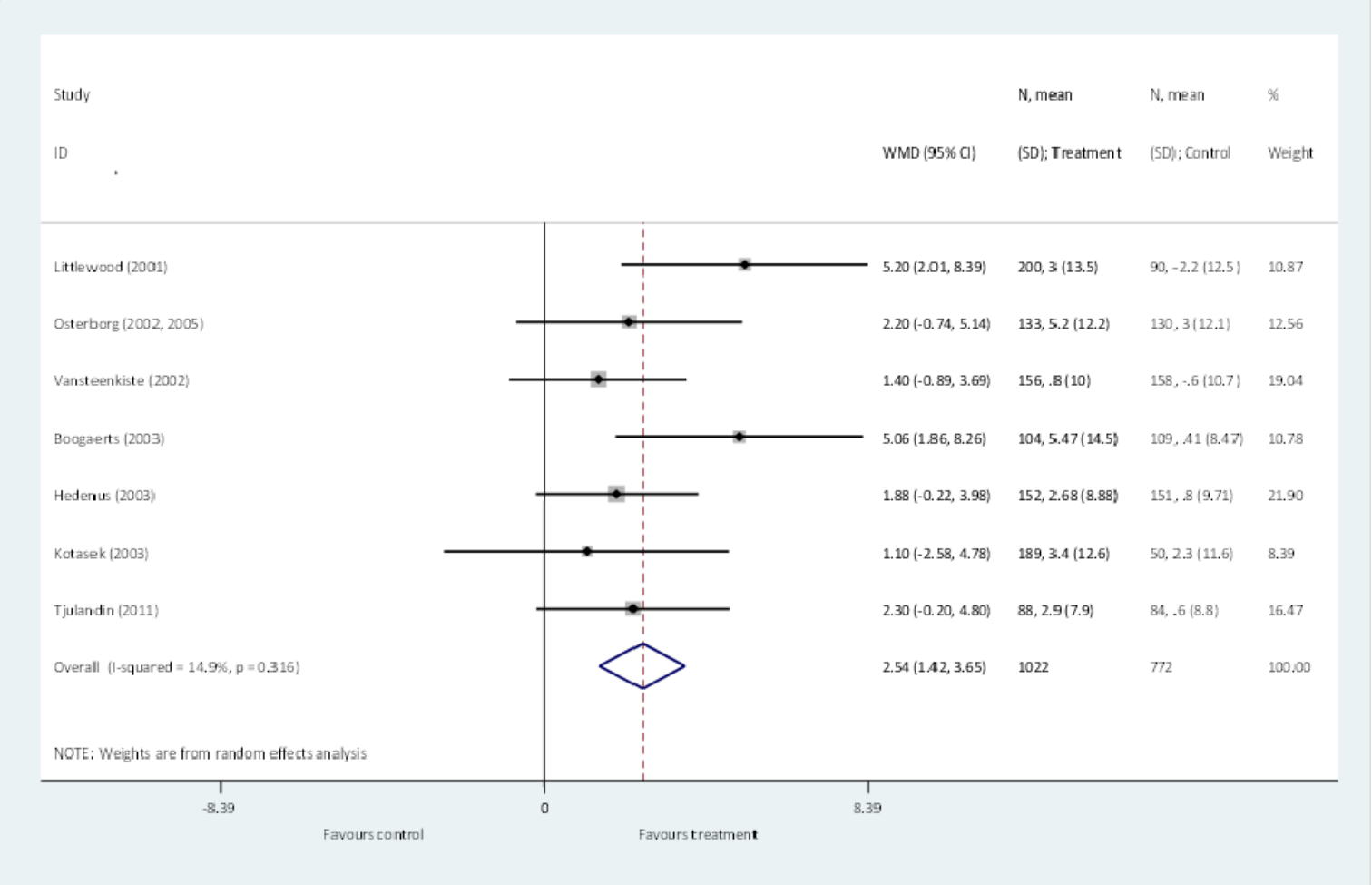
Any subgroup effect	NR	Yes: imputed vs. non-imputed data, baseline Hb level, type of anti-cancer therapy, duration of ESA treatment and ITT analysis.	–	Possible: malignancy, intervention and duration
FACT-F 13 item (score 0-52) without Boogaerts, 2003	–	–	–	MD 2.21 95% CI 1.13, 3.28 $X^2_{(het)}$4.31; df 5 (p=0.000) 6 trials, n= 1,581
FACT-G 27 item (score 0-108)	NR	NR	MD 3.16[e] 95% CI 1.11, 5.21 $X^2_{(het)}$6.82; df 2 (p=0.003) 3 trials, n=686	MD 2.98[e] 95% CI -0.83, 6.78 $X^2_{(het)}$6.82; df 2 (p=0.13) 3 trials, n=686
FACT-An 7 item (score 0-28)	NR	NR[d]	MD 1.05[f] 95% CI 0.93, 1.12 $X^2_{(het)}$80.66; df 2 (p=0.00) 3 trials, n=686	MD 2.60[f] 95% CI -0.52, 5.72 $X^2_{(het)}$80.66; df 2 (p=0.00) 3 trials, n=686

Key: CI, confidence interval; df, degrees of freedom; het, heterogeneity; ITT, intention-to-treat; MD, minimal difference; WMD, weighted mean difference

Notes: (a) change from baseline to end of study; (**b)** fixed effects (Mantel-Haenszel); **(c)** random effects (Der-Simonian Laird); **(d)** FACT-An (47 item) only used gy Tjulandin (2011) and Osterborg (2005), so no meta-analysis performed on this scale. Three studies analysed the FACT-An subscale (7 items). Tonia (2012) refer to a FACT-An (20 items) which is likely to be FACT-F subscale + FACT-An 7which they may have been able to use dueto additional information received by them. The reports of included studies here confirm 7-item FACT-An; **(e)** Standard deviation for Littlewood (2001) imputed from Tjulandin (2011) and Osterborg (2005); **(f)** Standard deviation for Littlewood (2001) imputed from Osterborg (2005);

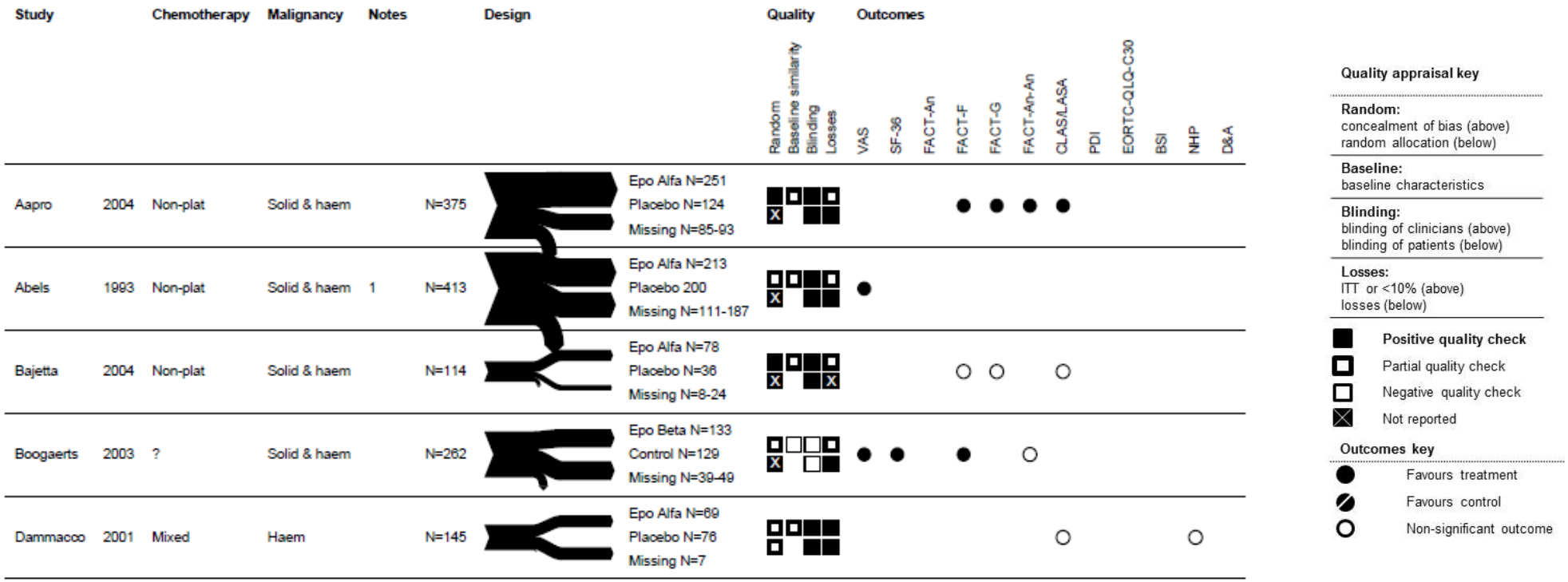
Overall, conclusions from the PenTAG review are in agreement with the Cochrane review (**Tonia and colleagues, 2012**)[10] in that there is a statistically significant difference between patients treated with ESAs and controls when combining HRQoL parameters, which is, however, most likely not clinically important (the threshold MD of 3.0 [Cella and colleagues, 2002])[96]. As with previous reviews, however, it should be noted that there are several methodological concerns which may result in bias; e.g. the substantial quantity of missing data, expecting patients to complete repeated questionnaires leading to a shift in patient response and various modes of administration of questionnaire.

Figure 24. HRQoL: overall (random effects)



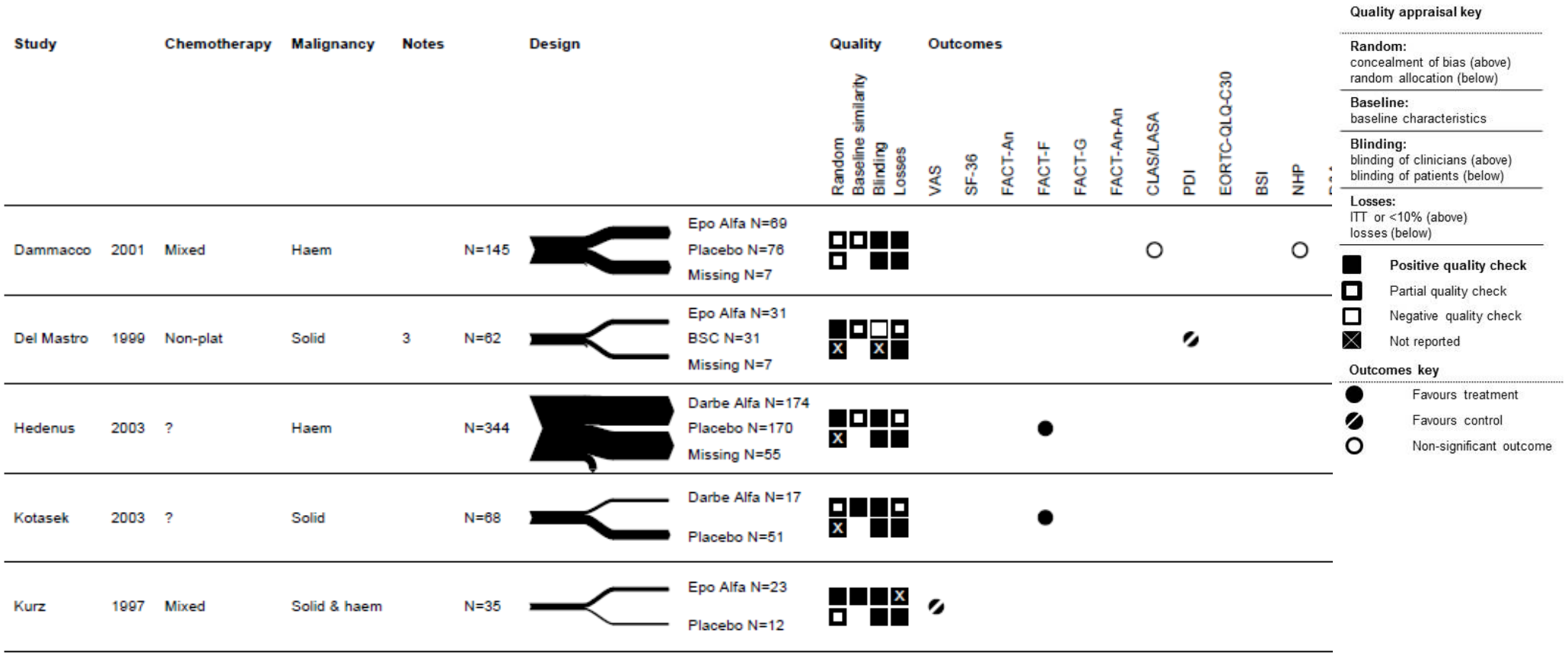
Key: CI, confidence interval; N number of events/participants in the treatment and control groups; ID, identification; WMD, weighted mean difference
Notes: (a) Random effects (Der-Simonian Laird pooled RR)

Figure 25. HRQoL: Graphical summary



Key: ?, unknown; BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analogue Score; EORTC QLQ C-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -F, Fatigue; G, General); HRQoL, health-related quality of life; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; PDI, Psychological Distress Inventory; SF-36, Short Form 36; VAS, Visual Analogue Scale; D&A, Depression and Anxiety subscale of BSI
Notes: 1 Study population included pts not receiving chemotherapy; **2** 87% and 84% participants were analysed in treatment and control groups, respectively, **3** 80% and 73% participants were analysed in treatment and control groups, respectively, **4** 54% and 57% participants were analysed in treatment and control groups, respectively, **5** 75% and 61% participants were analysed in treatment and control groups, respectively, **6** 90-98% and 86-97% participants were analysed in treatment and control groups, respectively, **7** 81% participants were analysed in treatment and control groups

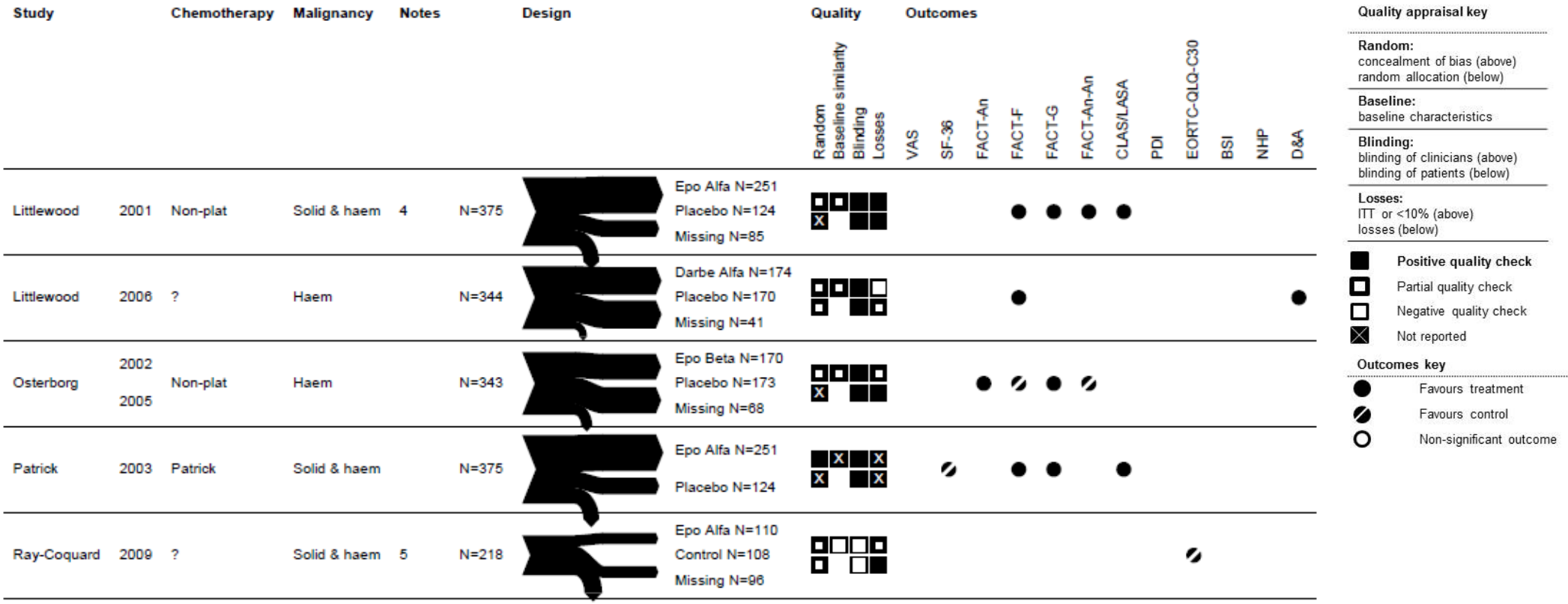
Figure 26. HRQoL: Graphical summary (continued)



Key: ?, unknown; BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analogue Score; EORTC QLQ C-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -F, Fatigue; G, General); HRQoL, health-related quality of life; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; PDI, Psychological Distress Inventory; SF-36, Short Form 36; VAS, Visual Analogue Scale; D&A, Depression and Anxiety subscale of BSI

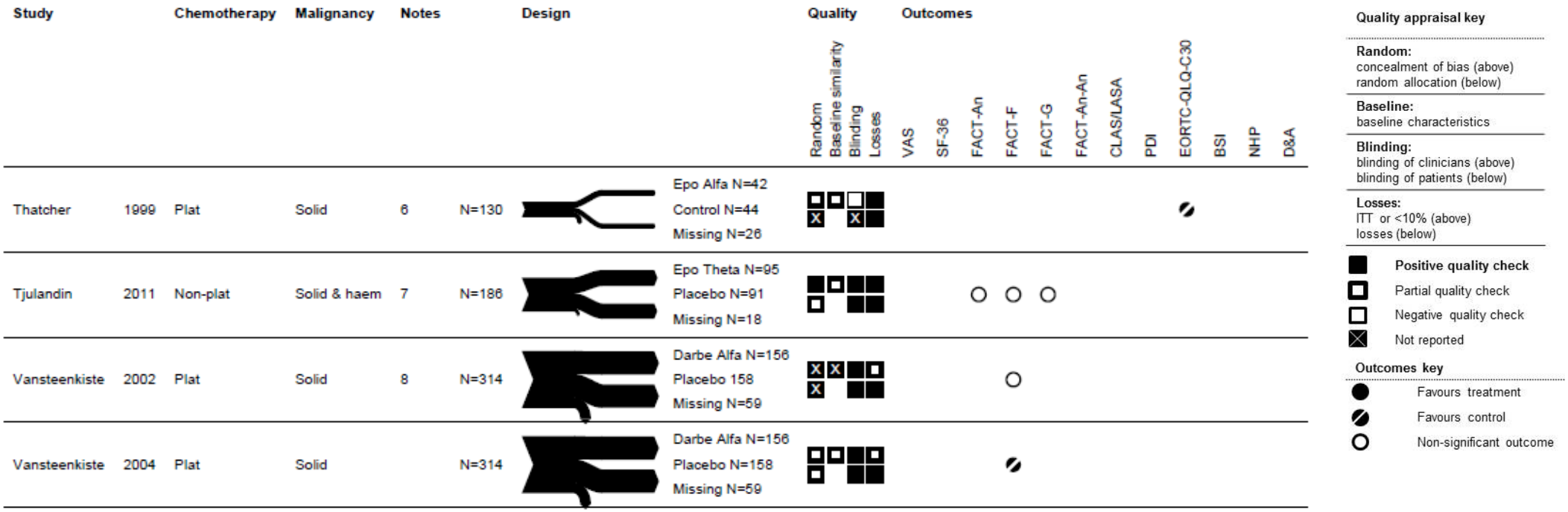
Notes: 1 Paediatric population evaluated; **2** Study population included pts not receiving chemotherapy; **3** 87% and 84% participants were analysed in treatment and control groups, respectively, **4** 80% and 73% participants were analysed in treatment and control groups, respectively, **5** 54% and 57% participants were analysed in treatment and control groups, respectively, **6** 75% and 61% participants were analysed in treatment and control groups, respectively, **7** 90-98% and 86-97% participants were analysed in treatment and control groups, respectively, **8** 81% participants were analysed in treatment and control groups

Figure 26. HRQoL: Graphical summary (continued)



Key: ?, unknown; BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analogue Score; EORTC QLQ C-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -F, Fatigue; G, General); HRQoL, health-related quality of life; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; PDI, Psychological Distress Inventory; SF-36, Short Form 36; VAS, Visual Analogue Scale; D&A, Depression and Anxiety subscale of BSI
Notes: 1 Paediatric population evaluated; **2** Study population included pts not receiving chemotherapy; **3** 87% and 84% participants were analysed in treatment and control groups, respectively, **4** 80% and 73% participants were analysed in treatment and control groups, respectively, **5** 54% and 57% participants were analysed in treatment and control groups, respectively, **6** 75% and 61% participants were analysed in treatment and control groups, respectively, **7** 90-98% and 86-97% participants were analysed in treatment and control groups, respectively, **8** 81% participants were analysed in treatment and control groups

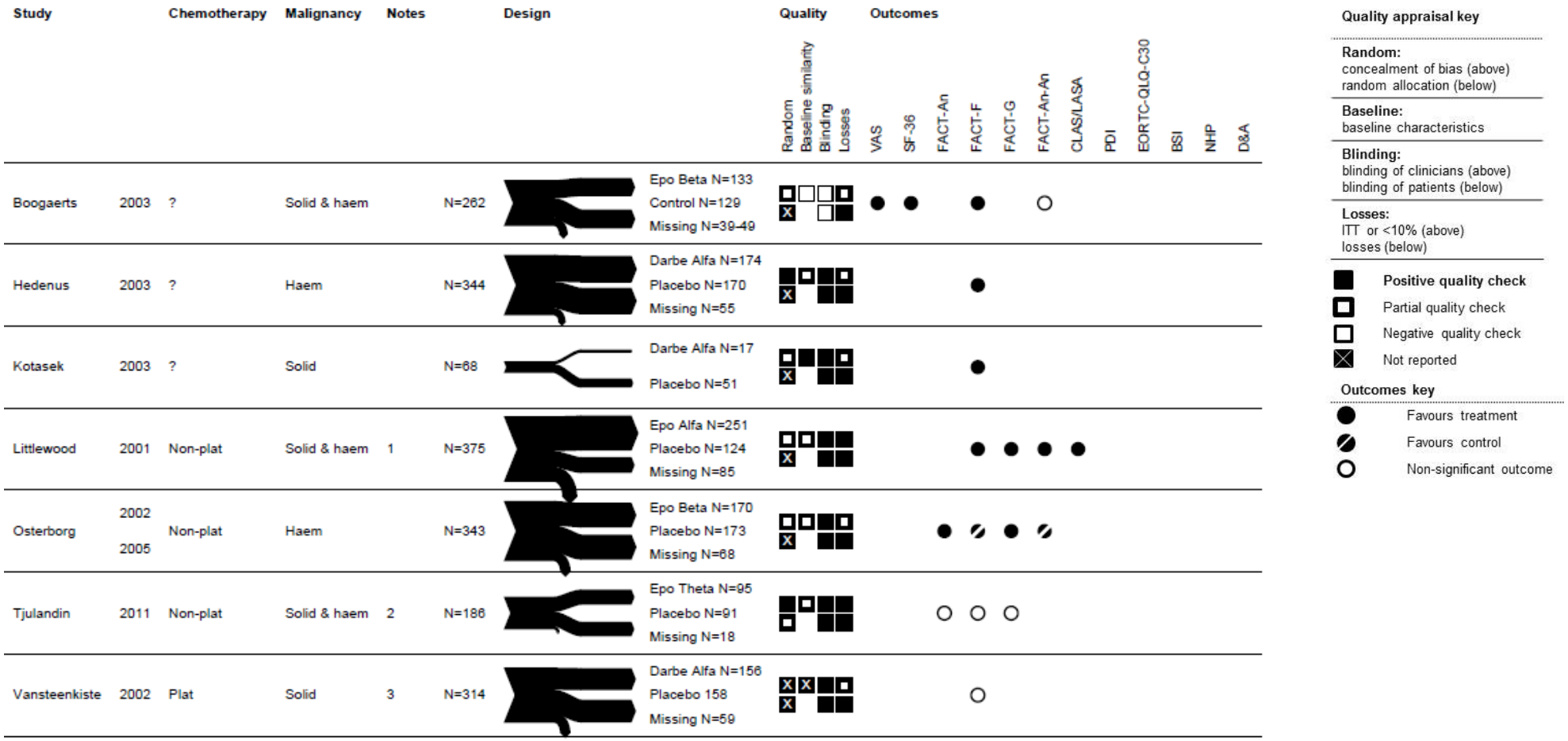
Figure 26. HRQoL: Graphical summary (continued)



Key: ?, unknown; BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analogue Score; EORTC QLQ C-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -F, Fatigue; G, General); HRQoL, health-related quality of life; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; PDI, Psychological Distress Inventory; SF-36, Short Form 36; VAS, Visual Analogue Scale; D&A, Depression and Anxiety subscale of BSI

Notes: 1 Paediatric population evaluated; **2** Study population included pts not receiving chemotherapy; **3** 87% and 84% participants were analysed in treatment and control groups, respectively, **4** 80% and 73% participants were analysed in treatment and control groups, respectively, **5** 54% and 57% participants were analysed in treatment and control groups, respectively, **6** 75% and 61% participants were analysed in treatment and control groups, respectively, **7** 90-98% and 86-97% participants were analysed in treatment and control groups, respectively, **8** 81% participants were analysed in treatment and control groups

Figure 26. FACT-F analysis



Key: ?, unknown; BSI, Brief Symptom Inventory; CLAS, Cancer Linear Analogue Score; EORTC QLQ C-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT, Functional Assessment of Cancer Therapy (-An, Anaemia; -F, Fatigue; G, General); HRQoL, health-related quality of life; LASA, Linear Analogue Scale Assessment; NHP, Nottingham Health Profile; PDI, Psychological Distress Inventory; SF-36, Short Form 36; VAS, Visual Analogue Scale; D&A, Depression and Anxiety subscale of BSI

Notes: 1 80% and 73% participants were analysed in treatment and control groups, respectively, **2** 90-98% and 86-97% participants were analysed in treatment and control groups, respectively, **3** 81% participants were analysed in treatment and control groups

5.4. Summary

KEY POINTS

- Fourteen trials measuring HRQoL were reported in 24 publications. Of these publications, 11 primary studies were included in the review by **Wilson and colleagues (2007).**[1] Three new primary studies were identified in the update searches
- The method of randomisation was unclear in seven of the primary studies with all reports having unclear allocation concealment. 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 of HRQoL assessed by self-reporting. HRQoL suffered significant losses for at least six trials.
- FACT-F 13 item data were extracted from review by **Tonia and colleagues (2012),**[10] given their greater access to data than that provided in the primary papers. FACT-F scores were available from seven studies with one new primary study identified.
- Overall, conclusions from the PenTAG review are in agreement with the Cochrane review (**Tonia and colleagues, 2012**)[10] in that there is a statistically significant difference between patients treated with ESAs and controls when combining HRQoL parameters, which is, however, most likely not clinically important (the threshold MD of 3.0 [Cella and colleagues, 2002])[96].
- 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 results between intervention and control.
- Meta-analysis was performed on FACT-G and FACT-An (7 items), however, only three studies were suitable for inclusion for each scale with high levels of heterogeneity.The results of no statistical difference between intervention and control must therefore be treated with caution.
- Publication bias was noted in the Cochrane review (**Tonia and colleagues, 2012**)[10], suggesting over reporting of studies that showed beneficial effects of ESAs. It was not possible to examine publication bias using funnel plots because <10 included studies. Therefore, it was not possible to confirm or refute the claims made in the Cochrane review.

Assessment of cost-effectiveness

6.1. Systematic review of existing cost-effectiveness evidence

The cost-effectiveness of erythropoiesis-stimulating agents (ESAs) within their licensed indications for the treatment of chemotherapy-induced anaemia (CIA) against each other and against best supportive care (BSC) 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 (2007)**[1] which informed previous NICE guidance TA142.[34] The methods and results of the previous systematic review are summarised in Section 6.1.1, the methods for this update review are described in Section 6.1.2 and the results of the update review are shown in Section 6.1.2.3.

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

6.1.1. Wilson and colleagues (2007): Summary

A systematic review of cost-effectiveness evidence was reported by **Wilson and colleagues (2007)** which informed previous NICE guidance TA142.[1,34]

6.1.1.1. 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.'

6.1.1.2. Methods

Searches were conducted in databases as detailed in Table 47. Industry submissions were also evaluated and searched for additional references.

Table 47. Databases searched in systematic review by Wilson and colleagues, 2007[1]

Database	Interface	Date range
MEDLINE	Ovid	1966 to July week 4 2004
EMBASE	Ovid	1980 to 2004 week 30
DARE		2004 Issue 3
NHS EED		2004 Issue 3
OHE HEED		July 2004 issue
Key: DARE, Database of Reviews and Effects; EED, Economic Evaluation Database; OHE EED, Office of Health Economics Health Economic Evaluations Database		

Separate search strategies were developed for costs, economic models and quality of life studies and are detailed in Appendix 3 of **Wilson and colleagues (2007)**.[1]

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.' Screening was performed by one reviewer.

Included studies were critically appraised using the checklist suggested by Drummond and colleagues.[114] Single points were also assigned to all but one criteria on the Drummond checklist when met and summed to give an overall quality score for a study.

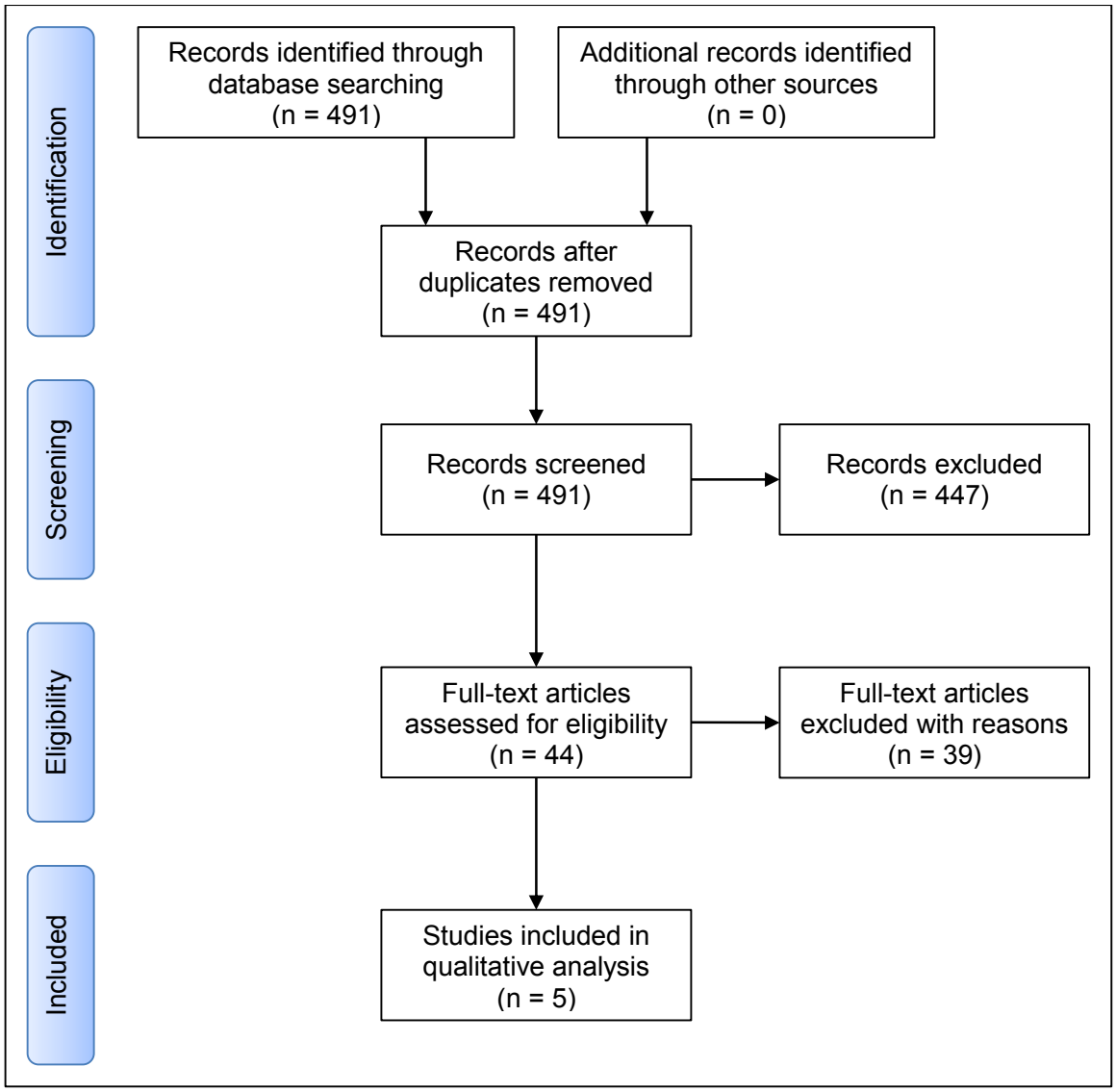
Data were abstracted from the studies using a framework used by the West Midlands group in previous technology appraisals. Data abstraction was performed by one reviewer and checked by another.

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

6.1.1.3. Results

Electronic database searches resulted in 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 (**Barosi and colleagues, 1998**; **Cremieux and colleagues, 1999**; **Martin and colleagues, 2003**; **Ortega and colleagues, 1998**; **Sheffield and colleagues, 1997**) were included following full text screening (the remainder generally being excluded for not considering both costs and benefits).[115-119] Figure 27 shows the study flow diagram for the systematic review.

Figure 27. Study flow diagram for systematic review of cost-effectiveness evidence reported by Wilson and colleagues (2007)[1]



Notes: Adapted from PRISMA flow diagram[120]

The results of three cost-utility studies included in the systematic review reported by **Wilson and colleagues (2007)**[1] are also included in the update review results in Section 6.1.2.3 (page 210) and are hence not reported here.

Two other studies were included, one by **Ortega and colleagues (1998)**[118] and one by **Sheffield and colleagues (1997)**.[119] **Ortega and colleagues (1998)**[118] 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 by 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 (1997)**[119] 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; i.e., it would be more expensive and produce worse outcomes. **Wilson and colleagues (2007)** highlighted several assumptions made which seemed implausible.[1]

6.1.2. Update review

6.1.2.1. Objective

The objective of the update review was specified in the appraisal protocol:

This systematic review aims to update the systematic review of cost-effectiveness studies which was conducted in 2004 as part of the review of evidence to inform NICE's earlier guidance on these drugs (TA142).[34]

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

Therefore, it will fully extract study data and assess study quality only for those economic evaluations or costing studies published since 2004 which are of relevance to the current decision problem.

6.1.2.2. Methods

6.1.2.2.1. 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 to economic evaluations (see Appendix B). Table 48 gives a summary of the databases searched. Where possible, searches were limited to publications since 2004.

Table 48. Databases searched in the update review

Database	Host	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 2013 week 21
NHS EED	Cochrane library	Issue 2 of 4, April 2013
Web of Science	Thomson Reuters	Searched 29/05/2013
CINAHL	EBSCO	Searched 29/05/2013
OHE HEED	Cochrane library	Searched 29/05/2013
Key: DARE, Database of Reviews and Effects; NHS EED, NHS Economic Evaluation Database; OHE EED, Office of Health Economics Health Economic Evaluations Database **Notes:** 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 B):

- Cochrane Database of Systematic Reviews (via the Cochrane Library): Issue 4 of 12, April 2013
- Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database (via the Cochrane Library): Issue 2 of 4, April 2013
- Health Management Information Consortium (HMIC) database (via Ovid): 1979 to March 2013.

6.1.2.2.2. Screening

Inclusion and exclusion criteria were the same as for the clinical effectiveness systematic review (Section 4.1.2, page 59), 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 which only report average cost-effectiveness ratios were only included if the incremental ratios could be easily calculated from the published data).
- Standalone 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 three 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 dosage and weight-based dosages were allowed; this is a different application of the licence to the systematic review of clinical effectiveness evidence (Section 6.1.2.2.7, page 209).

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 were screened for eligibility by the same reviewers, with disagreements resolved by discussion.

The bibliographies of review articles not judged 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 database searches.

6.1.2.2.3. Data extraction

Study characteristics and results were abstracted by one reviewer (TS) using a template adapted from the systematic review by **Wilson and colleagues (2007)**.[1] In addition, parameters which could be used in the construction of an independent economic model were identified and noted.

6.1.2.2.4. Selection of studies for detailed appraisal and reporting

Data extraction was conducted for all included studies, but for reasons of expediency, not all studies which 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).

6.1.2.2.5. Quality appraisal

Selected studies (all new systematic reviews and cost-utility studies) were quality assessed using the checklist developed by Evers and colleagues (2005)[121] by one reviewer (TS). In line with the instructions accompanying the final checklist, where there was insufficient

information available in the article to assess quality 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.

Where these studies were based on decision models, they were further quality assessed using the checklist developed by Philips and colleagues (2006).[122]

6.1.2.2.6. Analysis

The results of 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.

6.1.2.2.7. Changes from 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 (1999)**,[116] **Fagnoni and colleagues (2006)**[123] and **Tonelli and colleagues (2009)**[112] 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 (2007)**[1];
- The de novo analysis in **Wilson and colleagues (2007)**[1] 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 due to unlicensed dose schedule, **Glaspy and colleagues (2002)**,[124] which was only published as an abstract and 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 most relevant studies to the appraisal given the significant number of non-QALY outcomes of limited utility to decision makers attempting to maximise the total health benefit across healthcare spending. This resulted in the exclusion of 12 studies in abstract form only (characteristics and results given in Appendix P) and six studies in full paper form (characteristics and results in Section 6.1.2.3, page 210).

6.1.2.3. Results

Figure 28 (page 212) shows the study flow diagram of this update review. The electronic database search for cost-effectiveness evidence identified 1,131 records, and the supplementary search identified 32 records. After de-duplication 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 (**Cornes and colleagues, 2007**; **Herrmann and colleagues, 2008**; **Marchetti and colleagues, 2004**; **Reeder and colleagues, 2007; Repetto and colleagues, 2006; Stasi and colleagues, 2005**)[125-130] (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 which could not be obtained was by **Roungrong and colleagues (2008)**[131] which is a cost-utility analysis of epoetin alfa for cancer patients with anaemia in Thailand. The Centre for Reviews and Dissemination produced a critical appraisal of the study for the NHS Economic Evidence Database (NHS EED),[132] which reveals that the study was generally well conducted except for the limited reporting of clinical data sources and that it concluded epoetin alfa would not be a cost-effective alternative to standard care with RBCT.

Three studies which could not be obtained were published in 1997/1998, one of which was by **Sheffield and colleagues (1997)**[119] and included in the previous systematic review by **Wilson and colleagues (2007)**.[1] Two studies by **Griggs and colleagues (1997** and **1998)**[133,134] also could not be obtained. One appears to be a conference abstract of a cost-utility study (**Griggs and colleagues, 1997**).[133] The other (**Griggs and colleagues, 1998**) appears to be a full paper but likely to be a review rather than a primary study.[134]

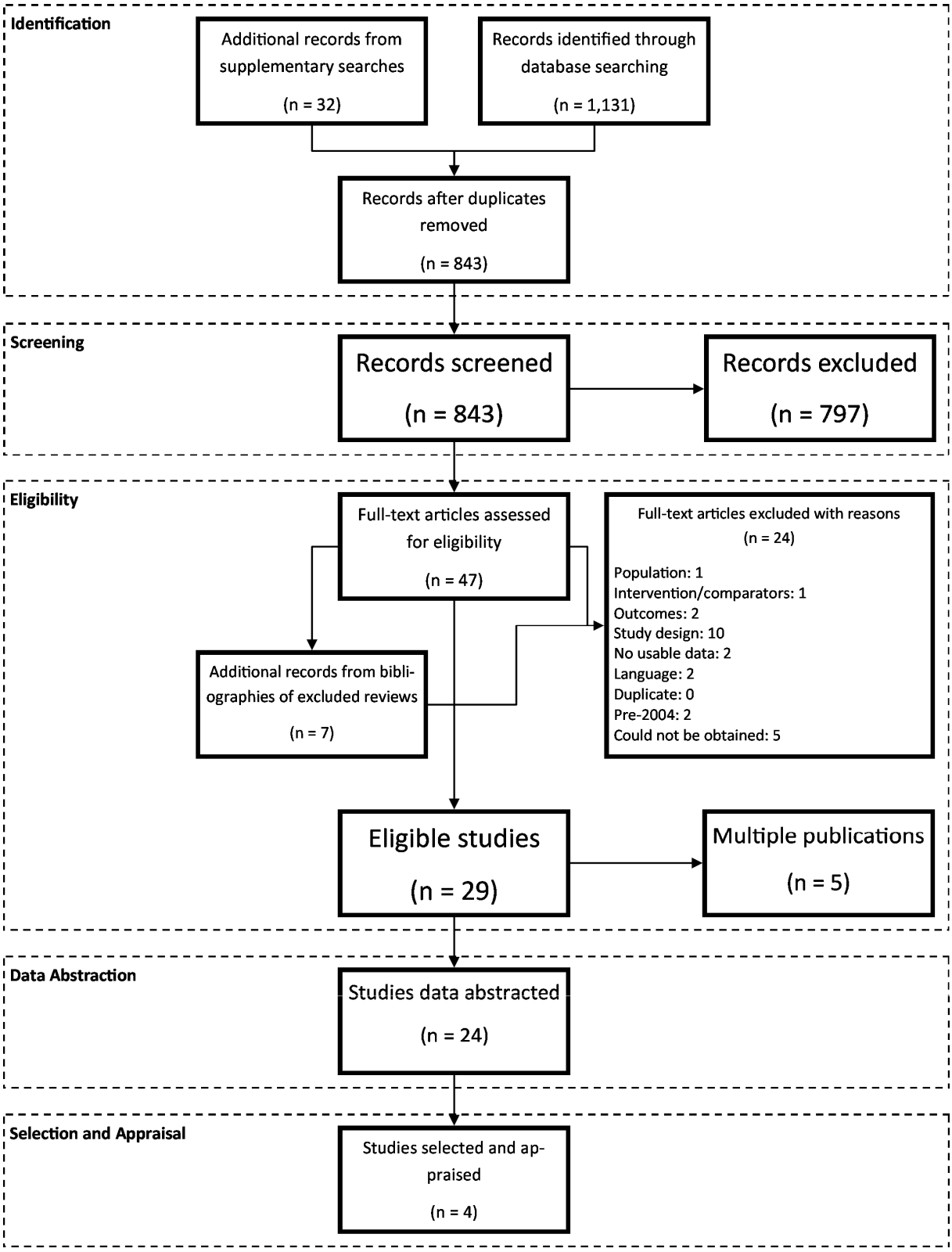
Finally one conference abstract by **Malonne and colleagues (2005)** could not be obtained, although the title suggests it may have only evaluated costs.[135]

Of the 47 full texts assessed for eligibility, 29 were deemed to meet the eligibility criteria. Reasons for exclusion after full text screening are detailed in Appendix N. Five texts (**Borget and colleagues, 2006; Borget and colleagues, 2007**; **Chouaid and colleagues, 2005**; **Finek and colleagues, 2010**; **Klarenbach and colleagues, 2010**)[136-140] were deemed to be multiple publications, including four abstracts and a peer-reviewed journal paper by **Klarenbach and colleagues (2010)**[140] deemed to be a multiple publication of the CADTH technology assessment report by **Tonelli and colleagues (2009)**[112] (see Appendix O), leaving 24 primary studies from which data was abstracted. Twelve primary publications were conference abstracts (**Szucs and colleagues, 2001**; **Cremieux and colleagues, 2003**; **Mark and colleagues, 2003**; **Hout and colleagues, 2004**; **Ben-Hamadi and colleagues, 2005**; **Van Bellinghen and colleagues, 2006**; **Esposito and colleagues, 2007**; **Van Bellinghen and colleagues, 2007**; **Finek and colleagues, 2010**; **Liwing and colleagues, 2010**; **Walter and colleagues, 2010**; **Fragoulakis and colleagues, 2011**);[141-152] three were or included systematic reviews (**Wilson and colleagues, 2007**; **Duh and colleagues, 2008**; **Tonelli and colleagues, 2009**),[1,112,153] and two were related to the previous NICE appraisal (**Wilson and colleagues, 2007**; **NICE TA142, 2007**);[1,34] these are described elsewhere in this report (Section 2.7.1, page 46) and are not appraised as a part of this update review, although the results of **Wilson and colleagues (2007)**[1] are considered as conclusions are drawn.

Summary tables of characteristics, key parameters and findings for abstracts are given in Appendix P. Summary tables of characteristics, key parameters and findings for full papers are shown in Table 56, Table 57 and Table 58 respectively.

Of the eligible studies, four (**Fagnoni and colleagues, 2006**; **Borg and colleagues, 2008**; **Duh and colleagues, 2008**; **Tonelli and colleagues, 2009**)[112,123,153,154] were selected for detailed appraisal. These comprised one standalone systematic review by **Duh and colleagues (2008)**[153] and three new cost-utility studies(**Fagnoni and colleagues, 2006**; **Borg and colleagues, 2008**; **Tonelli and colleagues, 2009**)[112,123,154] of which one also contained a systematic review (**Tonelli and colleagues, 2009**).[112]

Figure 28. PRISMA flow diagram of update review



6.1.2.3.1. Summaries of identified systematic reviews

Duh and colleagues, 2008[153]

Duh and colleagues (2008) 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 journals 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 comprising ESA therapy.

The authors identified 67 studies in the field of oncology in addition to 39 in chronic kidney disease 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 were identified through conferences (meetings of ASCO, ASH, ESMO and EHA in the period 2003–2006) 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 utilising textual descriptions and tabulation.

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

Various outcome measures were found, 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 where cost-effectiveness results are presented epoetin alfa has a lower average cost-effectiveness ratio than darbepoetin alfa.

The authors made a number of arguments which seemed to be designed to undermine results from existing cost-utility studies which produced 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 only approach acceptable cost-utility thresholds when a survival benefit is assumed. As 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.'

The authors also suggested that cumulative changes in haemoglobin 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 is claimed to achieve 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, 2009[112]

Tonelli and colleagues 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):

- 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) was extracted.

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

The combined searches produced 1,134 citations, of which 58 were identified for scrutiny by full text. Forty-seven studies were excluded to leave 11 primary studies included in the systematic review.

Five of the 11 studies were cost-utility analyses:

- **Wilson and colleagues (2007)**,[1] produced for the previous NICE appraisal
- **Fagnoni and colleagues (2006)**,[123] also identified in this update review
- **Martin and colleagues (2003)**,[117] **Cremieux and colleagues (1999)**[116] and **Barosi and colleagues (1998)**;[115] all included in the systematic review reported in **Wilson and colleagues (2007)**[1]

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

Narrative review identified that only one study, by **Martin and colleagues (2003)**,[117] reported an attractive incremental cost-utility ratio (ICUR). **Tonelli and colleagues (2009)**[112] note that this was an industry-sponsored study and that a subgroup of RCT patients with Stage IV breast cancer were identified to inform the model who demonstrated a survival advantage with epoetin use (although this survival advantage did not reach statistical significance), and

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:

- **Ossa and colleagues (2007)**,[155] a discrete choice experiment to ascertain the utility of anaemia-related health states and the willingness-to-pay for epoetin alfa
- **Borget and colleagues (2006)**,[156] a model-based cost-effectiveness analysis of darbepoetin alfa versus standard care without ESA use in patients with lung cancer with an effectiveness measure related to the final haemoglobin level achieved
- **Reed and colleagues (2006)**,[157] a cost-consequences analysis based on an open-label RCT of epoetin alfa once weekly and darbepoetin alfa every two weeks in patients with solid malignancies
- **Casadevall and colleagues (2004),**[158] a study of epoetin and rHuG-CSF and supportive care in patients with myelodysplastic syndrome (this was excluded from this review due to concomitant treatment with G-CSF)
- **Ortega and colleagues (1998)**[118] and **Sheffield and colleagues (1997)**;[119] both identified in the systematic review reported by **Wilson and colleagues (2007)**[1]

Tonelli and colleagues (2009)[112] noted in their discussion that ESA use leads to large incremental costs which do not tend to be significantly altered across a range of costs for RBCT. They noted that where 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 (2009)[112] 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.

6.1.2.3.2. Characteristics of new cost-utility studies

Fagnoni and colleagues, 2006[123]

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 which 91 were treated before the use of EPO was allowed (1999–2001), and 101 could have received EPO (2002–2004). 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 healthcare 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 54, page 226). 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 transfusion per red blood cell transfusion unit. Double counting owing to the tariff for blood transfusion was avoided by removing costs already collected for blood transfusions from hospitalisation costs.

Quality of life was modelled as a function of haemoglobin level, according to the Linear Analog Scale Assessment (LASA) methodology described by **Crawford and colleagues (2002)**[159] after being placed in discrete sections. Haemoglobin levels were measured at least every three weeks (i.e., at least once per chemotherapy cycle). The lowest haemoglobin level measured was taken as the haemoglobin 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 haemoglobin 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, 2008[154]

In this study the authors constructed an economic model based on the model presented by **Wilson and colleagues (2007)**[1] to evaluate the cost-utility (measured in euros or Swedish kronor per QALY) of epoetin alfa compared to red blood cell transfusion.

Two epoetin alfa strategies were included, in both of which red blood cell transfusion was 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 EPO 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 four weeks) before being discontinued. No dose doubling was included in the base case analysis.

Three red blood cell transfusion strategies were included, with trigger Hb levels of 9, 10 and 11 g/dL for transfusion of two units red blood cells.

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

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

A healthcare perspective was adopted and the following costs were included: drug acquisition, nurse-led hospital oncology clinic (one-off drug administration for epoetin alfa), filtered red blood cells acquisition, red blood cell transfusion administration. Unit costs for drug acquisition were derived from Pharmaceutical Specialities in Sweden, 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 (2007)**.[1]

Tonelli and colleagues, 2009[112]

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 consists of two submodels, one which represents the fifteen weeks during which ESA is administered in RCTs and another which represents the following year, during which the impact of ESAs on long-term survival are 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 haemoglobin levels and health-related quality of life)
- Haemoglobin level improvement from baseline to end of trial period
- Reduction in RBC units transfused
- Short-term mortality (within 15 weeks)
- Long-term mortality (within one year)

Although an increase in all adverse events was found in the systematic review of clinical effectiveness this was not included in the base-case analysis due to the heterogeneous nature of those adverse events and the lack of data regarding resource utilisation and costs of these adverse events.

A healthcare perspective was adopted and costs were included for:

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

In the base-case analysis, gains in haemoglobin 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 from 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.

6.1.2.3.3. Quality of new cost-utility studies

The quality appraisal checklist developed by Evers and colleagues[121] was applied to the three new cost-utility studies (see Table 49). 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 **Tonelli and colleagues (2009)**[112] were judged to have included sensitivity analyses of all important variables. No study produced a probabilistic sensitivity analysis.

The reviewer (TS) believes the only item where quality was not indicated which would materially affect conclusions is that **Borg and colleagues (2008)**[154] did not subject many of the key parameters, the values of which were uncertain, to sensitivity analyses.

Table 49. Quality appraisal of new cost-utility studies using the checklist developed by Evers and colleagues[121]

	Fagnoni, 2006[123]	Borg, 2008[154]	Tonelli, 2009[112]
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
Notes: (a) For this decision problem, a healthcare perspective was deemed to be appropriate			

Table 50. Quality appraisal of new model-based cost-utility studies using the checklist developed by Philips and colleagues[122]

	Borg, 2008[154]	Tonelli, 2009[112]
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	N/A
Data (D)		
D1: Data identification	No	Yes
D2: Pre-model data analysis	(No)	(Yes)
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)	(No)
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
Notes: (a) Assuming no survival benefit from ESAs		

6.1.2.3.4. Key parameters of all cost-utility studies

ESA dosage

ESA dosing strategies vary significantly in the literature 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

These aspects of dosing will potentially affect clinical effectiveness (Section 4.1.2.3.1, page 60 and Appendix C) and 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 (2008)**[154] to 13 g/dL in **Wilson and colleagues (2007)**.[1] Target Hb level was only reported in two studies, 13 g/dL in Wilson and colleagues[1] and 12 g/dL in Borg and colleagues.[154]

Dose escalation was included in the analyses by **Martin and colleagues (2003)**[117] and by **Fagnoni and colleagues (2006)**,[123] in both case doubling the dose, after four and six weeks of inadequate response respectively. Dose escalation may improve clinical effectiveness but adds costs, which may lead to an overall worsening of cost-effectiveness (indeed **Borg and colleagues (2008)**[154] found that dose doubling was not cost-effective relative to non-escalated dosing).

ESA abandonment was included in the analyses by **Wilson and colleagues (2007)**[1] at 12 weeks, **Fagnoni and colleagues (2006)**[123] at 12 weeks and **Borg and colleagues (2008)**[154] at eight weeks. Abandoning ESA therapy for non-responders is likely to improve cost-effectiveness as such patients are unlikely to benefit from further therapy which would incur significant costs. Earlier abandonment may improve the cost-effectiveness of ESA therapy.

Continuation of ESA therapy following chemotherapy cessation was only explicitly reported in the study by **Martin and colleagues (2003)**,[117] where patients were expected to receive ESA therapy for four weeks following chemotherapy cessation, although delays in chemotherapy treatment would reduce the duration of continued use. Continuation of ESA therapy is allowed for in the ESA licenses up to four weeks, which could hasten the return to normal Hb levels for patients receiving ESA and increase the QALY benefit estimated to arise in the normalisation period.

Table 51. Dosage in primary cost-utility analyses

	Start dose	Trigger Hb	Target Hb	Dose escalation	ESA abandon-ment	Duration of continued use
Barosi, 1998[115]	**Epo-a Q3W:** 150 IU/kg	10.7 g/dL	None	None	None	NR
Cremieux, 1999[116]	**Epo-a Q3W:** 10,000 IU	NR	None	None	None	None
Martin, 2003[117]	**Epo-a Q3W:** 150 IU/kg	10.5 g/dL	None	After 4 weeks (no further details)	NR	4 weeks (expected)
Amgen model[1]	**Darb-a:** 2.25 µg/kg *per week*	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]
Ortho Biotec model[1]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]
Roche model[1]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]
Wilson, 2007[1]	Not clear	13 g/dL	13 g/dL[a]	None	12 weeks	NR
Fagnoni, 2006[123]	**Epo-a QW:** 40,000 IU	11.5 g/dL	NR	Dose ×2 if no response after 6 weeks	12 weeks	NR
Borg, 2008[154]	**Epo-a Q3W:** 150 IU/kg	10 g/dL	12 g/dL	None	8 weeks	NR[b]
Tonelli, 2009[112]	**Epo-a QW:** 42,148 IU	None[c]	None	None	None	NR

Key: Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Epo-b, epoetin beta; ESA, erythropoiesis stimulating agent; Hb, haemoglobin
Notes: (a) Half dose was assumed if Hb 12–13 g/dL; **(b)** A possible interpretation is that use was continued until target Hb reached; **(c)** In the base case patients were assumed to start with Hb 10.3 g/dL; **(c)** Not reported in Wilson and colleagues, 2007[1]

Impact of ESA use on utility/health-related quality of life

The impact of ESA use on utility or health-related quality of life (HRQoL) in all cost-utility studies is shown in Table 52.

All cost-utility studies except **Martin and colleagues (2003)**[117] include an improvement in utility or HRQoL due to ESA use. Several studies (those published most recently) estimate utility or HRQoL as a function of Hb level and therefore indirectly estimate the impact of ESA use on utility or HRQoL by estimating the impact of ESA use on Hb levels. **Fagnoni and**

colleagues (2006)[123] estimate the impact of Hb level on QoL as measured by the linear analog scale assessment (LASA). **Barosi and colleagues (1998)**[115] and **Cremieux and colleagues (1999)**[116] both estimate the impact of ESA use on HRQoL directly.

It was not always clear whether the impact of ESA use on utility/HRQoL was instantaneous. **Wilson and colleagues (2007)**[1] and **Borg and colleagues (2008)**[154] explicitly model the proportion of patients in different haemoglobin levels over time which results in a gradual improvement in utility for patients responding to ESA treatment. A gradual improvement in utility is also seen in the Amgen model in the previous NICE appraisal.[1] **Tonelli and colleagues (2009)** explicitly state that the improvement in Hb levels and hence utility is assumed to be instantaneous (which acts in favour of ESA use in their analysis). **Fagnoni and colleagues (2006)**[123] map the Hb levels of patients in a retrospective observational study to HRQoL, and hence the improvement in Hb levels is translated exactly into HRQoL improvement.

Table 52. Methods for short-term QALY estimation in primary cost-utility analyses

	Utility/HRQoL estimation method	Utility profile over time
Barosi, 1998[115]	Baseline HRQoL from Glaspy, 1997[160] adjusted according to Abels, 1992[161] (visual analog scale)	Instantaneous improvement (not explicitly stated)
Cremieux, 1999[116]	HRQoL reported by randomised placebo-controlled trial patients (LASA method)[54]	Not clear
Martin, 2003[117]	N/A[a]	N/A
Amgen model[1]	Hb level (6 levels) mapped to utility using unpublished data from Amgen study (EQ-5D from Phase III active controlled darbepoetin alfa trial, data collected weekly from around 100 patients over 16 weeks)[1]	Gradual improvement[1]
Ortho Biotec model[1]	Hb level (4 levels) mapped to utility using unpublished data from Ortho Biotec study (TTO from community values of different levels of fatigue)[1]	NR[b]
Roche model[1]	Hb level (4 levels) mapped to utility using unpublished data from Roche study (TTO study of general population)[1]	–
Wilson, 2007[1]	Hb level (7 levels) mapped to utility using unpublished data provided by Ortho Biotec	Gradual improvement for responders
Fagnoni, 2006[123]	Hb level (11 levels ever experienced by patients) mapped to HRQoL (LASA) following Crawford, 2002[159]	Clincal study
Borg, 2008[154]	Hb level (7 levels) mapped to utility following Wilson, 2007[1]	Gradual improvement for responders
Tonelli, 2009[112]	Hb increment linearly mapped to utility following Ossa, 2007[155]	Instantaneous improvement

Key: ESA, erythropoiesis stimulating agent; Hb, haemoglobin; HRQoL, health-related quality of life; LASA, linear analog scale assessment; N/A, not applicable

Notes: (a) ESA use is assumed to have no impact on quality of life; QALY benefits are obtained through improved survival for patients receiving ESA; **(b)** Not reported in Wilson and colleagues, 2007[1]

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 (2007)**.[1] **Wilson and colleagues (2007)** also assumed normalisation in their base case analysis, although they assumed a slightly faster reversion to normal Hb levels.[1] **Borg and colleagues (2008)**[154] followed the model design of **Wilson and colleagues (2007)**[1] and as a result used the same rate of recovery. Earlier studies did not include normalisation.

Fagnoni and colleagues (2006)[123] produced a cost-utility analysis based on a retrospective observational study, in which patients were followed-up for up to seven weeks following chemotherapy cessation. If normalisation did occur this would have been measured and included in the analysis, but there is no mention of normalisation in the text.

Tonelli and colleagues (2009)[112] 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 increasing costs.

Table 53. Normalisation in primary cost-utility analyses

	Timeframe for normalisation	Rate of normalisation (slower rate favours ESA use)	Normal Hb level (higher level favours ESA use)	Duration of continued ESA use
Amgen model[1]	12 weeks	0.1 g/dL per week	NR[a]	NR[a]
Ortho Biotec model[1]	Overall timeframe 36 months	0.2 g/dL per week	13 g/dL	NR[a]
Roche model[1]	NR in Wilson, 2007[1]	0.2 g/dL per week	Solid tumours: 13 g/dL Haem tumours: 11.9 g/dL	NR[a]
Wilson, 2007[1]	NR	0.25 g/dL per week	13 g/dL	NR

Borg, 2008[154]	32 weeks	0.25 g/dL per week	13 g/dL	NR

Key: ESA, erythropoiesis stimulating agent; haem, haematological; Hb, haemoglobin; NR, not reported
Notes: (a) Not reported in Wilson and colleagues, 2007[1]

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 total incremental costs. Quality of reporting was variable, notably with Wilson and colleagues[1] reporting cost per dose rather than unit costs for epoetin alfa and epoetin beta. None of the studies appear to be outliers in respect of 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 54. Drug acquisition unit costs in primary cost-utility studies

	Price year; currency	Epo-a (per 1,000 IU)	Epo-b (per 1,000 IU)	Darb-a (per µg)
Barosi, 1998[115]	NR; USD	≈ 10.00	–	–
Cremieux, 1999[116]	1997; USD	9.50	–	–
Martin, 2003[117]	2000; GBP	8.38	–	–
Amgen model[1]	NR[c]		–	1.68
Ortho Biotec model[1]	NR[c]	83.30 *per dose* (Q3W)	–	–
Roche model[1]	NR[c]		83.80 *per dose* (Q3W)	–
Wilson, 2007[1]	NR; GBP	83.30 *per dose* (Q3W)	83.80 *per dose* (Q3W)	1.68
Fagnoni, 2006[123]	2004; EUR	8.90	–	–
Borg, 2008[154]	2007; EUR	10.55	–	–
Tonelli, 2009[112]	2008; CAD	14.40	–	2.88
NHS list price[162]	2013; GBP	Eprex: 5.53 Binocrit: 5.09	7.01	1.47

Key: Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Epo-b, epoetin beta; IU, international unit
Notes: (a) Note that in several places in the paper euro signs (€) are used without any apparent conversion and that in an abstract publication[156] euros were used throughout again without any apparent conversion. The reviewer (TS) concluded it was more likely US dollars were the actual currency; **(b)** Calculated from cost in Swedish kronor per IU epoetin alfa; **(c)** Not reported in Wilson and colleagues, 2007[1]

6.1.2.3.5. Results of all cost-utility studies

Table 55 compares the base case results across the cost-utility studies identified in this review. More detailed reporting of results for the studies is given below.

Table 55. Base case results for all cost-utility studies

	Costs	QALYs	Inc. costs	Inc. QALYs	ICER (cost per QALY)
Barosi, 1998[115]	Epo-a: $4,568 No ESA: $206		+$4,362	+0.023	$190,000
Cremieux, 1999[116]	Epo-a: $7,551 No ESA: $1,416	No base case	+$6,135	No base case	$111,000–$214,000
Martin, 2003[117]	Epo-a: £10,768 No ESA: £6,515	Epo-a: 1.0375 No ESA: 0.5570	+£4,253	+0.4805	£8,851
Amgen model[1] (short-term analysis)	Darb-a: £3,570 No ESA: £1,156	Darb-a: 0.0309 No ESA: 0.0146	+£2,594	+0.0163	£159,000
Amgen model[1] (long-term analysis)	–	–	–	–	£23,600
Ortho Biotec model[1]	–	–	+£4,021	–	£13,000
Roche model[1] (solid tumours)	–	–	+£3,727	+0.132	£28,200
Roche model[1] (haematological tumours)	–	–	+£3,510	+0.042	£83,700
Wilson, 2007[1]	–	–	+£4,450	+0.030	£150,000
Fagnoni, 2006[123]	Epo-a: €1,649 No ESA: €34	–	+€1,615	+0.0052	€311,000
Borg, 2008[154]	Epo-a: €3,750 No ESA: €2,881	Epo-a: 0.5687 No ESA: 0.5334	+€870	+0.035	€24,700
Tonelli, 2009[112] (short-term analysis)	–	–	+$8,643	+0.03	$267,000
Tonelli, 2009[112] (long-term analysis)	–	–	+$8,643	−0.086	ESA use dominated by no ESA use

Key: Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Epo-b, epoetin beta; ESA, erythropoiesis stimulating agent; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Barosi and colleagues (1998)[115]

The combination of improved quality of life and reduced risk from blood-borne diseases transmitted through RBC transfusions resulted in a gain of 0.023 QALYs (8.4 quality-adjusted life days) at an additional cost of $4,362, resulting in an ICER of $190,000 per QALY.

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

Cremieux and colleagues (1999)[116]

Patients in the epoetin alfa arm accrued total costs of $7,551 compared to total costs of $1,416 for patients in the standard care arm. 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 $723 in the epoetin alfa arm and $176 in the standard care arm. Reduced transfusion usage in the epoetin alfa arm resulted in cost savings of $428 but these were more than offset by epoetin alfa costs of $6,563. Drug acquisition was the most expensive resource, accounting for $4,560 in the epoetin alfa arm.

Cumulative haemoglobin was measured as an objective effectiveness measure, measured as 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).

Effectiveness in terms of quality of life was measured at baseline and at the end of the study using the Linear Analog Scale Assessment (LASA). Epoetin alfa patients gained 8.3 mm (the scale is 100 mm in length) versus standard care patients losing 1.0 mm, therefore the incremental effectiveness was 9.3 mm. Two methods were suggested for converting LASA measurements to “utilities”: the first assuming that a 9.3 mm gain would correspond to a 0.093 gain in utility; the second assuming 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 which provided the LASA measurements results in ICERs of $214,000 per QALY when the utility gain of 0.093 is assumed and $111,000 per QALY when the utility gain is assumed to be 0.184.

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

Martin and colleagues (2003)[117]

In their base case analysis epoetin alfa use results in greater discounted mean costs (£10,768 vs £6,515; difference +£4,253) and greater discounted QALYs (1.0375 versus 0.5570; difference +0.4805). The base case ICER was £8,851 per QALY.

The increased costs for epoetin alfa patients were due to epoetin alfa costs (£3,995) and increased costs in the follow-up phase (due to greater time spent in the follow-up phase). Increased costs were partially compensated by decreased costs in the active, supportive and terminal phases and a very small reduction in blood unit costs.

The difference in QALYs comes about solely through improved survival, i.e., there is no QALY gain due to relieving 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 below £30,000 per QALY except in one case where an ICER of £39,300 per QALY was obtained in which all patients from the RCT (rather than only Stage IV breast cancer patients) were included to estimate effectiveness of epoetin alfa.

Fagnoni and colleagues (2006)[123]

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)." The initial haemoglobin and haematocrit levels were very similar for both patient groups. The median number of haemoglobin level measurements per patient was the same (six) for both groups.

In the group with possible use of EPO, 46/101 (45.5%) actually received EPO. The mean haemoglobin level at initiation of EPO treatment was 11.3 g/dL (range 9.4–12.5). No red blood cell transfusions occurred in either group, and a similar proportion of patients were hospitalised related to anaemia in both groups (2.0% possible EPO versus 2.2% no EPO). On average patients with possible EPO spent almost 6 weeks with haemoglobin level over 13.49 g/dL compared to just over 3 weeks for patients with no EPO. Mapping haemoglobin levels to quality of life resulted in an increase of 0.0052 QALYs after the introduction of EPO over the 22-week study period.

The average cost of EPO treatment was €1,593 per patient for the group with possible use of EPO. The average cost of hospitalisation was €56 per patient for the group with possible use of EPO versus €34 for the group with no EPO, 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 EPO versus no EPO below €160,000 per QALY. The different methodologies for estimating quality of life according to haemoglobin level produced some differences in the QALY difference between the groups: using the relationship between haemoglobin level and FACT-General resulted in the greatest QALY difference (0.0099 QALYs), while an alternative LASA methodology resulted in the smallest (0.0046 QALYs). It should be noted that none of these HRQL measures are preference-based.

Borg and colleagues (2008)[154]

The base case comparison was between the EPO arm with a target Hb of 12 g/dL and the RBCT arm with a trigger level of 10 g/dL (the same trigger level as in the EPO arm). Patients in the EPO arm were estimated to incur total costs of €3,750 versus expected total costs of €2,881 in the RBCT arm (difference +€870). The additional cost of epoetin alfa (€2,054) was partially compensated for by savings in RBCT costs (€1,185). Patients were expected to accrue 0.5687 QALYs in the EPO 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 four-week model cycle to 2 g/dL per cycle; the resulting ICER (EPO versus RBCT) was €29,500 per QALY.

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

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

RBCT strategies with trigger levels of 9 and 11 g/dL were also considered. Increased trigger levels led to increased costs and QALYs. With a trigger level of 9 g/dL, RBCT cost €2,360 and resulted in 0.4948 QALYs. With a trigger level of 11 g/dL, RBCT cost €3,340 and resulted in 0.5605 QALYs. All strategies were on the cost-effectiveness frontier (i.e. no strategies were dominated or extended dominated), and therefore if RBCT with a trigger level of 11 g/dL were to be considered a valid comparator the ICER of EPO would be €50,000 per QALY.

Tonelli and colleagues (2009)[112]

In the base case analysis epoetin alfa use resulted in increased costs ($8,643) and increased benefits (0.03 QALYs) over 15 weeks, resulting in an ICER of $267,000 per QALY. Over a one-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% confidence intervals ESA use remained not cost-effective even at a threshold of $100,000 per QALY. When alternative methods of estimating the relationship between haemoglobin 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 ≤ 12 g/dL and/or an initial Hb level ≤ 10 g/dL, but even in these the ICERs remained above $70,000 per QALY.

6.1.2.3.6. Summary tables for other studies

Summary tables for other studies are summarised in Table 56.

Table 56: Study characteristics of full non-selected studies

	Ben-Hamadi, 2005[163]	Persson, 2005[164]	Borget, 2006[137]
Evaluation type	Cost-effectiveness analysis	Cost-consequences analysis	Cost-effectiveness analysis
Modelling used	Limited	Yes	Yes
Nature of modelling	Integration of drug acquisition costs based on dose escalation rate	Calculation of drug costs	Markov model
Perspective	Payer	Healthcare[a]	Healthcare perspective
Country (setting)	USA (not explicitly stated)	Sweden	France (not explicitly stated)
Intervention/comparator	**Epo-a QW:** 40,000 IU, escalated to 60,000 IU after 4 weeks if Hb increase < 1 g/dL **Darb-a QW:** 2.25 µg per kg, escalated to 4.5 µg per kg if Hb increase < 1 g/dL and/or given RBCT	**Epo-a TIW:** 150 IU/kg[b] **Darb-a QW:** 2.25 µg/kg[b]	**Darb-a QW** **Standard care:** RBCT if Hb < 8 g/dL or 8–10 g/dL and signs of poor tolerance of anaemia
Population	Patients with chemotherapy-induced anaemia	Patients with cancer therapy-related anaemia receiving Epo-a or Darb-a	Lung cancer patients
Outcomes considered	Treatment success (proportion of patients not requiring RBCT)	Haematologic response AUC_{HB} Proportion of patients receiving RBC transfusion Number of RBC units transfused	Proportion of patients receiving RBCT Number of RBC units transfused Mean Hb level
Time-frame	16 weeks	16 weeks	36 weeks
Discounting	Not stated	Not stated	Not stated
Funding	Ortho-Biotec (manufacturers of Epo-a)	Johnson & Johnson (manufacturers of Epo-a)	Not stated

Key: AUC_{HB}, area under Hb change curve; Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Hb, haemoglobin; IU, international unit; QW, once weekly; RBC(T), red blood cell (transfusion); TIW, three times weekly
Notes: (a) Included costs: drug acquisition, hospitalisation, RBCT; **(b)** Swedish treatment guidelines; dose doubled if inadequate response after four weeks; treatment discontinued if Hb > 14 g/dL

Table 52: Study characteristics of full non-selected studies (continued)

	Spaepen, 2008[165]	Aapro, 2012[166]	Pashos, 2012[167]
Evaluation type	Cost-consequences analysis	Cost-minimisation study	Cost-consequences analysis
Modelling used	Limited	Minimal	No
Nature of modelling	Statistical matching of patients receiving different ESAs to estimate costs	Multiplication of dosing level by unit price	
Perspective	Healthcare	Healthcare	Drug costs only
Country (setting)	Belgium (hospital)	Germany, France, UK, Italy, Spain	USA
Intervention/comparator	**Darb-a** **Epo-a** **Epo-b**[a]	**Originator Epo-a QW:** 40,000 IU; 450 IU/kg **Biosimilar Epo-a QW:** 30,000 or 40,000 IU; 450 IU/kg **Epo-b QW:** 30,000 IU; 450 IU/kg **Darb-a QW:** 150 µg; 2.25 µg/kg **Darb-a Q3W:** 500 µg; 6.75 µg/kg	**Epo-a QW:** 40,000 IU **Darb-a Q3W:** 500 µg
Population	Adult cancer patients receiving ESA support at some point	Patients with chemotherapy-induced anaemia	Adult cancer patients receiving ESA therapy
Outcomes considered	TA-free survival (composite of transfusion-free survival and anaemia-related readmission-free survival)	None (costs only)	Proportion of patients requiring packed RBC transfusion Units of packed RBC transfused per patient Increase in Hb from baseline
Time-frame	For duration of records until loss of follow-up at end of calendar year	18 weeks	Duration of ESA treatment up to maximum 16 weeks
Discounting	Not stated	Not discounted	Not stated
Funding	Amgen (manufacturers of Darb-a)	Sandoz Biophamaceuticals (manufacturers of biosimilar Epo-a, Binocrit)	Ortho Biotec (manufacturers of Epo-a)

Key: Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Epo-b, epoetin beta; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IU, international units; QW, once weekly; Q3W, once every three weeks; RBC(T), red blood cell (transfusion)
Notes: (a) Reimbursed only if administered to patients with Hb < 11 g/dL and/or receiving platinum-based chemotherapy

Table 57: Key parameters of full non-selected studies

	Ben-Hamadi, 2005[163]	Persson, 2005[164]	Borget, 2006[156]
Effectiveness (source): transfusion, response rate, survival, QALYs	**Epo-a:** Witzig et al. (J Clin Oncol 2005;23[12]:2606-2617) **Darb-a:** Kotasek et al. (Poster presentation, American Society of Hematology, December 4-7, 2004, San Diego, CA)	Retrospective chart review performed at three Swedish hospitals	Two-year retrospective study
Effectiveness (data): transfusion, response rate	**Treatment success (proportion of patients not requiring RBCT)** Weeks 0-16: Epo-a, 75%; Darb-a, 63% Weeks 5-16: Epo-a, 85%; Darb-a, 73%	**[Results by day 112[a]]** **Haem. response (Hb increase ≥ 1 g/dL):** Epo-a, 100%; Darb-a, 80% **Haem. response (Hb increase ≥ 2 g/dL):** Epo-a, 86%; Darb-a, 63% **AUC_{HB} (Hb g / day / dL; mean ± SD):** Epo-a, 203.0 ± 122.9; Darb-a, 157.0 ± 162.3 **Patients receiving 1+ RBCT:** Epo-a, 14/29; Darb-a, 14/30 **Mean units RBC transfused:** Epo-a, 1.71; Darb-a, 1.95	**Proportion of patients receiving RBCT:** Darb-a, 19.1%; standard care, 33.6% **Mean number of RBC units transfused:** Darb-a, 2.11 ± 0.47; standard care, 2.97 ± 1.47
Effectiveness (data): survival, QALYs	N/A	N/A	N/A
HRQoL/utility (source)	N/A	N/A	N/A
HRQoL/utility (data)	N/A	N/A	N/A
Costs (source)	Medi-Span Master Drug Data Base (MDDB) May 2005	**Drug acquisition:** List price in 2003 Swedish Pharmacopeia **Hospitalisation and RBCT:** Official list of regional administrative prices	Transfusion costs from national unit costs. Darb-a drug costs from drug purchase prices paid by hospital.
Cost year	2005	2003	Not stated

Key: AUC_{HB}, area under the Hb change curve; Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Hb, haemoglobin; HRQoL, health-related quality of life; RBC(T), red blood cell (transfusion)
Notes: (a) Results also presented at 28, 56 and 84 days

Table 53: Key parameters of full non-selected studies

	Spaepen, 2008[165]	Aapro, 2012[166]	Pashos, 2012[167]
Effectiveness (source): transfusion, response rate, survival, QALYs	Retrospective analysis of Belgian national patient database	Assumed equivalent	Dosing and Outcomes Study of Erythropoiesis-Stimulating Therapies (DOSE)
Effectiveness (data): transfusion, response rate	**TA-free survival:** Darb-a, 84.37% (79.22%-88.35%); Epo-a, 84.60% (80.72%-87.75%); Epo-b, 84.94% (80.03%-88.72%) **Transfusion-free survival:** Darb-a, 84.46% (79.29%-88.43%); Epo-a, 84.86% (81.00%-87.99%); Epo-a, 85.51% (80.70%-89.19%) **Anaemia-readmission-free survival:** Darb-a, 89.16% (84.71%-92.38%); Epo-a, 88.66% (85.18%-91.36%); Epo-b, 87.91% (83.31%-91.29%)	N/A	**Proportion of patients requiring RBCT:** Epo-a, 13.9%; Darb-a, 22.5% (p=0.026) **RBC units:** Epo-a, 0.4; Darb-a, 0.7 (p=0.020) **Increase in Hb from baseline (g/dL) at week 12:** Epo-a, 0.6; Darb-a, 0.1 (p=0.032)
Effectiveness (data): survival, QALYs	N/A	N/A	N/A
HRQoL/utility (source)	N/A	N/A	N/A
HRQoL/utility (data)	N/A	N/A	N/A
Costs (source)	Belgian national databases	This study; list price (Germany, France, Italy, Spain); negotiated price (UK)	Wholesale acquisition costs
Cost year	2003-2005 (patient-specific); 2006 across all patients in sensitivity analysis	2010	2009 (May)

Key: Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Epo-b, epoetin beta; Hb, haemoglobin; HRQoL, health-related quality of life; RBC(T), red blood cell (transfusion)

Table 58: Results of full non-selected studies

	Ben-Hamadi, 2005[163]	Persson, 2005[164]	Borget, 2006[156]
Measure	Cost per 1% successful treatment	Cost	Cost per g/dL Hb
Cost year; currency	2005; US dollars (USD; $)	2003; Swedish kronor (SEK)	Not stated; US dollars (USD; $)
Base case	***Epo-a dominates*** **Average cost-effectiveness ratios** Weeks 0-16: Epo-a, $121; Darb-a, $215 Weeks 5-16: Epo-a, $106; Darb-a, $186	**Total treatment cost at day 112:** Epo-a, SEK 74,701 Darb-a, SEK 85,285	**Darb-a:** mean Hb, 13.0 ± 0.5; mean cost, $1,732 ± 897 **Standard care:** mean Hb, 11.9 ± 1.0; mean cost, $996 ± $643 **ICER:** $669 per g/dL Hb
Probabilistic results	NR	NR	N/A
Sensitivity analyses	[Using average sale price + 6% (as used for reimbursement for Medicare Part B covered drugs)] ***Epo-a dominates*** **Average cost-effectiveness ratios** Weeks 0-16: Epo-a, $97; Darb-a, $159 Weeks 5-16: Epo-a, $86; Darb-a, $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 cost-effectiveness ratio

Key: Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Hb, haemoglobin

Table 54. Results of full non-selected studies

	Spaepen, 2008[165,166]	Aapro, 2012[166]	Pashos, 2012[167]
Measure	Cost per patient	Relative savings with use of biosimilar Epo-a[a]	Cumulative drug cost per patient
Cost year; currency	2003-2005; euros (EUR; €)	2010; euros (EUR; €)	2009; US dollars (USD; $)
Base case	**Overall costs** Darb-a, €16,949 ± €1,025 Epo-a, €19,472 ± €901 Epo-b, €19,295 ± €1,048	*Fixed dosing using biosimilar Epo-a 40,000 / 30,000 IU per week* **Originator Epo-a:** 13.8% / 35.4% **Epo-b:** 16.4% / 37.3% **Darb-a QW:** 25.5% / 44.2% **Darb-a Q3W:** 33.0% / 49.7% *Weight-based dosing using biosimilar Epo-a* **Originator Epo-a:** 13.8% **Epo-b:** 16.4% **Darb-a QW:** 44.2% **Darb-a Q3W:** 44.2%	**Epo-a:** $4,261 **Darb-a:** $8,643
Probabilistic results	N/A	N/A	N/A
Sensitivity analyses	Applying 2006 prices does not alter conclusion that Darb-a significantly cheaper than Epo-a and Epo-b	Results presented individually for five treatment scenarios; relative savings are unchanged	N/A

Key: Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Epo-b, epoetin beta; QW, once weekly; Q3W, once every three weeks
Notes: (a) Results presented are calculated from costs for each treatment averaged (unweighted) across five treatment scenarios. Costs represent European G5 cost as calculated by calculating weighted average of price, weighted by population of European G5 countries.

6.1.2.4. Discussion

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

Martin and colleagues (2003)[117] produced an analysis demonstrating good cost-effectiveness in a subgroup of cancer patients on the basis of a substantial survival advantage in an 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, indeed the RCT was not powered to detect survival differences and survival was added as a supplementary outcome after the trial started;[79] 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 placebo arms

The three industry submissions in the previous NICE appraisal achieved ICERs below £30,000 per QALY only by the inclusion of survival benefits which have not generally been reproduced in more recent meta-analyses.

Analyses not including survival benefit seem to predict small incremental benefits of ESA therapy in the range of 0.0052 to 0.035 QALYs.

The only analysis not including a survival benefit and producing a favourable estimate of cost-effectiveness was by **Borg and colleagues (2008)**,[154] which demonstrated a significantly lower incremental cost of ESAs than other analyses, including others funded or produced by industry. The average cumulative dose predicted by the model may be calculated by dividing the total cost of epoetin alfa (€2,054) by the cost of epoetin alfa per four week cycle (€1,329) to estimate an average 1.546 cycles, approximately 195,000 IU (based on 70 kg patient weight as chosen by the authors) whereas data from the clinical study informing the model by **Persson and colleagues (2005)**[164] suggests a cumulative dose of 460,000 IU. Dose doubling was included in the clinical study, but this would not account for the discrepancy – indeed maximum mean dosage for those receiving epoetin alfa was 37,143 IU versus the start mean dosage of 31,786 IU. This suggests that the analysis by **Borg and colleagues (2008)** assumes 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.

6.1.2.5. 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 Hb level improvement
- Low cumulative dose of ESA
- Normalisation period in which benefits of ESA persist beyond chemotherapy cessation (and beyond ESA cessation)

A significant survival advantage has not been shown in general either by the recent Cochrane review (**Tonia and colleagues, 2012**)[10] or by the systematic review in Section 0, page 56.

The primary claimed benefit of ESA therapy is improved health-related quality following correction of anaemia, but this has not been demonstrated on general health-related quality of life measures (such as EQ-5D) in published and peer-reviewed RCT. Significant predicted improvements in utility have resulted from the application of results of **Ossa and colleagues (2007)**[155] but this study has several methodological weaknesses (see Section 7.1.2.1, page 258). **Tonelli and colleagues (2009)**[112] have noted that as a result of using utility estimates derived from **Ossa and colleagues (2007)**[155] a 0.15 difference in utility between the ESA and non-ESA arm were predicted, on a par with the utility associated with 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 ESA (without sacrificing significant clinical effectiveness) will likely result from: identifying non-responders as early as possible and discontinuing ESA therapy in them; focussing ESA therapy on patients with moderate to severe anaemia likely to impact on quality of life and survival rather than continuing ESA therapy to achieve Hb levels over 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 (2007)[1] concluded that adverse events relating to ESA therapy or RBCT would be unlikely to impact on cost-effectiveness. The two new model-based cost-utility analyses do not include adverse events and provide no further insight on this. **Fagnoni and colleagues (2006)**[123] include anaemia-related hospitalisation costs but it appears these costs are valued according to average costs of hospitalisation rather than adverse event-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 incremental costs in all analyses any discounts would be expected to impact total incremental costs but 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 (2007)**.[1] 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 results from **Wilson and colleagues (2007)**,[1] **Borg and colleagues (2008)**[154] and **Tonelli and colleagues (2009)**.[112] This could be an overestimate as there is a lack of high quality evidence that ESA therapy improves health-related quality of life on generic measures such as 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 which still remains.

6.1.2.6. 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 (2008)**[153] which excluded standard care without ESAs as a comparator. The two systematic reviews by **Duh and colleagues (2008)**[153] and **Tonelli and colleagues (2009)**[112] did not identify cost-utility studies which were not identified in this review. The full text of one cost-utility study by **Roungrong and colleagues (2008)**[131] could not be obtained but the Centre for Reviews and Dissemination critical appraisal of this study suggests that it would not change the conclusions of the review.[132]

The methods and results of 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 in **Wilson and colleagues (2007)**.

The reviewers (TS and NH) excluded darbepoetin alfa given once every two weeks as an allowed intervention as biweekly administration is not allowed within the licence of darbepoetin alfa. This could be viewed as a limitation of the review, but at the full paper screening stage this only resulted in the exclusion of 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 and 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 due to 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.

6.1.2.7. 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. The cost of RBCT in the NHS has not been recently evaluated by studies identified but there is evidence that cost-effectiveness may not be particularly sensitive to the cost of RBCT (although this is from studies where drug acquisition costs dominate to a greater extent than would now be expected). Studies did not include costs of blood tests or outpatient clinics so it is not clear how these might impact on cost-effectiveness. Cumulative doses of ESAs when given in line with 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 which 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.

6.1.2.8. Update searches

Update searches were conducted on 2nd December using the same methodology as described earlier. Fifty-three records were screened by two reviewers (TS and LC) and one record was selected for full-text retrieval. The study was judged 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 Q for further details.

6.2. Economic evaluations submitted by manufacturers

No economic evaluations were submitted by any of the manufacturers.

6.3. Summary

KEY POINTS

- Ten cost-utility analyses and two systematic reviews were identified by updating an existing review by **Wilson and colleagues (2007)**[1]
- Five cost-utility analyses suggested that ESA therapy is cost-effective, these were all funded by industry (**Martin and colleagues, 2003**; **Borg and colleagues, 2006**) or conducted by industry (submissions by Amgen, Roche and Ortho Biotec as reported by **Wilson and colleagues, 2007**)
- The inclusion of survival benefits was common to four favourable analyses (**Martin and colleagues, 2003** and the industry submissions as reported by **Wilson and colleagues, 2007**) although no statistically significant survival benefit has been shown
- The fifth favourable analysis (**Borg and colleagues, 2006**) may suffer from problems of internal validity as it appears 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 analyses was that raising Hb levels would improve health-related quality of life, though 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 quality of life over patients in the no ESA arm; no evidence for or against normalisation has been presented
- 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 ESA therapy cost and improve cost-effectiveness

Independent economic assessment

7.1. Methods

7.1.1. 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 modeling 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 to patients not receiving ESA therapy (referred to as the ESA arm and control arm from here) 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, red blood cell transfusion costs and costs of adverse events. 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 and control arms (the potential ramifications of this assumption are discussed in Section 8.3.4.6, page 388). Short-term QALYs are accrued as health-related quality of life (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 due to potential differences in overall survival between the two arms; it is assumed that health-related quality of life is equal for both arms in this phase as patients no longer have cancer treatment-induced anaemia and health-related quality of life 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), as these are highly uncertain (due to the wide range of cancers 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 overall survival, these costs are not modelled in the base case. The potential ramifications of this assumption are explored through a univariate sensitivity analysis in Section 7.2.7.1 (page 367) and discussed in Section 8.3.4.6 (page 388).

7.1.1.1. Short-term costs and QALYs

Short-term costs in the model include ESA drug acquisition and administration, red blood cell transfusion related costs and costs relating to adverse events. In all cases resource use and unit costs are estimated separately. Resource uses of ESA drug acquisition and administration are estimated in Sections 7.1.2.1.2 (page 266) and 7.1.2.1.3 (page 268). Resource uses of red blood cell transfusion related costs are estimated in Section 7.1.2.1.1 (page 266). Resource uses of adverse events are estimated in Section 7.1.2.3.6 (page 304). Unit costs are estimated in Section 7.1.2.3 (page 298).

We have considered three possible model structures for the estimation of short-term QALYs (Table 59, page 248):

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:

- Whilst many RCTs report outcomes measured by disease-specific health questionnaires, such as FACT-An, FACT-Fatigue, EORTC QLQ C-30, no RCTs report generic preference-based health-related quality-of-life measures, such as EQ-5D or SF-6D, which are required to estimate health utilities. Indeed, this limitation has been noted by Grant and colleagues (2013).[59]

- Very little information can be gained from mapping from the disease-specific health questionnaires to the EQ-5D, see Section 7.1.2.2.4 (page 295).

Despite this, some previous cost-effectiveness analyses (e.g., **Cremieux and colleagues (1999)**[116]) have taken this approach, using quality of life based on visual analogue scales or linear analogue self-assessment (LASA) scales, 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.[168]

A variant of this method is seen in **Fagnoni and colleagues (2006)**[123] 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 health-related quality of life measures such as EQ-5D.

2. Mechanistic modelling of 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. Hb responses to ESAs.
- Times when RBCTs 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 (a) data for many required parameters is simply not available; and, (b) it is not possible to incorporate many of the outcomes from the systematic review of clinical effectiveness (Table 61).

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 (a) good estimates of all necessary parameters are available and (b) the method can use many of the outcomes from the systematic review of clinical effectiveness (see Section 0, page 56).

Table 59: Possible model structures for short-term economic evaluation of ESAs

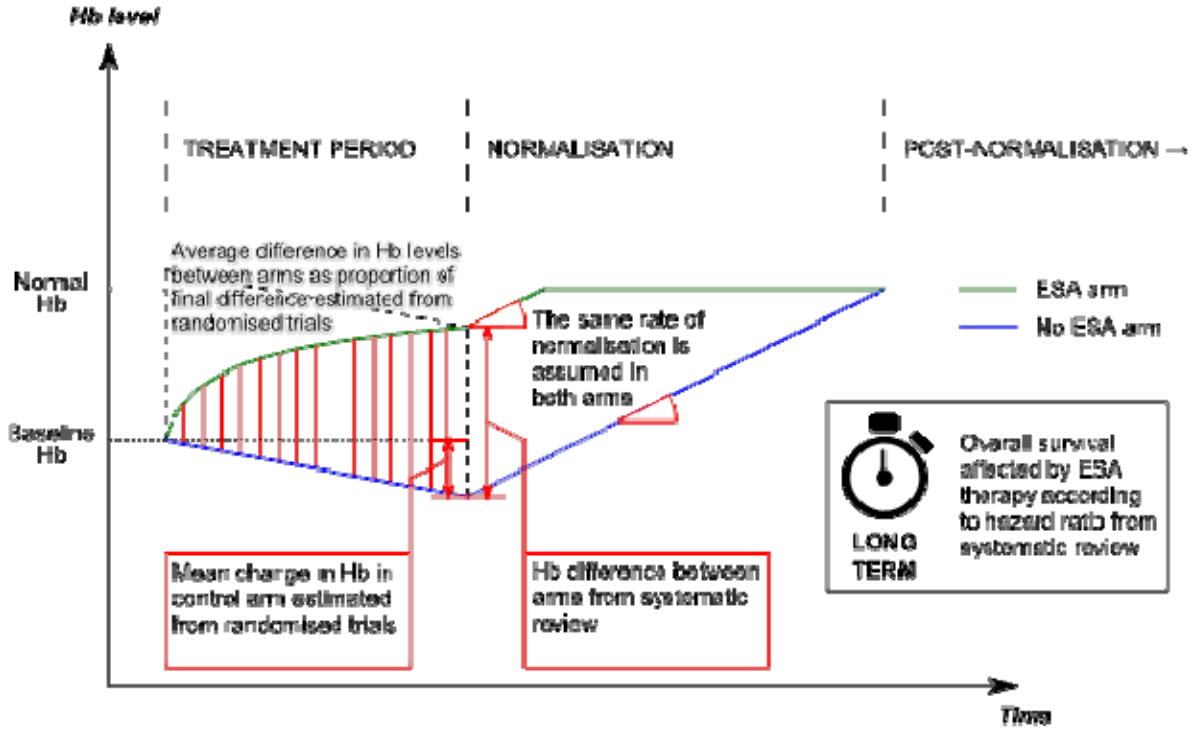
	Model structures		
	QoL from trial	**Mechanistic modelling of Hb over time**	**Empirical observation of Hb over time**
Complexity	Simplest	Complex, more parameters required.	Intermediate.
Flexibility to depart from characteristics of the RCTs, e.g. patient age, initial Hb level, subsequent Hb level, ESA doses.	Less flexibility.	More flexibility, e.g. to mirror difference in clinical practice compared to RCTs, changes in licence.	Less flexibility.
Data availability	Preference-based HRQoL not available from RCTs.	Quality data for many parameters not available. e.g. impact of Hb of increase in ESA dose.	Yes, taken from 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 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 via Hb level. QoL due to AEs captured independently.	
Examples of previous economic evaluations	Barosi (1998),[115] Cremieux (1999)[116]	Wilson (2007)[1], Borg (2008)[154]	Tonelli (2009),[112] Fagnoni (2006)[123]
Key: AEs, adverse events; ESAs, erythropoiesis stimulating agents; Hb, haemoglobin; HR, hazard ratio; HRQoL, health-related quality of life; OS, overall survival; QoL, quality of life; RCTs, randomised controlled trials			

A summary model diagram is presented in Figure 29 (page 249). This diagram demonstrates how Hb levels are modelled according to the baseline Hb level (Section 7.1.2.1.4, page 269), the expected change in Hb level for patients not receiving ESA therapy (Section 7.1.2.1.5, page 271) the expected final difference in Hb level between arms (Table 61, page 262), and the average difference in Hb levels between arms as a proportion of the final difference

(Section 7.1.2.1.6, page 273). The concept of normalization, which takes place after cancer treatment has ended, is described fully in Section 7.1.2.1.7 (page 275).

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

Figure 29. Diagram indicating model assumptions about Hb levels by model stage



Key: ESA, erythropoiesis stimulating agent; Hb, haemoglobin
Note: Hb levels mapped to utility to calculate short-term QALYs

7.1.1.2. Long-term QALYs

Long-term QALYs are calculated by estimating overall survival in each arm and applying a long-term utility common to both arms, i.e., it is assumed long-term QALY differences only come about through a difference in survival due to ESA therapy, not through any enduring impact on health-related quality of life. Long-term utility is estimated in Section 7.1.2.2.6 (page 297).

The systematic review of clinical effectiveness provided estimates for the hazard ratio (HR) for survival between the ESA and control arms, but to implement this in the model required baseline survival for patients without ESA treatment. As ESAs can be administered to

individuals with a range of cancers a wide range of overall survival estimates appear in clinical studies.

7.1.1.2.1. Review of best practice

Here we briefly outline key points from **Latimer (2011)**[169] which suggests some points for best practice, as they apply in 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. […]

7.1.1.2.2. Modelling approach

We examined overall survival curves from all studies included in the systematic review of clinical effectiveness where 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, e.g., if the cumulative hazard curve is a straight line then an exponential distribution may be appropriate; if the cumulative hazard function has a sigmoid shape this suggests the need for a survival function with non-monotonic hazard.

Where overall survival figures were provided as vector graphics (as was the case for **Ray-Coquard and colleagues, 2009**[74] and **Moebus and colleagues, 2013**[62]) the exact survival curve was extracted using Inkscape [freely available from http://www.inkscape.org/] and transformed appropriately using Excel® (Microsoft, Redmond, Washington, USA). Where overall survival figures were provided as raster graphics the underlying image was extracted using Inkscape and then transformed using GNU Image Manipulation Program [freely available from http://www.gimp.org/] and MathMap [freely available from http://www.complang.tuwien.ac.at/schani/mathmap/] as outlined in Appendix T. This approach means that no data points were excluded.

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

The extracted survival curves and calculated cumulative hazard and Weibull plots are shown in Table 60 (page 253).

Visual inspection of the cumulative hazard plots suggests that an exponential survival function would fit both arms in **Vansteenkiste and colleagues (2002)**[72] and **Osterborg and colleagues (2005)**.[70]

The plots for **Littlewood and colleagues (2001)**[68] suggest that neither a Weibull nor 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.

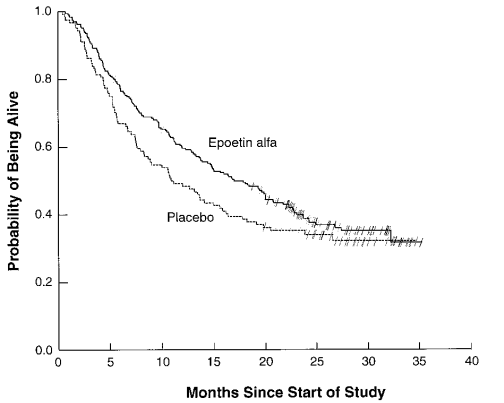
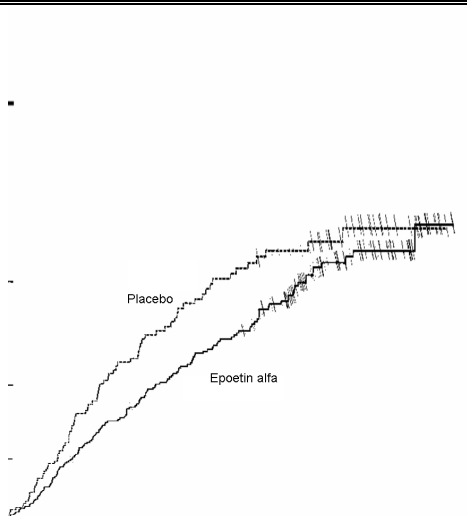
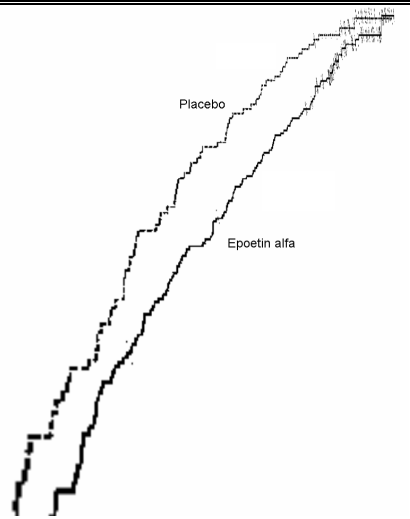
The plots for **Grote and colleagues (2005)**[73] suggest an exponential survival function could be valid as the cumulative hazard plot only diverges from being linear after significant censoring, although if the Kaplan–Meier curve beyond divergence is considered informative it could suggest a delayed treatment effect on overall survival.

The survival plot **Ray-Coquard and colleagues (2009)**[74] suggests that overall survival data is 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.

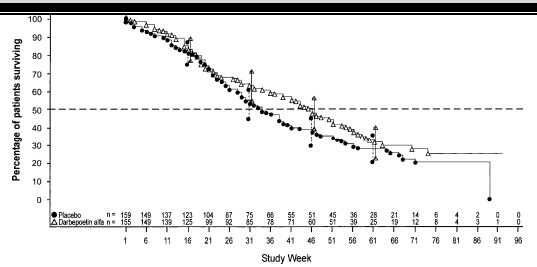
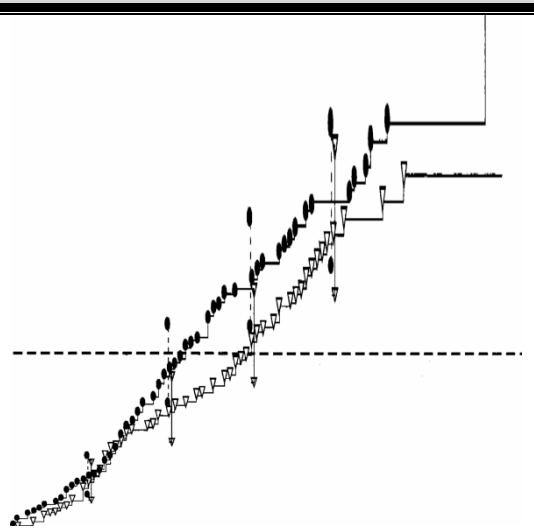
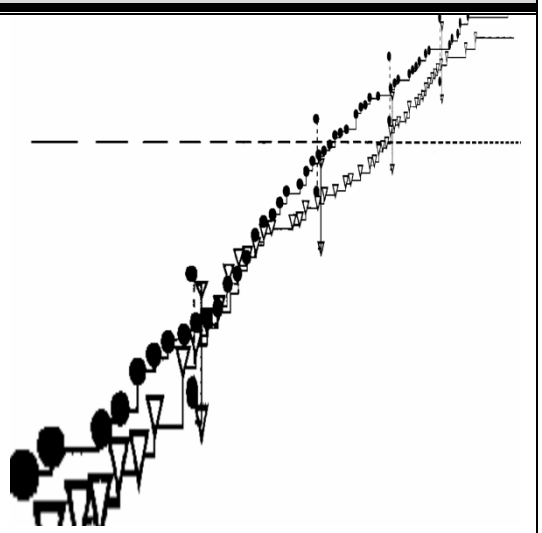
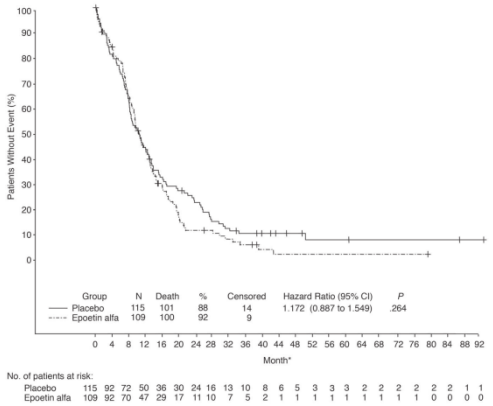
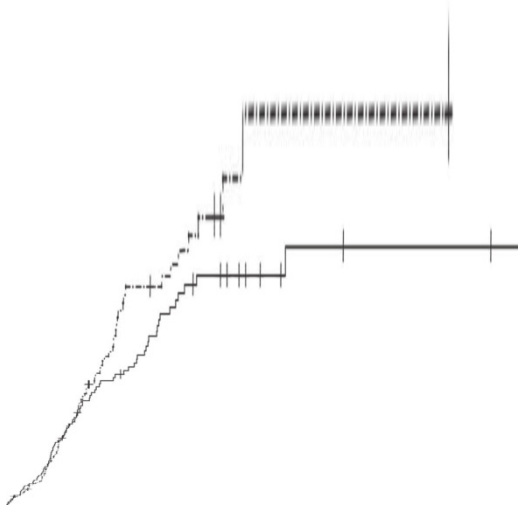
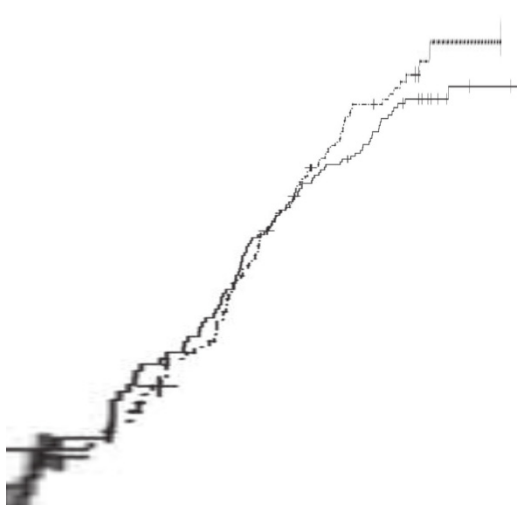
The plots for **Untch and colleagues (2011)**[78] suggest that exponential survival may not be appropriate. Examination of the Weibull plot suggests a Weibull survival function may be appropriate. It might also be appropriate to use piecewise exponential survival with very low hazard rate for the first year and then a higher hazard rate thereafter given the rightmost upturn in the cumulative hazard plot only occurs after significant censoring. A proportional hazards assumption would not be unreasonable given the Weibull plot.

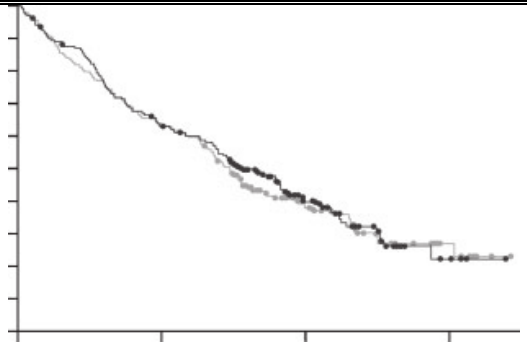
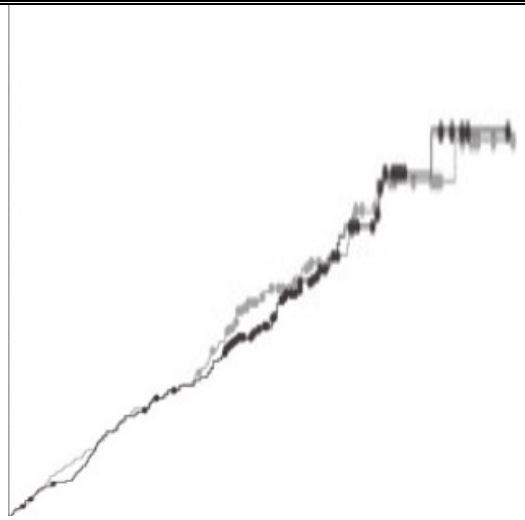
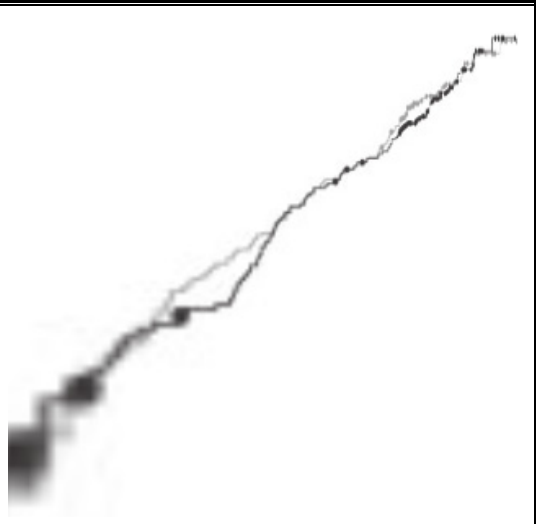
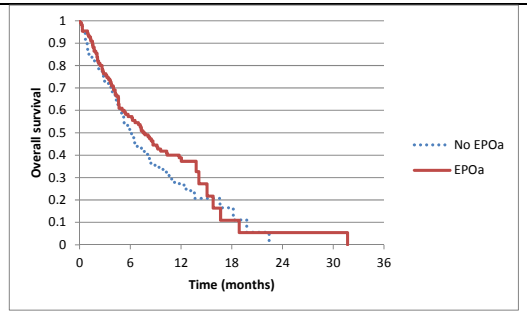
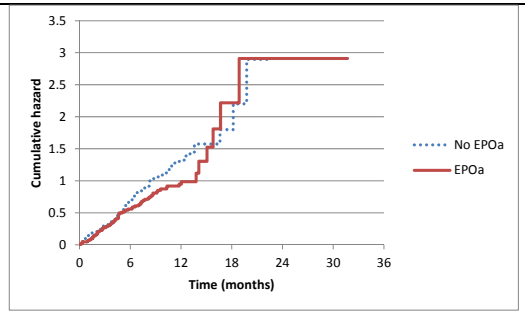
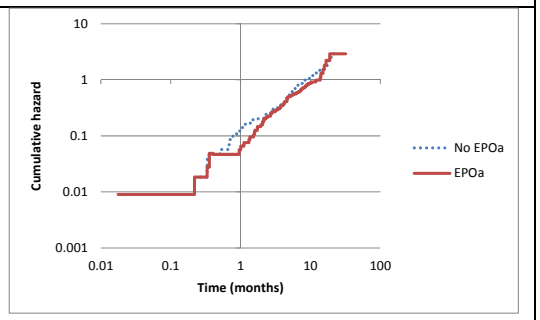
The plots for **Moebus and colleagues (2013)**[62] are noteworthy as they seem to suggest a non-monotonic hazard function, ruling out exponential, Weibull and Gompertz distributions for fitting. This study evaluated performance in breast cancer (stages II to IIIa) patients, who might be expected to have 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.

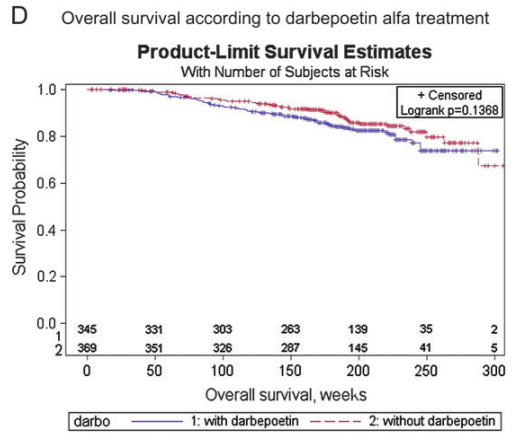
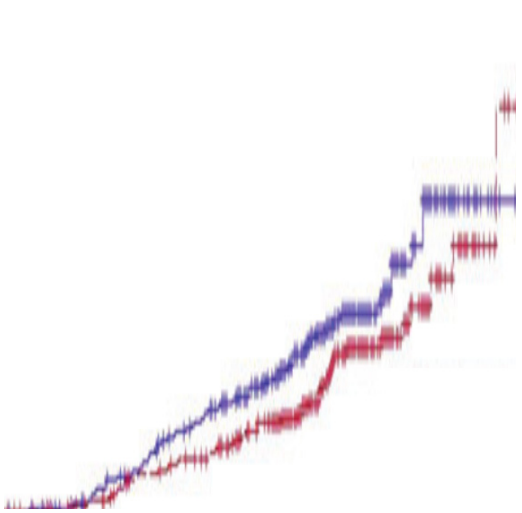
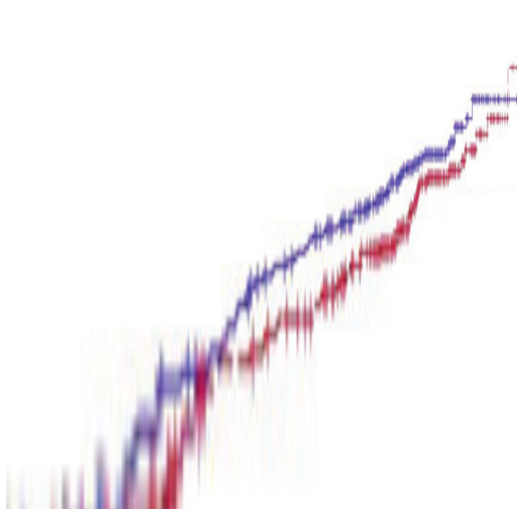
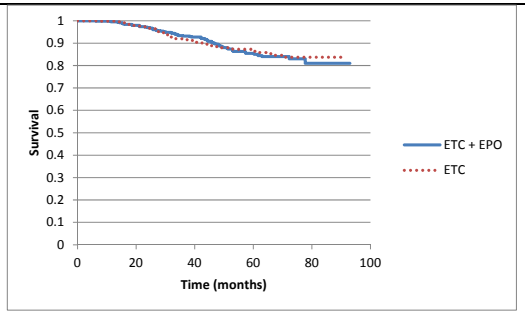
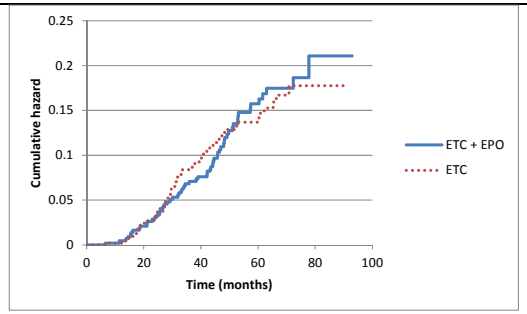
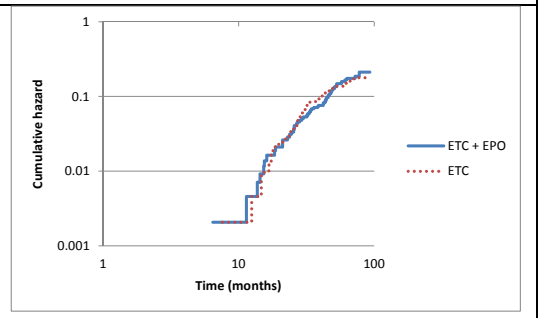
Table 60. Overall survival curves extracted from RCTs

Study	Survival curve	Cumulative hazard curve	Weibull plot
Littlewood, 2001[68]			

Safety Population	Alive	Dead	Lost to follow-up
Epoetin alfa (n=251)	94 (38%)	155 (62%)	2 (1%)
Placebo (n=124)	41 (33%)	82 (66%)	1 (1%)

Study	Survival curve	Cumulative hazard curve	Weibull plot
Vansteenkiste, 2002[72]			
Grote, 2005[73]			

Study	Survival curve	Cumulative hazard curve	Weibull plot
Osterborg, 2005[70]			
Ray-Coquard, 2009[74]			

Study	Survival curve	Cumulative hazard curve	Weibull plot
Untch, 2011a,b[77,78]			
Moebus, 2013[62]			

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

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

1. The survival in the control arm is unchanged from the base case and survival for patients receiving ESA therapy is estimated by using proportional hazards for the first three years followed by equal hazard rate to that of the control arm (as though the effect of ESA therapy on mortality lasts only three years). The length of follow-up is not reported for a number of studies contributing to the hazard ratio for overall survival although it is likely for a number of studies that follow-up was extremely limited. Of the studies giving Kaplan–Meier curves follow-up was only over three years for **Untch and colleagues (2011)**[78] (median follow-up 43.5 months) and **Moebus and colleagues (2013)**[62] (median follow-up 62 months)

2. A Weibull survival function is fitted to the control arm survival curve from **Untch and colleagues (2011)**[78] and a proportional hazards assumption is applied, using the same hazard ratio as applied in the base case.

3. Two log-normal survival functions are fitted to the two arms in **Littlewood and colleagues (2001)**[68] and are extrapolated to 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 is to approximate the inclusion of background mortality, which is not otherwise modelled and would not have been adequately represented in the Kaplan–Meier curve (which only covers approximately three years of follow-up).

We are able to perform a probabilistic sensitivity analysis for the first two scenarios (although the OS in the control arm is not varied probabilistically in the second scenario) but a probabilistic sensitivity analysis is not performed for the third scenario as we had no adequate information to incorporate uncertainty about overall survival in this instance.

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

Mean discounted life years in control arm (base case and first scenario; λ = mortality rate) = $1/(\lambda + r_c)$;

Mean discounted life years in ESA arm (base case; λ = mortality rate, β = hazard ratio) = $1/(\lambda \times \beta + r_c)$;

Mean discounted life years (first scenario; λ = mortality rate, β = hazard ratio) = $(1 - \exp(-(\lambda \times \beta + r_c) \times 3.0))/(\lambda \times \beta + r_c) + \exp(-(\lambda + r_c) \times 3.0)/(\lambda + r_c)$.

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

Section 7.1.2.1.8 (page 277) describes how the overall survival models are parameterised.

7.1.2. Model parameters

On guidance from NICE, and so that a larger set of clinical study results can be used, clinical effectiveness parameters are not given for individual ESAs, but for ESAs as 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 R provides a summary table including all model parameters.

7.1.2.1. Clinical effectiveness parameters

As explained in Section 7.1.1 (page 245), 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.

In order to ensure consistency between costs and benefits, all parameters are estimated on the basis of intention-to-treat. For example, we use 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. 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 and control arms, as these quantities are also estimated from all randomised patients.

The ESA withdrawal rate and mean weekly dose are two parameters that are used in the economic model, but which are often reported only indirectly. The derivations of these parameters, shown in Table 62 (page 263), are given in Section 7.1.2.1.1 (pages 266–269). 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 for the economic model, but which is often reported only indirectly. The derivation of this parameter is given in Section 7.1.2.1.6 (pages 273–275).

The mean weekly dose and frequency of administering can differ between ESAs, due to differences in their licensing. These differences are discussed in Section 7.1.2.1.1 (pages 266–269) and Section 7.1.2.3.4 (page 302), respectively.

Some parameters are taken directly from random effects meta-analyses in the PenTAG systematic review of clinical evidence (see Table 61, page 262):

- Overall survival hazard ratio;
- Difference in Hb change from baseline;
- Difference in RBC units transfused;
- Relative risk of adverse events (thromboembolic events, hypertension and thrombocytopenia).

Other parameters are calculated from the inputs in those meta-analyses (Table 61, page 262):

- Hb change from baseline in control arm;
- RBC units transfused in control arm;
- Absolute risk of adverse events in control arm.

Further parameters were not extracted as a part of the systematic review of clinical effectiveness evidence and needed to be additionally extracted for the economic analysis:

- Overall survival in 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 final difference in Hb change from baseline;
- Duration of ESA treatment;
- Age;
- Weight.

Table 62 (page 263) gives the estimates of these outcomes from clinical studies which are then pooled as described in later sections.

We found no evidence from RCTs for normalization of Hb levels following chemotherapy cessation, so this part of the model had to be parameterised on the basis of clinical expert opinion (Section 7.1.2.1.7, page 275).

In the base case we use all 24 studies included in the systematic review of clinical effectiveness evidence (Section 0).

There is some heterogeneity in this collection of studies which may be due to treatment intention differences, e.g., in some studies the intention may be to correct anaemia while in others the intention may be to prevent anaemia.

To attempt to produce an analysis more consistent with the licensed use of ESAs (for anemia correction) we perform a scenario analysis where the subgroup of studies with inclusion Hb level ≤ 11.0 g/dL (or lower) is used. While this subgroup still includes 13 studies the precision of some effectiveness estimates is 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 is chosen.

If target Hb level is used to identify subgroups, the number of included studies falls significantly; only two studies have inclusion Hb level ≤ 11.0 g/dL and target Hb level ≤ 13.0 g/dL: **Tjulandin and colleauges (2010)**[45] and **Tjulandin and colleagues (2011)**.[76] Only one additional study, **Untch and colleagues (2011)**[78] had target Hb level ≤ 13.0 g/dL (but did not have inclusion Hb level ≤ 11.0 g/dL). We did not believe these subgroups to be adequate to

inform the model due to lack of precision and possible bias as **Untch and colleagues (2011)**[77,78] 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 do not use this outcome in the model for two reasons. First, we use more detailed information on the change in Hb from the RCTs. Second, as far as we are aware, the impact of haematocrit on quality of life is unknown. Tumour response rate RCT data are not used in the PenTAG model, because the tumour response rate is modelled indirectly by its impact on survival and we do 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 perform a probabilistic sensitivity analysis (PSA) in which model parameters are varied according to probability distributions with expected values equal to the deterministic parameter values. While it would be best practice for certain parameters to be correlated in the PSA there is not enough data for such an approach and as such all parameters are 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 use the sample standard deviation of the extracted outcomes from studies as the standard error in the model. This is preferable to using the sample standard error as this would underestimate uncertainty (as it would not incorporate the within-study variance). The sample standard deviation is also weighted using the same weights as the central estimate.

Table 61. Clinical parameters used in economic model taken directly from the PenTAG systematic review

Parameter	Pooled mean used in PenTAG model base case (SE)	Pooled mean used in scenario analysis (SE)	Section in report
Overall survival (HR)	0.967 (0.079)	0.914 (0.137)	Section 4.2.6.2.2 (page 117)
Change in Hb from baseline to end of ESA treatment: difference between ESA and control arms	1.59 (0.130)	1.52 (0.115)	Section 4.2.6.1.1 (page 85)
Mean number of units transfused in control arm	2.09	2.30	Calculated from reported outcomes of the RBC units meta-analysis, Section 4.2.6.1.4 (page 104)
Mean difference # units RBCs transfused ESA vs. control arm	−0.87 (0.21)	−0.99 (0.22)	Section 4.2.6.1.4 (page 104)
Relative risk of adverse event rates 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)	Section 4.2.6.3.1 (page 131)
Hypertension	ln(1.8) = 0.588 (0.234)	ln(1.68) = 0.519 (0.250)	Section 4.2.6.3.2 (page 134)
Thrombocytopenia	ln(0.93) = −0.073 (0.185)	ln(0.73) = −0.315 (0.350)	Section 4.2.6.3.3 (page 138)
Probability of adverse event in control arm			
Thromboembolic events	3.3% (0.4%)	3.7% (0.8%)	Calculated from reported numbers of adverse events in Section 4.2.6.3 (page 131)
Hypertension	2.9% (0.5%)	1.8% (1.0%)	
Thrombocytopenia	6.4% (0.8%)	2.5% (0.8%)	

Key: ESA, erythropoiesis stimulating agents; HR, hazard ratio; RBCs, red blood cells; RBCT, red blood cell transfusion; SE, standard error

Table 62. Additional clinical effectiveness outcomes from RCTs

Study, year	Mean weekly ESA dose[a]	Hb			Mean overall survival
		Mean baseline Hb level (g/dl)	Mean increase Hb (g/dl) control	Mean difference in Hb levels between treatment arms as a proportion of difference at end of trial[b]	
Wilson and colleagues (2004 [HTA]) included studies meeting inclusion criteria for the PenTAG review					
Abels, 1993[54]	307 IU/kg[c]	NR	NR	NR	NR
Aravantinos, 2003[63]	NR	EA, 9.80 No tx, 9.32	+1.23	23%	NR
Boogaerts, 2003[52]	463 IU/kg	EB, 9.0 No tx, 9.2	+0.9[d]	68%[d]	NR
Dammacco, 2001[64]	496 IU/kg	EA, 9.3 PBO, 9.6	0.0	56%	NR
Del Mastro, 1997[65]	429 IU/kg	EA, 13.0 No tx, 13.1	−3.05	73%	NR
Dunphy, 1999[66]	467 IU/kg	14.1	−2.8	77%	NR
Hedenus, 2002[49]	2.20 µg/kg	DA (2.25 µg/kg QW), 9.4 (1.3) PBO, 9.5 (1.0)	+1.00	59%	NR
Hedenus, 2003[16]	NR	9.54	+0.19	NR	NR
Kotasek, 2003[46]	2.025 µg/kg	DA, 9.93[e] PBO, 9.87	−0.02	NR	NR
Kurz, 1997[67]	NR	EA, 9.88 No tx, 9.85	+0.25	50%	NR
Littlewood, 2001[68]	NR	9.8	+0.5	110%	**12-month survival:** EA, 60% PBO, 49%

Study, year	Mean weekly ESA dose[a]	Hb			Mean overall survival
		Mean baseline Hb level (g/dl)	Mean increase Hb (g/dl) control	Mean difference in Hb levels between treatment arms as a proportion of difference at end of trial[b]	
					Median survival: EA, 17 mths PBO, 11 mths
Osterborg, 2002, 2005[69,70]	NR	EB, 9.2 PBO, 9.3	NR	NR	EB, 17.4 mths[d] PBO, 18.0 mths[d]
Silvestris, 1995[71]	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, 1998[47]	302 IU/kg	EA (150 IU/kg TIW), 12.0[d] No tx, 11.8[d]	NR	NR	NR
Thatcher, 1999[48]	335 IU/kg	EA, 13.7[d] PBO, 13.4[d]	NR	92%	NR
Vansteenkiste, 2002[72]	161 µg[f]	10.11	NR	NR	DA, 46 wks[d] PBO, 36 wks[d]
PenTAG review update 2004 onwards					
Grote, 2005[73]	(Cannot be calculated as intended treatment duration not fixed)	EA, 12.8; PBO, 13.0	−2.7	232%[g]	EA, 10.5 mths[d] PBO, 10.4 mths[d]

Study, year	Mean weekly ESA dose[a]	Hb			Mean overall survival
		Mean baseline Hb level (g/dl)	Mean increase Hb (g/dl) control	Mean difference in Hb levels between treatment arms as a proportion of difference at end of trial[b]	
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[74]	NR	EA, 10.0 No tx, 10.0	NR	NR	EA, 7.6 mths[d] No tx, 6.0 mths[d]
Strauss, 2008[75]	26,338 IU	EB, 11.4, No tx, 11.6	−0.7	76%	NR
Tjulandin, 2010[45]	ET: 23,594 IU EB: 31,251 IU	ESA, 9.5 PBO, 9.4	+0.2	ET: 62% EB: 60%	NR
Tjulandin, 2011[76]	ET: 22,235 IU	ET, 9.2 PBO, 9.1	+0.65	50%	NR
Untch, 2011a,b[77,78]	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%

Key: DA, darbepoetin alfa; diff, difference; EA, epoetin alfa; EB, epoetin beta; ESA, erythropoiesis stimulating agents; est., estimated; ET, epoetin theta; Hb, haemoglobin; IQR, interquartile range; IU, International Units; No tx, No treatment; NR, not reported; OS, overall survival; PBO, placebo

Notes: Study and baseline characteristics are reported in Appendix G; and, dose administered (application of licence) within the studies is reported in Appendic C; **(a)** See Section 7.1.2.1.2 (page 242) for description of estimation methods; **(b)** See Appendix S for calculation details; **(c)** Reported in **Henry and colleagues (1994)**[56]; **(d)** Median; **(e)** Includes patients randomized to unlicensed doses; **(f)** Calculated from data reported in **Vansteenkiste and colleagues (2004)**[81]; **(g)** The final Hb levels shown in Figure 2 of **Grote and colleagues (2005)**[73] do not coincide with those described in the text – data has been extracted from the graph for the mean diff Hb over time and from the text for the mean increase in Hb level in the control arm.

7.1.2.1.1. Number of red blood cell transfusions

The systematic review of clinical effectiveness evidence provides a summary estimate for the difference in RBC units transfused per patient between patients receiving and not receiving ESAs of −0.87 (95% CI, −1.28 to −0.46). The confidence interval corresponds to a standard error of 0.21 units. This summary estimate is from a random effects meta-analysis and we use the same weights to estimate the absolute mean RBC units transfused for patients not receiving ESA therapy (2.09 units). Since the absolute mean RBC units transfused does not affect cost-effectiveness this is not varied in the PSA.

In the scenario analysis with the subgroup of studies in which inclusion Hb level was ≤ 11.0 g/dL the difference in RBC units transfused was −0.99 (95% CI, −1.41 to −0.56) and the absolute mean RBC units transfused in the no ESA arm was 2.30 units.

Assuming the average number of red blood cell (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 take an average number of units per transfusion to be 2.7 units.[170] A Normal distribution is used for this parameter in the PSA, with SE equal to 20% of the mean.

7.1.2.1.2. ESA withdrawal rate and mean weekly dose

ESA dosages are adaptive, in many cases being increased when an inadequate initial response is obtained and being 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 is calculated on an intention-to-treat basis (the general exception being adverse event data), it is important that the amount of ESA drug use is commensurate.

The modelling approach adopted is to combine the withdrawal rate, dose escalation, dose reduction, etc. into a single parameter, the ITT mean weekly dose.

This was estimated where 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 and so are 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, 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 63 lists the clinical effectiveness studies with estimates of ITT mean weekly dose and the corresponding weights of those studies in the random effects meta-analyses of Hb change. In the base case the weights are taken from the full set of RCTs. As a scenario analysis the weights are used from the subgroup when initial Hb level must be ≤ 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 64. As no studies were found with epoetin zeta ITT mean weekly doses we assumed the same mean weekly dose as epoetin alfa due to the similarity of their licences.

As there is significant uncertainty in the ITT mean weekly dose we assumed a Gamma distribution with means as shown in Table 64 and standard errors equal to 20% of means.

Table 63. Mean weekly doses from clinical effectiveness studies

Study	ESA	ITT mean weekly dose	Weight[a]	
			Base case[b]	Scenario analysis[c]
Abels, 1993[54]	Epoetin alfa	307 IU/kg[d]	10.72[f]	14.61[f]
Boogaerts, 2003[52]	Epoetin beta	463 IU/kg	6.69	11.14
Dammacco, 2001[64]	Epoetin alfa	496 IU/kg	5.71	8.11
Del Mastro, 1997[65]	Epoetin alfa	429 IU/kg	5.28	n/a
Dunphy, 1999[66]	Epoetin alfa	467 IU/kg	n/a	n/a
Hedenus, 2002[49]	Darbepoetin alfa	2.20 µg/kg	4.81	6.01
Kotasek, 2003[46]	Darbepoetin alfa	2.025 µg/kg	4.32	5.07
Silvestris, 1995[71]	Epoetin alfa	733 IU/kg	n/a	n/a
ten Bokkel, 1998[47]	Epoetin alfa	302 IU/kg	4.77	n/a
Thatcher, 1999[48]	Epoetin alfa	335 IU/kg	n/a	n/a
Vansteenkiste, 2002[72]	Darbepoetin alfa	161 µg[e]	n/a	n/a
Moebus, 2013[62]	Epoetin alfa	414 IU/kg	n/a	n/a
Strauss, 2008[75]	Epoetin beta	26,338 IU	n/a	n/a
Tjulandin, 2010[45]	Epoetin theta	23,594 IU	5.34	7.18
	Epoetin beta	31,251 IU	5.10	6.64
Tjulandin, 2011[76]	Epoetin theta	22,235 IU	6.29	9.78

Key: ESA, erythropoiesis stimulating agent; Hb, haemoglobin; IU, international units
Notes: (a) Weighting taken from random effects meta-analysis of mean Hb change in systematic review; **(b)** Studies with licensed start dose; **(c)** Studies with licensed start dose and initial Hb < 11 g/dL; **(d)** Reported in Henry and colleagues (1994); **(e)** Reported in Vansteenkiste and colleagues (2004); **(f)** Sum of weights for cisplatin and non-cisplatin chemotherapy

Table 64. ESA doses in model

ESA	Base case	Scenario analysis
Epoetin alfa (IU per week)	24,729	24,745
Epoetin beta (IU per week)	31,021	30,840
Epoetin theta (IU per week)	22,859	22,810
Epoetin zeta (IU per week)	24,729	24,745
Darbepoetin alfa (µg per week)	141.1	140.1

7.1.2.1.3. Duration of ESA treatment

As stated in Section 7.1.2.1 (page 258), clinical effectiveness parameters are estimated on an intention-to-treat basis. As such the duration of ESA treatment is taken to be 12 weeks in

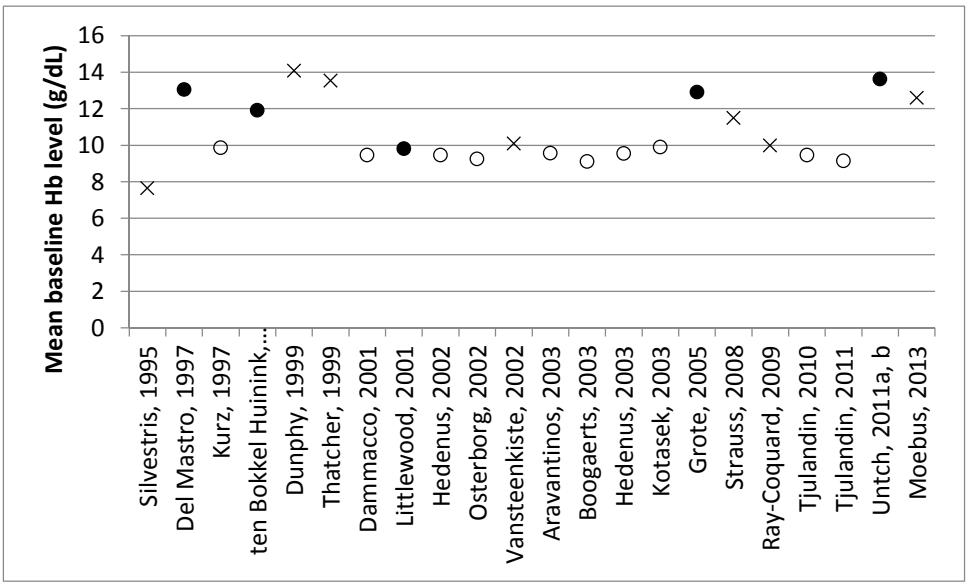
this analysis as this is the estimate acquired from the majority (13 of 23) of the RCTs included in the PenTAG meta-analysis. Some RCTs included longer treatment durations, but 17 of 23 reported durations of 18 weeks or less and all but one study with unambiguous reporting reported durations of 24 weeks or less. In a univariate sensitivity analysis we explore the impact of varying treatment duration up to 24 weeks, which is also the maximum duration included in Wilson and colleagues (2007).[1] 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.

ESA drug administration is modelled per protocol rather than on intention-to-treat basis (i.e., withdrawals are not incorporated. This does, in the base case, give a higher cost of administration for ESAs than we would otherwise expect, however, this increase in cost of drug administration is small enough that it does not greatly influence the overall costs. This cost is further discussed in Section 7.1.2.3.4 (page 302).

7.1.2.1.4. Initial (baseline) Hb 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 level is well reported in the included RCTs. Figure 30 (page 270) shows the range of baseline Hb levels. There is heterogeneity in the initial Hb levels which is likely due to different inclusion criteria.

Figure 30. Initial Hb level, by study



Key: Hb, haemoglobin; ○, Study included in base case and scenario analysis; ●, Study not included in scenario analysis; ×, Study excluded (not included in meta-analysis of Hb level change)

In the base case we calculate a weighted average baseline Hb level with weights taken from the random effects meta-analysis of mean Hb change. As a scenario analysis the weights from the subgroup with inclusion criteria of Hb ≤ 11.0 g/dL is used.

The resulting baseline Hb levels are 10.38 g/dL (base case) and 9.40 g/dL (scenario analysis), as shown in Table 65. The standard error in the base case is estimated from the weighted standard deviation of baseline Hb levels and calculated as 1.59 g/dL such that 95% of simulated values fall in the range [7.28, 13.49]. The standard error in the scenario analysis is calculated as 0.22 g/dL such that 95% of simulated values fall in the range [8.97, 9.84].

Table 65. Calculation of baseline Hb level parameter

Study		Weight	
	Baseline Hb level	Base case[b]	Scenario analysis[c]
Aravantinos, 2003[63]	9.56	4.46	5.34
Boogaerts, 2003[52]	9.1	6.69	11.14
Dammacco, 2001[64]	9.45	5.71	8.11
Del Mastro, 1997[65]	13.05	5.28	n/a
Dunphy, 1999[66]	14.1	n/a	n/a
Hedenus, 2002[49]	9.45	4.81	6.01

Hedenus, 2003[16]	9.54	6.79	11.51
Kotasek, 2003[46]	9.90	4.32	5.07
Kurz, 1997[67]	9.865	2.81	2.78
Littlewood, 2001[68]	9.8	6.57	n/a
Osterborg, 2002, 2005[69,70]	9.25	6.87	11.82
Silvestris, 1995[71]	7.65	n/a	n/a
ten Bokkel, 1998[47]	11.9	4.77	n/a
Thatcher, 1999[48]	13.55	n/a	n/a
Vansteenkiste, 2002[72]	10.11	n/a	n/a
Grote, 2005[73]	12.9	6.05	n/a
Moebus, 2013[62]	12.60	n/a	n/a
Ray-Coquard, 2009[74]	10.0	n/a	n/a
Strauss, 2008[75]	11.5	n/a	n/a
Tjulandin, 2010[45]	9.45	10.44[d]	13.82[d]
Tjulandin, 2011[76]	9.15	6.29	9.78
Untch, 2011a,b[77,78]	13.625	7.42	n/a
Summary estimate (base case)	**10.38**	89.28 (100%)	
Summary estimate (scenario)	**9.40**		85.38 (100%)

Key: Hb, haemoglobin
Notes: (a) Weighting taken from random effects meta-analysis of mean Hb change in systematic review; **(b)** Studies with licensed start dose; **(c)** Studies with licensed start dose and initial Hb <11 g/dL; **(d)** Weights summed over epoetin beta and epoetin theta arms

7.1.2.1.5. Change in Hb for patients not receiving ESA 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 to be expected that the Hb trajectories for patients in different studies would vary due to the differing effects of chemotherapy regimens and cancers on haemoglobin levels.

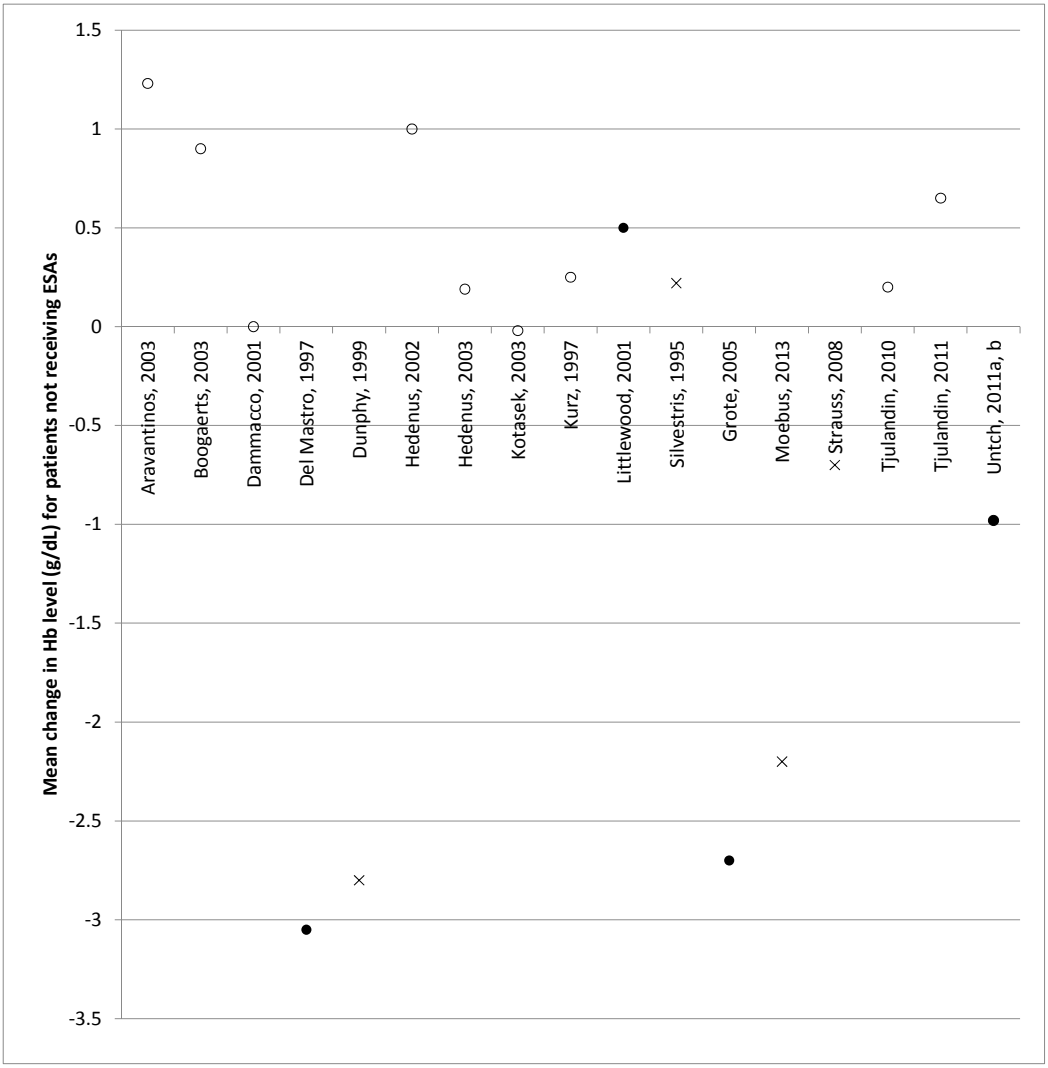
Figure 31 (page 272) shows the data from RCTs and

Table **66** (page 272) shows how these are combined to form the parameter values in the model base case and scenario analysis with inclusion Hb level ≤ 11.0 g/dL.

The resulting change in Hb 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 standard deviation was used to estimate the standard error in the base case and was calculated as 1.25 g/dL meaning 95% of simulated values fall in the range [−2.60, 2.29]. In the scenario analysis the

standard error was estimated as 0.41 g/dL meaning 95% of simulated values fall in the range [−0.33, 1.27].

Figure 31. Change in Hb level for patients not receiving ESAs at end of study period



Key: ESAs, erythropoiesis stimulating agents; Hb, haemoglobin; ○, Study included in base case and scenario analysis; ●, Study not included in scenario analysis; ×, Study excluded (not included in meta-analysis of Hb level change)

Table 66. Change in Hb level for patients not receiving ESAs

Study		Weight[a]	
	Change in Hb level for patients not receiving ESAs	Base case[b]	Scenario analysis[c]
Aravantinos, 2003[63]	1.23	4.46	5.34
Boogaerts, 2003[52]	0.9	6.69	11.14

Dammacco, 2001[64]	0.0	5.71	8.11
Del Mastro, 1997[65]	-3.05	5.28	n/a
Dunphy, 1999[66]	-2.8	n/a	n/a
Hedenus, 2002[49]	1.00	4.81	6.01
Hedenus, 2003[16]	0.19	6.79	11.51
Kotasek, 2003[46]	-0.02	4.32	5.07
Kurz, 1997[67]	0.25	2.81	2.78
Littlewood, 2001[68]	0.5	6.57	n/a
Osterborg, 2002, 2005[69,70]	NR	6.87	11.82
Silvestris, 1995[71]	0.22	n/a	n/a
ten Bokkel, 1998[47]	NR	4.77	n/a
Thatcher, 1999[48]	NR	n/a	n/a
Vansteenkiste, 2002[72]	NR	n/a	n/a
Grote, 2005[73]	-2.7	6.05	n/a
Moebus, 2013[62]	-2.20	n/a	n/a
Ray-Coquard, 2009[74]	NR	n/a	n/a
Strauss, 2008[75]	-0.7	n/a	n/a
Tjulandin, 2010[45]	0.2	10.44[d]	13.82[d]
Tjulandin, 2011[76]	0.65	6.29	9.78
Untch, 2011a,b[77,78]	-0.98	7.42	n/a
Summary estimate (base case)	**−0.155**	77.64 (100%)	
Summary estimate (scenario analysis)	**0.469**		73.56 (100%)

Key: Hb, haemoglobin
Notes: (a) Weighting taken from random effects meta-analysis of mean Hb change in systematic review; **(b)** Studies with licensed start dose; **(c)** Studies with licensed start dose and initial Hb < 11 g/dL; **(d)** Weights summed over epoetin beta and epoetin theta arms

7.1.2.1.6. Mean difference in Hb levels between treatment arms as a proportion of difference at end of trial

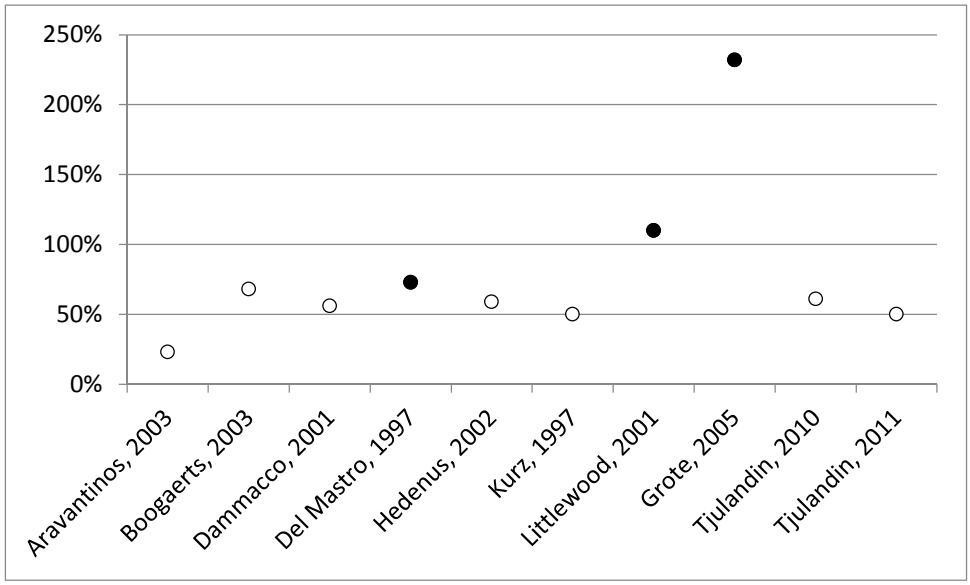
The mean difference in Hb levels between treatment arms over the entire ESA treatment period, as a proportion of difference at the end of the trial is another key parameter for the economic model, but which is often reported only indirectly.

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 end of treatment. We then took an average to give mean difference over the treatment period. See Appendix S for details.

Figure 32 (page 274) 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 67 (page 274) 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 standard deviation was used to estimate the standard error, 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%].

Figure 32. Mean difference in Hb levels between treatment arms as a proportion of difference at end of trial



Key: ESAs, erythropoiesis stimulating agents; Hb, haemoglobin; ○, Study included in base case and scenario analysis; ●, Study not included in scenario analysis; ×, Study excluded (not included in meta-analysis of Hb level change)

Table 67. Mean difference in Hb level over time from RCTs

Study	Mean diff Hb over time / mean final diff Hb	Weight[a]	
		Base case[b]	Scenario analysis[c]
Aravantinos, 2003[63]	23%	4.46	5.34

Boogaerts, 2003[52]	68%	6.69	11.14
Dammacco, 2001[64]	56%	5.71	8.11
Del Mastro, 1997[65]	73%	5.28	n/a
Dunphy, 1999[66]	77%	n/a	n/a
Hedenus, 2002[49]	59%	4.81	6.01
Hedenus, 2003[16]	NR	6.79	11.51
Kotasek, 2003[46]	NR	4.32	5.07
Kurz, 1997[67]	50%	2.81	2.78
Littlewood, 2001[68]	110%	6.57	n/a
Osterborg, 2002, 2005[69,70]	NR	6.87	11.82
Silvestris, 1995[71]	84%	n/a	n/a
ten Bokkel, 1998[47]	NR	4.77	n/a
Thatcher, 1999[48]	92%	n/a	n/a
Vansteenkiste, 2002[72]	NR	n/a	n/a
Grote, 2005[73]	232%	6.05	n/a
Moebus, 2013[62]	77%	n/a	n/a
Ray-Coquard, 2009[74]	NR	n/a	n/a
Strauss, 2008[75]	76%	n/a	n/a
Tjulandin, 2010[45]	ET: 62% EB: 60% Midpoint: 61%	10.44[d]	13.82[d]
Tjulandin, 2011[76]	50%	6.29	9.78
Untch, 2011a,b[77,78]	NR	7.42	n/a
Summary estimate (base case)	**80.6%**	59.11 (100%)	
Summary estimate (scenario analysis)	**55.5%**		56.98 (100%)

Key: EB, epoetin beta; ET, epoetin theta; Hb, haemoglobin; NR, not reported
Notes: (a) Weighting taken from random effects meta-analysis of mean Hb change in systematic review; **(b)** Studies with licensed start dose; **(c)** Studies with licensed start dose and initial Hb < 11 g/dL; **(d)** Weights summed over epoetin beta and epoetin theta arms

7.1.2.1.7. Normalisation of haemoglobin levels following chemotherapy cessation

It has been assumed in some previous economic evaluations of ESAs[1,154] that after chemotherapy cessation haemoglobin levels would return to 'normal' (see Section 0 , page 203). While this is an intuitive assumption that is generally supported by clinical expert opinion, we have not found direct evidence of the process (termed normalisation) in the published literature. Given that approximately half the QALY gain from ESA therapy could be accrued during normalisation,[1] 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.

Table 68 gives normalisation parameters in previous economic evaluations and those suggested by clinical experts. A normal Hb level of 12 g/dL appears to be a good compromise of the values suggested (the figure may be lower for haematological cancers but this is not modelled). This is varied in the PSA with distribution $\mathcal{N}(\mu, \sigma^2)$, with μ = 12.0, σ = 0.51 such that 95% of simulated values lie in the range (11.0, 13.0). It is possible for patients receiving ESA in the model to finish ESA therapy with Hb level higher 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 assume that the same utility gradient with respect to Hb level is observed (contrary to some studies which show levelling off), on the basis that clinicians would only raise Hb levels in such patients to improve HRQoL and therefore utility. If it is actually the case that utility levels off this method will overestimate the short-term QALY gain when Hb levels above 12 g/dL are modelled.

Given the base case initial Hb is 10.38 g/dL and the base case change in Hb for patients not receiving ESA is −0.15 g/dL, normalisation is expected to take Hb 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 per week, which is consistent with other estimates.

A normalisation rate of 0.2 g/dL per week is broadly consistent with previous evaluations and clinical expert opinion and this is the PenTAG base case value. In PSA this is varied according to $\mathcal{N}(\mu, \sigma^2)$ with μ = 0.2 and σ = 0.051 such that 95% of simulated values lie in the range (0.1, 0.3).

It is assumed on the basis of clinical opinion that normalisation will be complete within three months and this is incorporated in the model as a cap on the maximum time to normalisation, with the rate of normalisation effectively being increased where necessary to meet this cap.

Table 68. Normalisation parameters

Source	Rate of normalisation (g/dL per week)	Normal Hb level (g/dL)
Previous economic evaluations		
Amgen model[1]	0.1	≥ 12
Roche model[1]	0.2	13 (Solid); 11.9 (Haem)
Ortho Biotec model[1]	0.2	13
Birmingham model[1]	0.25	13
Borg et al. (2008)[154]	0.25	13
Clinical expert opinion		
Expert 1 (KS)	*(Normalised within 3 mths)*	
Expert 2 (CR)	0.125	11
Expert 3 (MN)	0.25	11
Expert 4 (NR)	*(Normalised within 6–8 wks)*	12
Key: Haem, haematological; Hb, haemoglobin; Solid, solid		

7.1.2.1.8. 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 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 overall survival hazard ratio) using the formula:

$$\bar{\lambda}_{GM} = \left(\prod_{i=1}^{n} \lambda_i^{w_i}\right)^{1/\sum_{i=1}^{n} w_i} = \exp\left(\frac{\sum_{i=1}^{n} w_i \ln \lambda_i}{\sum_{i=1}^{n} w_i}\right)$$

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 taken.

Table 69 gives the calculation of the summary estimates in the base case (all studies included) and in the scenario analysis (only including studies with Hb level ≤ 11.0 g/dL inclusion criteria).

Table 69. Calculation of OS parameter

Study	Reported OS	Calculated λ	Weight[a]	
			Base case[b]	Scenario analysis[c]
Littlewood, 2001[68]	KM at 1y: 49%	0.713	11.32	n/a
Vansteenkiste, 2002[72]	Median: 34w	1.060	11.22	21.13
Grote, 2005[73]	Median: 10.4m	0.800	6.05	n/a
Osterborg, 2005[70]	Median: 18.0m	0.462	12.40	22.46
Ray-Coquard, 2009[74]	Median: 6.0m	1.386	10.22	n/a
Untch, 2011a,b[77,78]	KM at 43.5w: 91.8%	0.024	8.48	n/a
Moebus, 2013[62]	KM at 5y: 83%	0.037	8.69	n/a
Summary estimate (base case)		**0.374**	100%	
Summary estimate (scenario analysis)		**0.691**		100%

Key: KM, Kaplan–Meier survival estimate; m, months; n/a, not applicable; OS, overall survival; w, weeks; y, years
Notes: (a) Weights taken from random-effects meta-analysis of OS hazard ratio; **(b)** Including only studies with licensed start dose; **(c)** Studies with licensed start dose and inclusion Hb level ≤ 11.0 g/dL

The resulting values for λ correspond to 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 is set to follow a Gamma distribution with SE 50% of the mean to capture the high level of uncertainty and the range of cancers from which patients receiving ESA therapy may suffer.

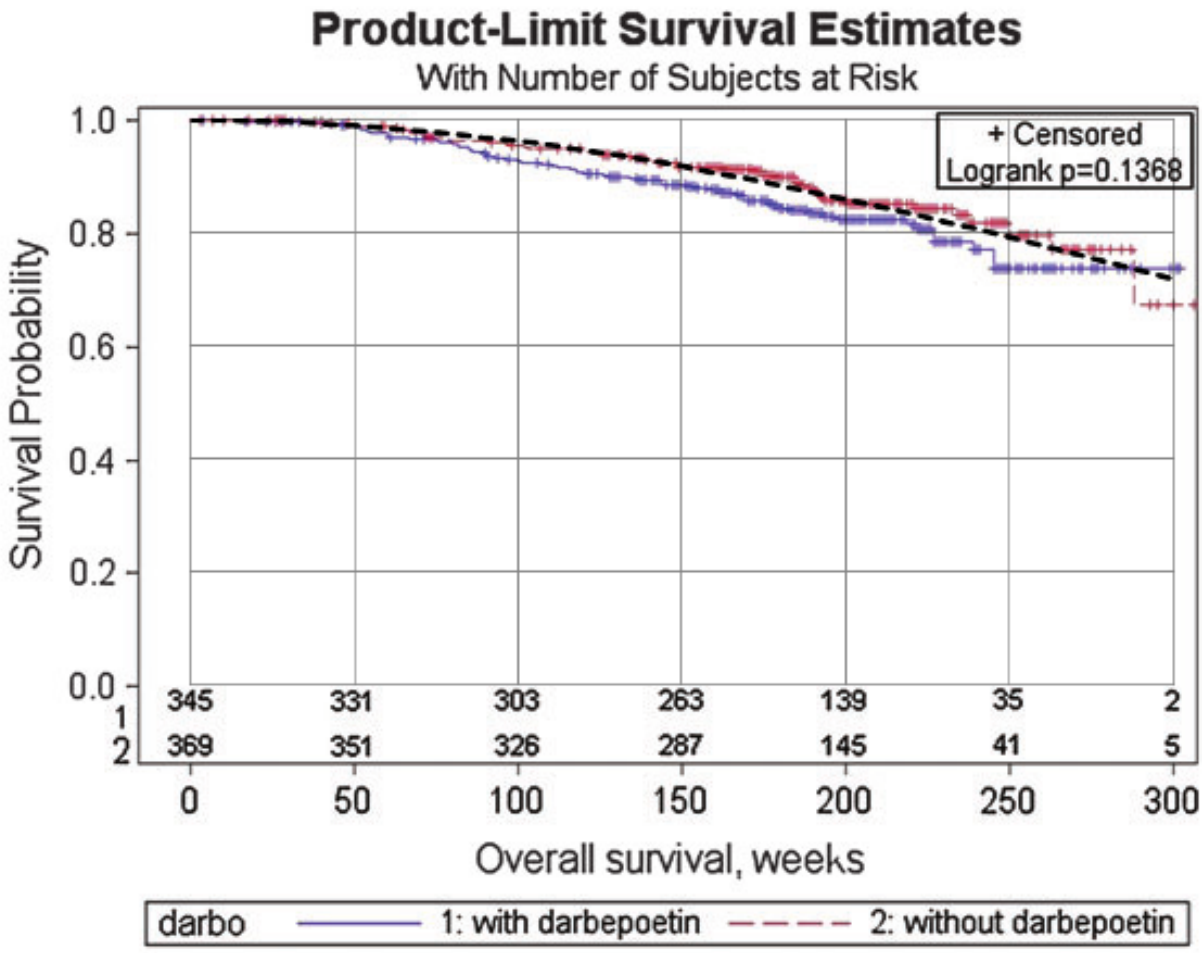
The overall survival for patients in the ESA arm is calculated by applying the hazard ratio provided in the clinical effectiveness review to the overall survival for patients not on ESAs. In the base case the hazard rate is 0.967, giving a mean undiscounted survival for patients on ESAs of 2.762 years. 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 hazard ratio is distributed as log-normal to match the result of the random effects meta-analysis (as the hazard ratio was meta-analysed following log transformation).Using a hazard ratio possibly derived from Cox proportional hazards and other non-parametric analyses to adjust a parametric survival function could result in a different result to derivation of the hazard ratio by parametric fitting, but given the limited data we believe this is the most appropriate approach. We allow for the alternative survival distributions to examine whether our results are 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 overall survival the hazard ratio for the first three years is equal to the hazard ratio used in the base case and thereafter a hazard ratio of exactly 1 is used.

In the second scenario analysis exploring structural uncertainty in the modelling of overall survival (where a Weibull curve is fitted to the control arm of **Untch and colleagues, (2011a,b)**[78] and a proportional hazards assumption is applied) the hazard ratio derived from the systematic review of clinical effectiveness evidence is 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 which minimized 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 $\lambda = 0.010987$; $\gamma = 1.950282$. Figure 33 shows the Weibull function overlaid on the original Kaplan–Meier curve and demonstrates very good fit.

Figure 33. Weibull distribution fitted to Kaplan–Meier survival from Untch and colleagues (2011a,b)[77,78]



Key: Black dashed line = Weibull fitted to control arm

In the third scenario analysis exploring structural uncertainty all parameters are estimated by fitting to the survival curves in **Littlewood and colleagues (2001)**.[68] The hazard ratio 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) are μ = 2.501676 in the control arm and 2.826619 in the ESA arm; σ = 1.483129 in the control arm and 1.348525 in the ESA arm. According to interim life tables for England and Wales (2010–12) the additional life expectancy for an individual aged 59 (the approximate mean age of patient in **Littlewood and colleagues [2001]**[68]) is 23.2 years for males and 26.0 years for females.[171] As 251 of 375 participants were female we estimate additional life expectancy of 25.1 years. Figure 34 shows the log-normal functions overlaid on the original Kaplan–Meier plot and

appears to demonstrate a reasonable fit. Under 2% of the population in both arms is modelled as still alive at 25.1 years after which it is assumed survival is zero.

Figure 34. Log-normal survival functions fitted to Kaplan–Meier survival curves from Littlewood and colleagues (2001)[68]

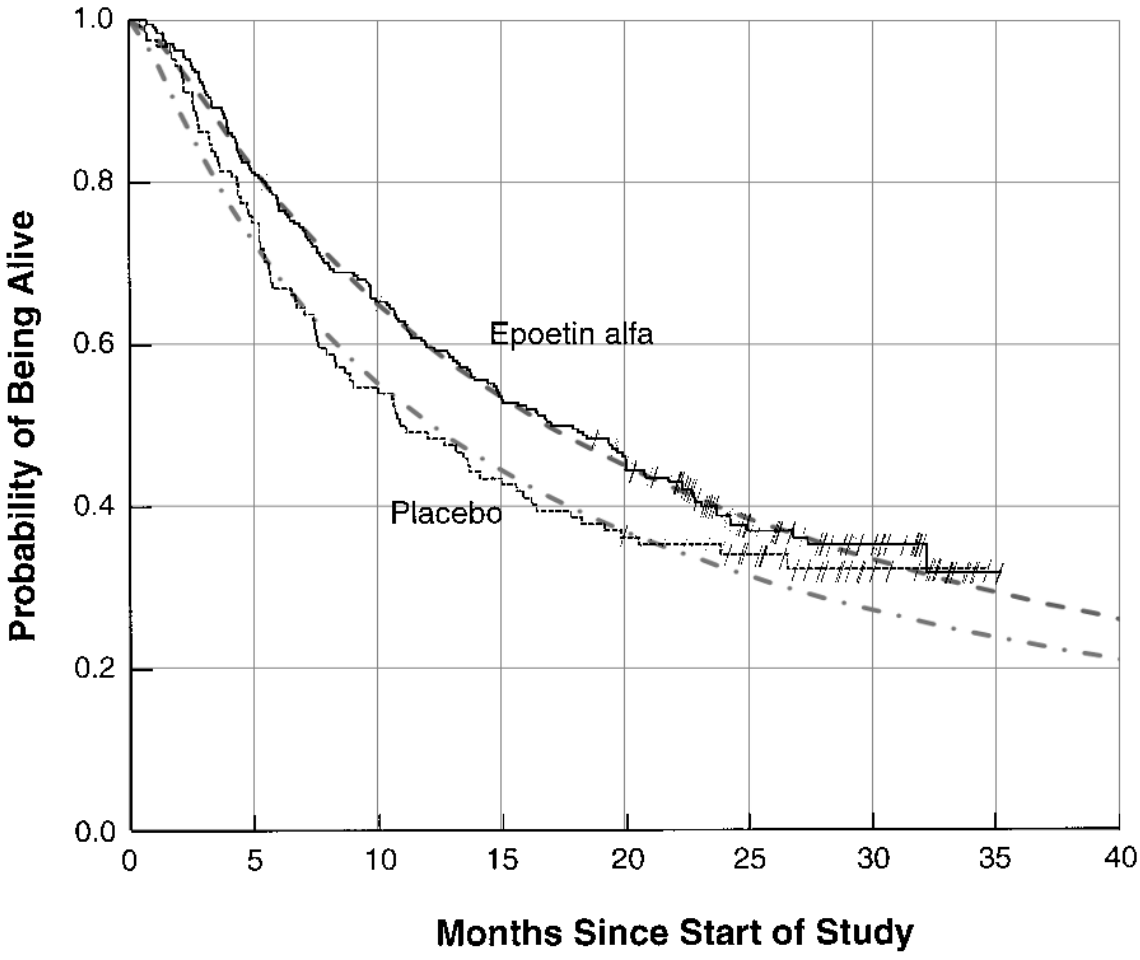


Figure 35 and Figure 36 show the various overall survival distributions employed for the control and ESA arms respectively.

Figure 35. Overall survival distributions used for the control arm

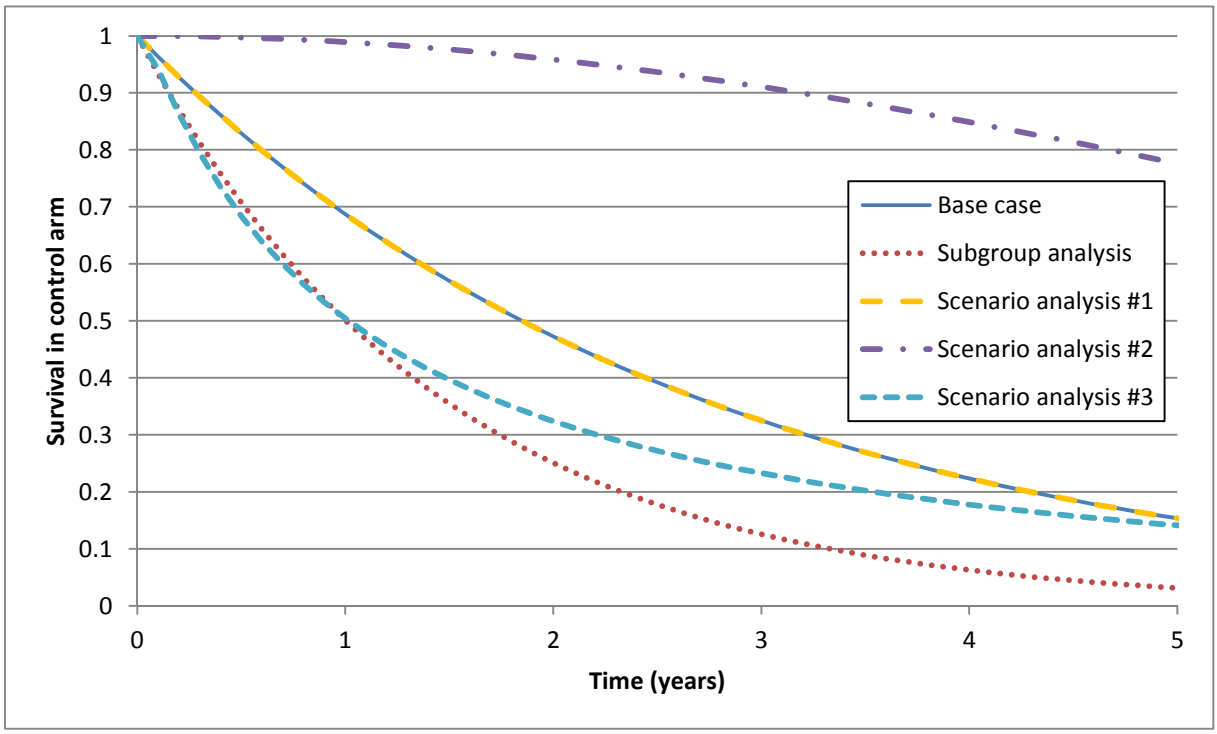


Figure 36. Overall survival distributions used for the ESA arm

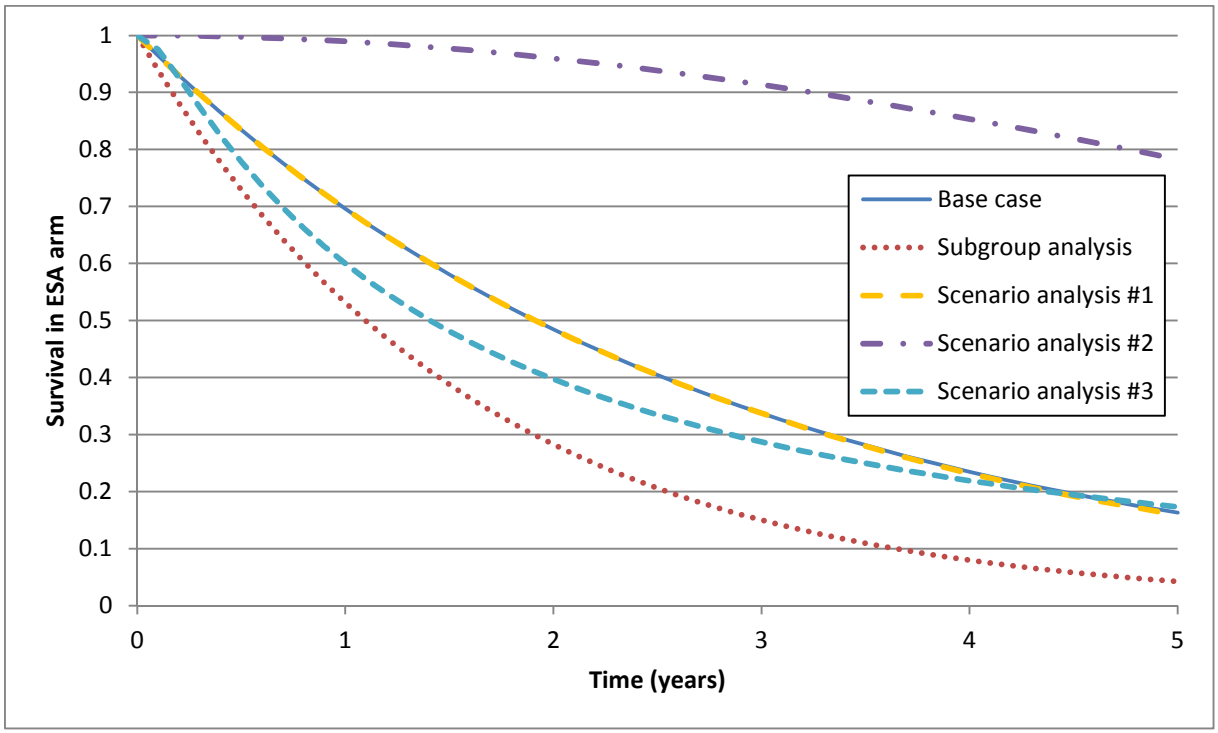


Figure 37 to Figure 41 show the overall survival distributions for both arms under each overall survival modelling assumption.

Figure 37. Overall survival distributions in the deterministic base case

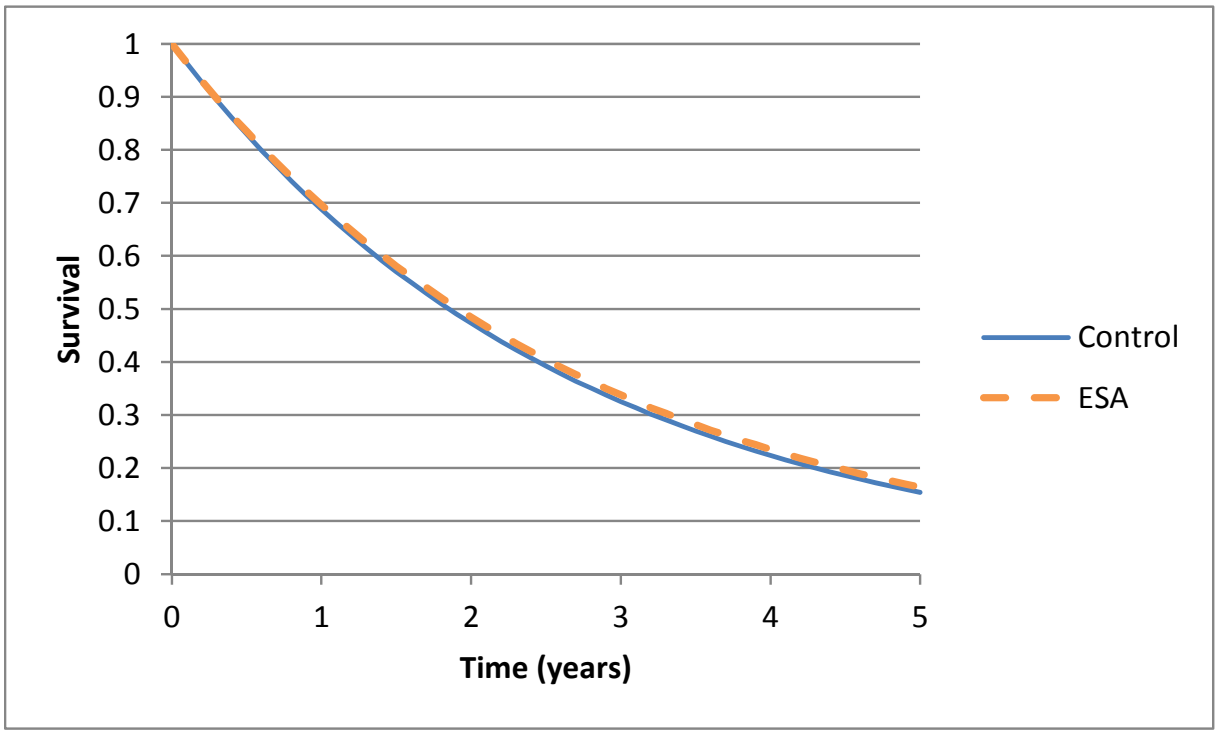


Figure 38. Overall survival distributions in the subgroup analysis where inclusion haemoglobin level ≤11.0 g/dL

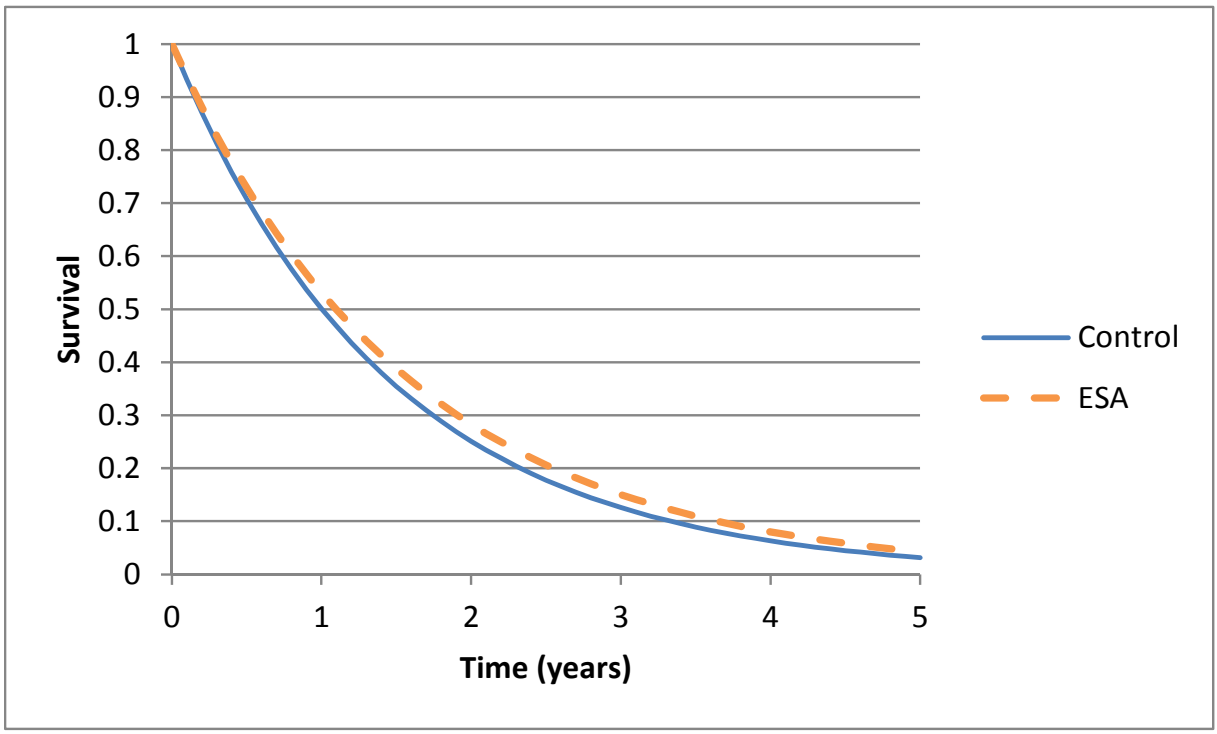


Figure 39. Overall survival distributions in the first scenario analysis (as the base case except hazard ratio only applies for first 3 years)

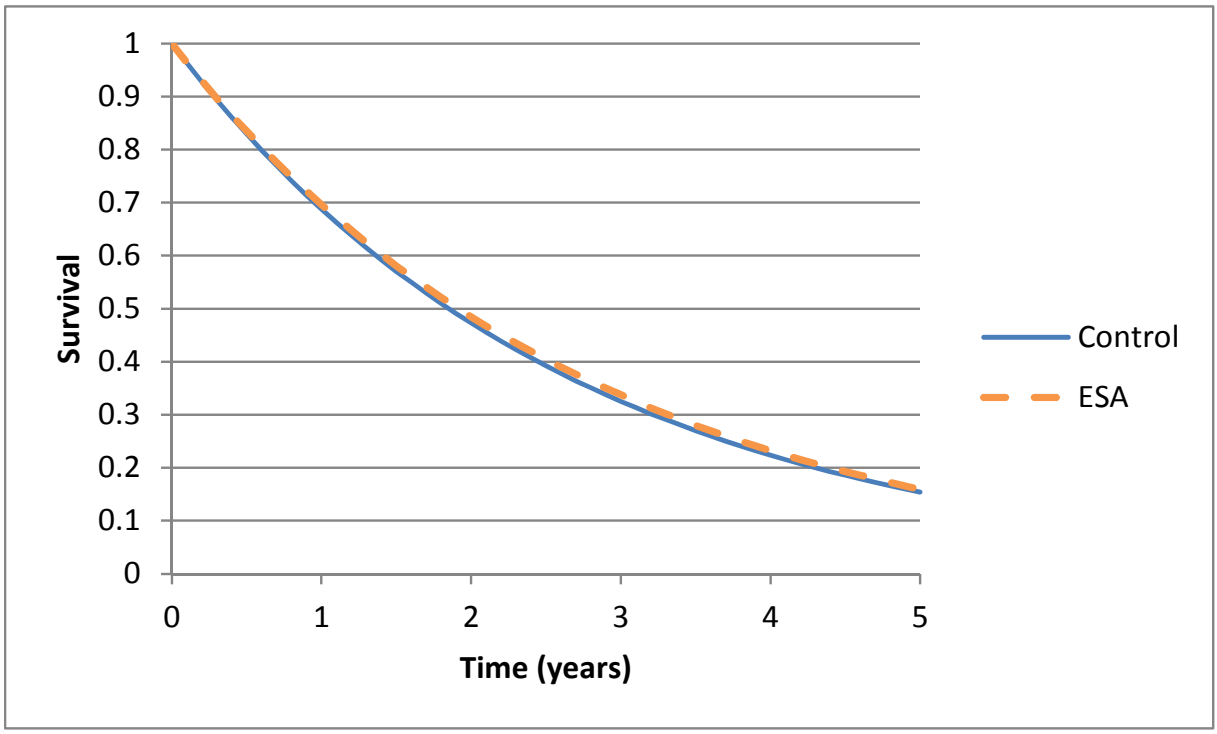


Figure 40. Overall survival distributions used in the second scenario analysis (Weibull distribution fitted to Untch and colleagues [2011a,b][77,78])

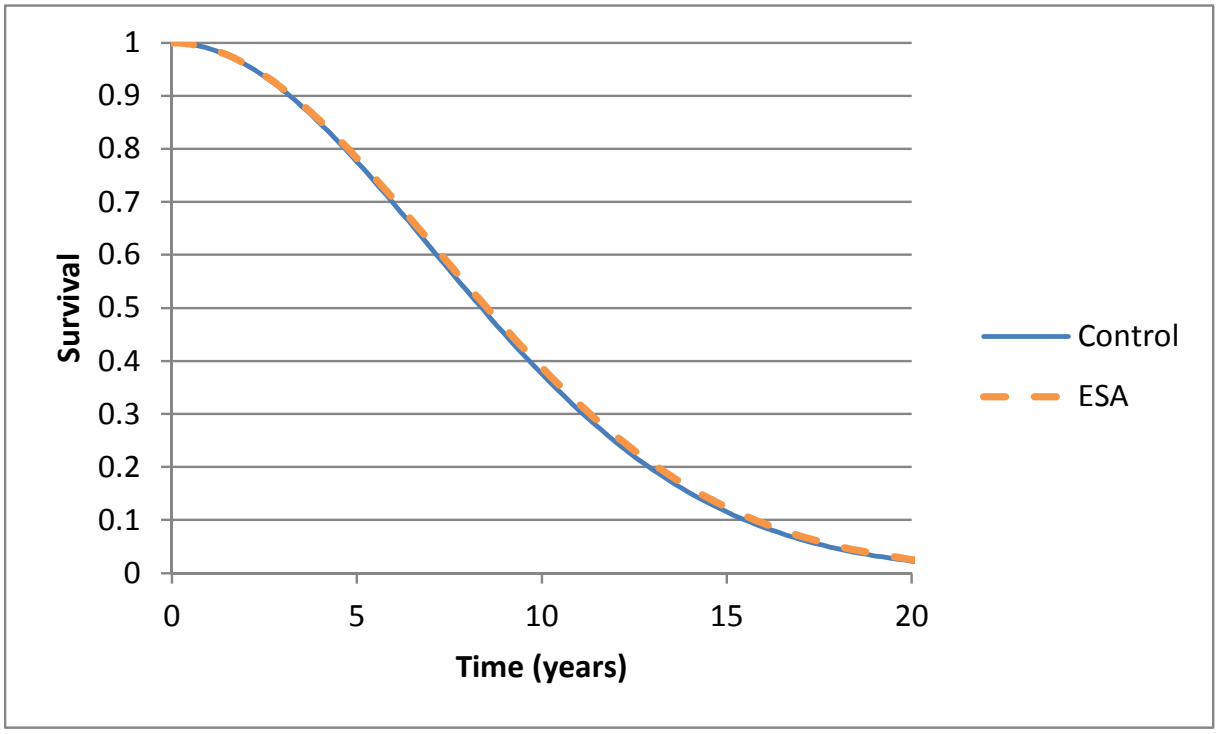
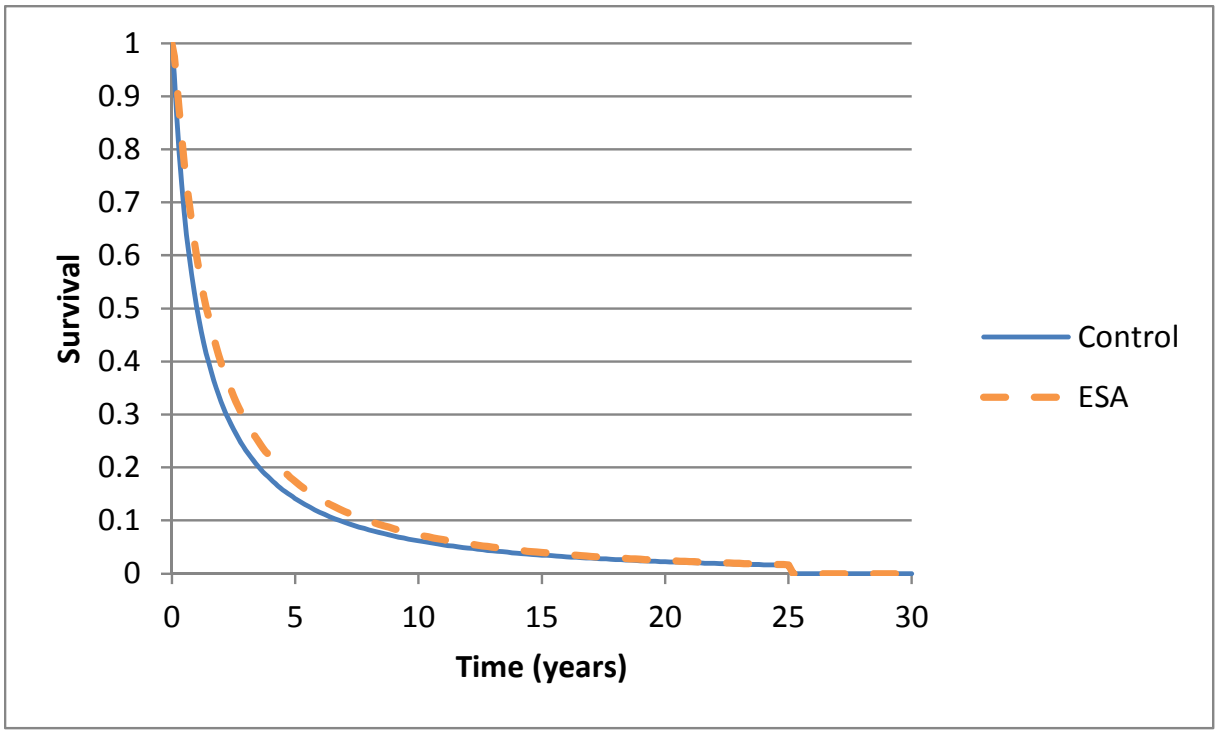


Figure 41. Overall survival distributions used in the third scenario analysis (log-normal distributions fitted to Littlewood and colleagues [2001][68] and truncated at 25.1 years)



7.1.2.2. Utilities

As explained in Section 7.1.1 (page 245), 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 impact of ESAs on HRQoL, and (2) constant utility value after normalisation, equal in all treatment arms.

The cost-effectiveness of ESAs is likely to be very sensitive to the 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 which has not been researched in depth for previous cost-effectiveness reviews. Therefore, it is necessary to research this carefully and in detail.

As explained in Section 7.1.1, p245, given that we model utilities during ESA treatment and during normalisation purely as a function of Hb level and due to disutilities due to ESAs, we implicitly assume that ESAs do not impact HRQoL in any other way. For example, it is

possible that ESAs affect some other aspect of health which is not captured by changes in Hb levels.

We used only randomised controlled trials (RCTs) to populate these parameters since only RCTs can support valid causal inferences about the effects of a particular treatment on quality of life.[59] With randomised studies potentially confounding factors, such as disease severity, that may affect both direct treatment outcome and quality of life should be distributed equally among trial arms and therefore do not bias estimates of the effect of treatment on quality of life.[59]

7.1.2.2.1. Utilities in cost-effectiveness models of ESAs

In Section 7.1.1 (page 245), we outlined approaches to estimating utilities in published economic evaluations of ESAs for cancer anaemia. Here, we elaborate on this (Table 70), in order to assess the usefulness of approaches to incorporation of utilities in published economic evaluations.

Table 70. Summary of use of utilities in previous models of the cost-effectiveness of ESAs for cancer anaemia

Cost-effectiveness analysis	During ESA treatment			After ESA treatment	
	Method of utility estimation	**Source data and method of utility estimation**	**Critique**	**Source data and method of utility estimation**	**Critique**
Barosi 1998[115]	ESAs affect HRQoL directly	VAS from Abels (1992)[161]	VAS method not recommended by NICE[a]	Not modelled, as short time horizon.	
Cremieux 1999[116]	ESAs affect HRQoL directly	LASA from Abels (1993)[54]	LASA scale not recommended.	Not modelled, as short time horizon.	
Martin 2003[117]	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 TA142 model[1]	Utility distribution per Hb level	Unpublished study of EQ-5D by Hb during Amgen RCT of darbepoetin. Data collected weekly from approx. 100 patients over 16 weeks. [1]	Details unpublished, therefore unable to critique.	0.66 (assumed same as baseline) [1]	Justification not given.
Ortho Biotec TA142 model[1]	Function of Hb level	Data from Ossa et al. 2004[172] from Ortho Biotec study (TTO from community values) by anaemia states..	Abstract only.Translation of anaemia states to Hb levels unreported	Not reported.	
Roche TA142 model[1]	Function of Hb level	Utilities from Ossa 2004, TTO, 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 (SG, TTO and EQ-5D)
Wilson 2007 TA142[1]	Function of Hb level	Unpublished data from Ortho Biotec	Unpublished, therefore unable to critique.	Not reported.	
Fagnoni 2006[123]	Function of Hb level	LASA from Crawford (2002)[159]	LASA not recommended as no value set.	Not modelled, as short time horizon.	
Borg 2008[154]	Function of Hb level	Following Wilson (2007) model[1]	Based on unpublished utilities study, therefore unable to critique.	Not modelled.	
Tonelli 2009[112]	Function of Hb level	Ossa, 2007[155]	See critique, Section 7.1.2.2.3, page 289	Not reported.	

Key: ESAs, erythropoiesis stimulating agents; Hb, haemoglobin; LASA, linear analogue scale assessment; HRQoL, health-related quality of life; VAS, visual analogue scale
[a]Not recommended as it does not reflect patient or public relative valuations or preferences for health states

All studies except Martin and colleagues (2003)[117] assume that ESAs affect HRQoL during ESA treatment. Most studies, including the previous technology assessment group's model (Wilson and colleagues, 2007[1]), estimate the impact of ESAs on HRQoL via the impact of ESAs on Hb levels.

Only two analyses modelled the impact of ESAs on health-related quality-of-life directly, rather than via the impact on Hb levels. One of these, Barosi and colleagues (1998)[115], used the Visual Analogue Scale, and the other, Cremieux 1999[116], the Linear Analog Scale Assessment (LASA) to estimate HRQoL. We believe both instruments are seriously flawed in assessing utilities as they do not allow trading off life expectancy with quality of life, as required by NICE.[168]

Of the seven studies that modelled the impact of ESAs on HRQoL via the impact of ESAs on Hb levels:

We consider the approach of Fagnoni and colleagues (2006)[123] to be inappropriate, because it also used the Linear Analog Scale Assessment (LASA).

Both the Ortho Biotec TA142 and Roche TA142 models use utility data from Ossa and colleagues (2004).[172] This is only reported in abstract form, but is reported fully in Ossa and colleagues (2007),[155] which we have identified and critiqued in Section 7.1.2.2.3, p289. The industry submissions differ in their partitioning of Hb levels into anaemia states.

The Amgen TA142 submission relied on unpublished data and used utility values elicited from patients on both experimental and licensed doses of Darbepoetin (patients who discontinued Darbepeotin were not followed up).

The data underlying the estimates of utilities as function of Hb levels from Borg and colleagues (2008)[154] also relied on unpublished data.

Utilities after ESA treatment are reported in only two cost-effectiveness studies: Martin 2003[117] and the Amgen TA142 model.[1] We do not consider the corresponding utilities further because the values from Martin and colleagues (2003)[117] relate to breast cancer only, and minimal detail is given for the value used in the Amgen TA142 model.[1] Some studies (e.g., Cremieux and colleagues, 1999[116] and Fagnoni and colleauges, 2006[123]) do not report utilities after ESA treatment because they consider only a short time horizon.

7.1.2.2.2. Principles for identification of studies to inform 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 recently by the NICE Decision Support Unit in the UK.[173] There are no agreed reporting standards for studies of utilities, but the following information is key to understand the nature and quantity and quality of evidence:[173]

- the population describing the health state (e.g. age, sex, disease severity),
- the approach used to describe the health state,
- utility value elicitation technique e.g. time trade-off, standard gamble, visual analogue score,
- sample size,
- respondent selection and recruitment, 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 is used.[168] Modification of utility values from the literature for use in economic models, and sensitivity analyses using less relevant utility values should be considered.[173]

A systematic search for studies reporting utilities should be undertaken.[173] For the current project, the search method is given in Appendix B. In addition, sources of utility values were obtained from published models on the cost-effectiveness of ESAs (Section 7.1.2.2.1, p286).

7.1.2.2.3. Studies reporting utilities as a function of Hb level

Our search for studies to inform utility values as a function of Hb levels yielded 235 publications. On inspection of titles and abstract, four papers were deemed sufficiently relevant to read in full: Harrow and colleagues (2011),[174] Lloyd and colleagues (2008),[175] Tajima and colleagues (2010),[176] and Wisloff and colleagues (2005).[177]

The first three papers reported studies that measured HRQoL as a function of Hb level. Wisloff and colleagues (2005)[177] did not provide estimates of utilities as a function of Hb. 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 in order to assess the impact of Hb on health-related quality of life.

In addition, we critiqued two further studies. Firstly, Ossa and colleagues (2007),[155] whose preliminary results (Ossa and colleagues, 2004[172]) 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 2007 model. It was also used in the cost-effectiveness analysis of Tonelli and colleagues (2009).[112] We also critiqued Crawford and colleagues (2002),[159] used in the cost-effectiveness analysis of Fagnoni and colleagues (2006).[123] The key characteristics and results of all five fully critiqued studies are given in Table 71 below. We do not critique the industry submissions from TA142 as the data underpinning the Roche and Ortho Biotec submissions are presented in Ossa and colleagues (2007) and the methods of the Amgen TA142 submission did not explicitly report utility as a function of Hb.

In the study by Harrow and colleagues (2011),[174] 13,433 women with cancer completed the SF-6D questionnaire at baseline. This represents a useful dataset as the sample size was very large, health was appropriately elicited by patients, and an appropriate preference elicitation instrument SF-6D was used (Table 71). However, the main weakness is that this was an observational study, which means that there could have been unmeasured covariates which contributed to the observed relationship between utility values and Hb levels. For example, patients with low Hb may have been more likely to have had more advanced cancer. This would tend to bias the apparent impact of Hb level on utilities, most likely 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 Hb 9 to 14 g/dl, and thereafter decrease (Figure 42, Figure 43, Table 71).

Tajima and colleagues (2010)[176] is also an observational study, which, amongst other factors, investigated the impact of Hb on utilities for patients with chronic kidney disease in Japan. This is also a useful dataset because, as preferred by NICE,[168] 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 also an observational study, which means that there could have been unmeasured covariates which contributed to the observed relationship between utility values and Hb levels, and (2) patients had chronic kidney disease, not cancer. Any bias due to (1) was minimised as several potentially confounding variables were included in the regression analysis. As for (2), it would only be a minor weakness if one could plausibly assume that the co-morbidity of anaemia impacts health-related quality of life 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 (Table 71). 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 (2007),[155] including the use of health state vignettes (Table 71). Hence, we attach little importance to the finding that utility increases steeply from Hb 7 to 11 g/dl (Figure 42).

The study by Lloyd and colleagues (2008)[175] also has many important weaknesses, including use of health state vignettes and very small sample size. Hence, we attach little importance to the finding that utility increases steeply from Hb 7.5 to 11.5 g/dl (Figure 42).

In the study by Crawford and colleagues (2002),[159] health was appropriately elicited from patients. However, the one important weakness of the study was that the health preference elicitation instrument was the Linear Analogue Scale Assessment (LASA), whose self-assessment consists of five questions on the physical, emotional, spiritual, intellectual and overall well-being, rated on a scale from 0-10. As suchutilities are not obtained by a choice-based method, such as the time trade-off or standard gamble, which is required by NICE.[168] Hence, we attach little importance to the finding that utility increases moderately from Hb 7 to 14 g/dl (Figure 42).

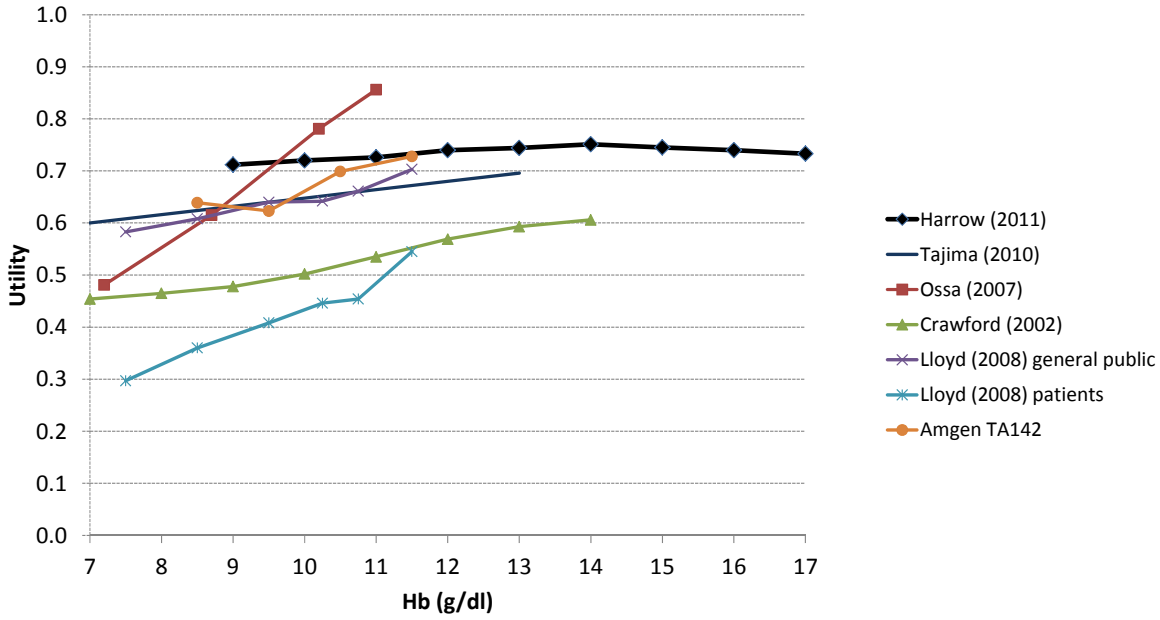
Table 71: Summary of characteristics of studies measuring utility as a function of Hb levels

Study	Harrow (2011)[174a]	Tajima (2010)[176]	Ossa (2007)[155]	Lloyd (2008)[175]	Crawford (2002)[159]	Amgen TA142 submission
Health elicitation by patients (pts)?	Yes	Yes	No	1st study: Yes, 2nd study: No.	Yes	Yes
Preference elicitation instrument	SF-6D	EQ-5D	Health state vignettes reflecting chemo-induced anaemia based on FACT-An and EQ-5D. Validated by 3 oncology specialists and 6 cancer anaemia pts.	Health state vignettes reflecting cancer anaemia. Reviewed by clinicians and QoL experts.	LASA	EQ-5D
Preference valuation	General public used SG	Japanese general publication used TTO	General public used TTO	1st study: General public used SG 2nd study: Cancer pts used TTO	None.	Not reported, presumably TTO
Study population size	13,433	537	110	1st study: 85 members of general public 2nd study: 26 cancer pts	Approx. 4,000	Not reported
Study population	Women with cancer aged 50-79, mean age 63	Chronic kidney disease pts.52% males, mean age 55, mean Hb 12.7	100 members of general population	1st study: General population. 2nd-study: Cancer pts received chemo;some anaemia, mean age 60	Cancer pts undergoing chemotherapy. Mean age 63	Pts on Darbepoetin, some on experimental dosing.
Country	US	Japan	UK	UK	US	Not reported
Year	1993-8	2008	2004	Not stated, but assume 2000s.	1990s	Not reported, pre 2004
Loss to follow up?	NA as measurement at baseline.	NA as measurement at baseline.	NA	NA	Appears not to be large	Numbers not reported, 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)

Study	Harrow (2011)[174a]	Tajima (2010)[176]	Ossa (2007)[155]	Lloyd (2008)[175]	Crawford (2002)[159]	Amgen TA142 submission
Results: ΔUtility for Δ1 Hb	0.009 over Hb 9-12 g.dl	0.016	0.109 over Hb 8.7-11.0	1st-study: 0.032, 2nd-study: 0.062. Over Hb 8.5-11.5.	0.029 over Hb 9-11.	0.030 over Hb 8.5-11.5
Major strengths	Sample size very large. Health elicited by pts, as required by NICE.[168] Generic preference elicitation instrument SF-6D.	EQ-5D is preferred by NICE.[168] Public valued using TTO, as preferred by NICE.[168] Sample size large. Health elicited by pts, as required by NICE[168]	None	In 2nd-study, health elicited by pts with experience of CIA	Sample size very large Health elicited by pts, as required by NICE[168] Pts with CIA	Health elicited by pts, as required by NICE[168] Pts with CIA EQ-5D is preferred by NICE.[168]
Minor strengths	Preference valuation SG appropriate (although TTO preferred by NICE[168]). Government funded.	Government funded	UK-based. TTO preferred by NICE[168].	UK-based		
Major weaknesses	Observational study, hence possibly unmeasured confounding variables[b]. However, many covariates were controlled for in analysis	Pts with chronic kidney disease, not cancer Observational study, hence possibly unmeasured confounding variables. However, many covariates were controlled for in analysis; e.g. albumin, creatinine, GFR, age, gender	Health status not elicited from pts. A requirement for NICE reference case[168] Health state vignettes assessed by experts, whereas NICE prefers pts self-reports using classifications systems of generic questionnairesSmall sample size of 110	Health state vignettes, whereas NICE prefer patient self-reports using generic questionnaires.[168] Very small sample size of 26 cancer pts	LASA instrument utilities are not obtained by a choice-based method, which is required by NICE[168]	Observational study, hence possibly unmeasured confounding variables[b]. All utilities taken from pts on some dose of ESA (utilities not taken when ESA use discontinued). Poorly reported
Minor weaknesses	Women only US, not UK NICE prefer EQ-5D to SF-6D Pts not necessarily taking 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-anaemia. Population under-represents ethnic minorities and over-represents wealthy people [b]. Industry funded.	Industry funded.	US, not UK. Industry funded.	Industry funded

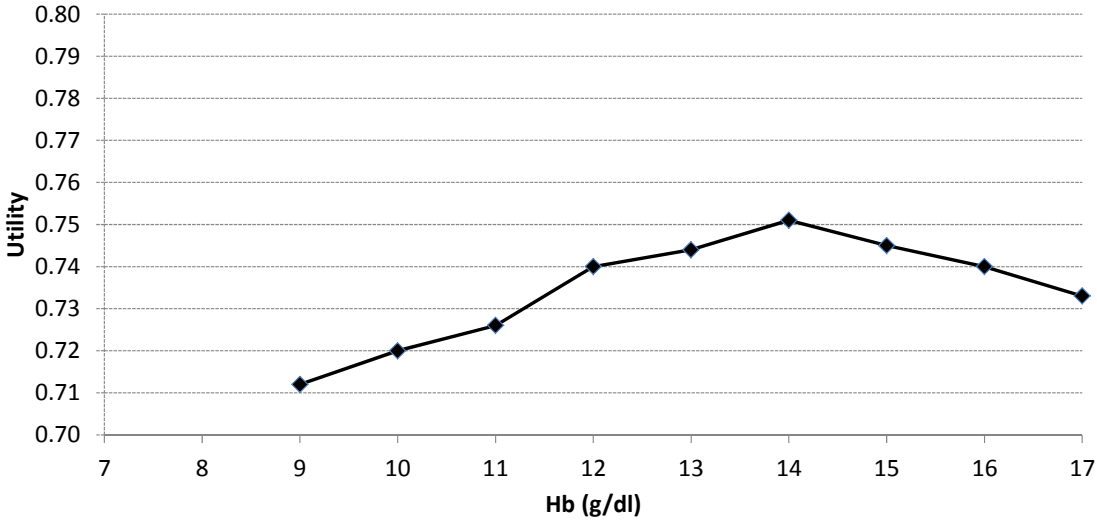
As stated above, the cost-effectiveness of ESAs may be very sensitive to the rate at which utilities change with respect to changes in Hb (i.e. the gradient of the utility / Hb graph). Cost-effectiveness is likely to be insensitive to the absolute utilities during the period of treatment with ESAs because mortality is assumed to be zero during this period for both the ESA and best supportive care treatment arms.

Figure 42. Utilities as a function of Hb level by study



Key: Hb, haemoglobin
Notes: For Tajima and colleagues (2010)[176], slope of line taken from regression and utility at Hb 7 arbitrarily assumed to equal 0.6. Utilities cannot be directly compared as they are reported on different scales and elicited through different tools.

Figure 43. Utilities as a function of Hb level from Harrow and colleagues (2011)[174]



Key: Hb, haemoglobin
Source: Harrow and colleagues (2011)[174]

7.1.2.2.4. Estimation of impact of ESAs on health utilities from mapping disease-specific questionnaires to EQ-5D

As mentioned in Section 7.1.2.1 (page 258), 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 (**Ray-Coquard and colleagues, 2009**)[74] used the EORTC QLQ C-30 questionnaire, and one **Tjulandin and colleagues (2011)[76]** used the FACT-G questionnaire. These have been mapped to EQ-5D by Dakin 2013.[178]

However, in the first case, it is not possible to perform such a mapping, because the required EORTC QLQ C-30 information is not provided.

In the second case, it is possible to make an approximate estimation of the impact of an epoetin alfa on utilities. At the end of treatment, we can estimate the difference in utilities between arms, in the case of Ray-Coquard and colleagues (2009)[74] this is 0.007 × 6.1 = 0.04, where 6.1 is the difference in FACT-G total score in Littlewood and colleagues (2001)[68] (2.5 + 3.6) and 0.007 is the coefficient from the utility mapping paper.[178] The authors of this paper found a better mapping function using the dimensions of the FACT-G questionnaire, rather than using total score.

All the other RCTs in the PenTAG systematic review that reported HRQoL use questionnaires for which we understand there is no mapping to EQ-5D nor to the SF-6D.[178]

7.1.2.2.5. PenTAG base case utilities by Hb level

As mentioned in the previous section, we consider the studies by Harrow and colleagues (2011)[174] and Tajima and colleagues (2010)[176] to be the most methodologically robust. The key differences between the two studies are:

- Harrow and colleagues (2011)[174] has the advantage of relating to people with cancer, whereas Tajima and colleagues (2010)[176] concerns people with chronic kidney disease.

- Tajima and colleagues (2010)[176] has the advantage of using the EQ-5D valued using Time Trade Off, both preferred by NICE,[173] whereas Harrow and colleagues (2011)[174] 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 (2011),[174] 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 (2004)[179] regression analysis. In Tajima and colleagues (2010),[176] 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 (2005),[177] and with our review of HRQoL that there is only weak evidence that ESAs improve HRQoL (Section 0, page 157).

The results are also consistent with the estimated impact of epoetin alfa on utilities (Section 7.1.2.2.4, page 295). At 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 difference between arms in Hb in Littlewood and colleagues (2001) was 1.7,[68] we would estimate difference in utility of 0.022 for Littlewood, which is plausibly close.

For our base case utilities we take the scaled utility value from Harrow and colleagues (2011). This is chosen over the EQ-5D results from Tajima and colleagues (2010) mainly on the basis that Harrow and colleague's population of people with cancer more closely matches our own. We therefore assume that utilities increase by 0.028 per unit increase in Hb. This utility is then applied until the end of normalization and adjusted for mean difference in Hb levels between ESA and no ESA arms, at the relevant time points, to calculate the short term QALY gain.

For the probabilistic sensitivity analysis, we assumed a gamma distribution with mean 0.028, standard error 20% of the mean, reflecting Harrow and colleagues (2011)[174]. We also perform univariate sensitivity analyses using the estimate from Tajima and colleagues (2010), 0.016, as well as using the unscaled value from Harrow and collegues, 0.009, and the estimate used in the previous HTA, 0.06.

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 due to unmeasured confounding variables. However, as suggested by Tonelli and colleagues (2009),[112] any such bias is likely to lead to an over-estimate of the rate of change of utility as a function of Hb. This is because: (1) people with low Hb 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 versus control.

7.1.2.2.6. PenTAG base case utilities after ESA 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 (2010)[180] (see below) and assuming the probability of being male to be 46% based on ONS Cancer Registration statistics for 2011 for people aged 50–60 years.

Equation 1. Formula for age related utility

$$U = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

Source: Ara and Brazier (2010) [180]

We can therefore surmise that the utility must be lower than this. In TA142, once people had returned to an Hb level of 13g/dL or higher, their utility was 0.810.[1] In this assessment people normalise to a lower Hb value than the previous HTA; and given the similarity of this value to people in the general population, we use a lower utility value for people in the long term. Tengs and Wallace (2000)[181] report a utility for cancer of 0.83-0.92 (irrespective of age) using a time trade off method. Applying these to the age-related utility gives a range of values of 0.68 to 0.76. Comparing this range to the values to those reported in the ESA specific utilities reported in Section 7.1.2.2.1 as well as to previous PenTAG cancer HTA

assessments,[182,183] we conclude that using the higher estimate of 0.76 is the most appropriate utility.

Again this is a parameter that is highly uncertain (due to 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 standard error 20% of the mean (0.184). The resulting standard error of the long-term utility is 0.830 × 0.184 = 0.153.

7.1.2.2.7. Utilties not included in the PenTAG 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 adverse events associated with ESA use. These utilities are not modelled explicitly and instead the disbenefit associated with adverse events is only accounted for by cost.

This decision was made for several reasons, the main reason being that adverse events data in the RCTs are extremely poorly defined. Firstly, the adverse events themselves are poorly defined and for example a thromboembolic event can refer to several events, including pulmonary embolism and deep vein thrombosis. These specific adverse events are often not specified within the RCTs or different RCTs will include different adverse events within their definition. Secondly, severity and length of impact of the adverse events 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 adverse events, but make it especially difficult to define the disutility of an adverse event and translate this into a QALY and indeed there was no data to define these results.

One area where the long term disbenefit of adverse events is implicitly included is in the survival. As with short term mortality, any mortality associated with adverse events 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 utility associated with adverse events as a limitation of the model and discuss this in Section 8.3.4.7 (page 388).

7.1.2.3. Costs

In this analysis we model the following costs: blood tests, ESA prices, red blood cell transfusion (RBCT) cost (unit cost of blood and cost of transfusion appointment) and costs of

adverse events. 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.

7.1.2.3.1. Adjustments to 2014/15 prices

All costs and prices in the model are inflated to 2011/12 prices using the Hospital and Community Health Services (HCHS) Pay and Prices index[184] and then further inflated by 3.65% per annum for two years to 2014/15 prices, where 3.65% is the average (geometric mean) inflation of the index between 2006/07 and 2011/12.

7.1.2.3.2. ESA prices

Table 72 presents the current drug prices for ESAs, which have been taken from the British National Formulary.[162] Separately we report the expected wholesale acquisition costs (Section 7.1.2.3.3, page 300), which we will use 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 72 demonstrates the various vial sizes for the ESAs which can make up a dose. Given the wide variety of vial sizes, we believe that drug wastage will be minimal and therefore do not account for it in our analysis.

Table 72. Available vial sizes and costs of ESAs

ESA BNF prices							
	Epo alfa		Epo beta	Epo theta	Epo zeta		Darbe alfa
Units	Eprex	Binocrit	NeoRecormon	Eporatio	Retacrit	mcg	Aranesp
500			£3.51			10	£14.68
1,000	£5.53	£5.09		£5.99	£5.66	15	£22.02
2,000	£11.06	£10.18	£14.03	£11.98	£11.31	20	£29.36
3,000	£16.59	£15.27	£21.04	£17.98	£16.97	30	£44.04
4,000	£22.12	£20.36	£28.06	£23.97	£22.63	40	£58.73
5,000	£27.65	£25.46	£35.07	£29.96	£28.28	50	£73.41
6,000	£33.19	£30.55	£42.08		£33.94	60	£88.09
8,000	£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
Notes: Sourced from British National Formulary 2013[162]							

Using the various vial sizes, we calculate the costs per 1,000 IU for the epoetin alfa, beta, theta and zeta; and per mcg for darbepoetin. These alter depending upon the vial size of the ESA for some of the ESAs; e.g. the cost of a vial size no greater than 20,000 IU for Eprex works out at £5.53 per 1,000 IU, but the larger vial sizes work out to be £6.64 per 1000IU. In the base case we used the lowest cost per 1,000 IU for each of the ESAs, as this covered the largest range of vial sizes. These base case costs are given in Table 73.

Table 73. PenTAG base case ESA costs

ESA base case unit cost (based on BNF prices)			
		per 1,000 IU	**per mcg**
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
Key: ESA, erythropoiesis stimulating agent			

The overall cost per dose for each ESA was then calculated using the number of units/ mcg per week.

ESA unit costs are not varied in the PSA.

7.1.2.3.3. 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. Due to different purchasing decisions by hospitals (due in part to 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; personal communication, 27 September 2013). These are understood to be from the most recent tendering process and therefore the most representative prices going forwards.

As can be seen in Table 74 all manufacturers were prepared to offer some level of discount from 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 74. ESA wholesale prices offered to London hospitals

ESA	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin alfa (Eprex)	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin alfa (Binocrit)	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin beta (NeoRecormon)	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin zeta (Retacrit)	[redacted]	[redacted]	[redacted]	[redacted]
Darbepoetin alfa (Aranesp)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

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 entered contracts committing to a volume of at least 8,000 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 which minimises total costs (i.e., 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 note 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 manufacturer and purchaser – in the case of London hospitals the contract was for twelve months with the option to extend by a further 24 months.

7.1.2.3.4. Cost of administering ESAs

There are multiple dosing options for most of the ESAs and we have chosen the base case dosing schedule for each on both the evidence available in the RCTs and on the advice of our clinical experts. This allows us to be consistent with our other evidence as well as clinical practice, including incorporating information on missed doses. In the base case we assume that dosing is given once a week, for all ESAs. Sensitivity analysis will investigate the different dosing schedules for each ESA as given in Table 75 (page 302).

Table 75. Dosing schedule for ESAs, based on licensed indications

	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

In the context of chronic kidney disease (CKD), ESAs are typically self-administered by the patient when possible (MN), and in the case of the industry submissions presented in this review, 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 in this disease area, with a comparatively short period of treatment, it may be more likely for patients to not self-administer. As our experts covered a range of cancers and backgrounds, we decided 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, 16.25% are administered during patients' chemotherapy appointments, 43.13% during a GP appointment or by a district nurse, and 40.63% self-administer in the base case (see Table 76). We do 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 we do not explicitly account for instances such as the weeks where 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 examine the situation where ESAs are administered to cancer patients in a similar manner to CKD patients. The costs of each type of administration and overall average cost for ESA administration are presented in Table 76. In the PSA the probabilities are drawn from a Dirichlet distribution.

As stated in Section 7.1.2.1.3 (page 268), duration of ESA treatment is calculated on an intention to treat 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 upon the results, compared to the cost of ESA drug price in the base case.

Table 76. ESA administration costs

ESA administration	Cost	Source	% of ESA	Source
Appointment with district nurse	£18.80	PSSRU	21.56%	Clinical experts NR, KS, MN, CR
Appointment with GP nurse	£10.74	PSSRU	21.56%	
Appointment with hospital staff nurse	£11.01	PSSRU	16.25%	
ESA self-administered	£0	Assumed	40.63%	
Average cost per ESA administration	**£8.16**			

Key: ESA, erythropoiesis stimulating agent; GP, general practitioner; PSSRU, Personal Social Services Research Unit
Notes: % of ESA may not add to 100% due to rounding

7.1.2.3.5. Additional blood tests for ESAs

Another additional cost for ESAs is incurred by an increase in blood tests, advised by our clinical experts (KS, NR). Opinion appears divided on how much of an increase this would be. In our base case we assume that blood tests would occur regularly for both patients who are on ESAs and those who are not whilst patients are undergoing chemotherapy treatment, but that additional blood tests would continue post-chemotherapy for those patients on ESAs. In our base case we cost for four additional blood tests. We assume this is administered by a GP nurse at a cost of £42.98 per hour (£40 in 2012/2013[185] inflated to 2014) and that the appointment takes 15.5 minutes of the GP nurse time, based on the average surgery consultation time,[186] resulting in a cost of £11.10. We also add the NHS Reference Cost for Phlebotomy (HRG DAPS08) of £3.91 (inflated from £3.64 in 2012/2013).[187] The total cost of a blood test is then £15.01. As the cost of blood tests is

relatively small compared to the other costs associated with cancer treatment induced anaemia, we do not expect any increase or reduction in the number of blood tests to have a significant impact upon the results. To represent uncertainty in these parameters all parameters are drawn from Gamma distributions in the PSA with SE equal to 20% of the mean.

7.1.2.3.6. Adverse event costs

The adverse events we account for in this cost-effectiveness analysis are identified through the clinical effectiveness review. In particular we account for the cost of:

- thromboembolic events
- hypertension, and
- thrombocytopenia.

Resource use for patients not receiving ESA therapy is 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 adverse event. A beta distribution was constructed on the basis of these figures for the PSA. Patients are assumed to experience at most one adverse event of each type. Resource use for patients receiving ESA therapy is calculated similarly but also applying the relative risk obtained from the systematic review of clinical effectiveness evidence (Section 0, page 56).

The unit costs of managing thromboembolic events (particularly pulmonary embolism and deep vein thrombosis), hypertension and thrombocytopenia are identified through NHS Reference Costs 2012-13[187] and updated to 2014/15 prices. These figures are presented in Table 77, p305 and are the weighted averages dependent on HRG code. No decision is made to specify HRG codes beyond the particular adverse event, to reflect that the relative risks identified in the PenTAG clinical effectiveness systematic review refer to any adverse event, regardless of severity. These costs are significantly larger than those reported in TA142, where the cost of an adverse event 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 at £4 a week and the Amgen submission a cost of £185 for a DVT, though sources of these costs were unclear. The NHS Reference costs themselves report a wide

range of costs for managing each of the adverse events and as such these costs will be altered in the PSA following a Gamma distribution with SEs equal to 20% of the means.

Table 77. Cost of adverse events

	PenTAG base case	HRG Codes
Thromboembolic events	£1,243	DZ09D, DZ09E, DZ09F, DZ09G, DZ09H (pulmonary embolus), QZ20A, QZ20B, QZ20C, QZ20D, QZ20E (DVT)
Hypertension	£826	EB04Z (hypertension)
Thrombocytopenia	£744	SA12G, SA12H, SA12J, SA12K (thrombocytopenia)
Key: DVT, deep vein thrombosis; HRG healthcare resource group		

7.1.2.3.7. Red blood cell acquisition costs

Unit costs for the supply of red blood cells (RBCs) are taken directly from NHSBT 2012/13 costs (£122 per unit)[188] and uprated to 2014/15 prices. This cost is significantly different to the cost of blood products in outpatient care that are reported in the NHS Reference costs 2013, where the average cost is around £1,300.[187] However this cost is for all blood products, not just red blood cells and as such has a skewed distribution: for HRG code XD05Z (Blood Products, Band 1) the average unit cost is £1,269, but the upper quartile cost is £482. We do not use the NHS Reference costs due to 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 National Commissioning Group for Blood meeting on 9th October 2007,[189] which detailed the cost of RBCs for 2008/9 as £139.72. A Gamma distribution is used for the cost of an RBC unit with SE equal to 20% of the mean.

7.1.2.3.8. Cost of transfusion appointment

The closest cost reported in NHS Reference costs for an outpatient blood transfusion appointment is the outpatient cost for 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 we find that the cost value reported originally came from the Varney and Guest (2003) paper.[170] Attempts were made to find updated versions of the figures reported in this paper, with marginal success. Audits from the NHSBT indicate that the numbers of transfusions as well as percentages of associated complications have decreased since the Varney and Guest study was conducted, but the associated costs were not available for this analysis. As such, we use the same figures as reported in Varney and

Guest 2003 and uprate this cost to 2014/15 costs. A Gamma distribution is used for the unit cost of a RBC transfusion appointment with SE equal to 20% of the mean.

Table 78. Unit costs of red blood cell transfusion

	PenTAG base case	Source
Unit cost of RBCs	£127	NHSBT
Cost of transfusion appointment	£688	Varney and Guest 2003
Key: NHSBT, NHD Blood & Transplant; RBCs, red blood cells		

7.1.2.3.9. Intravenous iron supplementation

NICE guidance from TA142 is that in circumstances where ESA therapy is recommended it should be used in combination with intravenous iron as this was associated with greater probability of haematological response.[34]

Intravenous iron supplementation was not included in any cost-utility studies identified in the update systematic review of cost-effectiveness (Section 6.1.2).

Iron supplementation is likely to be given to anaemic patients independently of whether they receive ESA therapy, so differences in resource use between patients receiving and 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 neglible in previous economic studies. To check that this is a reasonable assumption we briefly estimated the cost of 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).[190]

Resource use for drug administration is difficult to estimate as patients may already be attending an outpatient clinic for chemotherapy and ESA therapy. We assume that the incremental resource use of intravenous iron supplementation is minimal and of the same order of magnitude as the drug acquisition cost.

Given resource use is likely to be very similar between patients receiving and not receiving ESA therapy (and that no clinical data would directly inform an estimate of the difference), and given unit costs are also small in comparison to the cost of ESA acquisition and RBCT, we assume that the cost of intravenous iron supplementation can be ignored as it will be very similar for all arms.

7.1.2.4. Other model characteristics

7.1.2.4.1. Time horizon, perspective and discounting

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

7.1.2.4.2. Patient characteristics

The age and weight of patients in the model are estimated from the age and weight reported in clinical studies included in the systematic review of clinical effectiveness evidence. A simple average was taken to estimate the mean and standard deviation across studies was used to estimate the standard error for the PSA.

The mean age in the base case is estimated as 59.1 years (SE 5.3 years) and in the scenario analysis with inclusion Hb ≤ 11.0 g/dL it is estimated as 60.8 years (SE 4.2 years).

The mean weight in the base case is estimated as 66.6 kg (SE 3.3 kg) and in the scenario analysis as 66.1 kg (SE 3.6 kg).

The proportion of patients who are male is estimated as 46% based on cancer registration statistics in England, 2011 (individuals aged 50–59).[191]

KEY POINTS

- Our economic model consists of two components: short term and long term.
- In the short-term component:
  - Mean Hb levels across the population are estimated as a function of time for those receiving and not receiving ESA therapy. Hb levels are mapped to utility to derive QALYs.
  - The difference in Hb levels between the ESA and non-ESA arms at the end of treatment is taken from the systematic review of clinical effectiveness (Section 0, page 56).

  - Anaemia correction is not assumed to be instantaneous in the ESA arm, instead the average difference in Hb levels between the ESA and non-ESA arms across the duration of treatment is set to a proportion of the final difference in Hb levels based on results from 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 and 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 intention-to-treat 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 utility 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 while the rest required an appointment with a nurse.
  - Thromboembolic events, hypertension and thrombocytopenia were included as adverse events which incurred costs, but which did not incur disutility.
  - Red blood cell transfusions
- In the long-term component:
  - A constant rate of mortality is 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 is adjusted for those receiving ESA therapy using the hazard ratio derived in the systematic review of clinical effectiveness (Section 0, page 56).
  - A constant utility of 0.76 was assumed for the whole population to derive QALYs.

7.2. 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 cancer treatment induced anaemia. The options for anaemia treatment are either red blood cell transfusions (RBCTs) only, or ESAs with red blood cell transfusions. Given the differing cost of ESAs, results for patients on ESAs are examined across the different manufacturers.

Next we present the cost-effectiveness results under a number of scenarios and their PSA results. These scenarios include:

- Analysis where the survival is assumed equal in both ESA and no ESA arms
- Impact of wholesale acquisition costs for ESAs, both when applied to base case results and to the scenario analysis where survival is assumed equal in both arms
- Subgroup analysis based on studies where the initial Hb level of patients was <= 11g/dL
- Analyses investigating the overall survival assumptions.

We also present a comparison of our base case to those presented in TA142.[34]

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 have blood transfusion (on medical or religious grounds). These analyses are not presented given the absence of suitable data on these two subgroups (see Section 0, page 56).

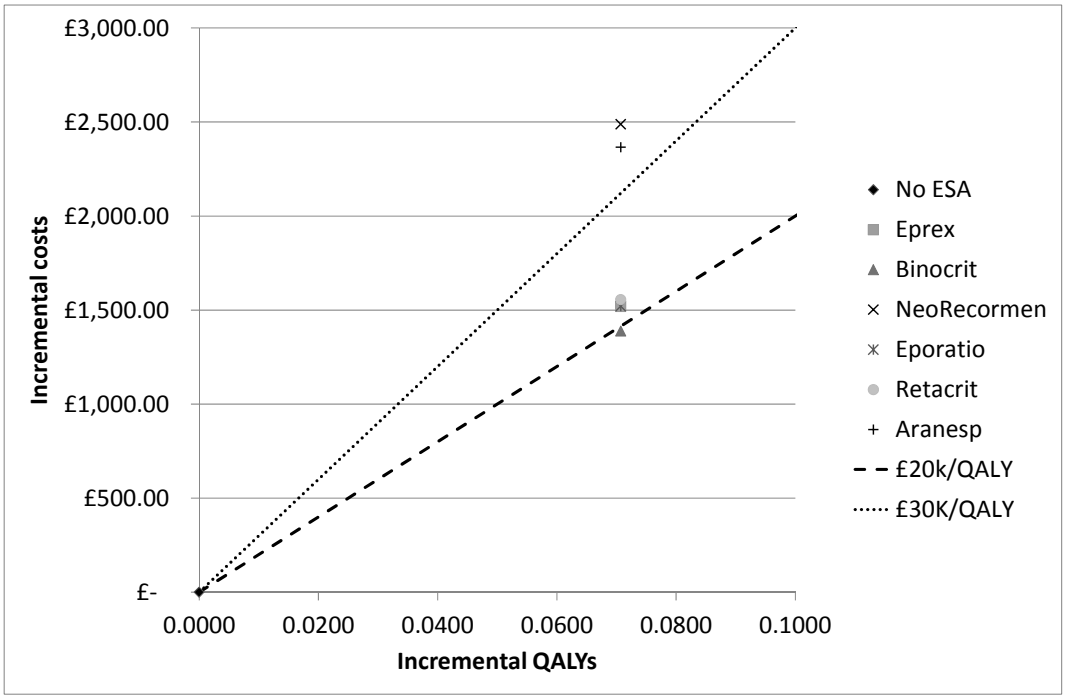
7.2.1. Base case

For our base case, we present the summary results, but emphasise the uncertainty in the model through scenario analyses and the PSA, since the deterministic results do not account for such uncertainty.

7.2.1.1. Cost-effectiveness results

The summary cost-effectiveness results are presented in Table 79 (page 312) and in Figure 44. Costs, which all occur within the first year, and short term QALY gain remain undiscounted, but QALYs gained in the long term are discounted.

Figure 44. Incremental costs and QALYs per patient, by anaemia treatment strategy



Key: ESA, erythropoiesis stimulating agent; QALYs, quality adjusted life years

As Table 79 shows, the incremental cost-effectiveness ratios for the ESA strategies versus no ESA use in the deterministic base case 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 limit of the £30,000 per QALY willingness to pay threshold. One ESA 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 44. As our ICERs cover a range from below £20,000 to above £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 to 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 thresholds, but only a net health benefit for one 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 to each other, they are dominated by the ESA with the lowest total ESA cost (in this case Binocrit® [Sandoz Ltd]). This is because the only model parameters that differ 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.

Table 79. Summary base case results

Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	–	Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Total costs per strategy	£912	£2,414	£2,283	£3,384	£2,416	£2,451	£3,258
Total incremental costs vs. no ESA	–	£1,502	£1,371	£2,472	£1,504	£1,539	£2,346
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® (Sandoz Ltd)	£19,429	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)
INHB vs. no ESA at WTP £20,000/QALY	–	-0.005	0.002	-0.053	-0.005	-0.006	-0.047
INHB vs. no ESA at WTP £30,000/QALY	–	0.021	0.025	-0.012	0.020	0.019	-0.008

Key: Darbe alfa, darbepoetin alfa; ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus; WTP, willingness to pay

We now briefly describe the breakdown of costs and QALY results that give our overall results.

7.2.1.2. Costs

In the base case, costs are only accrued in the short term (within the first year), so that long term costs unrelated to anaemis do not disadvantage a treatment with survival benefit. The costs reported in the base case are therefore not discounted.

Table 80 (page 314) shows the total cost per patient in all arms is not particularly large, implying that small changes to these costs may have large impacts to the overall results. The largest cost for all ESA arms is the cost of the ESA itself (£1,510–£2,485). The largest cost for a patient not on ESA is the cost of red blood cell transfusions (£799).

Adverse events (AEs) have the one of the smallest total costs, in both the ESA and no ESA arms. However, it is important to note that the data from the RCTs used to populate the values of the adverse event model parameters were only available as 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 adverse events data, we explore its impact on the results in sensitivity analyses (see Section 7.2.7.6, page 369).

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, due to assumptions of equal effectiveness, the cost of adverse events, RBCTs and additional blood tests are the same for all ESAs.

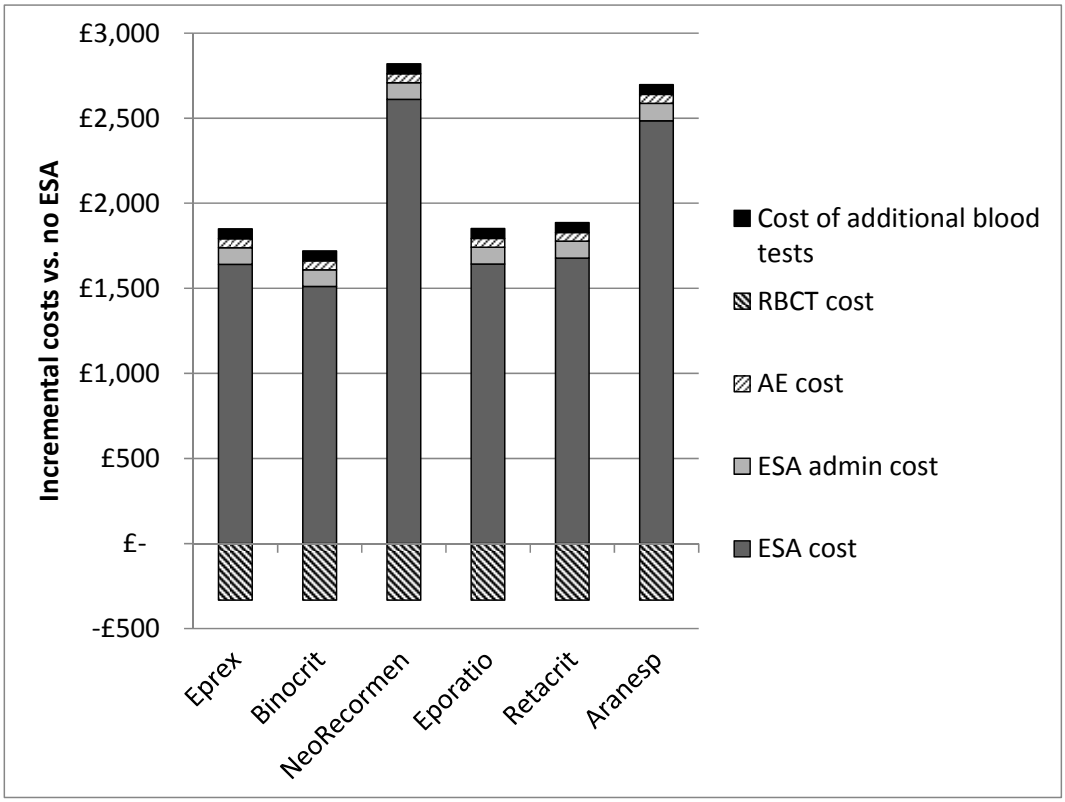
Table 80. Summary of costs in the base case

Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	–	Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Total costs per strategy	£912	£2,414	£2,283	£3,384	£2,416	£2,451	£3,258
ESA cost	£0	£1,641	£1,510	£2,611	£1,643	£1,678	£2,485
ESA administration cost	£0	£98	£98	£98	£98	£98	£98
Adverse event 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	-	£1,502	£1,371	£2,472	£1,504	£1,539	£2,346
ESA cost	-	£1,641	£1,510	£2,611	£1,643	£1,678	£2,485
ESA administration cost	-	£98	£98	£98	£98	£98	£98
Adverse event 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

Key: Darbe alfa, darbepoetin alfa; ESA, erythropoiesis stimulating agent; RBCT, red blood cell transfusion

Incremental results (Table 80 and Figure 45) demonstrate that though there is an estimated cost saving of £332 for RBCTs avoided, this is outweighed by the additional costs accrued in each ESA arm.

Figure 45. Incremental costs versus no ESA use in the base case



Key: AE, adverse event; ESA, erythropoiesis stimulating agents; RBCT, red blood cell transfusion

7.2.1.3. QALY and survival gain

As Table 81 (page 316) demonstrates, there is a life year (LY) and QALY gain for patients on ESA compared to no ESAs, both in the short term (QALY gain as a consequence of Hb level increase) and 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 to 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 1g/dL. We therefore do not calculate the short term utility for the patients who do not have ESAs, instead calculating the difference in utility between arms using the Hb levels. QALYs gained (or lost) by the ESA arm compared to 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 new meta-analyses of PenTAG's clinical effectiveness review, these results are not conducted separately for each ESA product.

Table 81. Incremental life years (LYS) and quality-adjusted life years (QALYs), ESA vs. no ESA

Treatment arm	Incremental LY and QALY gain (ESA vs. no ESA)
Undiscounted LY gained vs. no ESA (undiscounted)	0.0911
Discounted life years gained vs. no ESA	0.0762
Total discounted QALYs gained vs. no ESA	**0.0706**
Total short term	0.0124
Short term- during cancer treatment	0.0083
Short term- during normalisation	0.0042
Long term	0.0582
Key: ESA, erythropoiesis stimulating agents; LY, life year(s); QALY, quality-adjusted life year	

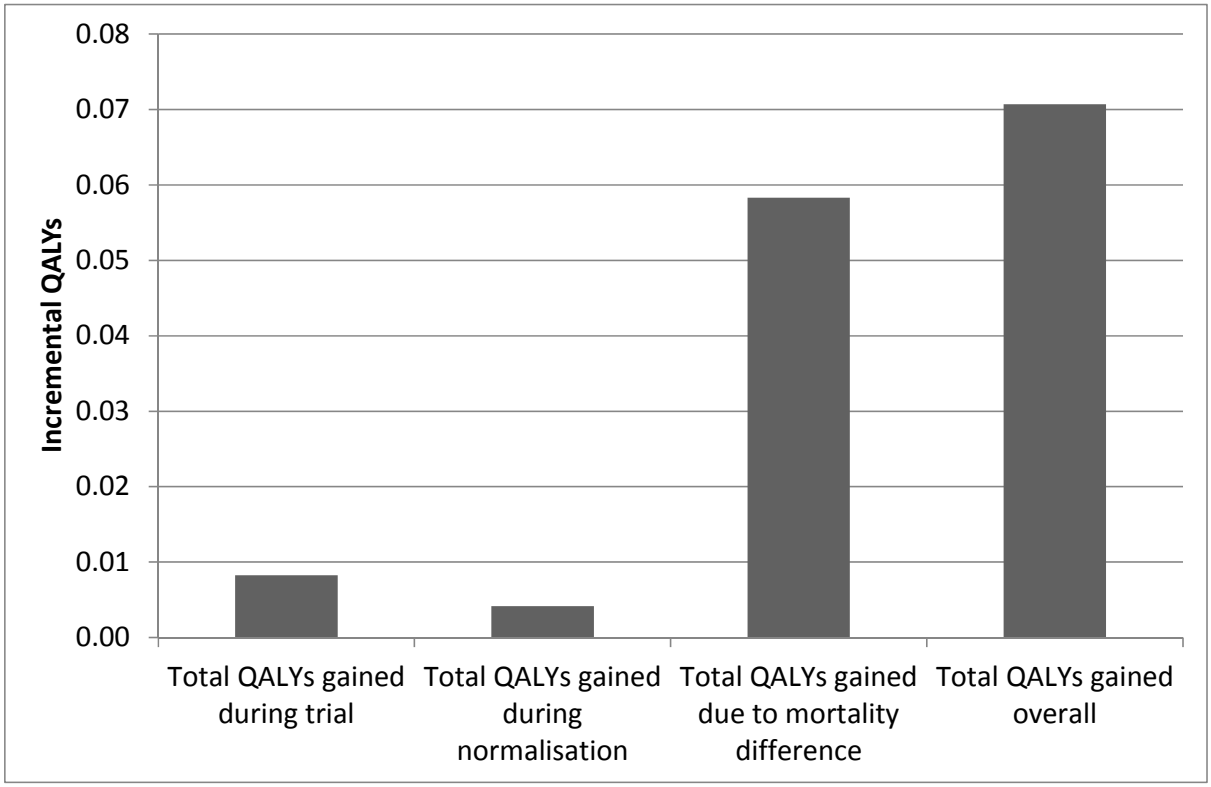
Figure 46 (page 317), demonstrates where these QALYs are accrued. Over three-quarters of the QALY gain is due to the modelled increased survival.

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 due to the short time frame they occur within. 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 for up to four weeks after chemotherapy) and therefore this QALY gain could be greater. Our estimated short term QALY gain, 0.0124, is lower than in other comparable studies (e.g. **Wilson and colleagues [2007]**,[1] where short term gain in the base case is 0.030), due to PenTAG's smaller utility gain associated with increase in Hb level.

The long term QALY gain for patients on ESA compared to those not on ESA is a direct result of the life years gained, as the utility is assumed the same in both arms once patients' Hb levels have normalised. Given the timeframe of this section of the model, the life years gained and associated QALYs are discounted in the final results. The discounted life years gained for patients on ESA are therefore 0.0762 years. 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. Though our base case includes a survival benefit associated with ESA use, this survival benefit is not demonstrated with statistical significance, as discussed in PenTAG clinical effectiveness review, and is one parameter that is investigated thoroughly in sensitivity analysis, in an attempt to quantify its effects on results. It is this parameter in particular that drives the cost-effectiveness results and emphasizes the importance of our PSA.

Figure 46. Incremental QALY gain versus no ESA



Key: ESA, erythropoiesis stimulating agent; QALYs, quality-adjusted life years

7.2.2. Probabilistic sensitivity analysis of PenTAG base case

Here we present the results of the probabilisitic sensitivity analysis (PSA) for our base case. Table 82 presents the average PSA results, with a comparison to the ICERs in the deterministic base case. On average the ICERs are slightly reduced in the probabilistic analysis compared to the deterministic base case. However, as we see from the 95% confidence intervals for the costs and QALYs, the true ICERs are likely to cover a wide range. Indeed the credible intervals cover a range of £2,500 per QALY to the point where they are dominated (with ESAs having higher costs and lower QALYs than the no ESA arm).

The average incremental net health benefit (INHB) for each ESA in the PSA are slightly higher than in the deterministic base case, especially in the case where ESAs were 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 are examined, they demonstrate that there is quite a range that each INHB can lie upon. The breakdown of costs and QALYs indicates where the majority of the uncertainty in the overall costs and QALYs is coming 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.

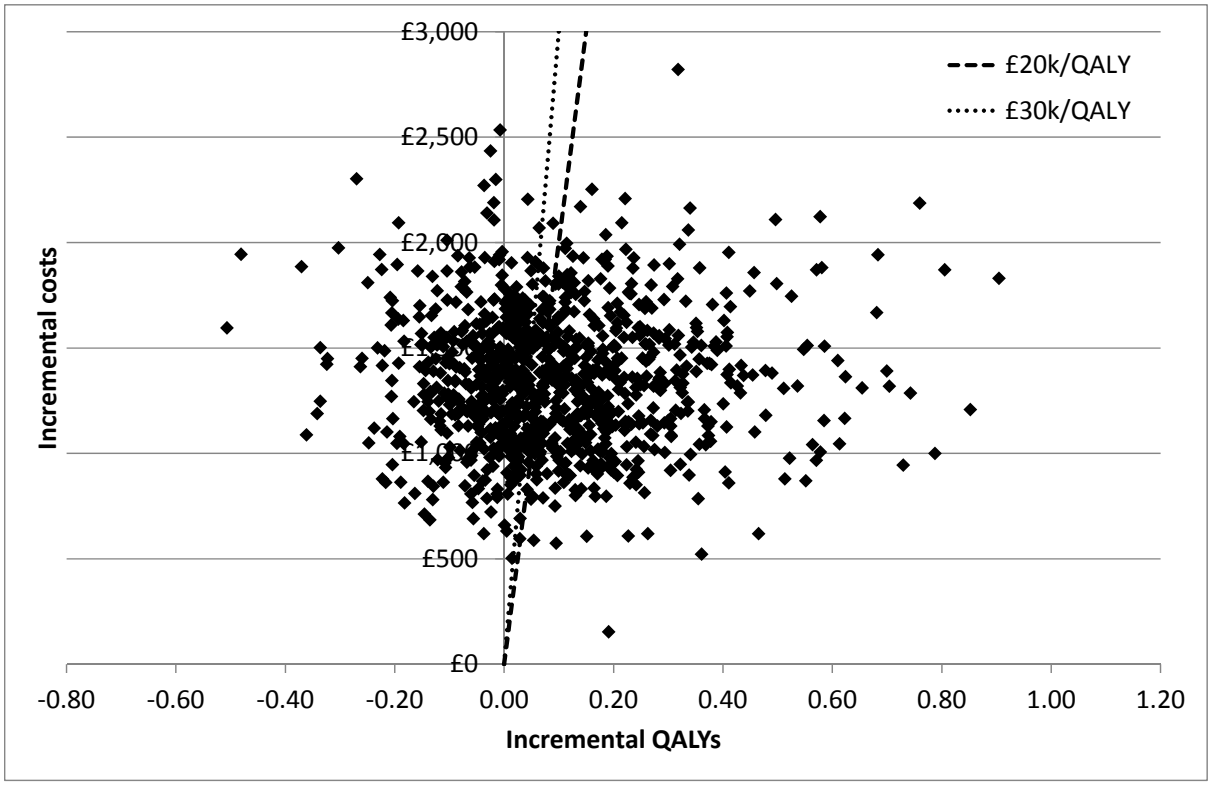
Table 82. Summary base case probabilistic results

Treatment arm	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	Eprex®	**Binocrit®**	**NeoRecormen®**	**Eporatio®**	**Retacrit®**	**Aranesp®**
Deterministic ICER vs no ESA	£21,279	£19,429	£35,018	£21,309	£21,804	£33,233
Mean probabilistic ICER vs no ESA (95% CrI)	**£16,135 (£2,529 – Dtd[a])**	**£14,724 (£2,322 – Dtd[a])**	**£27,226 (£4,067 – Dtd[a])**	**£16,312 (£2,581 – Dtd[a])**	**£16,484 (£2,439 – Dtd[a])**	**£25,684 (£3,841 – Dtd[a])**
Incremental QALYs vs. no ESA (95% CI)	**0.092 (-0.264 – 0.447)**	**0.092 (-0.264 – 0.447)**	**0.092 (-0.264 – 0.447)**	**0.092 (-0.264 – 0.447)**	**0.092 (-0.264 – 0.447)**	**0.092 (-0.264 – 0.447)**
Incremental short term QALYs vs. no ESA (95% CI)	0.014 (0.001 – 0.028)	0.014 (0.001 – 0.028)	0.014 (0.001 – 0.028)	0.014 (0.001 – 0.028)	0.014 (0.001 – 0.028)	0.014 (0.001 – 0.028)
Incremental long term QALYs vs. no ESA (95% CI)	0.077 (-0.278– 0.433)	0.077 (-0.278– 0.433)	0.077 (-0.278– 0.433)	0.077 (-0.278– 0.433)	0.077 (-0.278– 0.433)	0.077 (-0.278– 0.433)
Incremental costs vs. no ESA (95% CI)	**£1,478 (£792 – £2,164)**	**£1,349 (£710 - £1,987)**	**£2,494 (£1,401 - £3,586)**	**£1,494 (£826 - £2,163)**	**£1,510 (£720 - £2,249)**	**£2,353 (£1,327- £3,379)**
Incremental ESA cost vs. no ESA (95% CI)	£1,624 (£986-£2,262)	£1,495 (£908 - £2,082)	£2,640 (£1,588 - £3,693)	£1,641 (£1,005 - £2,277)	£1,656 (£953 - £2,360)	£2,499 (£1,492 - £3,507)
Incremental ESA admin cost vs. no ESA (95% CI)	£97 (£4 - £191)	£97 (£4 - £191)	£97 (£4 - £191)	£97 (£4 - £191)	£97 (£4 - £191)	£97 (£4 - £191)
Incremental AE cost	£37 (£1- £74)	£37 (£1- £74)	£37 (£1- £74)	£37 (£1- £74)	£37 (£1- £74)	£37 (£1- £74)
Incremental RBCT cost vs. no ESA (95% CI)	-£341 (-£556 - -£125)	-£341 (-£556 - -£125)	-£341 (-£556 - -£125)	-£341 (-£556 - -£125)	-£341 (-£556 - -£125)	-£341 (-£556 - -£125)
Cost of additional blood tests vs. no ESA (95% CI)	£60 (£41 - £79)	£60 (£41 - £79)	£60 (£41 - £79)	£60 (£41 - £79)	£60 (£41 - £79)	£60 (£41 - £79)
INHB vs no ESA at WTP £20,000 per QALY (95% CI)	**0.018 (-0.339 – 0.375)**	**0.024 (-0.332– 0.381)**	**-0.033 (-0.392 – -0.326)**	**0.017 (-0.338 – 0.372)**	**0.016 (-0.342 – 0.374)**	**-0.026 (-0.386 – -0.334)**

Key: AE, adverse event; CI, confidence interval; CrI, credible interval; darbe alfa, darbepoetin alfa; Dtd, dominated (more expensive and less QALYs than relevant comparator); ESA, erythropoiesis stmulating agent; ICER, incremental cost effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; RBCT, red blood cell transplantation; WTP, willingness to pay

Notes: a Not applicable as ESA is dominated by no ESA in more than 2.5% of simulations regardless of cost-effectiveness threshold

Figure 47. Probabilistic sensitiyic analysis base case incremental cost and QALYs, scatterplot



Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

To represent the uncertainty further, we plot the simulation results for Binocrit (currently the cheapest of the different ESAs) in Figure 47.

The scatterplot demonstrates that all datapoints fall within the north-west and north-east quadrants, so that none of the simulations resulted in a cost-saving from ESA use. We have summarised the four quadrants and their proportion of data points in 83. From examining the costs results of the model, in 100% of simulations the ESA arm had higher costs for ESA use, reduced costs for RBCTs and in 0.8% of simulations, there was a reduction in costs for adverse events compared to 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 the adverse events does not produce an overall cost saving (the cost saving for ESA in these occurrences is less than £10).

A significant proportion (31.4%) of the datapoints also reflect an estimated loss in QALYs. This suggests the possibility that ESAs may actually reduce QALYs whilst still having an

increased cost. There is always a QALY gain from ESA use in the short term, as the confidence interval for difference in Hb level at end of trial between ESA and no ESA arms never favours no ESA use, and therefore this loss of QALYs is a direct result of the wide confidence interval for the overall survival hazard ratio. The model shows that 36% of simulations have a QALY loss in the long term (as a result of the overall survival HR favouring no ESA over ESA use), and in the majority of these simulations (~87.2%) this is larger than the QALY gain from the short term, resulting in an overall QALY loss. This suggests that the overall survival HR is the primary driver of the QALY results for the simulations.

Table 83. Percentage of probabilistic sensitivity analysis simulations, by cost increase/saving and health loss/gain

	Health loss	Health gain
Cost increase	31.4%	68.6%
Cost saving	0%	0%
Key: PSA, probabilistic sensitivity analysis		

Table 84 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 £20,000 per QALY is 48.1%. Comparing this value to the 31.4% of simulations where ESA use is dominated, we can conclude that the likelihood of ESAs being cost-effective is highly uncertain.

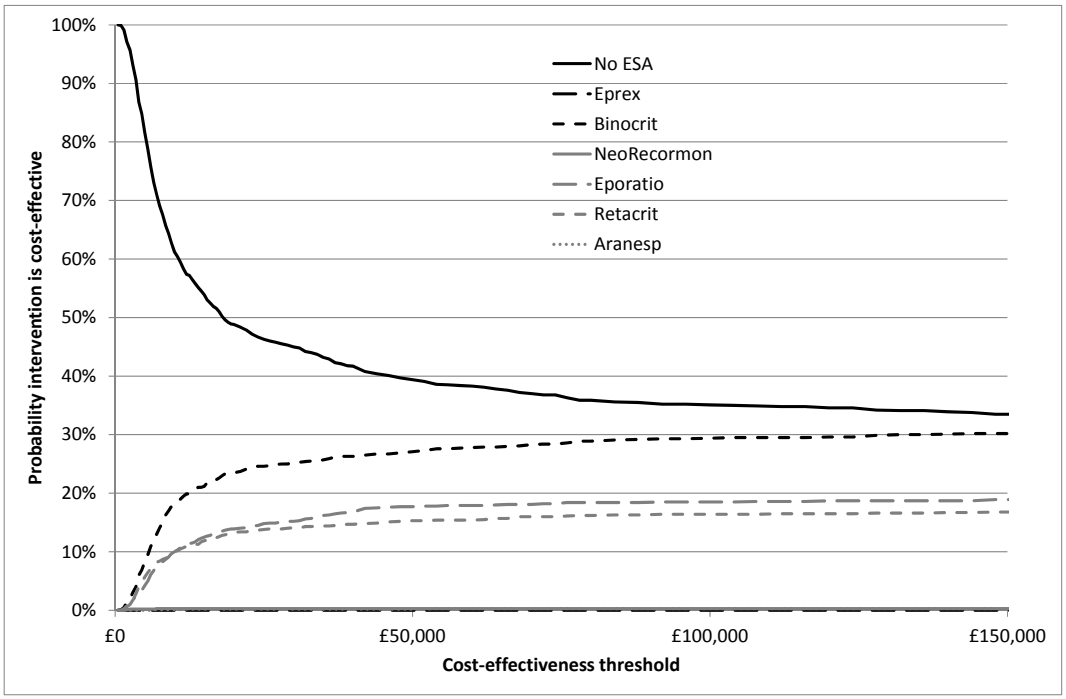
Table 84. Percentage of probabilistic sensitivity analysis simulations where ESA is not cost-effective.

	ESA dominated vs. No ESA	ICERs >£20,000 per QALY vs. no ESA	Total where ESA is not cost-effective (at £20,000 threshold)
Probability	31.4%	19.5%	50.9%
Key: ESA, erythropoiesis stimulating agent; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year			

When we compare the CEACs (cost-effectiveness acceptability curves) of all the ESA strategies, Figure 48, 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 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 increases, such that by a willingness to pay of £20,000 per QALY this falls to below 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 less than 25% probability of being cost-effective. All other ESA arms have a probability of being cost-effective of less than 20% for any willingness to pay threshold less than £150,000 per QALY.

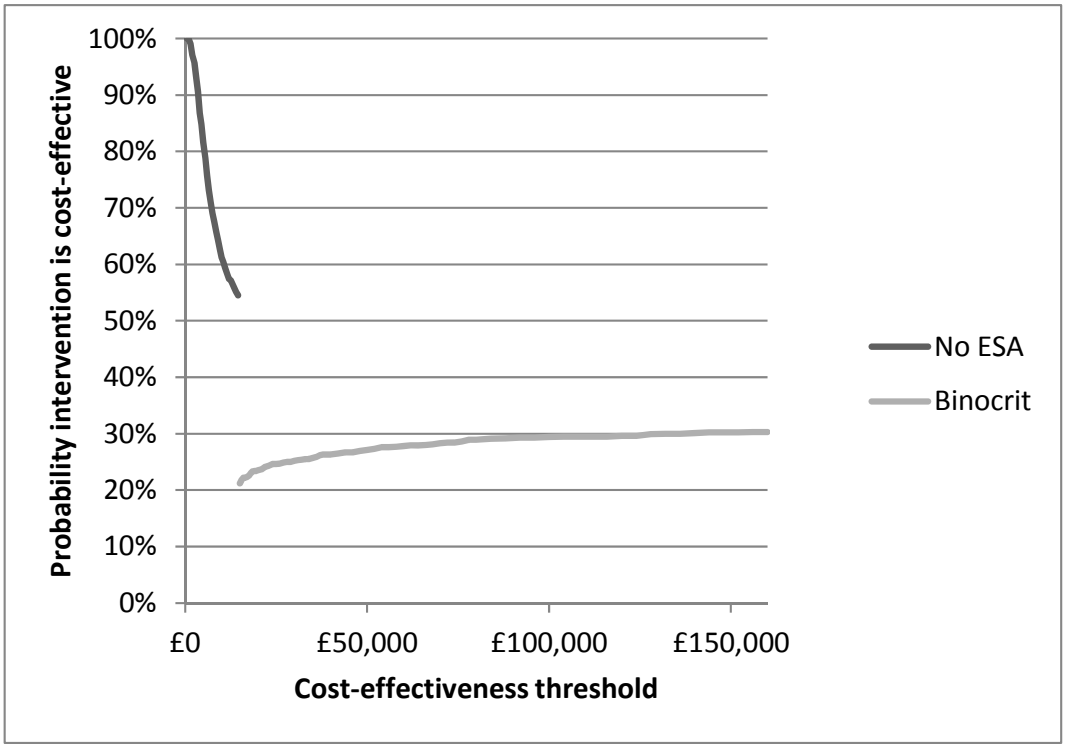
Figure 48. Cost effectiveness acceptability curves from base case probabilistic sensitivity analysis



Key: ESA, erythropoiesis stimulating agent; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

The cost-effectiveness acceptability frontier (CEAF), Figure 49, compares the expected net health benefit of strategies at various willingness to pay thresholds. Given the higher average costs and equal QALY gains of the other ESAs, Binocrit consisitently 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 most net health benefit).

Figure 49. Cost-effectiveness acceptability frontier for probabilistic sensitivity analysis of base case



Key: ESA, erythropoiesis stimulating agent; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

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 potential for ESAs to be cost-effective at a £20,000 per QALY threshold, depending upon their cost, but this is to be viewed with caution, given that there is also the possibility of ESAs producing a survival loss and there is also uncertainty which ESA would be cost-effective.

7.2.3. Scenario analysis 1: Setting overall survival 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 statistical significance of any survival benefit may be disputed, we present the scenario where the overall survival hazard ratio 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 mean weekly cost to establish the cost at

which ESAs become cost-effective; and a probabilistic sensitivity analysis to investigate how removing the long term survival benefit of the model affects the model results.

7.2.3.1. Deterministic analysis (scenario 1)

As this scenario is identical to the base case, but with the long term aspect effectively removed, the costs and short term QALYs of the deterministic analysis are the same as those from the base case, but long term incremental QALYs become equal to 0. This can be demonstrated by comparing Table 85, p325 to Table 79, p312 .

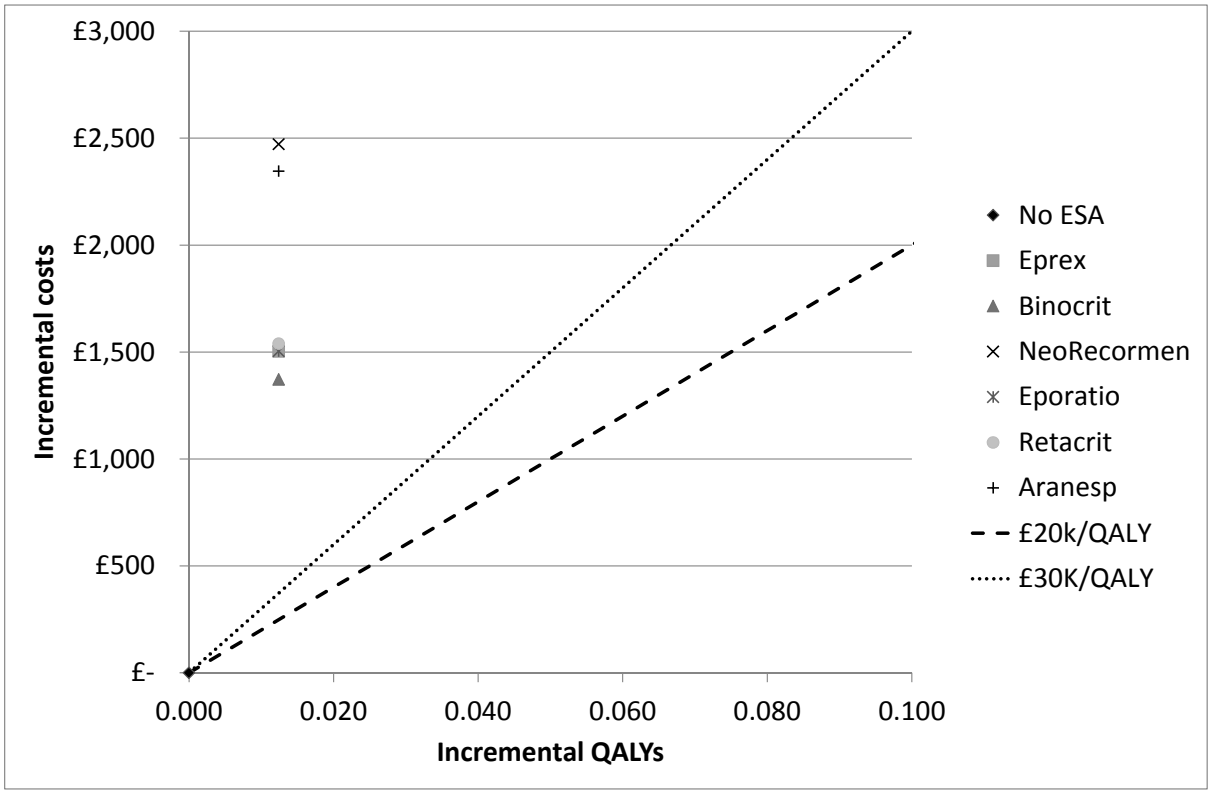
The overall QALY gain is now greatly reduced from 0.0706 in the base case to 0.0124, a reduction of 82%. As the costs have remained the same we see that the ICERs are greatly increased, such that all ESAs have an ICER greater than £110,000 per QALY compared to the non ESA arm. These ICERs lie well above the £30,000 per QALY threshold depicted in Figure 50 (page 326). This therefore suggests that if no survival benefit is assumed, ESAs do not appear to be cost-effective compared to current practice.

Table 85. Summary cost-effectiveness results for scenario analysis 1

Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
		Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Total costs per strategy	£912	£2,414	£2,283	£3,384	£2,416	£2,451	£3,258
Total incremental costs vs. no ESA	–	£1,502	£1,371	£2,472	£1,504	£1,539	£2,346
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® (Sandoz Ltd)	£110,477	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)
INHB vs. no ESA at WTP £20,000/QALY	–	-0.063	-0.056	-0.111	-0.063	-0.065	-0.105
INHB vs. no ESA at WTP £30,000/QALY	–	-0.038	-0.033	-0.070	-0.038	-0.039	-0.066

Key: Darbe alfa, darbepoetin alfa; ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus; WTP, willingness to pay

Figure 50. Incremental costs and QALYs for scenario analysis 1



Key: ESA, erythropoiesis stimulating agent; QALYs, quality-adjusted life years

7.2.3.2. Threshold analysis of ESA costs

As part of this scenario analysis that assumes no impact on overall survival, we considered what ESA cost would bring down the ICERs to below the £20,000 per QALY threshold. As ESA dose cost relies on both unit cost and size of 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, we see that for an ICER to fall below £20,000 per QALY gained in this scenario, the weekly cost of ESAs must fall below £32. Since any alteration in dose would likely affect the effectiveness of ESAs, the only variation to the base case analysis implied by this scenario is a reduction in unit cost of roughly between 75-85%.

[redacted]. An analysis of the wholesale acquisition costs is provided separately in Section 7.2.4 (page 332), but this analysis does indicate that for a certain cost, ESAs may be cost-effective, even without a modelled survival gain.

Table 86. Threshold analysis results for ESA cost per week

Dose cost per week	Total ESA cost	ICER
£30	**£360**	**£17,799**
£31	**£372**	**£18,765**
£32	**£384**	**£19,732**
£33	£396	£20,699
£34	£408	£21,666
£35	£420	£22,632
Min. base case value: £137	£2,283	£110,477
Key: ESA, erythropoiesis stimulating agent; ICER, incremental cost-effectiveness ratio; min., minimum		

7.2.3.3. Probabilistic analysis (scenario analysis 1)

We also perform a PSA on this scenario, to see how uncertain the results remain once the uncertainty around the survival is removed. As the results in Table 87 show, the 95% CIs around the incremental QALYs and INHB are much reduced compared to the base case, suggesting a large component of the uncertainty has been removed by eliminating the uncertainty surrounding overall survival. This is also consistent with no ESA being cost-effective at the highest CE threshold. The lower limit of the 95% credible interval 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.

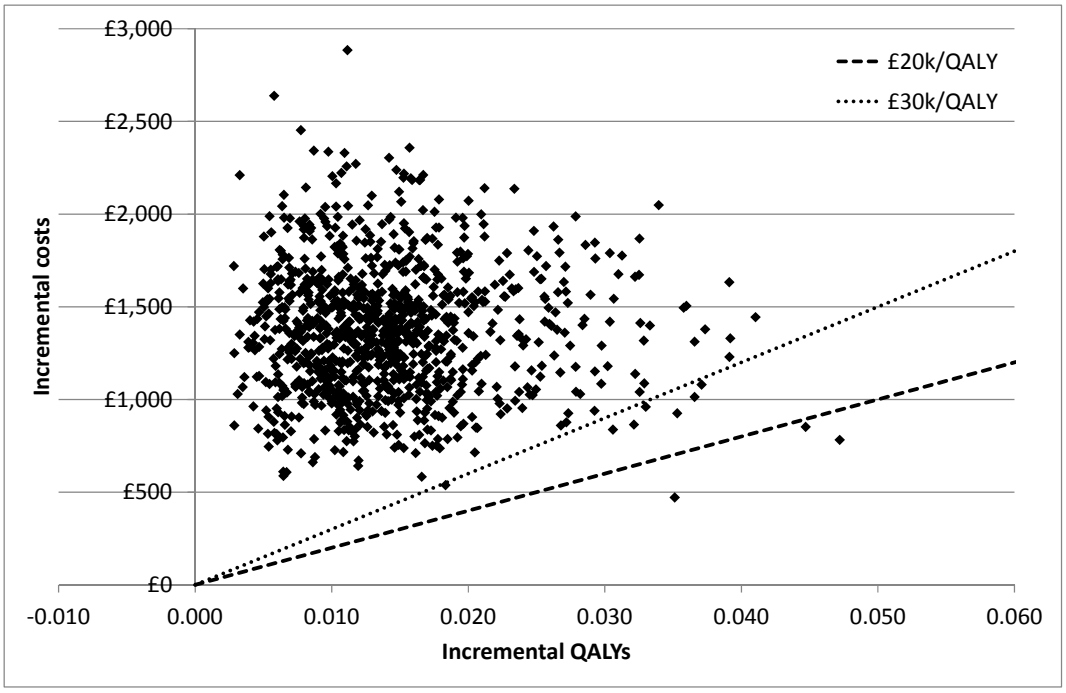
Table 87. Summary PSA results for scenario analysis 1

Treatment arm	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Deterministic ICER vs no ESA	£120,995	£110,477	£199,118	£121,166	£123,983	£188,968
Mean probabilistic ICER vs no ESA (95% CrI)	£106,007 (£40,506 - >£300,000)	£96,754 (£36,897 - >£300,000)	£174,193 (£71,732- >£500,000)	£104,706 (£41,987 - >£300,000)	£106,745 (£40,827 - >£300,000)	£166,848 (£69,324 - >£500,000)
Inc. QALY (95% CI)	0.014 (0.001 – 0.027)	0.014 (0.001 – 0.027)	0.014 (0.001 – 0.027)	0.014 (0.001 – 0.027)	0.014 (0.001 – 0.027)	0.014 (0.001 – 0.027)
Inc. cost (95% CI)	£1,504 (£777 - £2,232)	£1,373 (£695- £2,051)	£2,472 (£1,387 - £3,556)	£1,486 (£816 - £2,156)	£1,515 (£787 - £2,242)	£2,368 (£1,311 - £3,425)
INHB vs no ESA at WTP £20,000 per QALY (95% CI)	-0.061 (-0.100 - -0.022)	-0.054 (-0.091 - -0.018)	-0.109 (-0.165- -0.054)	-0.060 (-0.096 - -0.024)	-0.062 (-0.100 - -0.023)	-0.104 (-0.159 - -0.050)

Key: CI, confidence interval; ESA, erythropoiesis stimulating agent; ICER, incremental cost effectiveness ratio; Inc., incremental; INHB, incremental net health benefit; QALY, quality-adjusted life year
Notes: NB: Results slightly different from base case due to a different simulation being run

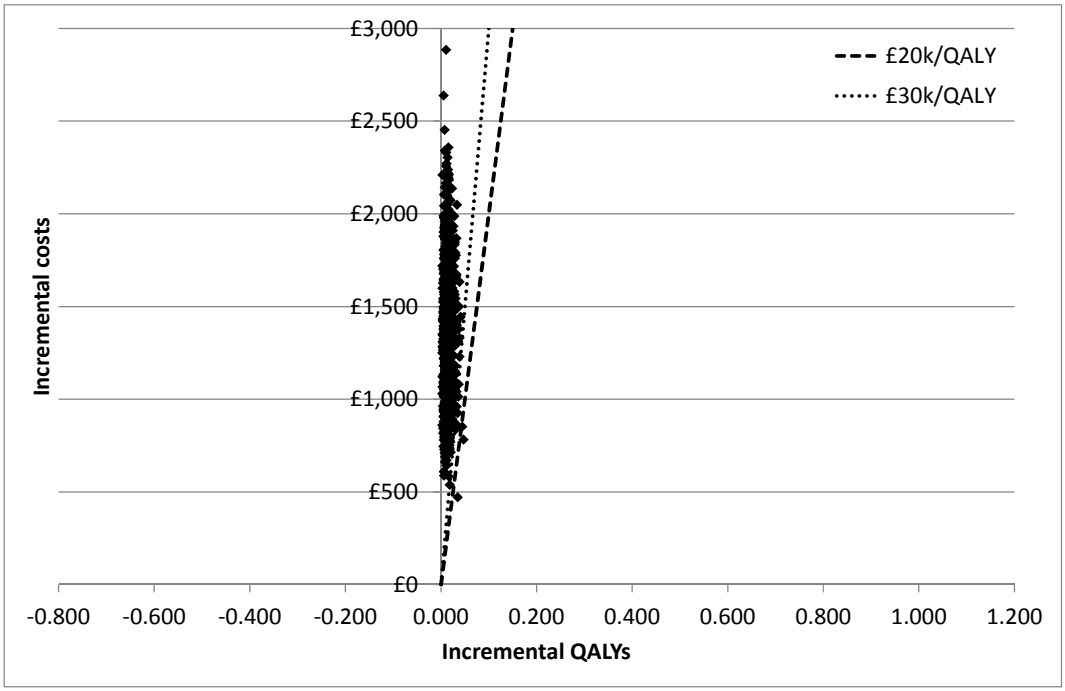
Indeed, when we examine the scatterplot of simulations (Figure 51) we see that the distribution of points along the horizontal axis as greatly reduced, both as there is no longer a QALY loss, nor is the QALY benefit spread across such a wide area. In fact if we consider the scatterplot on the same axes as the base case result (Figure 52), we see a much narrower distribution of QALY estimates. Given the much smaller QALY difference estimates in this case and the same size costs differences from the base case, we find that 99.7% of the data points lie above the £20,000 per QALY threshold.

Figure 51. Incremental costs and QALYs, by probabilistic sensitivity analysis simulation for scenario 1



Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

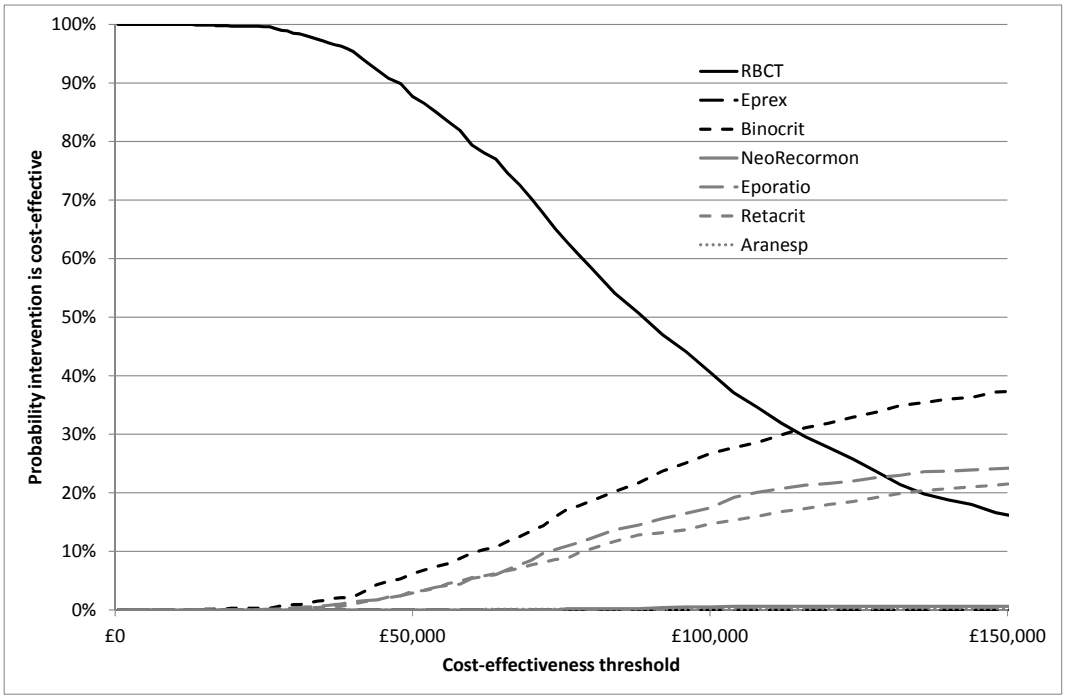
Figure 52. Incremental costs and QALYs, by probabilistic sensitivity analysis simulation for scenario analysis 1 and scaled to axes of base case



Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

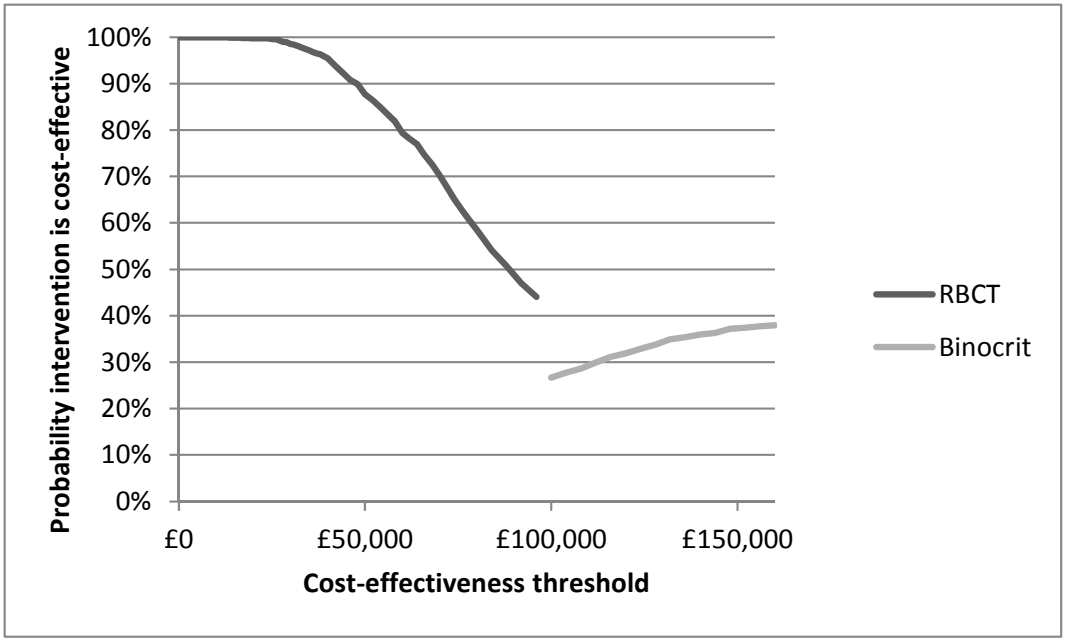
The CEAC for this scenario (Figure 53) demonstrates a much more gradual decline in probability of cost-effectiveness for the no ESA arm, as well as increase in the ESA arms, compared with that of the base case. The ESA arms also begin to converge to a higher probability than in the base case, though this still well below 50%. The CEAF (Figure 54) also demonstrates a much higher willingness to pay threshold, £100,000 per QALY, at which one of ESAs may produce a higher net health benefit compared to the no ESA arm.

Figure 53. Cost effectiveness acceptability curve for scenario analysis 1



Key: CEAC, cost-effectiveness acceptability curve; RBCT, red blood cell transfusion

Figure 54. Cost effectiveness acceptability frontier for scenario analysis 1



Key: CEAF, cost-effectiveness acceptability frontier; RBCT, red blood cell transfusion

The results from this PSA suggest that if ESA use is assumed to have exactly no impact upon survival, then 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.

7.2.4. Scenario analysis 2: Using ESA wholesale acquisition costs

Though we have partly investigated the impact of reducing the cost of ESAs in Scenario 1, we also consider it important to apply the actual costs we have available into the model. To give a complete picture, we apply these costs both in the base case and to Scenario 1, where 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, we omit this from these results.

7.2.4.1. Scenario analysis 2a): application to base case results

As Table 88 shows, all costs in this scenario are greatly reduced compared to the base case and the ICERs range from [redacted] 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. Though the ICERs indicate that the most cost-effective ESA is Retacrit (having the lowest cost), the INHB PSA results indicate that the 95% confidence intervals for INHB overlap for all ESAs, suggesting that the cost-effectiveness of the ESAs is similar.

[redacted]

Table 88. Summary results for scenario analysis 2a), wholesale acquisition costs applied in the base case, deterministic and probabilistic

Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin zeta	Darbe alfa
	–	Eprex®	Binocrit®	NeoRecormen®	Retacrit®	Aranesp®
Deterministic results						
Total costs per strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total incremental costs vs. no ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total discounted QALYs gained vs. no ESA	–	0.0706	0.0706	0.0706	0.0706	0.0706
ICER vs. no ESA (£/QALY)	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results						
Total costs per strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total incremental costs vs. no ESA (95% CI)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total discounted QALYs gained vs. no ESA (95% CI)		0.083 (-0.251 – 0.418)	0.083 (-0.251 – 0.418)	0.083 (-0.251 – 0.418)	0.083 (-0.251 – 0.418)	0.083 (-0.251 – 0.418)
ICER vs. no ESA (£/QALY)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INHB vs. no ESA at WTP £20,000/QALY (95% CI)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; Dtd, dominated (more expensive and less QALYs than relevant comparator); Dts, dominates (less expensive and more QALYs than relevant comparator); ESA, erythropoiesis stimulating agent; ICER, incremental cost effectiveness ratio; Inc., incremental; INHB, incremental net health benefit; QALY, quality-adjusted life year; WTP willingness to pay
Notes: a Not applicable as ESA dominates no ESA in more than 2.5% of simulations regardless of cost-effectiveness threshold, **b** Not applicable as ESA is dominated by no ESA in more than 2.5% of simulations regardless of cost-effectiveness threshold

If we examine the PSA results for the most cost-effective ESA in this scenario (Figure 55), we see that the majority of datapoints lie around the origin. A summary of where the datapoints lie is available in Table 89 and shows that 26.4% of simulations the ESA was dominated by no ESA (cost increase and QALY gain), but in 5% of cases the ESA dominated the no ESA arm (cost saving and QALY gain). In the case where ESA dominates, this occurs when the cost saving from RBCT reduction outweighs the additional costs from ESA use. For a significant proportion of the simulations (37.1%) the cost of ESA (dose and administration) is smaller than the cost saving from RBCT use, but the additional adverse event costs and blood test costs prevent the majority of these simulations from having an overall cost-saving. Therefore, when the unit costs of ESA are reduced, the other potential costs associated with ESA use become more important.

Figure 55. Incremental costs and QALYs, probabilistic sensitivity analysis results for scenario analysis 2a)

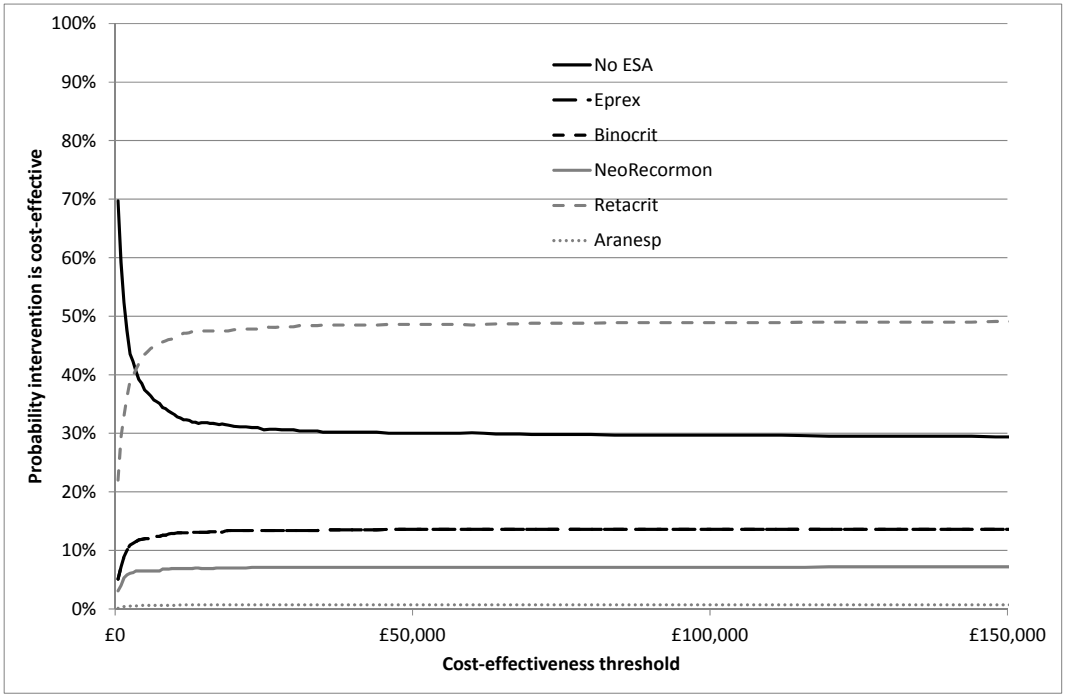
Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Table 89. Percentage of probabilistic sensitivity analysis simulations by cost increase/saving and health loss/gain for scenario analysis 2a) applied to base case

	Health loss	Health gain
Cost increase	26.4%	65.9%
Cost saving	2.7%	5.0%
Key: PSA, probabilistic sensitivity analysis		

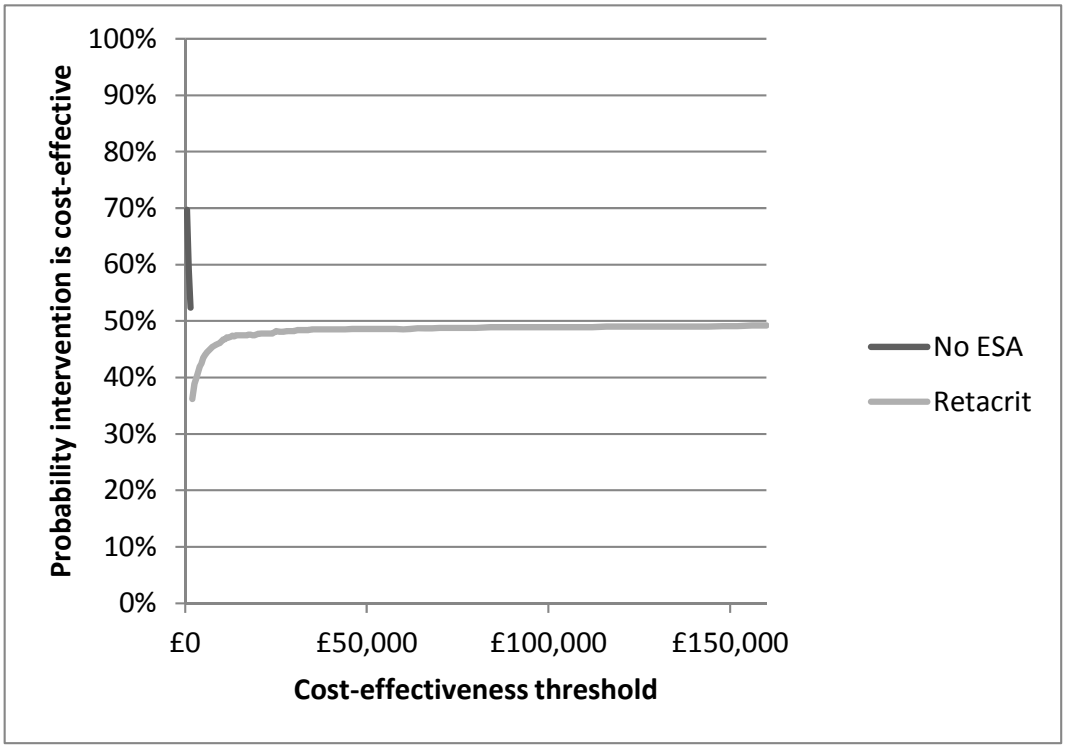
The CEAC for this scenario shows that at a willingness to pay of at least £3,500 per QALY, Retacrit has the highest probability of being cost-effective. Furthermore the probability of no ESA use being cost-effective is greatly reduced for all thresholds and the CEAF demonstrates that the the Retacrit becomes the optimal strategy, at a willingness to pay threshold of £2,000 per QALY.

Figure 56. Cost effectiveness acceptability curve scenario analysis 2a)



Key: CEAC, cost-effectiveness acceptability curve; ESA, erythropoiesis stimulating agent

Figure 57. Cost effectiveness acceptability frontier scenario analysis 2a)



Key: CEAF, cost-effectiveness acceptability frontier; ESA, erythropoiesis stimulating agent

The results of this scenario suggest that the ESAs appear are more cost-effective than in the base case. However, the long term QALYs are still highly uncertain and the reduction of costs has now made the impact of their uncertainty more influential than in the base case. As such the probability of ESAs being cost-effective is still uncertain.

7.2.4.2. Scenario analysis 2b): application to scenario analysis 1 results, no survival benefit

The summary results of the wholesale acquisition costs applied to scenario analysis 1, such that survival is assumed equal for both ESA and no ESA arms, are presented in Table 90. As expected, the ICERs in both the deterministic and 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 less than £20,000 per QALY and there is therefore an indication that at the prices ESAs can be paid for, ESAs could be cost-effective, regardless of survival benefit. However, the upper limit of the 95% credible intervals is still above £30,000 per QALY for all ESAs. It is noted that there is still much crossover in INHB 95% confidence intervals, suggesting that it is difficult to choose between ESAs.

Table 90. Summary results for scenario analysis 2b), wholesale acquisition costs applied with no survival benefit, deterministic and probabilistic

Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin zeta	Darbe alfa
	–	Eprex®	Binocrit®	NeoRecormen®	Retacrit®	Aranesp®
Deterministic results						
Total costs per strategy						
Total incremental costs vs. no ESA						
Total discounted QALYs gained vs. no ESA						
ICER vs. no ESA (£/QALY)						
Probabilistic results						
Total costs per strategy						
Total incremental costs vs. no ESA (95% CI)						
Total discounted QALYs gained vs. no ESA (95% CI)						
ICER vs. no ESA (£/QALY)						
INHB vs. no ESA at WTP £20,000/QALY (95% CI)						

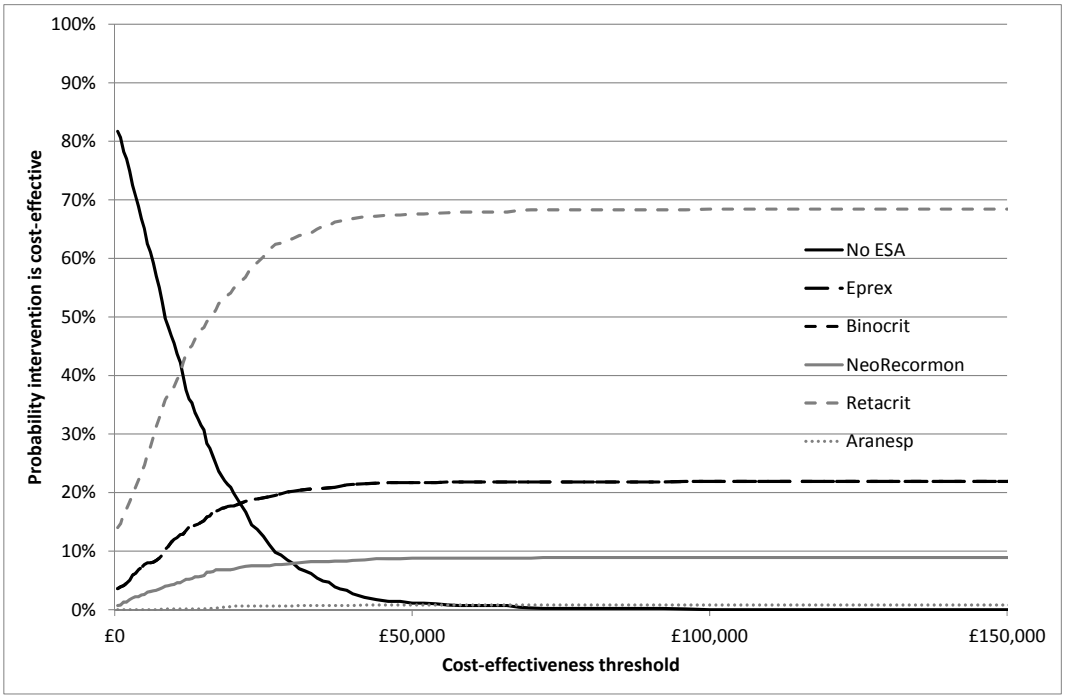
Key: CI, confidence interval; Dts, dominated (less expensive and more QALYs than relevant comparator); ESA, erythropoiesis stimulating agent; ICER, incremental cost effectiveness ratio; Inc., incremental; INHB, incremental net health benefit; QALY, quality-adjusted life year; vs, versus; WTP willingness to pay
Notes: Some results differ between this and Section 7.2.5.1 due to simulation run, **a** Not applicable as ESA dominates no ESA in more than 2.5% of simulations regardless of cost-effectiveness threshold

As with scenario analysis 1, when the survival component is removed from the model, the distribution of datapoints is greatly reduced. In this scenario, 8.2% 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 (dose and administration) is smaller than the cost saving from RBCT use, but the additional adverse event costs and blood test costs prevent the majority of these simulations from having an overall cost-saving. This value is slightly different to the case when wholesale acquisition costs are applied in the base case, due to a different run of the simulations.

Figure 58. Incremental costs and QALYs, probabilistic sensitivity analysis results for scenario analysis 2b), equal survival assumed

Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 59. Cost effectiveness acceptability curve for scenario analysis 2b), equal survival assumed

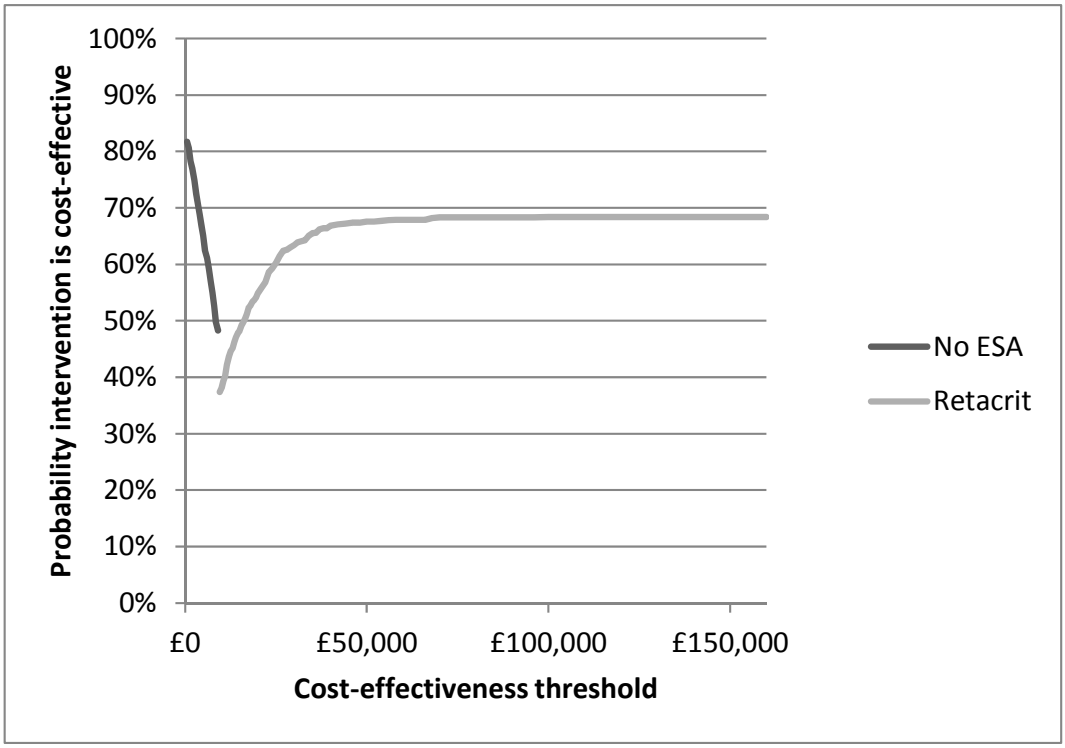


Key: CEAC, cost-effectiveness acceptability curve; ESA, erythropoiesis stimulating agent; QALYs, quality-adjusted life years

The CEAC for this scenario (Figure 59) appears to be quite different from those in the previous scenarios. By a willingness to pay 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 above 50%, higher than in other scenarios.

The CEAF for this scenario indicates the Retacrit is the most optimal choice at a willingness to pay threshold of £9,500 per QALY (Figure 60).

Figure 60. Cost-effectiveness acceptability frontier for scenario analysis 2b), equal survival assumed



Key: ESA, erythropoiesis stimulating agent

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 appear much improved, regardless of whether survival is accounted for in the model. If the survival is assumed equal in both the ESA and no ESA arms then the use of ESA being cost-effective seems plausible, but equally plausible that it is not cost-effective. Even if survival is not assumed equal, there is still a significant proportion of the simulations where a survival disbenefit occurs and as such the possibility of ESAs being dominated by current practice.

7.2.5. Scenario analysis 3: Subgroup of RCTs based on initial Hb level

7.2.5.1. Deterministic analysis (scenario 3)

We next present a scenario analysis that uses only data from RCTs where only patients with Hb level ≤ 11 g/dL are included. This subgroup was used in an attempt to get closer to the licensed indication, whilst maintaining a large enough subgroup of studies to gain estimates for all parameters. Summary estimates are presented in Table 28 (page 154). The input

parameters for this scenario are given in Appendix R and described in Section 7.1 (page 245). One of the main changes in input parameters in this scenario analysis is a higher estimated gain in overall survival due to ESAs (HR reducing from 0.97 [95% CI 0.83–1.13] to 0.91 [95% CI 0.70–1.20])

As Table 91 shows, the incremental cost-effectiveness ratios for the ESA strategies versus 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 limit of the £30,000 per QALY willingness to pay threshold. These results are represented pictorially in Figure 61. As with our base case, the ICERs cover a range around the £20,000 per QALY threshold, so we felt it important that we 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 incremental net health benefit (INHB) compared to no ESA use, the INHB ranges from -0.016 to 0.039 QALYs at a willingness to pay of £20,000 per QALY, and from 0.024 to 0.060 QALYs at a willingness to pay 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 thresholds, and a net health benefit for most ESAs at the £20,000 per QALY threshold.

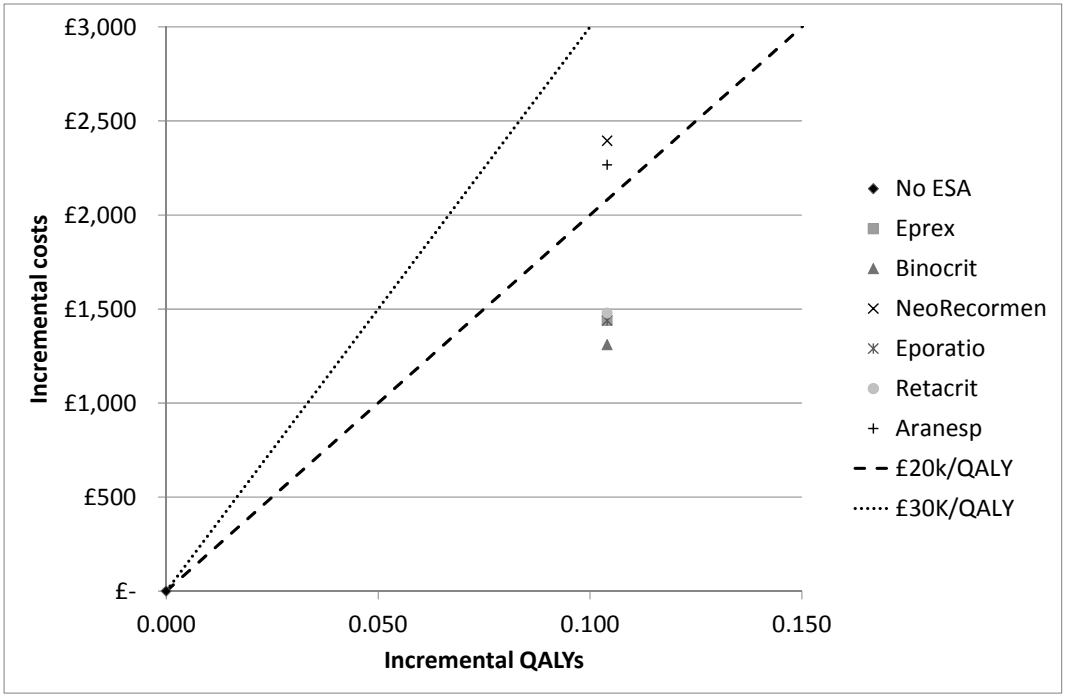
When the ESA strategies are compared to each other, we find that as in the base case they are dominated by the ESA with the lowest total ESA cost (in this case Binocrit® [Sandoz Ltd]). This is mostly expected as the parameters altered from the base case are those relevant to effectiveness, but there are also differences in the mean weekly dose of each ESA compared with the base case.

Table 91. Summary cost-effectiveness results for scenario analysis 3

Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
		Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Total costs per strategy	£956	£2,396	£2,266	£3,350	£2,394	£2,434	£3,222
Total incremental costs vs. no ESA	–	£1,441	£1,310	£2,394	£1,438	£1,478	£2,267
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® (Sandoz Ltd)	£12,593	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)
INHB vs. no ESA at WTP £20,000/QALY	–	0.032	0.039	-0.016	0.032	0.030	-0.009
INHB vs. no ESA at WTP £30,000/QALY	–	0.056	0.060	0.024	0.056	0.055	0.028

Key: Darbe alfa, darbepoetin alfa; ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus; WTP, willingness to pay

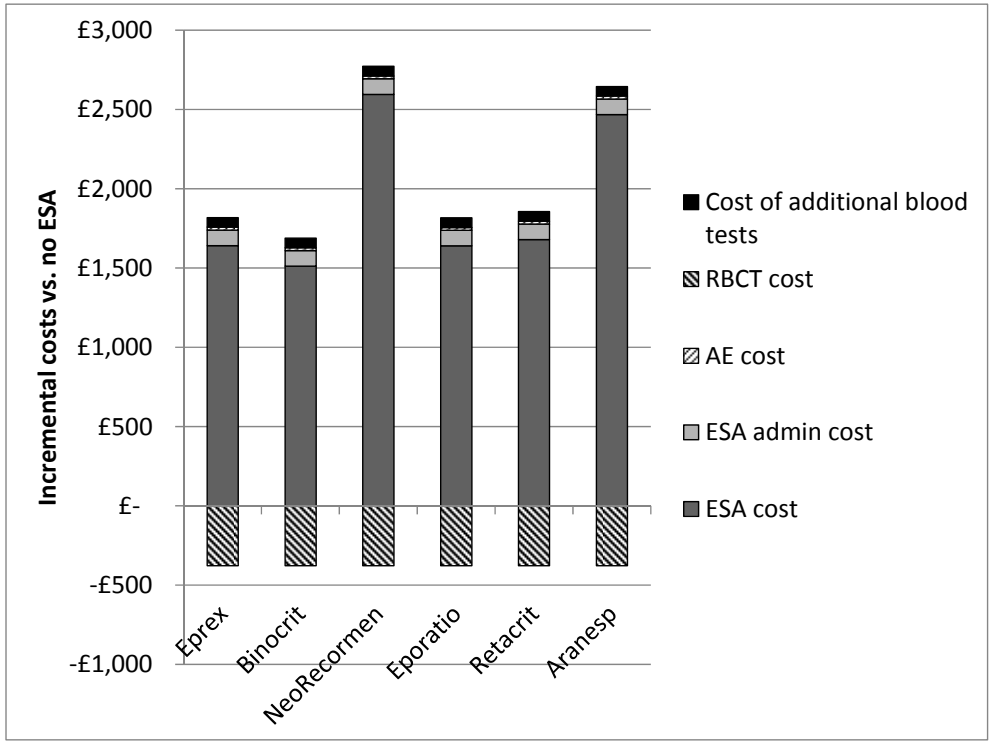
Figure 61. Incremental costs and QALYs for scenario analysis 3



Key: ESA, erythropoiesis stimulating agent; QALYs, quality-adjusted life years

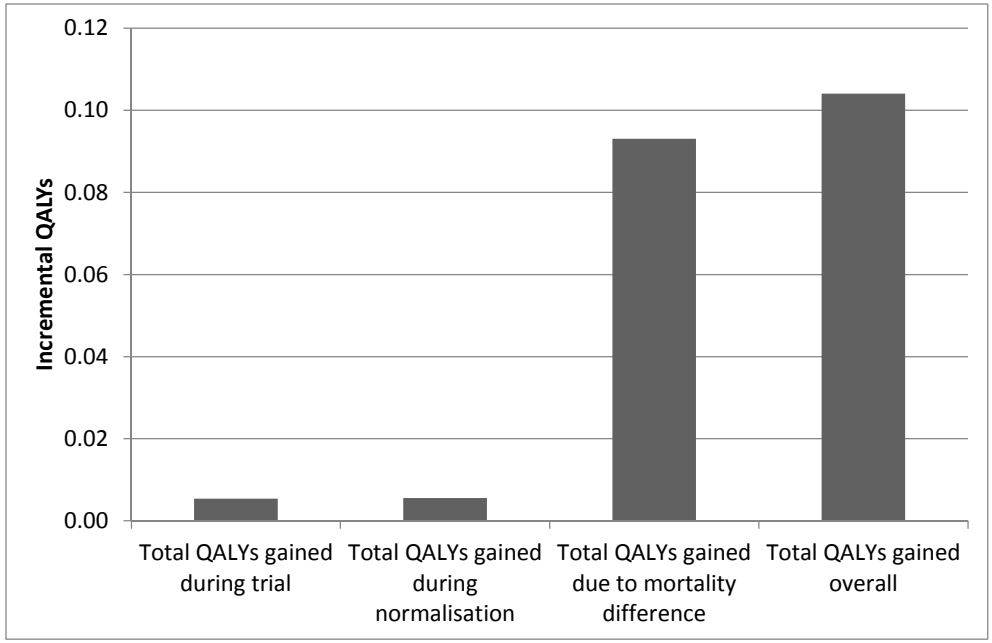
Figure 62 shows that the incremental costs in this scenario are similar to those in the PenTAG base case (Figure 44, page310). The incremental QALYs in the short term are more equal (Figure 63), due to a lower start Hb and longer normalisation period, but are a similar value to those in the base case (0.011 as opposed to 0.012). The total QALYs gained due to the mortality difference is 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 to 0.071 in the base case) and explains why the ICERs appear much reduced.

Figure 62. Incremental costs versus no ESA for scenario analysis 3



Key: AEs, adverse events; ESA, erythropoiesis stimulating agent; RBCT, red blood cell transfusion

Figure 63. Incremental QALYs gained vs no ESA in scenario analysis 3



Key: ESA, erythropoiesis stimulating agent; QALYs, quality-adjusted life years

7.2.5.2. Probabilistic analysis (scenario 3)

We also conducted a PSA for this scenario, to see the effect that limiting the subgroup had on the uncertainty of the results. A summary of the average results is presented in Table 92, where, as in the base case, the average PSA ICERs are slightly less than the estimates from the deterministic results, bu the upper limit of their credible intervals are still dominated by no ESA use.

Figure 64 shows that, compared to 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.

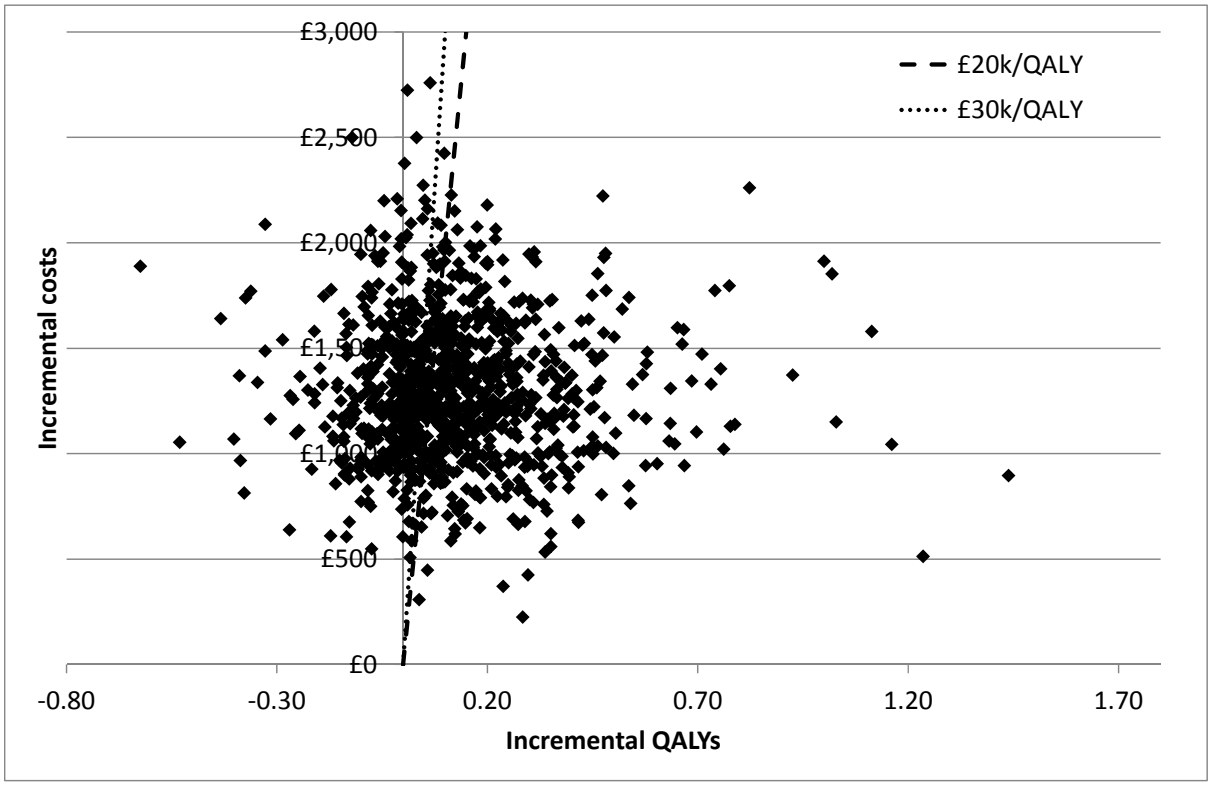
As with the base case, we see that a significant proportion (23.1%) of datapoints incur an increase in cost with a loss in QALYs and another 19.4% have a health gain but are above the £20,000 per QALY threshold. 3.2% of simulations had an overall QALY gain, but a survival disbenefit, with QALYs gained only in the short term. The percentage of simulations where ESAs are within the region of being cost-effective at £20,000 per QALY is 57.5%, which is slightly larger than the base case.

Table 92. Summary results from probabilistic sensitivity analysis of scenario analysis 3

Treatment arm	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Deterministic ICER vs no ESA	£13,849	£12,593	£23,013	£13,826	£14,206	£21,785
Mean probabilistic ICER vs no ESA (95% CrI)	£11,403 (£1,916- Dtd[a])	£10,363 (£1,706 – Dtd[a])	£19,157 (£3,473- Dtd[a])	£11,339 (£1,888 – Dtd[a])	£11,573 (£1,929- Dtd[a])	£17,745 (£3,351 – Dtd[a])
Inc QALY (95% CI)	0.126 (-0.276 – 0.528)	0.126 (-0.276 – 0.528)	0.126 (-0.276 – 0.528)	0.126 (-0.276 – 0.528)	0.126 (-0.276 – 0.528)	0.126 (-0.276 – 0.528)
Inc cost (95% CI)	£1,436 (£701 - - £2,171)	£1,305 (£620- £1,991)	£2,413 (£1,305 – £3,521)	£1,428 (£729 - £2,128)	£1,458 (£722 - £2,193)	£2,235 (£1,193 – £3,277)
INHB vs no ESA at WTP £20,000 per QALY (95% CI)	0.054 (-0.350 – 0.458)	0.061 (-0.343 – 0.465)	0.005 (-0.399 – 0.409)	0.055 (-0.350 – 0.459)	0.053 (-0.352 – 0.458)	0.014 (-0.390 – 0.418)

Key: Darbe alfa, darbepoetin alfa; Dtd, dominated (more expensive and less QALYs than relevant comparator); ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus; WTP, willingness to pay
Notes: a Not applicable as ESA is dominated by no ESA in more than 2.5% of simulations regardless of cost-effectiveness threshold

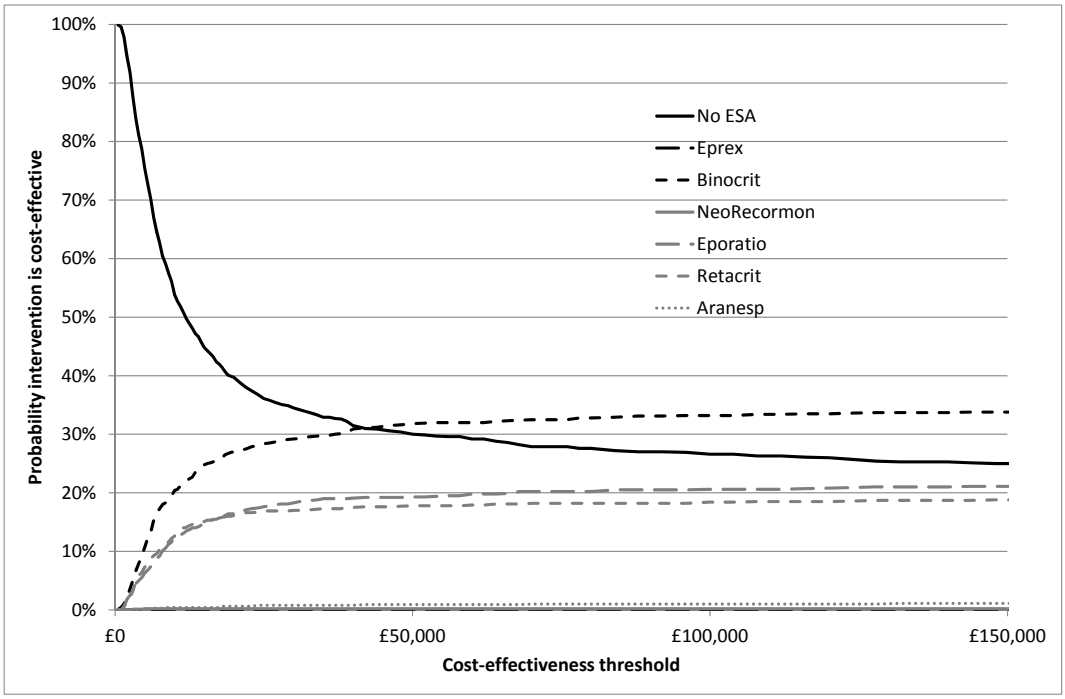
Figure 64. Incremental cost and QALYs of PSA simulations for scenario analysis 3



Key: PSA, probabilistic sensitivity analysis; QALYS, quality-adjusted life years

The CEAC for this PSA (Figure 65) suggests that Binocrit® (Sandoz Ltd) may have a higher probability of being cost-effective compared to no ESA use, at a willingness to pay of £42,000 per QALY, but that this probability if still fairly low (less than 35%). All other ESA arms have a probability of being cost-effective of less than 25% for any willingness to pay threshold less than £150,000 per QALY.

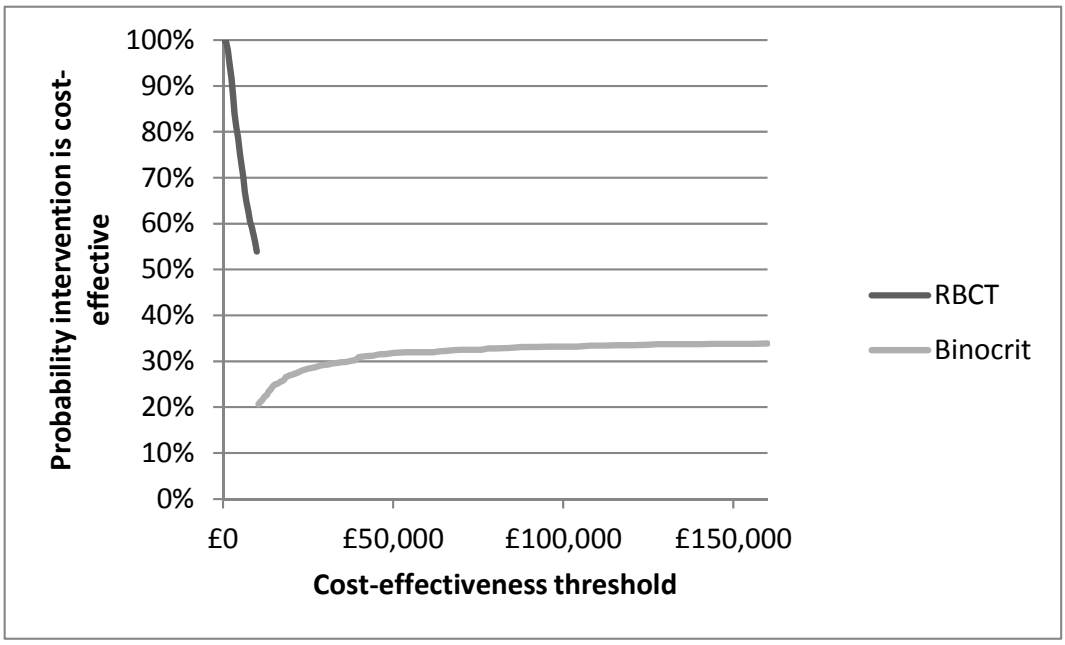
Figure 65. Cost effectiveness acceptability curve for scenario analysis 3



Key: CEAC, cost-effectiveness acceptability curve; ESA, erythropoiesis stimulating agent

The cost-effectiveness acceptability frontier, Figure 66 suggests that at a willingness to pay of at least £10,500 per QALY Binocrit appears to be the most favourable option.

Figure 66. Cost effectiveness acceptability frontier for Scenario analysis 3



Key: CEAF, cost-effectiveness acceptability frontier; ESA, erythropoiesis stimulating agent; RBCT, red blood cell transfusion

The implications of this scenario suggest that ESAs may appear more cost-effective when patients are limited to this subgroup. This could be interpreted as an indication that when ESAs are used within correct licensing, they appear to be more cost-effective. However, the PSA clearly shows that there is still a high level of uncertainty within this subgroup, and as such this should be kept in mind when considering these results. In particular, in 23.1% of the simulations for Binocrit® (Sandoz Ltd), ESA use is dominated, having fewer QALYs and higher costs than no ESA use.

7.2.6. Overall survival scenario analyses

As described in Section 7.1.1.2 (page 249) we perform three scenario analyses exploring the structural assumptions regarding overall survival.

7.2.6.1. Hazard ratio applying only for three years

Overall survival in the base case is estimated for both arms using an exponential distribution, with the overall survival in the control arm estimated by synthesising outcomes from included RCTs and the overall survival in the ESA arm estimated by applying a constant hazard ratio to the survival in the control arm, with the hazard ratio taken from the systematic review of clinical effectiveness evidence. As follow-up is limited for trials we explore the impact of assuming the hazard ratio only applies for the first three years, after which patients in both arms experience the same rate of mortality. Deterministic and probabilistic results are both available in this scenario.

7.2.6.1.1. 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:

- Mean incremental undiscounted life years are estimated at 0.028 years, reduced from 0.091 years in the base case;
- Mean incremental discounted long-term QALYs are estimated at 0.0198, reduced from 0.0582 in the base case;
- 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 three 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 thresholds of £20,000 or £30,000 per QALY (Table 93). Binocrit® (Sandoz Ltd) remains the most cost-effective of the ESAs but its ICER is estimated at £42,584 per QALY.

Table 93. Summary deterministic cost-effectiveness results for scenario analysis in which the OS hazard ratio applies for only three years

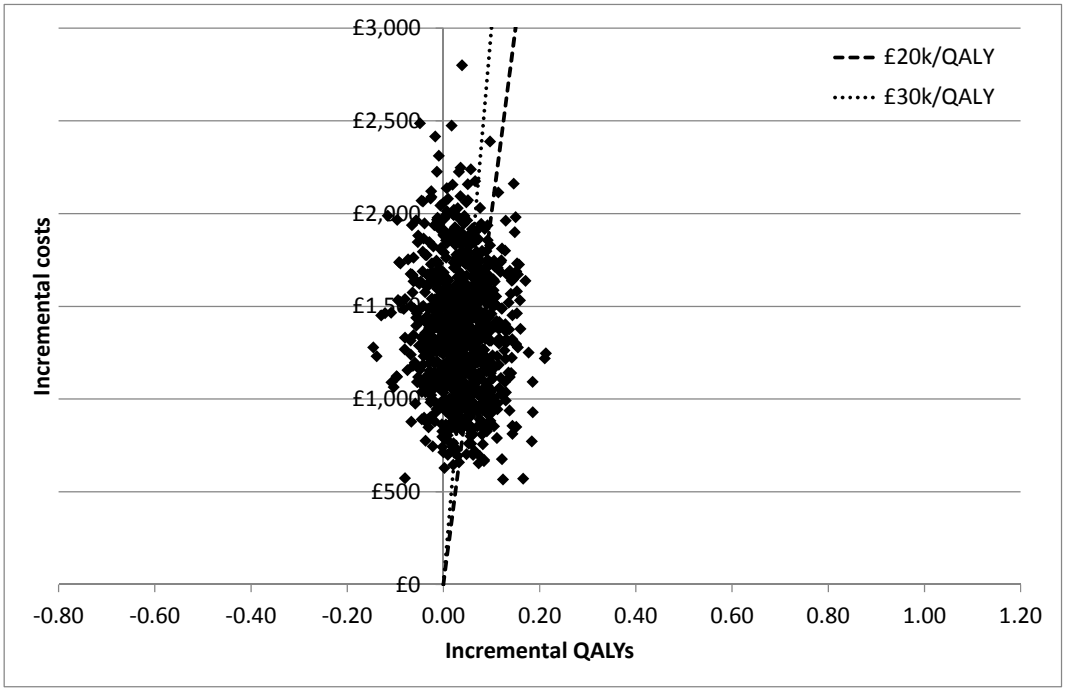
Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	–	Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Total costs per strategy	£912	£2,414	£2,283	£3,384	£2,416	£2,451	£3,258
Total incremental costs vs. no ESA	–	£1,502	£1,371	£2,472	£1,504	£1,539	£2,346
Total 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® (Sandoz Ltd)	£42,584	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)
INHB vs. no ESA at WTP £20,000/QALY	–	-0.043	-0.036	-0.091	-0.043	-0.045	-0.085
INHB vs. no ESA at WTP £30,000/QALY	–	-0.018	-0.014	-0.050	-0.018	-0.019	-0.046

Key: Darbe alfa, darbepoetin alfa; ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus; WTP, willingness to pay

7.2.6.1.2. Probabilistic analysis

The PSA scatter plot for the incremental cost-effectiveness of Binocrit® (Sandoz Ltd) versus no ESA is given in (with the same axis scales as presented in the base case). The scatter plot shows that a considerable amount of uncertainty about the incremental QALYs has been eliminated by assuming a hazard ratio of 1 from three years onwards. Even so, approximately 1 in 4 simulations predicts an overall QALY loss for patients receiving ESA therapy due to adverse impact on overall survival in the first three years (Figure 67).

Figure 67. Incremental costs and QALYs, PSA results for scenario analysis in which the OS hazard ratio applies for only three years



Key: OS, overall survival; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

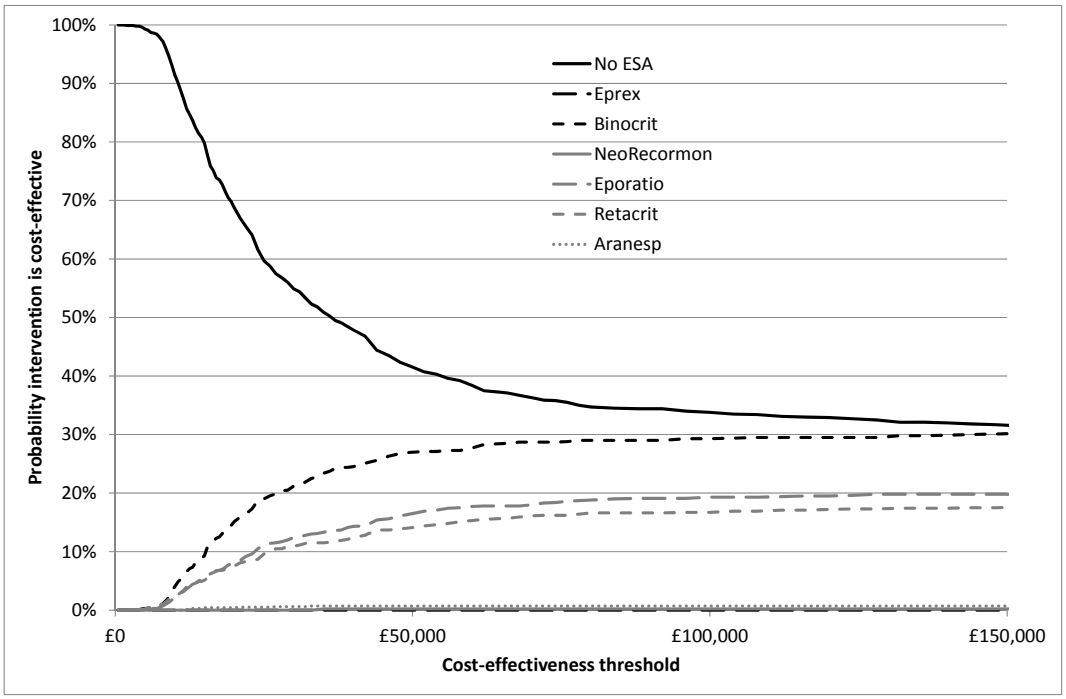
Table 94. Percentage of PSA simulations, by cost increase/saving and health loss/gain

	Health loss	Health gain
Cost increase	24.9%	75.1%
Cost saving	0%	0%
Key: PSA, probabilistic sensitivity analysis		

The summary probabilistic cost-effectiveness results are shown in Table 95 and show that ICERs are not changed significantly from the deterministic results, with the ICER for Binocrit® (Sandoz Ltd) remaining lowest versus no ESA therapy at £39,836 per QALY

Cost-effectiveness acceptability curves and the cost-effectiveness acceptability frontier are given in Figure 68 and Figure 69. The cost-effectiveness acceptability frontier switches from no ESA to Binocrit® (Sandoz Ltd) at WTP ≥ £40,000 per QALY.

Figure 68. CEAC for scenario analysis in which the overall survival hazard ratio applies for only three years



Key: CEAC, cost-effectiveness acceptability curve; ESA, erythropoiesis stimulating agent; OS, overall survival

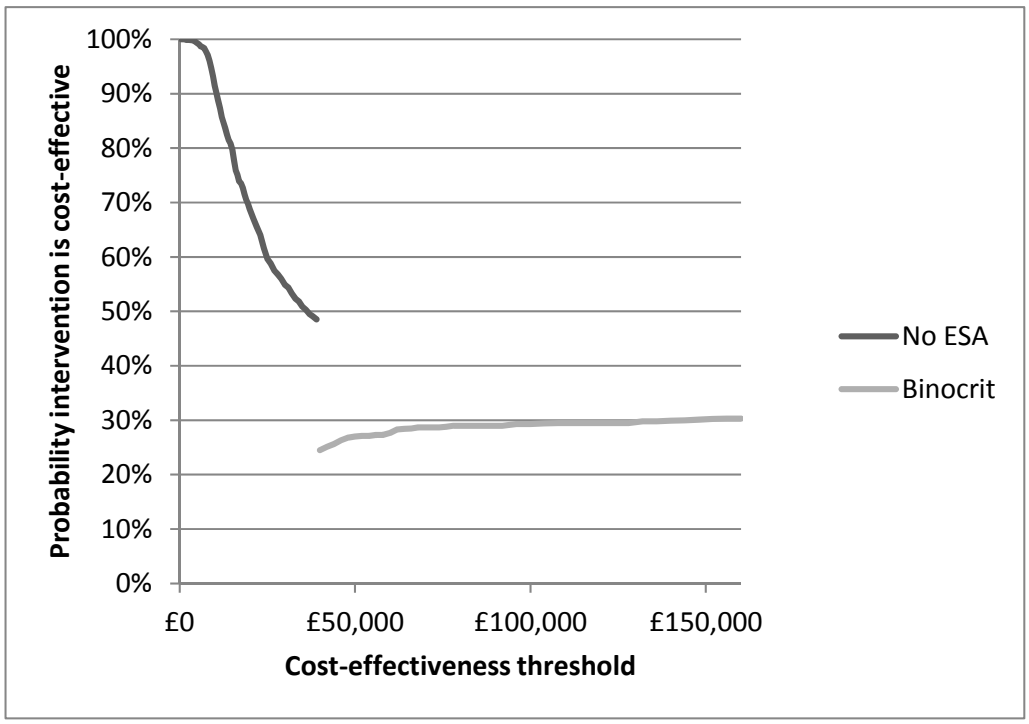
.

Table 95. Summary probabilistic cost-effectiveness results for scenario analysis in which the OS hazard ratio applies for only three years

Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	–	Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Total costs per strategy	£941	£2,440	£2,308	£3,398	£2,436	£2,475	£3,293
Total incremental costs vs. no ESA	–	£1,499	£1,367	£2,457	£1,495	£1,534	£2,352
Total discounted QALYs gained vs. no ESA	–	0.0343	0.0343	0.0343	0.0343	0.0343	0.0343
ICER vs. no ESA (£/QALY)	–	£43,667 (£9,371–Dtd[a])	£39,836 (£8,523–Dtd[a])	£71,589 (£15,002–Dtd[a])	£43,568 (£9,422–Dtd[a])	£44,689 (£8,795–Dtd[a])	£68,532 (£14,287–Dtd[a])
INHB vs. no ESA at WTP £20,000/QALY	–	-0.041	-0.034	-0.089	-0.040	-0.042	-0.083
INHB vs. no ESA at WTP £30,000/QALY	–	-0.016	-0.011	-0.048	-0.016	-0.017	-0.044

Key: Darbe alfa, darbepoetin alfa; Dtd, dominated (more expensive and less QALYs than relevant comparator); ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus; WTP, willingness to pay
Notes: a Not applicable as ESA is dominated by no ESA in more than 2.5% of simulations regardless of cost-effectiveness threshold

Figure 69. Cost-effectiveness acceptability frontier for scenario analysis in which the overall survival hazard ratio applies for only three years



Key: CEAF, cost-effectiveness acceptability frontier; ESA, erythropoiesis stimulating agent; OS, overall survival

7.2.6.2. Weibull curve fitted to Untch and colleagues (2011a,b)

In this scenario the hazard ratio from the systematic review of clinical effectiveness is maintained as in the base case, but the overall survival in the control arm is set to a Weibull distribution fitted to the overall survival in **Untch and colleagues (2011a,b)**.[78] Deterministic and probabilistic results are given for this scenario analysis, although the overall survival in the control arm is not varied in the PSA.

7.2.6.2.1. Deterministic results

The short-term costs and QALYs remain unchanged for both arms. The long-term incremental life years and QALYs are increased:

- Mean incremental undiscounted life years are estimated at 0.156 years, increased from 0.091 years in the base case;
- Mean incremental discounted long-term QALYs are estimated at 0.0807, increased from 0.0582 in the base case;

- 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 threshold of £20,000 per QALY (Table 96). Binocrit® (Sandoz Ltd) remains the most cost-effective of the ESAs with its ICER is estimated at £14,726 per QALY.

Table 96. Summary deterministic cost-effectiveness results for scenario analysis in which control arm overall survival is fitted to Untch and colleagues (2011)[77,78]

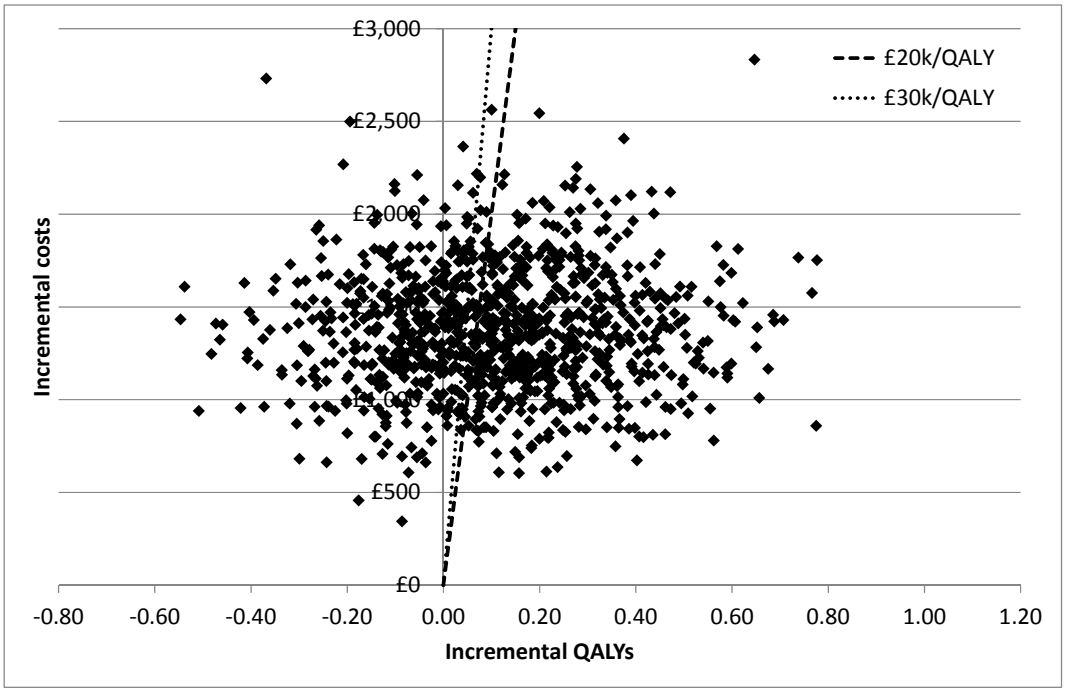
Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	–	Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Total costs per strategy	£912	£2,414	£2,283	£3,384	£2,416	£2,451	£3,258
Total incremental costs vs. no ESA	–	£1,502	£1,371	£2,472	£1,504	£1,539	£2,346
Total 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® (Sandoz Ltd)	£14,726	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)
INHB vs. no ESA at WTP £20,000/QALY	–	0.018	0.025	-0.030	0.018	0.016	-0.024
INHB vs. no ESA at WTP £30,000/QALY	–	0.043	0.047	0.011	0.043	0.042	0.015

Key: Darbe alfa, darbepoetin alfa; Dtd, dominated (more costly and less QALYs than relevant comparator); ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus; WTP, willingness to pay

7.2.6.2.2. Probabilistic analysis

The PSA scatter plot for the incremental cost-effectiveness of Binocrit® (Sandoz Ltd) versus no ESA is given in Figure 70 (with the same axis scales as presented in the base case). The scatter plot shows that a considerable amount of uncertainty about the incremental QALYs has been eliminated by assuming a hazard ratio of 1 from three years onwards. Even so, approximately 1 in 4 simulations predicts an overall QALY loss for patients receiving ESA therapy due to adverse impact on overall survival in the first three years (Table 97).

Figure 70. Incremental costs and QALYs, PSA results for scenario analysis in which control arm overall survival is fitted to Untch and colleagues (2011a,b)[77,78]



Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Table 97. Percentage of PSA simulations, by cost increase/saving and health loss/gain

	Health loss	Health gain
Cost increase	30.7%	69.3%
Cost saving	0%	0%
Key: PSA, probabilistic sensitivity analysis		

The summary probabilistic cost-effectiveness results are shown in Table 98 and show that ICERs are not changed significantly from the deterministic results, with the ICER for Binocrit® (Sandoz Ltd) remaining lowest versus no ESA therapy at £12,649 per QALY.

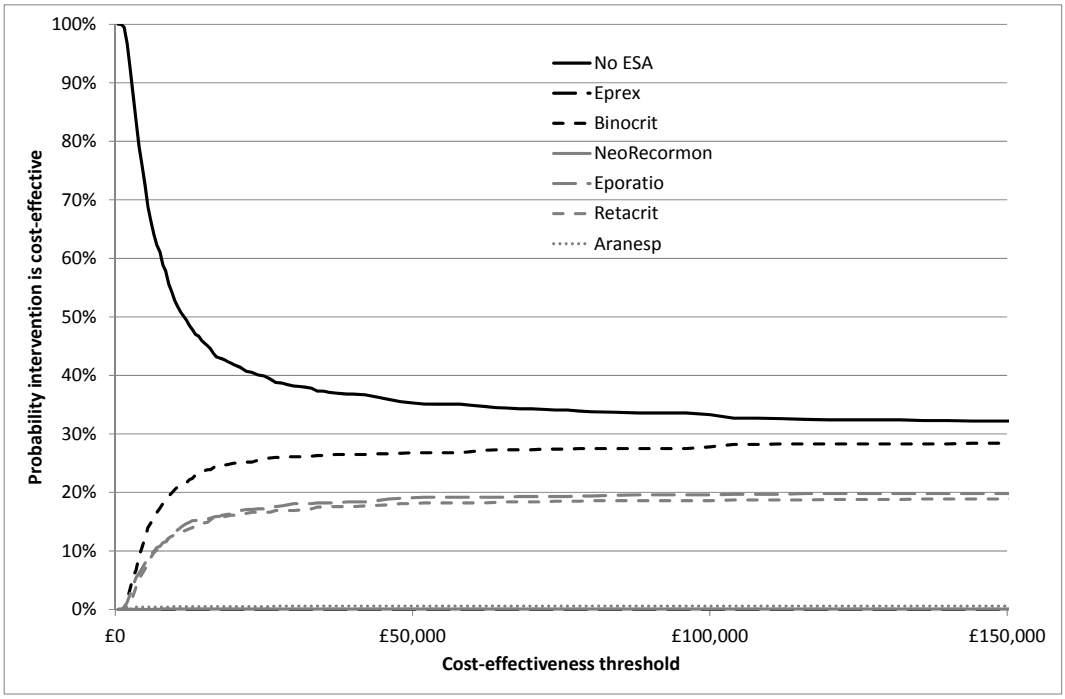
Table 98. Summary probabilistic cost-effectiveness results for scenario analysis in which control arm overall survival is fitted to Untch and colleagues (2011a,b) [77,78]

Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	–	Eprex®	Binocrit®	NeoRecormen®	Eporatio®	Retacrit®	Aranesp®
Total costs per strategy	£932	£2,438	£2,307	£3,379	£2,428	£2,471	£3,279
Total incremental costs vs. no ESA	–	£1,506	£1,375	£2,447	£1,496	£1,539	£2,347
Total discounted QALYs gained vs. no ESA	–	0.1087	0.1087	0.1087	0.1087	0.1087	0.1087
ICER vs. no ESA (£/QALY)	–	£13,857 (£2,297, Dtd)	£12,649 (£2,091, Dtd)	£22,516 (£4,004, Dtd)	£13,767 (£2,243, Dtd)	£14,160 (£2,319, Dtd)	£21,590 (£3,573, Dtd)
INHB vs. no ESA at WTP £20,000/QALY	–	0.033 (−0.400, 0.467)	0.040 (−0.393, 0.473)	−0.014 (−0.449, 0.422)	0.034 (−0.402, 0.470)	0.032 (−0.405, 0.468)	−0.009 (−0.447, 0.429)
INHB vs. no ESA at WTP £30,000/QALY	–	0.058 (−0.374, 0.491)	0.063 (−0.370, 0.496)	0.027 (−0.407, 0.461)	0.059 (−0.376, 0.494)	0.057 (−0.378, 0.492)	0.030 (−0.405, 0.466)

Key: Darbe alfa, darbepoetin alfa; Dtd, dominated; ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus; WTP, willingness to pay

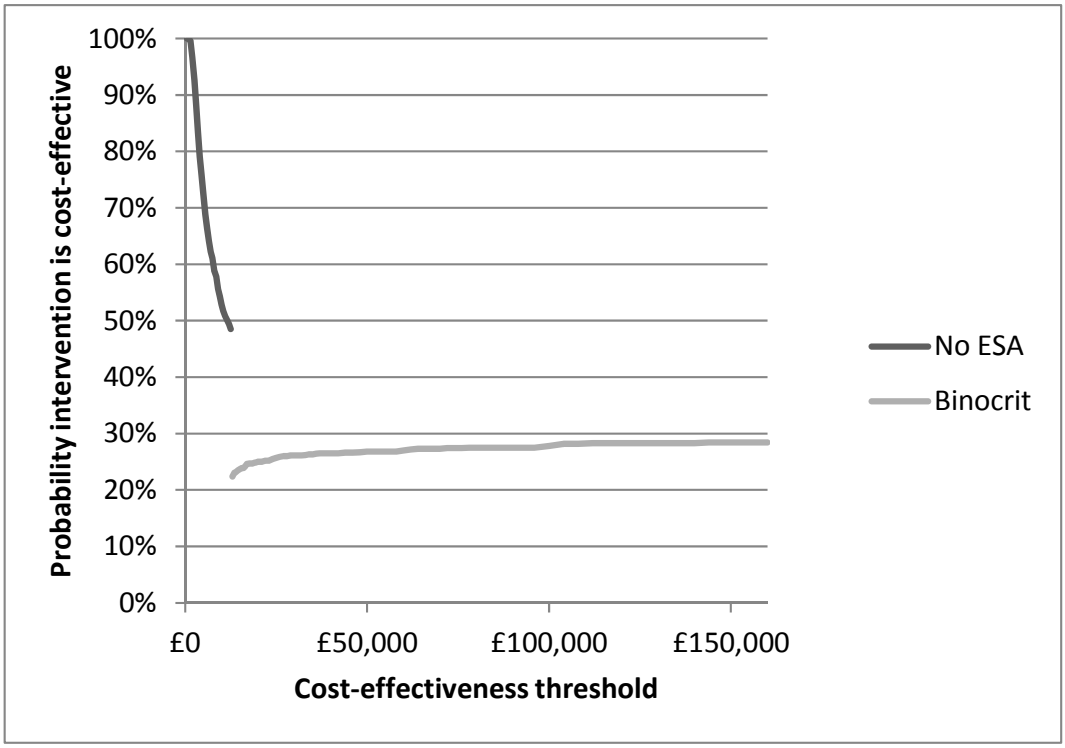
Cost-effectiveness acceptability curves and the cost-effectiveness acceptability frontier are given in Figure 71 and Figure 72. The cost-effectiveness acceptability frontier switches from no ESA to Binocrit at WTP ≥ £13,000 per QALY. It is notable that no ESA is cost-effective in more simulations than any of the ESAs at cost-effectiveness thresholds up to £150,000 per QALY.

Figure 71. Cost effectiveness acceptability curve for scenario analysis in which control arm overall survival is fitted to Untch and colleagues (2011a,b)[77,78]



Key: CEAC, cost-effectiveness acceptability curve; ESA, erythropoesis stimulating agent

Figure 72. Cost-effectiveness acceptability frontier for scenario analysis in which control arm overall survival is fitted to Untch and colleagues (2011a,b)



Key: CEAF, cost-effectiveness acceptability frontier; ESA, erythropoiesis stimulating agent

7.2.6.3. Log-normal curves fitted to Littlewood and colleagues (2001)

Kaplan–Meier curves from **Littlewood and colleagues (2001)**[68] suggest that neither exponential nor Weibull curves would fit overall survival 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 hazard ratio 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 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 overall survival 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:

- Mean incremental undiscounted life years are estimated at 0.471 years, increased from 0.091 years in the base case;
- Mean incremental discounted long-term QALYs are estimated at 0.3087, increased from 0.0582 in the base case;
- 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 99). Binocrit remains the most cost-effective of the ESAs with its ICER is estimated at £4,271 per QALY.

It is worth noting that Littlewood and colleagues (2001) is just one study out of a number of studies to which we could have fitted overall survival curves, including two (**Grote and colleagues, 2005**[73]; **Untch and colleagues, 2011**[78]) suggesting a survival disbenefit from ESA use (though not statistically significant) and two (**Osterborg and colleagues, 2005**[70]; **Moebus and colleagues, 2013**[62]) showing 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 assumptions about overall survival have on cost-effectiveness.

Table 99. Summary deterministic cost-effectiveness results for scenario analysis in which overall survival curves are fitted to Littlewood and colleagues (2001)[68]

Treatment arm	No ESA –	Epoetin alfa Eprex®	 Binocrit®	Epoetin beta NeoRecormen®	Epoetin theta Eporatio®	Epoetin zeta Retacrit®	Darbe alfa Aranesp®
Total costs per strategy	£912	£2,414	£2,283	£3,384	£2,416	£2,451	£3,258
Total incremental costs vs. no ESA	–	£1,502	£1,371	£2,472	£1,504	£1,539	£2,346
Total discounted QALYs gained vs. no ESA	–	0.3211	0.3211	0.3211	0.3211	0.3211	0.3211
ICER vs. no ESA (£/QALY)	–	£4,678	£4,271	£7,698	£4,684	£4,793	£7,306
ICER (£/QALY)	–	Dominated by Binocrit® (Sandoz Ltd)	£4,271	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)
INHB vs. no ESA at WTP £20,000/QALY	–	0.246	0.253	0.197	0.246	0.244	0.204
INHB vs. no ESA at WTP £30,000/QALY	–	0.271	0.275	0.239	0.271	0.270	0.243

Key: Darbe alfa, darbepoetin alfa; ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus; WTP, willingness to pay

7.2.7. Univariate sensitivity analysis

As the scenario analyses examine in depth the impact of the ESA cost and the overall survival, 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 are given in Table 100.

Table 100. Summary results for univariate sensitivity analysis

Parameter	Value in base case	Sensitivity analysis alternative values	ICERs vs. no ESA					
			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/yr	£42,877	£41,027	£56,616	£42,907	£43,402	£54,831
Utility associated with Hb level increase of 1g/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	1 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/wk	£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] & 16.3%[b] nurse; 40.6% self administer	25% nurse, 75% self administer	£20,519	£18,669	£34,258	£20,549	£21,045	£32,473
RBCT appointment costs	£688	£344 appt	£22,849	£20,999	£36,588	£22,879	£23,375	£34,803
		£1,376	£18,138	£16,288	£31,877	£18,168	£18,663	£30,092
Adverse event costs								
Thromboembolic event	£1,243	£621	£21,144	£19,294	£34,883	£21,174	£21,670	£33,098
		£2,486	£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
		£1,652	£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
		£1,488	£21,231	£19,381	£34,970	£21,261	£21,757	£33,185
Duration of ESA treatment	12 wks	24 wks	£41,108	£37,796	£65,710	£41,162	£42,049	£62,514
		24 wks with wholesale acq costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: acq, acquisition; appt, appointment; DA, darbepoetin alfa; EA, epoetin alda; EB, epoetin beta; EZ, epoetin zeta; ESA, erythropoiesis stimulating agent(s); Hb, haemoglobin; ICER, incremental cost effectiveness ratio; QW once per week; Q3W, once every three weeks; RBCT, red blood cell transfusion; TIW, thrice weekly; wks, weeks; yr, year
Notes: (a) GP or District; **(b)** Nurse at chemotherapy appointment

7.2.7.1. Long term costs

As discussed in Section 7.1 (page 245), 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 and to set an equal annual cost to 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 above £30,000 per QALY gained.

7.2.7.2. Utility associated with Hb level increase of 1g/dL

There was a range of values available for the utility associated with Hb level that were investigated in the methods section. PenTAG's chosen base case value was based on a cancer population and 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 Wilson value are (0.060) are used as alternatives.

As the model is quite sensitive to changes in the QALYs, by reducing the utility to 0.009 or 0.016, the ICERs of the ESAs increase, such that they all lie above the £20,000 per QALY threshold, with the most cost-effective ICERs calculated at £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 TA142 model, increase the short term QALY gain to 0.027 QALYs and reduces the ICERs such that all ESAs have an ICER below £30,000 per QALY compared to no ESA.

7.2.7.3. ESA dosing schedule

The licenced 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 with both what licensing allows and what occurred most frequently in the RCTs. However, previous assessments, including TA142, assumed that doses would be given three times a week. As such we explore the alternative dosing schedules for each of the ESAs, as applicable.

Darbepoetin alfa has the option of being given once every three weeks, reducing its total administration cost to £33, from £98. 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. As none of the other ESAs were affected, their ICERs remained the same as the base case

Epoetins alfa and zeta can be given three times a week, increasing their total administration cost to £294. In the scenario where epoetin alfa is increased to a three times a week schedule and the other ESAs 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).

Epoetin beta can be given either once weekly or have the dose divided and administered 3-7 times per week. This dosing schedule gives ICERs 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 a 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 cost-effective at this threshold.

Though this sensitivity analysis demonstrates the impact of changes to the administration costs, it is possible that when the dosing schedule is altered in practice, then 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.

7.2.7.4. ESA administration

As was dicussed in Section 7.1 (page 245) who administers ESAs is not entirely agreed by clincians. This may be due to many factors, 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 examine the possibility that ESAs would be given on a schedule closer to that of CKD patients, 25% of the time by a nurse and 75% of the time self-administering. If this approach was adopted for cancer patients, the overall cost of ESA administration

reduces to £44 and the ICERs for all ESAs are reduced such that in particular Eprex and Eporatio have ICERs of £20,500 per QALY gained (rounded to the nearest hundred), very close to the £20,000 per QALY threshold.

7.2.7.5. Red blood cell transfusion appointment costs

The cost of the transfusion appointment was taken from a very old source and uprated to 2014/15 prices. As such the true cost may vary considerably. Therefore this sensitivity analysis attempts to investigate the impact that altering the cost of RBCT has, by halving and then doubling the cost a transfusion appointment.

When the cost of an RBCT transfusion appointment is halved to £344, the ICERs for the ESAs compared to no ESA increase by around £1,500 each, such that all lie 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 RBCT costs are doubled to £1,376, the cost saving between ESA and no ESA arms increases and the ICERs are reduced, such that four of the ESAs lie below the £20,000 per QALY ICER.

It is therefore shown that the cost of an RBCT appointment can have an effect on the ICER, particularly if in the base case they are close to a willingness to pay threshold.

7.2.7.6. Adverse event costs

Another cost parameter for which limited data were found in the base case was that of the adverse events and as such this sensitivity analysis investigates the impact of changing these costs. As with the RBCT costs, they are halved and doubled to demonstrate the impact, rather than to demonstrate alternative values.

The results in Table 100 (page 366) show that altering individual adverse events cost has very little impact on the overall cost-effectiveness, 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 to the other adverse events, with a reduction in cost of thrombocytopenia causing an increase in the ICERs for the ESAs versus no ESA use.

The reason that the adverse events cost appears to have such a small impact is due to how similar the costs are for both patients in the ESA and no ESA arms. This is primarily driven by the lack of information on the number of each type of adverse event that occur in each

arm and the severity of the adverse events, as both are likely to affect the overall cost of the adverse event. In the model the arms are assumed to have the same level of severity and the number of adverse events is only set to cost for one instance of any individual adverse event, rather than multiple instances. As such further information would be required to properly evaluate the effect of a change in adverse event costs on the overall results.Duration of ESA treatment

Another parameter that varied quite substantially in the RCTs was the duration of the ESA therapy. As such we assess the impact of increasing the duration to 24 weeks, as described in the Section 7.1 (page 245).

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 ESAs versus no ESA use are greatly increased when the treatment duration increases. All ICERs lie above the £30,000 per QALY threshold, with the lowest ICER at £7,796 per QALY versus no ESA use.

Of note, when the ESA costs are reduced to that of their wholesale wholesale acquisition costs, the ICERs all fall below £13,000 per QALY.

7.2.8. Comparison with Wilson and colleagues (2007; TA142)

As we are conducting an update of the **Wilson and colleagues (2007)** HTA review, we attempt to compare our results to those previously reported. Table 101 demonstrates that there is a large difference between the most cost-effective ESA in the PenTAG base case and the base case reported in TA142: with ICERs of £19,429 and £150,342 per QALY respectively.

To attempt to account for these differences, we have adjusted the PenTAG model to incorporate parameters used in the TA142 report. Parameters 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, overall survival hazard ratio, ESA weekly cost (dose and administration), transfusion costs and probabilities, adverse event costs and probability, and ESA duration.The values for these parameters are reported in Appendix R.

Preferably we would have updated the TA142 model to match our parameters, but no model copy was available. We have attempted to discover whether the differences in the results are primarily due to model structure or due to the updated parameters. To make the results of our adjusted model comparable, costs are kept as reported in the TA142 monograph.

Unfortunately, as only limited outputs were reported in **Wilson and colleagues (2007)**, 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. One specific example of this is the mean difference in Hb levels between treatment arms as a proportion of difference at end of trial, which as a parameter in our model identifies when the benefit to 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 101. Comparison of base case results between PenTAG and TA142

	PenTAG base case (Binocrit)	TA142 base case	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 QALY, ESA vs no ESA	0.071	0.030	0.059
Incremental cost, ESA vs no ESA	£1,371	£4,450	£6,448
ICER, ESA vs no ESA	£19,429	£150,342	£109,055

Key: ESA, erythropoiesis stimulating agent; QALY, quality-adjusted life year
Notes: Costs of TA142 and adjusted PenTAG model are given at TA142 prices, but PenTAG base case is reported for 21014/15 prices

Table 101 shows, that when the PenTAG model is adapted to use parameters reported in TA142, the ICER rises to £110,680 per QALY gained, a value much closer to 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 that reported in TA142. We believe this is mostly the result of not being able to substitute all the parameters from TA142 into the PenTAG model or having to use parameters from the TA142 model in a different manner than 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, as an average value could not be calculated, which would result in both higher costs and 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, but the Wilson model approaches this mechanistically, adjusting the dose depending on the health state. Unfortunately, no information on the size of initial dose was reported in the TA142 model and therefore we do not know what size dose the cost is equivalent to. Comparing our weekly ESA dose cost (£126–£218) to 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 the TA142, which is partly due to a change in the unit cost, but would primarily be due to the difference in size of the dose.

As previously discussed, one parameter that greatly affects the QALY gains in the short term of the PenTAG model, but was not available from the TA142 monograph is the mean difference in Hb levels between treatment arms as a proportion of difference at end of trial. The larger this value is, the larger the benefits of ESA 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 in Table 102, p372. 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 is likely to be different and as such has an impact on the ICERs.

Table 102. Sensitivity analysis of mean difference in Hb levels between treatment arms as a proportion of difference at end of trial, when applied to TA142 parameters

Value	Total QALY gain	ICER
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
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year		

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 fromt TA142 could not be converted to the EQ-5D, so this 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 Section [Utilities]

We believe these model differences account for the difference between the adjusted PenTAG model and the TA142 base case.

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 main ones are:

- 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 due to a modelled favourable impact on survival, which was not assumed in the TA142 modelling. The overall survival hazard ratio, 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, due to a reduction in the cost of ESAs (both in terms of unit cost and dose reduction), a reduction in the number of administrations of ESAs and a reduced time frame where ESAs are administered.

7.3. Summary

KEY POINTS

- Cost of ESA is the largest cost component in any ESA arm and cost of red blood cell transfusions (RBCTs) is the largest cost for no ESA use.

- Costs of adverse events, RBCTs and additional blood tests are the equal across ESA arms.
- When ESA are used there cost savings in RBCTs
- Incremental cost-effectiveness ratios (ICERs) for ESA treatment versus no ESA treatment range from £19,429–£35,018 per QALY gained in the deterministic caseThe PSA gave ICERs that were lower than the deterministic base case (£14,724–£27,226 per QALY gained). The QALYs gained for ESA treatment compared to no ESA treatment had an average of 0.092 with a confidence interval of (-0.264 – 0.447). The incremental costs for the most-cost-effective ESA (Binocrit® [epoetin alfa]) were £1,349 (£710-£1,987, 95% CI)The ICER for Binocrit had a 95% credible interval (CrI) that was dominated by no ESA use (had fewer QALYs and higher costs) at its upper interval, with a lower value of £2,332 per QALY gained 36% of simulations from the PSA had an overall survival loss, with 31.4% of simulations having an overall QALY loss
- Three important scenario analyses considered are: (1) Setting the overall survival hazard ratio to exactly 1, such 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; (3) Setting the overall survival hazard ratio to exactly 1 and the ESA costs to wholesale acquisition
- In the first of these scenarios, where survival is assumed equal for both treatment arms, the QALY gain has greatly reduced (as well as the confidence interval: 0.014 (0.001–0.027)) compared to the base case. The most cost-effective ESA achieving an ICER of £96,754 per QALY gained (95% CrI: £36,897 to over £300,000 per QALY gained) in the PSA.
- In the second scenario, where wholesale acquisition costs were implemented, there was a reduction in the expected mean ICER from the PSA to [redacted] (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, where survival is assumed equal for both treatment arms and wholesale acquisition costs are used the expected ICER from the PSA for Retacrit® is [redacted].
- We also conduct scenario analyses on a subgroup of studies where initial Hb level for participants was ≤11 g/dl. This meant changes to many of the parameters and in particular the overall survival HR reduced to 0.91 in the determinstc results. Expected ICERs were reduced compared to base case, but the level of uncertainty was maintained.
- Scenario analyses were conducted on the overall survival modelling assumptions. Though all affected the ICERs, the most significant result showed that when the impact of survival benefit is only included for 3 years, ESAs appear to become much less cost-effective, with all ICERs above £30,000 per QALY.
- Univariate sensitivity analyses are also conducted, the most significant of these appeared to be the duration of ESA treatment.

Discussion

8.1. Aim

The remit for this report has been to up-date the evidence used to inform the previous NICE guidance on erythropoietin stimulating agents (ESAs) for the treatment of anaemia in cancer patients, particularly as laid out in the report by the West Midlands Health Technology Assessments Centre (WMTAC). In general they considered evidence up to 2004, and this is the start date we have used for this report.

Based on the previous assessment current NICE guidance (TA142)[34] recommends ESAs: "in combination with intravenous iron as an option for: the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin level of 8 g/dl or lower. The use of ESAs does not preclude the use of existing approaches to the management of anaemia, including blood transfusion where necessary".[34] The use of ESAs is also recommended: "in combination with intravenous iron in people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival."[34]

Initially all ESAs were recommended for use at Hb level ≤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 Summary of Product Characteristics for all ESAs at the European Medicines Agency's request. These changes came into effect in 2008 – after the previous guidance was issued – and included: decrease in haemoglobin value for treatment initiation to Hb ≤10 g/dl (to either increase haemoglobin by <2 g/dl or to prevent further decline); to amend haemoglobin target values to 10–12 g/dl and haemoglobin levels for stopping treatment to >13 g/dl.

The scope of this update review differed from the previous HTA review (**Wilson and colleagues, 2007**[1]) in respect of the population under consideration. Whereas the review conducted by Wilson and colleagues (2007)[1] considers cancer-related anaemia, the population covered in the PenTAG review is narrower, restricting to cancer patients with treatment-induced anaemia (specifically chemotherapy treatment). Similarly, the recent Cochrane review (**Tonia and colleagues, 2012**[10]) considers the broader population. Given 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 start dose administered irrespective of other criteria specified in the license; e.g. Hb levels (start and target Hb). In sensitivity analyses the definition of 'within licence' was tightened to: (1) start dose administered plus inclusion haemoglobin level ≤11 g /dl; and, (2) start dose administered plus inclusion haemoglobin level ≤11 g /dl plus target haemoglobin level l≤13 g /dl.

8.2. Clinical effectiveness

From 1,458 titles and abstract screened, 11 systematic reviews (reported in 14 papers), and 23 RCTs (reported in 35 publications), were found that matched our inclusion criteria. These combined studies eligible for inclusion from the previous HTA review (**Wilson and colleagues, 2007**[1]) with more recent studies identified by the PenTAG review team. Included studies were cross-checked with the recent Cochrane review (**Tonia and colleagues, 2012**[10]) to ensure completeness. Only one study (**Moebus and colleagues, 2013**[62]) was identified that was not included in the 2012 Cochrane review; it was included in abstract format (**Moebus and colleagues, 2007**[32]).

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 due to 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 as per the current licence specifications. However, none of the included studies evaluated ESAs entirely within the remit of their marketing authorisations; in particular, start and target Hb levels, and stopping levels were all generally higher than specificed in the licence. Thirteen studies compared ESAs plus supportive care (including transfusions) with placebo plus supportive care (including transfusions). The remaining studies compared ESAs plus supportive care (including transfusions) with supportive care (including transfusions) alone.

Analysis of haematological response (haemR) (defined as and improvement of 2 g/dl or a 6% increase in haematocrit level) showed a statistically significant difference in Hb response in favour of treatment (RR 3.29; 95% CI 2.84, 3.81; 12 trials, n=2,228). Sixty three per cent (n/N=759/1,213) of participants who received ESAs achieved a haemR compared with 18% (n/N=182/1,015) 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% 0.86, 1.41; 7 trials, n=1,909). 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, 1.13; 18 studies, n=4,399). Although this estimate differed from those reported by **Wilson and colleagues (2007)**[1] and **Tonia and colleagues (2012)**[10] – 1.05 (95% CI 1.00, 1.11; 76 trials, n=18,754) and 1.03 (95% CI 0.83, 1.13; 28 trials, n=5,308) respectively – there was considerable uncertainty around this 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 overall survival remains inconclusive.

On-study mortality was defined as deaths occurring up to 30 days after the active study period. Data, extracted from the Cochrane review (**Tonia and colleagues, 2012**[10]), were available from 21 studies including 5,085 participants. Analyses suggest that treatment with ESAs in patients with cancer treatment induced anaemia did not have a significant effect on mortality (HR 0.86, 95% CI 0.67 to 1.11; 14 trials, n=2,967). Eleven per cent (174/1,586) participants who received ESA had died within 30 days of the active study period, compared to 12% (164/1,381) of patients in control groups.

In agreement with the Cochrane review (**Tonia and colleagues, 2012**[10]), there is a statistically significant difference between patients treated with ESAs and controls when combining HRQoL parameters, although this is most likely 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 results between intervention and control, however, the number of included studies was small, therefore results must be treated with caution.

All AEs were relatively rare compared to 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 control groups reported thrombocytopenia/haemorrhage.. The summary

estimate from the random effects meta-analysis for thrombocytopenia/haemorrhage in the PenTAG review was RR 0.93 (95% CI 0.65, 1.34) compared with RR 1.21 (95% CI 1.04, 1.42) in the Cochrane review (**Tonia and colleagues, 2012**[10]). The data are insufficient to rule out detrimental effects. Overall, data suggest increased risk for thromboembolic events, hypertension, seizures and pruritus (skin rash, irritation and pruritus were combined in the analyses) consistent with previous estimates. Analyses suggest that treatment with ESA in people with chemotherapy induced anaemia 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) and suggests a non-significant increase in the number of seizures (RR of 1.19; 95% CI 0.33 to 4.38).

Important gaps in the evidence remain with respect to survival, mortality, adverse events, and impact on quality of life

8.2.1.1. 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 blood transfusion.

Only one included trial (**Ten Bokkel and colleagues, 1998**[47]) evaluated the use of ESAs in women with ovarian cancer; all participants received platinum-based chemotherapy. Data confirm results from prior analyses that ESAs reduce the risk of RBCT (RR 0.11 [95% CI 0.03–0.47), improve physiologic parameters such as Hb level (Hb change WMD 1.23 (95% CI 0.48–1.98), but increase the risk for thromboembolic events (RR 3.70 (95% CI 0.18–74.51). Overall survival was not measured in this study. No trials were identified that evaluated people unable to receive blood transfusions. However, it is reasonable to generalize from the wider RCT pool that ESAs are likely to work in improving Hb level 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 RBCT. Fortunately this is a small group (Jehovah's Witnesses and people who have multiple antibodies to red cells because they have required regular transfusions in the past).

In addition, subgroups 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 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; i.e. improved haematological response and reduction in RBCT requirements and are different compared to the results reported in the Cochrane review (**Tonia and colleagues, 2012**[10]). Similar to the overall analysis, results for the malignancy-related outcomes (overall survival and on-study mortality) suggest 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 confidence intervals remain wide. It is also important to remember that multiple testing issues arise when subgroups are tested and that confidence intervals 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. Usage of iron supplementation varied between the studies hindering comparison of results. No trials were identified that considered the use of ESAs in people with head and neck malignancies receiving platinum-based chemotherapy

8.2.1.1.1. The impact of "within licence"

In addition, post hoc sensitivity analysis considered the impact of administering ESAs 'closer to licence'. For the purposes of these analyses this was defined as: licensed start dose plus inclusion Hb criteria ≤11 g/dl, and licensed start dose plus inclusion Hb criteria ≤11 g/dl plus target Hb ≤13 g/dl. It appeared that the effectiveness of some outcomes was improved when ESAs were evaluated closer to their licenced indications. Results for anaemia-related outcomes showed improvements consistent with prior analyses. The effectiveness of malignancy-related outcomes did appear to be affected by the licence application and point estimates were notably lower to those reported in prior analyses when ESAs were administered in accordance with licence recommendations (licensed start dose plus inclusion Hb level ≤11 g/dl). Importantly, although the results for thromboembolic events from the PenTAG review agree with the Cochrane review (**Tonia and colleagues, 2012**[10]),

suggesting an increase in thromboembolic events in patients with ESA compared to controls, 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 hypothesise that anaemia in cancer patients is associated with a worse prognosis. According to Bohlius and colleagues, 2009, one explanation may be that, as a result of a low Hb, the tumour cells become hypoxic and are subsequently less sensitive to cytotoxic drugs, in particular oxygen-dependent chemotherapies. [9,192,193] Evidence for this, as reported in **Tonia and colleagues (2012)**,[10] exists in studies where tumour control and overall survival are improved in solid tumour patients with better tumour oxygenation (Hockel 1993; Knocke 1999). 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 overall survival.[194] 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,{Vaupel, 2008 #667 and thromboembolic events.

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.[13,14,16-19,195] This effect is postulated to be due to the presence of erythropoietin receptors on various cancers,[20,23,24,196,197] whereby the endogenously produced or exogenously administered erythropoietin promotes the proliferation and survival of erythropoietin receptor expressing cancer cells[194]. However, controversy about the functionality of these receptors remains,[25-29] and there are several studies which show no effect on tumour progression for patients receiving ESAs.[16,30,32,198]

It should be noted that the majority of studies examined in the systematic reviews by **Bohlius and colleagues (2009)[194]** and **Tonia and colleagues (2012)**,[10] have used a wide range of administration frequencies and dosage of ESAs (generally exceeding the license), which may cause a rise in adverse events and mortality. This knowledge, along with the generally poor reporting and data omission on factors such as tumour stage and method of assessment, have lead to the conclusion by (**Tonia and colleagues, 2012**[10]) 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 confidence intervals remain wide. The analyses may not have statistical power to detect the effects of license application on the effectiveness of outcomes,

if such effects exist. Furthermore, we have not sought to address multiple testing issues which arise when considering subgroups and so inference is not straightforward.

8.3. Cost effectiveness

8.3.1. Published economic evaluations

Ten cost-utility analyses and two systematic reviews were identified by updating an existing review by **Wilson and colleagues (2007)**[1] Five cost-utility analyses suggested that ESA therapy is cost-effective, these were all funded by industry (Martin and colleagues, 2003; Borg and colleagues, 2006) or conducted by industry (submissions by Amgen, Roche and Ortho Biotec as reported by **Wilson and colleagues, 2007**)

The inclusion of survival benefits was common to four favourable analyses (Martin and colleagues [2003] and the industry submissions as reported by **Wilson and colleagues [2007]**) although no statistically significant survival benefit has been shown

The fifth favourable analysis (Borg and colleagues, 2006) may suffer from problems of internal validity as it appears 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 analyses was that raising Hb levels would improve health-related quality of life, though 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 quality of life over patients in the no ESA arm; no evidence for or against normalisation has been presented

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 ESA therapy cost and improve cost-effectiveness

8.3.2. Strengths and limitations of the systematic review of studies of effectiveness

The overview of clinical effectiveness systematic reviews were conducted by an independent, experienced research team using the latest evidence and working to a pre-specified 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 the fact that no studies were completely aligned with the current UK authorization, we identified studies which were closest to the current marketing UK authorization, focusing initially on the starting dose. It is important to note that beyond the start dose there was still a significant differences from the current licence recommendations of the included studies. Also we did not pre-specify the criteria used to define closest to the current UK authorization, 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 done 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 topicwas greatly assisted by the recent Cochrane review (**Tonia and colleagues, 2012).** The authors had gathered further information from Investigators and manufacturers, which were used in the meta-analysis for the current review.

- **Heterogeneity:** There is considerable considerable unexplained statistical heterogeneity for a number of outcomes, particularly survival .

- **Publication bias:** There was some evidence in both the previous review and the Cochrane review 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 ie HRQoL this could not be further investigated because of the small number of included studies, in 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 close as possible to current UK authorization. 95% confidence intervals were in consequence often wide and include values indicating no difference in effect. The problem was compounded by the fact that total number of patients in the trials included were insufficient to establish the true presence of or absence of an effect, either because events are uncommon ie adverse events, or because the effect size which 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 sub-groups analyses done, we did not formally make adjustments for this

The limitations identified above impact on the key outcomes as follows:

- Haematological response and numbers transfused seem 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

- 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 confidence intervals.

- Survival is also subject to all 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 availableans as result there was a mix of short- and long-term studies.

8.3.3. 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 pre-specified protocol. Two new systematic reviews were identified, neither of which identified studies which would have been eligible for this review but were not included.

- Limitations were identified as follows:

- The searches were limited to English language due to 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 in **Wilson and colleagues (2007)**;Studies using darbepoetin alfa once every two weeks were excluded as out of licence although these could have usefully contributed to the review.

8.3.4. Strengths and limitations of the economic modelling by PenTAG

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, which has been acquired through a systemic review of current evidence. As such, though 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, where possible, attempted to address some of these limitations. These limitations are discussed below:

8.3.4.1. Data quality for ESA 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 patients' Hb level rises at an unacceptable pace or to an unacceptable level.

We estimated the mean weekly dose for patients on an intention-to-treat 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 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 (2009)**[112] 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 did not attempt to model dose adjustment and this combined with the assumption of three weeks extra treatment may explain the difference.

8.3.4.2. Uncertainty in overall survival

Differing assumptions regarding overall survival (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 conducted meta-analyses of hazard ratios for OS, but to our knowledge the assumption of proportional hazards (which must be made when calculating hazard ratios) has never been formally tested. Furthermore, it is likely that follow-up for a number of trials for which hazard ratios have been estimated has been very short and therefore there is considerable uncertainty in the effect of ESA therapy on long-term mortality. Individual patient data has been shared with the Cochrane review group on this subject and this could potentially be scrutinised to address these concerns.

Even when the assumption of proportional hazards is made and the random effects meta-analysis hazard ratio is used, there remains significant parameter and structural uncertainty.

Parameter uncertainty exists in that the confidence interval for the OS hazard ratio is very wide (0.83–1.13). There have not been sufficiently many studies powered to detect differences in OS for this parameter to be estimated precisely. Parameter uncertainty also exists in that the OS hazard ratio appears to be somewhat sensitive to the choice of inclusion criteria for studies. Further parameter uncertainty exists regarding the overall survival estimated for patients not receiving ESA therapy – this also has a significant impact on cost-effectiveness but is uncertain and likely to differ according to patient population.

Structural uncertainty exists in that even when assuming proportional hazards there are a number of distributions which permit 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 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, since there are biologically plausible explanations for beneficial and detrimental effects of ESA therapy on OS, and there is no reason to suppose these would cancel out.

8.3.4.3. Normalisation of Hb 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, so 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 portion of the predicted benefits to be largely based on clinical expert opinion, even though the expert opinion was at least not conflicting.

8.3.4.4. Exclusion of transfusion-dependent Hb level measurements

Some clinical studies (e.g., **Tjulandin and colleagues, 2010**[45]) excluded Hb level 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 to include measurements which 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 has been stripped from effectiveness results then we model the costs but not the benefits of transfusion. Since there is greater utilisation of

transfusion in patients not receiving ESA therapy it is possible that the cost-effectiveness of ESA therapy is 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 with recent transfusion), but there is 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 overall survival, and so small biases such as these in the estimation of short-term QALYs are unlikely to materially affect cost-effectiveness.

8.3.4.5. Hb to utility mapping

The short term QALYs associated with anaemia require mapping of Hb to utility. This is a surrogate outcome and requires several assumptions. Firstly, the relationship between Hb level and utilities is assumed linear. Whilst our review of previous studies into this are suggest that this is appropriate for Hb levels below 12 g/dL, the model does allow for normalization above 12g/dL in the PSA, where this assumption of linearity no longer seems to hold. Furthermore, review of previous studies showed that the evidence base for mapping Hb 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, 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 another 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 to 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. This meant that the study examined the association of anaemia and utility rather than association of anaemia correction and utility improvement, which our analysis was attempting to model. Furthermore, the study design was observational, though this appeared to be the case for most of the studies identified in our review. This does mean that the estimated relation between utility and Hb level may be biased due to unmeasured confounding variables. As discussed in Section 7.1 (page 245), results from **Tonelli and**

colleagues (2009)[112], suggest that it is likely that this would bias the results in favour of ESAs versus controls. Bias may also have occurred in the mapping study of SF-6D to EQ-5D due to measurement error in SF-6D values, which would result in an underestimation of the relationship between the two measures (i.e. attenuation bias).

8.3.4.6. Chemotherapy costs

The PenTAG model assumes that chemotherapy costs are equal both in the short term and 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 and control arms for on-study mortality the overall estimate (HR 0.87, 95% CI 0.70, 1.09), suggests a trend to improved survival under ESA. 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 RBCTs and this may impact patient attitude to their treatment. It is difficult to speculate what this impact may be on costs, as there appears to be no evidence currently to make any claim. Furthermore, in the long term results, if an impact on overall survival 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, or it might mean 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 the chemotherapy adherence from the short term. Without a clear clinical understanding of the impact on ESAs on survival and patient preferences, it is difficult to address how chemotherapy costs may alter, which is why they are assumed equal in both arms for the base case.

8.3.4.7. Adverse events

Adverse events rates associated with ESAs are also highly uncertain. The level of severity and specificity of each event is not well reported. The model specifically does not include rash or seizure as adverse events, even though they are reported in the clinical effectiveness systematic review, as these cover a wide, non-specific symptom base. The model included the adverse events of thromboembolic events, hypertension and thrombocytopenia, which cover a more specific symptom base, but 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 the adverse events at all levels of severity. This makes it problematic to assign either costs or disutilities to these adverse events in the model. Base costs were extracted from the NHS Reference costs 2012-13 for events likely to fall into the categories of adverse events, but these costs are averages from a wide variety of scenarios and as such highly uncertain. Our sensitivity analysis, 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 adverse events are the same in both arms. The model only identifies the proportion of patients who had at least one adverse event, regardless of severity or number. As such, the costs in the model only reflect one adverse event and do not account for the possibility that adverse events may be more severe in one arm than another. It is therefore probable that the unit cost for an adverse event 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 adverse events is even more problematic, both in estimating the utility and the time that the disutility should apply for. As such the model does not account for utility loss associated with the adverse events and the disbenefit of adverse events is only reflected in their costs. Given the sensitivity of the model to changes in the QALYs, this could likely 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 for patients on ESAs, but thrombocytopenia appeared to be common for the control arm. As such the addition of adverse event 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 higher risk of adverse events had a better survival outcome. This could be explained by the lack of detail on the adverse events (the higher risk may not actually correspond to the more severe adverse events) or to the possible spurious nature of the survival benefit. Again, without a clear clinical understanding of the possible difference in overall survival, it is difficult to speculate.

8.3.4.8. 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 use 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 is not adjusted for missed doses in the model, which therefore gives an increased cost for patients in the ESA arm. The sensitivity analysis where alternative dosing schedules are considered does not address this issue directly, but does demonstrate that altering these costs does not have a big impact on the model. Similarly, though it appears that there could be debate over how or who should administer the ESAs amongst clinicians, our results demonstrate that if ESAs were administered similar to the case of CKD patients, there is still little impact on the overall results.

There is also uncertainty over implications for other tests that may occur during ESA use. Some clinicians caution additional blood tests and one of the manufacturer submissions from the previous HTA, TA142, 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 the adverse events associated with red blood cell transfusions. However, we believe this risk to be minimal and the consequences are not easily defined or accounted for.

The cost of red blood cell transfusions 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 alter it sensitivity analyses to show the potential impact that changing this costs 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 assumes that the number of red blood cell units per transfusion is equal both in the ESA and no ESA arm, as we have 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 it is likely that the number of units transfused per transfusion is less for the ESA arm than the no ESA arm, then the number of transfusions for the ESA arm will increase and their cost-effectiveness will reduce.

Assessment of factors relevant to the NHS and other parties

9.1. 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 due to concerns about safety and effectiveness (overall survival), alongside restrictions set by the previous NICE guidance (TA142).

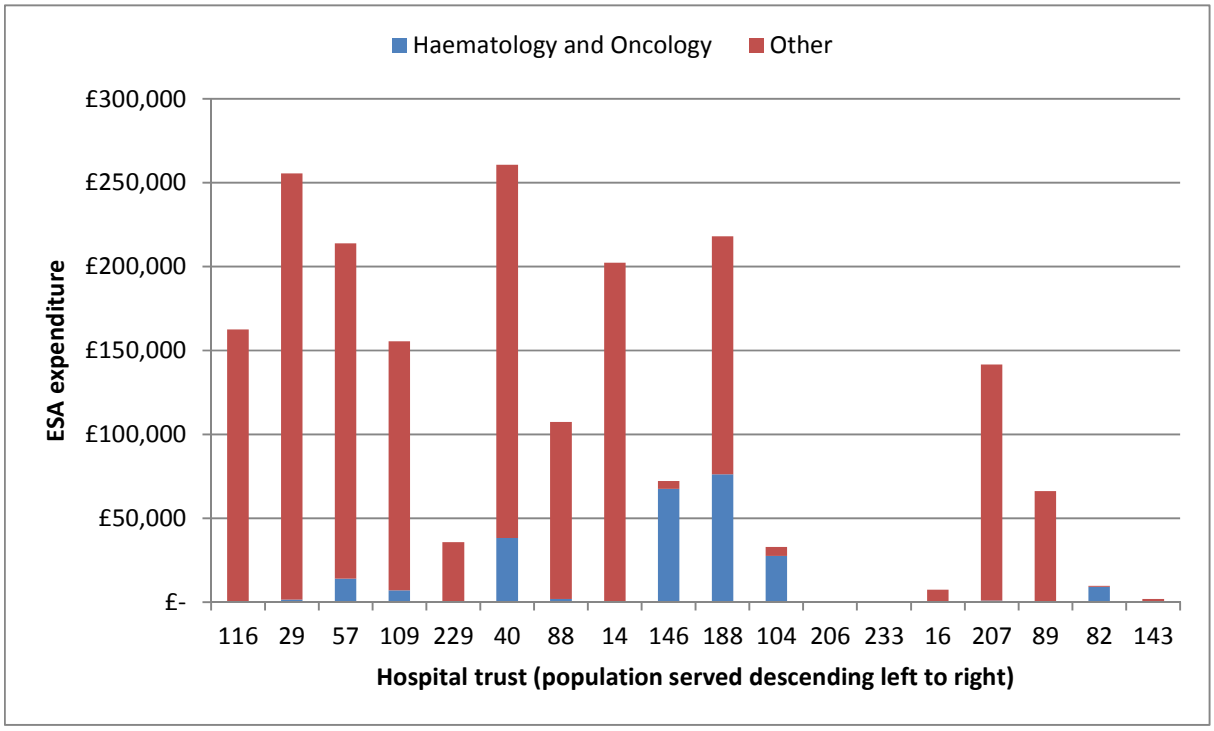
As this assessment is unlikely to reduce safety concerns it is relevant to the NHS that many clinicians aoppear to have judged that the potential risks of ESAs outweight the potential benefits.

9.2. Current usage

It is difficult to assess how frequently ESA therapy is used within the indication of cancer treatment-induced anaemia because prescription records do not routinely link medication with indication and ESA therapy is widely used in individuals with chronic kidney disease. Some indirect evidence of the use of ESA therapy for cancer treatment-induced anaemia is available from the use of cost centres against which ESAs are recorded.

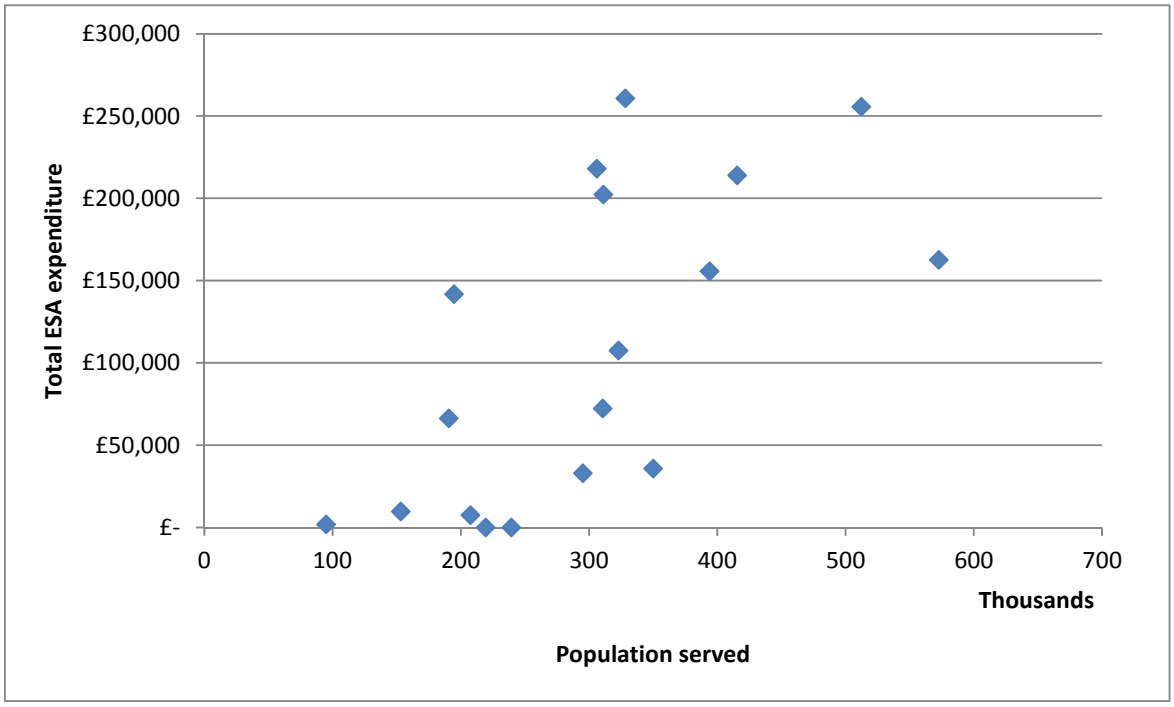
We were provided data (Personal communication, South East England Specialist Pharmacy Services, 3 October 2013) detailing how much had been spent on erythropoietin and darbepoetin alfa by hospital trusts (anonymised) in the East of England. This data was provided for the cost centres haematology and oncology. The oncology cost centre would be unlikely to include CKD patients but would not necessarily include all patients with cancer treatment-induced anaemia. 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 (see Figure 73), which suggests the trusts may record ESA prescriptions differently. Total ESA expenditure is highly variable but appears to be somewhat correlated with the size of population served (see Figure 74). This correlation disappears when only haematology and oncology are considered (see Figure 75). This is suggestive of significant variability in current usage, consistent with the experience that many clinicians do not use ESAs due to safety concerns (see Section 0), although data quality is low and interpretation challenging.

Figure 73: Total ESA expenditure for hospital trusts in East of England



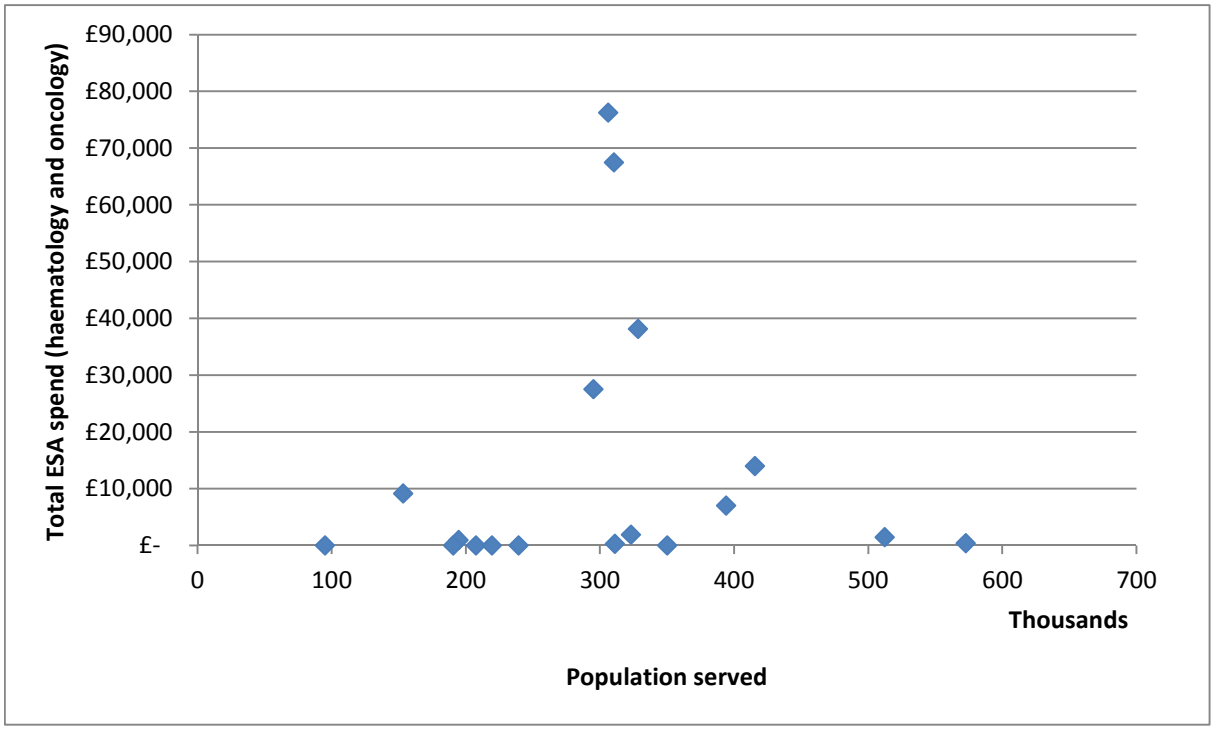
Key: ESA, erythropoiesis stimulating agent(s)

Figure 74: Comparison of total ESA expenditure with population served



Key: ESA, erythropoiesis stimulating agent(s)

Figure 75: Comparison of ESA expenditure in haematology and oncology with population served



Key: ESAs, erythropoiesis stimulating agent(s)

9.3. Acquisition cost of ESAs

As noted in Section 0 (page 245), the cost at which hospitals acquire ESAs may be significantly lower than the list price for the drugs. These prices are the subject of confidential negotiations and are commercially sensitive.

The NICE Process Methods Guide[168] states the following:

"*5.5.1 For the reference case, costs should relate to resources that are under the control of the NHS and personal and social services. These resources should be valued using the prices relevant to the NHS and personal and social services. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.*"

"*5.5.2 The public list prices for technologies (for example, pharmaceuticals or medical devices) should be used in the reference-case analysis. When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS. The*

Commercial Medicines Unit publishes information on the prices paid for some generic drugs by NHS trusts through its Electronic Marketing Information Tool (eMIT); focusing on medicines in the National Generics Programme Framework for England. Analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and consistently available across the NHS, and if the period for which the specified price is available is guaranteed. When a reduced price is available through a patient access scheme that has been agreed with the Department of Health, the base-case analysis should include the costs associated with the scheme. The review date for the appraisal will be informed by the period of time over which the manufacturer or sponsor can guarantee any such pricing agreements."

At the time of writing no manufacturer has agreed a Patient Access Scheme (PAS) with the Department of Health and there are no contracts 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 were developments in the management of CKD or if demand for ESAs increased for patients with cancer treatment-induced anaemia (as might be expected following positive NICE guidance).

In the event of positive NICE guidance for ESAs for cancer treatment-induced anaemia at list prices there would be no need for local decision analysis (pharmacists would simply attempt to obtain ESAs at the lowest price). However, if NICE were to issue negative guidance, local decision makers may be required to perform decision analyses with the offered prices from manufacturers. Such decisions would likely not perfectly match the counterfactual decision that would have been made by NICE had such offered prices been guaranteed and presented as reference case.

Conclusions

The previous HTA review (**Wilson and colleagues, 2007**[1]) concluded: "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."

Additional clinical effectiveness evidence identified in this update systematic review continues to suggest that there is clinical benefit from ESAs with respect to anaemia-related outcomes; i.e. improvements in haematological response and reduction in RBCT requirement. Data also suggest an improvement in HRQoL and this is better quantified compared with 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% confidence intervals are wide and not statistically significant.

Conclusions concerning cost-effectiveness are also no clearer. Base case ICERs for ESA treatment versus no ESA treatment ranged from £19,429–£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, survival was an influential parameter. If the survival benefit reported in the clinical effectiveness review (0.97 [95% CI 0.83–1.13]) 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 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 1 in 5 simulations give an ICER over £30,000 per QALY and approximately 1 in 3 simulations give an ICER over £20,000 per QALY..

In summary, ESAs could be cost-effective but there is considerable uncertainty mainly due to unknown impacts on overall survival.

10.1. Suggested research priorities

- If ESAs are thought to have major potential in 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 haemoglobin 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. If clinical studies of normalisation are conducted it would also be valuable for HRQoL outcomes to be measured, preferably using EQ-5D or another universal HRQoL questionnaire, such that incremental QALYs due to 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 re-visit Cochrane IPD meta-analysis 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 i.e. do ESAs allow better compliance with chemotherapy

References

1. Wilson J, Yao GL, Raftery J *et al*. (2007). 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. **11,** 1-202, iii-iv.

2. Schrijvers D, De Samblanx H, Roila F. (2010). Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO Clinical Practice Guidelines for use. Annals of Oncology. **21,** v244-v247.

3. Mercadante S, Gebbia V, Marrazzo A, Filosto S. (2000). Anaemia in cancer: pathophysiology and treatment. Cancer Treat Rev. **26,** 303-311.

4. Scrijvers D, Roila F, Group EGW. (2009). Erythropoiesis-stimulating agents in cancer patients: ESMO recommendations for use. Ann Oncol. **20 Suppl 4,** 159-161.

5. Groopman JE, Itri LM. (1999). Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst. **91,** 1616-1634.

6. Bohlius J, Schmidlin K, Brillant C *et al*. (2009). Erythropoietin or Darbepoetin for patients with cancer--meta-analysis based on individual patient data. Cochrane Database Syst Rev. CD007303.

7. Vaupel P, Mayer A. (2005). Hypoxia and anemia: effects on tumour biology and treatment resistance. Transfusion Clinique et Biologique. **12,** 5-10.

8. Schrijvers D, Highley M, De Bruyn E, Van Oosterom A, Vermorken J. (1999). Role of red blood cells in pharmacokinetics of chemotherapeutic agents. Anticancer Drugs. **10,** 147-153.

9. Hockel M, Knoop C, Schlenger K *et al*. (1993). Intratumoral pO2 predicts survival in advanced cancer of the uterine cervix. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. **26,** 45-50.

10. Tonia T, Mettler A, Robert N *et al*. (2012). Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev. **12,** CD003407.

11. Knocke TH, Weitmann HD, Feldmann HJ, Selzer E, Potter R. (1999). Intratumoral pO2-measurements as predictive assay in the treatment of carcinoma of the uterine cervix. Radiotherapy and Oncology. **18,** 156-169.

12. Vaupel P, Thews O, Mayer A, Hockel S, Hockel M. (2002). Oxygenation status of gynecologic tumors: what is the optimal hemoglobin level?. Strahlentherapie und Onkologie. **178,** 727-731.

13. Leyland-Jones B. (2003). Breast cancer trial with erythropoietin terminated unexpectedly. Lancet. **4,** 459-460.

14. Henke M, Laszig R, Rube C *et al*. (2003). Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet. **362,** 1255-1260.

15. Smith RE, Jr., Aapro MS, Ludwig H *et al*. (2008). Darbepoetin alpha for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. Journal of Clinical Oncology. **26,** 1040-1050.

16. Hedenus M, Adriansson M, San Miguel J *et al*. (2003). Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. Br J Haematol. **122,** 394-403.

17. Overgaard J, Hoff C, Sand Hansen H *et al*. (2007). 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. European Journal of Cancer Supplements. **5,** Abs 6LB.

18. Wright JR, Ung YC, Julian JA *et al*. (2007). Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. Journal of Clinical Oncology. **25,** 1027-1032.

19. Goss G, Feld R, Bezjak A *et al*. (2005). 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. **49,** S53-S53.

20. McBroom JW, Acs G, Rose GS *et al*. (2005). Erythropoeitin receptor function and expression in epithelial ovarian carcinoma. Gynecologic Oncology. **99,** 571-577.

21. Arcasoy MO, Jiang X, Haroon ZA. (2003). Expression of erythropoietin receptor splice variants in human cancer. Biochemical Biophysical Research Communications. **307,** 999-1007.

22. Arcasoy MO, Amin K, Vollmer RT *et al*. (2005). Erythropoietin and erythropoietin receptor expression in human prostate cancer. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. **18,** 421-430.

23. Dagnon K, Pacary E, Commo F *et al*. (2005). Expression of erythropoietin and erythropoietin receptor in non-small cell lung carcinomas. Clin Cancer Res. **11,** 993-999.

24. Leo C, Horn LC, Rauscher C *et al*. (2006). Expression of erythropoietin and erythropoietin receptor in cervical cancer and relationship to survival, hypoxia, and apoptosis. Clin Cancer Res. **12,** 6894-6900.

25. Feldman L, Wang Y, Rhim JS *et al*. (2006). Erythropoietin stimulates growth and STAT5 phosphorylation in human prostate epithelial and prostate cancer cells. The Prostate. **66,** 135-145.

26. Yasuda Y, Fujita Y, Matsuo T *et al*. (2003). Erythropoietin regulates tumour growth of human malignancies. Carcinogenesis. **24,** 1021-1029.

27. Mohyeldin A, Lu H, Dalgard C *et al*. (2005). Erythropoietin signaling promotes invasiveness of human head and neck squamous cell carcinoma. Neoplasia. **7,** 537-543.

28. Henke M, Mattern D, Pepe M *et al*. (2006). Do erythropoietin receptors on cancer cells explain unexpected clinical findings? Journal of Clinical Oncology. **24,** 4708-4713.

29. Jelkmann W, Bohlius J, Hallek M, Sytkowski AJ. (2008). The erythropoietin receptor in normal and cancer tissues. Critical Reviews in Oncology Hematology. **67,** 39-61.

30. Machtay M, Pajak TF, Suntharalingam M *et al*. (2007). Radiotherapy With or Without Erythropoietin for Anemic Patients With Head and Neck Cancer: A Randomized Trial of the Radiation Therapy Oncology Group (RTOG 99-03). International Journal of Radiation Oncology Biology Physics. **69,** 1008-1017.

31. Chang J, Couture F, Young S, McWatters KL, Lau CY. (2005). Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. J Clin Oncol. **23,** 2597-2605.

32. Moebus V, Lueck H, Thomssen C *et al*. (2007). 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). Journal of Clinical Oncology. **25,** Suppl:569.

33. Schrijvers D. (2011). Management of anemia in cancer patients: transfusions. Oncologist. **16 Suppl 3,** 12-18.

34. National Institute for Health and Care Excellence. (2008). Anaemia (cancer-treatment induced) - erythropoietin (alfa and beta) and darbepoetin (TA142). London: http://guidance.nice.org.uk/TA142/Guidance/pdf/English

35. Janssen-Cilag Ltd. (2012). Summary Product Characteristics: Eprex 40,000 IU/ml solution for injection in pre-filled syringe. High Wycombe, Bucks, England:

36. Sandoz Ltd. (2012). Summary of Product Characteristics: Binocrit Solution for Injection in a pre-filled syringe. Camberley, Surrey, England:

37. Hospira UK Ltd. (2012). Summary of Product Characteristics: Retacrit solution for injection in pre filled syringe. Leamington Spa, Warks, England:

38. Roche Products Ltd. (2012). Summary of Product Characteristics: Neorecormon Solution for Injection in Pre-Filled Syringe. Welwyn Garden City, Herts, England:

39. Teva Pharmaceuticals Ltd. (2012). Summary of Product Characteristics: Eporatio 1,000 IU/0.5 ml solution for injection in pre-filled syringe. Harlow, Essex, England: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001033/WC500043300.pdf

40. Amgen Ltd. (2012). Summary of Product Characteristics: Aranesp PFS. Cambridge, Cambs, England:

41. British Columbia Cancer Agency. BCCA Protocol Summary Guidelines for the Use of Erythropoiesis-Stimulating Agents (ESAs) in Patients with Cancer.

42. National Institute for Health and Care Excellence. FINAL SCOPE: Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA 142). London: NICE; 2013.

43. Bohlius J, Schmidlin K, Brillant C *et al*. (2009). Mortality in cancer patients receiving recombinant human erythropoiesis-stimulating agents: Individual patient data meta-analysis based on randomized trials. 8th Int Luebeck Conference Pathophysiology and Pharmacology of Erythropoietin and other Hemopoietic Growth Factors Luebeck Germany. **84,** E19.

44. Parmar MK, Torri V, Stewart L. (1998). Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in medicine. **17,** 2815-2834.

45. Tjulandin SA, Bias P, Elsasser R *et al*. (2010). Epoetin Theta in Anaemic Cancer Patients Receiving Platinum-Based Chemotherapy: A Randomised Controlled Trial. Arch Drug Inf. **3,** 45-53.

46. Kotasek D, Steger G, Faught W *et al*. (2003). 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. **39,** 2026-2034.

47. Ten Bokkel Huinink WW, de Swart CA, van Toorn DW *et al*. (1998). 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. **15,** 174-182.

48. Thatcher N, De Campos ES, Bell DR *et al*. (1999). Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer. Br J Cancer. **80,** 396-402.

49. Hedenus M, Hansen S, Taylor K *et al*. (2002). Randomized, dose-finding study of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies. Br J Haematol. **119,** 79-86.

50. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions (vn 5.1.0) [updated March 2011]*. The Cochrane Collaboration, 2011.

51. Dias S, Welton NJ, Sutton AJ, Ades AE (eds). *NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment (last updated April 2012)*. 2011.

52. Boogaerts M, Coiffier B, Kainz C. (2003). Impact of epoetin beta on quality of life in patients with malignant disease. Br J Cancer. **88,** 988-995.

53. Coiffier B, Boogaerts M, Kaine C. Impact of epoetin beta versus standard care on quality of life in patients with malignant disease. 6th Congress of the European Haematological Association. 2001

54. Abels R. (1993). Erythropoietin for anaemia in cancer patients. Eur J Cancer. **29A Suppl 2,** S2-8.

55. Case DC, Jr., Bukowski RM, Carey RW *et al*. (1993). Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. J Natl Cancer Inst. **85,** 801-806.

56. Henry DH, Abels RI. (1994). Recombinant human erythropoietin in the treatment of cancer and chemotherapy-induced anemia: results of double-blind and open-label follow-up studies. Semin Oncol. **21,** 21-28.

57. Henry DH, Brooks BJ, Jr., Case DC, Jr. *et al*. (1995). Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy. The cancer journal from Scientific American. **1,** 252-260.

58. Abels RI, Larholt KM, Krantz KD, Bryant EC. (1996). Recombinant Human Erythropoietin (rHuEPO) for the Treatment of the Anemia of Cancer. Oncologist. **1,** 140-150.

59. Grant MD, Piper M, Bohlius J *et al*. (2013). Epoetin and darbepoetin for managing anaemia in patients undergoing cancer treatment: Comparative effectiveness update. Chicago (IL), USA: http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1481#7457

60. Patrick DL, Gagnon DD, Zagari MJ *et al*. (2003). Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients receiving epoetin alfa. Eur J Cancer. **39,** 335-345.

61. Wagner LM, Billups CA, Furman WL, Rao BN, Santana VM. (2004). 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. Journal of Clinical Oncology. **22,** 1886-1893.

62. Moebus V, Jackisch C, Schneeweiss A *et al*. (2013). Adding Epoetin Alfa to Intense Dose-Dense Adjuvant Chemotherapy for Breast Cancer: Randomized Clinical Trial. J Natl Cancer Inst. **105,** 1018-1026.

63. Aravantinos G, Linardou H, Makridaki D *et al*. (2003). Recombinant human erythropoietin for platinum-based chemotherapy-induced anaemia: A single-centre randomised study. Journal of BUON : official journal of the Balkan Union of Oncology. **8,** 127-132.

64. Dammacco F, Castoldi G, Rodjer S. (2001). Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. Br J Haematol. **113,** 172-179.

65. Del Mastro L, Venturini M, Lionetto R *et al*. (1997). Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. J Clin Oncol. **15,** 2715-2721.

66. Dunphy FR, Harrison BR, Dunleavy TL *et al*. (1999). Erythropoietin reduces anemia and transfusions: A randomized trial with or without erythropoietin during chemotherapy. Cancer. **86,** 1362-1367.

67. Kurz C, Marth C, Windbichler G *et al*. (1997). Erythropoietin treatment under polychemotherapy in patients with gynecologic malignancies: a prospective, randomized, double-blind placebo-controlled multicenter study. Gynecol Oncol. **65,** 461-466.

68. Littlewood TJ, Bajetta E, Nortier JW *et al*. (2001). 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. **19,** 2865-2874.

69. Osterborg A, Brandberg Y, Molostova V *et al*. (2002). Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin Beta, in hematologic malignancies. J Clin Oncol. **20,** 2486-2494.

70. Osterborg AB, Yvonne; Hedenus, Michael. (2005). Impact of epoetin-beta on survival of patients with lymphoproliferative malignancies: long-term follow up of a large randomized study. British Journal of Haematology. **129,** 206-209.

71. Silvestris F, Romito A, Fanelli P, Vacca A, Dammacco F. (1995). Long-term therapy with recombinant human erythropoietin (rHu-EPO) in progressing multiple myeloma. Ann Hematol. **70,** 313-318.

72. Vansteenkiste J, Pirker R, Massuti B *et al*. (2002). Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst. **94,** 1211-1220.

73. Grote TY, Allen L.; Castillo, Rene; Butler, Dean; Fishkin, Ellioth; Henry, David H.; DeLeo, Michael; Fink, Kenneth; Sullivan, Daniel J. (2005). Efficacy and safety analysis of epoetin alfa in patients with small-cell lung cancer: a randomized, double-blind, placebo-controlled trial. Journal of Clinical Oncology. **23,** 9377-9386.

74. Ray-Coquard I, Dussart S, Goillot C *et al*. (2009). 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. **20,** 1105-1112.

75. Strauss HG, Haensgen G, Dunst J *et al*. (2008). Effects of anemia correction with epoetin beta in patients receiving radiochemotherapy for advanced cervical cancer. Int J Gynecol Cancer. **18,** 515-524.

76. Tjulandin SA, Bias P, Elsasser R *et al*. (2011). Epoetin Theta with a New Dosing Schedule in Anaemic Cancer Patients Receiving Nonplatinum-Based Chemotherapy: A Randomised Controlled Trial. Arch Drug Inf. **4,** 33-41.

77. Untch M, Fasching PA, Konecny GE *et al*. (2011). 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. Annals of Oncology. **22,** 1988-1998.

78. Untch M, Minckwitz G, Konecny GE *et al*. (2011). 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. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. **22,** 1999-2006.

79. Bajetta E, Vercammen E, Reinhardt U *et al*. (2004). Efficacy of epoetin alfa in a retrospective non-stratified subgroup analysis of a breast cancer cohort receiving non-platinum chemotherapy. Tumori. **90,** 449-457.

80. Aapro M, Bajetta E, Freund M *et al*. (2004). Is there a possible survival benefit to increasing hemoglobin levels with epoetin alfa during chemotherapy? European Journal of Cancer, Supplement. **2,** 20-28.

81. Vansteenkiste J, Tomita D, Rossi G, Pirker R. (2004). Darbepoetin alfa in lung cancer patients on chemotherapy: a retrospective comparison of outcomes in patients with mild versus moderate-to-severe anaemia at baseline. Supportive Care in Cancer. **12,** 253-262.

82. Littlewood TJ, Kallich JD, San Miguel J, Hendricks L, Hedenus M. (2006). 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. **31,** 317-325.

83. Sorgel F, Thyroff-Friesinger U, Vetter A, Vens-Cappell B, Kinzig M. (2009). Bioequivalence of HX575 (recombinant human epoetin alfa) and a comparator epoetin alfa after multiple intravenous administrations: an open-label randomised controlled trial. BMC clinical pharmacology. **9,** 10.

84. Sorgel F, Thyroff-Friesinger U, Vetter A, Vens-Cappell B, Kinzig M. (2009). Bioequivalence of HX575 (recombinant human epoetin alfa) and a comparator epoetin alfa after multiple subcutaneous administrations. Pharmacology. **83,** 122-130.

85. Sorgel F, Thyroff-Friesinger U, Vetter A, Vens-Cappell B, Kinzig M. (2009). Biosimilarity of HX575 (human recombinant epoetin alfa) and epoetin beta after multiple subcutaneous administration. International journal of clinical pharmacology and therapeutics. **47,** 391-401.

86. Weigang-Kohler KV, Andrea; Thyroff-Friesinger, Ursula. (2009). HX575, recombinant human epoetin alfa, for the treatment of chemotherapy-associated symptomatic anaemia in patients with solid tumours. Onkologie. **32,** 168-174.

87. Haag-Weber M, Vetter A, Thyroff-Friesinger U, Group IN-S. (2009). Therapeutic equivalence, long-term efficacy and safety of HX575 in the treatment of anemia in chronic renal failure patients receiving hemodialysis. Clin Nephrol. **72,** 380-390.

88. Desrame J, Stamerra O, Labourey JL *et al*. Haemoglobin outcomes with biosimilar epoetin alfa in the management of chemotherapy-induced anaemia in cancer patients: first results from OnCoBOS, a French observational study: Abstract 1312. European Cancer Congress. Amsterdam, The Netherlands, 2013

89. Rodriguez Garzotto A, Cortijo Cascajares S, Pernaut Sanchez C *et al*. Use of erythropoiesis-stimulating agents and comparison of different products for the treatment of chemotherapy-induced anaemia (CIA): Abstract 1320. European Cancer Conference. Amsterdam, The Netherlands, 2013

90. Lorenz A, Heine O. First comparison of biosimilar epoetin alfa and darbepoetin alfa for the treatment of chemotherapy-induced anaemia: Abstract 1392. European Cancer Congress. Amsterdam, The Netherlands, 2013

91. Delarue R, Haioun C, Coiffier B *et al*. (2011). Survival effect of darbepoetin alfa in patients with diffuse large B-cell lymphoma (DLBCL) treated with immunochemotherapy: The LNH03-6B study. ASCO Annual Meeting 2011 Chicago, IL United States. **29 (15 SUPPL. 1**.

92. Hartmann JT, Metzner B, Binder C *et al*. (2012). Addition of darbepoetin alfa to sequential high-dose VIP chemotherapy for patients with advanced metastatic germ cell cancer. 2012 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. **30 (15 SUPPL. 1)**.

93. Katsumata N, Fujiwara Y, Katakami N *et al*. (2009). 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, Asia Nagoya Japan. **97,** 58.

94. Nitz U, Oberhoff C, Reimer T *et al*. (2009). Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: a safety analysis from the phase III ARA plus trial. Cancer Research. **69,** 4100-4100.

95. Suzuki Y, Tokuda Y, Okamoto R *et al*. (2008). 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. **19,** 277.

96. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. (2002). 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. **24,** 547-561.

97. Cella DF, Tulsky DS, Gray G *et al*. (1993). The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. **11,** 570-579.

98. Ware JE, Jr., Sherbourne CD. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. **30,** 473-483.

99. Hunt SM, McEwen J, McKenna SP. (1985). Measuring health status: A new tool for clinicians and epidemiologists. The Journal of the Royal College of General Practitioners. **35,** 185-188.

100. Bowling A. *Measuring health, a guide to rating scales and questionnaires*. Buckingham: Oxford University Press, 1997.

101. Bretscher M, Rummans T, Sloan J *et al*. (1999). Quality of life in hospice patients. A pilot study. Psychosomatics. **40,** 309-313.

102. Sloan JA, Loprinzi CL, Kuross SA *et al*. (1998). Randomized comparison of four tools measuring overall quality of life in patients with advanced cancer. J Clin Oncol. **16,** 3662-3673.

103. Derogatis LR, Melisaratos N. (1983). The Brief Symptom Inventory: an introductory report. Psychological medicine. **13,** 595-605.

104. Morasso G, Costantini M, Baracco G, Borreani C, Capelli M. (1996). Assessing psychological distress in cancer patients: validation of a self-administered questionnaire. Oncology. **53,** 295-302.

105. de Haes J, Curran D, Young T *et al*. (2000). Quality of life evaluation in oncological clinical trials - the EORTC model. The EORTC Quality of Life Study Group. Eur J Cancer. **36,** 821-825.

106. Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. (2004). Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. J Natl Cancer Inst Monogr. **Monographs.,** 40-50.

107. Bokemeyer C, Aapro MS, Courdi A *et al*. (2007). EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. Eur J Cancer. **43,** 258-270.

108. Ross SD, Allen IE, Probst CA *et al*. (2007). Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: a systematic review and meta-analysis. Oncologist. **12,** 1264-1273.

109. Shehata N, Walker I, Meyer R *et al*. (2008). The use of erythropoiesis-stimulating agents in patients with non-myeloid hematological malignancies: a systematic review. Ann Hematol. **87,** 961-973.

110. Kvam AK, Fayers P, Hjermstad M, Gulbrandsen N, Wisloff F. (2009). Health-related quality of life assessment in randomised controlled trials in multiple myeloma: A critical review of methodology and impact on treatment recommendations. European journal of haematology. **83,** 279-289.

111. Minton O, Stone P, Richardson A, Sharpe M, Hotopf M. (2008). Drug therapy for the management of cancer related fatigue. Cochrane Database Syst Rev. CD006704.

112. Tonelli M, Lloyd A, Weibe N *et al*. (2009). Erythropoiesis-stimulating agents for anemia of cancer or of chemotherapy: systematic review and economic evaluation. Ottawa:

113. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. (2010). Drug therapy for the management of cancer-related fatigue. Cochrane Database Syst Rev. CD006704.

114. Drummond MF. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press, 1997.

115. Barosi G. (1998). Cost-effectiveness of recombinant human erythropoietin in the prevention of chemotherapy-induced anaemia. **78(6):781-787**.

116. Cremieux PY. (1999). Cost effectiveness, quality-adjusted life-years and supportive care: recombinant human erythropoietin as a treatment of cancer-associated anaemia. **16,** 459-472.

117. Martin SC, Gagnon DD, Zhang L *et al*. (2003). Cost-utility analysis of survival with epoetin-alfa versus placebo in stage IV breast cancer. Pharmacoeconomics. **21,** 1153-1169.

118. Ortega A, Dranitsaris G, Puodziunas AL. (1998). What are cancer patients willing to pay for prophylactic epoetin alfa? A cost-benefit analysis. **83,** 2588-2596.

119. Sheffield RE. (1997). Cost comparison of recombinant human erythropoietin and blood transfusion in cancer chemotherapy-induced anemia. **31,** 15-22.

120. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj. **339,** b2535.

121. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. (2005). Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. Int J Technol Assess Health Care. **06/01,** 240-245.

122. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. (2006). Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. **24,** 355-371.

123. Fagnoni P, Limat S, Chaigneau L *et al*. (2006). Clinical and economic impact of epoetin in adjuvant-chemotherapy for breast cancer. Support Care Cancer. **14,** 1030-1037.

124. Glaspy J, Tchekmedyian N, Gupta S. (2002). 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 in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. **5,** 543.

125. Cornes P, Coiffier B, Zambrowski JJ. (2007). Erythropoietic therapy for the treatment of anemia in patients with cancer: a valuable clinical and economic option. Curr Med Res Opin. **23,** 357-368.

126. Herrmann R. (2008). Erythropoietin therapy in cancer-related anaemia, yes or no? Intern Med J. **38,** 749-750.

127. Marchetti M, Barosi G. (2004). Clinical and economic impact of epoetins in cancer care. **22,** 1029-1045.

128. Reeder CE. (2007). Anemia in cancer and critical care patients: Pharmacoeconomic considerations. **64,** S22-S27.

129. Stasi R, Amadori S, Littlewood TJ *et al*. (2005). Management of cancer-related anemia with erythropoietic agents: doubts, certainties, and concerns. Oncologist. **10,** 539-554.

130. Repetto L, Moeremans K, Annemans L. (2006). European guidelines for the management of chemotherapy-induced anaemia and health economic aspects of treatment. **32,** S5-S9.

131. Roungrong J. (2008). Cost utility analysis of recombinant human erythropoietin in anemic cancer patients induced by chemotherapy in Thailand. J Med Assoc Thai. **91(Suppl 2):S119-S125**.

132. Centre for Reviews and Dissemination. (2010). Cost-utility analysis of recombinant human erythropoietin in anaemic cancer patients induced by chemotherapy in Thailand. NHS Economic Evaluation Database (NHS EED).

133. Griggs JJ. (1997). Cost-utility of erythropoietin in the treatment of cancer-related anemia. Medical Decision Making. **17(4):529**.

134. Griggs JJ. (1998). Recombinant erythropoietin and blood transfusions in cancer chemotherapy-induced anemia. Anti-Cancer Drugs. **9:925-932**.

135. Malonne H. Cost evaluation of erythropoiesis stimulating agents in the treatment of platinum chemotherapy induced anaemia. 20th Annual meeting of the Belgian Hematology Society. 2005

136. Borget I, Tilleul P, Baud M, Joly AC, Chouaid C. (2007). Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. Pharm World Sci. **29,** 454-454.

137. Borget I, Tilleul P, Joly AC, Chouaid C. (2006). Incremental cost-effectiveness ratio of darbepoetin alfa (Aranesp (R)) in the treatment of chemotherapy-induced anemia in lung cancer patients. Value in Health. **9,** A278-A279.

138. Chouaid C, Borget I, Baud M *et al*. (2005). Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: A Markov analysis. **49,** S23-S23.

139. Finek J, Holubec L, Wiesnerova A, Pav Z, Dusek V. (2010). Darbepoetin alfa versus epoetin alfa for treatment of chemotherapy-induced anemia: A health economic evaluation. Ann Oncol. **21,** 344.

140. Klarenbach S, Manns B, Reiman T *et al*. (2010). Economic Evaluation of Erythropoiesis-Stimulating Agents for Anemia Related to Cancer. **116,** 3224-3232.

141. Szucs TD, Boogaerts M, Coiffier B, Kainz C. (2001). 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. 59-59.

142. Cremieux P, Greenberg P, Piech CT. (2003). 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. **22,** 559.

143. Fragoulakis V, Maniadakis N. (2011). Economic evaluation of darbepoetin alpha in the management of patients with chemotherapy induced anemia (CIA) in Greece (ISPOR 14th Annual European Congress Madrid Spain). **14,** A440.

144. Mark TL, McKenzie SR, Piech CT. (2003). Better early and overall hematologic outcomes and lower drug cost with epoetin alfa (EPO) compared with darbepoetin alfa (DARB). Blood. **102,** 510B-510B.

145. van Hout BA, Gagnon DD. (2004). The cost-effectiveness of epoetin alfa (EPREX) and darbepoetin alfa (ARANESP) in the treatment of chemotherapy-related anemia. Hematol J. **5,** S176-S177.

146. Ben-Hamadi R, Duh MS, Henckler A *et al*. (2005). Cost-effectiveness of once weekly epoetin alfa and darbepoetin alfa in treating chemotherapy-induced anemia. J Clin Oncol. **23,** 551S.

147. Van Bellinghen LA, Demarteau N, Annemans L, Bracco A. (2006). 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. **9,** A286-A286.

148. Esposito G, Lamotte M, Annemans L, Bracco A. (2007). 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. **10,** A324-A324.

149. Van Bellinghen LA, Esposito G, Lamotte M *et al*. (2007). 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. **10,** A328-A328.

150. Finek J, Holubec L, Wiesnerova A, Pav Z, Dusek L. (2010). Darbepoetin alfa versus epoetin alfa for treatment of chemotherapy-induced Anemia: A health economic evaluation (ISPOR 13th Annual European Congress Prague Czech Republic). Value Health. **13,** A465.

151. Liwing J, Nasman P, Kernell H, Gagnon DD, Wu Y. (2010). Cost-Effectiveness Modelling of Epoetin Alfa and Darbepoetin Alfa in the Treatment of Chemotherapy-Related Anaemia in Sweden. Value Health. **13,** A38-A38.

152. Walter ER, E.; Kutikova, L. (2010). 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 in Health. **13,** A377.

153. Duh MS. (2008). Management of anaemia: a critical and systematic review of the cost effectiveness of erythropoiesis-stimulating agents. Pharmacoeconomics. **26,** 99-120.

154. Borg S, Glenngard AH, Osterborg A, Persson U. (2008). The cost-effectiveness of treatment with erythropoietin compared to red blood cell transfusions for patients with chemotherapy induced anaemia: a Markov model. Acta Oncologica. **47,** 1009-1017.

155. Ossa DF, Briggs A, McIntosh E *et al*. (2007). 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. **25,** 223-237.

156. Borget I, Tilleul P, Baud M *et al*. (2006). Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. Lung Cancer. 369-376.

157. Reed SD, Radeva JI, Daniel DB *et al*. (2006). Economic evaluation of weekly epoetin alfa versus biweekly darbepoetin alfa for chemotherapy-induced anaemia: evidence from a 16-week randomised trial. Pharmacoeconomics. **24,** 479-494.

158. Casadevall N, Durieux P, Dubois S *et al*. (2004). 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. **104,** 321-327.

159. Crawford J, Cella D, Cleeland CS *et al*. (2002). Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. Cancer. **95,** 888-895.

160. Glaspy J, Bukowski R, Steinberg D *et al*. (1997). 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. **15,** 1218-1234.

161. Abels RI. (1992). Recombinant human erythropoietin in the treatment of the anaemia of cancer. Acta Haematol. **87 Suppl 1,** 4-11.

162. British Medical Association and Royal Pharmaceutical Society. British National Formulary. British Medical Journal Publishing Group and Pharmaceutical Press; 2013.

163. Ben-Hamadi R, Duh MS, Aggarwal J *et al*. (2005). The cost-effectiveness of weekly epoetin alfa relative to weekly darbepoetin alfa in patients with chemotherapy-induced anemia. Curr Med Res Opin. **21,** 1677-1682.

164. Persson U, Borg S, Jansson S *et al*. (2005). 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. Advances in Therapy. **22,** 208-224.

165. Spaepen E, Demarteau N, Van Belle S, Annemans L. (2008). Health economic evaluation of treating anemia in cancer patients receiving chemotherapy: a study in Belgian hospitals. Oncologist. **13,** 596-607.

166. Aapro M, Cornes P, Sun D, Abraham I. (2012). 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. Therapeutic advances in medical oncology. **4,** 95-105.

167. Pashos CL, Larholt K, Fraser KA *et al*. (2012). Outcomes of erythropoiesis-stimulating agents in cancer patients with chemotherapy-induced anemia. Supportive Care in Cancer. **20,** 159-165.

168. National Institute for Health and Care Excellence. (2013). Guide to the Methods of Technology Appraisal.

169. Latimer N. (2011). NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Available from http://www.nicedsu.org.uk/.

170. Varney SJ, Guest JF. (2003). The annual cost of blood transfusions in the UK. Transfusion medicine (Oxford, England). **13,** 205-218.

171. Office for National Statistics. (2013) Interim Life Tables, 2010-2012. [cited; Available from: http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2010-2012/index.html

172. Ossa DF, Briggs A, Cowell W, Littlewood T, Sculpher M. (2004). Utility associated with severity of cancer-related anaemia (CRA): A societal valuation. Value in Health. **7,** 680-680.

173. Papaioannou D, Brazier J, Paisley S. (2010). NICE DSU Technical Support Document 9: The identification, review and synthesis of health state utility values from the literature. http://www.nicedsu.org.uk/TSD9%20HSUV%20values_FINAL.pdf

174. Harrow BS, Eaton CB, Roberts MB *et al*. (2011). Health utilities associated with hemoglobin levels and blood loss in postmenopausal women: the Women's Health Initiative. Value Health. **14,** 555-563.

175. Lloyd A, van Hanswijck de Jonge P, Doyle S, Cornes P. (2008). Health state utility scores for cancer-related anemia through societal and patient valuations. Value in Health. **11,** 1178-1185.

176. Tajima R, Kondo M, Kai H *et al*. (2010). Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D). Clin Exp Nephrol. **14,** 340-348.

177. Wisloff F, Gulbrandsen N, Hjorth M, Lenhoff S, Fayers P. (2005). Quality of life may be affected more by disease parameters and response to therapy than by haemoglobin changes. European Journal of Haematology. **75,** 293-298.

178. Dakin H. (2013). Review of studies mapping from quality of life or clinical measures to EQ-5D: an online database. Health and quality of life outcomes. **11,** 151.

179. Brazier J, Roberts J, Tsuchiya A, Busschbach J. (2004). A comparison of the EQ-5D and SF-6D across seven patient groups. Health economics. **13,** 873-884.

180. Ara R, Brazier JE. (2010). Populating an economic model with health state utility values: moving toward better practice. Value Health. **13,** 509-518.

181. Tengs TO, Wallace A. (2000). One thousand health-related quality-of-life estimates. Medical care. **38,** 583-637.

182. Hoyle M, Crathorne L, Peters J *et al*. (2013). 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. **17,** 1-237.

183. Pavey T, Hoyle M, Ciani O *et al*. (2012). Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. Health Technol Assess. **16,** iii-iv, 1-277.

184. Curtis L. (2012). Unit costs of Health and Social Care 2012 (PSSRU). Canterbury (Kent) and London (UK):

185. Curtis L. (2013). Unit costs of Health and Social Care 2013 (PSSRU). Canterbury (Kent) and London (UK):

186. Information Centre. *2006/07 UK General Practice Workload Survey*. Leeds: The Information Centre, 2007.

187. NHS. (2013). NHS reference costs 2012 to 2013. London: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/260403/nhs_reference_costs_2012-13.pdf

188. NHS Blood and Transplant. (2013). NHSBT Price List 2013/2014. London:

189. 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.

190. Joint Formulary Committee. *British National Formulary,* 66 edn. London: BMJ Group and Pharmaceutical Press, 2013.

191. Office for National Statistics. (2011) Statistical bulletin: Cancer Registration Statistics, England, 2011. [cited; Available from: http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--42--2011/stb-cancer-statistics-registrations-2011.html

192. Vaupel P. (2008). Hypoxia and aggressive tumor phenotype: Implications for therapy and prognosis. Oncologist. **13,** 21-26.

193. Schrijvers DH, M. De Bruyn, E. Van Oosterom, AT. Vermorken, JB. (1999). Role of red blood cells in pharmacokinetics of chemotherapeutic agents. Anticancer Drugs. **10,** 147-153.

194. Bohlius JS, Kurt; Brillant, Corinne; Schwarzer, Guido; Trelle, Sven; Seidenfeld, Jerome; Zwahlen, Marcel; Clarke, Mike J.; Weingart, Olaf; Kluge, Sabine; Piper, Margaret; Napoli, Maryann; Rades, Dirk; Steensma, David; Djulbegovic, Benjamin; Fey, Martin F.; Ray-Coquard, Isabelle; Moebus, Volker; Thomas, Gillian; Untch, Michael; Schumacher, Martin; Egger, Matthias; Engert, Andreas. (2009). Erythropoietin or Darbepoetin for patients with cancer--meta-analysis based on individual patient data. Cochrane Database of Systematic Reviews. CD007303.

195. Smith, Jr., R.E, Aapro MS *et al*. (2008). 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. Journal of Clinical Oncology. **26,** 1040-1050.

196. Arcasoy MO, Amin K, Chou SC *et al*. (2005). Erythropoietin and erythropoietin receptor expression in head and neck cancer: Relationship to tumor hypoxia. Clinical Cancer Research. **11,** 20-27.

197. Arcasoy MOJ, X. Haroon, Z.A. (2003). Expression of erythropoietin receptor splice variants in human cancer. Biochemical Biophysical Research Communications. **307,** 999-1007.

198. Chang JC, Felix; Young, Scott; McWatters, Kara-Lee; Lau, Catherine Y. (2005). Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy.[Erratum appears in J Clin Oncol. 2005 Aug 1;23(22):5276]. Journal of Clinical Oncology. **23,** 2597-2605.

199. Moher D, Cook DJ, Eastwood S *et al*. (1999). Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. **354,** 1896-1900.

200. Bamias A, Aravantinos G, Kalofonos C *et al*. (2003). 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. **64,** 102-110.

201. Cascinu S, Fedeli A, Del Ferro E, Luzi Fedeli S, Catalano G. (1994). Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double-blind trial with placebo. J Clin Oncol. **12,** 1058-1062.

202. Cazzola M, Messinger D, Battistel V *et al*. (1995). Recombinant human erythropoietin in the anemia associated with multiple myeloma or non-Hodgkin's lymphoma: dose finding and identification of predictors of response. Blood. **86,** 4446-4453.

203. Iconomou G, Koutras A, Rigopoulos A, Vagenakis AG, Kalofonos HP. (2003). Effect of recombinant human erythropoietin on quality of life in cancer patients receiving chemotherapy: results of a randomized, controlled trial. J Pain Symptom Manage. **25,** 512-518.

204. Kunikane H, Watanabe K, Fukuoka M *et al*. (2001). Double-blind randomized control trial of the effect of recombinant human erythropoietin on chemotherapy-induced anemia in patients with non-small cell lung cancer. International journal of clinical oncology. **6,** 296-301.

205. Oberhoff C, Neri B, Amadori D *et al*. (1998). 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. **9,** 255-260.

206. Osterborg A, Boogaerts MA, Cimino R *et al*. (1996). 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. **87,** 2675-2682.

207. Rosen FR, Haraf DJ, Kies MS *et al*. (2003). 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. **9,** 1689-1697.

208. Throuvalas N, Antonadu D, Boufi M, Lavey RS, Malamos N. Erythropoietin decreases transfusion requirements during radiochemotherapy [abstract 1558]. American Society of Clinical Oncology Annual Meeting. New Orleans (USA), 2000

209. Welch RS, James RD, Wilkinson PM, Belli F, Cowan RA. (1995). Recombinant human erythropoietin and platinum-based chemotherapy in advanced ovarian cancer. The cancer journal from Scientific American. **1,** 261-266.

210. Aapro M, Scherhag A, Burger HU. (2008). 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. British Journal of Cancer. **99,** 14-22.

211. Aapro M, Scherhag A, Osterwalder B, Ukarma L, Burger HU. (2009). 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. **17,** 1036-1037.

212. Berndt E, Kallich J, McDermott A *et al*. (2005). Reductions in anaemia and fatigue are associated with improvements in productivity in cancer patients receiving chemotherapy. Pharmacoeconomics. **23,** 505-514.

213. Blohmer JU, Paepke S, Sehouli J *et al*. (2011). 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. **29,** 3791-3797.

214. Cabanillas ME, Kantarjian H, Thomas DA *et al*. (2012). 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. **118,** 848-855.

215. Chang J, Couture FA, Young SD, Lau CY, Lee McWatters K. (2004). Weekly administration of epoetin alfa improves cognition and quality of life in patients with breast cancer receiving chemotherapy. Support Cancer Ther. **2,** 52-58.

216. Charu V, Belani CP, Gill AN *et al*. (2007). Efficacy and safety of every-2-week darbepoetin alfa in patients with anemia of cancer: a controlled, randomized, open-label phase II trial. Oncologist. **12,** 727-737.

217. Christodoulou C, Dafni U, Aravantinos G *et al*. (2009). Effects of epoetin-alpha on quality of life of cancer patients with solid tumors receiving chemotherapy. Anticancer Res. **29,** 693-702.

218. Engert A, Josting A, Haverkamp H *et al*. (2010). Epoetin alfa in patients with advanced-stage Hodgkin's lymphoma: results of the randomized placebo-controlled GHSG HD15EPO trial. J Clin Oncol. **28,** 2239-2245.

219. Fujisaka Y, Sugiyama T, Saito H *et al*. (2011). Randomised, phase III trial of epoetin-beta to treat chemotherapy-induced anaemia according to the EU regulation. Br J Cancer. **105,** 1267-1272.

220. Glaspy J, Vadhan-Raj S, Patel R *et al*. (2006). 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. **24,** 2290-2297.

221. Gupta S, Singh PK, Bisth SS *et al*. *Role of recombinant human erythropoietin in patients of advanced cervical cancer treated "by chemoradiotherapy".* http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/324/CN-00723324/frame.html

222. Hernandez E, Ganly P, Charu V *et al*. *Randomized, double-blind, placebo-controlled trial of every-3-week darbepoetin alfa 300 micrograms for treatment of chemotherapy-induced anemia.* http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/646/CN-00732646/frame.html; http://informahealthcare.com/doi/abs/10.1185/03007990903084164

223. Leyland-Jones B, Semiglazov V, Pawlicki M *et al*. (2005). 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. **23,** 5960-5972.

224. Milroy R, Bajetta E, van den Berg PM *et al*. (2011). Effects of epoetin alfa on anemia and patient-reported outcomes in patients with non-small cell lung cancer receiving chemotherapy: Results of a European, multicenter, randomized, controlled study. European journal of Clinical and Medical Oncology. **3,** 49-56.

225. Nagel S, Kellner O, Engel-Riedel W *et al*. (2011). 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. **12,** 62-69.

226. O'Shaughnessy JA, Vukelja SJ, Holmes FA *et al*. *Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy.* http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/941/CN-00512941/frame.html

227. Pirker R, Ramlau RA, Schuette W *et al*. (2008). Safety and efficacy of darbepoetin alpha in previously untreated extensive-stage small-cell lung cancer treated with platinum plus etoposide. J Clin Oncol. **26,** 2342-2349.

228. Pronzato P, Cortesi E, van der Rijt CC *et al*. (2010). 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. **15,** 935-943.

229. Razzouk BI, Hord JD, Hockenberry M *et al*. (2006). 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. **24,** 3583-3589.

230. Reed SD, Radeva JI, Daniel DB *et al*. (2005). Early hemoglobin response and alternative metrics of efficacy with erythropoietic agents for chemotherapy-related anemia. Curr Med Res Opin. **21,** 1527-1533.

231. Rosenzweig MQ, Bender CM, Lucke JP, Yasko JM, Brufsky AM. (2004). The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. J Pain Symptom Manage. **27,** 185-190.

232. Savonije JH, 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.* http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/597/CN-00562597/frame.html; http://theoncologist.alphamedpress.org/content/11/2/197.full.pdf

233. Savonije JH, 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. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/598/CN-00562598/frame.html

234. Savonije JH, van Groeningen CJ, van Bochove A *et al*. (2005). 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. **41,** 1560-1569.

235. Schwartzberg LS, Yee LK, Senecal FM *et al*. (2004). 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. **9,** 696-707.

236. Senecal FM, Yee L, Gabrail N *et al*. (2005). 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. **6,** 446-454.

237. Thomas G, Ali S, Hoebers FJ *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.* http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/280/CN-00621280/frame.html; http://ac.els-cdn.com/S0090825807008244/1-s2.0-S0090825807008244-main.pdf?_tid=7e46d8de-efcd-11e2-be1c-00000aacb362&acdnat=1374167844_d3bcd040ca37e724604869070bf9f3bb

238. Tsuboi M, Ezaki K, Tobinai K, Ohashi Y, Saijo N. (2009). 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. **39,** 163-168.

239. Waltzman R, Croot C, Justice GR *et al*. (2005). 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. **10,** 642-650.

240. Wilkinson PM, Antonopoulos M, Lahousen M, Lind M, Kosmidis P. (2006). Epoetin alfa in platinum-treated ovarian cancer patients: results of a multinational, multicentre, randomised trial. Br J Cancer. **94,** 947-954.

241. Winquist E, Julian JA, Moore MJ *et al*. (2009). Randomized, double-blind, placebo-controlled trial of epoetin alfa in men with castration-resistant prostate cancer and anemia. J Clin Oncol. **27,** 644-646.

242. Witzig TE, Silberstein PT, Loprinzi CL *et al*. (2005). Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. J Clin Oncol. **23,** 2606-2617.

243. Bokemeyer C, Aapro MS, Courdi A *et al*. (2004). EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. European journal of cancer. **40,** 2201-2216.

244. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. (2008). A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. J Natl Cancer Inst. **100,** 1155-1166.

245. Bohlius J, Wilson J, Seidenfeld J *et al*. (2006). Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev. CD003407.

246. Bohlius J, Langensiepen S, Schwarzer G *et al*. (2005). Recombinant human erythropoietin and overall survival in cancer patients: results of a comprehensive meta-analysis. Journal of the National Cancer Institute. **97,** 489-498.

247. Bohlius J, Wilson J, Seidenfeld J *et al*. (2006). Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. Journal of the National Cancer Institute. **98,** 708-714.

248. Bohlius JF, Langensiepen S, Engert A, Schwarzer G, Bennett CL. (2005). Effectiveness of erythropoietin in the treatment of patients with malignancies: methods and preliminary results of a Cochrane review. Best Pract Res Clin Haematol. **18,** 449-454.

249. Michallet M, Goldet K, Sobh M *et al*. (2013). Prospective study of erythropoietin use on quality of life and cost effectiveness in acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation patients. Cancer. **119,** 107-114.

APPENDICES

Appendix A	Protocol
Appendix B	Literature search strategy
Clinical effectiveness	
Appendix C	Application of license in included primary studies
Appendix D	Data extraction forms
Appendix E	Excluded studies (clinical-effectiveness review)
Appendix F	Study and baseline characteristics (unlicensed studies)
Appendix G	Study and baseline characteristics (licensed studies)
Appendix H	Multiple publications in clinical effectiveness review
Appendix I	Included studies: Systematic reviews
Appendix J	Comparison of search results with the manufacturer submissions
Appendix K	Ongoing studies
Appendix L	Supplementary analyses: clinical effectiveness
Appendix M	Supplementary material: quality of life
Cost effectiveness	
Appendix N	Excluded studies (cost-effectiveness review)
Appendix O	Multiple publications in cost-effectiveness review
Appendix P	Study characteristics, key parameters and results of conference abstracts identified in the cost-effectiveness review
Appendix Q	Critical appraisal of cost-effectiveness studies
Appendix R	Summary of parameters used in PenTAG cost-effectiveness model
Appendix S	Mean difference in Hb level as a proportion of final difference in Hb level
Appendix T	Use of MathMap to construct cumulative hazard and Weibull plots

Appendix A: Protocol

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta; and, darbepoetin alfa) for treating cancer-treatment induced anaemia (including review of TA142)

Technology Assessment Report commissioned by the NETSCC HTA Programme on behalf of the National Institute for Health and Care Excellence: HTA 12/42/01

19 July 2013

12.1. Title of the project:

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta; and, darbepoetin alfa) for treating cancer-treatment induced anaemia (including review of TA142)

12.2. Name of TAR team and project 'lead'

TAR Team	PenTAG, University of Exeter Medical School
Name	Louise Crathorne
Title	Research Fellow in HTA
Address	Veysey Building, Salmon Pool Lane, Exeter, EX2 4SG
Telephone number	01392 726084
Email	L.Crathorne@exeter.ac.uk

Address for correspondence: All correspondence should be sent to the project lead (Louise Crathorne, L.Crathorne@exeter.ac.uk), the TAR Team Director (Chris Hyde, C.J.Hyde@exeter.ac.uk), and Sue Whiffin (S.M.Whiffin@exeter.ac.uk)

12.3. Plain English Summary

This project will review and update the evidence presented to the National Institute of Health and Care Excellence in 2004 reviewing the effectiveness and cost-effectiveness of erythropoietin-stimulating agents (ESAs) epoetin alfa (Eprex [Janssen-Cilag], Binocrit

[Sandoz]), epoetin beta (NeoRecormon [Roche Products]), epoetin theta (Eporatio [Teva UK]), epoetin zeta (Retacrit [Hospira UK]), and darbepoetin alfa (Aranesp [Amgen]). The assessment will also assess whether the reviewed drugs are likely to be considered good value for money for the NHS.

12.4. Background

Anaemia is defined as a reduction of haemoglobin concentration, red cell count or packed cell volume to below normal levels. The World Health Organization has defined anaemia as a haemoglobin level of less than 12 g/dl in women and less than 13 g/dl in men. A reduction in the red blood cells can result from either the defective production of red blood cells or an increased rate of loss of cells, either by premature destruction or bleeding. Production of red blood cells (erythropoiesis) is primarily stimulated and regulated by a hormone called erythropoietin. Erythropoietin is a glycoprotein hormone that is produced naturally in the kidneys, but can also be manufactured for clinical use using recombinant DNA technology.

Anaemia can lead to a marked reduction in aspects of quality of life, such as increased fatigue, reduced exercise capacity and decreased sense of wellbeing. Fatigue is one of the commonest symptoms of anaemia. Anaemia is a common side-effect of cancer treatments and the anaemia-related fatigue has been shown to have a significant impact on cancer patients. Nearly 60% of patients with solid tumours undergoing chemotherapy became anaemic with a haemoglobin (Hb) <11 g/dl during their treatment. Anaemia is also common in haematological malignancies; up to 75% of patients with multiple myeloma are anaemic at diagnosis, and 70% of patients with lymphoma are anaemic by Cycles 3-4 of their chemotherapy.

Cancer treatment-induced anaemia is managed by adjustments to the cancer treatment regimen, iron supplementation and blood transfusion in cases of severe anaemia. NICE Technology Appraisal Guidance 142: *"Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia' recommends erythropoietin analogues [ESAs] only for women receiving platinum-based chemotherapy for ovarian cancer who have a blood haemoglobin level of 8 g/100 ml or lower, and also for people who have very severe anaemia and cannot receive blood transfusions."*[34]

12.5. Current evidence

The conclusions from the previous review were:[1]

- ESAs are effective in improving haematological response and red blood cell transfusion requirements, and appears to have a positive effect on health-related quality of life.

- The incidence of side-effects and effects on 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.

A recent Cochrane Review (2012) was identified in background searches:

- Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, Hyde C, Engert A, Bohlius J. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database of Systematic Reviews 2012, Issue 12.[10]

This review assessed the effects of ESAs to either prevent or treat anaemia in cancer patients. It included a total of 91 trials with a total of 20,102 participants. The review found that ESAs: *"… reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve QoL. Whether and how ESAs affect tumour control remains uncertain. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient's clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumour progression. 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."* (Tonia T et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database of Systematic Reviews 2012, Issue 12).[10]

12.6. Decision problem

12.6.1. Purpose of the decision to be made

The assessment will address the question: "What is the effectiveness and cost-effectiveness of ESAs (epoetin alfa, beta, theta and zeta; and, darbepoetin alfa) for treating cancer-treatment induced anaemia (including review of TA142)?"

12.6.2. Interventions

Exogenously administered erythropoietin is the intervention under assessment. It is used in addition to, rather than a complete replacement of the existing components of management. Since the last appraisal (2004), an additional two types of recombinant human erythropoietin are available: epoetin theta and epoetin zeta; the latter is referenced to epoetin alfa. Epoetin alfa, beta, theta and zeta are recombinant human erythropoietin analogues, Epoetins are used to shorten the period of symptomatic anaemia in patients receiving cytotoxic chemotherapy. Darbepoetin alfa is a hyperglycosylated derivative of epoetin that stimulates erythropoiesis by the same mechanism as the endogenous hormone. For the treatment of anaemia associated with cancer treatment, they are administered by injection.

This technology assessment report (TAR) will consider six pharmaceutical interventions: epoetin alfa (Eprex [Janssen-Cilag], Binocrit [Sandoz]), epoetin beta (NeoRecormon [Roche Products]), epoetin theta (Eporatio [Teva UK]), epoetin zeta (Retacrit [Hospira UK]), and darbepoetin alfa (Aranesp [Amgen]).[42]

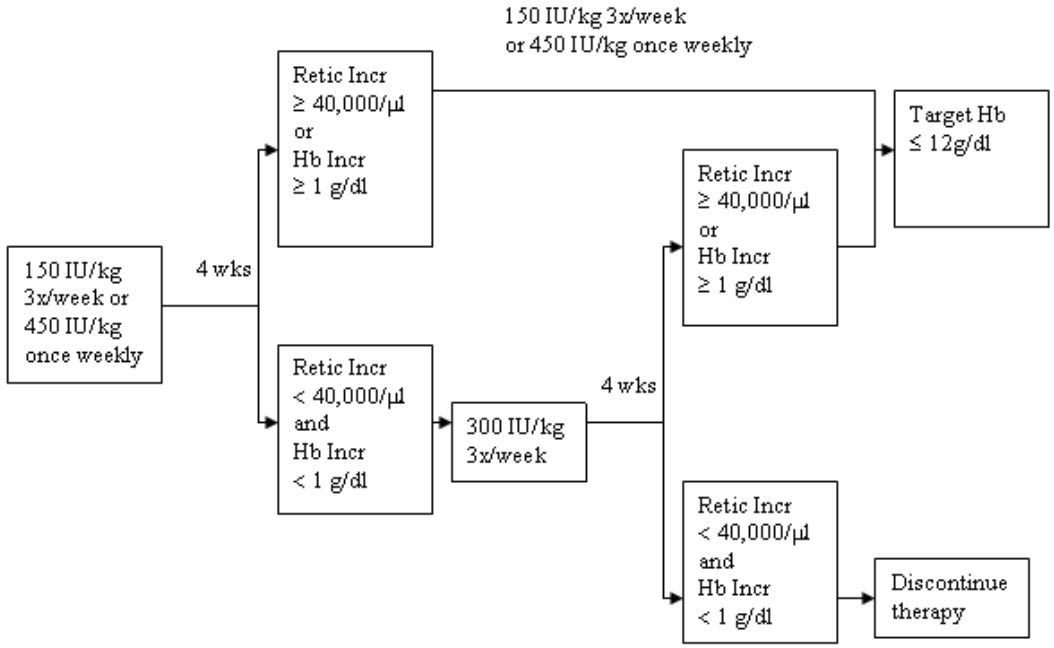
Epoetin alfa (Eprex®, [Janssen-Cilag] and Binocrit® [Sandoz]), and **epoetin zeta** (Retacrit® [Hospira UK]) have UK marketing authorisations for the treatment of anaemia and for the reduction of transfusion requirements in adults receiving chemotherapy for solid tumours, malignant lymphoma, or multiple 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).[35-37] Binocrit® (Sandoz) and epoetin zeta (Retacrit®, Hospira UK) are biosimilar medicines references to Eprex which contains epoetin alfa. **Epoetin beta** (NeoRecormon®, Roche Products), **epoetin theta** (Eporatio® [Teva UK]), and **darbepoetin alfa** (Aranesp [Amgen]) have UK marketing authorisations for the treatment of symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy.[38-40] A summary of the UK marketing authorisation for each intervention along with a description of administration method is given below.

12.6.2.1. UK marketing authorisations

All interventions of interest in this review are administered by administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤10 g/dl (6.2 mmol/l)) in order to increase haemoglobin to not greater than 12 g/dl (7.5 mmol/l). All therapies should be continued up to four weeks after the end of chemotherapy.

Epoetin alfa (Eprex [Janssen-Cilag], Binocrit [Sandoz], and epoetin zeta (Retacrit, Hospira UK): the initial dose is 150 IU kg^{-1} given subcutaneously three times per week.[35-37] Alternatively, epoetin alfa can be administered at an initial dose of 450 IU kg^{-1} subcutaneously once weekly.[35-37] The maximum recommended dose is 900 IU kg^{-1} body weight per week.[35-37] Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10g/dl (6.2 mmol/l) to 12g/dl (7.5mmol/l).[35-37] A sustained haemoglobin level of greater than 12g/dl (7.5mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceed 12g/dl (7.5mmol/l) (see Figure 76).[35,36,120] Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to maintain haemoglobin at that level.[35-37]

Figure 76. Epoetin alfa and epoetin zeta administration guidance[35-37]



Epoetin beta (NeoRecormen, Roche Products): the weekly dose can be given as one injection per week or in divided doses three to seven times per week.[38] The recommended initial dose is 450 IU kg^{-1} body weight per week.[38] If, after four weeks of therapy, the haemoglobin value has increased by at least 1 g/dl (0.62 mmol/l), the current dose should be continued. If the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), a doubling of the weekly dose should be considered. If, after eight weeks of therapy, the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), response is unlikely and treatment should be discontinued.[38] The maximum recommended dose is 900 IU kg^{-1}

body weight per week.[38] Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l).[38] A sustained haemoglobin level of greater than 12 g/dl (7.5 mmol/l) should be avoided.[38] Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to maintain haemoglobin at that level.[38] Appropriate dose titration should be considered.[38]

Epoetin theta (Eporatio, Teva UK): the recommended initial dose is 20,000 IU, independent of bodyweight, given once-weekly.[39] Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l).[39] A sustained haemoglobin level of greater than 12 g/dl (7.45 mmol/l) should be avoided.[39] If, after four weeks of therapy, the haemoglobin value has increased by at least 1 g/dl (0.62 mmol/l), the current dose should be continued. If the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l) a doubling of the weekly dose to 40,000 IU should be considered.[39] If, after an additional four weeks of therapy, the haemoglobin increase is still insufficient an increase of the weekly dose to 60,000 IU should be considered. The maximum dose should not exceed 60,000 IU per week.[39] If, after 12 weeks of therapy, the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), response is unlikely and treatment should be discontinued.[39]

Darbepoetin alfa (Aranesp, Amgen): the recommended initial dose is 500 µg (6.75 µg kg^{-1}) given once every three weeks, or once weekly dosing can be given at 2.25 µg kg^{-1} body weight.[40] The maximum recommended dose is 4.5 µg kg^{-1} per week.[40] If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy may not be effective.[40] Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25% to 50% in order to ensure that the lowest approved dose of is used to maintain haemoglobin at a level that controls the symptoms of anaemia.[40] Appropriate dose titration between 500 µg, 300 µg, and 150 µg should be considered.[40] Patients should be monitored closely, if the haemoglobin exceeds 12 g/dl (7.5 mmol/l), the dose should be reduced by approximately 25 to 50%.[40] Treatment with darbepoetin alfa should be temporarily discontinued if haemoglobin levels exceed 13 g/dl (8.1 mmol/l).[40] Therapy should be reinitiated at approximately 25% lower than the previous dose after haemoglobin levels fall to 12 g/dl (7.5 mmol/l) or below.[40] If the rise in haemoglobin is greater than 2 g/dl (1.25 mmol/l) in four weeks, the dose should be reduced by 25 to 50%.[40]

12.6.2.2. Place of the interventions in the treatment pathway

NICE guidance (Technology Appraisal Guidance 142)[34] currently recommends ESAs in combination with intravenous iron as an option for:

- the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin level of 8 g/100 ml or lower. The use of ESAs does not preclude the use of existing approaches to the management of anaemia, including blood transfusion where necessary.[34]

- people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.[34]

Where indicated the ESA used should be the one with the lowest acquisition cost.[34]

In addition, the NICE guidance recommends ESAs for people who are currently being treated with ESAs for the management of cancer treatment-related anaemia but who do not fulfil either of the above criteria should have the option to continue their therapy until they and their specialists consider it appropriate to stop.[34]

12.6.3. Relevant comparators

The main comparators of interest are:[42]

- placebo

- best supportive care (including adjustment to the cancer treatment regimen, blood transfusion, and iron supplementation)

- one of the other interventions under consideration, compared in line with their marketing authorisations.

12.6.4. Population

The population will be:[42]

- people receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, 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)
- people with non-myeloid malignancies who are receiving chemotherapy

There are no age restrictions; however, it is recognised that all licences for all drugs do not cover erthyropoietin use in children.

The scope issued by NICE states that if evidence allows subgroups should be considered; e.g. by cancer type and status, by chemotherapy, or by best supportive care received (see Section 12.7.5, page 428 for more information).

12.6.5. Outcomes to be addressed

Evidence in relation to the following kinds of outcomes will be considered:[42]

- haematological response to treatment
- need for blood transfusion after treatment
- tumour response (time to cancer progression)
- survival
- adverse effects of treatment
- health-related quality of life.

12.7. Methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for the clinical effectiveness of epoetin alfa (Eprex® [Janssen-Cilag], Binocrit® [Sandoz]), epoetin beta (NeoRecormon® [Roche Products]), epoetin theta (Eporatio® [Teva UK]), epoetin zeta (Retacrit® [Hospira UK]), and darbepoetin alfa (Aranesp® [Amgen]).

The review will update the previous review of clinical effectiveness undertaken in 2004 to inform NICE's TA142 Guidance.[34] The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[132]

12.7.1. Search strategy

The search strategy will comprise the following main elements:

- searching of electronic databases using an appropriately sensitive search strategy designed and executed by an information specialist
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

The following electronic databases will be searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid); The Cochrane Library including the Cochrane Database of Systematic Reviews, CENTRAL, DARE, NHS EED, HEED and HTA databases; CINAHL (EBSCO); British Nursing Index (ProQuest); Web of Science (Thomson Reuters); HMIC (Ovid); Current Controlled Trials; Clinical Trials.gov; FDA website; EMA website.

In addition the following websites will be searched for background information:

Medical societies

British Society for Haematology	http://www.b-s-h.org.uk/
The Association of Cancer Physicians	http://www.cancerphysicians.org.uk/
American Society of Hematology	http://www.hematology.org/
American Society of Clinical Oncology	http://www.asco.org/
The Canadian Oncology Societies	http://www.cos.ca/
Haematology Society of Australia and New Zealand	http://www.hsanz.org.au/
Clinical Oncology Society of Australia	http://www.cosa.org.au/
New Zealand Society for Oncology	http://www.nzsoncology.org.nz/

UK charities

Cancer Research UK	http://www.cancerresearchuk.org/home/
Macmillan	http://www.macmillan.org.uk/
Marie Curie	http://www.mariecurie.org.uk/

Non-UK charities

American Cancer Society	http://www.cancer.org/
Canadian Cancer Society	http://www.cancer.ca/
Cancer Council Australia	http://www.cancer.org.au/
Cancer Society of New Zealand	http://www.cancernz.org.nz/

World Cancer Research Fund http://www.wcrf-uk.org/

The databases will be searched from search end-date of the last MTA on this topic (2004).

The searches will be developed using the search strategies detailed in the MTA by Wilson *et al* as the starting point (see Appendix A for more information).[1] Search filters will be used to find clinical effectiveness, cost effectiveness and quality of life studies, and all searches will be limited to English language studies.

All references will be exported into Endnote X5 (Thomson Reuters) where automatic and manual de-duplication will be performed.

12.7.2. Inclusion/exclusion criteria

12.7.2.1. Inclusion criteria

The inclusion criteria are as reported in Table 103. The review of clinical effectiveness will include any randomised controlled trial (RCT) reporting at least one of the outcomes of interest. However, if there are no RCTs reporting one of the listed outcomes of interest or if there are no RCTs with over 12 months' follow up, we will extend our inclusion criteria to controlled clinical trials to search for studies with missing outcomes or longer follow up. Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of the results to be undertaken. Systematic reviews and clinical guidelines will be included as sources of references for finding further RCTs and to compare with our systematic review. These criteria may be relaxed for consideration of adverse events, for which non-randomised and observational studies may be included.

For the purpose of this review, a systematic review[120,132,199] will be defined as one that has:

a focused research question

- explicit search criteria that are available to review, either in the document or on application
- explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest

- a critical appraisal of included studies, including consideration of internal and external validity of the research

- a synthesis of the included evidence, whether narrative or quantitative.

Table 103. Inclusion criteria (PICOS) as per the final scope and accompanying notes[42]

Population	People receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, 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). People with non-myeloid malignancies who are receiving chemotherapy	There are no age restrictions; however, it is recognised that the licences for all three drugs do not cover eruthropoietin use in children. Exclude studies where erythropoietin was 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.
Intervention(s)	**Epoetin alfa** (Eprex, [Janssen-Cilag] and Binocrit [Sandoz]) **Epoetin beta** (NeoRecormon, Roche Products) **Epoetin theta** (Eporatio [Teva UK]) E**poetin zeta** (Retacrit [Hospira UK]) **Darbepoietin alfa** (Aranesp [Amgen]).	These interventions will be assessed as administered in accordance with licensed indications. <u>Concomitant anaemia therapy</u> such as granulocyte colony-stimulating factor (G-CSF) supplementation was permitted should be given equally in the control arm. This criterion was relaxed for iron supplementation which can be used in the experimental but not in the control arm as well.
Comparator(s)	Placebo Best supportive care (including adjustment to the cancer treatment regimen, blood transfusion and iron	<u>Concomitant anaemia therapy</u> such as granulocyte colony-stimulating factor (G-CSF) supplementation was permitted should be given equally in the intervention arm. This criterion was relaxed for iron

	supplementation) One of the other interventions under consideration; compared in line with their marketing authorisations	supplementation which can be used in the experimental but not in the control arm as well.
Outcomes	Haematological response to treatment	Defined as a transfusion free increase of Hb of ≥2 g dl^{-1} or a haematocrit increase of 6%
	Need for blood transfusion after treatment	Number of patients transfused, number of units transfused per patient, and number of patients transfused per patient per four weeks
	Tumour response	Time to cancer progression
	Survival	Overall survival
	Adverse effects of treatment	Hypertension, rash/irritation, pruritus, mortality, thromboembolic events, seizure, haemorrhage / thrombocytopenia, fatigue, pure red cell aplasia. Particular interest thromboembolic events A note will be made of other adverse events described within the trial reports
	Health-related quality of life	Health-related quality of life – data on validated quality of life measures; e.g. FACT (FACT-General, FACT-Fatigue, FACT-Anaemia); EQ-5D, SF-36
Study design	RCTs SRs of RCTs (to be used to cross-check for any	For the purpose of this review, a systematic review will be defined as one that has: a

	additional RCTs and to compare the findings of our review with)	focused research question; explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest; a critical appraisal of included studies, including consideration of internal and external validity of the research synthesis of the included evidence, whether narrative or quantitative. If insufficient data are available from RCTs, observational studies or non-randomised trials may be considered. For example this criterion will be relaxed for the consideration of adverse events and long term evidence of effectiveness, for which observational studies and disease registers of sufficiently long follow-up and good quality may be included **Exclude:** non-randomised studies; animal models; preclinical and biological studies; narrative reviews, editorials, opinions; non-English language papers; reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

12.7.2.2. Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. Studies which are considered

methodologically unsound in terms of either study design or the method used to assess outcomes will be excluded from the results.

The following publication types will also be excluded from the analysis:

- non-randomised studies
- animal models
- preclinical and biological studies
- narrative reviews, editorials, opinions
- non-English language papers
- reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

12.7.3. Data extraction strategy

Studies retrieved from the update searches will be selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified in Table 103. First, abstracts and titles returned by the search strategy will be screened for inclusion independently by two researchers. Disagreements will be resolved by discussion, with involvement of a third reviewer when necessary. Full texts of identified studies will be obtained and screened in the same way. At each step studies which do not satisfy those criteria; abstract-only studies will be included provided sufficient methodological details are reported to allow critical appraisal of study quality. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

In addition, if time and resources permit, studies included in the 2004 review may be re-abstracted using the data extraction process detailed below. This will facilitate examination of sub-groups not examined in detail in the original report.

Included full papers will be split between two reviewers for the purposes of data extraction using a standardised data specification form, and checked independently by another. Information extracted and tabulated will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events if reported. Where there is incomplete information on key data, we will attempt to

contact the study's authors to gain further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

Included studies and industry submissions will be analysed to ensure the saturation of relevant studies (see Section 12.9 [page 432]).

12.7.4. Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, using the Cochrane Risk of Bias tool,[50]or criteria based on those proposed by the NHS Centre for Reviews and Dissemination for randomised controlled trials (RCTs).[132]

12.7.5. Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. If appropriate (i.e. if a number of studies which report data relating to a given outcome are comparable in terms of key features such as their design, populations, and interventions), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention-to-treat analyses.

Where appropriate, meta-analysis will be carried out using STATA and/or WinBugs software, with the use of fixed- and/or random-effects appropriate to the assembled datasets. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

A network meta-analysis was considered but not thought to be particular relevance to this topic.

We will investigate the likelihood of publication bias using funnel plots if there are sufficient included studies.

If evidence allows, the following subgroups will be considered:

- iron supplementation given with erythropoiesis-stimulating agents
- people with any type of cancer receiving platinum-based chemotherapy

- people with head and neck malignancies receiving platinum-based chemotherapy
- women with ovarian cancer
- women with ovarian cancer receiving platinum-based chemotherapy
- people unable to receive blood transfusions.

12.7.6. Publication bias

If time and resource permit, reporting bias[1] in our systematic review and meta-analyses will be assessed. We will follow best practice as recommended in the Cochrane Handbook for Reviewers, who have dedicated a whole chapter to the avoidance, identification and investigation of possible reporting bias.[50] This may include researching trials that have only ever appeared as conference abstracts in previous reviews.

12.8. Methods for synthesising evidence of cost-effectiveness

12.8.1. Review of economic studies

This review aims to update the systematic review of cost-effectiveness studies which was conducted in 2004 as part of the review of evidence to inform NICE's earlier guidance on these drugs (TA142).[34]

A review, using a systematic approach, will be of economic evaluations of erythropoietin stimulating agents for the treatment of cancer treatment induced anaemia will be undertaken. Full economic evaluations will be included where they meet the inclusion criteria set out for the review of clinical effectiveness (see Section 12.7.2). Exceptions include: (a)non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies.); (b) full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data); and, (c) standalone cost analyses based in the UK NHS will also be sought and appraised.

[1] Where the term 'reporting bias' covers all types of publication, language, outcome, location etc biases defined in the Cochrane Handbook.

The sources to be searched will be similar to those in the clinical effectiveness review (see Section 12.7.1), and extend to NHS EED and HEED. Searches will be limited to English language sources.

Key included economic evaluations identified in the search will be critically assessed using accepted frameworks, such as the consensus-developed list of criteria developed by Evers and colleagues[121] For included economic evaluations based on decision models, critical appraisal of these studies will make use of guidelines for good practice in decision analytic modelling in HTA.

Methods and findings from key included economic evaluations will be summarised in a tabular format and synthesised in a narrative review. Economic evaluations carried out from the perspective of the UK NHS and Personal Social Services (PSS) perspective will be particularly highlighted.

12.8.2. Economic modelling

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and PSS using a decision analytic model. The evaluation will be constrained by available evidence.

Model structure will be determined on the basis of available research evidence and clinical expert opinion.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other relevant research literature. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from sponsor submissions to NICE.

Resource use will be specified and valued from the perspective of the NHS and PSS. The resource use associated with different health states or clinical events will be obtained or estimated either from trial data, sponsor submissions, other published sources, or – where published sources are unavailable – relevant expert contacts or NHS Trusts. Unit cost data will be identified from national NHS and PSS reference cost databases for the most recent year, or, where these are not relevant, will be extracted from published work and/or sponsor submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

Analysis of uncertainty will focus on cost utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

Search strategies for additional information regarding model parameters or topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the methodological discussion paper 'Methods for establishing parameter values for decision analytic models' commissioned by the UK Dept. of Health and produced by InterTASC (January 2005). In addition to systematic reviews and RCTs other UK studies will be considered if appropriate.

ICERs estimated from Consultee models will be compared with the respective ICERs from the Assessment Group's model, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

12.8.2.1. Methods for measuring and valuing health effects

Ideally, the measurement of changes in health-related quality of life (HRQL) should be reported directly from patients. The value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D will be the preferred measure of HRQL for the purposes of estimating QALYs. In the absence of reliable EQ-5D utility data from relevant trials or patient groups, the use of alternative sources for utility weights for health states will be informed by the NICE Guide to the methods of technology appraisal (2013).[168]

12.8.2.2. Time horizon, perspective and discounting

The time horizon of our analysis will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%.[168]

12.9. Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the ERG no later than 02/10/2013. Data arriving after this date may not be considered.

Any economic evaluations included in the company submission will be assessed against NICE's guidance on the Methods of Technology Appraisal and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. Where the TAR team have undertaken further analyses, using models submitted by manufacturers/sponsors or via de novo modelling and cost effectiveness analysis, a comparison will be made of the alternative models used for the analysis.

Tabulated summaries and technical commentaries on the economic models used in the manufacturer submissions will be provided. This will not be a full critique as for a single technology appraisal but will be used to reflect on the results from the PenTAG *de novo* model and to discuss any differences identified in the outcomes provided.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be [redacted] in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be [redacted] in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

12.10. Expertise in this TAR team

Name	Institution	Expertise
Simon Briscoe	PenTAG, University of Exeter Medical School	Information Specialist
Helen Coelho	PenTAG, University of Exeter Medical School	Assessment of publication bias
Louise Crathorne	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical effectiveness review) and project management
Marcela Haasova	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical effectiveness review)
Martin Hoyle	PenTAG, University of Exeter Medical School	Health economics and economic modelling (lead)
Nicola Huxley	PenTAG, University of Exeter Medical School	Economic modelling and economic evaluation

Chris Hyde	PenTAG, University of Exeter Medical School	Systematic reviewing and economic evaluation. Director of TAR group and project guarantor
Tracey Jones-Hughes	PenTAG, University of Exeter Medical School	Lead systematic reviewer (quality of life review)
Linda Long	PenTAG, University of Exeter Medical School	Systematic reviewing (quality of life review)
Ruben Mujica-Mota	PenTAG, University of Exeter Medical School	Health Economist
Mark Napier	Royal Devon & Exeter Hospital, Devon	Clinical Medical Oncologist
Jaime Peters	PenTAG, University of Exeter Medical School	Advising re publication bias and mixed treatment comparison
Claudius Rudin	Royal Devon & Exeter Hospital, Devon	Consultant Haematologist
Kate Scatchard	Royal Devon & Exeter Hospital, Devon	Consultant Oncologist
Tristan Snowsill	PenTAG, University of Exeter Medical School	Economic modelling and economic evaluation

Other external experts: We are also collaborating with Simon Stanworth of the NHS Blood and Transplant Centre (NHSBT), and Julia Bohlius and Thomy Tonia from the Cochrane Haematological Malignancies Group.

Other PenTAG resources: Depending on the agreed scope of work we will draw on other PenTAG resources as required.

12.11. TAR centre

12.11.1. About PenTAG:

The Peninsula Technology Assessment Group is part of the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme, systematic reviews and economic analyses for the NICE Centre for Public Health Excellence, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Institute of Health Research is made up of

discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

Health technology assessment projects include:

- A systematic review and economic evaluation of intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer
- Dasatinib and Nilotinib for the 1st line treatment of chronic phase chronic myeloid Leukaemia (CML): a systematic review and economic model
- Bevacizumab, Cetuximab, and Panitumumab for in colorectal cancer (metastatic) after failure of 1st line chemotherapy: a systematic review and economic model
- The psychological consequences of false positive mammograms: a systematic review
- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp
- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK
- Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: a critique of the submission from Novartis
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer

12.12. Competing interests of authors

None

12.13. Timetable/milestones

Action	Expected due date
Draft protocol due	3 June 2013
Comments on draft protocol sent to AG	10 June 2013
Final protocol due	13 June 2013
Sign-off of final protocol	24 June 2013
Consultee information meeting	12 August 2013
Manufacturers submissions due	2 October 2013
Progress report due	9 October 2013
Draft assessment report due	10 December 2013
Comments on draft assessment report	17 December 2013
Assessment report due	14 January 2014
1st Appraisal Committee meeting	19 March 2014

Appendix B: Literature search strategies

13.1. Clinical Effectiveness

Database: MEDLINE(R)
Host: OVID
Data Parameters: 1946 to May Week 3 2013
Date Searched: 24/5/2013
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")

Database: MEDLINE(R) In-Process & Other Non-Indexed Citations
Host: OVID
Data Parameters: May 23, 2013
Date Searched: 24/5/2013
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"

Database: EMBASE
Host: OVID
Data Parameters: 1980 to 2013 Week 21
Date Searched: 29/5/2013
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")

Database: CENTRAL
Host: Cochrane Library
Data Parameters: Issue 4 of 12, April 2013
Date Searched: 24/5/2013
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

Database: Web of Science
Host: Thomson Reuters
Data Parameters: N/A
Date Searched: 28/5/2013
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

Database: CINAHL
Host: EBSCO
Data Parameters: N/A
Date Searched: 29/5/2013
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 de-duplicated: clinical effectiveness

Database	Hits
MEDLINE	342
MEDLINE-in-Process	28
EMBASE	865
CENTRAL	219
Web of Science	745
CINAHL	79
Total	**2278**
Automatically de-duplicated	**845**
Manually de-duplicated	**97**
Total records to screen	**1,336**

13.2. Cost effectiveness

Database: MEDLINE(R)
Host: OVID
Data Parameters: 1946 to May Week 3 2013
Date Searched: 29/5/2013
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")

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Host: OVID
Data Parameters: May 28, 2013
Date Searched: 29/5/2013
Searcher: SB
Hits: 13
Strategy:

Lines 1-9: see MEDLINE-in-Process 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"

Database: EMBASE
Host: OVID
Data Parameters: 1980 to 2013 Week 21
Date Searched: 29/5/2013
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")

Database: NHS EED
Host: Cochrane Library
Data Parameters: Issue 2 of 4, April 2013

Date Searched: 24/5/2013
Searcher: SB
Hits: 10
Strategy: See CENTRAL clinical effectiveness strategy

Database: Web of Science
Host: Thomson Reuters
Data Parameters: N/A
Date Searched: 29/5/2013
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

Database: CINAHL
Host: EBSCO
Data Parameters: N/A
Date Searched: 29/5/2013
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

Database: HEED
Host: Cochrane Library
Data Parameters: N/A
Date Searched: 29/5/2013
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 de-duplicated: cost effectiveness

Database	Hits
MEDLINE	144
MEDLINE-in-Process	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**

13.3. Quality of Life

Database: MEDLINE(R)
Host: OVID
Data Parameters: 1946 to May Week 4 2013
Date Searched: 30/5/2013
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")

Database: MEDLINE(R) In-Process & Other Non-Indexed Citations
Host: OVID
Data Parameters: May 29, 2013
Date Searched: 30/5/2013
Searcher: SB
Hits: 19
Strategy:

Lines 1-9: see MEDLINE-in-Process 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"

Database: EMBASE
Host: OVID
Data Parameters: 1980 to 2013 Week 21
Date Searched: 30/5/2013
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")

Database: Web of Science
Host: Thomson Reuters
Data Parameters: N/A
Date Searched: 30/5/2013
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

Database: CINAHL
Host: EBSCO
Data Parameters: N/A
Date Searched: 30/5/2013
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

Database: BNI
Host: ProQuest
Data Parameters: N/A
Date Searched: 31/5/2013
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 de-duplicated: quality of life

Database	Hits
MEDLINE	369
MEDLINE-in-Process	19
EMBASE	952
Web of Science	646
CINAHL	111
BNI	43
Total	**2140**
Automatically de-duplicated	**805**
Manually de-duplicated	**67**
Total records to screen	**1268**

13.4. Update searches

Numbers of references retrieved and de-duplicated

All update searches were run on 2nd December 2013 and date limited from 1st January 2013 – 2nd December 2013.

Clinical effectiveness

Database	Hits
MEDLINE	11
MEDLINE-in-Process	8
EMBASE	44

CENTRAL	2
Web of Science	32
CINAHL	1
Total	**98**
Automatically de-duplicated	**30**
Manually de-duplicated	**0**
Total records to screen	**68**

Cost effectiveness

Database	Hits
MEDLINE	8
MEDLINE-in-Process	5
EMBASE	47
NHS EED	2
Web of Science	11
CINAHL	0
HEED	0
Total	**73**
Automatically de-duplicated	**17**
Manually de-duplicated	**5**
Total records to screen	**51**

Quality of Life

Database	Hits
MEDLINE	9
MEDLINE-in-Process	8
EMBASE	46
Web of Science	25
CINAHL	0
BNI	0
Total	**88**
Automatically de-duplicated	**24**
Manually de-duplicated	**3**
Total records to screen	**61**

13.5. Supplementary searches (1): reviews and reports

Database: CDSR, DARE and HTA
Host: Cochrane Library
Data Parameters: CDSR: Issue 4 of 12, April 2013; DARE and HTA: Issue 2 of 4 Apr 2013
Date Searched: 24/5/2013
Searcher: SB
Hits: CDSR=8; DARE=16; HTA=6

Strategy: See CENTRAL clinical effectiveness strategy

Database: HMIC
Host: OVID
Data Parameters: 1979 to March 2013
Date Searched: 30/5/2013
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 de-duplicated: reviews and reports

Database	Hits
CDSR	8
DARE	16
HTA	6
HMIC	2
Total	**32**
Manually de-duplicated	**3**
Total records to screen	**29**

13.6. Supplementary searches (2): Hb level

The references for these two searches were not de-duplicated because they were only searched in MEDLINE and each search was sent to the review team as a separate Endnote file.

Hb level over time after stopping chemotherapy

Database: MEDLINE(R)
Host: Ovid
Data Parameters: 1946 to September Week 1 2013
Date Searched: 17/9/2013
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 Hb level

Database: MEDLINE(R)
Host: Ovid
Data Parameters: 1946 to September Week 1 2013
Date Searched: 18/9/2013
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 C: Application of license in included studies

Study, year	n	Arms	Malignancy	Treatment	Initial treatment	Start Hb level	Target Hb level	Dose adjustment
Licence details ***Epoetin Alfa*** ***Epoetin Beta***[a]		**Initial treatment: 150 IU/kg SC TIW or 450 IU/kg SC QW** **Start Hb level: Hb ≤10 g/dl** **Target HB level: 10−12 g/dl** **Dose adjustment: 4 wks: 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 Hb: reduce dose 25-50%** **Hb ≥12 g/dl: reduce dose 25-50%** **Hb ≥13 g/dl: stop & re-initiate at Hb 12 g/dl at 25% lower dose**						
Abdelrazik, 2007[b]	60	Epoetin alfa vs Standard	Haem	Chemo: NR	**450 IU/kg QW**	<10.5 g/dl	11−13 g/dl	From Wk 5: dose **increased in 50%** if Hb ≤11.5 g/dl; if transfusion was needed; **if ≤ 1 g/dl increase.** Hb >15 g/dl or rapid increase (>1.3 g/dl in any 2 wks period): decrease dose by 50%. If Hb >16 g/dl dose withheld until Hb <12 g/dl or in the event of complications (deep vein thrombosis, hypertension, flushing).
Abels, 1993	413[c]	Epoetin alfa vs Placebo	Solid & haem	Chemo: mixed	**150 IU/kg TIW**	≤10.5 g/l or haematocrit ≤32%	NR	No dose escalation used. Dosing continued for 12 wks; if haematocrit ≥ 38% withheld until haematocrit fell below 38%.
Aravantinos, 2003	47	Epoetin alfa vs Standard	Solid	Chemo: mixed	**150 IU/kg TIW**	**<10.5 g/dl**	NR	No dose escalation used. Hb >14 g/dl: stop & re-initiate Hb <12.5 g/dl at 25% lower than start dose.
Boogaerts, 2003	262	Epoetin beta vs Standard	Solid & haem	Chemo: NR	**150 IU/kg TIW**	≤11 g/dl	12-14 g/dl	3-4 wks Hb increase <0.5 g/dl Hb, or Hb increase <1 g/dl Hb at 6- wks: dose doubled. **Hb increase >2 g/dl: dose reduced by 50%.** Hb > 14 g/dl: stop & re-initiate at Hb <12 g/dl at 50% lower than start dose.
Dammacco, 2001	145	Epoetin alfa	Haem	Chemo: mixed	**150 IU/kg TIW**	<11 g/dl	12-14 g/dl	**4 wks Hb increase <1 g/dl: dose doubled**. **4 wks Hb increase ≥2 g/dl: dose reduced by 25**%.

Study, year	n	Arms	Malignancy	Treatment	Initial treatment	Start Hb level	Target Hb level	Dose adjustment
		vs Placebo						Hb >14 g/dl stop & re-initiate at Hb ≤12 g/dl at 25% lower than start dose.
Del Mastro, 1999	62	rHuEPO[d] vs Standard	Solid (breast)	Chemo: non-plat	**150 IU/kg TIW**	≤12 g/dl	NR	If Hb >15.0 g/dl in 2 consecutive weekly assays, treatment stopped until Hb <13.0 g/dl.
Dunphy, 1999	30	rHuEPO[d] vs Standard	Solid (head & neck, lung)	Chemo: mixed	**150 IU/kg TIW**	NR; note rHuEPO was initiated if Hb≤16g/dl	NR	1st course of chemo: Hb increase <1 g/dl: dose doubled. 2nd course of chemo: Hb increase <1 g/dl: dose increased to 450 IU/kg. Hb ≥18 g/dl stop & re-initiate at Hb ≤16 g/dl.
Grote, 2005	224	Epoetin alfa vs Placebo	Solid (SCLC)	Chemo: mixed	**150 IU/kg TIW**	≤14.5 g/dl	14-16 g/dl	Dose escalation not permitted. Hb >16 g/dl: stop & re-initiate at Hb <14 g/dl at 50% lower dose.
Kurz, 1997	35	Epoetin alfa vs Placebo	Solid (cervix, ovary, uterus)	Chemo: mixed	**150 IU/kg TIW**	<11 g/dl	NR	**4 wks Hb increase <1 g/dl: dose doubled.**
Littlewood, 2001	375	Epoetin alfa vs Placebo	Mixed	Chemo: non-plat	**150 IU/kg TIW**	≤10.5g/dl, or >10 and ≤ 12g/dl with ≥1.5 g/dl decrease in Hb per/cycle, per/month	12-15 g/dl	4 wks Hb increase <1 g/dl and reticulocyte count increase <40 000 cells/µl: dose was doubled to 300 IU/kg **4 wks Hb increase ≥2 g/dl: reduce dose by 25%.** If Hb >15 g/dl: stop & re-initiate at Hb <12 g/dl at 25% lower dose.
Moebus, 2013	643	Epoetin alfa vs Standard	Solid (breast)	Chemo: non-plat	**150 IU/kg TIW**	NR	12.5−13 g/dl	**4 wks Hb increase <2 g/dl: dose doubled.** If Hb >14 g/dl: stop & re-initiate at Hb <13 g/dl.
Osterborg, 2002, 2005	349	Epoetin beta vs	Haem	Chemo: non-plat	**150 IU/kg TIW**	**<10g/dl** [e]	13-14 g/dl	4 wks Hb increase <0.5 g/dl : dose doubled. 4 wks Hb <8.5 g/dl or transfusion: dose doubled.

Study, year	n	Arms	Malignancy	Treatment	Initial treatment	Start Hb level	Target Hb level	Dose adjustment
		Placebo						**4 wks Hb increase >2 g/dl: reduce dose by 50%.** If Hb >14 g/dl: stop & re-initiate at Hb ≤13 g/dl at 50%.
Ray-Coquard, 2009	218	Epoetin alfa vs Standard	Mixed	Chemo: NR	**150 IU/kg TIW**	<12 g/dl	**12-14 g/dl**	4 wks Hb increase <1 g/dl and Hb <10.5 and reticulocyte count <40 000 cells/µl: dose increased to 60 000 UI weekly. 4 wks Hb increase ≥2 g/dl: reduce dose by 25%. If Hb >12 g/dl: stop & re-initiate at ≤12 g/dl
Silvestris, 1995	54	Epoetin alfa vs Standard	Haem	Chemo: NR	**150 IU/kg TIW**	**≤8 g/dl**	NR	By 6th week: dose doubled
Strauss, 2008	74	Epoetin beta vs Standard	Solid (cervix)	Chemo + Radio	**150 IU/kg TIW**	9−13 g/dl	14-15 g/dl	4 wks Hb increase <0.5 g/dl: dose doubled. **4 wks Hb increase >2 g/dl: reduce dose by 50%.** If Hb >15 g/dl: stop & re-initiate at ≤14 g/dl at 50%. If Hb <8.5 g/dl: dose doubled.
Ten Bokkel, 1998	122	Epoetin beta vs Standard	Solid (ovary)	Chemo: plat	**150 IU/kg TIW**	<13 g/dl	14-15 g/dl	**4 wks Hb increase ≥2 g/dl: reduce dose by 50%.** Hb >15 g/dl: stop & re-initiate at Hb ≤14 g/dl at 50% dose. Epo withheld while platelet counts were < 20 000µg/l.
Thatcher, 1999	130	Epoetin alfa vs Standard	Solid (SCLC)	Chemo: plat	**150 IU/kg TIW**	≥10.5 g/dl	≥10 g/dl	Hb >15 g/dl: stop & re-initiate at Hb ≤13 g/dl at 50% dose.
Licence details ***Epoetin Theta***		**Dose: 20 000 IU QW** **Start Hb level:** ≤10 g/dl **Target HB level: 10−12 g/dl** **Dose adjustment: 4 wks Hb increase <1 g/dl dose is doubled; increase to 60 000 IU if Hb increase insufficient at 8 wks** **Hb >12 g/dl: should be avoided** **12 wks Hb increase <1 g/dl: discontinue.**						
Tjulandin, 2010	223	Epetin theta,	Solid	Chemo: plat	**Epoetin theta:**	≤11 g/dl	NR	**4 wks Hb increase <1 g/dl: dose doubled; further increase to 60 000 IU if no response at 8 wks.**

Study, year	n	Arms	Malignancy	Treatment	Initial treatment	Start Hb level	Target Hb level	Dose adjustment
		Epoetin beta vs Placebo			**20 000 IU QW**			4 wks 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 wks Hb increase <1 g/dl: dose doubled**; no further increase allowed. 4 wks Hb increase >2 g/dl: dose reduced by 50%. Hb >13 g/dl: stop or reduce dose by 50%.
Tjulandin, 2011	186	Epoetin theta vs Placebo	Mixed	Chemo: non-plat	**20 000 IU QW**	≤11 g/dl	NR	**4 wks Hb increase <1 g/dl: dose doubled; further increase to 60 000 IU if no response at 8 wks.** 4 wks Hb increase >2 g/dl: reduce dose by 50%. Hb >13 g/dl: stop or reduce dose by 50%.
Licence details ***Darbepoetin Alfa***		**Dose: 2.25 µg/kg SC QW; 500 µg (6.75 µg/kg) SC Q3W** **Start Hb level: Hb ≤10 g/dl** **Target HB level:10−12 g/dl** **Dose adjustment: 4 wks <1 g/dl Hb inc. dose doubled** **4 wks ≥2 g/dl Hb reduce dose 25-50%** **Dose adj Hb ≥12 g/dl: reduce dose 25-50%** **Dose adj Hb ≥13 g/dl: stop & re-initiate at Hb 12 g/dl at 25% lower dose**						
Hedenus, 2002	33[e]	Darb alfa vs Placebo	Haem	Chemo: NR	**2.25 µg/kg QW**	≤11 g/dl	NR	**4 wks Hb increase ≥2 g/dl: 50% dose reduction.** If Hb >15.0 g/dl (men) or >14.0 g/dl (women): stop & re-initiate at Hb ≤13.0 g/dl dose reinitiated at 50%.
Hedenus, 2003	349	Darb alfa vs Placebo	Haem	Chemo: NR	**2.25 µg/kg QW**	≤11 g/dl	13-14 g/dl	**4 wks Hb increase ≤1 g/dl: dose doubled.** If Hb >15.0 g/dl (men) or >14.0 g/dl (women): stop & re-initiate at Hb ≤13.0 g/dl at 50% dose.
Kotasek, 2003	249	Darb alfa vs Placebo	Solid	Chemo: 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 & re-initiate at Hb ≤13.0 g/dl at 50% dose.
Untch, 2011	733	Darb alfa vs Standard	Solid (breast)	Chemo: non-plat	4.5 µg/kg (ev. 2 wks) [f]	NR	12.5−13 g/dl	**4 wks Hb increase <1 g/dl: dose doubled.** If Hb >14.0 g/d: stop & re-initiate at Hb ≤13.0 g/dl at 50% dose.
Vansteenkiste	314	Darb alfa	Solid (lung)	Chemo: plat	**2.25 µg/kg**	≤11 g/dl	13-14 g/dl	6 wks Hb increase <1 g/dl: dose doubled.

Study, year	n	Arms	Malignancy	Treatment	Initial treatment	Start Hb level	Target Hb level	Dose adjustment
, 2002		vs Placebo			**QW**		(women), 13-15 g/dl (men)	If Hb >15.0 g/dl (men) or >14.0 g/dl (women): stop & re-initiate at Hb ≤13.0 g/dl at 50% dose.

Key: ; Darb, darbepoetin; Hb, haemoglobin; NR, not reported ; IU, international units; QW, once weekly; Q3W, once every three weeks; RBCT, plat, platinum-based chemotherapy ; red blood cell transfusion; SC, subcutaneous; TIW, thrice weekly;

Notes: (a) Dose increase to 300IU/kg SC TIW **(b)** Intervention evaluated in paediatric population **(c)** Study population included patients not receiving chemotherapy (n=124); beyond the scope for the current review; **(d)** Assumed to epoetin alfa or epoetin beta based on date of study and dose administered **(e)** >9 to <10g/dl (if serum epo ≤100IU/L); >8 to ≤9 g/dl (if serum epo ≤180 IU/L; or, ≤8 g/dl (if serum epo 300 IU/L); **(f)** dose correct but frequency given not. **Highlighted text =** following licence**.** (unclear whether dose reduced).

Appendix D: Data extraction forms

15.1. 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	**r-HuEPO (Amgen; assumed epo alfa)**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Abels 1993	N	413: Three populations: Cyclic non-cisplatin chemotherapy (n=157) and cyclic cisplatin-chemotherapy (n= 132) and no chemo (n=124) vs Placebo (n=200)*
Objective	to examine the safety of r-HuEPO 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 a **haemoglobin ≤10.5 g/l** • ECOG ≤3 • Life expectancy ≥3 months • cyclic cisplatin an d non-cisplatin chemotherapy was to be 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 • B12 and/or iron deficiency • Autoimmune haemolysis or presence of gastrointestinal bleeding	
# centres	NR		
Other references/aliases	Abels 1996; Henry 1994; Henry 1995; Case 1993; see notes 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 r-HuEPO on an open-label basis Henry 1994 provides results for the first 6 month of EPO therapy (combined double-blind and open-label data: the mean duration of epo therapy was 17.1, 18.2 and 15.8 weeks for no chemo, no-cisplatin and cisplatin chemotherapy respectively.		
Country of corresponding author	USA		
Language of publication	English		
Sources of funding	NR		

RANDOMISATION & ALLOCATION	Series of double-blind, placebo-controlled trials: three populations of anemic cancer patients were randomized to rHuEPO or placebo. The three populations were: A) patients not receiving concomitant chemotherapy, B) patients receiving chemotherapeutic regimens which did not contain cisplatin, and C) patients receiving chemotherapeutic regimens which contained cisplatin.

TREATMENT ARMS

ARM Drug name/s	**Epo**	**Placebo**
N	206 (efficacy population)	190 (efficacy population)
Dose & freq (od, bd etc)	150 U/kg 3 times a week	150 U/kg 3 times a week
Dose adjustment Y/N	Y	
Route of administration	subcutaneously	subcutaneously
Duration of epo tx		
Adj 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); haemR (haematocrit: change from baseline, mean weekly haematocrit,# correctors and responders** neutrophil analyses; platelet analyses; HRQL (100 mm VAS: energy level, ability to perform daily activities and overall quality of life)

NOTES:
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
* 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 noncisplatin chemotherapy (Protocols I88-037, 87-016, 87-017), and treatment with cisplatin chemotherapy (Protocols I88-036, 87-018, 87-019*)*
** **Correctors**= patients who attained a haematocrit ≥38% unrelated to transfusion; **Responders**= patients whose haematocrit increased ≥6% unrelated to transfusion. Unrelated to transfusion: means that no transfusion was administered in the month prior to documenting attainment of the criterion

ANALYSIS

Statistical technique used?	Fischer's exact test was used for statistical inference for dichotomous variables (e.g. sex by treatment group) formulated as 2x2 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 via 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 EPO level, haematocrit, performance score, etc.

	All statistical tests were two-sided, with α = 0.05.
Intention to treat analysis?	Patients were considered evaluable for efficacy if they completed >15 days on study. All patients were evaluable for safety.
Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	Unclear: ITT=413; epo =213 and placebo =200; Efficacy population = 396; epo =206, placebo =190
Was attrition rate adequately dealt with?	NR
Number (%) followed up from each condition?	Unclear; Henry 1994 provides results for first 6 month of EPO therapy (combined double-blind and open-label data): n=363, efficacy population =347.

BASELINE CHARACTERISTICS				
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*			Anaemic cancer (primary myeloid malignancies and acute leukaemias excluded)	
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*			Cyclic non-cisplatin chemotherapy (n=157) and cyclic cisplatin-chemotherapy (n= 132)	
Adjuvant anaemia treatment	**Iron**		NR	
	G-CSF		NR	
	Transfusion trigger		NA; assessing RBCT req	
	Hb inclusion criteria level		Anaemia: haematocrit of ≤32% or a haemoglobin ≤10.5 g/l	
	Arm 1 = EPO N=213	**Arm 2 = Placebo N=200**	**Arm 3 = N =**	
Baseline demographics and clinical characteristics reported for the entire enrolled patient population, and are not separated out by chemotherapy treatment				
male, n	102	95		
female, n	111	105		
Age years	61.2 (13)	62.5 (14.1)		
patients evaluable for efficacy	**Arm 1 = EPO N=206**	**Arm 2 = Placebo N=190**		
Patients transfused, n (%)	44.7%	48.4%		
# RBC units transfused per patient per month prior to study	0.67 (1.08)	0.73 (1 .04)		
Mean Haematocrit, n (%)	29.1 (4)	28.5 (3.8)		
Haematocrit, (%):				
Non-cisplatin Chemo	N=79	N=74		
	28.6 (3.9)	29.4 (3)		
Cisplatin chemo	N=64	N=61		
	29.4 (4)	28.4 (14.5)		
Endogenous EPO level, mU/mL, mean (SD) [median]	146 (260) [76]	149 (217) [85]		

Median Serum EPO (mU/ml)				
Overall quality of life (mm)	50 (24)	50.4 (26)		
Tumour type:				
Haematologic, n (%)	**32%**	**32.1%**		
Non-haematologic, n (%):	**68%**	**67.9%**		
Prostate, n (%)	11.2%	9%		
Breast, n (%)	10.7%	12.6%		
Gastrointestinal, n (%)	10.2%	5.3%		
Lung, non-small cell, n (%)	10.2%	9%		
Gynaecological, n (%)	9.2%	12.1%		
Lung, small cell, n (%)	3.9%	8%		
Head and neck, n (%)	2.4%	1.6%		
Oesophagus, n (%)	1.0%	1.6%		
Unknown primary, n (%)	3.4%	1.1%		
Other, n (%)	5.8%	7.9%		

Were intervention and control groups comparable?	No p values reported, authors stated “Pooling patients across all trials shows equivalent emographic characteristics between the patients randomised to r-HuEPO and the patients andomised to placebo”

RESULTS
Reported for plat chemo & non-plat chemo (data available for no chemo but outside of scope for this appraisal)

patients evaluable for efficacy	**Arm 1 = EPO N=206**	**Arm 2 = Placebo N=190**	**Arm 3 = N =**	**p**
Response of haematocrit therapy				
Non-cisplatin Chemo	**N=79**	**N=74**		
Change in haematocrit	6.9 (6)	1.1 (4.3)	Fig 2, pS5 represents Mean weekly haematocrit (+S.E.) comparing EPO and placebo in all three populations.	<0.004
Final haematocrit	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 versus time (cells x week/µl)	30 203	34 189	As reported in Case 1993	
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 or more rise in haematocrit from baseline unrelated to transfusion	46 (58.2%)	10 (13.5%)		
Cisplatin chemo	**N=64**	**N=61**		

Change in haematocrit	6 (7)	1.3 (5)	Fig 2p S5 represents Mean weekly haematocrit (+S.E.) comparing EPO and placebo in all three populations.	<0.004
Final haematocrit	35.4 (7)	29.7 (4.5)		
Correctors	35.9	1.6		<0.008
Responders	48.4	6.6		<0.008
HaemR (≥6% points HcT withour a transfusion in the four weeks prior to that Hct value); chg from BL (mean ± SD)	6.0 ± 7.0	1.3 ± 5.0	As reported in Henry 1995; also reports BL Hct 29.4 ± 4.0 (rHuEPO) and 28.4 ± 4.5 (PBO).	
	Diff. 4.7; p<0.0001 (favours epo)			
Transfusions				
Non-cisplatin Chemo	**N=79**	**N=74**		
Proportion of pts transfused (%); overall	40.5	48.6	When the non-Cisplatin and cisplatin Chemo populatins were combined there was sig difference for Proportion of pts transfused at Month 2-3 (p≤0.005) and mean units per patients at month 2-3 (p=0.009; Table 7 page S5).	
Mean units per patients; overall	2.03 (3.88)	2.75 (4.15)		
Proportion of pts transfused (%) ; Month 1	25.3	27		
Mean units per patients; Month 1	0.69 (N=70)	0.71(N=68)		
Proportion of pts transfused (%); Month 2-3	28.6 (N=70)	36.8 (N=68)		
Mean units per patients; Month 2-3	0.91	1.65		0.056
Patients transfused, n (%)			As reported in Case 1993	
Month1 (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				
Month1 (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 chemo	**N=64**	**N=61**		
Proportion of pts transfused (%); overall	53.1	68.9	When the non-cisplatin and cisplatin chemo populations were combined there was sig difference for Proportion of pts transfused at Month 2-3	
Mean units per patients; overall	3.56 (7.01)	4.01 (4.87)		
Proportion of pts transfused (%) ; Month 1	43.8	44.3		
Mean units per patients; Month 1	1.71	1.2		

Proportion of pts transfused (%); Month 2-3	26.8 (N=56)	56.4 (N=55)	(p≤0.005) and mean units per patients at month 2-3 (p=0.009; Table 7, pS5).	≤0.005
Mean units per patients; Month 2-3	1.2 (N=56)	2.02 (N=55)		0.089
Neutrophil and platelet analyses , and mean haematocrit were similar across all groups at time of transfusion (see Table 7 & 8, p S5 and S6 for more details.				
RBCT least squares mean				
Patients transfused, n (%)				As reported in Henry 1995
N	**64**	**61**		
All patients	34 (53.1)	42 (68.9)	p>0.05	
Month1 (n=64)	28 (43.8)	27 (44.3)	p>0.05	
Month 2 (n=56)	12 (21.4)	27 (49.1)	p<0.005	
Month 3 (n=47)	8 (17.0)	13 (28.3)		
Months 2 & 3 (n=56)	15 (26.8)	31 (56.4)		
Mean units transfused ± SE				
N	**56**	**53**		
Mean units transfused ± SE	4.01 ± 0.85	3.95 ± 0.84	p>0.05	
Month1 (n=79)	1.71 ± 0.28	1.20 ± 0.29	p>0.05	
Month 2	0.71 ± 0.22	1.30 ± 0.22	p=0.0572	
Month 3	0.42 ± 0.16	0.62 ± 0.16	-	
Months 2 & 3 (n=70)	1.20 ± 0.33	2.02 ± 0.33	P=0.0893	
Haematological vs. non-haematological tumour				
Change in haematocrit from baseline to final value by tumour type (%)				
• CLL	6 (N=7)	0.9 (N=9)	Since the data for any turnout type may include patients from the NC, NCC and CC treatment groups, duration of therapy can range from 8 (NC) to 12 (NCC, CC) weeks.	0.077
• Myeloma	3.7 (N=19)	0.3 (N=23)		0.058
• Lymphoma	6 (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)		
• GI cancer	5.8 (N=21)	1.6 (N=10)		≤0.05
• Gynaecological cancer	7.7 (N=18)	-0.3 (N=23)		≤0.05
Tumour type and bone marrow infiltration was similar at baseline and among responders (Table 10 p S6).				
Health-related QoL				
• reported for the entire enrolled patient population, and are not separated out by chemotherapy treatment. Data presented graphically: Fig 3 and 4, pS6				
As reported in Case 1993:				
Prestudy and post study QoL assessments were available for 124 patients (rHuEPO n=63; placebo n=61); rHuEPO-treated population as a whole had a statistically significant (p≤0.05) increase in 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 QoL. No similar improvements in QoL assessments were seen in placebo-treated patients. The changes in QoL scores were of somewhat greater magnitude in the rHuEPO-				

treated populations with an increase in haematocrit to 38% or more or an increase of 6 % points or more (both unrelated to transfusion) than in the rHuEPO-treated population as a whole. DATA NOT SHOWN; DATA REPORTED GRAPHICALLY					
As reported in Henry 1995					
Patients in the rHuEPO-treated group experienced a significant p≤0.05 prestudy to poststudy improvement in energy level, ability to perform daily activities, and overall QoL. Patients in the PBO group also experienced a significant (p≤0.05) prestudy to poststudy improvement in their energy levels, but not in their ability to perform daily activities or overall QoL. Comparing the two treatment arms , there was a significantly greater prestudy to poststudy change in the overall QoL 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, QoL changes were even greater in favour of rHuEPO, but did not achieve significance, because of smaller numbers. DATA NOT SHOWN; DATA REPORTED GRAPHICALLY					
Adverse effects of tmt: **reported for the entire enrolled patient population, and are 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%			
no antibodies against r-HuEPO developed during the course of therapy.					
Hypertension	5%	3.5%			>0.05
Non-cisplatin Chemo	As reported in Case 1993:				
ITT population	N=81	N=76			>0.05
# patients completed the study	63 (78%)	63 (83%)			>0.05
# pts who discontinued study prematurely because of an adverse experience, death, or disease progression	13 (16%)	8 (11%)			=0.05
Diarrhoea, n (%)	18 (22%)	8 (10%)			<0.05
Diaphoresis, n (%)	9 (11%)	1 (1%)			
Hypertension, n (%)*	4	2			
Seizure, n (%)**	2	2			
Thromboembolic events, n (%)	4	4			
No statistically significant difference in the incidence of any adverse experience in rHuEPO –treated patients compared with placebo –treated patients except for Diarrhoea (p=0.05) and Diaphoresis (p<0.05).					

* 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 mm Hb. The haematocrit in this patient increased from 31% at baseline to 43% at the time the hypertension was reported (Day 57) ** 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) .					
Cisplatin Chemo	As reported in Henry 1995				
	rHuEPO	**PBO**			
N	**67**	**65**			
Overall	58 (87)	58 (89)			
≥10% patients					
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)			
Edema	9 (13)	6 (9)			
Anorexia	7 (10)	10 (15)			
Bacterial infection	7 (10)	7 (11)			
Paresthesia	7 (10)	5 (8)			
Med site RXN	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% patients selected AEs					
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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear (states randomised but no details given)				
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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 “Pooling patients across all				

	trials shows equivalent demographic characteristics between the patients randomised to r-HuEPO and the patients randomised to placebo"
4. WERE THE ELIGIBILITY CRITERIA SPECIFIED?	Y
5. WERE THE PARTICIPANTS BLIND TO TREATMENT ALLOCATION?	Y (states double-blind)
6. WERE THE OUTCOME ASSESSORS BLIND TO TREATMENT ALLOCATION?	Y (states double-blind)
7. WERE THE POINT ESTIMATES AND MEASURE OF VARIABILITY PRESENTED FOR THE PRIMARY OUTCOME MEASURE?	Partially
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	N
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Unclear
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	After completion of double-blind therapy, patients were eligible to receive r-HuEPO on an open-label basis,

NOTES:

References:

Abels, 1996: Reports pooled data from the three chemotherapy populations:

Abels, R. I., Larholt, K. M., Krantz, K. D., & Bryant, E. C. (1996). Recombinant Human Erythropoietin (rHuEPO) for the Treatment of the Anemia of Cancer. *Oncologist*, 1(3), 140-150.

Henry, 1994: After completion of double-blind therapy, patients were offered to receive r-HuEPO on an open-label basis, this paper reports open-label follow up data:

Henry, D. H. and R. I. Abels (1994). "Recombinant human erythropoietin in the treatment of cancer and chemotherapy-induced anemia: results of double-blind and open-label follow-up studies." Semin Oncol 21: 21-28.

Subgroup analysis

Case, 1993: Analysis of non-cisplatin chemotherapy subgroup:

Case, D. C., Jr., Bukowski, R. M., Carey, R. W., Fishkin, E. H., Henry, D. H., Jacobson, R. J., . . . et al. (1993). Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. J Natl Cancer Inst, 85(10), 801-806.

Henry, 1995: Analysis of cisplatin chemotherapy subgroup:

Henry, D. H., B. J. Brooks, Jr., D. C. Case, Jr., E. Fishkin, R. Jacobson, A. M. Keller, J. Kugler, J. Moore, R. T. Silver, A. M. Storniolo, R. I. Abels, D. S. Gordon, R. Nelson, K. Larholt, E. Bryant and S. Rudnick (1995). "Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy." Cancer J Sci Am 1(4): 252-260. Data for plat chemo subgroup

OTHER	
Generalisability	
Author conclusions	r-HuEPO increases haematocrit and corrects anaemia in cancer patients whether or not they are receiving chemotherapy, and apparently without regard to type of cancer. In a dose of 150 U/kg three times weekly, r-HuEPO 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. r-HuEPO also appears to be well-tolerated in this patient population.

Reviewer comments	

Endnote Ref ID	**2685**	**Malignancy type**	**Solid (ovarian, lung & stomach)**
		Treatment	**rHuEPO: epoetin alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Aravantinos, 2003	N	47
Objective	To evaluate the safety of 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 due to malignant disease, performance status of 0-2 according to the ECOG, and life expectancy ≥3 mths. Patients with **Hb values <10.5 g/dL** before initiation or during chemotherapy, receiving platinum-based combinations on a 3-4 weekly schedule lasting for not more than 5 days per cycle. Lab requirements WBC >3,500/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 (DBP >100 mg Hb), and suspicion of iron, folic or B_{12} deficiency. Patients who had received radiotherapy or had undergone surgery 2 weeks prior to study entry, or had received a red blood cell transfusion the week before	
# centres	1		
Other references/aliases	NA		
Geographical setting	Greece		
Duration of treatment	Unclear; median 5 cycles		
Length of follow-up (if different)	NR		
Country of corresponding author	Greece		
Language of publication	English		
Sources of funding	Not reported		
RANDOMISATION & ALLOCATION	Randomised, unblinded, single centre Stratified: type of malignancy, type of platinum compound (cisplatin or carboplatin), & chemo cycle number at study entry (1st vs 2nd vs 3rd)		

TREATMENT ARMS		
ARM Drug name/s	**rHuEPO**	**Control: No rHuEPO**
N	24	23
Dose & freq (od, bd etc)	150 IU/kg Q3W	NA
Dose adjustment Y/N	Y: Hb value >14 g/dL rHuEPO administration was interrupted and re-initiated in a dose reduced by 25% when Hb was <12.5 g/dL. No escaliation of the rHuEPO dose was attempted in case of failure to increase Hb >1 g/dL in a month. Dose adjustments were made according to body weight on the first day of the following chemo cycle.	NA
Route of administration	Subcutaneous	NA
Duration of epo tx	NR	NR
Adj anaemia treatment	200 mg elementary iron daily	200 mg elementary iron daily
Transfusion trigger	Discretion of treating physician but	Discretion of treating physician but

	avoided if Hb was >9 g/dL		avoided if Hb was >9 g/dL
OUTCOMES			
Primary outcome	**the reduction of transfusion requirement: # transfusions (per grp & per patient)**	**Other outcomes**	Hb level (chg per cycle); Ht level (chg per cycle); RBC (chg per cycle);# patients requiring transfusion;

ANALYSIS	
Statistical technique used?	ANOVA with 2 parameters was used for the administration of EPO, follow-up, RBC transfusions and cycle number. Statistical significance was tested in relation to EPO administration (with or without EPO) and in relation to Cycle number ANOVA with 1 parameter was used to identify statistically significant differences in relation to the use of EPO and in relation to Cycle number Post-hoc comparisons and Scheffe-tests followed in order to assess the statistical significance of difference between the 2 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 P value <0.05 considered significant
Intention to treat analysis?	Unclear; likely ITT as no crossover and results reported for full data set but not mentioned in the study write-up
Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	Not reported
Attrition rate (loss to follow-up)?	Not reported
Was attrition rate adequately dealt with?	Unclear; attrition rate not reported
Number (%) followed up from each condition?	NA

BASELINE CHARACTERISTICS		
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		**Solid – ovarian, lung, stomach, other**
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		**Platinum-based(cisplatin or carboplatin)**
Adjuvant anaemia treatment	**Iron**	**200 mg elementary iron daily**
	G-CSF	**Not reported**
	Transfusion trigger	**Discretion of treating physician but avoided if Hb**

					was >9 g/dL	
	Hb inclusion criteria level				**Hb <10.5 g/dL**	
	Arm 1 = rHuEPO N = 24		**Arm 2 = No rHuEPO N = 23**		**Arm 3 = N =**	
Sex						
male (%)	2	(8%)	7	(30%)		
female (%)	22	(92%)	16	(70%)		
Age years median (range)	59 (18-76)		64 (23-75)			
Performance status: ECOG						
0	11	(45.8%)	14	(60.9%)		
1	8	(33.3%)	4	(17.4%)		
2	5	(20.9%)	5	(21.7%)		
Type of solid tumour						
Ovarian	16	(67%)	10	(43%)		
Lung	3	(12.5%)	5	(22%)		
Stomach	2	(8%)	2	(9%)		
Other	3	(12.5%)	6	(26%)		
# of chemotherapy cycle at study entry						
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 baseline (g dl^{-1})	NR		NR			
Hb at cycle 1	9.8	0.5	9.32	0.8	Reported values are assumed to be means and SD	
Iron baseline (U/l median (range)	NR		NR			
Epo baseline (mU ml^{-1})	NR		NR			
Target Hb	NR		NR			
Were intervention and control groups comparable?	No p values reported, authors stated “all characteristics were well-balanced between the two groups”.					

RESULTS

	Arm 1 = rHuEPO	**Arm 2 = No rHuEPO**	**Arm 3 = N =**		**p**
	N = 24	**N = 23**			
Median # of chemo cycles	5	5			

Mean Hb by cycle (Reported values are assumed to be means and SD)						
Cycle 1	9.8 ± 0.5		9.32 ± 0.8			
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 to controls: P<0.03		10.31 ± 1.56			
Cycle 5	12.11 ± 1.39 Hb increase compared to controls P<0.03		10.55 ± 1.83			
P value for all cycles						<0.0002
Mean haematocrit by cycle						
Cycle 1	28.56 ± 4.92		28.74 ± 2.68			
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 Ht increase compared to controls P<0.002		31.58 ± 4.54			
Cycle 5	36.43 ± 4.33		32.2 ± 5.63			
RBC count (x $10^4/mm^3$) by cycle						
Cycle 1	3.46 ± 0.42		3.46 ± 0.59			
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						
# patients requiring RBCT	9	(37.5%)	23	(100%)		<0.0001
# 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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear; stratification
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially	NR

numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was alternate, or based on information known to the triallist)	
3. WERE THE GROUPS SIMILAR AT BASELINE IN TERMS OF PROGNOSTIC FACTORS; E.G. SEVERITY OF DISEASE?	Unclear; p values not reported authors stated “all characteristics were well-balanced between the two 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?	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)
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes; results reported for full population, no crossover so appears to be ITT but not mentioned in study description
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	NR

NOTES:

Levels of Hb within rHuEPO group increased with cycle number becoming statistically significant in Cycle 5. Similarly there was a trend for increase in the no rHuEPO group (<0.06)

There was statistically significant increase of the Ht level in rHuEPO compared to no rHuEPO especially in Cycle 4 ($p<0.002$), with a statistically significant increase of Ht level during cycles, more significant in Cycles 4 and 5

A tendency towards higher RBC numbers per cycle was seen in Group A patients

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 compared to 4.2% in Cycle 5). Similarly in no-rHuEPO there was a decrease in transfusion requirements from 65.2% in Cycle 2 to 30.4% in Cycle 5. Not statistically significant for either group

For the 9 patients in the rHuEPO group requiring transfusion, 56% of them received their first transfusion in Cycle 2 of chemotherapy, while only 22.2% in Cycles 3 or 4. There was a significant fluctuation of the % of patients requiring transfusion per cycle (21.7% Cycle 1; 47.8% in Cycle 2; 8.7% in Cycle 3; 13% in 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 Ht levels proved reliable indicators for response to rHuEPO treatment.
Reviewer comments	Trial unblinded

Endnote Ref ID	2710	Malignancy type	haem & solid
		Treatment	Epoetin beta

STUDY DESIGN		PARTICIPANTS	
Author, year	Boogaerts, 2003	N	262
Objective	To assess the impact of epoetin beta on QoL compared with standard care in anaemic patients with lymphoid or solid tumour malignancies	**Inclusion criteria:** Adult outpatients; **Hb ≤11 g/dl** associated with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia and any solid tumour treated with myelosuppressive chemotherapy with at least 3 cycles remaining; WHO performance status of ≤2 & a life expectancy of 6 mths **Exclusion criteria:** Anaemia arising for other reasons (iron or Vitamin B12 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 child bearing age who were practising unreliable contraception. Any patient scheduled to undergo bone marrow or peripheral stem cell transplantation during the study period or 4 wks prior to the study.	
# centres	Multicentre, conducted between October 1996 and September 1998.		
Other references/aliases	Coiffier 1999 (abstract) **see notes**		
Geographical setting	8 countries: Austria, Belgium, Franec, Germany, Italy, South Africa, Sweden, UK)		
Duration of treatment	12 wks (plus run in period of up to 2 weeks)		
Length of follow-up (if different)	26 wks?		
Country of corresponding author	Belgium		
Language of publication	English		
Sources of funding	NR		
RANDOMISATION & ALLOCATION	Patients were randomised 1:1 stratified according to centre to receive either epoetin beta or standard care with transfusion support		

TREATMENT ARMS

ARM Drug name/s	**Epoetin beta**	**Standard care**
N	133	129
Dose & freq (od, bd etc)	150 U/kg/Q3W Average dose of epo over the study period was174 IU/kg per administration.	–
Dose adjustment Y/N	Dose increased to 300 U/kg/Q3W for those patients in whom Hb levels increased by <0.5 g/dl after 3-4 wks or <1 g/dl after 6-8 wks. The dose was reduced by 50% if the Hb level increased by >2 g/dl per mth, while treatment was interrupted if Hb levels increased to >14 g/dl.Treatment was recommenced at half the previous dose once the Hb level had declined to <12 g/dl.	–
Route of administration	Subcut.	–
Duration of epo tx	12 wks	NR
Adj anaemia treatment	Oral iron supplementation (200–300	Oral iron supplementation (200–300

	mg elemental iron per day) as indicated (transferrin sat. <15%)	mg elemental iron per day) was indicated (transferrin sat. <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	**HRQL (chg from BL to Wk 12 in SF-36, FACT-An, FACT-F)**	**Other outcomes**	HaemR (defined as ≥2 g/dl without transf. req. after the first 4 wks (lso measured HaemR as inc in ≥2 g/dl or increase to ≥12 g/dl); Change in Hb BL to Wk 12 (+ changes in Hb& corresponding changes in QoL); RBCT; HRQL* (chg from BL to Wk 12 VAS; FACT-An Global); AEs** (incl # of hospitalisations)

NOTES:
Clinic visits were every 3 or 4 weeks for pts off chemotherapy. Clinical outcomes were collected at each psot baseline visit. QoL was assessed at baseline, after 3-4 wekke sand 6-8 weeks and et the end fo the study.
* All QoL assessments were performed immediately prior to the clinic visits so that patients could not eb influenced by reference to Hb levels
** 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 drug-related or not

ANALYSIS

Statistical technique used?	Psychometric evaluation was performed to evaluate how well the QoL 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 a. Cronbach's a, 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 equal to or greater than 0.70 have been recommended for group level comparisons (Nunnaly, 1978). For QoL 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 its raw form and using the last observation carried forward (LOCF) approach, for patients with missing values at the final visit. For the percentage of clinical responders, Kaplan–Meier estimates and corresponding confidence intervals (CIs) for time to treatment response were determined, and curves were compared using the log-rank test. The O/P log serum erythropoietin ratio was derived from reference regression at the particular Hct or Hb level, and was calculated for responders and nonresponders to epoetin b. The relation between endogenous erythropoietin level and response to treatment was explored using the odds ratio (OR) and relative risks (RR) (Cazzola and Beguin, 1992). Appropriate parametric and nonparametric 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.
Intention to treat analysis?	Yes, ITT=262
Does statistical technique adjust for confounding?	NR
Power calculation (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 an SD of 10 using a two-sided test with a statistical power of 80% and α 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 in the study (epoetin beta, n=30; control (n=21); 20 of them were for 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
Number (%) followed up from each condition?	NR

BASELINE CHARACTERISTICS		
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		Haem & solid
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		Chemo, NR
Adjuvant anaemia treatment	**Iron**	Oral iron supplementation (200–300 mg elemental iron per day) was indicated (transferrin sat. <15%)
	G-CSF	NR
	Transfusion trigger	Hb 8.5 g/dl
	Hb inclusion criteria level	Hb ≤11 g/dl

Evaluable population	**Arm 1 = EPO N=133**	**Arm 2 = Controls N=129**	**p**	
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)		
EPO, mU/mL mean (SD) (N=25)	54 (7–1,650)	58 (5–4,300)		
Iron, serum, mg/dL mean (SD) (N=26)	63.7 (6–472)	78.8 (4–510)		
Iron saturation, % mean (SD) (N=26)	20.6 (1–97)	29.0 (2–100)		
Folic acid, mg/mL mean (SD) (N=25)	NR	NR		
B12, pg/mL mean (SD)	NR	NR		

(N=24)				
BL QoL 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)		P=0.02
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)" With respect to QoL measures, BL scores on the FACT-An subscale were comparable between treatment groups, although those randomised to epoetin beta therapy had lower **Fact-F subscale** score relative to the control group (p=0.02).			

RESULTS					
	Arm 1= EPO n=133	**Arm 2 = Controls n=129**			**p**
HaemR, n (%)					
Responders increase ≥2 g/dl	63 (47)	17 (13)			<0.001
Responders increase ≥2 g/dl or increase to ≥12 g/dl	65 (49)	19 (15)			
Graph showing response Figure 2					
Hb BL to Wk 12, median increase (range) (n)					
All patients	2.1 (-3 to 8) (n=112)	0.9 (-3 to 6) (n=112)			<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)	1.0 (NR) (n=88)			
Without chemotherapy	2.0 (NR) (n=38)	0.2 (NR) (n=24)			
Graph showing Hb change Figure 3 add the figure here?					
Transfusions					
Hb level before transfusion, median	7.64g/dl	7.8g/dl			
Pts transfused, in last 8 weeks of study, %	22%	43%			<0.001
Pts transfused, overall, %	32%	52%			=0.001
Units transfused per patient was reduced by 45% during the treatment period with epo beta.					
Health-related QoL					
Cronbach α: 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, while the FACT-An 7-item subscale reached 0.68 using the pooled population.					
Median change BL to Wk 12	LOCF data	LOCF data			vs control

• SF-36 PCS	+3.1 (n=104)	NR (n=109)			P<0.05
• FACT-F	+3.0 (n=104)	NR (n=109)			P<0.05
• FACT-AN	+1.0 (n=104)	NR (n=109)			p-0.076
• VAS	+10.0 (n=111)	+1.0 (n=112)			P=0.004
Median change BL to Wk 12	Data without LOCF	Data without LOCF n=129			Vs control
• SF-36 PCS	+3.3 (n=77)	NR			P=0.01
• FACT-F	+4.0 (n=90)	NR			P=0.001
• FACT-AN	+1.0 (n=89)	NR			P=0.068
• VAS	+10.0 (n=89)	+3.0 (n=98)			P=0.001

Patients with lymphoproliferative malignancies derived at least as much QoL benefit from epoetin b therapy as patients with solid tumours; likewise, patients previously exposed to chemotherapy showed similar QoL benefit with epoetin b as chemotherapy-naıve patients (data not shown). However, patients who responded to epoetin b therapy (i.e. achieved the target Hb response) experienced a greater improvement in QoL from baseline to final visit than patients who were nonresponders (i.e. did not achieve the target Hb response). Patients who responded to epoetin b 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 scores; the corresponding improvements in the nonresponder 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 where epoetin b treatment, QoL increase and Hb increase were used as dependent variables in turn.

Mean change in QoL scores from baseline in the epoetin b and control groups for the without LOCF population are reported graphically.

Adverse events 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)			
Number of hospitalisations per patient, menaq SD	3.8 (4.5)	4.1 (4.9)			=0.52
Number 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, n (mostly oral)	30	28			
Parenteral iron, n	9	2			
Serum iron deficit BL to study end	4.5µg/dl	16.8mg/dl			<0.01
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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear: randomised but method not specified.
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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 that had received prior chemotherapy (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?	Y
5. WERE THE PARTICIPANTS BLIND TO TREATMENT ALLOCATION?	N (open label)
6. WERE THE OUTCOME ASSESSORS BLIND TO TREATMENT ALLOCATION?	N (open label)
7. WERE THE POINT ESTIMATES AND MEASURE OF VARIABILITY PRESENTED FOR THE PRIMARY OUTCOME MEASURE?	Y
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	N
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Y.
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Partially; # total per group reported & # withdrawing due to AEs reported per group. Other reasons stated but # not reported
NOTES:	

Also presented in abstract: Coiffier, B., et al. (2001). Impact of epoetin beta versus standard care on quality of life in patients with malignant disease. 6th Congress of the European Haematological Association. Coiffier included in Wilson review	
OTHER	
Generalisability	
Author conclusions	Compared with transfusion therapy, epoetin beta produces a clinically significant improvement in QoL 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 QoL accompany and are mediated through improvements in Hb concentration, and can be achieved after a few weeks of epoetin beta therapy.In addition, baseline epo serum levels and the O/P ratio might identify those patients with lymphoproliferative malignancies who are more likely respond to epoetin beta; however, this required further study
Reviewer comments	Included in Wilson HTA as Coiffier, B., M. Boogaerts and C. Kaine (2001). Impact of epoetin beta versus standard care on quality of life in patients with malignant disease. 6th Congress of the European Haematological Association. We have included the full paper (Boogaerts et al, 2003) in this review

Endnote Ref ID	2689	Malignancy type	Haem (multiple myeloma)
		Treatment	epoetin alfa

STUDY DESIGN		PARTICIPANTS	
Author, year	Dammacco, 2001	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, a 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; those who had received a blood transfusion within 7 days of study entry; patients with a major infection within 1 month or an acute illness within 7 days of study entry	
# centres	31		
Other references/aliases	None		
Geographical setting	12 countries (Italy, Poland, Gt Britain, Norway, Sweden, Czech Republic, Hungary, Belgium, Israel, Denmark, Spain and 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 & ALLOCATION	Stratified according to receipt of blood transfusion within the preceding three 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 epo 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 & freq (od, bd etc)	150 IU/kg Q3W (each dose separated by at least 1 day)	Matched to epoetin alfa dose
Dose adjustment Y/N	Y: if Hb level had not increased by ≥1 g/dl after 4 wks of tmt the dose was doubled to 300IU/kg Q3w for the remaining 8 wks of study; if Hb level increased to >14 g/dl treatment withheld until Hb level was <12 g/dl and then reinitiated at does approx.. 25% lower than start dose; increased by ≥2 g/dl within a 4-wk period dose	Matched to epoetin alfa dose

	reduced by approx.. 25% to maintain an increase of <2 g/dl	
Route of administration	Subcutaneous	Subcutaneous
Duration of epo tx	12 weeks (double blind)	12 weeks (double blind)
Adj 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 (chg in QoL scores (Nottingham Health Profile & CLAS/LASA)); *AEs REPORTED:* AEs – questioning patients at study visits . All AEs together with investigators assessment of its seriousness, severity and presumed relationship to study medication were recorded

Vital signs, clinical lab tests (eg complete blood and reticulocyte count), serum chemistry and urinalysis were competed 7 days prior study, on day 1 and weekly. Serum erythropoietin was evaluated prior study entry, at day 1 and weeks 2, 4, 8. Serum iron, transferrin, total iron-binding capacity and ferritin evaluated prior study entry, at day 1 and every 4 weeks.

Responders = proportion of patients during d-blind phase with increase of ≥2 g/dl in Hb level

Correctors = achieved an 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, scoail isolation & physical mobility. Pts respond yes/no. Scale calculated by counting the number of items rated as a yes within each scale. Scale is then converted to a scale (0 good to 100 bad.

CLAS = 100 mm scale separately evaluates energy level, ability to do daily activities, and overall QoL

Also measured pre study and at the end were complete physical examination, clinical signs and symptoms of multiple myeloma, bone marrow biopsy, skeletal radiography, serum M-component, urine light-chain M-component, folate , B12, myeloma staging and physician ‘s performance score and global assessment.

ANALYSIS

Statistical technique used?	Proportion of patients transfused stratified by prestudy transfusion history was analysed by the Cochran-Mantel-Haenszel test. Only data for Month 2 and 3 were analysed (effects not expected before this time [Abels, 1992]) 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 the Fisher exact test QoL : Kruskal-Wallis test were performed to ensure no bias had been introduced by deleting patients. Assessments evaluated by 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_Haenzel tests. Between-group differences in the physician's global assessment were analysed using the Kruskal-Wallis test. All statistical tests were 2-sided
Intention to treat analysis?	Results for primary efficacy evaluation of transfusion requirements & 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 Wk 4 sufficient time to respond). QoL analyses were performed for the ITT population minus patients who died during the double-blind phase of the study for whom QoL data were incomplete.
Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	Yes: 5 Epo patients discontinued (2 AEs [death due to septic shock n=1 & disease progression n=1] and 3 for personal reasons). 15 PBO patients discontinued (3 AEs [pneumonia n=1, death due to septic shock n=1, death due to acute renal failure n=1]; 6 disease progression; 3 personal reasons; 3 other unspecified reasons
Was attrition rate adequately dealt with?	Partially: ITT population was not used for secondary efficacy parameters and HRQL data
Number (%) followed up from each condition?	NA

BASELINE CHARACTERISTICS				
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		Haem: multiple myeloma		
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		Unclear: though most commonly used non-plat based chemo		
Adjuvant anaemia treatment	**Iron**	NR		
	G-CSF	NR		
	Transfusion trigger	to be avoided if possible, if Hb >8 g/dl		
	Hb inclusion criteria level	**<11.0 g/dL**		
	Arm 1 = Epo Alfa N=69	**Arm 2 = Placebo N=76**	**Arm 3 = N =**	
male (%)	34 (49%)	31 (41%)		

female (%)	35 (51%)	45 (59%)		
Age years median (range)	67.3 (43.0-80.4)	65.0 (38.2-88.9)		
Performance score (0-4; higher score the worse the performance status): ECOG				
Missing	1	0		
0	9	8		
1	51	50		
2	33	34		
3	6	8		
Creatinine µmol/l, mean	106.3 ± 42.29	102.4 ± 35.60		
# chemotherapy cycles within 6 months prestudy: mean ± SD (range)	N=68	N=75		
	3 ± 2.5 (0-15)	4 ± 2.0 (0-8)		
Malignancy staging (Durie & Salmon 1975), %				
IA	4	5		
IB	0	1		
IIA	33	34		
IIB	4	0		
IIIA	46	54		
IIIB	12	5		
Hb baseline (g dl^{-1}), 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 pts receiving transfusions at baseline), mean ± SD	N=25	N=28		
	8.1 ± 1.08	8.1 ± 0.93		
Serum Epo level (mU ml-1), median (range)	N=36	N=36		
	116 (18-5,220)	93 (10-408)		
Were intervention and control groups comparable?	No p values reported but authors state “baseline demographic and clinical characteristics were comparable between treatment groups”. Based on the reported values the groups appear comparable.			

RESULTS					
	Arm 1 = Epo Alfa	**Arm 2 = Placebo**	**Arm 3 = N =**		**p**
ITT POPULATION	**Epo alfa N=69**	**Placebo N=76**			
RBCT					
Pts transfused during Month 2 & 3 (double-blind study), n (%)	19 (27.5%)	36 (47.4%)			=0.017
Transfused (by transfusion history) [either having or not having received 1+ transfusions during the prior 3 months], n (%):					
Transfused prestudy	14 (56.0)	22 (78.6)			=0.006

Not transfused prestudy	5 (11.4)	14 (29.2)			
Hb level g/dL triggering RBCT, mean (range)	7.66 g/dl (6.1-9.7 g/dl)	7.89 g/dl (6.47-9.45 g/dl			
Adverse effects of tmt (reported in 10% or more of patients in any treatment group)					
Any adverse event, n (%)	50 (72.5)	57 (75.0)			
Fever, n (%)	5 (7.2)	10 (13.2)			
Pain, n (%)	9 (13.0)	3 (3.9)			
Skeletal pain, n (%)	5 (7.2)	2 (2.6)			
Leukopenia, n (%)	9 (13.0)	6 (7.9)			
Granulocytopenia, n (%)	3 (4.3)	4 (5.3)			
Dyspnoea, n (%)	2 (2.9)	3 (3.9)			
Hypertension, n (%)	3 (4.3)	1 (1.3)			
Infection, n (%)	1 (1.4)	4 (5.3)			
Deaths*	1	7			
* No deaths were attributed to the study drug (reasons reported for double-blind and open-label phases not reported separately. FYI reasons included disease progression (50% of deaths for both periods); septic shock/infection; acute renal failure or cardiogenic shock. **FYI** Disease response comparable between patients receiving epoetin alfa & those receiving placebo (epo alfa did not appear to influence effects of chemotherapy, treatment or disease status) – data not reported					
ECOG	N=66	N=66			
Change from baseline	NR	NR			=0.038
I point improvement	13 (19.7%)	4 (6.1%)			
2 point deterioration	1 (1.5%)	5 (7.6%)			
Response to anaemia treatment rated by physician : excellent, 19.7 vs 0%; very good, 19.7 vs 3%; good,13.6 vs 9.1%; fair,18.2 vs 24.2%; and poor, 28.8 vs 63.6% for epo and placebo arms respectively (it is not clear if results are provided for the double blind phase of the study only):					
EFFICACY POPULATION	Epo alfa N=66	Placebo N=66			
Hb					
Chg Hb level g/dl (baseline to last value), mean ± SD	1.8 ± 2.05 g/dl	0.0 ± 1.18 g/dl			<0.001
Mean Hb level g/dl Wk 12	11.2 g/dl	9.7 g/dl			
Responders, n (%)	38 (57.6%)	6 (9.1%)			<0.001
Mean time for responders to achieve Hb level ≥2 g/dl above baseline	46 days	35 days*			
Correctors, n (%)	30 (45.5%)	2 (3%)			<0.001
Mean time for correctors to achieve Hb level ≥12 g/dl	50 days	23 days*			
* most likely due to the small numbers of placebo treated responders and correctors					
Health-related QoL					

QoL POPULATION	Epo alfa N=66	Placebo N=72			
Health state utility scale = Nottingham Health Profile; CLAS					
DATA NOT REPORTED Both treatment groups showed some improvement in QoL but multivariate analysis did not show a significant difference between the groups for Wk 12 change scores, although nearly all trends favoured patients treated with epoetin alfa (data not reported). Univariate analyses of within-group meand changes from baseline to Wk 12 indicated significant improvement in 4 QoL scales for the epoetin alfa group (NHP scale emotional reaction p<0.001 & social isolation p=0.05; & for the CLAS energy level (p=0.01) & ability to do daily activities (p<0.001)) and 1 QoL scale for the placebo group (NHP scale sleep p=0.03). A trend towards improvement was also noted for CLAS Overall QoL for the Epoetin alfa treated group whereas for the placebo group scores were virtually unchanged since baseline						

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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 in the table
4. WERE THE ELIGIBILITY CRITERIA SPECIFIED?	Yes
5. WERE THE PARTICIPANTS BLIND TO TREATMENT ALLOCATION?	Yes (though not blinded to dose – placebo dose matched epoetin alfa dose)
6. WERE THE OUTCOME ASSESSORS BLIND TO TREATMENT ALLOCATION?	Yes (though 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)
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Partially: primary endpoint and HRQoL only
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes

NOTES:	
OTHER	
Generalisability	Haem cancer
Author conclusions	Epo 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 QoL
Reviewer comments	

Endnote Ref ID	**2700**	**Malignancy type**	**Solid (breast)**
		Treatment	**EPO (assumed epo alfa)**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Del Mastro, 1997	N	62
Objective	To evaluate the ability of EPO in preventing 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 RBC (within 80 to 100 fL) **Exclusion criteria:** uncontrolled hypertension; inadequate iron reserves as evidenced by serum iron level less than normal (37 µg/dL) associated with ferritin level <10 ng/mL and/or transferrin saturation < 20%	
# centres	1 (February 1993-June 1995)		
Other references/aliases	None		
Geographical setting	Italy		
Duration of treatment	12 weeks: 6 cycles and 2 weeks (starting on day 1 of chemo, until 2 weeks after last chemo cycle); 36 administrations planned per participant		
Length of follow-up (if different)	A blood count was performed 6 months after the last chemo cycle.		
Country of corresponding author	Italy		
Language of publication	English		
Sources of funding	Supported in part by a grant from Associazione Italiana per la Ricerca sul Concro, Milan (ITALY)		
RANDOMISATION & 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	**Epo**	**Best supportive care**
N	31	31
Dose & freq (od, bd etc)	150 U/kg Q3W	NA
Dose adjustment Y/N	Y. Hb increased to 15 g/dl in two consecutive weekly assays; EPO treatment was stopped until Hb <13 g/dl (N=4)	NA
Route of administration	Subcutaneous	NA
Duration of epo tx	12 weeks: 6 cycles and 2 weeks (starting on day 1 of chemo, until 2 weeks after last chemo cycle); 36 administrations planned per pts	12 weeks
Adj 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 mcg/dL; serum ferritin <10 ng/ml; or transferrin saturation <20% (N=4)	G-CSF 5 mcg/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		**Other outcomes** RBC (MCV, MCH, MCHC); haematocrit; reticulocyte; HRQoL (PDI)
At day 1 of each cycle: blood cell count, reticulocyte count, serum iron, transferrin, ferritin, total iron binding capacity. Assay of EPO serum at baseline and 2 weeks post last chemo cycle only for first 15 pts. in each arm		
NOTES: MCV, mean corpuscular volume; MCH, mean corpuscular Hb level; MCHC, mean corpuscular Hb concentration PDI = Psychological Distress Inventory score; 5-point, 13-item self-assessment scale, developed and validated in Italy to measure psychological distress in cancer patients. Measured before randomisation, after 3rd cycle of chemo. And at the first follow-up visit (approx. 6 mths after randomisation AEs severity assessed by 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 EPO: observed/predicted ratio (predicted was derived from a 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 & psychologic	

	distress after adjustment for baseline values. The probability of maintaining Hb levels >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 RBCT were considered as events
Intention to treat analysis?	Yes (HRQL- PDI available only in 53 (85.5%) pts.
Does statistical technique adjust for confounding?	NR
Power calculation (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% patients, 30 patients per arm had to be randomised to ensure a significance of .05, 2-sided, and a power of .90
Attrition rate (loss to follow-up)?	Partially: 2 patients in the control group and 3 in the EPO group did not complete all 6 cycles of chemotherapy. 2 patients refused accelerated chemotherapy and EPO treatment. They were treated with CEF at the same doses but every 3 weeks, no attrition rate for last measurement (2 weeks post 6th cycle) and for HRQoL data
Was attrition rate adequately dealt with?	Unclear as attrition rate not fully reported
Number (%) followed up from each condition?	Yes

BASELINE CHARACTERISTICS			
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*			Solid (breast)
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*			Chemo: 6 cycles of CEF (cyclophosphamide and epirubicin and fluoroacil), cycles repeated every 2 weeks (unless delayed until hematologic recovery)
Adjuvant anaemia treatment	**Iron**		Oral iron supplement (ferrous sulphate 325 mg/d) was started at the occurrence of: serum iron < 37 mcg/dL; serum ferritin <10 ng/ml; or transferrin saturation <20%
	G-CSF		G-CSF 5 mcg/kg SC Day 4 to Day 11 during the first 5 cycles; it was withdrawn after the sixth cycle
	Transfusion trigger		Hb <8 g/dl or in presence of anaemia related symptoms (dyspnea, tachycardia, severe asthenia)
	Hb inclusion criteria level		Hb≥12 g/dl
	Arm 1 = EPO N=31	**Arm 2 = Control N=31**	**Arm 3 = N =**

Age years median (range)	54 (31-68)	56 (29-68)	
Hb (g dl^{-1}), mean ± SD	13.0 ± 0.7	13.1 ± 0.6	
WBC count (x 10^9/L), mean ± SD	7.2 ± 2.0	7.1 ± 2.0	
Platelet count (x 10^9/L) , mean ± SD	247 ± 60.7	241 ± 51.3	
RBC count (x 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	
Mean corpuscular volume (fL)	91.2 ± 3.7	90.7 ± 4.7	
Mean corpuscular Hb (pg)	29.9 ± 1.1	29.8 ± 1.6	
Mean corpuscular Hb concentration (g/dL), mean ± SD	32.7 ± 1.1	32.8 ± 1.0	
Serum iron (mmol/L)	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 (mcg/dL), mean ± SD	348 ± 55.6	352 ± 51.3	
Serum EPO (mU/mL) , median (range)	21.0 (0-512)	25.5 (0-800)	Evaluated in 16 pts per arm, note that methods section states 15 pts.
Observed/Predictive ratio, median (range)	1.13 (0.82-1.31)	1.19 (0.87-2.34)	
# received conservative surgery	22 (71%)	26 (84%)	
HRQoL	N=27	N=26	
PDI, mean ± SD	27.5 ± 8.6	27.1 ± 7.3	
Were intervention and control groups comparable?	Unclear. P values not reported but authors state “no statistically significant difference in baseline haematologic and iron-related parameters”		

RESULTS

	Arm 1 = EPO N=31	**Arm 2 = Control N=31**	**Arm 3 =**	**p**
RBC-related parameters, mean ± SD at EOTP				
RBC count (x10^{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 chemo*	0.8 ± 1.4 (CI:0.3-1.4)	3.05 ± 1 (CI:2.6-3.5)		<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)**	0 (0%) 95% CI 0 to 14	16 (52%) 95% CI 33 to 69		=0.00001
RBCT (# patients requiring)		2		
Haematocrit (%)	37.8 ± 3.9	31.0 ± 3.8		0.000

Reticulocytes count (%)	10.1 ± 9.8	11.8 ± 8.7		0.6
MCV (fL)	91.9 ± 6.7	94.7 ± 4.3		0.08
MCH (pg)	29.6 ± 2.3	30.7 ± 1.8		0.07
MCHC (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 pts per arm, note that methods section states 15 pts.	
Serum EPO (mU/mL)*, median (range)	83 (18-774)	66 (14.5-469)		
<1, %	1	37		

* RBC and haematocrit values showed a similar course to Hb data, but data not reported in the paper.
** In the control group, patients developing anaemia had mean baseline Hb level significantly lower than those who did not (12.8 g/dl ± 0.6 g/dl [treatment group] vs 13,4 ± 0.5 [control group]; p=0.005). Probability of maintaining Hb level >10 g/dl significantly lower in the control group compared with the EPO group (p<0.0001 (no data reported; reported graphically Fig 3)

Reticulocytes increased in both arms from baseline to Wk 2 (treatment arm 8% to 17% and control arm 7% to 11%). After this early increase reticulocytes decreased and in both arms final value not significantly different from baseline (treatment arm 10% and control arm 12%).

Iron metabolism	Throughout 6 cycles of treatment serum iron (p<0.001) and transferrin saturation (p=0.0002) significantly decreased, regardless 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 chemo. A sharp increase in mean serum ferritin was observed in both arms. After that ANCOVA showed that the ferritin values did not significantly change (p=0.14) during the treatment, but its levels were significantly lower in the EPO group compared with thecontrol group (p=0.0015). Results graphically presented.				
Total iron binding capacity, (mean ± SD) at the end of chemo	356.4 ± 62.0	338.5 ± 58.6			

HRQoL

Health state utility scale = **Psychological Distress Inventory 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			

Psychological distress increased during treatment and decreased at first follow-up visit p=0.03.
Treatment groups did not differ in terms of psychological distress p=0.4

Adverse effects of tmt

	WHO grade						No Grade IV toxicity reported
Leukopenia	I-II	-		4	(13%)		No statistically

	III	2	(7%)	-	-		significant difference in main toxicities observed between the 2 arms
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%)		

EPO-related toxicities included: facial rash (n=2) after the first administrations. In 1 of these patients, dyspnea and headache requiring dose reduction also occurred. Almost all patients experienced mild or moderate local burning during EPO administration

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Yes
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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 “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.
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	Partial; some evidence e.g. WBC mentioned but data not reported
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	yes, however for HRQoL

	only 87 and 84% participants analysed in epo and control groups respectively
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	partially
NOTES:	

OTHER	
Generalisability	Women only (breast cancer patients)
Author conclusions	EPO prevents anaemia in patients undergoing chemotherapy. Further trials are required to identify subsets of patients in which the preventive use of this drug could be cost-effective
Reviewer comments	

Endnote Ref ID	**2701**	**Malignancy type**	**advanced head and neck or lung carcinoma**
		Treatment	**EPO (assumed epo alfa)**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Dunphy 1999	N	30
Objective	The effects of paclitaxel and carboplatin with or without concurrent EPO in the treatment of patients with head and neck carcinoma and lung carcinoma, on anemia and # of transfusions.	**Inclusion criteria:** • patients with head and neck carcinoma and lung carcinoma treated at Saint Louis University Health Sciences Center on a Phase II trial using paclitaxel and carboplatin • histologically confirmed advanced head and neck carcinoma (clinical Stage III and IV) or advanced nonsmall cell lung carcinoma (Stage IV) • No prior 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/uL; • platelet count > 100,000/uL; • life expectancy > 4 months. • **Hb level:** NR; see dose adjustment	
# 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		

Language of publication	English	**Exclusion criteria:** NR; see inclusion criteria
Sources of funding	NR	
RANDOMISATION & ALLOCATION	Patients were randomized in a non-blinded fashion either to receive or not receive EPO	

TREATMENT ARMS		
ARM Drug name/s	**Epo**	**Control**
N	15	15
Dose & freq (od, bd etc)	150 U/kg, 3 times per week (Mon, Wed and Fri).	NA
Dose adjustment Y/N	Y: If the Hb fell ≥1 g/dL (Course 1) dose was escalated to 300 U/kg (Course 2); if the Hb fell ≥1 g/dL, the dose was escalated to 450 U/kg (Course 3). EPO was not initiated if the Hb was ≥16 g/dL. Once EPO was initiated the Hb was checked weekly. If theHb level rose to 18 g/dL, EPO was discontinued until it fell to 16 g/dL, at which point treatment was re-initiated	NA
Route of administration	NR	NR
Duration of epo tx	NR	NR
Adj anaemia treatment	Oral iron and folic acid for the duration of chemotherapy (ferrous sulfate, 325 mg orally, 3 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, 3 times per day and folic acid, 1 mg orally, twice per day
Transfusion trigger	<8.0 g/dL or cardiovascular symptoms of anemia developed	<8.0 g/dL or cardiovascular symptoms of anemia developed

OUTCOMES			
Primary outcome		**Other outcomes**	HaemR, RBCT

NOTES
CBC 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 ANOVA was used to compare the difference in post-chemotherapy Hb levels between the two groups during the first two courses of chemotherapy. The Fisher exact test was used to compare the difference in the rate of transfusion between the two groups. The Mann–Whitney U test and Fisher 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.		
Intention to treat analysis?		Evaluable population used in data analyses 2 pts (noncompliance and EPO was initiated on Day 8) in EPO group and 1 participant (early death) in control group were not evaluable)		
Does statistical technique adjust for confounding?		NR		
Power calculation (priori sample calculation)?		Y : A minimum of 20 evaluable patients was required to a difference of 2.5 g/dL in post-chemotherapy Hb levels between EPO and controls with a power of >90% at a significance level of 0.05.		
Attrition rate (loss to follow-up)?		Partially: 2 pts (noncompliance and EPO was initiated on Day 8) in Epo group and 1 participant (early death) in control group were not evaluable.		
Was attrition rate adequately dealt with?		NR		
Number (%) followed up from each condition?		NR		
BASELINE CHARACTERISTICS				
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		advanced head and neck or lung carcinoma		
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		paclitaxel and carboplatin, repeated every 21 days: Patients with advanced **lung carcinoma** were treated until best response or six courses of chemotherapy. After 2–3 preoperative chemo 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 then were followed 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, 3 times per day and folic acid, 1 mg orally, twice per day		
	G-CSF	NR		
	Transfusion trigger	<8.0 g/dL or cardiovascular symptoms of anemia developed		
	Hb inclusion criteria level	NR		
Evaluable population	**Arm 1 = EPO N=13**		**Arm 2 = Controls N=14**	**p**
male, n	12 (92%)		7 (50%)	Gender was not Distributed equally between the two treatment groups (P = 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)	P = 0.68

EPO, 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)		
B12, pg/mL mean (SD) (N=24)	552 (243)	445 (139)		
Type of solid tumour of randomised pts:				
Head and neck, n (%)	**10**	**11**		
Lung, n (%)	5	4		
Were intervention and control groups comparable?	No			

RESULTS					
	Arm 1= EPO n=13	**Arm 2 = Controls n=14**	**Arm 3 = N =**		**p**
Hb					
Change in Hb; after 2 courses of chemotherapy g/dl	1.2	2.8			=0.037
There was a highly significant decrease inHb over time (2 courses of chemotherapy or 6 weeks) in patients who did not receive EPO compared with those who did (p=0.008) (Fig. 1).					
Transfusions					
# transfused pts during 2 courses of chemo	1 (8%)	2 (14%)			>0.05
# transfused pts at 4 courses of chemo	2 (15%)	5 (36%)	These differences were not compared statistically because after the second chemo fewer patients were treated in subsequent courses (Fig. 2)		
Units received per pts at 4 courses of chemo	3	2.8			
Serum EPO	N=10	N=10	3 epo and 4 control participants have no follow up serum epo data.		
	EPO levels increased significantly over time for both groups (P =0.007); however, the increase in the group treated with EPO was significantly greater than the increase in the control group (P = 0.002) (Fig. 3).				
Health-related QoL					
NR					
Adverse effects of tmt					
NR					

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear: not specified.
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded	NR

vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was alternate, or based on information known to the triallist)	
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?	Y
5. WERE THE PARTICIPANTS BLIND TO TREATMENT ALLOCATION?	N
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
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	N
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	N
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	yes
NOTES:	
OTHER	
Generalisability	Gender was not distributed equally between the two treatment groups (P = 0.003).
Author conclusions	There was significantly less anemia and transfusions were reduced by 50% in patients randomized to receive EPO during chemotherapy with paclitaxel and carboplatin.
Reviewer comments	No Hb inclusion criteria; EPO was not initiated if the Hb was ≥16 g/dL. In addition head and neck pts interrupted treatment after 2-3 chemo courses with no further treatment until they developed a recurrence.

Endnote Ref ID	**362**	**Malignancy type**	**Small cell lung cancer (SCLC)**
		Treatment	**Epo alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Grote 2005	N	224
Objective	To evaluate tumour response in pts receiving etoposide and cisplatin after third chemo cycle. The study hypothesis was that epo alfa overall tumour response rate won't be ≥15% below placebo group.	**Inclusion criteria:** age ≥18years; newly diagnosed both extensive stage and limited stage SCLC scheduled for at least 3 chemo cycles; ECOG=0-2; life expectancy ≥3 months; Hb≤14.5g/dl **Exclusion criteria:** Previous cytotoxic chemo or radiotherapy, or scheduled curative-intent radiotherapy during the first three chemo cycles; uncontrolled underlying disease not attributable to malignancy; uncontrolled hypertension; evidence of untreated iron, folate or vitamin B12 deficiency or on-going haemolysis.	
# centres	35 sites		
Other references/aliases	N93-004		
Geographical setting	USA		

Duration of treatment	12 wks = from start of treatment until 3 weeks after chemotherapy completed (the mean number of chemo cycles was 4 and 4.1 in epo 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 & 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	**Epo alfa**	**Placebo**
N	109	115
Dose & freq (od, bd etc)	150U/kg three times a week	150U/kg three times a week
Dose adjustment Y/N	Y: epo stopped if Hb>16 till Hb<14 and resumed at 75U/kg, no dose escalation	
Route of administration	Subcutaneous	Subcutaneously
Duration of epo tx	Approx. three weeks after final chemo	Approx. three weeks after final chemo
Adj anaemia treatment	NR	NR
Transfusion trigger	NR	NR

OUTCOMES

Primary outcome		**Other outcomes**	HaemR (weekly Hb, after 3 cycles and final cycle); RBCT (patients, units, time to first transfusion); tumour response (after 3 cycles and final cycle); survival (up to 3 years); AEs

NOTES:
Study early terminated because of slow recruitment and suboptimal enrolment: enrolled 224 from 400 planned pts. Thus some power issues.

ANALYSIS

Statistical technique used?	Overall tumour response rate (complete response (CR) plus partial response (PR)) and 95% confidence intervals reported.. Kaplan-Meier estimates for survival data.
Intention to treat analysis?	Yes for all efficacy data. Safety data analysed patients receiving at least one dose of study drug with available safety data.

Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	Yes, (based on 15% one sided decrease in overall tumour response rate in epo arm). However trial was terminated early, thus power issues.
Attrition rate (loss to follow-up)?	Number of patients and reasons for treatment discontinuation reported for both arms.
Was attrition rate adequately dealt with?	NR except to say ITT was conducted
Number (%) followed up from each condition?	NR

BASELINE CHARACTERISTICS

Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		**SCLC**
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		**etoposide and cisplatin**
Adjuvant anaemia treatment	**Iron**	**NR**
	G-CSF	**NR**
	Transfusion trigger	**NR**
	Hb inclusion criteria level	**Hb≤14.5**

	Arm 1 = Epo N =109		**Arm 2 = Placebo N = 115**			
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 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%		
Mean Hb baseline (g dl^{-1}) (SD)	12.8 (1.5)		13 (1.5)			
Iron baseline (U/l median) (range)	75.3	(65.41)	81.6	(66.35)		
Mean Feritin, ng/dL (SD)	471.7	(856.3)	460.3	(632.9)		
Number of Chemo cycles received	4 (2.1)	4 (1-10)	4.1 (2.2)	4 (1-12)		
Radiotherapy received	16	14.7%	14	12.2%		
Extensive stage SCLC	72	66.1%	68	59.1%		

Were intervention and control groups comparable?	No p-values reported, authors stated that "demographics and clinical characteristics were generally similar between groups"

RESULTS

	Arm 1 = Epo N = 109	**Arm 2 = Palacebo N = 115**	**Diff:** Epo-placebo:	**95% CI**
Tumour response				

Tumour response; CR or PR at final cycle	65	59.6%	64	55.7%	4%		-9 to17 %
Tumour response; CR at final cycle	20	18.3%	21	18.3%			
Hb							
(Mean Hb at cycle 3)	12.5		10.6		1.9 g/dl		1.4 to 2.4 g/dl
Mean Hb at final cycle	12.2		10.3		1.9 g/dl		1.4 to 2.4 g/dl
Change from baseline to end of treatment	-0.6		-2.7				
Mean Hb change at 13 weeks-median drug exposure	-0.2		-2.9				
Health-related QoL	NR						
Overall survival							
Median survival (Kaplan-Meier)	10.5	months	10.4	months			
Transfusions	Difference in Kaplan-Meier estimates of time to first transfusion showed that probability of transfusion was greater in Placebo group starting at month 3.						
Participants	26	24%	42	37%	HR=0.597, 95%CI(0.365 -0.977)		
Mean number of units (SD)	0.5	(3.6)*	0.4	(0.7)			
Safety data$							
Discontinued chemo because of AE	23	21%	32	28%			
Deaths (at 3 years follow up)	100	91.7%	101	87.8%			
Cause of death = disease progression:		91%		84%			
Nausea	80	73.4%	79	68.7%			
Vomiting	56	51.4%	58	50.4%			
Fatigue	32	29.4%	40	34.8%			
Constipation	34	31.2%	40	34.8%			
Clinically relevant thrombo-vascular events	12	11%	11	9.6%			
Thromoboembolic events	1	0.9%	0	0.9%			
Hypertension	NR; Patients with uncontrolled hypertension were excluded.						
ECOG	At baseline 98 % and 100% patients had ECOG ≤2 in Epo and Placebo groups respectively, at the end of treatment 71 % of patients had ECOG ≤2 in both groups.						
* One patient in EPO arm had abdominal aortic aneurysm requiring 37 units of blood $ 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 = for patients number, date of							yes

birth, alternate; Unclear = if the method not stated)	
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	no
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	yes
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes, during treatment period only

NOTES:
Complete tumour response (CR)=total disappearance of all all known malignant disease.

Partial tumour response (PR)= defined as a ≥ 50% decrease in total tumour area (added products of bidimensional measurements of all measurable disease) and as no growth of any measurable lesion by more than 25% and no estimated growth of any unmeasurable but assessable lesions by more than 25% and as no new lesions.

Patients without a date of death were censored on the date that the patient was last known to be alive.

RESULTS

Fig 1 page 9382: Kaplan-Meier plot of survival over time. (*) One month = 28 days.
Fig 2 page 9382: mean Hb values and 95% CI (estimates based on graph reading reported below)

Hb estimated from Figure 2	**Arm 1 = Epo N=64**	**Arm 2 = Placebo N=58**
Week 13 mean (SD)	12.5 (0.6)	10.24 (0.4)

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 (figure 1). The author notes, that there is no information on patients medication after the end of the treatment, and 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.

Endnote Ref ID	**2703**	**Malignancy type**	**Lymphoproliferative**
		Treatment	**Darbepoetin alpha**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Hedenus, 2002	N	66
Objective	To assess the safety and dose-response relationship of darbepoetin alpha in patients with different types of lymphoproliferative malignancies receiving multicyle chemo	**Inclusion criteria:** • Pts with a diagnosis of lymphoproliferative malignancy (MM, low- and intermediate-grade NHL, Hodgekin's disease or CLL) • Life expectancy of ≥6 months • ECOG performance status of 0-2 • At least 12 more weeks of chemo • Adequate iron stores (transferrin saturation ≥15% or ferratin ≥10µg/l) • Normal serum vit B12 and folate concentrations • Adequate liver function (serum bilirubin ≤1.5 times the upper limit of the normal range • Adequate renal function (serum creatinine ≤177µmol/l) • Not received two RBC transfusions within 4 wks of randomisation or any RBC transfusion within 2 wks of randomisation • **Hb level: ≤11.0 g/dl** **Exclusion criteria:** • High-grade NHL • Myleoablative chemo or radiotherapy for transplantation or chemo regimens using investigational agents • Primary or metastatic malignancy involving the CNS • Clinical evidence of active infection or inflammatory disease • Other disorders that could potentially interfere with the response of darbe
# 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 & ALLOCATION	Multicentre, randomized (1:2:2:1 ratio, see notes), double-blind, placebo-controlled, dose-finding study. Randomization was performed using a central computerised system and was stratified to balance the treatment groups with respect to malignancy type (myeloma vs lymphoma).		

TREATMENT ARMS		
ARM Drug name/s	**Darbepoetin alpha**	**Placebo**
N	**22**	11
Dose & freq (od, bd etc)	2.25 µg/kg once weekly	NR

Dose adjustment Y/N	Y; doses reduced by 50% for pts who had ≥2g/dl increase in Hb during any 28 day period in the absence of RBC transfusion; withheld for pts with Hb concentrations >15.0g/dl (men) or >14.0g/dl (women) and reinstated at 50% of weekly dose once Hb concentrations decreased to ≤13.0g/dl.	NR
Route of administration	Subcutaneous	Sub cut
Duration of epo tx	12 weeks	12 weeks
Adj anaemia treatment	NR	NR
Transfusion trigger	RBC transfusions were recommended for pts with Hb concentrations ≤8.0g/dl.	NR but assumed to match darbe group

OUTCOMES			
Primary outcome	**HaemR** (haem response defined as an increase in Hb of ≥2.0 g/dl from baseline in the absence of RBC transfusion; haematopoietic response defined as Hb response or increase in Hb concentration to ≥12.0 g/dl in the absence of RBC transfusion; sustained Hb response defined as Hb response maintained for 28 days or until the end of treatment; Hb concentrations measured weekly	**Other outcomes**	**RBCT (f**rom Wk 5 until the end of the treatment period); AEs (AEs, excess increases in Hb, changes in lab variables and vital signs, antibody formation resulting from darbe administration)

ANALYSIS	
Statistical technique used?	Rates of Hb and Hb response estimated using the Kaplan-Meier method. Logistic regression was used to assess treatment effect, dose response relationships and the effect of covariates.
Intention to treat analysis?	Described as ITT, 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), RBC transfusions in 4 weeks before randomisation, baseline serum endogenous erythropoietin concentration (categorical vaiable)
Power calculation (priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	N=3 of the 66 recruited to the four study groups (two pts in darbe groups withdrawn due to delay in chemo; one in placebo group withdrew consent)
Was attrition rate adequately dealt with?	Not clear, although attrition rate low
Number (%) followed up from each condition?	NR

BASELINE CHARACTERISTICS

Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		**Lymphoproliferative**
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		Chemo (type NR)
Adjuvant anaemia treatment	**Iron**	NR
	G-CSF	NR
	Transfusion trigger	RBC transfusions were recommended for pts with Hb concentrations ≤8.0g/dl.
	Hb inclusion criteria level	≤11.0 g/dl

	Arm 1 = Darbe N=22	**Arm 2 = Placebo N=11**	**Arm 3 = N =**	
Sex				
male, n (%)	14 (64)	2 (18)		
female, n (%)	8 (36)	9 (82)		
Age years median (range)	69 (20-84)	63 (25 -80)		
Mean (SD) neutrophil count ($X10^9$/l)	2.9 (2.2)	7.0 (7.5)		
RBC tfn during 4 wks pre-randomisation, n (%)	4 (18)	2 (18)		
Haemoglobin g/dl, Mean (SD)	9.4 (1.3)	9.5 (1.0)		
Mean (SD) platelet count ($X10^9$/l)	232.4 (157.6)	283.1 (188.6)		
Median (range) Endogenous serum erythropoietin (U/l)	69 (12-1362)	45 (12-132)		
Lymphoma, n (%)				
Hodgkin's disease	4 (18)	3 (27)		
NHL	11 (50)	3 (27)		
CLL	1 (5)	2 (18)		
Multiple myeloma, n (%)	6 (27)	3 (27)		
Median (range) Serum ferritin µg/l	430 (15-1288)	524 (14-2178)		
Median (range) Transferrin saturation (%)	25 (6-71)	18 (9-37)		

Were intervention and control groups comparable?	No; Stated that there was a higher proportion of women in placebo group, and that neutrophil and platelet counts were higher in placebo group. No analyses presented to support these statements.

RESULTS						
	Arm 1= Darbe n=22		**Arm 2 = Placebo n=11**		**Arm 3 = N =**		**p**
Haematology							
Proportion pts with haematologic response	55%		10%				Analysis comparing these two groups NR
Median time to response	13 weeks (1-13)		Not estimated				
% pts with a haematopoietic response (95% CI)	60 (39-81)		19 (0-43)				
Mean change (95% CI) in Hb from baseline to wk 13	1.64 (1.05-2.24)		1.00 (0.55-1.45)				
Transfusions							
% patients transfused (95% CI))	27 (9-46)		45 (16-75)				
Health-related QoL							
NR							
Adverse effects of tmt							
Note: safety data given for all three darbe groups combined versus placebo. Most AEs are presented graphically (bar chart), and it is not possible to extract exact data from the chart.							
	Darbe n=55		Placebo n=11				
At least one AE during study period, n (%)	52 (95%)		10 (91%)				
Rapid rise in Hb ≥2g/dl within 28 day period	22 (40%)		1 (9%)				
Changes in lab measures and vital signs were reported as ‘similar between patients receiving darbepoetin alpha and placebo’.							

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Yes, computerised stratified system
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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 placebo group (but sex included as confounder in models), neutrophil and platelet counts

	higher in 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
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Partially*

NOTES:

- Four study groups: darbe 1.0µg/kg (n=11); darbe 2.25 µg/kg (n=22); darbe 4.5µg/kg (n=22); placebo (n=11). Only darbe 2.25 µg/kg (n=22) and placebo (n=11) relevant to this review.
- Withdrawals given for the three darbe groups combined (n=2), although only one of these groups is relevant to this review

OTHER	
Generalisability	Small sample sizes. Analyses conducted using combined data from the three darbe groups versus placebo, but only one of the darbe groups is relevant to this review
Author conclusions	The results of the study indicated that darbepoetin alpha, administered once weekly at doses of 1.0, 2.25, and 4.5 µg/kg, was associated with greater effects on haemoglobin than placebo in patients with lymphoproliferative malignancies.
Reviewer comments	Difficult to interpret results specifically for the dosage relevant to this review

Endnote Ref ID	**2704**	**Malignancy type**	**Lymphoproliferative**
		Treatment	**Darbepoetin alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Hedenus 2003	N	
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 or over • lymphoproliferative malignancies (Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, or multiple myeloma) • Anaemia (**Hb ≤11 g/dl**), primarily due to cancer or chemotherapy (i.e. serum folate ‡ 4Æ5 nmol/l and vitamin B12 ‡ 148 pmol/l, no haemolysis, and no gastrointestinal bleeding • ECOG performance status 0-3. • Pts scheduled to receive cytotoxic chemo for at least 12 additional weeks	
# centres			
Other references/aliases	49		

Geographical setting		• Pts anaemia was primarily due to cancer or chemotherapy • Pts had adequate renal and liver function (serum creatinine concentration ≤177 lmol/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, • were scheduled toreceive a stem cell • transplant within 16 weeks of randomization • had received myeloablative chemotherapy, • radiotherapy for transplantation, or chemotherapy regimenscontaining investigational agents • transferrin saturation <15% and ferritin • <10 lg/l • significant central nervous system, cardiac, or • inflammatory diseases; • or any known primary haematological • disorders that could cause anaemia • Patients were not to have received epoetin • within 8 weeks, >2 RBC transfusion within 4 weeks, or any RBC transfusion within 2 weeks before randomization.
Duration of treatment	Secondary analysis in Littlewood 2006 (#375)	
Length of follow-up (if different)	Europe, Australia and Canada	
Country of corresponding author	12 weeks	
Language of publication	Unclear, a median follow-up period of approximately 11 months	
Sources of funding	Sweden	
RANDOMISATION & ALLOCATION	Central randomization 1:1 to receive DA or placebo. Randomization 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 randomization (heavily pre-treated vs not heavily pretreated; NB * patients were considered heavily pre-treated if they received two or more lines of chemotherapy, or one line of chemotherapy and a stem cell transplant)	
TREATMENT ARMS		
ARM Drug name/s	**Darbepoetin alfa**	**Placebo**
N	174	170
Dose & freq (od, bd etc)	2.25 ug/kg	
Dose adjustment Y/N	Y: doubled for patients who had ≤ 1 g/dl Hb increase from baseline after 4 weeks of treatment. It was withheld if a patient's haemoglobin value increased to > 15g/dl for men or > 14 g/dl for women, and was to be reinstated at 50% once Hb ≤13 g/dl.	
Route of administration	Subcut	
Duration of epo tx	12 weeks	
Adj anaemia treatment	Iron therapy were 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	**HaemR (proportion of pts with Hb response*)**	**Other outcomes**	**HaemR (proportion of pts with haematopoietic response); RBCT (**incidence of transfusions from week 5 to the end of the treatment (and from Wk 1 to the end of the treatment); tumour response (continue to be collected during a long-term follow-up period); survival (continue to be collected during a long-term follow-up period); AEs (AE and antibody formation); HRQL (FACT-Fatigue (every 4 weeks on d 1 of each cycle of chemotherapy, before any other study procedures)

NOTES:
* haemoglobin response, defined as an increase in haemoglobin of ≥2 g/dl from baseline in the absence of any RBC transfusions during the previous 28 days
$ haematopoietic response=haemoglobin response or a haemoglobin concentration ≥12 g/dl in the absence of any RBC transfusions during the previous28 days
£ completers analysis= pts with ≥ 12 weeks of treatment (had a week 13 Hb with no transfusions during the preceding 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 RBC transfusion, because of the anticipated withdrawal rate and approximate 95% CI 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 (±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 completers analysis£. Efficacy endpoints were analysed with and without adjusting for the stratification factors of malignancy type, region and chemotherapy before randomization. Results of these analyses were similar; thus, only the results of the unadjusted analyses are presented. Exploratory analyses of changes in the FACT-Fatigue subscale were conducted using ANOVA. The relationship between the change in the FACT-Fatigue subscale and the change in Hb was investigated using simple linear regression
Intention to treat analysis?	Y: ITT population (N=344) = all patients who received at least

	one dose of study drug, was used in the analyses of efficacy and safety; With the exception of transfusion endpoints,valuated during week 5 to the end of the treatment phase: these endpoints, 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 RBC transfusion endpoints, 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 (priori sample calculation)?	Y: sample size to detect an increase in Hb response rates 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 weeks study)
Attrition rate (loss to follow-up)?	Y: until the end of treatment
Was attrition rate adequately dealt with?	Yes
Number (%) followed up from each condition?	NR

BASELINE CHARACTERISTICS

Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		**Lymphoproliferative**
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		**Chemotherapy – no further details given**
Adjuvant anaemia treatment	**Iron**	Iron therapy were 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 criteria level	**≤11 g/dl**

	Darbe N =174		**Placebo N = 170**		**Arm 3 = N =**	
male (%)	87	50%	78	46%		
female (%)	87	50%	92	54%		
Age years, mean (SD)	64.8	13.8	64.6	12.2		
ECOG : 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^{-1} , 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, %	26.5	5-95	25	4-95		

Median, range						
Serum Epo baseline (mU ml^{-1}) Median, range	68.99	2.3-1522.7	54.49	10.9-3169.1		
Prior chemotherapy, n (%) Heavily pretreated**	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 "baseline demographic and clinical characteristics were generally well balanced between the treatment groups".					

RESULTS							
	Darbe N =174		**Placebo N = 170**		**Difference**		**p**
Haemoglobin response * % (95% CI)	60%	52-68%	18%	12-24%	42% (32-52%)		P<0.001
Haematopoietic response$	65%	57-73	24%	18-31			P<0.001
Mean change in Hb (SEM) ; ITT	1.8	0.17	0.19	0.1			P<0.001
Mean change in Hb (SEM) ; completers analysis£	2.66	0.2	0.69	0.14			P<0.001
Lymphoma subgroup	**N =85**		**N = 86**				
Haemoglobin response % (95% CI)	64%		13%		51%		P<0.001
Myeloma subgroup	**N =89**		**N = 84**				
Haemoglobin response % (95% CI)	56%		23%		33%		P<0.001
baseline serum erythropoietin levels ≤ 100 IU/l,	**N =89**		**N = 84**				
Haemoglobin response % (95% CI)	69%	60-79%	16%	9-22%			
baseline serum erythropoietin levels > 100 IU/l,	**N =89**		**N = 84**				
Haemoglobin response % (95% CI)	44%	31-58%	25%	11-39%	19% (0-38%)		
	N =167		**N = 165**				
Transfusions ; from week 5 to end of treatment	31%	24-38%	48%	41-56%			P<0.001
When the data were analysed within each malignancy type, darbe was associated with a reduction in transfusions compared with placebo both in pts with lymphoma (27% vs 49%,P =0.002) and pts with myeloma (35% vs 48%, P =0.042)							
Transfusions ; from week 1 to end of treatment					17% (6-27%)		P<0.001
This reduction in transfusions with darbe compared with placebo was observed both in pts with lymphoma (P =0.011) and pts with myeloma (P=0.018)							
Change in FACT Fatigue subscale score from baseline to EOTP: (84% of pts completed the FACT-Fatigue subscale at week 13)							

Improvement in FACT-Fatigue subscale score compared with placebo, regardless of their level of fatigue at baseline. Patients with the lowest baseline FACT-Fatigue subscale scores reported the largest improvement in FACT-Fatigue subscale score at EOTP. After adjusting for the effect of baseline score, increases in FACT-Fatigue subscale scores with darbepoetin alfa treatment were significantly greater than those observed with placebo (P=0.032).							
For every 1 g/dl increase in haemoglobin, the estimated mean increase in FACT-Fatigue subscale score was 1Æ39 (95% CI 0.83-1.94); p<0.001.							
For FACT change scores in the Lymphoma and Myeloma subgroups, see Littlewood 2006.							
Adverse effects							
Deaths(during the study or within 30 d after the last dose of study drug)	**10**	6%	4	2%			
Withdrawal due AE (not including death)		3%		4%			
No evidence of neutralizing antibodies to darbepoetin alfa was detected for any patient.							
Iron supplementation received; oral		6%		7%			
Iron supplementation received; subcutaneous		0%		1%			
Survival a median follow-up period of approximately 11 months							
PFS	82	47%	76	45%			

NOTES:
One patient was randomized 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.
** Prior chemotherapy: Heavily pre-treated = Two or more lines of chemotherapy or one line of chemotherapy and a stem cell transplant

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Y
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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 “baseline demographic and clinical characteristics were generally well balanced between the treatment groups”.
4. WERE THE ELIGIBILITY CRITERIA SPECIFIED?	Y

5. WERE THE PARTICIPANTS BLIND TO TREATMENT ALLOCATION?	Y
6. WERE THE OUTCOME ASSESSORS BLIND TO TREATMENT ALLOCATION?	Y
7. WERE THE POINT ESTIMATES AND MEASURE OF VARIABILITY PRESENTED FOR THE PRIMARY OUTCOME MEASURE?	Y
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPORTED?	N
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes, ITT defined as all randomised who received ≥ 1 dose of
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Y: until the end of treatment

NOTES:
References: investigates the effects of HB levels on fatique and examines the relationship between improvement in fatigue andHRQoL:
Littlewood, Timothy J.; Kallich, Joel D.; San Miguel, Jesus; Hendricks, Lisa; Hedenus, Michael. (2006). Efficacy of darbepoetin alfa in alleviating fatigue and the effect of fatigue on quality of life in anemic patients with lymphoproliferative malignancies. *Journal of Pain & Symptom Management*, 31, 317-325

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 as consistent with that expected for this patient population. Darbepoetin alfa significantly increased haemoglobin and reduced red blood cell transfusions 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	

Endnote Ref ID	**2705**	**Malignancy type**	**Solid – breast, gynae, GI, lung, other**
		Treatment	**Chemo: darbepoetin alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Kotasek, 2003	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 & to characterise the dose-repsonse relationships for darbepoetin alfa when given Q3W	**Inclusion criteria:** Patients ≥18 years of age with solid tumours receiving cyclic chemotherapy ; ≥6 month life expectancy, ECOG performance status of 0-2; adequate liver and renal function; anaemia (**Hb level ≤11.0 g/dl**) due to cancer and/or chemotherapy **Exclusion criteria:** Patients who: were iron-deficient (transferrin saturation <15% and ferritin 10 mcg/l; had received recombinant human erythropoietin within 8 weeks before randomisation; >2 RBCTs within 4 weeks of randomisation; any RBCT within 2 weeks of randomisation; known primary haematological	
# centres	26		
Other references/aliases	None		
Geographical setting	Australia, Canada, Costa		

	Rica, & Europe	disorders that could cause anaemia & central nervous system, cardiac, or inflammatory diseases
Duration of treatment	12 weeks (double-blind treatment. *NB: study in 2 parts (Part B open-label treatment period Wk 12 to 24)*	
Length of follow-up (if different)	Unclear: 8-week observation period after last dose of study drug at Wk 12 (Fig 1 shows Part A of study has obs period running to Wk 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 & ALLOCATION	Randomised, double-blind, placebo-controlled, dose-finding study of darbepoetin alfa Randomised 4:1 to receive darbepoetin alfa (4.5, 6.75, 9.0 or 13.5 µg/kg) or placebo. Later, after review of data by the safety monitoring committee, dose cohorts of 12.0 and 15.0 µg/kg were added, thus a 5-arm study.	

TREATMENT ARMS		
ARM Drug name/s	**Darbepoetin alfa**	**Placebo**
N	17	51
Dose & freq (od, bd etc)	6.75 µg/kg Q3W * *(2.2 mcg/kg QW)* The mean administered number of darbepoetin alfa doses over the 12-week treatment phase was 3.6.	NR
Dose adjustment Y/N	Y: 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 & reinstated at a lower dose level when Hb level was ≤13.0 g/dl	NR
Route of administration	Subcutaneous	NR
Duration of epo tx	12 weeks	12 weeks
Adj anaemia treatment	NR	NR
Transfusion trigger	NR	NR

OUTCOMES			
Primary outcome	**AEs (incidence of AE by dose and treatment group and formation of antibodies)**	**Other outcomes**	HaemR (responders; HaemR; Hb level (chg from baseline); RBCT ((Wk 5 to EOTP); HRQL (FACT-General, FACT-Fatigue)

NOTES:
Pre-dose and 48-h post-dose serum samples (darbe concentration) were collected at Weeks 1, 4, 10; QOL assessments at Weeks 1, 4, 7, 10 (to assess the feasibility,reliability, validity, sensitivity and timing of QOL, rather than to evaluate fatigue
Responders = increase in Hb of ≥2.0 g/dl during the treatment phase in the absence of any RBCTs in the previous 28 days
Haematopoietic response = haematologica response and/or haemoglobin concentration of ≥12.0 g/dl during the treatment phase in the absence of any RBCT in the previous 28 days
AEs- classified using a modified WHO AE term dictionary

ANALYSIS	
Statistical technique used?	Proportion of patients per dose group (haemoglobin response, haematopoietic response) estimated by taking 1 minus the Kaplan-Meier estimate of the survivor function at the time of the last observed endpoint. Approx. 95% CI for the Kaplan-Meier estimate of the proportion were calculated using Greenwood's estimate of the variance & assuming a normal distribution for the Kaplan-Meier estimate. Incidence of **RBCT** a subset was used (transfusions from week 5 to EOTP): all patients who received at least one dose of study drug and who ended their treatment phase during week 5 or later. Patients who have more than one transfusion were counted only once in calculating the incidence of transfusions. **Chg 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 chg in Hb. All patients had an observed or imputed value for this analysis (pts who withdrew after one dose were given a chg 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 2-sided Jonckheere-Terpstra test) to investigate the dose relationship of darbepoetin alfa: • mean chg in Hb at EOTP across dose groups • mean change in FACT-F across categorised chg in Hb (chg in Hb at last available QoL assessment)
Intention to treat analysis?	Analyses conducted on patients randomised to study drug who received at least one dose
Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	Statistically based on the secondary objectives to determine a clinically effective dose, by means of estimating Hb response rates. 4:1 randomisation allowed for 36 darbepoetin alfa patients per dose cohort. Anticipated premature withdrawal rate of approximately

	20%, a sample size of 29 allows estimation of the Hb response rate within a standard error of 0.09. Exact number of patients in each cohort was determined by the rate of enrolment & 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 Fig 2 of paper)			
Was attrition rate adequately dealt with?	Yes			
Number (%) followed up from each condition?	NR			
BASELINE CHARACTERISTICS				
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*			Solid – breast, gynae, GI, lung, other	
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*			Chemo: NR	
Adjuvant anaemia treatment	**Iron**		NR	
	G-CSF		NR	
	Transfusion trigger		NR	
	Hb inclusion criteria level		**≤11.0 g/dl**	
	Arm 1 = Darbepoetin alfa N-198	**Arm 2 = Placebo N=51**	**Arm 3 = N =**	
Baseline demographics and clinical characteristics reported for all darbepoetin alfa patients not separated out by dose				
Sex				
Male, n (%)	56 (28%)	16 (31%)		
Female, n (%)	142 (72)	35 (69)		
Age years mean (SD)	58.3 (11.9)	56.2 (12.4)		
Performance status; ECOG				
<2, n (%)	180 (91)	45 (88)		
Type of solid tumour				
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^{-1}), mean (SD)	99.3 (10.0)	98.7 (11.2)		
Hb (g dl^{-1}), mean (SD)	*9.93 (1.00)*	*9.87 (1.12)*	*PenTAG calculated*	
Ferritin(mcg/l) <50, mean (SD)	21 (11)	3 (6)		
Endogenous epo baseline (pts with ≥100 mU ml-1); n (%)	N=183	N=47		
	32 (17)	7 (15)		
Mean (SD) FACT-F Score; Darbe and placebo combined	QoL population N=239			
	27.2 (12.4)			
Were intervention and	No p values reported, authors stated: “In general, baseline demographic			

control groups comparable?	and clinical characteristics of patients were well balanced between the darbepoetin alfa and placebo groups. A slightly higher proportion of patients in the 12.0-mg/kg group had breast cancer (61%) compared with the other groups, which ranged from 15 to 38%. The 12.0-mg/kg group also had a slightly higher mean baseline Hb concentration (104 g/l) compared with mean concentrations between 97 and 102 g/l for the other groups. No clinically meaningful differences in pretreatment chemotherapy were seen between the darbepoetin alfa and placebo patients (data not shown)".

RESULTS: data extraction for 6.75 mcg/kg Q3W and placebo arms only

	Arm 1 = Darbepoetin alfa 6.75 mcg/kg Q3W N=17 ***(of total 198)***	**Arm 2 = Placebo N=51**	**Arm 3 = N =**	**p**
Hb				
Responders, K-M proportion (95% CI)	52 (27-78)	31 (16-45)	Haemoglobin values within 28 days of a red blood cell transfusion have been omitted	
Chg in Hb from baseline to EOTP (g/l), mean (SE)	8.6 (3.8)	-0.2 (2.0)		
g/dl PenTAG calculated	*0.86 (0.38)*	*-0.02 (0.2)*		
Chg in Hb from baseline after 12 weeks (g/l)*, mean (SE)	n=11	n=37		
	10.2 (5.4)	3.1 (2.4)		
g/dl PenTAG calculated	*1.02 (0.54)*	*0.31 (0.24)*		
* Chg after 12 weeks, a window was used allowing Wk 12 or 14 to be sued in the absence of an evaluable Wk 13 Hb value (Using the set of patients who completed at least 12 weeks of treatment).				
Safety: withdrawal due to:				
Deaths	7 (4%)	3 (6%)		
Tumour progression	6 (3%)	0		
AE	1 (1%)	0		

Adverse events are not reported by dose.
Authors state: "No relationship between the dose and adverse events was noted." AND " AEs reported were comparable between the darb alfa and placebo patients and generally consistent with those expected for patients being treated with myelosuppressive chemotherapy."

Results presented graphically

Fig. 3. Adverse events that occurred with 515% incidence in patients receiving darbepoetin alfa or placebo. Grey bars, darbepoetin alfa (n=198);solid bars, placebo (n=51).

RBCT (Wk 5 to EOTP)	**N=188**	**N=50**		
	Results presented graphically			

Results presented graphically

FOR ALL DOSES FYI: A lower percentage of patients in the darbepoetin alfa group required RBCT Wk 5 to EOTP compared with patients receiving placebo (46% (95% CI 32-61). No differences between the darbepoetin alfa groups could be observed: transfusion rates varied from 19% (95% CI 6-32) to 30% (95% CI 16-44).

HRQoL: Chg in QoL FACT-F score baseline to EOTP by change in haemoglobin

Results presented graphically	
FOR ALL DOSES FYI: Mean chg in FACT-F score appears 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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear; process not described
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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;* No p values reported, authors state: " In general, … well balanced between groups" and "a slightly higher proportion of patients in the 12.0-mg/kg group had breast cancer (61%) and higher mean baseline Hb concentration (104 g/l) compared with the other groups.
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: presented AEs ≥15% incidence in pts for all darb alfa doses don't separate out by dose
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes, all randomised who received ≥ 1 dose of study drug were analysed (100% and 95% participants in epo and placebo respectively).
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Partially; only until the end of the double blind study.
NOTES: *** yes for the placebo and 6.75 µg/kg Q3W (2.2 mcg/kg QW) darbe subgroup**	
OTHER	
Generalisability	Dose-finding study
Author conclusions	Administration of darbepoetin alfa Q3W is well-tolerated & effective in the treatment of anaemic patients receiving chemotherapy. Need for further research to investigate proportion of patients responding to treatment and the time to achieve 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	

Endnote Ref ID	**2691**	**Malignancy type**	**Solid**
		Treatment	**rHuEPO assume epoetin alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Kurz, 1997	N	
Objective	To evaluate the effectiveness of rHuEPO with respect to increasing Hb levels and decreasing RBCT requirements & to assess the influence on QoL parameters	**Inclusion criteria:** Patients between 18 and 75 years; **Hb level <11 g/dl**; ferritin serum levels >29 ng/ml; stool negative for occult blood; life expectancy >3 mths **Exclusion criteria:** clinically significant disease or dysfunction of the pulmonary, cardiovascular, endocrine, neurological, GI or genitourinary system not attributable to the underlying malignancy; uncontrolled hypertension (DBP >100 mmHb; anaemia attributable to factors other than chronic neoplastic disease, such as vitamin B_{12} deficiency, iron deficiency, and ferritin serum levels <29 ng/ml, GI bleeding or autoimmune haemolysis, acute illness within the last 7 days, & creatinine >2.5 mg/dl	
# 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 & ALLOCATION	Random permuted blocks and a corresponding randomisation list was used in the randomisation office at Cilag-Janssen. A 2:1 ratio between rHuEPO and placebo was implemented Randomisation code broken after documentation of all data		

TREATMENT ARMS		
ARM Drug name/s	**rHuEPO (Erypo® EPO ALFA)**	**Placebo**
N	23	12
Dose & freq (od, bd etc)	150 U/kg Q3W	150 U/kg Q3W
Dose adjustment Y/N	Y: Hb levels at Wk 4 were <1 g/dl above the baseline value each dose was increased to 300 U/kg Q3W. If at Wk 4 Hb levels were >1 g/dl above the baseline value but still within the anaemic range, the patient received 150 U/kg SC Q3W for the next 8 wks	Y: Hb levels at Wk 4 were <1 g/dl above the baseline value each dose was increased to 300 U/kg Q3W. If at Wk 4 Hb levels were >1 g/dl above the baseline value but still within the anaemic range, the patient received 150 U/kg SC Q3W for the next 8 wks
Route of administration	Subcutaneous	Subcut.
Duration of epo tx	12 wks	12 wks
Adj 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 level <8 g/dl		Hb level <8 g/dl
OUTCOMES			
Primary outcome		**Other outcomes**	**HaemR (**Hb levels measured every 4 weeks); **RBCT (**number of transfusions documented); HRQoL (VAS, beginning of treatment and then every 4 weeks before receiving chemotherapy patients completed a standardise questionnaire (10-item); VAS (1-5). Self administration; collected by a nurse but results not read immediately and physician did not comment on the results)
NOTES:			

ANALYSIS	
Statistical technique used?	Significance of the # responders & the # transfusions evaluated by X^2 test. Differences between the treatment and control group shown in Kruskall-Wallis test for variables with a non-parametric distribution QoL described per patient by 10 different scores each of which was calculated as the average value of 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 by Student's t test for unpaired samples. A multivariate evaluation of all 10 different scores was obtained by Hotelling's T^2 test Effect of achieving response from a state of non-response is described for each responding patient (n=13) by the difference of average QoL score values for the items for feeling of wellbeing, level of activity, physical ability, and social activities under response and non-response
Intention to treat analysis?	Assumed ITT: Unclear; results reported for total patient population and no reported crossover however not reported explicitly in the paper
Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	Not reported
Attrition rate (loss to follow-up)?	Not reported
Was attrition rate adequately dealt with?	Unclear as attrition rate not reported
Number (%) followed up from each condition?	NA

BASELINE CHARACTERISTICS	
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*	Solid – ovarian; cervical; uterine
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*	Plat-based chemother (n=28 (17 EPO; 11 PBO)) & non-plat based chemother (n=7 (6 EPO; 1

		PBO))
Adjuvant anaemia treatment	**Iron**	Iron saccharate substitution following each dose of chemotherapy beginning with the next cycle
	G-CSF	NR
	Transfusion trigger	Hb level <8 g/dl
	Hb inclusion criteria level	Hb level <11 g/dl

	Arm 1 = rHuEPO EPO ALFA N=23	**Arm 2 = PLACEBO N=12**	**P value**
Age years mean ± SD (range)	54.4 ± 9.7 (32-68)	52.7 ± 7.5 (43-63)	0.36*
Performance status; WHO			
0 - 1	17	9	0.88**
1 - 2	6	3	
Type of solid tumour, n			
Ovarian	17	8	0.64**
Uterine sarcoma	3	1	
Cervical carcinoma	3	3	
Hb baseline (g dl^{-1}), mean ± SD	9.88 ± 0.889	9.85 ± 0.60	0.63*
Haematocrit baseline (ng/ml), mean ± SD	29.9 ± 3.1	29.9 ± 1.7	0.95*
Ferritin baseline (ng/ml), mean ± SD	300 ± 255	245 ± 196	0.71*
* Kruskall-Wallis test; ** X^2test			
Were intervention and control groups comparable?	Yes; no statistically significant differences between the groups were reported		

RESULTS

	Arm 1 = rHuEPO EPO ALFA N=23		**Arm 2 = PLACEBO N=12**				**p**
Hb level, mean							
Wk 4	11.3 g/dL		No chg				
Wk 8	11.9 g/dL		No chg				
Wk 12	13.1 g/dL		No chg				
Haem response							
Yes	13	(56.5%)	0	(0%)	X^2 =10.79		0.001
No	10	(43.5%)	12	(100%)			

Of the 13 responders, 9 responded after 4 weeks of treatment, 2 after 8 weeks of treatment, and after 12 weeks of treatment in the EPO ALFA arm
RESPONDER = if HB levels at Wk 4, 8, 12 were >2 g/dl above the baseline value and/or >12 g/dl the patient was classified as a responder
NON-RESPONDERS = pts receiving RBCT (those with Hb level <8 g/dl; erythrocytes <3 x 10^6/ml; or clinical symptoms of anaemia which made transfusion necessary)

Values estimated from figure:

Hb	**EPO ALFA N=23**		**PLACEBO N=12**	
4 weeks (mean and SD)	11.34	1.75	9.82	1.75
8 weeks (mean and SD)	11.87	2.25	10.32	2.25
12 weeks (mean and SD)	13.14	2.25	10.1	2.25

RBCT requirement, n (%)	5	(21.7%)	8	(66.6%)	$X^2 = 6.81$	0.009

The 5 patients receiving RBCT in the treatment group, received 33 units for transfusion; whereas 8 of the placebo group received 44 blood units
None of the responding patients had to be transfused during the study period. A 2.5 times increased demand of transfusions in the placebo-treated group in comparison to the rHuEPO group

Health-related QoL – NOT VALIDATED QUESTIONNAIRE

Health state utility scale = See notes in Outcomes re questionnaire used

					p value*
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

* t test
Multivariate Hotelling's $T^{p=0.34}$

Adverse effects of tmt	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

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Yes
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was alternate, or based on information known to the triallist)	Unclear, Randomisation was performed in the randomisation office, 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?	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 not reported, unclear what the primary endpoint was
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes; results report response for all patients & no crossover so assume ITT
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Not reported
NOTES:	
OTHER	
Generalisability	Women only
Author conclusions	rHuEPO significantly increases Hb levels and decreases RBCT requirements while maintaining QoL in patients with gynaecological malignancies who are undergoing polychemotherapy
Reviewer comments	rHuEPO is Epo Alfa (Erypo, Janssen-Cilag)

Endnote Ref ID	**2692**	**Malignancy type**	**solid or non-myeloid haematologic malignancies**
		Treatment	**epoetin alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Littlewood, 2001	N	
Objective	To assess the effects of epoetin alfa on RBCT requirements, haematopoetic parameters, QoL, and safety in patients receiving non-platinum based chemotherapy	**Inclusion criteria:** age ≥18 years; confirmed diagnosis of solid or nonmyeloid hematologic malignancy and receiving or scheduled to receive nonplatinum chemotherapy (with a minimum cycle duration of 3 weeks); life expectancy ≥ 6 months; Hb level: **Hb≤10.5 or > 10.5 g/dL but ≤ 12.0 g/dL with at least 1.5-g/ decrease in Hb per cycle/month since beginning chemotherapy** **Exclusion criteria:** Patients with acute leukemia and myeloid malignancies; uncontrolled hypertension or untreated iron,folate, or vitamin B12 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.	
# centres	73 sites		
Other references/aliases	Patrick 2005 (#300), Aapro 2004 (#755) and Bajetta 2004 (#376) and – all retrospective analyses of this trial		
Geographical setting	15 countries (Germany, The Netherlands , United Kingdom and Ireland, Belgium, Luxembourg, Italy , South Africa, France, Greece, Switzerland, Poland, Portugal, Hungary, Czech Republic)		

Duration of treatment	Up to 28 weeks 12 to 24 weeks (3-6 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	Research grant JohRW Johnson Research Institute and Ortho Biotech Europe / Janssen Cilag	
RANDOMISATION & ALLOCATION	Stratified by tumor stratum (solid or ematologic) and haemoglobin level (≤10.5 g/dL, or ≤ 12.0 but > 10.5 g/dL). Double blind trail, but concealed allocation not reported.	

TREATMENT ARMS		
ARM Drug name/s	**Epo alfa**	**Placebo**
N	251	124
Dose & freq (od, bd etc)	150 IU/kg three times a week	Matching volume to epo alfa
Dose adjustment Y/N	Y : at 4 weeks: Dose was doubled if Hb increase <1 and the reticulocyte count increase <40,000 above BL. Dose reduction by 25% if Hb increased ≥2 per month or cycle. If at any time Hb >15, medication was interrupted till Hb <12, restarted with 25% dose reduction.	
Route of administration	Subcutaneously	Subcutaneously
Duration of epo tx	Up to 28 weeks	Up to 28 weeks
Adj 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**	**HaemR (**chg in Hb level (baseline to last value); proportion of responders); Survival; HRQoL (chg in QoL score (baseline to last value) on 5 cancer specific scales [FACT-An, FACT-G Total, FACT-An Fatigue, CLAS, LASA])

NOTES:
RESPONDERS = patients with an increase in Hb level ≥2 g/dl unrelated to transfusion; i.e. no transfusion within 28 days before measurement

ANALYSIS	
Statistical technique used?	Primary endpoint analysed for ITT and EFF populations (see below). Patients on study 28 days or less 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 haem), and haematologic stratum (≤10.5 g/dl or >10.5 g/dl). Since the interaction terms for treatment by tumour stratum and treatment by haemoglobin stratum were not significant at the 10% level, they were not included in the model Secondary efficacy variables (other than QoL) were analysed for the EFF population. Chgs in Hb level from baseline to last value were compared by t tests, and the proportions of responders were compared by the Fisher's exact test. Univariate analysis was performed to test within-group mean QoL 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 (2-sided). The p values for the primary QoL 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 QoL scores for each primary QoL 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 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 (haem 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. 8 factors were tested for; 4 – tumour stratum, baseline Hb level, age and area under the curve for neutrophils were found to be significant and included in the model

	For all analyses p<0.05 was considered significant. The study was not powered for subgroups
Intention to treat analysis?	Partially. Three populations were used for the efficacy analyses: the intent-to-treat population, which included all randomized patients; the efficacy group, which included all randomized patients on study >28 days (EFF); and the QoL population, which was defined as all patients who had been randomized, received the study drug, and had a baseline and at least one follow-up QoL assessment. Safety population was same as for ITT population. Baseline demographics and primary efficacy variable analyses for both the ITT and EFF population. Secondary variables other than QoL domains were analysed for the EFF population
Does statistical technique adjust for confounding?	Not reported
Power calculation (priori sample calculation)?	Not reported
Attrition rate (loss to follow-up)?	Yes:16 pts (7 receiving epo alfa and 9 receiving PBO) were excluded from the efficacy evaluation; 14 (6 receiving epo alfa and 8 receiving placebo) because they discontinued before completing treatment (no reasons reported); and 2 (1 per patient group) because the blind on their treatment codes was broken permanently. The remaining 359 patients were assessable for efficacy. #s also reported for QoL data set.
Was attrition rate adequately dealt with?	Yes: Patients on study 28 days or less were counted as transfused for the ITT analysis (although no sensitivity analysis)
Number (%) followed up from each condition?	Yes; 2 epo alpha patients and 1 placebo patient lost to follow up for 12 month survival analysis

BASELINE CHARACTERISTICS		
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		Solid: breast
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		Non-platinum chemotherapy
Adjuvant anaemia treatment	**Iron**	An oral daily dose of 200 mg of iron was recommended, if transferrin saturation ≤ 20%, intravenous iron was recommended, use of iron dextran was not allowed
	G-CSF	No
	Transfusion trigger	At the discretion of the physician with recommended Hb < 8 g/dL unless clinically indicated
	Hb inclusion criteria level	Haemoglobin levels ≤ 10.5

					g/dL, or levels greater than 10.5 g/dL but ≤ 12.0 g/dL after a 1.5-g/dL or greater decrease in haemoglobin level per cycle or month since beginning chemotherapy.	
	Arm 1 = Epoetin alfa N =251		**Arm 2 = Placebo N = 124**		**Arm 3 = N =**	
male (%)	85	(34)	39	(31)		
female (%)	166	(66)	85	(69)		
Age years mean ± SD	58.3±14.2		59.5±13.9			
Performance status WHO / ECOG /	NR					
Hb baseline (g dl^{-1}), mean ±SD	9.9±1.1		9.7±1.1			
Hb stratum						
≤10.5 g/dL	209	(83)	109	(88)		
>10.5 g/dL	42	(17)	15	(12)		
Chemo within 3 mths before study	231	(92)	114	(92)		
Pre-study transfusions (within 3 mths before study start	71	28	44	36		
Iron baseline (U/l median (range)	NR		NR			
Epo baseline (mU ml^{-1})	NR		NR			
Target Hb	NR		NR			
Tumour stratum (Littlewood 2001)						
Solid	136	(54)	66	(53)		
Haematologic	115	(46)	58	(47)		
Were intervention and control groups comparable?	No p values reported, authors stated “Demographic and baseline characteristics of the patients in the ITT population were generally comparable between the epoetin alfa and placebo treatment groups …although a further 12% of the placebo arm received prestudy transfusions”					

RESULTS ITT AND EFFICACY POPULATION							
	Arm 1 = Epoetin alfa		**Arm 2 = Placebo**		**Arm 3 = N =**		**p**
	N=251		N=124				
Pts transfused (%) (ITT population)	Overall						
	62/251	(24.7)	49/124	(39.5)			0.0057 (adjusted)
	Solid tumour						
	33/136	24.3	24/66	36.4			
	Haematologic						
	29/155	(25.2%)	25/58	(43.1)			
	N=244		N=115				

Mean change in Hb after 28 wks(g/dl) (SD) (efficacy pop)	2.2	(2.18)*	0.5	(1.79)			*<0.001 – chg from BL to 28 wks
Hb levels increased for first 10-14 weeks on epoetin alfa, while the Hb levels in the placebo group did not differ significantly from BL over the same period							
Responders (increase of Hb level by 2 g/dl during the study without transfusion 30 days prior) (%) (efficacy pop)	N=244		N=115				
	172	(70.5)	22	(19.1)			<0.001 (Fisher exact test)
	Solid tumour						
	87/131	(66.4)	13/61	(21.3)			
	Haematologic						
	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%)			
	127/203	(62.6)	14/100	(14.0)			
	Hb > 10.5 g/dl						
	38/41	(92.7)	4/15	(26.7)			
Survival 12 months after the last patient enrolled completed the study (median follow-up, 26 months) SAFETY POP							
	N = 251		N = 124				
Overall survival at 12-month assessment (median follow-up, 26 months)							
Alive	94	(37%)	41	(33%)			
Dead	155	(62%)	82	(66%)			
Lost to follow-up	2	(1%)	1	(1%)			
Median survival (ITT population)	17 mths*		11 mths				
Overall survival (note study insufficiently powered for this outcome) Kaplan-Meier 12 month survival estimates (%) (ITT population)	60%		49%				0.13
Estimated hazard ratio (placebo v epoetin alfa)	1.309						0.052
HR in favour of epo alfa; during the entire follow-up period the risk of dying was approximately 31% higher for placebo-treated patients compared with epo alfa treated patients							
Overall survival at 12-month assessment (median follow-up, 26 months): **HAEM MALIGNANCIES (n=173)** SAFETY POP							
	N=115		N=58				
Alive	60	(52%)	28	(48%)			
Dead	54	(47%)	30	(52%)			
Lost to follow-up	1	(1%)	0	(0%)			

Overall survival at 12-month assessment (median follow-up, 26 months):
SOLID TUMOURS (n=202)
SAFETY POP

	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 QOL parameters
Presented as change from baseline to last assessment (unclear when)

- Results for FACT and CLAS

	N=200	N=90			
Mean change score FACT-An:fatigue	3.0	-2.2			0.004
Mean change score FACT-An:anaemia	4	-2.6			0.0007 (not adjusted for multiple comparisons
Mean change score FACT-G	N=194	N=88			0.004
	2.5	-3.6			
	N=228	N=108			
CLAS-ENERGY	8.1	-5.8			0.0007
CLAS-DAILY ACTIVS	7.5	-6.0			0.0018
CLAS-OVERALL QoL	N=228	N=107			0.0048
	4.8	-6.0			

Adverse effects of tmt	**SAFETY POPULATION**						
	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%)			

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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear: stratified by tumour stratum (solid or haematologic) and haemoglobin level (≤10.5 g/dL, or ≤12.0 but >10.5 g/dL)
2. WAS THE TREATMENT ALLOCATION ADEQUATELY	NR

CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was alternate, or based on information known to the triallist)	
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 no variability
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes, apart from HRQoL (only 80% and 73% participants analysed in epo and placebo groups respectively)**
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes numbers given but detailed reasons not provided

NOTES:
*no p values reported; authors report "Demographic and baseline characteristics of patients in ITT pop generally comparable between groups"

**secondary endpoints (other than QoL) analyses using Efficacy population (see Stats section above)

OTHER	
Generalisability	Yes – broad population
Author conclusions	Epoetin alfa safely and effectively ameliorates anaemia and significantly improves QoL in cancer patients receiving non-platinum chemotherapy. Encouraging results regarding increased survival warrant another trial designed to confirm these findings
Reviewer comments	Caution required with survival results due to being underpowered. Also concern with lack of explanation for drop out/withdrawal; some explanation reported in Littlewood 2001 but reasons for withdrawals not specified in detail

Endnote Ref ID	**2680**	**Malignancy type**	**Breast Cancer**
		Treatment	**Epoetin Alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Moebus 2013	N	1,284 of which 643 in the IDD-ETC arm randomised to EPO A (n=324) or No EPO (n=319)
Objective	AGO-ETC trial compared intense dose-dense sequential chemotherapy every 2 weeks vs conventional scheduled	**Inclusion criteria:** women aged 18-65 years, histologically confirmed primary breast cancer of stages II to IIIa with four or more tumor-infiltrated axillary lymph nodes, M0 status, and R0 resection of the primary tumor and axilla with a	

	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 randomization of the intense dose-dense arm (IDD arm).**	minimum of 10 axillary lymph nodes removed, ECOG performance status of 0 to 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 tumor therapy, and simultaneous contralateral breast cancer or any other cancer except for basal cell skin carcinoma
# centres	165 (recruitment between November 1998 and April 2003)	
Other references/aliases	EPO-GER-10 AGO-ETC trial Moebus 2010 (in Tonia as abstracts Moebus 2005 and 2007)	
Geographical setting	Germany	
Duration of treatment	Median 18 weeks (mean=16.9 weeks)	
Length of follow-up (if different)	Median follow-up duration 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, Pharmacia, and Johnson& Johnson	
RANDOMISATION & ALLOCATION	Pts stratified by center, menopausal status (pre- vs postmenopausal),and the number of affected lymph nodes (4–9 vs≥10) at the central fax randomization. Computer-generated lists with permuted blocks of randomly variable size were used	
TREATMENT ARMS		

ARM Drug name/s	**Epo alfa**	**Controls, standard care**
N	324	319
Dose & freq (od, bd etc)	150 IU/kg three times weekly	NA
Dose adjustment Y/N	To maintain Hb level of 12.5 to 13.0 g/dL. Dose doubled if Hb dropped >2 g/dL within a 4-week period. Epo was withdrawn when the Hb >14.0 g/dL was restarted when the Hb level <13.0 g/dL.	NA
Route of administration	Subcutaneously	NA
Duration of epo tx	Started on Day 1 and continued up to 14 days after the last dose of cyclophosphamide.	NA
Adj anaemia treatment	200 mg/day oral iron	200 mg/day oral iron.
Transfusion trigger	Pts with an Hb level <9.0 g/dL were	Pts with an Hb level < 9.0 g/dL were

	evaluated for transfusions by the physician. The indication for RBC transfusion depended on the symptoms of the patients and was at the discretion of the physician.	evaluated for transfusions by the physician

OUTCOMES			
Primary outcome	**Hb levels BL to Cycle 9**	**Other outcomes**	RBCT (# blood transfusions); Survival (OS, recurrence-free survival); HRQoL (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, version [assessed at before the start of treatment, at every second cycle, at the end of treatment, and at each follow-up visit]); AEs

NOTES:
Primary outcome (as specified by study authors) is highlighted in bold
Complete blood counts were obtained at each cycle, and Hb level was measured at least weekly during chemotherapy.
Follow-up visits performed every 3 months for 3 years, every 6 months during years 4 and 5, and annually thereafter.
M0 status: ie, 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 endpoint of transfusions for which a one-sided hypothesis was prospectively defined. Comparison of Hb levels evaluated with ANOVA and Wilcoxon tests. Numbers of at least one on-study RBC transfusions were compared between the two groups using Fisher exact test. On-study defined as the period from randomisation to the date of the last cycle of chemo plus 14 days or the date of withdrawal, whichever occurred first. Kaplan-Meier estimates of the relapse-free survival were compared using a 2-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% CI.
Intention to treat analysis?	Yes: ITT and per-protocol analyses for primary outcomes and relapse-free survival. The safety population included 627 subjects (309 in epo arm 318 in control arm); all epo ptc receiving epo and all controls with no epo treatments. The per-protocol population included 511 subjects, 258 ptc in the epoetin alfa group and 253 ptc in the control group. Ptc excluded if unknown ECOG/WHO

	performance status; < four positive lymph nodes at baseline; not receiving the assigned treatment (the majority of ptc excluded if they failed to received 9 cycles of chemotherapy).
Does statistical technique adjust for confounding?	NA
Power calculation (priori sample calculation)?	Yes, based on the size needed to detect any difference in Hb levels and proportions needing transfusion. In addition, the 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
Number (%) followed up from each condition?	Yes

BASELINE CHARACTERISTICS

Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		Solid tumour: breast cancer
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		9 cycles of: three sequential cycles of epirubicin (150 mg/m2), paclitaxel (225 mg/m2), and cyclophosphamide (2500 mg/m2), 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	Pts with an Hb level < 9.0 g/dL were evaluated for transfusions by the physician
	Hb inclusion criteria level	NR

	Arm 1 = epo N =324		**Arm 2 = controls N = 319**		**Arm 3 = N =**	
Age years median (range)	50	29-65	52	28-67		
ECOG	315		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)		
Median Hb baseline (g/dL)	313		303			
median (IQR)	12.4	(11.7-13.3)	12.8	(12.2-13.6)		
Tumour stage:						
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 “the two treatment groups were generally similar with respect to the demographic and baseline

			characteristics".				
RESULTS							
	Arm 1 = epo N =324		**Arm 2 = controls N = 319**		**Arm 3 = N =**		**p**
Change in Hb (cycle 9)	0		-2.2*				*<0.001 chg from BL
Mean Hb values presented graphically Hb level (g/dL) by cycle (intent-to-treat population). Based on available measurements in the patients receiving the respective chemotherapy cycle. Results from similar to those of the per-protocol population Analysis of variance and Wilcoxon test: p<0.001							
Transfusions: Numbers of transfusions: assessed during the period from randomization to the date of the last cycle of chemotherapy plus 14 days or the date of withdrawal, whichever occurred first							
Transfusions (ITT)	41	12.8%	86	28.1%			<0.0001
HR: 0.37 (95% CI = 0.25 to 0.57). Similar results were obtained when the per-protocol population was analysed. Most transfusions, regardless of treatment group, occurred during Cycles 7 to 9. # of subjects in the control group who received transfusions increased steadily from Cycle 1 to Cycle 9; # of subjects in the epoetin alfa who received transfusions increased mainly during Cycles 7 to 9							
Health-related QoL							
Results for health-related patient-reported outcome analyses are not presented because of the large amount of missing baseline data (in excess of 40% of baseline measurements were missing).							
Survival (ITT)	324		317				
5-yr relapse-free survival (95% CI)	71% (66-76%)		72% (67-77%)				
	HR= 1.03 (95% CI = 0.77 to 1.37)						P = 0.86
5 yr overall survival (95% CI)	81% (76-86%)		83% (78-87%)				
	HR= 0.97 (95% CI = 0.67 to 1.41)						P = 0.89
Safety Incidence is based on the number of pts experiencing at least one AE, not the number of AE							
	309		318				
Total # subjects with AEs	10	(3%)	22	(7%)			
Embolism	1	<1%	0	0%			
Pts with thromboembolic vascular event while on chemotherapy	39	13%	22	7%			
Pts with clinically relevant thromboembolic vascular events	22	7%	10	3%			P = 0.03
Vascular disorders							
Thrombosis	21	(7%)	9	(3%)			
Venous thrombosis	2	(1%)	0				
Arterial thrombosis	1	(<1%)	0				
Deep vein thrombosis	1	(<1%)	0				
Embolism	0		1	(<1%)			
Subclavian vein thrombosis	0		1	(<1%)			
Respiratory, thoracic, and mediastinal disorders							
Pulmonary embolism	0		1	(<1%)			
Serious AE	10%		13%				

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Yes
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	Yes; this study was a Latin Square design and this paper reports second randomisation (first randomisation results published in an alternative ref [2010] excluded as epo vs epo not measured
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes

NOTES:

Moebus 2010 reference:

Moebus, V., Jackisch, C., Lueck, H. J., du Bois, A., Thomssen, C., Kurbacher, C., . . . Untch, M. (2010). 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, 28(17), 2874-2880. doi: 10.1200/jco.2009.24.7643

OTHER	
Generalisability	Females only (breast cancer)
Author conclusions	Epoetin alfa resulted in improved hemoglobin levels and decreased transfusions without an impact on relapsefree or overall survival. 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-kilogram dose was calculated using the subject's body weight.

Endnote Ref ID	2693	Malignancy type	Lymphoproliferative malignancies: Non-Hodgkin's lymphoma (NHL) Chronic lymphocytic leukaemia (CLL) Multiple myeloma (MM)
		Treatment	ESA- epoetin beta

STUDY DESIGN		PARTICIPANTS	
Author, year	Osterborg 2005	N	349 (ITT=343)
Objective	To investigate the efficacy of epoetin beta in eliminating severe anaemia and transfusion dependency and concomitant effects on QOL, with the FACT scale in pts with advanced MM, low grade NHL and CLL.	**Inclusion criteria:** • 18 years and over • Confirmed diagnosis of NHL, CLL, MM • **Hb less than 10 g/dl** with a transfusion requirement of ≥ 2 U RBCs in the 3 months before the study • Pts required to have an inadequately low endogenous serum erythropoietin concentration ≤100 IU/l (if Hb was >9 to <10 g/dl), ≤180 IU/l (if Hb level was >8 to ≤9 g/dl) or ≤ 300 IU/l (if Hb level was ≤8 g/dl) • Pts must have been scheduled to receive antitumour therapy for the next 4 months • Life expectancy of more than 4 months • WHO performance score of 0 to 3 **Exclusion criteria:** • Therapy resistant hypertension • Relevant acute or chronic bleeding in 3 months before study commencement • Thrombocytopenia or thrombocytosis (platelets <20 and >450 x 10^9/L, respectively) • Vitamin B_{12} or folic acid deficiencies • Creatinine levels more than 2.5 mg/dl • Haemolysis (haptoglobin level <50 mg/dl) • Epilepsy • Known hypersensitivity to preservatives used in study medication injection formulation • Pts with evidence of functional iron deficiency (transferring <25%)	
# centres	63, conducted between June 1997 and July 1999		
Other references/aliases	Osterborg, 2002 (#682)		
Geographical setting	12 countries		
Duration of treatment	16 weeks		
Length of follow-up (if different)	Pts followed up for at least one year after EOTP. The minimum length of follow up was approx 17.5 months in both treatment groups, with only 4 pts in each gp having a shorter follow up (reported in Osterborg 2005)		
Country of corresponding author	Sweden		
Language of publication	English		
Sources of funding	F.Hoffman-La Roche		
RANDOMISATION & ALLOCATION	Randomised, double-blind, placebo controlled. Stratified according to malignancy type and study centre. After a run-in period of approximately 2 weeks, patients suitable for inclusion were randomized.		

TREATMENT ARMS		
ARM Drug name/s	**Epoetin beta**	**Placebo**
N	170	173

Dose & freq (od, bd etc)	150 IU/kg three times a week	
Dose adjustment Y/N	The dose was increased to 300 IU/kg if Hb < 8.5g/dl, or if Hb increase from baseline < 0.5 g/dl after 4 weeks. Dose was decreased by 50% if Hb increased > 2 g/dL within this period. If Hb >14 g/dL, the study medication was suspended until Hb declined to ≤13 g/dL, when epo was reinstated at 50% of the previous dose.	
Route of administration	Subcutaneous	Sub cut
Duration of epo tx	16 weeks	16 wks
Adj anaemia treatment	Enrolled pts with a baseline transferring saturation of less than 25% received IV iron substitution (100mg Fe) before the start of study treatment. Where transferring saturation levels decreased to below 25% during the course of the study, IV Fe substitution therapy was administered at a dose of 100 mg Fe per week until transferrin saturation reached ≥25%. Oral Fe substitution therapy (200-300 mg Fe) was administered to those in whom IV Fe was precluded.	Enrolled pts with a baseline transferring saturation of less than 25% received IV iron substitution (100mg Fe) before the start of study treatment. Where transferring saturation levels decreased to below 25% during the course of the study, IV Fe substitution therapy was administered at a dose of 100 mg Fe per week until transferrin saturation reached ≥25%. Oral Fe substitution therapy (200-300 mg Fe) was administered to those in whom IV Fe was precluded.
Transfusion trigger	If Hb was less than 8.5 g/dL or at higher levels if medically indicated—that is, the presence of marked anemic symptoms such as angina pectoris.	If Hb was less than 8.5 g/dL or at higher levels if medically indicated—that is, the presence of marked anemic symptoms such as angina pectoris.

OUTCOMES

Primary outcome	**Transfusion-free survival (during weeks 5 to 16 of study. Also analysed severe anaemia free survival (Hb≥8.5 g/dl) during weeks 5 to 16. Death without previous event was considered a failure)**	**Other outcomes**	HaemR (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 QoL was assessed at baseline and every 4 weeks during the study via FACT-An. Questionnaires were completed before any examination or treatment so that pts assessment could not be influenced by references to current Hb level.; AEs (Adverse events, hematologic parameters, concomitant medications, blood transfusions, and antitumor therapy were documented throughout the course of the study)

NOTES:
Although the anemia 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 (α = 0.05) should be performed if the difference in the total study population was significant and no significant interaction between study treatment and strata were present (P>.1 Hazard ratios 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 on 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 QoL and Hb data, where baseline values were considered as covariates. **Long term Survival data: Osterborg 2005:** Survival data were analysed by standard Kaplan-Meier methods and differences in survival between groups were assessed using a log-rank test. Median time to patients being censored was 27.8 months in the epoetin beta group and 27.5 months in the placebo group.
Intention to treat 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 ITT population is defined as all participants receiving study treatment N= 343, while 349 pts were randomised. ITT = safety population in this study (n=343).
Does statistical technique adjust for confounding?	Yes
Power calculation (priori sample calculation)?	Yes –150 patients with low-grade NHL, CLL, or MM 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: Enroll at least 100 pts per stratum (MM, NHL, CLL; 50 pts 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 pts in each treatment group were withdrawn prior to receiving study medication due to withdrawal of consent (n=5) and protocol violation (n=1). In total, of 349 pts, 281 completed the study. The main reasons for withdrawal were death (n=35), withdrawal of consent (n=12) and adverse events (n=11).
Was attrition rate adequately dealt with?	In case or premature withdrawal from study treatment, pts were observed and Hb level, blood transfusions and vital status were recorded whenever possible until study week 16.
Number (%) 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 / haem / MDS / mixed)*	**Non-Hodgkin's lymphoma (NHL)** **Chronic lymphocytic leukaemia (CLL)** **Multiple myeloma (MM)**
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*	Non-plat chemo

Adjuvant anaemia treatment	**Iron**	Yes, see treatment description above for more details
	G-CSF	NR
	Transfusion trigger	If Hb was less than 8.5 g/dL or at higher levels if medically indicated—that is, the presence of marked anemic symptoms such as angina pectoris.
	Hb inclusion criteria level	**<10 g/dl**

	Epoetin beta N= 170	**Placebo N= 173**	**Arm 3 = N =**	
male, n (%)	91 (54.0)	82 (47.0)		
female, n(%)	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				
CLL, n (%)	59 (35.0)	66 (38.0)		
MM, n (%)	58 (34.0)	58 (33.5)		
NHL, n (%)	53 (31.0)	49 (28.5)		
Transfusion requirement (%)				
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				
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, x 10^9/L, mean±SD	2.8±2.5	3.0±3.1		
Platelet count, x 10^9/L, mean (IQR)	149 (100-195)	141 (94-190)		
Serum EPO, 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		
QoL scores				
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 “There			

	were no major differences in the demographics and clinical characteristics of the two treatment groups ".

RESULTS

	Epo Beta n=170	Placebo n=173			p
Haematological					
Hb response (≥ 2 g/dl increase in Hb without transfusion) at 16 weeks	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 CII patients (n=125)	63%	26%			<0.0001
Fig2 p 2490 represents time to response graphically					
Hb nadir Mean ± SD (g/dl)	**Epo Beta n=170**	**Placebo n=173**	Epoetin (N)	Placebo (N)	
1-4 weeks	9.1±1.4	8.7±1.2	169	173	0.0003
5-8 weeks	10.0±1.9	8.8±1.5	161	165	0.0001
9-12 weeks	10.5±2.0	8.9±1.5	152	153	0.0001
13-16 weeks	10.8±2.0	9.2±1.6	146	147	0.0001

The difference in mean Hb nadir was 0.4 g/dl at week 1 to 4, increasing to 1.6 g/dl at wk 13 to 16 (P=0.001 v placebo). Similar findings were observed for mean Hb levels and haematocrit, which increased significantly in epo group from wk 2 onward (both P<0.005 v placebo) during the course of the study.

Prediction of Response (Cox's multivariate regression analysis of factors in transfusion free survival during weeks 5 to 16):

Treatment, epopetin beta v placebo	HR 0.555 95%CI (0.369-0.776), p=0.0006
Platelet count, ≥100 v <100 x 10^9 g/L	HR 0.416 95%CI (0.292-0.592), p=0.0001
Hb level, ≥ 9 v <9 g/dl	HR 0.589 95%CI (0.423-0.821), p=0.0018
Pretreatment transfusion requirement, ≤ 2 v 3 units	HR 0.645 95%CI (0.458-0.909), p=0.0123
Underlying malignancy	HR 0.803 95%CI (0.565-1.140p=0.2198

Baseline platelet count ≥ 100 x 109/L, Hb levels ≥ 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 pts versus placebo was stronger in pts with a high platelet count (55%) and high Hb levels (51%) than in pts with a low platelet count (21%) and low Hb levels (26%).The type of underlying malignancy (MM, NHL, CLL), sex, age, baseline neutrophil count, transferrin saturation, WHO performance score, or QOL score had no significant effect ineither analysis.

Severe Anemia and Transfusion free survival					
	Epo Beta n=170	**Placebo n=173**			**p**
Pts with blood transfusions in first 4 weeks of study treatment (%)	29.0	27.2			0.707
Transfusion free survival during 16 weeks treatment (%)	66.7	47.6	Risk reduction favouring Epo of 43%		0.0012
Severe anaemia and transfusion free survival			Risk reduction favouring Epo of 51%		0.0001

Interaction between underlying malignant disease and treatment					>0.1

Fig1 p 2490 represents severe anaemia free survival graphically:
The difference in transfusion- and severe anaemia-free survival was statistically significant across all malignancy subtypes and was particularly apparent in pts 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 ~ 40% in both groups (P=0.02 and P=0.03, respectively).

Survival (long-term follow up Osterborg 2005):

	Epoetin beta N= 170	Placebo N= 173	p
number of deaths	110 (65%) censored, n =60	109 (63%) censored, n =64	
Kaplan–Meier : Median survival (months)	17.4 95% CI: 15.0-20.5	18 95% CI: 16-22.3	
	HR: 1.04, 95% CI: 0.8-1.36		0.76

Fig1 p 207 Osterborg 2005 represents graphically OS

Health-related QoL

Baseline and Change From Baseline in Quality-of-Life Questionnaires:

	Baseline		Week 4		Week 8		Week 12		Week 16	
Variable	Mean Score ±SD	No. pts	Mean Score ±SD	No. pts	Mean Score ±SD	No. pts	Mean Score ±SD	No. pts	Mean Score ±SD	No. pts
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***	114	**14.8±28.0***	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***	114	**6.5±13.8***	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, 7 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

***P<0.5** (After 12 and 16 weeks, the improvement in FACT-An and FACT-G score was greater in epo arm). Analysis of the dimensions of the FACT-G scale revealed statistically significant differences after 12 weeks: P<0.01 and P<0.05 favouring epo for social and family wellbeing and emotional wellbeing, respectively.

QOL results at baseline and change from baseline in epoetin beta responders and non-responders:

	Baseline		Week 4		Week 8		Week 12		Week 16	
Variable	Mean Score ±SD	No. pts	Mean Score ±SD	No. pts	Mean Score ±SD	No. pts	Mean Score ±SD	No. pts	Mean Score ±SD	No. pts
FACT-An, 49 items, range 0-196										
Responder	118.9±25.1	92	5.1±21,6	91	**9.7±25.2***	87	**15.2±26.3***	88	**17.4±25.9***	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***	87	**6.9±14.3***	88	**7.8±13.4***	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***	108	**5.3±10.5***	110	**6.3±10.5***	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, 7 items, range 0-28										
Responder	17.8±4.4	114	1.0±3.2	112	1.3±4.3	108	**2.1±3.9***	110	**2.2±4.0***	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

***P<0.05**

Analysis of the relationship between final Hb in wk 16 and change in total FACT-An score from baseline in the epoetin 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 pts was considerable and a uniform target Hb value associated with an optimal QoL could not be identified.

Adverse effects

	Epoetin beta		Placebo				
Pts reporting at least on adverse event, n (%)	122 (72)		132 (76)				
Hypertension	9%		5%				
Local transient reaction after injection	1%		0%				
SAE, n (%)	57 (33)		55 (32)				
Deaths, n (%)	28 (16)		22 (13)				
Death due to PE	1		0				
stable disease or partial remission	68%		68%		Reported in Osterborg 2005		
Remission	9	5%	5	3%			
Progressive disease	31	18%	40	23%			

No antibodies to erythropoietin were detected in any patient.

Iron

The proportion of patients who developed transferrin saturations of less than 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). 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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes, until the end of treatment only

NOTES:

References:

Osterborg, Anders; Brandberg, Yvonne; Hedenus, Michael. (2005). Impact of epoetin-beta on survival of patients with lymphoproliferative malignancies: long-term follow up of a large randomized study. British *Journal of Haematology*, 129, 206-209.

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 QoL in severely anaemic, transfusion dependent pts with advanced phase NHL, CLL and MM. Overall, the improvement in QoL was particularly apparent in pts with Hb increases of ≥2 g/dl. This suggests that the minimum increase in Hb may be a more important determinant of improved QoL than a uniform and close to normal target Hb level. Osterborg 2005: The treatment of severe, transfusion-dependent anaemia with epoetin-beta had 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.
Reviewer comments	

Endnote Ref ID	1119	Malignancy type	solid tumours and hematologic cancer
		Treatment	Epo alfa

STUDY DESIGN		PARTICIPANTS	
Author, year	Ray-Coquard 2009	N	218
Objective	This randomized phase III study aimed to identify the effects of epo alfa in patients at high risk for anemia requiring RBC: patients receiving chemotherapy with Hb level <12, and PS >1, or ≤Ly £700/ll (score of 4 and more according to the ELYPSE risk model).	**Inclusion criteria:** histologically documented cancer necessitating chemotherapy; age≥ 18 years with solid tumours or hematologic cancer requiring CT; **Hb<12g/dl (@ Day 1 of chemo)**, and Ly ≤700/ µl, or PS >1; negative HIV test in patients with non–Hodgkin's lymphoma; chemotherapy not requiring hematopoietic 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 epo during chemotherapy; uncontrolled hypertension (i.e. diastolic blood pressure >95 mmHg), patient refusal; anemia in cancer patients not receiving chemotherapy; history of nervous or psychiatric disorder that would preclude informed consent or compliance; anemia resulting from factors other than cancer or its treatment untreated folate or vitamin B12 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.	
# centres	9 sites; September 200-January 2005		
Other references/aliases			
Geographical setting	France		
Duration of treatment	12 weeks		
Length of follow-up (if different)	median follow-up of 12 months (95% CI: 12–12.4)		
Country of corresponding author	France		
Language of publication	English		
Sources of funding	The Ministry of Health; the Ligue contre le cancer (Ain, Rhoˆne and Savoie		
RANDOMISATION & ALLOCATION	Randomization was centralized and stratified according to the participating centers and the number of prognostic factors for severe anemia, with two versus three of the following criteria: Hb level at day 0 <12 g/dl, Ly <700/ll, and PS >1.		

TREATMENT ARMS		
ARM Drug name/s	**Epo alfa**	**No treatment**
N	110	108
Dose & freq (od, bd etc)	150UI/kg TIW	
Dose adjustment Y/N	Decrease to 75% if Hb increased >2 g/dl. If after 4 weeks the Hb was <10.5 with <1 g/dl decrese, and is retriculocyte count was <40 000 cells/µl , Epo was increased to 60 000UI weekly. If Hb increased >12g/dl, it was interrupted till it got back to 12 g/dl.	
Route of administration	Subcutaneous injections	NA
Duration of epo tx	12 weeks	Oral iron supplementation was administered to support erythropoiesis in patients with iron

		deficiency since no information on the improved efficacy of i.v. iron treatment was available at the initiation of the trial
Adj anaemia treatment	Oral iron supplementation was administered to support erythropoiesis in patients with iron deficiency since no information on the improved efficacy of i.v. iron treatment was available at the initiation of the trial	Incidence of severe anemia
Transfusion trigger	Incidence of severe anemia	

OUTCOMES			
Primary outcome		**Other outcomes**	RBCT (rate of transfusion; number of transfusions); survival (OS, time to disease progression); HRQoL (EORTC QLQ-C30); AEs

NOTES:
Not clear what PS used, assumed ECOG as ECOG reported in results section.
Ly= lymphocyte count
PS=performance status
severe anemia= grade III anemia (Hb <8 g/dl) or grade II anemia (Hb <10 g/dl and ≥8 g/dl) in patients with grade III symptomatic cardiopathy, tachycardia (>100 beats/min), symptomatic angina with electric signs (modification of ST segment), grade III dyspnea, symptomatic pneumopathy (PaO2, 50–64; diffusion of carboxy oxygen, 54%–40%; volume capacity, 54%–40%), and grade III asthenia.
Elypse model: Score of 4 or more: scoring based on Hb <12g/dl (score of three), and Lymphocyte count ≤700/ µl or performance status >1 (score of one each).
reference: Ray-Coquard I, Le Cesne A, Rubio MT 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: 2840–2846.
prognostic factors for no RBC: The final model showed that no previous history of RBC transfusion [odds ratio (OR): 0.36; 95% CI: 0.135–0.978] and Hb level >10 g/dl at baseline (OR: 0.27; 95% CI: 0.09–0.84) were independent risk factors for no RBC.

ANALYSIS	
Statistical technique used?	OS was the time interval from randomization to date of death or last follow-up. Kaplan–Meier survival estimates, and differences were assessed by the log-rank test. Safety variables were analyzed using the safety population (all randomly assigned patients with at least one safety assessment). QoL 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.
Intention to treat analysis?	Yes
Does statistical technique adjust for confounding?	NA
Power calculation (priori sample calculation)?	Yes, to detect a 15% difference in RBC transfusions with a power of 80% and a one-sided significance level of 5%.
Attrition rate (loss to follow-up)?	NR; numbers of patient and reasons for treatment discontinuation reported (but not by study arm):

Was attrition rate adequately dealt with?	NR
Number (%) followed up from each condition?	NR

BASELINE CHARACTERISTICS

Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		solid tumours and hematologic cancer
Treatment*(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		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 anemia
	Hb inclusion criteria level	Hb<12g/dl

	Arm 1 = Epo N =110		**Arm 2 = control N = 108**		**Arm 3 = 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 /: 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^{-1}) mean (SD)	10	1.2	10	1.2		
Haematocrit (%) mean (SD)	30.3	3.4	30.4	3.8		
Mean Feritin, µg/dL (SD)	585	697	701	1005		
Stage (%): Local	16	14.5%	12	11.1%		
Metastatic stage	92	83.6%	94	94%		
NA	2	1.8 %	2	1.9%		
2 Strata (prognostic factor)	84	76.4%	79	73.1%		
3 Strata (prognostic factor)	26	23.6%	29	26.9%		
Health state utility scale = EORTC QLQ-C30						P=0.048

Were intervention and control groups comparable?	No p-values reported aprt from HRQoL data, authors stated “Patients distribution was well balanced between the two groups of treatments”.

RESULTS

	Arm 1 = Epo A N = 110		**Arm 2 = controls N = 108**		**Arm 3 = N =**		**p**
Health-related QoL[$]							
Health state utility scale = EORTC QLQ-C30.							
Baseline							P=0.048
Follow up	no statisticallydetectable 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.						

Survival							
Overall survival*	Ly was found to be correlated to OS, with a median OS of 4.2 months (95% CI: 3.0–5.5) for patients with £700/ll lymphocytes versus 8.3 months (95% CI: 6.6–10.4) otherwise. And patients with two prognostic factors had a significantly better OS than patients with three factors (median 8.3 versus 3.6 months, P < 0.0001; hazard ratio: 2.36, 95% CI: 1.7–3.3) However, Hb counts <10 versus ≥10 were not.						
Median survival (months ; CI)	7.6	5.3 to 10.4	6	5.0 to 8.0			P = 0.148
PFS (months ; CI)	5	4.3–6.6	4.4	3.8–5.2			P=0.17
Transfusions*							
Participants (%)	39	36.1%	61	58%			P=0.001
	relative risk: 0.62 [95% confidence interval (CI): 0.46–0.84						
Safety data$							
At least one AE	59	(53.6%)	50	(46.7%)			P=0.31
At least one SAE	54	(49.1%)	49	(45.4%)			P=0.58
Fatal AE	20	18.2%	20	18.5%			P=0.95
Deaths	A majority (73%) of patients had died at the time of 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 adverse events were considered related to the study drug		4.6%		2.9%			P=0.72
incidence of serious adverse events, including deaths		50%		46.7%			P=0.63

* 213 patients were assessable primary criteria (rate of RBC transfusions) and toxicity; Five patients (2.3%) were enrolled but did not receive chemotherapy (four died before the beginning of treatment).
$ Only 54% of the questionnaires (118) were available for QoL evaluation, 57% in arm 1 (n = 63) and 51% in arm 2 (n = 55).
85% of the patients were metastatic at inclusion in the study; and the majority was in the stratum for two prognostic factors

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear – method was centralised but not reported
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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 and no for from HRQL scores 9 Significant differences in favour of the EPO arm were noted for QoL scores at inclusion)

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
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes, apart from HRQoL (54% and 57% participants analysed in epo and control groups respectively).
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	NR, see stats section above
NOTES:	
OTHER	
Generalisability	A very specific population group.
Author conclusions	Patients at high risk for RBC transfusion according to Hb<12g/dl, and Ly ≤700/ µl and/or PS >1could be given prophylactic Epo. with significantly reduced RBC transfusions and no significant impact on side-effects, progression-free survival, and OS
Reviewer comments	Not very well reported trial, e.g. data in results and methods section only partially reported.

Endnote Ref ID	**2695**	**Malignancy type**	**Multiple myeloma**
		Treatment	**Second induction chemo** **rHU-EPO – assume epoetin alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Silvestris, 1995	N	54
Objective	Not stated – paper reports the results of a long term trial using rHuEPO in MM pts undergoing second-induction chemo	**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 lower than 50 **Exclusion criteria:** NR	
# centres	NR		
Other references/aliases	None		
Geographical setting	NR		
Duration of treatment	NR – according to graph 24 wks		
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 & ALLOCATION	Randomisation was obtained directly by the biostatistical department of the pharmaceutical company providing the recombinant hormone (Cilag AG, Schaffhausen, Switzerland).	
TREATMENT ARMS		
ARM Drug name/s	**rHU-EPO**	**Control (assumed as this arm is not mentioned)**
N	30	24
Dose & freq (od, bd etc)	150 IU/kg, three times a week, started within first month of conventional cytotoxic protocol	
Dose adjustment Y/N	This dose was increased to 300 IU/kg by the 6th week of treatment.	
Route of administration	Sub cut	
Duration of epo tx		
Adj anaemia treatment	Regular iron supplementation was provided throughout the study	
Transfusion trigger	9.5 g/dl	

OUTCOMES			
Primary outcome		**Other outcomes**	HaemR (An increase of 2 g/dl or more of the original Hb level, or no further red cell supplementation in TD pts was taken as response to the treatment)

NOTES:
No outcomes clearly identified in Methods.
Weekly controls included a thorough physical examination (including monthly assessment of performance status), a complete blood count, Hb and haematocrit levels, iron, transferring and ferritin concentrations, electrolytes and kidney function tests.

ANALYSIS	
Statistical technique used?	Since the majority of laboratory parameters 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 nonparametric method to compare different groups
Intention to treat analysis?	NR
Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	4 pts withdrawn, although the results table suggests 5
Was attrition rate adequately dealt with?	Yes
Number (%) followed up from each condition?	NR

BASELINE CHARACTERISTICS	
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*	Multiple myeloma
Treatment	Second induction chemo

(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)		
Adjuvant anaemia treatment	**Iron**	Regular iron was provided
	G-CSF	NR
	Transfusion trigger	NR
	Hb inclusion criteria level	≤8.0 g/dl

	Arm 1 = rHuEPO 30	**Arm 2 = control 24**	**Arm 3 = N =**	
Sex				
male, n	NR			
female, n	NR			
Age years median (range)	NR			
Median neutrophil count, cell/μL				
Patients transfused, n (%)				
# RBC units transfused per patient over 3 mths prior to study, mean (range)				
Mean haematocrit, n (%)				
Endogenous EPO level, mU/mL, mean (median) [range]				
Type of solid tumour:				
Haematologic, n (%)				
Breast, n (%)				
Gynaecologic, n (%)				
Gastrointestinal, n (%)				
Lung (SCLC & NSCLC), n (%)				
Prostate, n (%)				
Head & neck, n (%)				
Other, n (%)				
Unknown primary, n (%)				

Were intervention and control groups comparable?	NR – no baseline characteristics reported

RESULTS

	Arm 1= rHuEPO n=30 (27 evaluable)				**Arm 2 = Control n=24 (22evalauble)**		**p**
Hb response (≥2g/dl)	21 (77.7%) after a median period of 8 weeks						
Chemotherapy groups	NTD (n)	Responders evaluable pts	TD (n)	Responders evaluable pts	NTD (n)	TD (n)	
VMCP	11	9/10	9	5/8	12[a]	5[b]	
VMCP + α-IFN	5	5/5	-	-	3	-	
VED	1		3	2/3	1	2	

CTX	-		1	-/1	-	1	

[a]Eleven pts were evaluable at the end of the study, [b]Four pts were evaluable at the end of the study
NTD – non transfusion dependant
TD – transfusion dependant
VMCP – vincristine+melphalan+cyclophosphamide+prednisone
IFN – interferon
VED – vincristine+epirubicin+dexamethasone
CTX – high dose cyclophosphamide

Median Hb (g%) (Approximate interpretation from graphs by PenTAG)

	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24
NTD - VMCP+EPO (9pts)	7.6	8.2	9.5	10.5	10.4	10.4	10.2
NTD- VCMP-EPO (11pts)	7.8	7.6	7.5	7.6	7.6	7.6	7.6
TD - VMCP+EPO (5pts)	7.4	9.0	9.5	9.4	9.4	9.2	9.4
TD- VCMP-EPO (4pts)	7.8	8.4	8.1	8.6	9.0	8.9	9.0

In NTD pts, rHu-EPO promoted a significant ($p<0.05$) and stable increase in Hb levels by the 12th week as compared with initial values.

Health-related QoL

NR

Adverse effects

Mild hypertension recorded in 4 cases.
The first of four withdrawals suffered a cerebral vascular stroke during the 5th week. One pt was lost to follow up at the 7th week and the remaining two pts were excluded at the 3rd and 11th week because of severe pneumonia and multiple bone fractures, respectively. No evident Hb increase was observed in the three EPO drop out pts during their inclusion in the trial.

Diarrhoea, n (%)					
Diaphoresis, n (%)					
Hypertension, n (%)*					
Seizure, n (%)**					
Thromboembolic events, n (%)					

QUALITY APPRAISAL

1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ;	NR

Inadequate = allocation was alternate, or based on information known to the triallist)	
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
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	No, ≥10% dropout in epo group.
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes
NOTES:	
OTHER	
Generalisability	Unable to assess
Author conclusions	Our data suggest that α-IFN plus rHu-EPO treatment in MM pts is effective in restoring normal B cell function. These results may reflect in vivo the modulation of normal human B cells and lymphoblasts by rHu-EPO observed in vitro
Reviewer comments	Small sample size, no baseline characteristics, poorly reported outcomes.

Endnote Ref ID	**341**	**Malignancy type**	**Cervical cancer**
		Treatment	**Epoetin beta**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Strauss, 2008	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 if there was a correlation between anaemia correction with	**Inclusion criteria:** • 18yrs or over • A histologically confirmed diagnosis of cervical cancer • FIGO 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 • A life expectancy of at least 3 months • Adequate bone marrow function (platelets >100 x10^9/L and leukocytes>3.0 x 10^9/L) • Adequate liver function (transaminases and/or alkaline phosphatises no greater than 2.5.x upper normal limit; bilirubin no greater than 1.5 x normal limit) • Adequate renal function (calculated	

	epoetin beta and treatment failure in women with cervical cancer receiving RCT. After the first stage had been analyzed the study protocol outlined a continuation of the study where a further 450 pts were to be enrolled to investigate the potential impact of anaemia correction with epoetin on survival.	creatinine clearance >60 ml/min) • No previous systemic antineoplastic therapy or RT for cervical cancer, except previous single brachytherapy fraction of the protocol prescribed RT course as clinically indicated **Exclusion criteria:** • Pts with distant metastasis (M1 disease) • Positive para-aortic lymph nodes • Chronic heart failure (NYHA ≥2) • Uncontrolled arterial hypertension (systolic ≥170 mm Hb, diastolic ≥100 mm Hb) • Known history of DVT • Thrombocytosis • Known haemoglobin opathies • Vitamin B12 and/or folic acid deficiencies • Haemolytic anaemia • Bleeding requiring transfusion within 3 months before planned start of treatment • Acute infection • Transferrin saturation less than 20% • Known presence of other neoplasias within the last five yrs • Pregnancy or lactation • Exposure to epoetins within 3 months • Contraindications against cisplatin therapy
# centres	20	
Other references/aliases	Full paper	
Geographical setting	Europe, Turkey and Thailand	
Duration of treatment	Unclear - pts scheduled to receive RT over 6 wks (to a maximum of 50 days), plus concomitant cisplatin	
Length of follow-up (if different)	447 – 513 days (unclear if this starts after EOTP)	
Country of corresponding author	Germany	
Language of publication	English	
Sources of funding	F-Hoffman-La Roche Ltd	
RANDOMISATION & ALLOCATION	Open, randomised, two arm, parallel group, two-stage, adaptive study. Patients were centrally randomised to epoetin arm or control arm. Open label. No details given on randomization procedure.	
TREATMENT ARMS		
ARM Drug name/s	**Epoetin beta**	**Control (standard care)**
N	34	40
Dose & freq (od, bd etc)	450 IU/kg in three divided doses	
Dose adjustment Y/N	Y. If insufficient Hb response (inc in Hb of <0.5 g/dl after 4 weeks of treatment, or requirement of RBCTin the fourth week of epoetin beta treatment) the dose could be doubled to 900 IU/kg If Hb >15 g/dl epo stopped and resumed at 50% of 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 epo tx	The median duration of epoetin beta treatment was 63 days (range: 3-98 days)	
Adj anaemia treatment	If transferrin saturation <20% IV iron supplementation with a dose of 100 mg $Fe^{3+.}$ was recommended. If contraindicated or not available, daily oral iron supplementation at a dose of 200-300 mg Fe^{3+} could be used Fe was received by 27 pts (79%) in epoetin group. Of these 15 received IV and 12 oral. In the control group, Fe was received by 22 pts (55%), 12 pts received IV and 10 pts received oral.	
Transfusion trigger	At physicians' discretion if Hb levels were <8.5 g/dl and were to be avoided in pts with an Hb >8.5 g/dl	

NOTES:
2-week pre-treatment period to ensure anaemic patients had 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 pts with no complete response or relapsing within 6 months after initiation of RCT)	**Other outcomes**	Tumour response; progression / relapse-free survival; overall survival; overall response rate; AEs

ANALYSIS

Statistical technique used?	The effect of Hb change from baseline on treatment failure (defined as pt with no complete response or relapsing within 6 months after initiation of RCT) was analysed using a logistical regression analysis (two-sided test at α = 5% with change from baseline in Hb 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 levels 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 pts. PFS 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 confidence intervals. Change from baseline in Hb at the end of the treatment period was tested in an analysis of covariance model, with Hb at baseline as covariate. Hb change from baseline was assessed at week 4 and at the end of the treatment period.
Intention to treat analysis?	Yes – all randomised patients were included in the ITT population and all efficacy results are provided for this population. The safety population comprised of all patients who received at least one dose of the trial medication with RCT and/or epoetin in the epoetin beta group and at least one dose of RCT in the control group.
Does statistical technique adjust for confounding?	NR (only baseline Hb values mentioned as covariate in ANCOVA)
Power calculation (priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	See below
Was attrition rate adequately dealt with?	Three pts were excluded from safety analysis (one from treatment arm and two from control arm), as they did not receive study treatment. A total of 12 pts (16%) were withdrawn prematurely from the study, 8 in the epoetin arm and 4 in control arm. There were no withdrawals due to adverse events 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.
Number (%) 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 / haem / MDS / mixed)*		**Cervical**
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; radio; no specific malignancy treatment; not reported)*		**Chemo+radio**
Adjuvant anaemia treatment	**Iron**	Enrolled pts with a transferrin saturation of less than 20% were recommended to receive IV 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 physicians' decision if Hb levels were less than 8.5 g/dl and were to be avoided in pts with an Hb greater than 8.5 g/dl
	Hb inclusion criteria level	Hb levels between 9 and 13 g/dl at screening

	Arm 1 = Epoetin beta N =34		**Arm 2 = Control N = 40**		**P-value**	
Sex						
male (%)	N/A		N/A			
female (%)	34	(100)	40	(100)	0.957	
Age years mean (SD)	48.8	(10.2)	49.2	(12.8)		
Performance status WHO , 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						
Hb baseline (g dl^{-1}) median (IQR)	11.4	(10.8-12.0)	11.6	(10.9-12.4)	0.371	
Hb before RCT (g dl^{-1}) (IQR)	11.8	(10.6-13.1)	11.7	(10.9-12.4)	0.633	
Epo baseline (mU ml^{-1})						
Were intervention and control groups comparable?	Yes.					

RESULTS

	Arm 1 = Epoetin beta N = 34		**Arm 2 = Control N = 40**		**Arm 3 = N =**		**p**
Haematological outcomes and transfusions							
Median change in Hb (baseline to last value)	1.3		-0.7				
Transfusion free pts (%)	25	(73.5)	28	(70)			
RBC units rec'd, median (range)	3.3	(0.9-6.4)	12	(0.9-6.0)			Not significant
Survival							
Overall survival, deaths (%)	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)			0.83
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	18		23				
Health-related QoL							
Health state utility scale = Not collected							
Adverse effects							
Total (%)	19	(58)	26	(68)			0.409
Deaths	8	(23.5)	5	(12.5)			0.22
Thromoboembolic events							
Hypertension							
Haemorrhage/thrombocytopenia	1	(3)	4	(11)			0.313
Rash/irritation/pruritus	1	(3)	0	(0)			
Seizures							

Notes: By week 4 after initiation of RCT, median Hb increased by 1.1 g/dl from baseline in the epoetin group, but decreased by 0.6 g/dl in the control group. An analysis of covariance 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 pts in the treatment group achieved target Hb levels of 13 g/dl than those in the control group (71% vs 25%).

Overall survival – RR 2.0, 95% CI 0.65-6.15, P=0.22

Seven pts reported SAE (epoetin arm: 5 pts (15%); control arm (2 pts (5%)). Only one SAE was considered by the investigator to be related to study treatment: a DVT in a pt receiving epoetin beta. This pt 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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was alternate, or based on information known to the triallist)	Unclear: although described as 'centrally randomized', 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)
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes

NOTES:	
OTHER	
Generalisability	
Author conclusions	This study shows that epoetin beta rapidly, effectively and safely increases Hb levels in pts with cervical cancer receiving RCT. Because no positive correlation of 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 RT.
Reviewer comments	Unsure how run-up to trial with Epo will affect results

Endnote Ref ID	**2696**	**Malignancy type**	**Ovarian carcinoma**
		Treatment	**Epoetin beta (assumed)**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Ten Bokkel Huinink 1998	N	122
Objective	To investigate the influence of rhEPO on anaemia and transfusion requirement in pts with ovarian carcinoma treated with platinum based therapy	**Inclusion criteria:** • 18 yrs or over • Ovarian cancer IIb-IV (according to the International Federation of Gynaecology and Obstetrician's classification) • Performance status 0-2 (WHO) • **Hb <13 g/dl** prior to treatment • Overall life expectancy > 2 months • Previously treated pts who had achieved a complete remission (CR) and had not received treatment for at least 1 yr could be enrolled into the study. • Pts receiving cisplatin ≥ 75 mg/m^2, or carboplatin ≥350 mg/m^2, because lower doses induce anaemia in only a small proportion of pts. **Exclusion criteria:** • Prior chemotherapy or radiotherapy for ovarian cancer if they did not meet the requirements for previously treated pts as detailed in incl criteria • White blood cell count ≤3.5 x 10^9/l • Platelet counts ≤ 100 x 10^9/l • Hypertension [SBP > 160mmHb or DBP >95 mmHb) • Impaired liver function (bilirubin >25 mmol/l) • Impaired renal function (creatinine >120 µmol/l) • Thrombocytosis (≥500 x 10^9/l)	
# centres	NR		
Other references/aliases	None		
Geographical setting	NR		
Duration of treatment	Treatment with EPO and chemo began 2 days after randomisation in most pts. EPO continued throughout the course of chemotherapy and for a further 3-24 weeks after the last cycle of treatment, depending on the duration of chemo. Median duration of observation (between randomisation and last examination) was 170 days in the control group and 167 days in group I.		
Length of follow-up (if different)			
Country of corresponding author	The Netherlands		

Language of publication	English	• Other reasons for anaemia • Severely impaired coagulation • Iron deficiency • Epilepsy • Blood transfusion less than 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
Sources of funding	NR	
RANDOMISATION & ALLOCATION	Pts 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 & freq (od, bd etc)	150 µg/kg three times a week	
Dose adjustment Y/N	The dose of EPO was reduced by 50% if Hb increased by more than 2 g/dl during chemo. If Hb exceeded 15 g/dl at any time, EPO administration was stopped until it returned to <14 g/dl and was then resuned at half the previous dose. EPO was withheld while platelet counts were $<20 \times 10^9$ g/l. If chemo was delayed due to thrombocytopaenia, but platelet count was $> 20 \times 10^9$ g/l, EPO was continued.	
Route of administration	Sub cut	
Duration of epo tx	Treatment with EPO and chemo began 2 days after randomisation in most pts. EPO continued throughout the course of chemotherapy and for a further 3-24 weeks after the last cycle of treatment, depending on the duration of chemo.	
Adj anaemia treatment	NR	
Transfusion trigger	<9.7 g/dl	

OUTCOMES			
Primary outcome	**Time from randomisation to first erythrocyte transfusion; RBCT (# patients study period)**	**Other outcomes**	# and vol of RBCT per patient and per chemo cycle; course of Hb per chemo cycle; response to chemo; number of deaths; AEs

NOTES:
SAE: fatal or life-threatening event; hospitalisation; pt 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), by log-rank tests based on months from randomisation and on number of cycles of chemo. 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.
Intention to treat analysis?	Described as ITT but two pts excluded from analysis due to insufficient data
Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	Numbers unclear – author states 84 pts completed protocol. From 120 pts, one pt in Gp 1 and one in Gp2 dropped out of study before start of treatment. Twenty nine plus seven withdrew (through death, non-compliance etc) to give 82 pts.
Was attrition rate adequately dealt with?	Safety was assessed according to ITT, but unclear how missing data was handled
Number (%) followed up from each condition?	NR

BASELINE CHARACTERISTICS

Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		Ovarian cancer
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		Platinum-based chemo
Adjuvant anaemia treatment	**Iron**	NR
	G-CSF	N/A
	Transfusion trigger	<9.7 g/dl
	Hb inclusion criteria level	**<13 g/dl**

	Arm 2 = rhEPO n=45		**Arm 1 = Control N=33**		**Arm 3 = N =**	
Sex	**All female**		**All female**			
male (%)						
female (%)						
Age years mean (range)	58.81		58.83			
WHO performance status (%);						
0	24	(53.3)	20	(60.6)		
1	19	(42.2)	13	(39.4)		
2	2	(4.4)	0			
Previous chemo (%)						
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-<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 appear to be a"typo" in the results (Table 1 p 177) for Bl Hb epo values: 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 (x 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 (x 10^9/l)	383	(304-433)	395	(302-505)		
Neutrophil count (x 10^9/l)	4.3	(3.3-5.7)	5.1	(3.4-6.2)		
Iron baseline (U/l median (range)	NR					
Epo baseline (mU ml^{-1})	NR					
Target Hb	NR					

Were intervention and control groups comparable?	No p values reported, authors stated "The three groups were comparable with respects to age, stage of disease, WHO performance status, primary and recurrent disease, previous chemotherapy and baseline haematological parameters".

RESULTS

	Arm 2 = Epo N=44[a]		**Arm 1 = Control N=33**		**Arm 3 = N =**		**p**
Response to chemo	**N=40**		**N=30**				
# Progression	6		2				
# Complete remission	23		19				
# Deaths	1		2				
Transfusion							
Time to first transfusion (mnts)	Longer in Epo group than control						0.0002
No pts receiving at least one transfusion (%)	2	(4.4)	13	(39.4)			
No units	15 units in 6 transfusion events		41 units in 19 transfusion events				
Haematological outcomes							
Pts with Hb <10g/dl (%)							
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)			
No. pts evaluable	31		19				
Median (range)	9	(9-584)	8	(2-29)			
No. pts evaluable	28		18				
O/P ratio [b] ≥0.8	16		7				
O/P ratio [b] <0.8	12		11				
Health-related QoL	NR						
Adverse effects (%)							
Thromoboembolic events	1						
Hypertension	1/43	(2.3	1/28	(3.6)			
No. pts suffering at least one adverse event (%)	39/45	(86.7)	28/33	(84.8)			
No. pts suffering more than one adverse event (%)		(20.0)		(15.2)			
Superficial thrombophlebitis	1						
Due to adverse events 25 pts in control group and 34 pts in group 1 completed the planned protocol. Seven pts (15.6% in group I and four (12.1%) in the control group were withdrawn due to adverse events.							
Notes: [a] One pt withdrew before start of treatment with Epo; [b] the ratio between observed serum EPO level and the level predicted from the degree of anaemia (O/P) was selected as a possible predictor of transfusion requirement because a relative EPO deficiency (O/P <0.8) is considered to indicate an inadequate eondogenous EPO concentration.							

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Partially; Number unclear
NOTES:	

OTHER	
Generalisability	Small sample size – all female population

Author conclusions	The use of rhEPO should be considered in pts with ovarian cancer receiving platinum based chemo, particularly if they have an endogenous EPO deficiency, to delay the onset of anaemia and reduce the need for blood transfusion.
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

Endnote Ref ID	**2697**	**Malignancy type**	**Small cell lung cancer**
		Treatment	**Epoetin alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Thatcher, 1999	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 RBC transfusion requirements could also be achieved. The impact of epoetin alfa therapy on pts quality of life was also assessed	**Inclusion criteria:** • Male or female pts aged 18-75 yrs • Planned for treatment with 4-6 cycles of combination chemo, primarily Pt based • Small cell lung cancer • All pts required to be ambulatory and capable of self care (WHO performance score ≤2) • **Hb ≤10.5 g/dl** • Neutrophil count >3000 mm^{-3} • Platelet count >100,000 mm^{-3} • 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 • Pts who had received androgen therapy within 2 months of study entry and those who had received any experimental treatment, immunosuppressive drugs or other agents known to affect haematocrit within 1 month prior to study entry • Pts receiving haematopoietic growth factors (including epoetin alfa) • Pts participating in another trial	
# 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 & ALLOCATION	Pts randomised to one of three groups – epoetin alfa 150 IU/kg, epoetin alfa 300 IU/kg (outside licence therefore N/A and control		
TREATMENT ARMS			
ARM Drug name/s	**Epoetin alfa**	**Control (standard care)**	

N	42	44
Dose & freq (od, bd 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 Y/N	If Hb level exceeded 15g/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 epo tx	Maximum study duration was 26 weeks	
Adj anaemia treatment	Transfusions were allowed as necessary. No pt received iron supplementation	
Transfusion trigger	NR	

OUTCOMES			
Primary outcome	**HaemR (prevention of anaemia defined as maintenance of a Hb ≥10 g/dl)**	**Other outcomes**	HRQoL (Pt well-being in the week prior to each cycle of chemo was assessed by QoL questionnaire where pt response to three levels (energy level, daily activity and overall QoL) were scored on a 100mm VAS, and WHO performance score); AEs (Safety assessments included pt discontinuation information, vital signs (recorded in the treated groups only) and the incidence and severity of adverse events, laboratory parameters at the start of each cycle and epoetin alfa antibody titre at study end compeared to baseline)

ANALYSIS	
Statistical technique used?	Comparability of the three groups with regard to demographic and clinical characteristics at baseline was tested by means of analysis of variance, Kruskal-Wallis 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 pts transfused was compared between treatment groups using a Cochran-Mantel-Haenszel analysis. For pairwise comparison 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.

Intention to treat analysis?	Yes
Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	NR
Attrition rate (loss to follow-up)?	**Reasons for premature study discontinuation** **Parameter** / **Control (n=42)** **Adverse events** 2 **Death** 3 **Intercurrent illness** 1 **Other**[a] 8 **Total** 14 [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
Number (%) followed up from each condition?	NR

BASELINE CHARACTERISTICS		
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*		Small Cell Lung Cancer
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*		Pt - based chemo
Adjuvant anaemia treatment	**Iron**	None
	G-CSF	None
	Transfusion trigger	NR
	Hb inclusion criteria level	Hb ≥10.5 g/dl

	Arm 2 = Epoetin alfa N=42	**Arm 1 = Control N=44**	**Arm 3 = N =**	
Sex				
male, n	26	27		
female, n	16	17		
Age years median (range)	59.0 (43-72)	60 (39-74)		
Median Hb, g/dl (range)	13.7 (10.7-16.1)	13.4 (10.9-16.4)		
Median Haematocrit, % (range)	41.0 (32.6-50.3)	39.4 (32.3 – 46.8)		
Median reticulocyte count, x 10^9 /l (range)	40.1 (1.0-76.2)	39.3 (0.1-109.1)		
Median neutrophil count, x 10^9 /l	6.0 (1.7-11.3)	5.9 (2.9-16.4)		
Median WHO performance score, 0-4 (range)	1.0 (0-3)	1.0 (0-2)		
Median QoL scores, 0-100 mm (range)				
Energy level	47.0 (11-100)	51.0 (0-94)		
Daily activity	46.0 (5-100)	32.0 (0-97)		

Overall QoL	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 “no statistically significant between-group differences”.

RESULTS

	Arm 2 = Epoetin alfa N=42	**Arm 1 = Control N=44**	**Arm 3 = N =**		**p**
Haematological and transfusion outcomes					
Pts experiencing Hb < 10g/dl, %	48	66			<0.05
Pt requiring of transfusion (%)	19/42 (20)	26/44 (59)			<0.05
Total number of transfusions	41	73			
Mean cumulative transfusion rate for 6 cycles of chemo (±sd)	3.84±5.58	6.13±7.13			<0.01
Median time to become anaemic/ require first transfusion, days	116/98	59/48			
Health-related QoL notes:					
Parameters assessed by the QoL 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 QoL 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 scores revealed similar findings, with no significant between- or within-group differences.					
Change in QoL parameter from baseline, 0-100mm (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 QoL	11.7 ± 30.6[a]	7.5 ± 29.1			
Notes: [a]P<0.05 vs baseline					
Adverse effects reported by ≥5% of pts in any treatment group					
Anaemia	19 (43%)	14 (33%)			
Thrombocytopenia	9 (20%)	11 (26%)			
Bacterial infection	10 (23%)	8 (19%)			
Nausea	6 (14%)	3 (7%)			
Neutropenia	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%)			
UTI	0	0			
Alopecia	3 (7%)	1 (2%)			
Oedema	0	4 (10%)			
Diarrhoea	2 (5%)	5 (12%)			
Rash	4 (9%)	5 (12%)			
Decreased WBC count	3 (7%)	1 (2%)			
Lethargy	3 (7%)	1 (2%)			

There was no evidence of a sustained increase in hypertension in the epoetin alfa arm. One patient had several recordings of a diastolic BP around 105 mmHg, while another patient with a history of hypertension experienced an elevation of BP to 180/120 after the second dose. Overall, there was significant reduction in mean systolic BP over time in the epoetin alfa treatment group.

Notes:
Low serum iron and transferring saturation values were seen in pts in the treatment group.

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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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)
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes (except for QoL)
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes
NOTES:	

OTHER	
Generalisability	Relatively small sample size.
Author conclusions	This study has demonstrated that epoetin alfa is effective and well tolerated in maintaining Hb level

	≥10 g/dl and reducing transfusion requirements in pts with SCLC undergoing pt-based cyclic combination chemo.
Reviewer comments	QoL of limited used due to unvalidated scale. Although WHO performance scores were measured.

Endnote Ref ID	**435**	**Malignancy type**	**solid tumours**
		Treatment	**epo theta & beta & placebo**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Tjulandin 2010	N	223
Objective	To assess effects of epoetin theta compared to placebo for efficacy and to compare the efficacy and safety profile of epoetin theta with epoetin beta	**Inclusion criteria:** secondary anaemia (**Hb ≤11g/dl**) related to platinum-containing chemotherapy; age ≥ 18 years; histologically or cytologically proven diagnosis of a solid tumour; at least 1 platinum-based chemotherapy cycle as treatment of the current malignancy during the last 4 weeks (Hb concentration of ≤11 g/dL after the last chemotherapy); ECOG≥3 **Exclusion criteria:** patients with head and neck tumours, uncontrolled severe hypertension and patients receiving concomitant radiotherapy	
# centres	54 sites; Between October 2005 and July 2007		
Other references/aliases	Trial reg # ISRCTN09530309 XM01-21		
Geographical setting	International, 10 countries (Argentina, Belarus, Brazil, Bulgaria, Croatia, India, Moldova, Romania, Russia, Ukraine)		
Duration of treatment	12 weeks The mean treatment duration ±SD was comparable in all 3 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 S. A.		
RANDOMISATION & 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 either epoetin theta, epoetin beta, or placebo. Randomisation list generated by the Department of Biostatistics, Merckle GmbH. Only the person administering study medication was unblinded (due to the		

	difference in dosing schemes). An unblinded data monitoring committee closely monitored the safety		
TREATMENT ARMS			
ARM Drug name/s	**epoetin theta**	**epoetin beta**	**placebo**
N	76	73	74
Dose & freq (od, bd etc)	20 000 IU once per week$	450 IU/kg three times per week*	NR*$
Dose adjustment Y/N	Y: after 4 weeks increase to 40 000 IU if Hb increase <1 g/dL, with further increase to 60 000IUif after next 4 weeks still insufficient response. Reduction by 50% if Hb increase >2 g/dL at 4 weeks. If Hb > 13 g/dl, dose interruption or 50 % dose reduction.	Y: after 4 weeks dose doubled if if Hb increase <1 g/dL. Reductions same as for Epo Theta.	three times per week*
Route of administration	Subcutaneously		
Duration of epo tx	12 weeks	subcutaneously	12 weeks
Adj anaemia treatment	Iron substitution was allowed during the study	12 weeks	NR**
Transfusion trigger	At the discretion of the investigator, but should have been avoided if Hb ≥8.5 g/dL,	Iron substitution was allowed during the study	At the discretion of the investigator, but should have been avoided if Hb ≥8.5 g/dL,
OUTCOMES			
Primary outcome	**HaemR (inc in Hb of ≥2 g/dL from BL without the benefit of a transfusion within previous 4 weeks)**	**Other outcomes**	HaemR (partial Hb response ≥1 g /dL from BL; # patients having complete Hb response with initial dose; time course of Hb, haematocrit and reticulocytes; dose of epo theta or epo beta at the time of complete/partial Hb response); RBCT (# patients requiring blood transfusion; # of blood units transfused); HRQoL (FACT-An (incl FACT-G and FACT-F)); AEs (Safety lab, vital signs, incidence of AEs, adverse drug reactions, overall tolerability & screening for anti-drug antibodies to epoetin theta & epoetin beta at the beginning and end of study & 60 days after the

			end of the individual treatment period)

NOTES:

ANALYSIS	
Statistical technique used?	Logistic regression analysis with treatment and BL Hb level as explanatory variables was performed to estimate the difference in the proportion of complete Hb responders for epo theta vs placebo, epo beta vs placebo, & epo theta vs epo beta in the confirmatory analysis of the primary endpoint. For other binary secondary efficacy endpoints same logistic regression model as for the primary endpoint. Changes of QoL (FACT score) from BL to EOTP were compared pairwise among treatment groups with the Wilcoxon-Mann-Whitney test, treatment groups for other secondary endpoints only compared descriptively
Intention to treat analysis?	Yes. Full analysis set used for efficacy endpoints, no crossover and endpoints reported for full patient numbers
Does statistical technique adjust for confounding?	NR, however logistic regression analysis was adjusted for baseline Hb to estimate the effects of treatment on Hb response.
Power calculation (priori sample calculation)?	Partial: sample size calculation given for statistical superiority test comparing epoetin theta and placebo but not overall (two-sided α = 5%, assuming the actual Hb response rates for Epoetin theta and placebo were 50% and 20% respectively)
Attrition rate (loss to follow-up)?	Y: Placebo n=21 withdrawals (4 due to AE, 12 patient request,2 loss to follow-up, 3 other); epo beta n=9 withdrawals (1 due to AE, 7 patient request, 1 other; epo theta n=12 withdrawals (2 due to AE, 2 patient request, 1 due to incl/excl criteria, 3 loss to follow-up, 4 other)
Was attrition rate adequately dealt with?	Unclear
Number (%) followed up from each condition?	NA: No follow-up reported

BASELINE CHARACTERISTICS						
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*					Solid tumours	
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*					Platinum containing chemotherapy	
Adjuvant anaemia treatment	**Iron**				Iron substitution was allowed during the study	
	G-CSF					
	Transfusion trigger				≤8.5 g/dL	
	Hb inclusion criteria level				≤11.0 g/dL	
	Arm 1 = Epo theta N = 76		**Arm 2 = Epo beta N = 73**		**Arm 3 = Placebo N = 74**	
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 to 76.0)		57.3±10.5 57.0 (28.0 to 83.0)		57.3±11.5 59.5 (26.0 to 76.0)	
Performance status ECOG						
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%)
Mean Hb baseline (g dl^{-1}) (SD)	9.6±1.1		9.5±0.8		9.4±1.2	
Iron baseline (U/l median (range)	NR	NR	NR	NR	NR	NR
Epo baseline (mU ml^{-1})	NR	NR	NR	NR	NR	NR
Target Hb	NR	NR	NR	NR	NR	NR
Most common tumour types						
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.					

RESULTS

	Arm 1 = Epo theta N = 76		**Arm 2 = Epo beta N = 73**		**Arm 3 = Placebo N = 74**		**p**
Hb							
Hb at the end of study, (g dl^{-1}), mean (SD)	11.2	2	11.4	2	9.6	1.2	
Change in Hb levels, g dl^{-1}), mean (SD)	1.6		1.9		0.2		
Notes: Results for Hb change from baseline presented graphically; Fig 3 p 50 in paper The changes of haematocrit values were very similar to the changes of Hb values over time. Absolute reticulocyte values showed a high degree of variability in all 3 treatment groups and at all timepoints.							
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, 22.83)				<0.0001
Epoetin theta vs placebo			OR 8.06 (95% CI: 3.89, 17.63)				<0.0001
Epoetin theta vs beta			OR 0.79 (95% CI: 0.39, 1.58)				0.5004
Complete Hb response without blood transfusion & dose adjustment, n, %	26	(34.2%)	29	(39.7%)	8	(10.8%)	

Epoetin beta vs placebo			OR 5.40 (95% CI: 2.35, 13.68)				0.0001
Epoetin theta vs placebo			OR 4.24 (95% CI: 1.84, 10.76)				0.0012
Epoetin theta vs beta			OR 0.79, 95% CI: 0.40, 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, 24.93)				<0.0001
Epoetin theta vs placebo			OR 9.8 (95% CI: 4.19, 26.00)				<0.0001
Epoetin theta vs beta			OR 1.04, 95% CI: 0.34, 3.20				0.9394
Notes: The mean ± SD average weekly dose was higher in the Epoetin beta group compared to the Epoetin theta group (36,973±13,967 vs. 26,425± 9,157 IU). This was to be expected as the weekly starting dose were different. Baseline Hb levels had no statistically significant effects on the response rates.							
Transfusions							
Patients received blood transfusions,n ,%	8	(10.5%)	9	(12.3%)	18	(24.3%)	
Epoetin beta vs placebo			NR				0.1042
Epoetin theta vs placebo			OR 0.38 (0.14, 0.95)				0.0433
Epoetin theta vs beta			OR 1.04, 95% CI: 0.34, 3.20				0.9394
Number of Blood Units Transfused, mean (SD)	3.3	2.2	1.8	0.7	2.8	2.9	
Baseline Hb levels had a statistically significant effect on the rate of blood transfusion (P = 0.0005) with an odds ratio of 0.53 (95% CI: 0.37, 0.75) per g/dL baseline Hb comparing Epoetin theta with placebo							
Health-related QoL							
Health state utility scale = FACT-An incl FACT-F and FACT-G **MEASURED NOT REPORTED**							
Adverse effects of tmt							
Any TEAE	58	(76.3%)	63	(86.3%)	63	(85.1%)	
Related TEAE = 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*	5	(6.6%)	4	(5.5%)	12	(16.2%)	
Discontinuation	4		3		6		
* Most frequent reason for death was disease progression (1 epoetin beta, 6 placebo, 3 epoetin theta) 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; 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 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%). Incidence of skin reactions possibly caused by SC administration was low and comparable across groups (epoetin theta 1, epoetin beta 3, placebo 1. Hypertension 2.6% in epoetin theta and 2.7% in epoetin beta and placebo groups							

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Yes
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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; similar ECOG scores between groups; other characteristics similar
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 presented in the paper)
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	Yes; quality of life data not reported
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes; however 4 and 3 pts withdrew for unspecified “other” reasons in epo and placebo groups respectively

NOTES:
$ e.g. Patients randomised to Epoetin theta received a starting dose of 20,000 IU Epoetin theta subcutaneously (s.c.) once weekly (e.g., on Mondays) and in addition the same volume of placebo twice weekly (e.g., on Wednesdays and Fridays) for blinding purposes
*”only the person administering study medication was unblinded” which might imply that the person allocating treatment was unaware of the next allocation, but there is nothing explicitly stated so remains unclear

OTHER	
Generalisability	Yes
Author conclusions	No conclusions re 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. Epo theta is a safe and effective treatment for the treatment of anaemia due to 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.

Endnote Ref ID	436	Malignancy type	solid tumour or non-myeloid haematological tumour
		Treatment	Epo theta

STUDY DESIGN		PARTICIPANTS	
Author, year	Tjulandin 2011	N	186
Objective	The objective of this study was to demonstrate superiority of Epoetin theta compared to placebo for efficacy during the treatment period of 12 weeks in patients with solid tumours or nonmyeloid haematological malignancies receiving nonplatinum chemotherapy.	**Inclusion criteria:** • patients ≥18 years of age with histologically or cytologically proven diagnosis of a solid tumour or non-myeloid haematological tumour • anaemia caused by nonplatinum-based chemotherapy defined by a documented **Hb concentration of ≤11 g/dl** after the last chemotherapy prior to inclusion • at least 1 previous nonplatinum-based chemotherapy cycle as treatment of the current malignancy during the last 4 weeks • ECOG= 0, 1, 2 or 3 **Exclusion criteria:** • any other primary haematologic disorder that would cause anaemia • headand neck tumours • uncontrolled severe hypertension • concomitant radiotherapy	
# centres	72 sites; Between November 2005 and May 2007		
Other references/aliases	Trial reg # ISRCTN08063129 XM01-22		
Geographical setting	International, 10 countries (Argentina, Belarus, Brazil, Bulgaria, Croatia, India, Moldova, Romania, Russia, Ukraine)		
Duration of treatment	**12 weeks** The mean treatment duration ± SD was comparable in both groups (71.9 ± 16.9 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 S. A.		
RANDOMISATION & 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 the safety in order to ensure that patients were not exposed to an unjustifiable risk.		

TREATMENT ARMS		
ARM Drug name/s	**Epo theta**	**Placebo**
N	95	**91**

Dose & freq (od, bd 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 Y/N	Y: after 4 weeks increase to 40 000 IU if Hb increase <1 g/dl, with further increase to 60 000IU if after next 4 weeks still insufficient response. Reduction by 50% if Hb increase >2 g/dl at 4 weeks. If Hb > 13 g/dl , dose interruption or 50 % dose reduction.	Y: according to the same schedule as for epoetin theta for blinding purposes
Route of administration	Subcutaneously	Subcutaneously
Duration of epo tx	12 weeks	12 weeks
Adj 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 have been avoided if Hb ≥ 8.5 g/dl	At the discretion of the investigator, but should have been avoided if Hb ≥ 8.5 g/dl

OUTCOMES			
Primary outcome	**HaemR (inc in Hb of ≥2 g/dL from BL without the benefit of a transfusion within previous 4 weeks**)	**Other outcomes**	HaemR (partial Hb response ≥1 g /dL from BL; # patients having complete Hb and partial response with initial dose; the time course of Hb,haematocrit and reticulocytes; dose of epo theta at the time of Hb response); RBCT (# patients requiring blood transfusion; # of blood units transfused); HRQoL (FACT-An; FACT-G; 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 and baseline haemoglobin value as continuous variables was performed to estimate the difference in the proportion of complete haemoglobin responders between Epoetin theta and placebo in the confirmatory analysis of the primary efficacy endpoint. For the primary efficacy endpoint a subgroup analysis with type of malignancy (solid, non-myeloid haematological) was performed. For the other binary secondary efficacy endpoints the same logistic regression model as for the primary endpoint was

	estimated. Changes of QoL from baseline to end of study were compared pairwise with the Wilcoxon-Mann-Whitney test. Other secondary efficacy endpoints were only compared descriptively. Descriptive P-values were calculated with appropriate statistical tests but were regarded as supportive only.
Intention to treat analysis?	Yes. Full analysis set used for efficacy endpoints, no crossover and endpoints reported for full patient numbers
Does statistical technique adjust for confounding?	NR, however logistic regression analysis was adjusted for baseline Hb to estimate the effects of treatment on Hb response.
Power calculation (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.
Attrition rate (loss to follow-up)?	Y: n=25 prematurely discontinued: n=15 in placebo group (AE=6 pts, patients request=4, lack of efficacy=2, lost to follow up=1 and other=2) and n=10 in epo theta group: (AE=4 pts, patients request=5, lack of efficacy=0, lost to follow up=1 and other=0).
Was attrition rate adequately dealt with?	Unclear. Full analysis set used for efficacy endpoints.
Number (%) followed up from each condition?	NA: No follow-up reported

BASELINE CHARACTERISTICS

Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*					solid tumour or non-myeloid haematological tumour	
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*					Nonplatinum-Based Chemotherapy	
Adjuvant anaemia treatment	**Iron**				Iron substitution was allowed during the study	
	G-CSF				**NR**	
	Transfusion trigger				≤8.5 g/dL at the discretion of the investigator	
	Hb inclusion criteria level				≤11.0 g/dL	
	Arm 1 = Epo theta N = 95		**Arm 3 = Placebo N = 91**			
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 to 83.0)		55.8±14.3 57.0 (18.0 to 82.0)			
Performance status ECOG						
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%)		
Mean Hb baseline (g dl^{-1}) (SD)	9.2±1.3		9.1±1.3			
Iron baseline (U/l median (range)	NR	NR	NR	NR		
Epo baseline (mU ml^{-1})	NR	NR	NR	NR		
Target Hb	NR	NR	NR	NR		
Most common malignancies						
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%)		
Most common on-study chemo						
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".					

RESULTS

	Arm 1 = Epo theta N = 95		**Arm 3 = Placebo N = 91**			**p**
Hb						
Hb at the end of study, (g dl^{-1}), mean (SD)	11.3	2	<10			
Change in Hb levels, g dl^{-1}), mean (SD)	2.1					<0.0001

Results for Hb change from baseline presented graphically; Fig 3 p 38

Hb estimated from above figure	**Arm 1 = Epo theta N = 95**			**Arm 3 = Placebo N = 91**		
at the end of study (g dl^{-1}),	mean	SEM	SD	mean	SEM	SD
	11.31	0.22	2.14	9.89	0.22	2.10

The changes of haematocrit values were very similar to the changes of Hb values over time. Absolute reticulocyte values showed a high degree of variability in both treatment groups and at all timepoints (results not reported).

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 odds ratio*:* OR 7.944 (4.182, 15.632)*, p* <0.0001							
Complete Hb response without blood transfusion & dose adjustment, n, %	43	45.3%	9	9.9%			
Epoetin beta vs placebo	OR 7.728(3.59, 18.285), p <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 (1.462, 5.694), p =0.0025						
Partial Hb response without blood transfusion & dose adjustment, n, %	56	58.9%	24	26.4%			
Epoetin beta vs placebo	OR 4.028 (2.179, 7.632), p <0.0001						
Type of cancer and baseline haemoglobin 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 it 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 complete Hb response in 66.7% of patients with complete response in the Epoetin theta group. In a further 23.2% of patients with complete response, response was achieved with a dose of 40,000 IU/week.							
Transfusions							
Patients received blood transfusions, n, %	13	13.7%	23	25.3%			
Epoetin beta vs placebo	OR 0.352 (0.133, 0.868), p =0.0277						
Number of Blood Units Transfused, mean (SD)	3.5	3.5	4.1	2.8			
Health-related QoL							
FACT-Anaemia Total, mean (SD)	6.3	21.7	0.6	22			0.243
FACT-Anaemia Trial outcome index, mean (SD)	5.6	17.1	1.2	18.8			0.222
FACT-Fatigue, mean (SD)	2.9	7.9	0.6	8.8			0.142
FACT-General scale, mean (SD)	3.0	12.7	-0.2	12.4			0.224
The completion rate of valid FACT-An questionnaires was high in both treatment groups: 89.5-97.9% in epo and 85.7 to 96.7% in the placebo group with only small decreases in completion rates observed over the course of the study in both groups.							
AE							
Any EAE	76	80.0 %	71	78.0 %			
Related EAE = EADR	27	28.4 %	18	19.8 %			
Serious EAE	11	11.6 %	14	15.4 %			
Serious EADR	0	0 %	1	1.1 %			
Death*	6	6.3 %	5	5.5 %			
Discontinuation$	4	4.2%	6	6.6%			
Hypertension	8	8.4	1	1.1%			<0.05
* Most frequent reason for death was disease progression (3 placebo, 2 epoetin theta) $ 1 patient in the placebo group discontinued due to a thrombophlebitis							

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 lab variables, vital signs, body weight, 12-lead ECG, physical examination, tolerability, 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) and 96.7% (placebo) of the 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 (13 Epoetin theta, 13.7% and 7 placebo, 7.7%). None of the skin reactions was severe or serious.

The incidence of anti-drug antibodies to Epoetin theta was assessed at the beginning and end of the study. Only 1 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 enclosed 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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Yes
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was 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”.
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 the safety in order 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)
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes, apart from HRQoL (89.5-97.9 and 85.7 to 96.7% participants analysed in epo and placebo groups respectively).
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Yes
NOTES:	

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 haemoglobin levels compared to placebo. The overall frequencies of adverse events were similar in both treatment groups
Reviewer comments	

Endnote Ref ID	**961**	**Malignancy type**	**Breast cancer**
		Treatment	**Darbepoetin alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Untch 2011	N	736 enrolled, with 733 randomly allocated
Objective	Latin square design : In a second randomization, the short- and long-term effects of primary use of darbepoetin alfa independent from Hb levels on tumor response and safety were investigated. **The toxicity and response data are described here (#961) and the effect on DFS and OS is reported in #962**	**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 X-ray, sonography, or computed tomography scan of upper abdomen and bone scan; ECOG <2; adequate organ function: aspartate aminotransferase and bilirubin = 1.5 x upper limit, white blood cells = 3000/µl, neutrophils = 1000/µl, platelets = 100 000/µl, and serum creatinine <2.0 mg/dl, and normal left ventricular ejection fraction. **Exclusion criteria:** NR (but see inclusion criteria above)	
# centres	78		
Other references/aliases	PREPARE trial Untch 2011(#962) NCT00544232		
Geographical setting	Germany		
Duration of treatment	26 weeks: There were 24 weeks of chemo. Darbe 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 of 43.5 months	
Country of corresponding author	Germany	
Language of publication	English	
Sources of funding	Amgen; Bristol Myers Squibb.	
RANDOMISATION & ALLOCATION	Latin square design: Patients were randomized in a 1:1 allocation to receive standard-dose or dose intensified preoperative chemotherapy. Patients within each treatment arm were further randomized in a 1:1 allocation to receive DA or no DA therapy.	
TREATMENT ARMS		
ARM Drug name/s	**Darbepoetin alfa**	**Controls (standard care)**
N	356	377
Dose & freq (od, bd etc)	4.5 µg/kg Q2W	NA
Dose adjustment Y/N	To achieve the target Hb level 12.5 - 13 g/dl, the dose was doubled if the increase was <1 g/dl during the first 4 weeks, or discontinued if Hb >14 g/dl. Treatment was re-induced with 50% of the dose, if Hb≤13.0 g/dl	NA
Route of administration	NR	
Duration of epo tx	starting with the first dose of epirubicin (day 1) until 14 days after the last dose of paclitaxel	NA
Adj anaemia treatment	200 mg oral iron daily	NA
Transfusion trigger	NR	None
NOTES: Of 318 patients receiving DA, 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)
NOTES: Other efficacy end points included lymph node status, clinical response at surgery, surgical outcome as well as effects of DA on DFS, OS, pCR, and anemia		
ANALYSIS		
Statistical technique used?	Comparisons between intensified or standard chemotherapy and between treatments with and without DA used the chi- square tests. All secondary end point tests were two sided, and 95% CI were provided for relevant estimates.	

	The change in Hb level difference between the treatments with and without DA used ANCOVA with baseline Hb level as covariate. Binary logistic regression analysis was employed in order 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 due to any cause. OS was the time from the date of informed consent to the date of death due to any cause. Local DFS was defined as time in weeks between thedate of signing informed consent and date of local recurrence. Patients with no local recurrence reported were censored at the date of the last contact.
Intention to treat 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 received at least one dose of study treatment were only included 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 in order 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 tumor size& nodal status,grade, chemotherapy arm, darbepoetin alfa application, and pCR.
Power calculation (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 equals an HR of 1.4 with a type I error of α 5% using a one-sided test
Attrition rate (loss to follow-up)?	Partially: Until the point of surgery (as reported in supplemental online materials). 733 participants were randomly allocated, 19 did not receive any study treatment: 318 of 356 patients randomly allocated to DA actually received the treatment. Most of the patients had surgery after chemotherapy: n=326 darbe and n=343 controls 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 analysis were difficult to follow and remain unclear.
Number (%) followed up from each condition?	NR
BASELINE CHARACTERISTICS	
Malignancy type	**Breast cancer**

(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)						
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*					Preoperative chemotherapy epirubicin, cyclophosphamide and paclitaxel each 3-weekly (N=370) for four cycles, or epirubicin, paclitaxel with pegfilgrastim, followed by CMF each 2-weekly and for three cycles (N=363).There were 8 and 9 planned cycles in the standard and intensified regimen respectively.	
Adjuvant anaemia treatment	**Iron**				200 mg oral iron in darbe arm	
	G-CSF				Yes in intensified regimen chemo only(5µg/kg/d)	
	Transfusion trigger				NR	
	Hb inclusion criteria level				NR	
	Arm 1 = darbe N =356		**Arm 2 = controls N = 377**		**Arm 3 = N =**	
Sex						
Age years median (range)	NR, median age reported for the separately for the intensified and standard chemotherapy arms only; the median age at randomization was 48 years (range 23–65years)					
<50 years	183	51.4%	213	56.4%		
≥50 years	173	43.6%	164	43.6%		
ECOG						
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%		
Mean Hb baseline (g dl^{-1}) (SD)	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, just stated that 'baseline characteristics were similar in the treatment arms'. It is assumed that this refers to the chemo arms, and it is not clear whether it also refers to the epo vs no epo arms.					

RESULTS				
	Arm 1 = darbe N =356	**Arm 2 = controls N = 377**	**Arm 3 = N =**	**p**
Hb				

Mean Hb at the end of chemotherapy (g dl-1) (SD)	n=342 13.59	(1.7)	n=368 12.61	(1.38)	as reported in supplemental online materials:
Mean change in Hb (g dl-1) (SD)	n=330 -0.07	(0.11)	n=359 -0.98	(0.07)	The Hb levels in the control group decreased significantly, whereas the levels in the Darbe 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 darbe, n=333 control; Hb at end of chemo n=368 darbe, n=342 control; change in Hb data from n=359 darbe, n=330 control). Could not find full analysis of the Hb data.
(95% CI)	-0.28; 0.14		-1.12; -0.84		
Tumour response					
Pathological CR	57	16%	60	15.9%	P=0.972 (pCR vs no pCR)
CR(by most appropriate method)	46	12.9%	54	14.3%	P=0.580
No difference for clinical response, or nodal response					
Toxicity (safety analysis set)	**Darbe n=318,**		**controls n=396**		
Cardiovascular and thromboembolic events	20	6.3%	17	4.3%	P=0.232
Thromboembolic events: Embolism/thrombosis/	18	5.7%	12	3%	P=0.055
Nausea grade 1-4	251	78.9%	315	79.5%	
Nausea grade 3-4	19	6.0%	19	4.8%	
Anaemia grade 1-4	31	9.7%	35	8.8%	
Anaemia grade 3-4	1	0.3%	1	0.3%	
Transfusions	1		0		
Survival	**At a median follow-up of 43.5 months**; as reported in Untch 2011b				
DFS	**Arm 1 = darbe N =345**		**Arm 2 = controls N = 369**		
DFS: estimated at 3 years		74.3%		78%	HR=1.31; 95% CI (0.99-1.74), P=0.061
DFS: events, n	106		90		

DFS: events adjusted for BL	104	30%	88	24%	as reported in supplemental online materials
DFS: events adjusted for BL : HR=1.23; 95% CI (0.83-1.83), p=0.296 in multivariate analyses adjusted for chemo, age, initial tumour size, grading, ER/PgR status.					
DFS Subgroup analyses: no pCR vs pCR (better outcome observed for patients who achieved a pCR): With darbe: HR=2.38; 95% CI (1.2-4.71), p=0.013 Without darbe: HR=2.13; 95% CI (1.03-4.41), p=0.041					as reported in supplemental online materials
OS					
OS: estimated at 3 years		88%		91.8%	HR=1.33; 95% CI (0.91-1.95), P=0.139
OS: events, n %	59		48		HR=1.33; 95% CI (0.91-1.95), P=0.139 in univariate analysis.
OS: events adjusted for BL	59	17%	48	13%	as reported in supplemental online materials
OS: events adjusted for BL HR=1.24; 95% CI (0.71-2.19), p=0.4502 multivariate analyses adjusted for chemo, age, initial tumour size, grading, ER/PgR status.					
OS Subgroup analyses: no pCR vs pCR (better outcome observed for patients who achieved a pCR): With darbe: HR=4.02; 95% CI (1.26-12.85), p=0.019 Without darbe: HR=3.08; 95% CI (0.95-9.92), p=0.060					as reported in supplemental online materials
A trend (without showing a relevant effect on the clinical and pathohistological response) toward s a worse DFS in the darbepoetin alfa arm compared with the darbepoetin free arm was found. The absolute DFS difference in the dose-dense arm between patients treated with and without darbepoetin alfa is larger than the difference between the two chemotherapy regimens. An unplanned subgroup analysis the study revealed poor prognostic factors to be associated with significantly decreased DFS and OS in patients who received darbepoetin In an unplanned subgroup analysis, the impact of darbe on DFS and OS was investigated. Patients with either grade 3 tumor or a tumor size ≥4 cm had significantly worse DFS when treated with darbepoetin alfa. This effect on OS was only significant for grade 3 tumors:					
NOTES: **pCR:** Regression **Grade 5** means no microscopic evidence of residual viable tumor cells (invasive or noninvasive) in all breast specimens and lymph nodes; **Grade 4,** no residual tumor in breast specimens but involved lymph nodes; **Grade 3**, only residual noninvasive (in situ) tumor in breast tissue irrespective of lymph node status; **Grade 2**, extensive tumor sclerosis with focal or multifocal evidence only of minimally invasive residual tumor (<0.5 cm), frequently extensive ductal carcinoma in situ; **Grade 1**, increased tumor sclerosis with focal resorptive inflammation and/or marked cytopathic effects; and **Grade 0**, no effect. pCR was defined as no residual tumor in the breast regardless of lymph node status.					

QUALITY APPRAISAL	
1. WAS THE METHOD USED TO GENERATE RANDOM ALLOCATIONS ADEQUATE? (Yes – random numbers; coin toss; shuffle etc; No = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was alternate, or based on information known to the	NR

triallist)	
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'. It is assumed that this refers to the chemo arms, and it is not clear whether it also refers to the epo vs no epo 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
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	No
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Partially: only until the point of surgery; n=326 darbe and n=343 controls.

Untch 2011 ref(#962) reports DFS and OS follow up data.
Untch, M., von Minckwitz, G., Konecny, G. E., Conrad, U., Fett, W., Kurzeder, C., . . . Fasching, P. A. (2011). 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,* 22(9), 1999-2006. doi: 10.1093/annonc/mdq713

OTHER	
Generalisability	
Author conclusions	Primary use of darbepoetin did not affect pCR, while darbepoetin might have detrimental effects on DFS. Patients should not be treated with ESA in the neoadjuvant setting under the assumption of better tumor 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.

Endnote Ref ID	**2698 (HTA)**	**Malignancy type**	**lung cancer**
		Treatment	**darbepoetin alfa**

STUDY DESIGN		**PARTICIPANTS**	
Author, year	Vansteenkiste 2002	N	314
Objective	The safety and efficacy of darbepoetin	**Inclusion criteria:**	

	alfa compared with placebo in patients with lung cancer receiving chemotherapy.	• lungcancer • expected to receive at least 12 additional weeksof platinum-containing chemotherapy • age≥18years • had a life expectancy of at least 6 months • ECOG= 0 -2 • **Anemia (i.e., Hb level of ≤11.0 g/dL)** primarily because of their cancer or chemotherapy • have adequate serum folate, vitamin B12, ferritin, and saturated transferrin levels • have adequate renal and hepatic functions **Exclusion criteria:** • iron deficient pts • primary or metastatic malignancy of the central nervous system • pts with more than two red blood cell transfusions within 4 weeks of randomization or had received any red blood cell transfusion within 2 weeks of randomization • pts with rHuEPO therapy within 8 weeks of randomization 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 hematologic disorder as the cause of their present anemia
# centres	70	
Other references/aliases	NESP 980297 Tchekmedyian 2003 Secondary analysis in Vantenkeenste 2004 (#240)	
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 a long-term follow-up to determine tumor status and surviva (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 has received research and travel grants and consulting fees from Amgen Inc. D. Tomita holds stock in Amgen Inc., the maker of darbepoetin alfa and erythropoietin alfa.	
RANDOMISATION & ALLOCATION	A double-blind, placebo-controlled, randomized phase III study; patients were randomly assigned, by a central randomization service for all sites, in a 1 : 1 ratio. Randomization was stratified by tumour type (small-cell lung cancer or non-small-cell lung cancer) and geographic region (Australia, Canada, Western Europe, or Central and Eastern Europe).	
TREATMENT ARMS		
ARM Drug name/s	**Darbepoetin alfa**	**Placebo**
N	156	158
Dose & freq (od, bd etc)	2.25 µg/kg/week	Volume equivalent to darbe treatment
Dose adjustment Y/N	Y: At Week 6: if baseline HB ≤ 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).	Y: same as darbepoetin (see above)

	Treatment withheld if Hb>15.0 g/dL (for men) or >14.0 g/dL (for women). After the patient's Hb decreased ≤13.0 g/dL, dose was reinstated at 50%.	
Route of administration	Subcutaneous	Subcutaneous
Duration of epo tx	12 weeks	
Adj anaemia treatment		
Transfusion trigger	Recommended when Hb≤8.0 g/dL and based on clinical judgment (transfusion policies can vary widely from country to country)	As darbepoetin alfa

OUTCOMES			
Primary outcome	**RBCT (proportion of pts who received a red blood cell transfusion during a specific time period—from week 5 until the end-of-treatment *)**	**Other outcomes**	**HaemR (**hematopoietic response$; Hb collected weekly); RBCT (the incidence of RBCT from Week 1 until the end-of-treatment, the incidence of transfusion or Hb concentrations ≤8.0 g/dL, and the 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); HRQL (FACT–Fatigue, collected every 3–4 weeks on the first day of each cycle of chemotherapy, before any other study procedures); AEs (adverse event profile; incidence and duration of hospitalization)

NOTES:
Antibody formation to darbepoetin alfa was assessed

*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 endpoint

$ hematopoietic response was defined as an increase in Hb concentration of greater than or equal to 2.0 g/dL or a Hb concentration of greater than or equal to 12.0 g/dL in the absence of a red blood cell transfusion within the previous 28 days.

ANALYSIS	
Statistical technique used?	Kaplan–Meier estimates were used for proportion of patients who received at least one transfusion during week 5 until the end of the treatment and for secondary transfusion-related endpoints and OS and PFS. The SE of the Kaplan–Meier proportion was calculated using Greenwood's formula; 95% CI were also reported.

	Efficacy endpoints were analysed with and without adjusting for the two factors used to stratify the randomization: tumour type and geographic region. Results of both types of analyses were consistent, so only results of the unstratified analyses are presented. Cox proportional hazards and logistic regression were used to compare treatment groups after adjusting for tumour type, geographic region, and other potentially prognostic factors after determining that data complied with assumption for this method. **No adjustments were made for multiple significance tests.** The percentage of change from baseline for the FACT–Fatigue 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 uncorrected chi-square test. Safety was evaluated in all patients who received at least one dose of study drug.
Intention to treat analysis?	NR All patients randomly assigned into the study who received at least one dose of study drug were included in the analyses. 314 pts received study drug and were included in the analysis for all Endpoints,(including OS and PFS). However this does not seem to apply to analyses of FACT. 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. 297 pts (93%) completed the first 28 days of the study and were included in the analysis of the primary endpoint.
Does statistical technique adjust for confounding?	NR
Power calculation (priori sample calculation)?	Y: 90% power to detect a 50% reduction (from 40% to 20%) in the proportion of pts 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; n=14 and n=11 for epo and placebo respectively withdrew consent, administrative decision, and loss to follow-up
Was attrition rate adequately dealt with?	NR
Number (%) followed up from each condition?	Partially
BASELINE CHARACTERISTICS	
Malignancy type *(e.g.solid / solid head neck, lung, ovarian, cervical / haem / MDS / mixed)*	**Lung cancer**
Treatment *(e.g. chemotherapy platinum / non-platinum based; chemo + radio; no specific malignancy treatment; not reported)*	**Pt based chemo**

Adjuvant anaemia treatment	**Iron**	**NR**
	G-CSF	**NR**
	Transfusion trigger	**Recommended when Hb≤8.0 g/dL and based on clinical judgment**
	Hb inclusion criteria level	**<11 g/dl**

	Arm 1 = darbe N =156		**Arm 2 = placebo N = 158**			
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]		
Performance status WHO / ECOG /						
0	22	14%	23	15%		
1	109	70%	98	62%		
2	24	15%	37	23%		
>2	1	1%	0	0%		
Hb baseline (g dl^{-1}) 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 baseline (U/l median (range)						
Epo baseline (mU ml^{-1})						
Target Hb						
Feritin 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:						
BL Hb, mean (SD)	**Arm 1 = darbe N =51**		**Arm 2 = placebo N = 69**			
Hb <10	9.1	(0.7)	9	(0.7)		
	Arm 1 = darbe N =105		**Arm 2 = placebo N = 89**			
Hb≥10	10.9	(0.7)	10.7	(0.5)		
Were intervention and control groups comparable?	No p-values are reported, stated “Baseline demographics and clinical characteristics were similar between the two treatment groups”.					

RESULTS						
	Arm 1 = darbe N =156		**Arm 2 = placebo N = 158**		**Arm 3 = N =**	**p**
Haematological & transfusions						
Transfusions	N=148 and N=149 for darbe and placebo respectively.					
Pts with RBC transfusions % (95%CI), from wk 5 to EOTP	27%	20-35%	52%	44-66%	The difference was 25% (CI 14 - 36%), p<.001.	P<0.001
First RBC transfusion or	32%	24-39%	62%	54-71%		P<0.001

HB≤8g/dl							
Mean RBC units transfused (SD)	0.67	1.7	1.92	3.27	The difference was 1.25 (CI 0.65-0.84), p<.001.		P<0.001
hematopoietic response$; % (95%CI)	66%	58-74%	24%	16-31%	The difference was 42% (CI 31-53%) , p<.001.		P<0.001
	103pts calculated		38pts calculated		As reported in Vansteenkiste 2004:		
Pts with RBC transfusions % (95%CI), from wk 1 to EOTP	28%	21-35%	57%	49-65%			
Time to disease progression or death, weeks, median (95% CI)	23	19-31	20	17-23			
Data from secondary analyses Vansteenkiste 2004:							
	Arm 1 = darbe N =51		**Arm 2 = placebo N = 69**				
Hb <10	65%	50-80%	31%	17-45%			P<0.002
	33pts calculated		21pts calculated				
	Arm 1 = darbe N =105		**Arm 2 = placebo N = 89**				
Hb≥10	67%	57-77%	20%	11-29%			P<0.001
	70pts calculated		17pts calculated				
The difference between epo and placebo change from BL was, the mean Hb change was 1.3 (p<0.001) and 1.4 (p<0.001) for the two Hb <10 and Hb≥10 groups respectively.							
Health-related QoL	N=127 and N=128 for darbe and placebo respectively completed the scale through study week 4, also completed baseline and at least one time from week 5 until the end-of-treatment phase.						
Improvement in FACT–Fatigue scale, % (CI)	56%	47-65%	44%	35-52%			P=0.052
patients with at least a 25% improvement from baseline in FACT–Fatigue scale, % (CI)	32%	23-40%	19%	12-26%	The difference was 13% (CI 2-23%), p=0 .019.		P=0.019
Adverse effects of tmt							
Deaths	22	14%	19	12%			
Deaths due to disease progression		61%		58%			
Thromobotic events	7	5%	5	3%			
Hypertension	9	6%	6	4%			
Hospitalizations for overnight stays: mean days (SD)	10.3	13.7	13	17.7			P=0.13
An analysis of the proportion of pts hospitalized was also done considering all hospitalizations (i.e., with or without an overnight stay), with similar results.							
an average of 1 year follow-up after pts first dose of study drug: (N=156 and N=158 for darbe and placebo respectively.)							
Median OS weeks, (95% CI)	46	39-53	34	29-39			
Deaths	92	59%	109	69%			
Median PFS weeks, (95% CI)	22	18-31	20	17-23			

Disease progression or died	129	83%	141	89%			

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-darbe antibodies were detected in 1054 serum samples (darbe N =531 and placebo N= 523).
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 = for patients number, date of birth, alternate; Unclear = if the method not stated)	Unclear; no randomisation details given.
2. WAS THE TREATMENT ALLOCATION ADEQUATELY CONCEALED? (Yes = central allocation at trials office/pharmacy; sequentially numbered coded vials; other methods where the triallist allocating treatment could not be aware ; Inadequate = allocation was alternate, or based on information known to the triallist)	Unclear; Randomisation was performed using a centralised system, but no 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, stated “Baseline demographics and clinical characteristics were similar between the two treatment groups”.
4. WERE THE ELIGIBILITY CRITERIA SPECIFIED?	Y
5. WERE THE PARTICIPANTS BLIND TO TREATMENT ALLOCATION?	Y
6. WERE THE OUTCOME ASSESSORS BLIND TO TREATMENT ALLOCATION?	Y
7. WERE THE POINT ESTIMATES AND MEASURE OF VARIABILITY PRESENTED FOR THE PRIMARY OUTCOME MEASURE?	Y
7. IS THERE EVIDENCE TO SUGGEST THAT THE AUTHORS COLLECTED MORE OUTCOME DATA THAN THEY REPOTED?	N
8. DID THE ANALYSES INCLUDE AN INTENTION-TO-TREAT ANALYSIS OR WERE LESS THAN 10% OF EACH STUDY ARM EXCLUDED?	Yes*, not for HRQoL; only 81% of patients analysed in both treatment groups
9. WERE WITHDRAWALS DROPOUTS AND LOSS TO FOLLOW-UP IN EACH GROUP STATED?	Partially

NOTES:
***** less than 10% dropout, but ITT defined as all randomised participants who received ≥ 1 dose of study drug

References:

- Vansteenkiste, J.; Tomita, D.; Rossi, G.; Pirker, R. (2004). Darbepoetin alfa in lung cancer patients on chemotherapy: a retrospective comparison of outcomes in patients with mild versus moderate-to-severe anaemia at baseline. Supportive Care in Cancer, 12, 253-262.

Objective: To determine if the degree of benefit obtained from treatment with DA is affected by patient’s Hb level at the start of treatment

- Tchekmedyian, N. S., Kallich, J., McDermott, A., Fayers, P., & Erder, M. H. (2003). The relationship between psychologic distress and cancer-related fatigue. Cancer, 98(1), 198-203. doi: 10.1002/cncr.11463

Objective: examined the correlation between psychologic distress (anxiety and depression) and fatigue over time

Note: 250 participants are analysed, data are collated (no separate results for darbe and placebo arm). Pts were included in the analysis if they completed at least 4 weeks of treatment and reported BSI at baseline and at least once after 4 weeks of treatment. The following confounding variables for evaluation of the relationship between psychologic outcomes and fatigue: age, gender, baseline ECOG, tumour type (small cell or nonsmallcell 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 and Conclusion: 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 Fatigue 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 Fatigue score was the only significant explanatory variable ($P < 0.001$). For every unit improvement in FACT Fatigue 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 associated significantly with reductions in anxiety and depression. For patients with anemia, fatigue can be improved or reversed with darbepoetin alfa therapy. Thus, less fatigued patients also may benefit from reduced levels of anxiety and depression.

OTHER	
Generalisability	The majority of pts were male
Author conclusions	Patients with chemotherapy-associated anemia can safely and effectively be treated with weekly darbepoetin alfa therapy. Darbepoetin alfa decreased blood transfusion requirements, increased hemoglobin 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	

Appendix E: Excluded studies

16.1. Clinical effectiveness: excluded studies

Abstract only	
Alexopoulos, C. G. K., A. A. (2004). "A randomized comparison of rHuEPO with darbepoetin for cancer related anaemia." Annals of Oncology 15: 219-219.	Abstract only
B.Sevinir, O. D. (2004) "Once aweek erythropoietin in children with cancer." Pediatr Blood Cancer, 491-492.	Abstract only
Canon, J. L. V., J.; Bodoky, G.; Mateos, M. V.; Bastit, L.; Ferreira, I.; Rossi, G. (2005). "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." Journal of Clinical Oncology 23: 799S-799S.	Abstract only
Canon, J. V., J.; Bodoky, G.; Mateos, M. V.; Bastit, L.; Ferreira, I.; Amado, R. (2005). "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 Supplements 3: 370-370.	Abstract only
Charu, V. B., C. P.; Gill, A. N.; Bhatt, M.; Ben-Jacob, A.; Tomita, D.; Katz, D. (2004). "A controlled, randomized, open-label study to evaluate the effect of every-2-week darbepoetin alfa for anemia of cancer." Journal of Clinical Oncology 22: 749S-749S.	Abstract only
Charu, V. B., C.; Gill, A.; Bhatt, M.; Ben-Jacob, A.; Tomita, D.; Katz, D. (2005). "A controlled, randomized, open-label study to evaluate the effects of every-2-week darbepoetin alfa for anemia of cancer." Journal of Supportive Oncology 3: 12-13.	Abstract only
Charu, V. S., B.; Ben-Jacob, A.; Justice, G. R.; Maniam, A. S.; Rearden, T.; Tomita, D.; Rossi, G. (2004) "Improvements in fatigue are associated with early treatment with darbepoetin alfa every 3 weeks (Q3W) Darbepoetin alfa (DA) Treatment in Anemic Patients (pts) Receiving Chemotherapy." Blood, abstract 233.	Abstract only
Crawford, J. G., J.; Vansteenkiste, J.; Henry, D. H.; Tomita, D.; Bridges, K.; Ludwig, H. (2010). "Use of erythropoiesis-stimulating agents (ESAs) in lung cancer patients: Study-level and patient-level meta-analyses of safety outcomes." Journal of Thoracic Oncology.Conference: Chicago Multidisciplinary Symposium in Thoracic Oncology Chicago, IL Un	Abstract only
Delarue, R. (2012). "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, ECCLU 2012 Lugano Switzerland 82: S12-S13.	Abstract only
Delarue, R. H., C.; Broussais-Guillaumot, F.; Sibon, D.; Fournier, M.; Mounier, N.; Petrella, T.; Bologna, S.; Fruchart, C.; Ferme, C.; Recher, C.; Picard, S.; Tilly, H.; Bosly, A. (2009). "Efficacy and safety of prophylactic use of darbepoetin alfa in patients with diffuse large B-cell lymphoma (DLBCL) treated with	Abstract only

immunochemotherapy: Results of	
Freemantle, N. Y., B.; Calvert, M.; Lillie, T. (2005). "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 106: 871A-871A.	Abstract only
Gupta, S. S., P. K.; Bhatt, M. L.; Pant, M. C.; Sundar, S.; Verma, J.; Negi Mp, S. (2011). "Clinical benefits of Epoetin beta in patients with advanced stage hormone refractory prostate cancer." 26th Annual Congress of the European Association of Urology, EAU Vienna Austria 10: 337.	Abstract only
Hartmann, J. T. M., B.; Binder, C.; Mergenthaler, H. G.; Rick, O.; Sayer, H. G.; Mayer, F.; Beyer, J.; Lorch, A.; Berdel, W. E.; Frickhofen, N.; Bokemeyer, C.; Schleicher, J.; Gauler, T. C. (2012). "Addition of darbepoetin alfa to sequential high-dose VIP chemotherapy for patients with advanced metastatic germ cell cancer." 2012 Annual Meeting of	Abstract only
Heras, P. H., A.; Karagiannis, S. (2006) "Efficacy and safety of epoetin beta 30,000 IU once weekly in patients with solid tumors and chemotherapy-induced anemia [abstract] 2035." Journal of Clinical Oncology : ASCO annual meeting proceedings, 697.	Abstract only
Heras, P. H., A.; Karagiannis, S.; Kritikos, K. (2007). "Epoetin beta (30000) vs. epoetin alfa (40000) for chemotherapy induced anemia in patients with colorectal cancer: A randomized comparative study." Annals of Oncology 18: VII77-VII77.	Abstract only
Hernandez, E. D., J.; Kotasek, D.; Ganly, P.; Silberstein, P.; Tomita, D.; Lillie, T.; Boccia, R. V. (2006) "Effectiveness of darbepoetin alfa 300 mcg every 3 weeks in patients with chemotherapy-induced anemia [abstract] 2032." Journal of Clinical Oncology : ASCO annual meeting proceedings, 691.	Abstract only
Hinds, P. S. H., Marilyn; Feusner, James; Hord, Jeffrey D.; Rackoff, Wayne; Rozzouk, Bassem I. (2005). "Hemoglobin response and improvements in quality of life in anemic children with cancer receiving myelosuppressive chemotherapy." The Journal of Supportive Oncology 3: 10-11.	Abstract only
Houben, R. P.-J., M.; Ramaekers, B.; Van Den Ende, P.; De Jong, J.; De Huysscher, D.; Lambin, P. (2010). "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 Barcelona S	Abstract only
Katsumata, N. F., Y.; Sugiyama, T.; Goto, I.; Ohmatsu, H.; Okamoto, R.; Ohashi, Y.; Saijo, N.; Hotta, T.; Ariyoshi, Y. (2011). "Erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anemia and mortality: A meta-analysis of individual patient data from Japanese randomized trials." 2011 European Multidisciplinary Cancer Congres	Abstract only
Kelada, O. J. M., L. (2010). "Does the use of erythropoiet in-st imulating agen ts 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 Barcelona Spain 96: S578.	Abstract only

Kotsori, A. A. A., C. G. (2006) "A randomized comparison of Darbepoetin alfa with Epoetin for chemotherapy induced anemia in nonhematological tumors [abstract]." Journal of Clinical Oncology : ASCO annual meeting proceedings, 692.	Abstract only
Langer, C. J. (2009). "Managing anemia in lung cancer." Journal of Thoracic Oncology 4: S144-S145.	Abstract only
Ludwig, H. C., J.; Osterborg, A.; Fleishman, A.; Lillie, T.; Sueto, T.; Glaspy, J. (2007). "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 Supplements 5: 142-143.	Abstract only
Marangolo, M. L., I.; Beato, C.; Colomer, R.; Ukarma, L. (2005) "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." European Journal of Cancer, 388.	Abstract only
Marangolo, M. M., N.; Pedrini, J. L.; Rotarski, M. (2005) "Epoetin beta in patients with metastatic breast cancer receiving chemotherapy: Results from the Breast Cancer - Anaemia and the Value of Erythropoietin (BRAVE) study." Journal of Clinical Oncology, 764s.	Abstract only
Marinaccio, M. M., E.; Poma, S.; Cantinieri, C.; Cocca, M.; Latiano, T. (2004) "Pretreatment normalisation of mild anemia with epoetin alfa predicts long-term outcome for women with epithelail ovarian cancer [abstract]." Proceedings of the American Society of Clinical Oncology, 480, Abstract 5132.	Abstract only
Markus, R. H., D.; Gascon, P.; Fleishman, A.; Borenstein, J. (2009). "Design and rationale of a double-blind, randomized, placebo-controlled study to evaluate the long-term safety and efficacy of darbepoetin alfa administered 500mcg once every three weeks (Q3W) in anemic patients with advanced non-small cell lung cancer (NSCLC) receiving multi-cyc	Abstract only
Mihaylov, G. T., V.; Koytchev, R. (2008) "EPOETIN ZETA: SAFETY DATA FROM AN OPEN-LABEL, PHASE III TRIAL IN PATIENTS WITH CHEMOTHERAPYINDUCED ANAEMIA [Abstract No. 907P]." Annals of Oncology, 278.	Abstract only
Moehler, M. G., M.; Raedle, J.; Ebert, M. D.; Flieger, D.; Seufferlein, T.; Galle, P. R.; Kanzler, S.; Hoehler, T. (2007) "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, 140-141.	Abstract only
Nitz, U. O., C.; Reimer, T.; Schumacher, C.; Hackmann, J.; Warm, M.; Uleer, C.; Runde, V.; Gluz, O.; Zuna, I. (2009). "Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: A safety analysis from the phase III ARA plus trial." 31st Annual San Antonio Breast Cancer Symposium San Antonio, TX United States 69 (2 Suppl. S.	Abstract only
Norris, L. M., D.; Qureshi, Z. P.; Bennett, C. (2011). "Location, location, location: Reassessing Erythropoiesis Stimulating Agents (ESAs) in the United States (US), Canada, and Europe (2007-	Abstract only

2011)." 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States 118 (21.	
Norris, L. Q., Z.; Barnato, S.; Lai, S.; Bennett, C. (2011). "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 United States 17: 20-21.	Abstract only
Ohmatsu, H. N., Y.; Ichinose, Y.; Ohe, Y.; Yamada, Y.; Takeda, K.; Saijo, N.; Hotta, T. (2006). "Randomized phaseii study of weekly administration of darbepoetin alfa (DA) in anemic patients with lung cancer and ovarian cancer receiving platinum-based chemotherapy." Annals of Oncology 17: 291-292.	Abstract only
Paladini, L. C., O.; Clark, L. G.; Engel, T.; Pegoretti, B.; Faleiros, E. (2009). "Erythropoiesis stimulating agents (ESA) for the treatment of chemotherapy induced anemia in patients with hemoglobin levels (HB) <11G/DL-A systematic review and meta-analysis." ISPOR 12th Annual European Congress Paris France 12: A493.	Abstract only
Pirker, R. C., H.; Legg, J. C.; Vansteenkiste, J. F. (2011). "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." ASCO Annual Meeting 2011 Chicago, IL United States 29 (15 SUPPL. 1.	Abstract only
Pollera, C. F. N., F.; Gamucci, T.; Sperduti, I.; Giampaolo, A. M.; Moscetti, L.; Tonini, G.; Mentuccia, L.; Nardi, M.; Cortesi, E. (2006) "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 Ita	Abstract only
Razzouk, B. I. H., Jeffrey D.; Hockenberry, Marilyn; Hinds, Pamela S.; Feusner, James; Williams, Denise; Rackoff, Wayne R. (2006). "Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy." Journal of Clinical Oncology 24: 3	Abstract only
Rearden, T. P. C., V.; Saidman, B.; Ben-Jacob, A.; Justice, G. R.; Manaim, A. S.; Tomita, D.; Rossi, G. (2004). "Results of a randomized study of every three-week dosing (Q3W) of darbepoetin alfa for chemotherapy-induced anemia (CIA)." Journal of Clinical Oncology 22: 745S-745S.	Abstract only
Reed, N. C., S.; Hayward, C.; Burger, H.; Bokkel Huinink, W. (2005) "Impact of epoetin beta on the survival of anemic patients with ovarian cancer receiving platinum-based chemotherapy [abstract]." Proceedings of the American Society of Clinical Oncology, Abstract 5102.	Abstract only
Rosti, G. S., S.; Giordano, L.; Garassino, I.; Gandini, C.; Auerbach, M.; Santoro, A.; Pedrazzoli, P. (2009). "Intravenous iron supplementation and erythropoiesis stimulating agents (ESAs): Mata-analysis of randomized trials in patients with chemotherapy-induced anemia." Joint ECCO 15 - 34th ESMO	Abstract only

Multidisciplinary Congress Berlin Germany 7: 256.	
Schwartzberg, L. Y., L.; Charu, V.; Tomita, D.; Rossi, G.; Senecal, F. (2005). "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." Journal of Supportive Oncology 3: 30-31.	Abstract only
Schwartzberg, L. Y., L.; Charu, V.; Tomita, D.; Rossi, G.; Senecal, F. (2005). "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." Journal of Supportive Oncology 3: 30-31.	Abstract only
Shah B. (2013). Darbepoetin in cancer related anemia. 54th Annual Conference of Indian Society of Haematology and Blood Transfusion, Haematacon 2013 Mumbai India. 29, 270-271.	Abstract only
Steensma, D. P. D., S. R.; Novotny, P. J.; Sloan, J. A.; Johnson, D. B.; Anderson, D. M.; Mattar, B. I.; Moore, D. F.; Nikcevich, D.; Loprinzi, C. L. (2009). "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 A	Abstract only
Strauss, H. H., G.; Dunst, J.; Hayward, C.; Koelbl, H. (2005) "Effects of anaemia correction with epoetin beta in patients with advanced cervical cancer and radiochemotherapy [abstract]." Proceedings of the American Society of Clinical Oncology, Abstract 5121.	Abstract only
Suzuki, Y. T., Y.; Okamoto, R.; Nakagawa, K.; Ando, K.; Iwata, H.; Tobinai, K.; Tanigawara, Y.; Hotta, T.; Saijo, N. (2008). "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 (ESM	Abstract only
Taylor, K. G., P.; Charu, V.; DiBenedetto, J.; Kracht, K.; Rossi, G.; Hernandez, E. (2005) "Randomized, Double-Blind, Placebo-Controlled Study of Darbepoetin alfa Every 3 Weeks for the Treatment of Chemotherapy-Induced Anemia [abstract]." Blood, 992-993.	Abstract only
Tesch, H. L., A. M.; Ifrah, N. (2006) "Assessment of cognitive effects of once-weekly epoetin alfa in anemic patients with hematologic malignancies receiving chemotherapy: results of the EPOLYM trial [Abstract No. 0022]." Haematologica, the hematology journal: abstract book.	Abstract only
Toma A, Chevret, S., Kosmider, O., Delaunay, J., Stamatoullas, A., Rose, C., Beyne-Rauzy, O., Banos, A., Guercy-Bresler, A., Jourdan, E., Sardnal, V., Caillot, D., Laribi, K., De Renzis, B., Bordessoule, D., Slama, B., Sanhes, L., Fontenay, M., Fenaux, P., Dreyfus, F. (2013). 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. 2013 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. 31 (15 SUPPL. 1.)	Abstract only
Tzekova, V. K., R. (2008) "Efficacy of epoetin zeta in patients with	Abstract only

chemotherapy-induced anemia and hematological malignancies: interim results [abstract no.1132]." Haematologica, the hematology journal: abstract book, 444.	
Tzekova, V. M., G.; Koytchev, R. (2008) "Epoetin zeta: efficacy data from an open-label, phase iii trial in patients with chemotherapyinduced anaemia [Abstract No. 906P]." Annals of Oncology, 278.	Abstract only
Van Groeningen, C. J. K., T. C.; Biesma, B.; Melissant, C. F.; De Klerk, G.; Brok, R. G. P. M.; Lahaye, M.; Milek, R. L. B. (2011). "Epoetin alfa and darbepoetin alfa in clinical practice in patients with chemotherapy induced anemia in the Netherlands (evaluate)." 2011 European Multidisciplinary Cancer Congress Stockholm Sweden 47: S237.	Abstract only
Vandebroek, A. G., B.; Altintas, S.; Smith, K.; Yao, B.; Schupp, M.; Bastit, L. (2006) "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 [abstract] 2015." Journal of Clinical Oncology : ASCO annual meeting proceedings,	Abstract only
Vandebroek, A. G., B.; Altintas, S.; Smith, K.; Yao, B.; Schupp, M.; Bastit, L. (2007). "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." Journal of Supportive Oncology 5: 24-26.	Abstract only
Walter, E. R., E.; Kutikova, L. (2010). "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." ISPOR 13th Annual European Congress Prague Czech Republic 13: A377.	Abstract only
Waltzman, R. J. F., M.; Justice, G. R.; Croot, C.; Williams, D. (2004) "Epoetin alfa 40,000 U QW vs darbepoetin alfa 200 mcg Q2W in anemic cancer patients receiving chemotherapy: Preliminary results of a comparative trial [abstract]." Journal of Clinical Oncology : ASCO annual meeting proceedings, 763.	Abstract only
Waltzman, R. W., D. (2004) "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, 144b.	Abstract only
Watanbabe, M. E., K.; Tobinai, K.; Tsuboi, M.; Ohashi, Y.; Hirashima, K.; Saijo, N. (2006). "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." Annals of Oncology 17: 294-294.	Abstract only
Youssef, L. A. H., D. H.; Sulaiman, S. (2011). "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 2011 San Diego, CA United States 118 (21.	Abstract only
Population	

Abdelrazik, N. F., Manal (2007). "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 12: 533-541.	Population ALL
Agnihotri, P. T., M.; Butt, Z.; Jella, A.; Cella, D.; Kozma, C. M.; Ahuja, M.; Riaz, S.; Akamah, J. (2007). "Chronic anemia and fatigue in elderly patients: Results of a randomized, double-blind, placebo-controlled, crossover exploratory study with epoetin alfa." Journal of the American Geriatrics Society 55: 1557-1565.	Population
Cella, D. K., J.; McDermott, A.; Xu, X. (2004). "The longitudinal of hemoglobin, fatigue and quality of life in anemic cancer patients: Results from five randomised clinical trials." Annals of Oncology 15: 979-986.	Population
Corwin, H. L. G., A.; Fabian, T. C.; May, A.; Pearl, R. G.; Heard, S.; An, R.; Bowers, P. J.; Burton, P.; Klausner, M. A.; Corwin, M. J. (2007). "Efficacy and safety of epoetin alfa in critically ill patients." New England Journal of Medicine 357: 965-976.	Population
Gordon, D. N., G.; Ben-Jacob, A.; Tomita, D.; Lillie, T.; Miller, C. (2008). "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 13: 715-724.	Population
Gurion, R. G.-G., Anat; Paul, Mical; Vidal, Liat; Ben-Bassat, Isaac; Yeshurun, Moshe; Shpilberg, Ofer; Raanani, Pia (2009). "Hematopoietic growth factors in aplastic anemia patients treated with immunosuppressive therapy-systematic review and meta-analysis." Haematologica 94: 712-719.	Population
Henke, M. M., D.; Pepe, M.; Bezay, C.; Weissenberger, C.; Werner, M.; Pajonk, F. (2006). "Do erythropoietin receptors on cancer cells explain unexpected clinical findings?" Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24: 4708-4713.	Population
Intervention	
Krzakowski, M. (2008). "Epoetin Delta: Efficacy in the Treatment of Anaemia in Cancer Patients Receiving Chemotherapy." Clinical oncology 20: 705-713.	Intervention
Lindholm, E. D., Peter; Korner, Ulla; Hyltander, Anders; Fouladiun, Marita; Lundholm, Kent (2004). "Effects of recombinant erythropoietin in palliative treatment of unselected cancer patients." Clinical Cancer Research 10: 6855-6864.	Intervention
Macdougall, I. C. (2005). "CERA (Continuous Erythropoietin Receptor Activator): a new erythropoiesis-stimulating agent for the treatment of anemia." Current Hematology Reports 4: 436-440.	Intervention
(2010) "Radiation therapy with or without epoetin alfa in treating anemic patients with head and neck cancer." ClinicalTrials.gov [accessed 17 Jul 2010], ClinicalTrials.gov ID: NCT00004917.	Intervention

Comparator	
Casadevall, N, Dubois, S., Hemery, F., *et al*. (2004). "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 104: 321-327.	Comparator (G-CSF in on treatment arm; study additive value of G-CSF)
Laurie, S. A. D., K.; Whitehead, M.; Feld, R.; Murray, N.; Shepherd, F. A.; Seymour, L. (2007). "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." Annals of Oncology 18: 1051-1055.	Comparator
Weigang-Kohler, K. V., Andrea; Thyroff-Friesinger, Ursula (2009). "HX575, recombinant human epoetin alfa, for the treatment of chemotherapy-associated symptomatic anaemia in patients with solid tumours." Onkologie 32: 168-174.	Comparator
Outcome	
Littlewood, T. J. S., Brad; Liss, Martin (2005). "Effect of patient exclusion criteria on the efficacy of erythropoiesis-stimulating agents in patients with cancer-related anemia." Oncologist 10: 357-360.	Outcome
Study design	
Aapro, M. (2012). "Emerging topics in anaemia and cancer." Annals of Oncology 23 Suppl 10: x289-293.	Study design
Aapro, M. C., B.; Dunst, J.; Osterborg, A.; Burger, H. U. (2006). "Effect of treatment with epoetin beta on short-term tumour progression and survival in anaemic patients with cancer: A meta-analysis." British Journal of Cancer 95: 1467-1473.	Study design
Aapro, M. J., W.; Constantinescu, S. N.; Leyland-Jones, B. (2012). "Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer." British Journal of Cancer 106: 1249-1258.	Study design
Aapro, M. O., B.; Scherhag, A.; Burger, H. U. (2009). "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." British Journal of Cancer 101: 1961-1971.	Study design
Aapro, M. S., Jerry L. (2009). "Update on erythropoiesis-stimulating agents and clinical trials in oncology." Oncologist 14 Suppl 1: 6-15.	Study design
Bennett, C. L. (2005). "The blue cross blue shield assessment technology review: summary of findings." Bailliere's Best Practice in Clinical Haematology 18: 423-431.	Study design
Bennett, C. L. S., Samuel M.; Djulbegovic, Benjamin; Samaras, Athena T.; Blau, C. Anthony; Gleason, Kara J.; Barnato, Sara E.; Elverman, Kathleen M.; Courtney, D. Mark; McKoy, June M.; Edwards, Beatrice J.; Tigue, Cara C.; Raisch, Dennis W.; Yarnold, Paul R.; Dorr, David A.; Kuzel, Timothy M.; Tallman, Martin S.; Trifilio, Steven M.; West, Dennis	Study design
Beutel, G. G., A. (2007). "Risks and benefits of erythropoiesis-stimulating agents in cancer management." Seminars in	Study design

Hematology 44: 157-165.	
Bohlius, J. T., Thomy; Schwarzer, Guido (2011). "Twist and shout: one decade of meta-analyses of erythropoiesis-stimulating agents in cancer patients." Acta Haematologica 125: 55-67.	Study design
Bohlius, J. W., Jayne; Seidenfeld, Jerome; Piper, Margaret; Schwarzer, Guido; Sandercock, Josie; Trelle, Sven; Weingart, Olaf; Bayliss, Sue; Djulbegovic, Benjamin; Bennett, Charles L.; Langensiepen, Simon; Hyde, Chris; Engert, Andreas (2006). "Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients." Journal of the National Cancer Institute 98: 708-714.	Study design
Boogaerts, M. O., C.; Ten Bokkel Huinink, W.; Nowrousian, M. R.; Hayward, C. R. W.; Burger, H. U. (2006). "Epoetin beta (NeoRecormon) therapy in patients with solid tumours receiving platinum and non-platinum chemotherapy: a meta-analysis." Anticancer Research 26: 479-484.	Study design
Booton, R. T., N. (2005). "The value of erythropoietin therapy in cancer patients." American Journal of Cancer 4: 87-103.	Study design
Boulaamane L, Goncalves A, Boutayeb S et al. (2013). Prognostic impact of the combination of erythropoiesis-stimulating agents to cancer treatment: Literature review. Supportive Care in Cancer. 21, 2359-2369.	Study design
Cersosimo, R. J. J., Daniel R. (2006). "Epoetin alfa versus darbepoetin alfa in chemotherapy-related anemia." Annals of Pharmacotherapy 40: 58-65; quiz 169-170.	Study design
Cheer, S. M. W., A. J. (2004). "Epoetin beta - A review of its clinical use in the treatment of anaemia in patients with cancer." Drugs 64: 323-346.	Study design
Coiffier, B. B., Marc; Aapro, Matti; Hayward, Colin; Burger, Hans-Ulrich (2006). "Effect of treatment with epoetin Beta on thromboembolic events in anemic patients with cancer: a metaanalysis." Supportive Cancer Therapy 4: 49-55.	Study design
Cornes, P. C., B.; Zambrowski, J. J. (2007). "Erythropoietic therapy for the treatment of anemia in patients with cancer: a valuable clinical and economic option." Current Medical Research and Opinion 23: 357-368.	Study design
Cortesi, E. G., Pere; Henry, David; Littlewood, Timothy; Milroy, Robert; Pronzato, Paolo; Reinhardt, Uwe; Shasha, Daniel; Thatcher, Nicholas; Wilkinson, Peter (2005). "Standard of care for cancer-related anemia: improving hemoglobin levels and quality of life." Oncology 68 Suppl 1: 22-32.	Study design
Couture, F. T., A. R.; Melosky, B.; Xiu, L.; Plante, R. K.; Lau, C. Y.; Quirt, I. (2005). "Prior red blood cell transfusions in cancer patients increase the risk of subsequent transfusions with or without recombinant human erythropoietin management." Oncologist 10: 63-71.	Study design
Crawford, J. (2006). "Erythropoiesis-stimulating protein support and survival." Oncology (Williston Park) 20: 39-43.	Study design
Crawford, J. R., F.; Perry, M. C.; Belani, C.; Williams, D. (2007). "A randomized trial comparing immediate versus delayed treatment of anemia with once-weekly epoetin alfa in	Study design

patients with non-small cell lung cancer Scheduled to Receive First-Line Chemotherapy." Journal of Thoracic Oncology 2: 210-220.	
De Los Santos, J. F. T., Gillian M. (2007). "Anemia correction in malignancy management: threat or opportunity?" Gynecologic Oncology 105: 517-529.	Study design
Desai, J. D., George D. (2005). "Recombinant human erythropoietin in cancer-related anemia: an evidence-based review." Bailliere's Best Practice in Clinical Haematology 18: 389-406.	Study design
Donato, H. (2005). "Erythropoietin: an update on the therapeutic use in newborn infants and children." Expert Opinion on Pharmacotherapy 6: 723-734.	Study design
Eton, D. T. C., D. (2011). "Do erythropoietic-stimulating agents relieve fatigue? A review of reviews." Hematopoietic Growth Factors in Oncology.Cancer Treatment and Research 157: 181-194.	Study design
Ferrario, E. F., L.; Bidoli, P.; De Candis, D.; Del Vecchio, M.; De Dosso, S.; Buzzoni, R.; Bajetta, E. (2004). "Treatment of cancer-related anemia with epoetin alfa: a review." Cancer Treatment Reviews 30: 563-575.	Study design
Feusner, J. (2009). "Guidelines for Epo Use in Children With Cancer." Pediatric Blood & Cancer 53: 308-309.	Study design
Folloder, J. (2005). "Effects of darbepoetin alfa administered every two weeks on hemoglobin and quality of life of patients receiving chemotherapy." Oncology Nursing Forum 32: 81-89.	Study design
Gao S, Ma JJ, Lu C. (2013). Venous thromboembolism risk and erythropoiesis-stimulating agents for the treatment of cancer-associated anemia: a meta-analysis. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine.	Study design
Gascon, P. (2005). "Evaluating erythropoietic agents for the treatment of anaemia in the oncology setting." European Journal of Cancer 41: 2601-2612.	Study design
Glaspy, J. A. (2011). "Randomized controlled trials of the erythroid-stimulating agents in cancer patients." Hematopoietic Growth Factors in Oncology.Cancer Treatment and Research 157: 195-215.	Study design
Glaspy, J. B., Y. (2005). "Anaemia management strategies: Optimising treatment using epoetin beta (NeoRecormon (R))." Oncology 69: 8-16.	Study design
Glaspy, J. C., J.; Vansteenkiste, J.; Henry, D.; Rao, S.; Bowers, P.; Berlin, J. A.; Tomita, D.; Bridges, K.; Ludwig, H. (2010). "Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes." British Journal of Cancer 102: 301-315.	Study design
Glaspy, J. R., G. (2004). "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 10: 1546-1546.	Study design
Goodnough LT, Shander, A. (2013). Update on erythropoiesis-stimulating agents. Best Practice and Research: Clinical	Study design

Anaesthesiology. 27, 121-129.	
Gosselin, A. M., R. S.; Lefebvre, P.; Mody, S. H.; Piech, C. T.; Duh, M. S. (2006). "Dose-conversion ratio for epoetin alfa and darbepoetin alfa in chemotherapy patients with anemia and cancer." P and T 31: 594-596601-596603.	Study design
Hedenus, M. O., Anders; Tomita, Dianne; Bohac, Chet; Coiffier, Bertrand (2012). "Effects of erythropoiesis-stimulating agents on survival and other outcomes in patients with lymphoproliferative malignancies: a study-level meta-analysis." Leukemia & Lymphoma 53: 2151-2158.	Study design
Hedenus, M. V., Johan; Kotasek, Dusan; Austin, Matthew; Amado, Rafael G. (2005). "Darbepoetin alfa for the treatment of chemotherapy-induced anemia: disease progression and survival analysis from four randomized, double-blind, placebo-controlled trials." Journal of Clinical Oncology 23: 6941-6948.	Study design
Henry, D. H. (2005). "Epoetin alfa for the treatment of cancer- and chemotherapy-related anaemia: product review and update." Expert Opinion on Pharmacotherapy 6: 295-310.	Study design
Henry, D. H. (2007). "Epoetin alfa treatment for patients with chemotherapy-induced anemia." Supportive Cancer Therapy 4: 78-91.	Study design
Heuser, M. G., A. (2006). "Recombinant human erythropoietin in the treatment of nonrenal anemia." Annals of Hematology 85: 69-78.	Study design
Jadersten, M. H.-L., E. (2009). "Myelodysplastic syndromes: biology and treatment." Journal of Internal Medicine 265: 307-328.	Study design
Jadersten, M. M., L.; Dybedal, I.; Della Porta, M. G.; Invernizzi, R.; Montgomery, S. M.; Pascutto, C.; Porwit, A.; Cazzola, M.; Hellstrom-Lindberg, E. (2008). "Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome." Journal of Clinical Oncology 26: 3607-3613.	Study design
Janecka, I. P. (2004). "Erythropoletin to treat anaemia in patients with head and neck cancer." Lancet 363: 993-994.	Study design
Jones, M. S., Brad; Just, Julie; Fallowfield, Lesley (2004). "Epoetin alfa improves quality of life in patients with cancer: results of metaanalysis.[Erratum appears in Cancer. 2005 May 1;103(9):1984]." Cancer 101: 1720-1732.	Study design
Juneja, V. K., Patricia; Gootenberg, Joseph E.; Rothmann, Mark D.; Shen, Yuan Li; Lee, Kyung Y.; Weiss, Karen D.; Pazdur, Richard (2008). "Continuing reassessment of the risks of erythropoiesis-stimulating agents in patients with cancer." Clinical Cancer Research 14: 3242-3247.	Study design
Kaanders, J. H. A. A., ; Haddad, R.; Posner, M.; Leyland-Jones, B.; Mahmud, S.; Blumberg, N.; Heal, J. M.; Freidlin, B.; Korn, E. L.; Henke, M.; Laszig, R.; Frommhold, H.; Powles, T.; Shamash, J.; Liu, W. (2004). "Erythropoietin to treat anaemia in patients with head and neck cancer... Henke M, Laszig R, Rübe C et al. Erythropoietin to treat head	Study design
Katodritou, E. D., M. A.; Zervas, K.; Terpos, E. (2009). "Update on the use of erythropoiesis-stimulating agents (ESAs) for the	Study design

management of anemia of multiple myeloma and lymphoma." Cancer Treatment Reviews 35: 738-743.	
Kelaidi, C. F., P. (2010). "Darbepoetin alfa in anemia of myelodysplastic syndromes: present and beyond." Expert Opinion on Biological Therapy 10: 605-614.	Study design
Kimel, M. L., Nancy K.; Mannix, Sally; Dixon, Julia (2008). "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 in Health 11: 57-75.	Study design
Klarenbach, S. M., B.; Reiman, T.; Reaume, M. N.; Lee, H.; Lloyd, A.; Wiebe, N.; Hemmelgarn, B.; Tonelli, M. (2010). "Economic Evaluation of Erythropoiesis-Stimulating Agents for Anemia Related to Cancer." Cancer 116: 3224-3232.	Study design
Kowalczyk, M. B., M.; Mikhailidis, D. P.; Rysz, J. (2011). "Erythropoietin update 2011." Medical Science Monitor 17: RA240-RA247.	Study design
Lambin, P. R., B. L.; van Mastrigt, G. A.; Van den Ende, P.; de Jong, J.; De Ruysscher, D. K.; Pijls-Johannesma, M. (2009). "Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer." Cochrane database of systematic reviews (Online): 006158.	Study design
Larsson, A. M. L., G.; Pahlman, S.; Albertsson, M. (2004). "Erythropoietin enhances response to treatment in patients with advanced breast cancer." Acta Oncologica 43: 594-597.	Study design
Leonard, R. C. U., M.; Von Koch, F. (2005). "Management of anaemia in patients with breast cancer: role of epoetin." Annals of Oncology 16: 817-824.	Study design
Littlewood, T. (2005). "Epoetin alfa (Eprex) and quality of life." Current Medical Research & Opinion 21 Suppl 2: S1-2.	Study design
Littlewood, T. C., G. (2005). "Epoetin alfa: basic biology and clinical utility in cancer patients." Expert Review of Anticancer Therapy 5: 947-956.	Study design
Lonnroth, C. S., Marie; Wang, Wenhua; Korner, Ulla; Daneryd, Peter; Nilsson, Ola; Lundholm, Kent (2008). "Survival and erythropoietin receptor protein in tumours from patients randomly treated with rhEPO for palliative care." Medical Oncology 25: 22-29.	Study design
Ludwig, H. C., Jeffrey; Osterborg, Anders; Vansteenkiste, Johan; Henry, David H.; Fleishman, Alex; Bridges, Ken; Glaspy, John A. (2009). "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." Journal of Clinic	Study design
Ludwig, H. W., U.; Van Belle, S. (2012). "Anaemia in elderly patients with cancer: Focus on chemotherapy-induced anaemia." Journal of Geriatric Oncology 3: 256-264.	Study design
Lyman, G. H. G., J. (2006). "Are there clinical benefits with early erythropoietic intervention for chemotherapy-induced anemia? A systematic review." Cancer 106: 223-233.	Study design
McKinney, M. A., Murat O. (2011). "Erythropoietin for oncology supportive care." Experimental Cell Research 317: 1246-1254.	Study design

Marec-Berard, P. C., P.; Kassab-Chahmi, D.; Casadevall, N.; Marchal, C.; Misset, J. L.; Ray-Coquard, I. (2009). "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." Pediatric Blood and Cancer 53: 7-12.	Study design
Melosky, B. L. (2008). "Erythropoiesis-stimulating agents: benefits and risks in supportive care of cancer." Current Oncology 15: S10-S15.	Study design
Metzger, N. L. F., K. E.; Voils, S. A. (2008). "A comparative review of erythropoiesis stimulating agents." Journal of Pharmacy Practice 21: 424-430.	Study design
Milano, M. S., Maurice (2007). "EPO in cancer anemia: benefits and potential risks." Critical Reviews in Oncology-Hematology 62: 119-125.	Study design
Miller, C. P. L., Kimberly A.; Valliant-Saunders, Karine; Kaiser, Joringel F.; Mattern, Dominik; Urban, Nicole; Henke, Michael; Blau, C. Anthony (2009). "Evaluating erythropoietin-associated tumor progression using archival tissues from a phase III clinical trial." Stem Cells 27: 2353-2361.	Study design
Minisini, A. A., G.; Bottomley, A.; Puglisi, F.; Piccart, M.; Biganzoli, L. (2004). "What is the effect of systemic anticancer treatment on cognitive function?" Lancet Oncology 5: 273-282.	Study design
Minton, O. R., Alison; Sharpe, Michael; Hotopf, Matthew; Stone, Patrick (2008). "A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue." Journal of the National Cancer Institute 100: 1155-1166.	Study design
Morere, J.-F. (2004). "Role of epoetin in the management of anaemia in patients with lung cancer." Lung Cancer 46: 149-156.	Study design
Morreale, A. P., Brian; DeLattre, Melissa; Boggie, Dan; Schaefer, Monica (2004). "Clinical and economic comparison of epoetin alfa and darbepoetin alfa." Current Medical Research & Opinion 20: 381-395.	Study design
Moyo, V. L., Patrick; Duh, Mei Sheng; Yektashenas, Behin; Mundle, Suneel (2008). "Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: a meta-analysis." Annals of Hematology 87: 527-536.	Study design
Mystakidou, K. P., Anna; Tsilika, Eleni (2007). "Erythropoietic growth factors for children with cancer: a systematic review of the literature." Current Medical Research & Opinion 23: 2841-2847.	Study design
Newland, A. M. B., C. D. (2008). "Tumor Progression Associated with Erythropoiesis-Stimulating Agents." Annals of Pharmacotherapy 42: 1865-1870.	Study design
Nowrousian, M. R. (2006). "Regarding "randomized comparison of epoetin alfa and darbepoetin alfa in anemic patients with cancer receiving chemotherapy"." Oncologist 11: 535-536; author reply 536-537.	Study design
Nowrousian, M. R. D., J.; Vaupel, P. (2008). "Erythropoiesis-stimulating agents: Favorable safety profile when used as indicated." Strahlentherapie Und Onkologie 184: 121-136.	Study design

Oberhoff, C. (2007). "Speed of haemoglobin response in patients with cancer: a review of the erythropoietic proteins." Supportive Care in Cancer 15: 603-611.	Study design
Ohashi, Y. U., Yukari; Fujisaka, Yasuhito; Sugiyama, Toru; Ohmatsu, Hironobu; Katsumata, Noriyuki; Okamoto, Rumiko; Saijo, Nagahiro; Hotta, Tomomitsu (2013). "Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: Individual patient data from Japanese randomized, placebo-controlled trials." Canc	Study design
Oster, H. S. H., Michael; Prutchi-Sagiv, Sara; Katz, Odelia; Neumann, Drorit; Mittelman, Moshe (2006). "Erythropoietin in clinical practice: current use, effect on survival, and future directions." Israel Medical Association Journal: Imaj 8: 703-706.	Study design
Oster, H. S. N., D.; Hoffman, M.; Mittelman, M. (2012). "Erythropoietin: The swinging pendulum." Leukemia Research 36: 939-944.	Study design
Osterborg, A. (2004). "New erythropoietic proteins: Rationale and clinical data." Seminars in Oncology 31: 12-18.	Study design
Ots, P. M. S. C., Concepcion Lopez; Perez, Aurora Rodriguez; de Dios Saez Garrido, Juan; Perez, Jose Ma Delgado (2008). "Darbepoetin versus epoetin alfa for the correction of anemia in cancer patients receiving radiotherapy or chemoradiotherapy treatment." Clinical Medicine Oncology 2: 393-399.	Study design
Parrish, C. O., R. G. (2012). "Waldenstrom macroglobulinemia with a durable clinical response to epoetin beta." Leukemia & Lymphoma 53: 1811-1813.	Study design
Pedrazzoli, P. C., S.; Lorusso, V.; Gamucci, T.; Secondino, S.; Silvestris, N. (2007). "Darbepoetin alpha coming of age." Anticancer Research 27: 4419-4424.	Study design
Pelegri, A. (2007). "Impact of erythropoietin treatment on the quality of life of oncologic patients." Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico 9: 645-651.	Study design
Petru, E. S., W.; Angleitner-Boubenizek, L.; Scholl, T.; Sevelda, P.; Benedicic, C.; Speiser, P.; Reinthaller, A. (2010). "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 und Frauenheilkunde 70: 646-657.	Study design
Pirker, R. (2004). "Darbepoetin alfa for the treatment of cancer-related anemia: an update." Expert Review of Anticancer Therapy 4: 735-744.	Study design
Pirker, R. (2007). "Safety considerations for erythropoietin treatment in patients with cancer." Expert Opinion on Drug Safety 6: 63-69.	Study design
Pirker, R. (2009). "Clinical use of erythropoiesis-stimulating agents: defining the benefits." Journal of Thoracic Oncology 4: S153-S155.	Study design
Pirker, R. (2009). "Erythropoiesis-stimulating agents in patients with cancer: update on safety issues." Expert Opinion on Drug	Study design

Safety 8: 515-522.	
Pronzato, P. J., J.; Mayordomo, J. (2006). "Epoetin beta therapy in patients with solid tumours." Critical Reviews in Oncology Hematology 58: 46-52.	Study design
Pujade-Lauraine, E. T., Clare (2005). "Once-weekly treatment of anemia in patients with cancer: a comparative review of epoetins." Oncology 68: 122-129.	Study design
Quercia, R. A. K., K. P.; Goldman, M. C. (2006). "Management of epoetin alpha use in the intensive care unit: a drug use evaluation." Formulary 41: 442-+.	Study design
Quirt, I. K., Michael; Couture, Felix; Turner, A. Robert; Noble, Michael; Burkes, Ronald; Dolan, Sean; Plante, Richard K.; Lau, Catherine Y.; Chang, Jose (2006). "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."	Study design
Rades, D. G., H.; Schild, S. E.; Kilic, E. (2008). "The impact of tumor expression of erythropoietin receptors and erythropoietin on clinical outcome of esophageal cancer patients treated with chemoradiation." International Journal of Radiation Oncology Biology Physics 71: 152-159.	Study design
Reed, S. D. R., Jasmina I.; Daniel, Davey B.; Mody, Samir H.; Forlenza, Jamie B.; McKenzie, R. Scott; Schulman, Kevin A. (2006). "Economic evaluation of weekly epoetin alfa versus biweekly darbepoetin alfa for chemotherapy-induced anaemia: evidence from a 16-week randomised trial." Pharmacoeconomics 24: 479-494.	Study design
Revicki, D. A. S., Donald; Vernon, Margaret; Rader, Michael; Tomita, Dianne; Viswanathan, Hema N. (2012). "Assessing the effect of darbepoetin alfa on patient-reported fatigue in chemotherapy-induced anemia in four randomized, placebo-controlled clinical trials." Quality of Life Research 21: 311-321.	Study design
Rigolin, G. M. C., G. (2005). "The role of rHuEpo in low-risk myelodysplastic syndrome patients." Leukemia & Lymphoma 46: 823-831.	Study design
Rizzo, J. D. (2005). "Evidence-based medicine: can it be applied to stimulation of erythropoiesis for patients with malignancy?" Bailliere's Best Practice in Clinical Haematology 18: 439-448.	Study design
Rizzo, J. D. B., M.; Hurley, P.; Seidenfeld, J.; Arcasoy, M. O.; Spivak, J. L.; Bennett, C. L.; Bohlius, J.; Evanchuk, D.; Goode, M. J.; Jakubowski, A. A.; Regan, D. H.; Somerfield, M. R. (2010). "American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult p	Study design
Rizzo, J. D. S., M. R.; Hagerty, K. L.; Seidenfeld, J.; Bohlius, J.; Bennett, C. L.; Cella, D. F.; Djulbegovic, B.; Goode, M. J.; Jakubowski, A. A.; Rarick, M. U.; Regan, D. H.; Lichtin, A. E. (2008). "Use of epoetin and darbepoetin in patients with cancer: 2007 American society of clinical oncology/American society of hematology clinical practice	Study design
Rosberg, J. H. B.-H., Rym; Cremieux, Pierre Y.; Fastenau,	Study design

John M.; Piech, Catherine Tak (2005). "Dose conversion and cost effectiveness of erythropoietic therapies in chemotherapy-related anaemia : a meta-analysis." Clinical Drug Investigation 25: 33-48.	
Ross, S. D. A., E.; Henry, D. H.; Seaman, C.; Sercus, B.; Goodnough, L. T. (2006). "Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature." Clinical Therapeutics 28: 801-831.	Study design
Saintigny, P. B., B.; Soria, L. C.; Bernaudin, J. F.; Callard, P. (2008). "Does erythropoietin promote tumor growth? Reply." Clinical Cancer Research 14: 1920-1921.	Study design
Santini, V. (2012). "Treatment of low-risk myelodysplastic syndrome: hematopoietic growth factors erythropoietins and thrombopoietins." Seminars in Hematology 49: 295-303.	Study design
Savona, M. R. S., S. M. (2008). "Erythropoietin-stimulating agents in oncology." Cancer Journal 14: 75-84.	Study design
Schrijvers, D. D. S., H.; Roila, F. (2010). "Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO Clinical Practice Guidelines for use." Annals of Oncology 21: v244-v247.	Study design
Schwartz, R. N. (2007). "Anemia in patients with cancer: Incidence, causes, impact, management, and use of treatment guidelines and protocols." American Journal of Health-System Pharmacy 64: S5-S13.	Study design
Siddiqui, M. A. A. K., G. M. (2006). "Darbepoetin alfa - A review of its use in the treatment of anaemia in patients with cancer receiving chemotherapy." Drugs 66: 997-1012.	Study design
Siddiqui, M. A. A. K., Gillian M. (2006). "Spotlight on darbepoetin alfa in the treatment of anemia in patients with cancer receiving chemotherapy.[Reprint of Drugs. 2006;66(7):997-1012; PMID: 16740021]." Biodrugs 20: 321-323.	Study design
Spaeth, D. (2008). "Epoetin beta once weekly: review of its efficacy and safety in patients with chemotherapy-induced anemia." Expert Review of Anticancer Therapy 8: 875-885.	Study design
Spano, J. P. K., D. (2008). "Treatment options for anemia, taking risks into consideration: Erythropoiesis-stimulating agents versus transfusions." Oncologist 13: 27-32.	Study design
Spivak, J. L. (2005). "The anaemia of cancer: Death by a thousand cuts." Nature Reviews Cancer 5: 543-555.	Study design
Stasi, R. A., Sergio; Littlewood, Timothy J.; Terzoli, Edmondo; Newland, Adrian C.; Provan, Drew (2005). "Management of cancer-related anemia with erythropoietic agents: doubts, certainties, and concerns." Oncologist 10: 539-554.	Study design
Steensma, D. P. L., C. L. (2005). "Erythropoietin use in cancer patients: A matter of life and death?" Journal of Clinical Oncology 23: 5865-5868.	Study design
Steensma, D. P. W., T. E. (2005). "Does treatment with recombinant human erythropoietin affect the survival of anemic patients with cancer?" Nature Clinical Practice Oncology 2: 444-445.	Study design

Straus, D. J. (2005). "Treatment of anemia with erythropoietic agents in patients with hematologic malignancies." Supportive Cancer Therapy 2: 215-224.	Study design
Straus, D. J. (2006). "Management of anemia in patients with hematologic malignancies." Oncology (Williston Park) 20: 8-11.	Study design
Szenajch, J. W., G.; Jeong, J. Y.; Szczylik, C.; Feldman, L. (2010). "The role of erythropoietin and its receptor in growth, survival and therapeutic response of human tumor cells. From clinic to bench - a critical review." Biochimica et Biophysica Acta - Reviews on Cancer 1806: 82-95.	Study design
Testa, U. (2010). "Erythropoietic stimulating agents." Expert Opinion on Emerging Drugs 15: 119-138.	Study design
Tonia, T. B., Julia (2011). "Ten years of meta-analyses on erythropoiesis-stimulating agents in cancer patients." Cancer Treatment & Research 157: 217-238.	Study design
Tonia T, Schwarzer G, Bohlius J. (2013). Cancer, meta-analysis and reporting biases: the case of erythropoiesis-stimulating agents. Swiss Medical Weekly. 143.	Study design
Tovari, J. P., R.; Timar, J.; Ostoros, G.; Kovacs, G.; Dome, B. (2008). "Erythropoietin in cancer: An update." Current Molecular Medicine 8: 481-491.	Study design
Vansteenkiste, J. H., Michael; Gascon, Pere; Bokemeyer, Carsten; Ludwig, Heinz; Vermorken, Jan; Hamilton, Lisa; Bridges, Ken; Pujol, Beatriz (2009). "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	Study design
Vansteenkiste, J. W., Isabelle (2005). "The use of darbepoetin alfa for the treatment of chemotherapy-induced anaemia." Expert Opinion on Pharmacotherapy 6: 429-440.	Study design
Vansteenkiste, J. W., Isabelle; Elliott, Steven; Glaspy, John; Hedenus, Michael (2013). "Chemotherapy-induced anemia: the story of darbepoetin alfa." Current Medical Research & Opinion 29: 325-337.	Study design
Vansteenkiste, J. G., John; Henry, David; Ludwig, Heinz; Pirker, Robert; Tomita, Dianne; Collins, Helen; Crawford, Jeffrey (2012). "Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: study-level and patient-level meta-analyses." Lung Cancer 76: 478-485.	Study design
Vansteenkiste J, Wauters I, Elliott S, Glaspy J, Hedenus M. (2013). Chemotherapy-induced anemia: the story of darbepoetin alfa. Curr Med Res Opin. 29, 325-337.	Study design
Vaupel, P. D., J.; Engert, A.; Fandrey, J.; Feyer, P.; Freund, M.; Jelkmann, W. (2005). "Effects of recombinant human erythropoietin (rHuEPO) on tumor control in patients with cancer-induced anemia." Onkologie 28: 216-221.	Study design
Vaupel, P. M., A.; Gemici, C.; Henke, M.; Pajonk, F.; Janecka, I. P. (2004). "Erythropoietin to treat anaemia in patients with head and neck cancer... Henke M, Laszik R, Rube C et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet 2003; 362:1255	Study design

Volgger, B. P., Edgar; Angleitner-Boubenizek, Lukas; Weigert, Monika; Reinthaller, Alexander; Lass, Harald; Stempfl, Anita; Gamper, Christian; Deibl, Martina; Marth, Christian (2008). "Erythropoetin beta twice weekly versus standard therapy in patients with gynaecological malignancies--a randomised Austrian AGO trial." Anticancer Research 28: 3977	Study design
Waltzman, R. J. (2004). "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 100: 1545-1546; author reply 1546.	Study design
Wauters, I. P., Karin; Vansteenkiste, Johan (2006). "Flexible dosing with Darbepoetin alfa for the treatment of chemotherapy-induced anemia." Therapeutics & Clinical Risk Management 2: 175-186.	Study design
Wauters, I. V., Johan (2009). "Darbepoetin alfa in the treatment of chemotherapy-induced anaemia." Expert Opinion on Biological Therapy 9: 221-230.	Study design
Wauters, I. V., Johan (2011). "Erythropoiesis-stimulating agents in cancer patients: reflections on safety." Expert Review of Clinical Pharmacology 4: 467-476.	Study design
Wauters, I. V., Johan (2012). "Darbepoetin alfa in the treatment of anemia in cancer patients undergoing chemotherapy." Expert Review of Anticancer Therapy 12: 1383-1390.	Study design
Wiffen, P. J. (2009). "Evidence-based pain management and palliative care in issue one for 2009 of the cochrane library." Journal of Pain and Palliative Care Pharmacotherapy 23: 166-168.	Study design
Ziegler, J. A. H., Jon D. (2006). "Current and future options for the treatment of chemotherapy-induced anaemia." Expert Opinion on Investigational Drugs 15: 1051-1065.	Study design
Duplicate	
Bohlius, J. L., S.; Schwarzer, G.; Seidenfeld, J.; Piper, M.; Bennet, C.; Engert, A. (2004). "Erythropoietin for patients with malignant disease." Cochrane Database of Systematic Reviews: CD003407.	Duplicate
Ohashi Y, Uemura, Yukari, Fujisaka, Yasuhito, Sugiyama, Toru, Ohmatsu, Hironobu, Katsumata, Noriyuki, Okamoto, Rumiko, Saijo, Nagahiro, Hotta, Tomomitsu. (2013). 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. 104, 481-485.	Duplicate
Schwartzberg, L. S. Y., L. K.; Senecal, F. M.; Charu, V.; Tomita, D.; Wallace, J.; Rossi, G. (2004). "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 9: 696-707.	Duplicate
Language	
Hernandez, M. A. L. L., E. U. (2008) "[Weekly beta erythropoietin high doses in patients with lymphoblastic acute	Language

leukemia in remission and under chemotherapy, its effects in transfusion requirements]." Medicina Interna de Mexico, 375-380.	
Liang, J. B., Q.; Shen, L. D.; Cheng, H. Y. (2009) "[The clinical study on recombinant human erythropoietin for chemotherapy-related anemia]." Tumor, 58-60.	Language
Meric, J. B. M., J. F. (2005). "Anemia in lung cancer patients." Bulletin Du Cancer 92: 439-444.	Language
Ray-Coquard, I. K.-C., D.; Casadevall, N.; Chastagner, P.; Marchal, C.; Marec-Berard, P.; Misset, J. L. (2008). "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)." Bulletin Du Cancer 95: 433-441.	Language
Ray-Coquard, I. K.-C., D.; Casadevall, N.; Chastagner, P.; Marchal, C.; Marec-Berard, P.; Misset, J. L. (2008). "Standards, Options: Recommendations for the use of erythropoiesis-stimulating agents (ESA : epoetin alfa, epoetin beta, darbepoetin) in anaemic patients with cancer: 2007 update." Oncologie 10: 160-166.	Language
Sanchez, C. O. G., G. P.; Sanchez, L. F. O. (2005). "Erythropoietin and cancer-related anaemia. Light and shade." Medicina Clinica 124: 186-195.	Language
Schipper, J. H., M. (2004) "[Erythropoietin in patients with head and neck carcinomas?]." Laryngo- rhino- otologie, 292-297 DOI: 10.1055/s-2004-814310.	Language
Spaeth, D. C., N.; Daouphars, M.; Marchal, C.; Marec-Berard, P.; Fabre, N.; Haugh, M. (2004). "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." Bulletin Du Cancer 91: 179-188.	Language
Zemelka, T. R., J.; Ziobro, M.; Michalczyk, A. (2007) "[Opinion on influence of erythropoietin on quality of life and survival in patients with advanced non-small cell lung cancer]." Wspolczesna Onkologia, 37-40.	Language
No usable data	
(2005). "Benefits of epoetin alfa for cancer patients' quality of life are confirmed after modelling to account for missing data." Current Medical Research & Opinion 21 Suppl 2: S6-8.	No usable data
Golshayan, A. R. J., T.; Maciejewski, J.; Fu, A. Z.; Bershadsky, B.; Kattan, M. W.; Kalaycio, M. E.; Sekeres, M. A. (2007). "Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes." British Journal of Haematology 137: 125-132.	No usable data
Coiffier, B. M., N.; Facon, T.; Beris, P. (2004) "Epoetin beta (NeoRecormon) once weekly or three-times weekly produces a rapid haemoglobin response in anaemic patients with lymphoproliferative malignancies." European Hematology Association Website - http://www.ehaweb.org.	Unobtainable
Costa, E. C. M., E. G.; Vilaplana, P. G. (2007). "Current approach in the use of erythropoietin." Cancer and	Unobtainable

Chemotherapy Reviews 2: 121-132.	
Littlewood, T. Z., M.; Schenkel, B. (2004) "Effects of population definitions and study endpoints on efficacy of epoetin alfa vs placebo in anemic patients with hematologic malignancies receiving chemotherapy." European Hematology Association Website - http://www.ehaweb.org.	Unobtainable
Vandebroek, A. A., S.; Gaede, B.; Smith, K.; Yao, B.; Schupp, M. (2006) "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 [Abstract No. 0029]." Haematologica, the hematology journal: abstract book.	Unobtainable
Wang, R. (2009). "Safety of erythropoiesis-stimulating agents: Lessons and limitations of meta-analyses." 2009 Annual Meeting Student Poster Abstract 43: 520.	Unobtainable
Unlicensed dose	
Aapro, M. L., Robert C.; Barnadas, Agusti; Marangolo, Maurizio; Untch, Michael; Malamos, Nikolaos; Mayordomo, Jose; Reichert, Dietmar; Pedrini, Jose Luiz; Ukarma, Lidia; Scherhag, Armin; Burger, Hans-Ulrich (2008). "Effect of once-weekly epoetin beta on survival in patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy: results of the Breast Cancer-Anemia and the Value of Erythropoietin (BRAVE) study." Journal of Clinical Oncology 26: 592-598	Unlicensed dose
Aapro, M. O., B.; Scherhag, A.; Burger, H. U. (2009). "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." British Journal of Cancer 101: 1961-1971.	Unlicensed dose
Berndt, E. K., Joel; McDermott, Anne; Xu, Xiao; Lee, Howard; Glaspy, John (2005). "Reductions in anaemia and fatigue are associated with improvements in productivity in cancer patients receiving chemotherapy." Pharmacoeconomics 23: 505-514.	Unlicensed dose
Blohmer, J. U. P., S.; Sehouli, J.; Boehmer, D.; Kolben, M.; Wurschmidt, F.; Petry, K. U.; Kimmig, R.; Elling, D.; Thomssen, C.; Von Minckwitz, G.; Mobus, V.; Hinke, A.; Kummel, S.; Budach, V.; Lichtenegger, W.; Schmid, P. (2011). "Randomized phase III trial of sequential adjuvant chemoradiotherapy with or without erythropoietin alfa in patients with high-risk cervical cancer: Results of the NOGGO-AGO intergroup study." Journal of Clinical Oncology 29: 3791-3797.	Unlicensed dose
Cabanillas, M. E. K., Hagop; Thomas, Deborah A.; Mattiuzzi, Gloria N.; Rytting, Michael E.; Bruera, Eduardo; Xiao, Lianchun; Bekele, B. Nebiyou; Foudray, Maria C.; Cortes, Jorge E. (2012). "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 118: 848-855.	Unlicensed dose

Chang, J. C., Felix; Young, Scott; McWatters, Kara-Lee; Lau, Catherine Y. (2005). "Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy.[Erratum appears in J Clin Oncol. 2005 Aug 1;23(22):5276]." Journal of Clinical Oncology 23: 2597-2605.	Unlicensed dose
Chang, J. C., Felix A.; Young, Scott D.; Lau, Catherine Y.; Lee McWatters, Kara (2004). "Weekly administration of epoetin alfa improves cognition and quality of life in patients with breast cancer receiving chemotherapy." Supportive Cancer Therapy 2: 52-58.	Unlicensed dose
Charu, V. B., Chandra P.; Gill, Ahmad N.; Bhatt, Mukesh; Tomita, Dianne; Rossi, Greg; Ben-Jacob, Ali (2007). "Efficacy and safety of every-2-week darbepoetin alfa in patients with anemia of cancer: a controlled, randomized, open-label phase II trial." Oncologist 12: 727-737.	Unlicensed dose
Christodoulou, C. D., U.; Aravantinos, G.; Koutras, A.; Samantas, E.; Karina, M.; Janinis, J.; Papakostas, P.; Skarlos, D.; Kalofonos, H. P.; Fountzilas, G. (2009). "Effects of epoetin-alpha on quality of life of cancer patients with solid tumors receiving chemotherapy." Anticancer Research 29: 693-702.	Unlicensed dose
Engert, A. J., A.; Haverkamp, H.; Villalobos, M.; Lohri, A.; Sokler, M.; Zijlstra, J.; Sturm, I.; Topp, M. S.; Rank, A.; Zenz, T.; Vogelhuber, M.; Nogova, L.; Borchmann, P.; Fuchs, M.; Flechtner, H. H.; Diehl, V. (2010). "Epoetin alfa in patients with advanced-stage Hodgkin's lymphoma: results of the randomized placebo-controlled GHSG HD15EPO trial." Journal of clinical oncology : official journal of the American Society of Clinical Oncology 28: 2239-2245.	Unlicensed dose
Fujisaka, Y. S., T.; Saito, H.; Nagase, S.; Kudoh, S.; Endo, M.; Sakai, H.; Ohashi, Y.; Saijo, N. (2011). "Randomised, phase III trial of epoetin-B to treat chemotherapy-induced anaemia according to the EU regulation." British journal of cancer 105: 1267-1272.	Unlicensed dose
Glaspy, J. V.-R., S.; Patel, R.; Bosserman, L.; Hu, E.; Lloyd, R. E.; Boccia, R. V.; Tomita, D.; Rossi, G. (2006). "Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia: The 20030125 study group trial." Journal of Clinical Oncology 24: 2290-2297.	Unlicensed dose
Gupta, S. S., P. K.; Bisth, S. S.; Bhatt, M. L.; Pant, M.; Gupta, R.; Singh, S.; Negi, M. P. (2009) "Role of recombinant human erythropoietin in patients of advanced cervical cancer treated "by chemoradiotherapy"." Cancer biology & therapy, 13-17.	Unlicensed dose
Hernandez, E. G., P.; Charu, V.; Dibenedetto, J.; Tomita, D.; Lillie, T.; Taylor, K. (2009) "Randomized, double-blind, placebo-controlled trial of every-3-week darbepoetin alfa 300 micrograms for treatment of chemotherapy-induced anemia." Current medical research and opinion, 2109-2120	Unlicensed dose
Leyland-Jones, B. S., Vladimir; Pawlicki, Marek; Pienkowski, Tadeusz; Tjulandin, Sergei; Manikhas, George; Makhson, Antoly; Roth, Anton; Dodwell, David; Baselga, Jose; Biakhov,	Unlicensed dose

Mikhail; Valuckas, Konstantinas; Voznyi, Edouard; Liu, Xiangyang; Vercammen, Els (2005). "Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study." Journal of Clinical Oncology 23: 5960-5972.	
Milroy, R. B., E.; van den Berg, P. M.; O'Brien, M. E. R.; Perez-Manga, G.; Georgoulias, V.; Greil, R.; Ramlau, R. (2011). "Effects of epoetin alfa on anemia and patient-reported outcomes in patients with non-small cell lung cancer receiving chemotherapy: Results of a European, multicenter, randomized, controlled study." European journal of Clinical and Medical Oncology 3: 49-56.	Unlicensed dose
Nagel, S. K., Olaf; Engel-Riedel, Walburga; Guetz, Sylvia; Schumann, Christian; Gieseler, Frank; Schuette, Wolfgang (2011). "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." Clinical Lung Cancer 12: 62-69.	Unlicensed dose
O'Shaughnessy, J. A. V., S. J.; Holmes, F. A.; Savin, M.; Jones, M.; Royall, D.; George, M.; Hoff, D. (2005) "Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy." Clinical breast cancer, 439-446.	Unlicensed dose
Pirker, R. R., R. A.; Schuette, W.; Zatloukal, P.; Ferreira, I.; Lillie, T.; Vansteenkiste, J. F. (2008). "Safety and efficacy of darbepoetin alfa in previously untreated extensive-stage small-cell lung cancer treated with platinum plus etoposide." Journal of Clinical Oncology 26: 2342-2349.	Unlicensed dose
Pronzato, P. C., E.; Cc,; Bols, A.; Moreno-Nogueira, J. A.; De Oliveira, C. F.; Barrett-Lee, P.; Ostler, P. J.; Rosso, R. (2010). "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 15: 935-943.	Unlicensed dose
Razzouk, B. I. H., Jeffrey D.; Hockenberry, Marilyn; Hinds, Pamela S.; Feusner, James; Williams, Denise; Rackoff, Wayne R. (2006). "Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy." Journal of Clinical Oncology 24: 3583-3589.	Unlicensed dose
Reed, S. D. R., Jasmina I.; Daniel, Davey B.; Fastenau, John M.; Williams, Denise; Schulman, Kevin A. (2005). "Early hemoglobin response and alternative metrics of efficacy with erythropoietic agents for chemotherapy-related anemia." Current Medical Research & Opinion 21: 1527-1533.	Unlicensed dose
Rosenzweig, M. Q. B., Catherine M.; Lucke, Joseph P.; Yasko, Joyce M.; Brufsky, Adam M. (2004). "The decision to prematurely terminate a trial of R-HuEPO due to thromboembolic events." Journal of Pain & Symptom Management 27: 185-190.	Unlicensed dose
Savonije, J. H. G., C. J.; Wormhoudt, L. W.; Giaccone, G.	Unlicensed dose

(2006) "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." The oncologist, 197-205	
Savonije, J. H., C. J. Groeningen, L. W. Wormhoudt and G. Giaccone (2006) "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." The oncologist, 206-216	Unlicensed dose
Savonije, J. H. V. G., C. J.; Van Bochove, A.; Honkoop, A. H.; Van Felius, C. L.; Wormhoudt, L. W.; Giaccone, G. (2005). "Effects of early intervention with epoetin alfa on transfusion requirement, hemoglobin level and survival during platinum-based chemotherapy: Results of a multicenter randomised controlled trial." European journal of cancer 41: 1560-1569.	Unlicensed dose
Schwartzberg, L. S. Y., Lorrin K.; Senecal, Frank M.; Charu, Veena; Tomita, Dianne; Wallace, Joel; Rossi, Greg (2004). "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 9: 696-707.	Unlicensed dose
Senecal, F. M. Y., Lorrin; Gabrail, Nashat; Charu, Veena; Tomita, Dianne; Rossi, Greg; Schwartzberg, Lee (2005). "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." Clinical Breast Cancer 6: 446-454.	Unlicensed dose
Thomas, G. A., S.; Hoebers, F. J.; Darcy, K. M.; Rodgers, W. H.; Patel, M.; Abulafia, O.; Lucci, J. A.; Begg, A. C. (2008) "Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer." Gynecologic oncology, 317-325	Unlicensed dose
Tsuboi, M. E., Kohji; Tobinai, Kensei; Ohashi, Yasuo; Saijo, Nagahiro (2009). "Weekly administration of epoetin beta for chemotherapy-induced anemia in cancer patients: results of a multicenter, Phase III, randomized, double-blind, placebo-controlled study." Japanese Journal of Clinical Oncology 39: 163-168.	Unlicensed dose
Wagner, L. M., C. A. Billups, W. L. Furman, B. N. Rao and V. M. Santana (2004). "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." Journal of Clinical Oncology 22: 1886-1893.	Unlicensed dose
Waltzman, R. C., Christopher; Justice, Glen R.; Fesen, Mark R.; Charu, Veena; Williams, Denise (2005). "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 10: 642-650.	Unlicensed dose
Wilkinson, P. M. A., M.; Lahousen, M.; Lind, M.; Kosmidis, P.	Unlicensed dose

(2006). "Epoetin alfa in platinum-treated ovarian cancer patients: Results of a multinational, multicentre, randomised trial." British journal of cancer 94: 947-954.	
Winquist, E. J., Jim A.; Moore, Malcolm J.; Nabid, Abdenour; Sathya, Jinka; Wood, Lori; Venner, Peter; Levine, Mark (2009). "Randomized, double-blind, placebo-controlled trial of epoetin alfa in men with castration-resistant prostate cancer and anemia." Journal of Clinical Oncology 27: 644-646.	Unlicensed dose
Witzig, T. E. S., Peter T.; Loprinzi, Charles L.; Sloan, Jeff A.; Novotny, Paul J.; Mailliard, James A.; Rowland, Kendrith M.; Alberts, Steven R.; Krook, James E.; Levitt, Ralph; Morton, Roscoe F. (2005). "Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy." Journal of Clinical Oncology 23: 2606-2617.	Unlicensed dose
Wright, J. R. U., Yee C.; Julian, Jim A.; Pritchard, Kathleen I.; Whelan, Timothy J.; Smith, Column; Szechtman, Barbara; Roa, Wilson; Mulroy, Liam; Rudinskas, Leona; Gagnon, Bruno; Okawara, Gord S.; Levine, Mark N. (2007). "Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia." Journal of Clinical Oncology 25: 1027-1032.	Unlicensed dose

16.2. Quality of life review: Excluded studies

Abstract only	
Epoetins and darbepoetin alfa in malignant disease. (2004). Drug and therapeutics bulletin. 42:21-23.	Abstract
Benefits of epoetin alfa for cancer patients' quality of life are confirmed after modelling to account for missing data. (2005). Current Medical Research & Opinion. 21 Suppl 2:S6-8.	Abstract
Meta-analysis of the effects of epoetin alfa treatment on quality of life in anaemic cancer patients. (2005). Current Medical Research & Opinion . 21 Suppl 2:S16-8.	Abstract
Treating anaemia with epoetin alfa is associated with improvements in quality of life in cancer patients receiving chemotherapy. (2005). Current Medical Research & Opinion. 21 Suppl 2:S9-11.	Abstract
Darbepoetin during RT boosts Hb level, with QOL benefit. (2006). Oncology News International.15:37-37.	Abstract
Retacrit (epoetin zeta) is an effective treatment for chemotherapy-induced anaemia. (2009). EJHP Practice.15:38.	Abstract
Anonymous. HIGHLIGHTS. (2009).Canadian Medical Association. Journal.180:1085-1085.	Abstract
Aapro MS, A.: Osterwalder, B.: Ukarma, L.: Burger, H. U. (2009) 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 .17:1036-1037.	Abstract

Addeo RC, Michele: Frega, Nicola: Del Prete, Salvatore. (2009). Two faces for Janus: recombinant human erythropoiesis-stimulating agents and cancer mortality. Expert Review of Hematology.2:513-5.	Abstract
Altintas SB, L.: Vandebroek, A.: Mossman, T.: Suto, T.: Gaede, B. (2007). 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-the Hematology Journal. 92:286-287.	Abstract
Antonadou DK, C.: Apostolou, D.: Coliarakis, N.: Athanasiou, H.: Papadopoulos, V.: Katsilieris, N.: Georgakopoulos, G.: Beroukas, C.: Karageorgis, P. (2005). A multicenter, open study evaluating the impact of darbepoetin alfa on anaemia and quality of life, in cancer patients undergoing radiotherapy. Ejc Supplements. 3:374-374.	Abstract
Auerbach MS, P. T.: Webb, R. T.: Averyanova, S.: Ciuleanu, T. E.: Cam, L.: Shao, J.: Lillie, T. (2008). Darbepoetin alfa (DA) 500MCG or 300MCG once every three weeks (Q3W) with or without iron in patients (PTS) with chemotherapy-induced anemia (CIA). 34th Congress of the European Society for Medical Oncology (ESMO) Stockholm Sweden . 19:3.	Abstract
Bennett, C. L. (2005). "The blue cross blue shield assessment technology review: summary of findings." Bailliere's Best Practice in Clinical Haematology 18: 423-431.	Abstract
Blumberg NH, J. M. (2004) Erythropoietin to treat anaemia in patients with head and neck cancer. The Lancet. 363:80-1	Abstract
Brett AS. (2008) An Erythropoietin-Stimulating Agent for Cancer-Related Anemia -- No Benefit. Journal Watch. General Medicine .	Abstract
Bruun KHN, 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). (2011) . 12th Annual NATA Symposium Dublin Ireland. 12:19-20.	Abstract
Burton MJD, D. G.: Rosenfeld, R. M. (2009). Extracts from The Cochrane Library: Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer. Otolaryngology - Head and Neck Surgery. 141:438-441.	Abstract
Caravita TS, A.: Montanaro, M.: Niscola, P.: Stasi, R.: Amadori, S.: De Fabritiis, P. (2009). High-dose epoetin alfa as induction treatment for severe anemia in multiple myeloma patients. International journal of hematology. 90:270-272.	Abstract
Charu, V. B., C.; Gill, A.; Bhatt, M.; Ben-Jacob, A.; Tomita, D.; Katz, D. (2005). A controlled, randomized, open-label study to evaluate the effects of every-2-week darbepoetin alfa for anemia of cancer. Journal of Supportive Oncology 3: 12-13.	Abstract
Charu VS, B.: Ben-Jacob, A.: Justice, G. R.: Maniam, A. S.: Rearden, T.: Tomita, D.: Rossi, G.(2005). Improvements in fatigue are associated with early treatment with darbepoetin alfa every 3 weeks in anemic patients receiving chemotherapy.	Abstract

Journal of Supportive Oncology. 3:14-15.	
Dintinjana RDN, A. D.: Dintinjana, M.: Petranovic, D.(2010). 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. 19:S234.	Abstract
Engert MH, H.: Borchmann, P.: Josting, A.: Fuchs, M.: Diehl, V. A (2009). 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. 94:438.	Abstract
Fagim MD, S.: Svetlana, D. (2011) Anaemic syndrome correction in patients receiving chemoradiation therapy with eprex for uterine cervical cancer. ESTRO Anniversary - GEC-ESTRO - EIOF - 11th Biennial London United Kingdom. 99:S308.	Abstract
Gabrilove JP, R.: Lyons, R. M.: Mushtaq, C.: Sekeres, M. A.: Lam, H.: Dreiling, L. (2007) The efficacy and safety of darbepoetin alfa for treating anemia in low-risk myelodysplastic syndrome patients: Results after 53/55 weeks. Journal of Supportive Oncology. 5:14-15.	Abstract
Gascon P. Intravenous iron : supplement or substitute to ESAs? (2012). 40th Congress of the International Society of Oncology and Biomarkers, ISOBM 2012 Jerusalem Israel . 33:S62-S63.	Abstract
Gregory SAB, D. W.: Vadhan-Raj, S.: Tomita, D. K.: Rossi, G.: Mirtsching, B. (2005) Efficacy of darbepoetin alfa in the treatment of chemotherapy-induced anemia in non-Hodgkin's lymphoma. Journal of Supportive Oncology. 3:24-25.	Abstract
Green D. Erythropoietin for Myelodysplastic Syndromes. Journal Watch. Oncology and Hematology 2009.	Abstract
Gupta, S. S., P. K.; Bhatt, M. L.; Pant, M. C.; Sundar, S.; Verma, J.; Negi Mp, S. (2011). "Clinical benefits of Epoetin beta in patients with advanced stage hormone refractory prostate cancer." 26th Annual Congress of the European Association of Urology, EAU Vienna Austria 10: 337.	Abstract
Hassan MAS, M. M. (2009). Phase II trial comparing darbepoetin alfa every 3-week versus weekly epoetin alfa for the treatment of chemotherapy-induced anemia. Journal of Clinical Oncology.Conference: 2009 Annual Meeting of the American Society of Clinical Oncology, ASCO Orlando. 27:e20724.	Abstract
Hellstrm-Lindberg E. (2010). Erythropoiesis-stimulating agents in myelodysplastic syndromes. Leukemia and Lymphoma. 51:1155-1156.	Abstract
Henry DHD, Naomi V.: Auerbach, Michael A. (2012).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. American Journal of Hematology. 87:308-10.	Abstract

Heras PH, A.: Mitsibounas, D. (2005). 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 Supplements. 3:373-373.	Abstract
Hinds, P. S. H., Marilyn; Feusner, James; Hord, Jeffrey D.; Rackoff, Wayne; Rozzouk, Bassem I. (2005). "Hemoglobin response and improvements in quality of life in anemic children with cancer receiving myelosuppressive chemotherapy." The Journal of Supportive Oncology 3: 10-11.	Abstract
Kaanders JHdK, van. (2004). Erythropoietin to treat anaemia in patients with head and neck cancer. The Lancet. 363:78-9; author reply 81-2.	Abstract
Katsumata, N. F., Y.; Sugiyama, T.; Goto, I.; Ohmatsu, H.; Okamoto, R.; Ohashi, Y.; Saijo, N.; Hotta, T.; Ariyoshi, Y. (2011). "Erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anemia and mortality: A meta-analysis of individual patient data from Japanese randomized trials." European Multidisciplinary Cancer Congres	Abstract
Katsumata NF, Y.: Saijo, N.: Ohashi, Y. (2005). Once-weekly epoetin beta improves hemoglobin and quality of life in anemic cancer patients receiving chemotherapy. Ejc Supplements. 3:375-375.	Abstract
Leyland-Jones BM, S. (2004). Erythropoietin to treat anaemia in patients with head and neck cancer. The Lancet. 363:80-2.	Abstract
Mel JRS, A.: Rodriguez, C. A.: Alegre, A.: Gonzalez, A.: Cassinello, J.: Montesinos, J.: Gasquet, J. A.: Sanchez, J.: Saigi, E. Title: Weekly fixed dose of darbepoetin alfa (DA) is efficacious and improves health-related quality of life in patients with chemotherapy induced anemia (CIA). (2006). On behalf of the AMG-DAR-2002-01 study group. Annals of Oncology 17:292-293.	Abstract
Mhaskar RW, H.: Kumar, A.: Miladinovic, B.: Djulbegovic, B.(2010). Role of iron supplementation to erythropoiesis stimulating agents in the management of chemotherapy-induced anemia in cancer patients: A systematic review and meta-analysis. 52nd Annual Meeting of the American Society of Hematology, ASH 2010 Orlando, FL United States. 116	Abstract
Michallet MG, K.: Morisset, S.: Sobh, M.: Chelghoum, Y.: Thomas, X.: Labussiere, H.: Ducastelle, S.: Barraco, F.: Vial, J.: Renzullo, C.: Paillet, C.: Pivot, C.: Straaten, P. B. V.: Denis, A.: Termoz, A.: Nicolini, F. E.: Jaisson-Hot, I. (2010). 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. 52nd Annual Meeting of the American Society of Hematology, ASH 2010 Orlando, FL United States .	Abstract
Michallet MG, K.: Morisset, S.: Sobh, M.: Ducastelle, S.: Chelghoum, Y.: Barraco, F.: Thomas, X.: Labussiere, H.: Vial, J.: Renzullo, C.: Paillet, C.: Pivot, C.: Badol-Van Straaten, P.: Denis, A.: Termoz, A.: Nicolini, F.: Jaisson-Hot, I. (2011). Erythropoietin use in patients undergoing allogeneic HSCT	Abstract

does not impact on quality of life, reduces red blood cells transfusions without any survival effect. European Group for Blood and Marrow Transplantation, EBMT 2011 Paris France. 46:S53-S54.	
Nitz, U. O., C.; Reimer, T.; Schumacher, C.; Hackmann, J.; Warm, M.; Uleer, C.; Runde, V.; Gluz, O.; Zuna, I. (2009). "Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: A safety analysis from the phase III ARA plus trial." 31st Annual San Antonio Breast Cancer Symposium San Antonio, TX United States 69 (2 Suppl. S.	Abstract
Oliva ENL, R.: Danova, M.: Vincelli, I.: Rovati, B.: Ronco, F.: Carmosino, I.: Specchia, G.: Breccia, M.: Impera, S.: Attolico, I.: Nobile, F. (2006) Darbepoetin for the treatment of anemia of myelodysplastic syndromes: Efficacy and improvements in quality of life. Blood . 108:754A-754A.	Abstract
Oliva ENL, R.: Danova, M.: Specchia, G.: Impera, S.: Rovati, B.: Vincelli, I.: Liso, V.: Alimena, G.: Ronco, F.: Carmosino, I.: Risitano, A.: Breccia, M.: Nobile, F. (2007) Darbepoetin for the treatment of anemia of myelodysplastic syndromes: efficacy and quality of life. Leukemia Research . 31:S117-S118.	Abstract
Ordonez AG-B, M.: De Castro, J.: Isla, D.: Sanchez, A.: Arrivi, A.: Manzano, J. (2005) Epoetin beta (NeoRecormon (R)) prevents anaemia and improves quality of life in lung cancer patients receiving platinum-based chemotherapy. Lung Cancer. 49:S339-S339.	Abstract
Patrick DG, D. D.: Zagari, M. J. (2005). Improvements in quality of life associated with epoetin alfa treatment are clinically, as well as statistically, significant. Current Medical Research and Opinion, Supplement . 21:S3-S5.	Abstract
Ross SDA, I. E.: Henry, D.: Seaman, C.: Sercus, B.: Goodnough, L. T. (2007). Clinical benefits and risks associated eith epoetin (alfa/beta) and darbepoetin alfa in patients with chemotherapy-induced anemia: A systematic review of the literature. Journal of Supportive Oncology. 5:20-21.	Abstract
Sakai HS, N.: Ohashi, Y. (2004). 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. Annals of Oncology.15:219-219.	Abstract
Steensma, D. P. D., S. R.; Novotny, P. J.; Sloan, J. A.; Johnson, D. B.; Anderson, D. M.; Mattar, B. I.; Moore, D. F.; Nikcevich, D.; Loprinzi, C. L. (2009). "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 A	Abstract
Suzuki YT, Y.: Okamoto, R.: Nakagawa, K.: Ando, K.: Iwata, H.: Tobinai, K.: Tanigawara, Y.: Hotta, T.: Saijo, N. Randomized, placebo-controlled phase II study of darbepoetin alfa (DA) administered every three weeks (Q3W) in patients with chemotherapyinduced anemia (CIA). (2008). 34th Congress of the European Society for Medical Oncology (ESMO) Stockholm Sweden.19:277.	Abstract

Wilkinson PMA, M.: Lahousen, M.: Lind, M.: Kosmidis, P. (2006). Epoetin alfa in platinum-treated ovarian cancer patients: Results of a multinational, multicentre, randomised trial. British journal of cancer. 94:947-954.	Abstract
Winquist EJ, Jim A.: Moore, Malcolm J.: Nabid, Abdenour: Sathya, Jinka: Wood, Lori: Venner, Peter: Levine, Mark. (2009) Randomized, double-blind, placebo-controlled trial of epoetin alfa in men with castration-resistant prostate cancer and anemia. Journal of Clinical Oncology. 27:644-6.	Abstract
Witzig TES, P. T.: Loprinzi, C. L.: Spigel, D. R. Weekly erythropoietin improves anemia associated with cancer treatment. Journal of Clinical Outcomes Management 2004;11:751-752.	Abstract
Yoshizaki AK, S.: Sugiyama, T.: Goto, I.: Saito, H.: Ariyoshi, Y.: Saijo, N.: Ohashi, Y. (2010) 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. 21:385.	Abstract
Youssef, L. A. H., D. H.; Sulaiman, S. (2011). "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 2011 San Diego, CA United States 118 (21.	Abstract
Population	
Abdelrazik, N. F., Manal (2007). "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 12: 533-541.	Population ALL
Casadevall ND, P.: Dubois, S.: Hemery, F.: Lepage, E.: Quarre, M. C.: Damaj, G.: Giraudier, S.: Guerci, A.: Laurent, G.: Dombret, H.: Chomienne, C.: Ribrag, V.: Stamatoullas, A.: Marie, J. P.: Vekhoff, A.: Maloisel, F.: Navarro, R.: Dreyfus, F.: Fenaux, P. (2004). 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. 104:321-327.	Population
Carroll JKK, S.: Mustian, K. M.: Roscoe, J. A.: Morrow, G. R. (2007). Pharmacologic treatment of cancer-related fatigue. Oncologist. 12:43-51.	Population
Lindholm ED, Peter: Korner, Ulla: Hyltander, Anders: Fouladiun, Marita: Lundholm, Kent. (2004). Effects of recombinant erythropoietin in palliative treatment of unselected cancer patients. Clinical Cancer Research. 10:6855-64.	Population
Hoskin PJR, M.: Slevin, N.: Morgan, D.: Harrington, K.: Gaffney, C. (2009). 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. Journal of Clinical Oncology . 27:5751-5756.	Population
Mystakidou KK, C.: Katsouda, E.: Parpa, E.: Kouskouni, E.:	Population

Chondros, C.: Tsiatas, M. L.: Vlahos, L. (2005). Evaluation of epoetin supplemented with oral iron in patients with solid malignancies and chronic anemia not receiving anticancer treatment. Anticancer Research . 25:3495-3500.	
Norager CBJ, M. B.: Madsen, M. R.: Qvist, N.: Laurberg, S. (2006). Effect of darbepoetin alfa on physical function in patients undergoing surgery for colorectal cancer - A randomized, double-blind, placebo-controlled study. Oncology. 71:212-220.	Population
Oliansky DMA, J. H.: Bennett, J. M.: Deeg, H. J.: Engelhardt, C.: Heptinstall, K. V.: de Lima, M.: Gore, S. D.: Potts, R. G.: Silverman, L. R.: Jones, R. B.: McCarthy,, Jr.: P.L,: Hahn, T. (2009)The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Myelodysplastic Syndromes: An Evidence-Based Review. Biology of Blood and Marrow Transplantation. 15:137-172.	Population
Smith REA, M. S.: Ludwig, H.: Pinter, T.: Smakal, M.: Ciuleanu, T. E.: Chen, L.: Lillie, T.: Glaspy, J. A. (2008). 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. Journal of Clinical Oncology. 26:1040-1050.	Population
Intervention	
Blair SB, W. A.: Podbelewicz-Schuller, Y.: Mortimer, J. E. (2008). Correlation Between Hemoglobin and Fatigue in Women Undergoing Adjuvant Chemotherapy Without Erythropoietin-Stimulating-Agent Support. Clinical Breast Cancer . 8:522-526.	Intervention
Berndt EK, J.: McDermott, A.: Xu, X.: Lee, H.: Glaspy, J. (2005). Reductions in anaemia and fatigue are associated with improvements in productivity in cancer patients receiving chemotherapy. PharmacoEconomics. 23:505	Intervention
Cheng ZW, J. L.: Chen, J. F. (2009). Clinical Observation on the Treatment of Male Neoplastic Anemia with Yixuesheng Capsule Combined with Recombination Human Erythropoietin. Chinese Journal of Integrative Medicine. 15:63-65.	Intervention
Gascon PP, R.: Del Mastro, L.: Durrwell, L. (2010). 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. Annals of Oncology. 21:2029-2039.	Intervention
Krzakowski, M. (2008). "Epoetin Delta: Efficacy in the Treatment of Anaemia in Cancer Patients Receiving Chemotherapy." Clinical oncology 20: 705-713.	Intervention
Comparator	
Auerbach MB, Harold: Trout, J. Richard: McIlwain, Marilyn: Ackerman, Alan: Bahrain, Huzefa: Balan, Stefan: Barker, Lance: Rana, Jeevindra. (2004). Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. Journal of Clinical Oncology.22:1301-7.	Comparator

Balleari ER, Edoardo: Clavio, Marino: Congiu, Angela: Gobbi, Marco: Grosso, Marco: Secondo, Vincenzo: Spriano, Mauro: Timitilli, Silvana: Ghio, Riccardo. (2006). 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. Annals of Hematology. 85:174-80.	Comparator
Bastit LV, A.: Altintas, S.: Gaede, B.: Pinter, T.: Suto, T. S.: Mossman, T. W.: Smith, K. E.: Vansteenkiste, J. F. (2008). 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. Journal of Clinical Oncology. 26:1611-1618.	Comparator
Canon JLV, J.: Bodoky, G.: Mateos, M. V.: Bastit, L.: Ferreira, J.: Rossi, G.: Amado, R. G. (2006). Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. Journal of the National Cancer Institute. 98:273-284.	Comparator
Courneya KSJ, Lee W.: Peddle, Carolyn J.: Sellar, Christopher M.: Reiman, Tony: Joy, Anil A.: Chua, Neil: Tkachuk, Linda: Mackey, John R. (2008). Effects of aerobic exercise training in anemic cancer patients receiving darbepoetin alfa: a randomized controlled trial. Oncologist. 13:1012-20.	Comparator
Crawford JR, Francisco: Perry, Michael C.: Belani, Chandra: Williams, Denise. (2007). 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. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2:210-20.	Comparator
Glaspy JH, D.: Patel, R.: Tchekmedyian, D.: Applebaum, S.: Berdeaux, D.: Lloyd, R.: Berg, R.: Austin, M.: Rossi, G. (2005). 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. European Journal of Cancer. 41:1140-1149.	Comparator
Gupta SS, P. K.: Bhatt, M. L.: Pant, M. C.: Sundar, S.: Verma, J.: Paul, S.: Kumar, D.: Shah, A.: Gupta, R.: Negi, M. P. (2010). Clinical benefits of two different dosing schedules of recombinant human erythropoietin in anemic patients with advanced head and neck cancer. Bioscience trends. 4:267-272.	Comparator
Justice GK, J. F.: Jadeja, J.: Campos, L.: Weick, J.: Chen, C. F.: Heatherington, A. C.: Amado, R. G. (2005). A randomized, multicenter study of subcutaneous and intravenous darbepoetin alfa for the treatment of chemotherapy-induced anemia. Annals of Oncology. 16:1192-1198.	Comparator
Larsson AML, G.: Pahlman, S.: Albertsson, M. (2004). Erythropoietin enhances response to treatment in patients with	Comparator

advanced breast cancer [2]. Acta Oncologica. 43:594-597.	
Steensma DPS, J. A.: Dakhil, S. R.: Dalton, R.: Kahanic, S. P.: Prager, D. J.: Stella, P. J.: Rowland,, Jr.: K.M,: Novotny, P. J.: Loprinzi, C. L. (2011). Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. Journal of Clinical Oncology. 29:97-105.	Comparator
Outcome	
Bell DG, D.: Gurney, H.: Dalley, D.: Blackwell, T.: Fox, R.: Jeffery, M. (2008). Outcomes and predicting response in anaemic chemotherapy patients treated with epoetin alfa. A multicentre, 4-month, open-label study in Australia and New Zealand. Internal Medicine Journal. 38:751-7.	Outcome
Bennett CLS, S. M.: Djulbegovic, B.: Samaras, A. T.: Blau, C. A.: Gleason, K. J.: Barnato, S. E.: Elverman, K. M.: Courtney, D. M.: McKoy, J. M.: Edwards, B. J.: Tigue, C. C.: Raisch, D. W.: Yarnold, P. R.: Dorr, D. A.: Kuzel, T. M.: Tallman, M. S.: Trifilio, S. M.: West, D. P.: Lai, S. Y.: Henke, M.(2008). Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. Jama-Journal of the American Medical Association. 299:914-924.	Outcome
Bohlius JT, S.: Weingart, O.: Schwarzer, G.: Brillant, C.: Clarke, M. J.: Djulbegovic, B.: Piper, M.: Rades, D.: Seidenfeld, J.: Somerfield, M.: Steensma, D.: Schumacher, M.: Engert, A.: Egger, M. (2008). Erythropoietin or Darbepoetin for patients with cancer - Meta-analysis based on individual patient data. Cochrane Database of Systematic Reviews.	Outcome
Bohlius JW, J.: Seidenfeld, J.: Piper, M.: Schwarzer, G.: Sandercock, J.: Trelle, S.: Weingart, O.: Bayliss, S.: Djulbegovic, B.: Bennett, C. L.: Langensiepen, S.: Hyde, C.: Engert, A. (2006). Recombinant human erythropoietins and cancer patients: Updated meta-analysis of 57 studies including 9353 patients. Journal of the National Cancer Institute. 98:708-714.	Outcome
Bohlius JL, S.: Schwarzer, G.: Seidenfeld, J.: Piper, M.: Bennett, C.: Engert, A. (2005). Recombinant human erythropoietin and overall survival in cancer patients: Results of a comprehensive meta-analysis. Journal of the National Cancer Institute. 97:489-498.	Outcome
Bohlius JS, Kurt: Brillant, Corinne: Schwarzer, Guido: Trelle, Sven: Seidenfeld, Jerome: Zwahlen, Marcel: Clarke, Michael: Weingart, Olaf: Kluge, Sabine: Piper, Margaret: Rades, Dirk: Steensma, David P.: Djulbegovic, Benjamin: Fey, Martin F.: Ray-Coquard, Isabelle: Machtay, Mitchell: Moebus, Volker: Thomas, Gillian: Untch, Michael: Schumacher, Martin: Egger, Matthias: Engert, Andreas. (2009). Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials.[Erratum appears in Lancet. 373:1532-42.	Outcome
Bohlius JS, K.: Brillant, C.: Schwarzer, G.: Trelle, S.:	Outcome

Seidenfeld, J.: Zwahlen, M.: Clarke, M. J.: Weingart, O.: Kluge, S.: Piper, M.: Napoli, M.: Rades, D.: Steensma, D.: Djulbegovic, B.: Fey, M. F.: Ray-Coquard, I.: Moebus, V.: Thomas, G.: Untch, M.: Schumacher, M.: Egger, M.: Engert, A. (2009). Erythropoietin or Darbepoetin for patients with cancer - Meta-analysis based on individual patient data. Cochrane Database of Systematic Reviews.	
Devon KMM, Robin S. Pre and peri-operative erythropoietin for reducing allogeneic blood transfusions in colorectal cancer surgery. Cochrane Database of Systematic Reviews 2009:CD007148.	Outcome
Duh MSW, J. R.: White, L. A.: Lefebvre, P.: Dreenberg, P. E. (2008). Management of anaemia - A critical and systematic review of the cost effectiveness of erythropoiesis-stimulating agents. Pharmacoeconomics. 26:99-120.	Outcome
Henry DHD, N. V.: Auerbach, M.: Tchekmedyian, S.: Laufman, L. R. (2007). Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist. 12:231-242.	Outcome
Henry DHG, L. N.: Charu, V.: Wilhelm, F. E.: Williams, D.: Xie, J.: Woodman, R. C. (2006). Randomized, open-label comparison of epoetin alfa extended dosing (80000U Q2W) vs weekly dosing (40000U QW) in patients with chemotherapy-induced anemia. Current Medical Research and Opinion. 22:1403-1413.	Outcome
Machtay MP, T. F.: Suntharalingam, M.: Shenouda, G.: Hershock, D.: Stripp, D. C.: Cmelak, A. J.: Schulsinger, A.: Fu, K. K. (2007). Radiotherapy with or without erythropoietin for anemic patients with head and neck cancer: A randomized trial of the radiation therapy oncology group (RTOG 99-03). International Journal of Radiation Oncology Biology Physics . 69:1008-1017.	Outcome
Moyo VL, P.: Duh, M. S.: Yektashenas, B.: Mundle, S. (2008). Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: a meta-analysis. Annals of Hematology. 87:527-536.	Outcome
Reed SDR, J. I.: Daniel, D. B.: Fastenau, J. M.: Williams, D.: Schulman, K. A. (2005). Early hemoglobin response and alternative metrics of efficacy with erythropoietic agents for chemotherapy-related anemia. Current Medical Research and Opinion. 21:1527-1533.	Outcome
Reed SDR, J. I.: Daniel, D. B.: Mody, S. H.: Forlenza, J. B.: McKenzie, R. S.: Schulman, K. A. (2006). Economic evaluation of weekly epoetin alfa versus biweekly darbepoetin alfa for chemotherapy-induced anaemia - Evidence from a 16-week randomised trial. Pharmacoeconomics. 24:479-494.	Outcome
Rosenzweig MQB, Catherine M.: Lucke, Joseph P.: Yasko, Joyce M.: Brufsky, Adam M. (2004). The decision to prematurely terminate a trial of R-HuEPO due to thromboembolic events. Journal of Pain & Symptom Management. 27:185-90.	Outcome

Schwartzberg LSY, L. K.: Senecal, F. M.: Charu, V.: Tomita, D.: Wallace, J.: Rossi, G. (2004). 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 . 9:696-707.	Outcome
Schwartzberg LY, 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. (2005) Journal of Supportive Oncology.3:30-31.	Outcome
Schwartzberg LSY, L. K.: Senecal, F. M.: Charu, V.: Tomita, D.: Wallace, J.: Rossi, G. (2004). 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. 9:696-707.	Outcome
Senecal FMY, L.: Gabrail, N.: Charu, V.: Tomita, D.: Rossi, G.: Schwartzberg, L. (2005) 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. Clinical Breast Cancer. 6:446-454.	Outcome
Strauss HGH, G.: Dunst, J.: Hayward, C. R. W.: Burger, H. U.: Scherhag, A.: Koelbl, H. Effects of anemia correction with epoetin beta in patients receiving radiochemotherapy for advanced cervical cancer. International Journal of Gynecological Cancer 2008;18:515-524.	Outcomes
Tonia TB, J. (2011). Ten Years of Meta-analyses on Erythropoiesis-Stimulating Agents in Cancer Patients. Hematopoietic Growth Factors in Oncology. Volume 157,217-238.	Outcomes
Study design	
Aapro, M. C., B.; Dunst, J.; Osterborg, A.; Burger, H. U. (2006). "Effect of treatment with epoetin beta on short-term tumour progression and survival in anaemic patients with cancer: A meta-analysis." British Journal of Cancer 95: 1467-1473.	Study design
Aapro MSD, David C.: Blasi, Michael: Sarokhan, Brenda: Ahmed, Fawzia: Woodman, Richard C. (2006). Epoetin alfa increases hemoglobin levels and improves quality of life in anemic geriatric cancer patients receiving chemotherapy. Supportive Care in Cancer. 14:1184-94.	Study design
Aapro MS, A.: Burger, H. U. (2008). 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. British Journal of Cancer. 99:14-22.	Study design
Aapro, M. O., B.; Scherhag, A.; Burger, H. U. (2009). "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." British Journal of Cancer 101: 1961-	Study design

1971.	
Ariganello OM, Andrea: Di Molfetta, Michele: Diana, Francesco: Beccaglia, Patrizia: Cortesi, Enrico: De Marinis, Filippo. (2004). A new induction schedule of epoetin alfa 40.000 IU in anemic patients with advanced lung cancer. Lung Cancer. 46:119-24.	Study design
Azzara AC, G.: Galimberti, S.: Barate, C.: Fazzi, R.: Cervetti, G.: Petrini, M. (2011). 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. American Journal of Hematology. 86:762-767.	Study design
Badzek SC, Zvonimir: Krajina, Zdenko: Plestina, Stjepko: Golubic-Cepulic, Branka: Radman, Ivo. (2008). Treatment of cancer-related anemia. Collegium Antropologicum. 32:615-22.	Study design
Beer TMB, Misty: Birt, Karlee: Higano, Celestia S. (2007). Darbepoetin alfa administered every 4 weeks for anemia in patients with advanced prostate cancer. Clinical Genitourinary Cancer. 5:329-33.	Study design
Boccia RL, Tom: Tomita, Dianne: Balducci, Lodovico. (2007). The effectiveness of darbepoetin alfa administered every 3 weeks on hematologic outcomes and quality of life in older patients with chemotherapy-induced anemia. Oncologist. 12:584-93.	Study design
Bogdanos JK, D.: Milathianakis, K.: Repousis, P.: Chloraki-Bobota, A.: Majed, H.: Pagalou-Thoua, E.: Tsintavis, A.: Koutsilieris, M. (2004). Epoetin beta (NeoRecormon (R)) corrects anaemia in patients with hormone-refractory prostate cancer and bone metastases. Anticancer Research . 24:1957-1961.	Study design
Boogaerts, M. O., C.; Ten Bokkel Huinink, W.; Nowrousian, M. R.; Hayward, C. R. W.; Burger, H. U. (2006). "Epoetin beta (NeoRecormon) therapy in patients with solid tumours receiving platinum and non-platinum chemotherapy: a meta-analysis." Anticancer Research 26: 479-484.	Study design
Bohlius, J. W., Jayne; Seidenfeld, Jerome; Piper, Margaret; Schwarzer, Guido; Sandercock, Josie; Trelle, Sven; Weingart, Olaf; Bayliss, Sue; Djulbegovic, Benjamin; Bennett, Charles L.; Langensiepen, Simon; Hyde, Chris; Engert, Andreas (2006). "Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients." Journal of the National Cancer Institute 98: 708-714.	Study design
Boulaamane L, Goncalves, A., Boutayeb, S., Viens, P., M'Rabti, H., Bertucci, F., Errihani, H. (2013). Prognostic impact of the combination of erythropoiesis-stimulating agents to cancer treatment: Literature review. Supportive Care in Cancer. 21, 2359-2369.	Study design
Burstein HJP, L. M.: Keshaviah, A.: Doherty, J.: Partridge, A. H.: Schapira, L.: Ryan, P. D.: Younger, J.: Harris, L. N.: Moy, B.: Come, S. E.: Schumer, S. T.: Bunnell, C. A.: Haldoupis, M.: Gelman, R.: Winer, E. P. (2005). Efficacy of pegfilgrastim and darbepoetin alfa as hematopoietic support for dose-dense	Study design

every-2-week adjuvant breast cancer chemotherapy. Journal of Clinical Oncology. 23:8340-8347.	
Cacic DLH, Tor: Seghatchian, Jerard. Anemia treatment of lymphoproliferative malignancies with erypoiesis: An overview of state of the art. (2013). Transfusion & Apheresis Science . 48:277-81.	Study design
Caocci GLN, G.: Efficace, F. (2009). Health-related quality of life and symptom assessment in patients with myelodysplastic syndromes. Expert Review of Hematology. 2:69-80.	Study design
Cella DV, Hema N.: Hays, Ron D.: Mendoza, Tito R.: Stein, Kevin D.: Pasta, David J.: Foreman, Aimee J.: Vadhan-Raj, Saroj: Kallich, Joel D. (2008). Development of a fatigue and functional impact scale in anemic cancer patients receiving chemotherapy. Cancer. 113:1480-8.	Study design
Cella DK, J.: McDermott, A.: Xu, X. (2004). The longitudinal of hemoglobin, fatigue and quality of life in anemic cancer patients: Results from five randomised clinical trials. Annals of Oncology. 15:979-986.	Study design
Eton DTC, D. (2011). Do erythropoietic-stimulating agents relieve fatigue? A review of reviews. Hematopoietic Growth Factors in Oncology.Cancer Treatment and Research. 157:181-194.	Study design
Cersosimo, R. J. J., Daniel R. (2006). "Epoetin alfa versus darbepoetin alfa in chemotherapy-related anemia." Annals of Pharmacotherapy 40: 58-65; quiz 169-170.	Study design
Chu EE, Lawrence H.: Lefebvre, Patrick. (2006). Clinical benefits of once-weekly epoetin alfa in anemic patients with colorectal cancer receiving chemotherapy. The Journal of Supportive Oncology. 4:243-50.	Study design
Corapcioglu FA, Gorkem: Basar, Evic Z.: Demirel, Atalay: Oncel, Selim: Mutlu, Ajda. (2008). Recombinant human erythropoietin beta therapy: an effective strategy to reduce transfusion requirement in children receiving anticancer treatment. Pediatric Hematology & Oncology . 25:509-21.	Study design
Cornes, P. C., B.; Zambrowski, J. J. (2007). "Erythropoietic therapy for the treatment of anemia in patients with cancer: a valuable clinical and economic option." Current Medical Research and Opinion 23: 357-368.	Study design
Couture, F. T., A. R.; Melosky, B.; Xiu, L.; Plante, R. K.; Lau, C. Y.; Quirt, I. (2005). "Prior red blood cell transfusions in cancer patients increase the risk of subsequent transfusions with or without recombinant human erythropoietin management." Oncologist 10: 63-71.	Study design
Durmaz OD, Metin: Sevinir, Betul. Recombinant human erythropoietin : the effect of weekly dosing on anemia, quality of life, and long-term outcomes in pediatric cancer patients. Pediatric Hematology & Oncology 2011;28:461-8.	Study design
Esquerdo GL, Cristina: Cervera, Jose Manuel: Orts, David: Juarez, Asuncion: Carrato, Alfredo. (2011). 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	Study design

scores and change in haemoglobin level. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico. 13:341-7.	
Fagnoni PL, S.: Chaigneau, L.: Briaud, S.: Schmitt, B.: Merrouche, Y.: Pivot, X.: Woronoff-Lemsi, M. C. (2006). Clinical and economic impact of epoetin in adjuvant-chemotherapy for breast cancer. Supportive Care in Cancer . 14:1030-1037.	Study design
Folloder, J. (2005). "Effects of darbepoetin alfa administered every two weeks on hemoglobin and quality of life of patients receiving chemotherapy." Oncology Nursing Forum 32: 81-89.	Study design
Gascon, P. (2005). "Evaluating erythropoietic agents for the treatment of anaemia in the oncology setting." European Journal of Cancer 41: 2601-2612.	Study design
Gaston KEK, E.: Moore, D. T.: Pruthi, R. S. (2006) The use of erythropoietin in patients undergoing radical prostatectomy: Effects on hematocrit, transfusion rates and quality of life. Urologia Internationalis. 77:211-215.	Study design
Glaspy, J. A. (2011). "Randomized controlled trials of the erythroid-stimulating agents in cancer patients." Hematopoietic Growth Factors in Oncology.Cancer Treatment and Research 157: 195-215.	Study design
Glaspy, J. C., J.; Vansteenkiste, J.; Henry, D.; Rao, S.; Bowers, P.; Berlin, J. A.; Tomita, D.; Bridges, K.; Ludwig, H. (2010). "Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes." British Journal of Cancer 102: 301-315.	Study design
Gregory SA. Efficacy of Darbepoetin Alfa in the Treatment of Chemotherapy-Induced Anemia in Non-Hodgkin's Lymphoma. (2006). Supportive Cancer Therapy.3:232-9.	Study design
Jones, M. S., Brad; Just, Julie; Fallowfield, Lesley (2004). "Epoetin alfa improves quality of life in patients with cancer: results of metaanalysis.[Erratum appears in Cancer. 2005 May 1;103(9):1984]." Cancer 101: 1720-1732.	Study design
Kallich JM, A.: Xu, X.: Fayers, P.: Cella, D. (2006). The relationship between patient knowledge of hemoglobin levels and health-related quality of life. Quality of Life Research. 15:57-68.	Study design
Kimel, M. L., Nancy K.; Mannix, Sally; Dixon, Julia (2008). "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 in Health 11: 57-75.	Study design
Larsson GJ, E. T. (2008). Anemia in patients with midgut carcinoid, treated with alpha interferon: effects by erythropoietin treatment on the perceived quality of life. European Journal of Cancer Care.17:200-4.	Study design
Latagliata RO, E. N.: Volpicelli, P.: Carmosino, I.: Breccia, M.: Vincelli, I.: Alati, C.: Napoleone, L.: Vozella, F.: Nobile, F.: Alimena, G. (2008). Twice-weekly high-dose rHuEpo for the treatment of anemia in patients with low-risk myelodysplastic	Study design

syndromes. Acta Haematologica. 120:104-107.	
Ludwig, H. C., Jeffrey; Osterborg, Anders; Vansteenkiste, Johan; Henry, David H.; Fleishman, Alex; Bridges, Ken; Glaspy, John A. (2009). "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." Journal of Clinic	Study design
Lyman, G. H. G., J. (2006). "Are there clinical benefits with early erythropoietic intervention for chemotherapy-induced anemia? A systematic review." Cancer 106: 223-233.	Study design
Maisnar VC, K. (2004). Treatment of associated anemia in different hematological disorders with epoetin alpha. Neoplasma. 51:379-84.	
Michallet MG, K.: Sobh, M.: Morisset, S.: Chelghoum, Y.: Thomas, X.: Barraco, F.: Ducastelle, S.: Labussiere, H.: Renzullo, C.: Paillet, C.: Pivot, C.: Badol-Van Straaten, P.: Denis, A.: Termoz, A.: Detrait, M.: Nicolini, F. E.: Jaisson-Hot, I. (2013). Prospective study of erythropoietin use on quality of life and cost effectiveness in acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation patients. Cancer . 119:107-114.	Study design
Moul JWD, N. (2012). Quality of life associated with treatment of castration-resistant prostate cancer: A review of the literature. Cancer investigation. 30:1-12.	Study design
Newland AMB, C. D. Tumor progression associated with erythropoiesis-stimulating agents.(2008). Annals of Pharmacotherapy 42:1865-1870.	Study design
Ohashi, Y. U., Yukari; Fujisaka, Yasuhito; Sugiyama, Toru; Ohmatsu, Hironobu; Katsumata, Noriyuki; Okamoto, Rumiko; Saijo, Nagahiro; Hotta, Tomomitsu (2013). "Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: Individual patient data from Japanese randomized, placebo-controlled trials." Canc	Study design
Oliva ENN, Francesco: Alimena, Giuliana: Specchia, Giorgina: Danova, Marco: Rovati, Bianca: Ronco, Francesca: Impera, Stefana: Risitano, Antonio: Alati, Caterina: Breccia, Massimo: Carmosino, Ida: Vincelli, Iolanda: Latagliata, Roberto. (2010). Darbepoetin alfa for the treatment of anemia associated with myelodysplastic syndromes: efficacy and quality of life. Leukemia & Lymphoma. 51:1007-14.	Study design
Ots, P. M. S. C., Concepcion Lopez; Perez, Aurora Rodriguez; de Dios Saez Garrido, Juan; Perez, Jose Ma Delgado (2008). "Darbepoetin versus epoetin alfa for the correction of anemia in cancer patients receiving radiotherapy or chemoradiotherapy treatment." Clinical Medicine Oncology 2: 393-399.	Study design
Palumbo AP, M. T.: Lauta, V. M.: Musto, P.: Caravita, T.: Barbui, A. M.: Nunzi, M.: Boccadoro, M. Correlation between fatigue and hemoglobin level in multiple myeloma patients: Results of a cross-sectional study. Haematologica 2005;90:858-860.	Study design
Palumbo AP, M. T.: Lauta, V. M.: Musto, P.: Caravita, T.: Barbui, A. M.: Nunzi, M.: Boccadoro, M. Correlation between	Study design

fatigue and hemoglobin level in multiple myeloma patients: Results of a cross-sectional study. Haematologica 2005;90:858-860.	
Petrelli FB, Karen: Cabiddu, Mary: Lonati, Veronica: Barni, Sandro. (2012). Addition of iron to erythropoiesis-stimulating agents in cancer patients: a meta-analysis of randomized trials. Journal of Cancer Research & Clinical Oncology. 138:179-87.	Study design
Quirt, I. K., Michael; Couture, Felix; Turner, A. Robert; Noble, Michael; Burkes, Ronald; Dolan, Sean; Plante, Richard K.; Lau, Catherine Y.; Chang, Jose (2006). "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."	Study design
Reed, S. D. R., Jasmina I.; Daniel, Davey B.; Mody, Samir H.; Forlenza, Jamie B.; McKenzie, R. Scott; Schulman, Kevin A. (2006). "Economic evaluation of weekly epoetin alfa versus biweekly darbepoetin alfa for chemotherapy-induced anaemia: evidence from a 16-week randomised trial." Pharmacoeconomics 24: 479-494.	Study design
da Silva Costa MTS, A.: Fontes, P.: Castro, V.: Fernandes, T.: Oliveira, A.: Silva, I. (2006). Erythropoiesis-stimulating agents in the treatment of anemia in patients with head and neck tumors ? Analysis of quality of life. Radiotherapy and Oncology. 81:S339-S339.	Study design
Steensma DPL, C. L. (2006). Epoetin alfa and darbepoetin alfa go head to head. Journal of Clinical Oncology. 24:2232-2236.	Study design
Stull DEV, Margaret K.: Legg, Jason C.: Viswanathan, Hema N.: Fairclough, Diane: Revicki, Dennis A. (2010). Use of latent growth curve models for assessing the effects of darbepoetin alfa on hemoglobin and fatigue. Contemporary Clinical Trials. 31:172-9.	Study design
Reinhardt UT, A.: Angermund, R.: Lutz, H. (2005). 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. 10:225-237.	Study design
Reinhardt UT, A.: Angermund, R.: Lutz, H. (2005). 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. 10:225-237.	Study design
Revicki, D. A. S., Donald; Vernon, Margaret; Rader, Michael; Tomita, Dianne; Viswanathan, Hema N. (2012). "Assessing the effect of darbepoetin alfa on patient-reported fatigue in chemotherapy-induced anemia in four randomized, placebo-controlled clinical trials." Quality of Life Research 21: 311-321.	Study design
Rizzo, J. D. B., M.; Hurley, P.; Seidenfeld, J.; Arcasoy, M. O.; Spivak, J. L.; Bennett, C. L.; Bohlius, J.; Evanchuk, D.; Goode, M. J.; Jakubowski, A. A.; Regan, D. H.; Somerfield, M. R. (2010). "American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult p	Study design

Ross, S. D. A., E.; Henry, D. H.; Seaman, C.; Sercus, B.; Goodnough, L. T. (2006). "Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature." Clinical Therapeutics 28: 801-831.	Study design
Stephens JMG, Paola: Laskin, Benjamin: Botteman, Marc F.: Pashos, Chris L. (2005). Chronic lymphocytic leukemia: economic burden and quality of life: literature review. American Journal of Therapeutics. 12:460-6.	Study design
Tonelli MH, Brenda: Reiman, Tony: Manns, Braden: Reaume, M. Neil: Lloyd, Anita: Wiebe, Natasha: Klarenbach, Scott.(2009). Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. CMAJ Canadian Medical Association Journal.180:E62-71.	Study design
Vansteenkiste, J. W., Isabelle; Elliott, Steven; Glaspy, John; Hedenus, Michael (2013). "Chemotherapy-induced anemia: the story of darbepoetin alfa." Current Medical Research & Opinion 29: 325-337.	Study design
Vansteenkiste, J. G., John; Henry, David; Ludwig, Heinz; Pirker, Robert; Tomita, Dianne; Collins, Helen; Crawford, Jeffrey (2012). "Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: study-level and patient-level meta-analyses." Lung Cancer 76: 478-485.	Study design
Yang SJ, M.: Hong-Li, Z.: Jian-Min, W.: Chun, W.: Lu-Gui, Q.: Yong-Qiang, Z.: Jun, Z.: Jian, H.: Zhi-Xiang, S. (2008). 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. International journal of hematology. 88:139-144.	Study design
Duplicate	
Vansteenkiste J, Wauters I, Elliott S, Glaspy J, Hedenus M. (2013). Chemotherapy-induced anemia: the story of darbepoetin alfa. Curr Med Res Opin. 29, 325-337.	Duplicate
Wilson JY, G. L.; Raftery, J.; Bohlius, J.; Brunskill, S.; Sandercock, J.; Bayliss, S.; Moss, P.; Stanworth, S.; Hyde, C. 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 Apr;11:1-202, iii-iv. PubMed PMID: 17408534. English.	Duplicate
Steensma DPD, S. R.: Dalton, R.: Kahanic, S. P.: Kugler, J. W.: Stella, P. J.: Rowland, K. M.: Novotny, P. J.: Sloan, J. A.: Loprinzi, C. L. (2009). 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 United States.114	Duplicate
Language	
Ludwig HA, T.: Burghuber, O. C.: Gnant, M.: Hopfinger, G.:	Language

Jager, U.: Keil, F.: Kornek, G.: Linkesch, W.: Petru, E.: Pirker, R.: Pittermann, E.: Reinthaller, A.: Samonigg, H.: Steger, G.: Stockenhuber, F.: Studnicka, M.: Weiss, G.: Zielinski, C. Replacement of Erythropoese stimulated protein in anemic patients with malignant disease. Wiener Klinische Wochenschrift 2008;120:507-513.	
Zemelka, T. R., J.; Ziobro, M.; Michalczyk, A. (2007) "[Opinion on influence of erythropoietin on quality of life and survival in patients with advanced non-small cell lung cancer]." Wspolczesna Onkologia, 37-40.	Language
No usable data	
Earlier initiation of treatment recommended in using erythropoietic agents for chemotherapy-induced anemia. The Journal of Supportive Oncology 2004;2:319.	No usable data
Anthony LBG, N. Y.: Ghazal, H.: Woytowitz, D. V.: Flam, M. S.: Drelichman, A.: Loesch, D. M.: Niforos, D. A.: Mangione, A. (2011). IV iron sucrose for cancer and/or chemotherapy-induced anemia in patients treated with erythropoiesisstimulating agents. Community Oncology. 8:270-278.	No usable data
Arcasoy MOA, K.: Chou, S. C.: Haroon, Z. A.: Varia, M.: Raleigh, J. A. (2005). Erythropoietin and erythropoietin receptor expression in head and neck cancer: Relationship to tumor hypoxia. Clinical Cancer Research. 11:20-27.	No usable data
Borg SG, Anna H.: Osterborg, Anders: Persson, Ulf. (2008). The cost-effectiveness of treatment with erythropoietin compared to red blood cell transfusions for patients with chemotherapy induced anaemia: a Markov model. Acta Oncologica. 47:1009-17.	No usable data
Clark JS, A. (2006). Advantages of every-3-week dosing of erythropoietic agents to manage chemotherapy-induced anemia. Oncology . 20:795-800.	No usable data
Dale DC. The benefits of haematopoietic growth factors in the management of gynaecological oncology. European Journal of Gynaecological Oncology 2004;25:133-44.	No usable data
Greaves PA, S. (2007). Safe and efficacious use of recombinant human erythropoietin in malignancy. Clinical Medicine, Journal of the Royal College of Physicians of London. 7:617-620.	No usable data
Jadersten MM, S. M.: Dybedal, I.: Porwit-MacDonald, A.: Hellstrom-Lindberg, E. (2005). Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. Blood. 106:803-811.	No usable data
Jadersten MM, L.: Dybedal, I.: Della Porta, M. G.: Invernizzi, R.: Montgomery, S. M.: Pascutto, C.: Porwit, A.: Cazzola, M.: Hellstrom-Lindberg, E.(2008). Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. Journal of Clinical Oncology. 26:3607-3613.	No usable data
Moebus V, Jackisch C, Schneeweiss A et al. (2013). Adding Epoetin Alfa to Intense Dose-Dense Adjuvant Chemotherapy	No usable data

for Breast Cancer: Randomized Clinical Trial. J Natl Cancer Inst. 105, 1018-1026.	
Roungrong JT, Yot: Chaikledkaew, Usa. (2008). Cost-utility analysis of recombinant human erythropoietin in anemic cancer patients induced by chemotherapy in Thailand. Journal of the Medical Association of Thailand. 91 Suppl 2:S119-25.	No usable data
Unobtainable	
ADAMSON, J. W. 2013. Iron, erythropoietic stimulating agents, and anemia in cancer. Critical reviews in oncogenesis, 18, 471-483.	No usable data
Dose outside licence	
Aapro ML, Robert C.: Barnadas, Agusti: Marangolo, Maurizio: Untch, Michael: Malamos, Nikolaos: Mayordomo, Jose: Reichert, Dietmar: Pedrini, Jose Luiz: Ukarma, Lidia: Scherhag, Armin: Burger, Hans-Ulrich. (2008). Effect of once-weekly epoetin beta on survival in patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy: results of the Breast Cancer-Anemia and the Value of Erythropoietin (BRAVE) study. Journal of Clinical Oncology. 26:592-8.	Dose outside license
Cabanillas MEK, Hagop: Thomas, Deborah A.: Mattiuzzi, Gloria N.: Rytting, Michael E.: Bruera, Eduardo: Xiao, Lianchun: Bekele, B. Nebiyou: Foudray, Maria C.: Cortes, Jorge E. (2012). 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. 118:848-55.	Dose outside license
Chang JC, Felix A.: Young, Scott D.: Lau, Catherine Y.: Lee McWatters, Kara. (2004). Weekly administration of epoetin alfa improves cognition and quality of life in patients with breast cancer receiving chemotherapy. Supportive Cancer Therapy. 2:52-8.	Dose outside license
Chang JC, Felix: Young, Scott: McWatters, Kara-Lee: Lau, Catherine Y. (2005). Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. Journal of Clinical Oncology 2005;23:2597-605.	Dose outside license
Charu VB, Chandra P.: Gill, Ahmad N.: Bhatt, Mukesh: Tomita, Dianne: Rossi, Greg: Ben-Jacob, Ali. (2007). Efficacy and safety of every-2-week darbepoetin alfa in patients with anemia of cancer: a controlled, randomized, open-label phase II trial. Oncologist . 12:727-37.	Dose outside license
Charu VS, B.: Ben-Jacob, A.: Justice, G. R.: Maniam, A. S.: Tomita, D.: Rossi, G.: Rearden, T.: Glaspy, J. (2007). A randomized, open-label, multicenter trial of immediate versus delayed intervention with darbepoetin alfa for chemotherapy-induced anemia. Oncologist 12:1253-1263.	Dose outside license
Christodoulou CD, U.: Aravantinos, G.: Koutras, A.: Samantas, E.: Karina, M.: Janinis, J.: Papakostas, P.: Skarlos, D.: Kalofonos, H. P.: Fountzilas, G. (2009). Effects of epoetin-alpha on quality of life of cancer patients with solid tumors	Dose outside license

receiving chemotherapy. Anticancer Research. 29:693-702.	
Engert AJ, A.: Haverkamp, H.: Villalobos, M.: Lohri, A.: Sokler, M.: Zijlstra, J.: Sturm, I.: Topp, M. S.: Rank, A.: Zenz, T.: Vogelhuber, M.: Nogova, L.: Borchmann, P.: Fuchs, M.: Flechtner, H. H.: Diehl, V. (2010). Epoetin alfa in patients with advanced-stage Hodgkin's lymphoma: Results of the randomized placebo-controlled GHSG HD15EPO trial. Journal of Clinical Oncology. 28:2239-2245.	Dose outside license
Fujisaka YS, T.: Saito, H.: Nagase, S.: Kudoh, S.: Endo, M.: Sakai, H.: Ohashi, Y.: Saijo, N. (2011). Randomised, phase III trial of epoetin- to treat chemotherapy-induced anaemia according to the EU regulation. British Journal of Cancer. 105:1267-72.	Dose outside license
Glaspy JV-R, S.: Patel, R.: Bosserman, L.: Hu, E.: Lloyd, R. E.: Boccia, R. V.: Tomita, D.: Rossi, G. (2006). Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia: The 20030125 study group trial. Journal of Clinical Oncology. 24:2290-2297.	Dose outside license
Greenberg PLS, Zhuoxin: Miller, Kenneth B.: Bennett, John M.: Tallman, Martin S.: Dewald, Gordon: Paietta, Elisabeth: van der Jagt, Richard: Houston, Jessie: Thomas, Mary L.: Cella, David: Rowe, Jacob M. (2009).Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). Blood. 114:2393-400.	Dose outside license
Gupta SS, P. K.: Bisth, S. S.: Bhatt, M. L.: Pant, M.: Gupta, R.: Singh, Sharad: Negi, M. P. S. (2009). Role of recombinant human erythropoietin in patients of advanced cervical cancer treated "by chemoradiotherapy". Cancer Biology & Therapy. 8:13-7.	Dose outside license
Hernandez EG, Peter: Charu, Veena: Dibenedetto, Joseph: Tomita, Dianne: Lillie, Tom: Taylor, Kerry: Group, Aranesp Study. Randomized, double-blind, placebo-controlled trial of every-3-week darbepoetin alfa 300 micrograms for treatment of chemotherapy-induced anemia. Current Medical Research & Opinion 2009;25:2109-20.	Dose outside license
Leyland-Jones BS, Vladimir: Pawlicki, Marek: Pienkowski, Tadeusz: Tjulandin, Sergei: Manikhas, George: Makhson, Antoly: Roth, Anton: Dodwell, David: Baselga, Jose: Biakhov, Mikhail: Valuckas, Konstantinas: Voznyi, Edouard: Liu, Xiangyang: Vercammen, Els. (2005). Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. Journal of Clinical Oncology.23:5960-72.	Dose outside license
Nagel SK, Olaf: Engel-Riedel, Walburga: Guetz, Sylvia: Schumann, Christian: Gieseler, Frank: Schuette, Wolfgang. (2011) Addition of darbepoetin alfa to dose-dense chemotherapy: results from a randomized phase II trial in small-cell lung cancer patients receiving carboplatin plus	Dose outside license

etoposide. Clinical Lung Cancer . 12:62-9.	
O'Shaughnessy JAV, Svetislava J.: Holmes, Frankie Ann: Savin, Michael: Jones, Monte: Royall, Donald: George, Martine: Von Hoff, Daniel. (2005). Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. Clinical Breast Cancer . 5:439-46.	Dose outside license
Pronzato PC, E.: Cc,: Bols, A.: Moreno-Nogueira, J. A.: De Oliveira, C. F.: Barrett-Lee, P.: Ostler, P. J.: Rosso, R. (2010). 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 . 15:935-943.	Dose outside license
Razzouk BIH, Jeffrey D.: Hockenberry, Marilyn: Hinds, Pamela S.: Feusner, James: Williams, Denise: Rackoff, Wayne R. Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy. Journal of Clinical Oncology 2006;24:3583-9.	Dose outside license
Savonije JHvG, Cees J.: Wormhoudt, Lars W.: Giaccone, Guiseppe. (2006). 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. 11:197-205.	Dose outside license
Savonije JH, van Groeningen CJ, Wormhoudt LW, Giaccone G. (2006). Early Intervention with epoetin alfa during platinum-based chemotherapy: an analysis of the results of a multicenter, randomized, controlled trial based on haemoglobin level. Oncologist. 11:206-16	Dose outside license
Savonije JHvG, C. J.: van Bochove, A.: Honkoop, A. H.: van Felius, C. L.: Wormhoudt, L. W.: Giaccone, G. (2005). Effects of early intervention with epoetin alfa on transfusion requirement, hemoglobin level and survival during platinum-based chemotherapy: Results of a multicenter randomised controlled trial. European Journal of Cancer. 41:1560-9.	Dose outside license
Tsuboi ME, Kohji: Tobinai, Kensei: Ohashi, Yasuo: Saijo, Nagahiro. (2009). Weekly administration of epoetin beta for chemotherapy-induced anemia in cancer patients: results of a multicenter, Phase III, randomized, double-blind, placebo-controlled study. Japanese Journal of Clinical Oncology . 39:163-8.	Dose outside license
Waltzman RC, Christopher: Justice, Glen R.: Fesen, Mark R.: Charu, Veena: Williams, Denise. (2005). 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. 10:642-50.	Dose outside license
Witzig TES, Peter T.: Loprinzi, Charles L.: Sloan, Jeff A.: Novotny, Paul J.: Mailliard, James A.: Rowland, Kendrith M.: Alberts, Steven R.: Krook, James E.: Levitt, Ralph: Morton, Roscoe F. (2005). Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. Journal of Clinical Oncology.	Dose outside license

23:2606-17.	
Wright JRU, Yee C.: Julian, Jim A.: Pritchard, Kathleen I.: Whelan, Timothy J.: Smith, Column: Szechtman, Barbara: Roa, Wilson: Mulroy, Liam: Rudinskas, Leona: Gagnon, Bruno: Okawara, Gord S.: Levine, Mark N. (2007). Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. Journal of Clinical Oncology.25:1027-32.	Dose outside license

16.3. Wilson et al, 2007: Excluded studies

Population	
Blohmer, J. U., Wurschmidt, F., Petry, W. U. et al (2003). 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 [abstract 1798]. ASCO.	Population; patients receiving radiotherapy only
Thompson, J. A., Gilliland, D.G., Prchal, J.T. et al (2000). "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 95(4): 1175-1179.	Population; patients not on chemotherapy
Henke, M., Guttenberger, R., Barke, A. et al (1999). "Erythropoietin for patients undergoing radiotherapy: a pilot study." Radiother Oncol 50(2): 185-190.	Population; patients not on chemotherapy
Henke, M., Laszig, R., Rube, C. et al (2003). "Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial." Lancet 362(9392): 1255-1260.	Population; patients receiving radiotherapy only
Henze, G., Michon, J.,Morland, B.,et al (2002). Phase III randomised study: efficacy of epoetin alfa in reducing blood transfusions in newly diagnosed pediatric cancer patients receiving chemotherapy [abstract 1547]. ASCO.	Population; patients receiving radiotherapy only
Italian Cooperative Study Group for rHuEpo in Myelodysplastic, Syndrome., P. R. Ferrini, A. Grossi, A. M. Vannucchi, G. Barosi, R. Guarnone, N. Piva, P. Musto and E. Balleari (1998). "A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes." Br J Haematol 103(4): 1070-1074.	Population; patients not on chemotherapy
Smith, R. E., Jr., Tchekmedyian, N.S., Chan, D. et al (2003). "A dose- and schedule-finding study of darbepoetin alpha for the treatment of chronic anaemia of cancer." Br J Cancer 88(12): 1851-1858.	Population; patients not on chemotherapy
Sweeney, P. J., Nicolae, D. Ignacio, L. et al (1998). "Effect of subcutaneous recombinant human erythropoietin in cancer patients receiving radiotherapy: final report of a randomised, open-labelled, Phase II trial." Br J Cancer 77: 1996-2002.	Population; patients receiving radiotherapy only

Wurnig, C., Windhager, R., Schwameis, E. et al (1996). "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 36(2): 155-159.	Population
Rose, E., Rai, K.R., Revicki D.A. et al (1994). "Clinical and health status assessments in anemia chronic lymphocytic leukemia (CLL) patients treated with epoetin alfa (EPO) " Blood 84(10Suppl A): 526a.	Population; patients not on chemotherapy
Abstract	
Janinis, D., Dafni, U., Aravantinos, G. et al (2003). "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 [abstract]." Proc Am Soc Clin Oncol 22: 789.	Abstract only (no paper identified)
Huddart, R. A., Welch, R. S., Chan, S et al (2002). "A prospective randomised comparative group evaluation of epoetin alfa for the treatment of anaemia in UK cancer patients receivin platinum-based chemotherapy." Ann Oncol 13: 177.	Abstract only (no paper identified)
Thomas, H., McAdam, K. F., Thomas, R. J. et al (2002). "Early intervention with Epoetin alfa for treatment of anaemia and improvement of quality of life in cancer patients undergoing myelotoxic chemotherapy." Ann Oncol 13: 177.	Abstract only (no paper identified)
Quirt, I., S. Micucci, L. A. Moran, J. Pater and J. Browman (1996). "The roel of recombinant human erythropoietin (EPO) ni 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 88: 347a.	Abstract only (no paper identified)
Carabantes, F. J., M. Benavides, R. Trujillo, M. Cobo, M. L. Herbrero and S. Garcia (1999). Epoetin alfa in the prevention of anaemia in cancer patients undergoing platinum-based chemotherapy (CT). A prospective randomised study [abstract 2303]. ASCO.	Abstract only (no paper identified)
Duplicate	
Casadevall, N. D., Dubois, S., Hemery, F et al. (2004). "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 104: 321-327.	Duplicate; study also identified and accounted for in update searches
Rosenzweig, M. Q. B., Catherine M.; Lucke, Joseph P.; Yasko, Joyce M.; Brufsky, Adam M. (2004). "The decision to prematurely terminate a trial of R-HuEPO due to thromboembolic events." Journal of Pain & Symptom Management 27: 185-190.	Duplicate; study also identified and accounted for in update searches
Unlicensed dose	
Bamias, A., G. Aravantinos, C. Kalofonos, N. Timotheadou, V. Siafaka, I. Vlahou, D. Janinis, D. Pectasides, N. Pavlidis, G. Fountzilas and G. Hellenic Cooperative Oncology (2003). "Prevention of anemia in patients with solid tumors receiving platinum-based chemotherapy by recombinant human	Unlicensed dose

Erythropoietin (rHuEpo): a prospective, open label, randomized trial by the Hellenic Cooperative Oncology Group." Oncology 64(2): 102-110.	
Cascinu, S., A. Fedeli, E. Del Ferro, S. Luzi Fedeli and G. Catalano (1994). "Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double-blind trial with placebo." J Clin Oncol **12**: 1058-1062.	Unlicensed dose
Cazzola, M., D. Messinger, V. Battistel, D. Bron, R. Cimino, L. Enller-Ziegler, U. Essers, R. Greil, A. Grossi, G. Jager, A. LeMevel, A. Najman, V. Silingardi, M. Spriano, A. van Hoof and B. Ehmer (1995). "Recombinant human erythropoietin in the anemia associated with multiple myeloma or non-Hodgkin's lymphoma: dose finding and identification of predictors of response." Blood 86(12): 4446-4453.	Unlicensed dose
Hedenus, M., S. Hansen, K. Taylor, C. Arthur, B. Emmerich, C. Dewey, D. Watson, G. Rossi, A. Osterborg and G. Darbepoetin alfa 990114 Study (2002). "Randomized, dose-finding study of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies." Br J Haematol 119(1): 79-86.	Dose-response study; licensed dose included in PenTAG but unlicensed doses excluded
Iconomou, G., A. Koutras, A. Rigopoulos, A. G. Vagenakis and H. P. Kalofonos (2003). "Effect of recombinant human erythropoietin on quality of life in cancer patients receiving chemotherapy: results of a randomized, controlled trial." J Pain Symptom Manage 25(6): 512-518.	Unlicensed dose
Kotasek, D., G. Steger, W. Faught, C. Underhill, E. Poulsen, A. B. Colowick, G. Rossi, J. Mackey and G. Aranesp 980291 Study (2003). "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 39(14): 2026-2034.	Dose-response study; licensed dose included in PenTAG but unlicensed doses excluded
Kunikane, H., K. Watanabe, M. Fukuoka, N. Saijo, K. Furuse, H. Ikegami, Y. Ariyoshi and S. Kishimoto (2001). "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 6(6): 296-301.	Unlicensed dose
Leyland-Jones, B., B. Investigators and G. Study (2003). "Breast cancer trial with erythropoietin terminated unexpectedly." Lancet Oncol 4(8): 459-460.	Unlicensed dose
Oberhoff, C., B. Neri, D. Amadori, K. U. Petry, T. Gamucci, U. Rebmann, M. R. Nowrousian, R. Voigtmann, S. Monfardini, J. P. Armand, R. Herrmann, J. Netter-Pinon, N. Tubiana-Mathieu and H. Zwierzina (1998). "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 9(3): 255-260.	Unlicensed dose
Osterborg, A., M. A. Boogaerts, R. Cimino, U. Essers, J. Holowiecki, G. Juliusson, G. Jager, A. Najman and D. Peest (1996). "Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma--a randomized multicenter study. The	Unlicensed dose

European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma." Blood 87(7): 2675-2682.	
Rosen, F. R., D. J. Haraf, M. S. Kies, K. Stenson, L. Portugal, M. A. List, B. E. Brockstein, B. B. Mittal, A. W. Rademaker, M. E. Witt, H. Pelzer, R. R. Weichselbaum and E. E. Vokes (2003). "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 9(5): 1689-1697.	Unlicensed dose
Ten Bokkel Huinink, W. W., C. A. de Swart, D. W. van Toorn, G. Morack, W. P. Breed and H. F. Hillen (1998). "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 15: 174-182.	Multi dose comparison study; licensed dose included but unlicensed doses excluded
Thatcher, N., E. S. De Campos, D. R. Bell, W. P. Steward, G. Varghese, R. Morant, J. F. Vansteenkiste, R. Rosso, S. B. Ewers, E. Sundal, E. Schatzmann and H. Stocker (1999). "Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer." Br J Cancer 80: 396-402.	Multi dose comparison study; licensed dose included but unlicensed doses excluded
Throuvalas, N., D. Antonadu, M. Boufi, R. S. Lavey and N. Malamos (2000). Erythropoietin decreases transfusion requirements during radiochemotherapy [abstract 1558]. American Society of Clinical Oncology Annual Meeting, New Orleans (USA).	Unlicensed dose
Welch, R. S., R. D. James, P. M. Wilkinson, F. Belli and R. A. Cowan (1995). "Recombinant human erythropoietin and platinum-based chemotherapy in advanced ovarian cancer." Cancer J Sci Am 1: 261-266.	Unlicensed dose

Appendix F: Study & baseline characteristics excluded unlicensed

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
WILSON AND COLLEAGUES, 2007								
Bamias, 2003[200] ROL	n = 72 Age, yrs: 60 (18–77) n (%) Male: 35 (49) Hb BL (g/dl): 11.5 (11.1–11.9) Epo mU/ml BL: 24.8 (16.6–37)	n = 72 Age, yrs: 62 (19–80) n (%) Male: 39 (54) Hb BL (g/dl): 11.5 (11.2–11.8) Epo mU/ml BL: 12.5 (8.7–18)	Brand: epoetin alfa Dose: 30,000 IU QW Dose adjustment: Y, ↓ Duration of epo tx: 21–24 wks (duration of chemo Duration of trial: duration of chemo + 3 wks Follow-up:	SC	Iron: NR G-CSF: NR RBCT trigger: prn (Hb incl. criteria level: <13 g/dl)	Disease: solid Treatment: chemo, plat	Hb, patients' RBCT HRQoL measured in a subset	Y
Cascinu, 1994[201] RCT	n = 50 Age, yrs: 58 (44–72)* n (%) Male: 24 (48) Hb BL (g/dl): 8.63 ± 0.62 Epo mU/ml L: 67.9 ± 66.6	n = 50 Age, yrs: 57 (45–68)* n (%) Male: 29 (58) Hb BL (g/dl): 8.73 ± 0.52 Epo mU/L BL: 49.3 ± 39.9	Brand: epoetin alfa Dose: 300 IU/kg QW Dose adjustment: Y Duration of epo tx: 9 wks Duration of trial: 9 wks Follow-up: NR	PBO	Iron: Y, oral (as indicated by serum iron, serum ferritin, transferrin sat.) G-CSF: NR RBCT trigger: <8 g/dl (Hb incl. criteria level: <9 g/dl)	Disease: solid Treatment: chemo, plat	Hb, RBCT,AE	Y
Cazzola, 1995[202] ROL	EPO BETA 5,000 IU/kg n = 31 (analysed 31) Age, yrs: NR n (%) Male: NR Hb BL (g/dl): ≤10 g/dl Epo mU/ml BL: NR EPO BETA 10,000 IU/kg n = 26 (analysed 326) Age, yrs: NR n (%) Male: NR Hb BL (g/dl): ≤10 g/dl Epo mU/ml BL: NR	n = 55 (analysed 55) Age, yrs: NR n (%) Male: NR Hb BL (g/dl): ≤10 g/dl Epo mU/ml BL: NR	Brand: epoetin beta Dose: 5,000 IU/day or 10,000 IU/day Dose adjustment: NR Duration of epo tx: 8 wks Duration of trial: NR Follow-up:	SC	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: NR)	Disease: haem Treatment: chemo, non-plat	HaemR, Hb, RBCT, AE	Y
Hedenus, 2002[49a] RCT Dose-response study, only licensed dose included in current review	DARBEPOETIN ALFA 1.0 µg/kg/QW[a] n = 11 Age, yrs: 64 (26–80) n (%) Male: 7 (64) Hb BL (g/dl): 9.7 (0.8) Epo mU/ml BL: 46 (12–208) DARBEPOETIN ALFA 4.5 µg/kg/QW[a]	n = 11 Age, yrs: 63 (25–80) n (%) Male: 2 (18) Hb BL (g/dl): 9.5 (1.0) Epo mU/ml BL: 45 (12–132	Brand: darbepoetin alfa Dose: 1.0 & 4.5 µg/kg QW[a] Dose adjustment: Y Duration of epo tx: 12 wks Duration of trial: 16 wks Follow-up: Unclear	PBO	Iron: NR G-CSF: RBCT trigger: Hb ≤8 g/dl (Hb incl. criteria level: ≤11.0 g/dl)	Disease: haem Treatment: chemo, NR	HaemR, Hb, RBCT, AE	Y

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
	n = 22 Age, yrs: 70 (52–84) n (%) Male: 14 (64) Hb BL (g/dl): 9.7 (0.9) Epo mU/ml BL: 57 (12–227)							
Iconomou, 2003[203] ROL	n = 57 Age, yrs: 60.6 (33–85) n (%) Male: 22 (39) Hb BL (g/dl): 10.1 ± 0.6 Epo mU/ml BL: NR	n = 55 Age, yrs: 62.6 (34–80) n (%) Male: 24 (44) Hb BL (g/dl): 10.1 ± 0.6 Epo mU/ml BL: NR	Brand: rHuEPO Dose: 30,000 IU QW Dose adjustment: Y Duration of epo tx: 12 wks Duration of trial: 12 wks Follow-up:	SC	Iron: Y G-CSF: NR RBCT trigger: Hb 7.5 g/dl or prn (Hb incl. criteria level: ≤11 g/dl)	Disease: solid Treatment: chemo, mixed	HaemR, HRQoL	Y
Kotasek, 2003[46a] RCT Dose-response study, only licensed dose included in current review	DARB ALFA 1.5 µg/kg/QW n = 32 n (%) Male: 9 (28) DARB ALFA 3.0 µg/kg/QW n = 46 n (%) Male: 13 (28) DARB ALFA 4.0 µg/kg/QW n = 28 n (%) Male: 8 (28) DARB ALFA 4.5µg/kg/QW n = 35 n (%) Male: 10 (28) DARB ALFA 5.0 µg/kg/QW n = 40 n (%) Male: 11 (28) Age, yrs: 58.3 (11.9)[c] Hb BL (g/dl): 9.93 (1.0)[c] Epo BL: 17% patients ≥100 mU/mL[c]	n = 51 Age, yrs: 56.2 (12.4) n (%) Male: 16 (31) Hb BL (g/dl): 9.87 (1.12) Epo mU/ml BL: NR	Brand: darbepoetin alfa Dose: 1.0, 3.0, 4.0, 4.5, 5.0 µg/kg QW Dose adjustment: Yes, ↓ Duration of epo tx: 12 wks Duration of trial: 12 wks Follow-up: Unclear	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤11.0 g/dl)	Disease: solid (breast, gynae., GI, lung) Treatment: chemo, NR	HaemR, Hb, RBCT, HRQoL[c], AE[c]	Y
Kunikane, 2001[204] RCT	EPOETIN BETA 300U/kg/QW n = 16 Age, yrs: n (%) Male: Hb BL (g/dl): >12 g/dl Epo mU/ml BL: EPOETIN BETA 600U/kg/QW n = 18 Age, yrs: n (%) Male: Hb BL (g/dl): >12 g/dl	n = 38 Age, yrs: n (%) Male: Hb BL (g/dl): >12 Epo mU/ml BL:	Brand: epoetin beta Dose: 300 IU/kg QW & 600 IU/kg QW Dose adjustment: NR Duration of epo tx: 6 wks Duration of trial: NR Follow-up:	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: NR)	Disease: solid (NSCLC) Treatment: chemo, plat	Hb, patients' RBCT	Y

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
	Epo mU/ml BL:							
Leyland-Jones, 2003[13]	n = NR (total for trial 939) Age, yrs: NR n (%) Male: NR Hb BL (g/dl): NR Epo mU/ml BL: NR	n = NR (total for trial 939) Age, yrs: NR n (%) Male: NR Hb BL (g/dl): NR Epo mU/ml BL: NR	Brand: epoetin alfa Dose: NR Dose adjustment: NR Duration of epo tx: NR Duration of trial: 12–19 mths Follow-up:	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: 13 g/dl (aim of study to keep Hb >12 <14 g/dl)	Disease: solid (metastatic breast) Treatment: NR	Survival	Y
Oberhoff, 1998[205] **ROL**	n = 114 Age, yrs: n (%) Male: Hb BL (g/dl): ≤10 Epo mU/ml BL:	n = 104 Age, yrs: n (%) Male: Hb BL (g/dl): ≤10 Epo mU/ml BL:	Brand: epoetin beta Dose: 5,000 IU/day Dose adjustment: 12 wks Duration of epo tx: Duration of trial: Follow-up:	SC	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level:)	Disease: solid Treatment: chemo, plat	HaemR, Hb, RBCT, AE	Y
Osterborg, 1996[206] **ROL**	EPOETIN BETA 10,000 U/OD n = 47 Age, yrs: n (%) Male: Hb BL (g/dl): ≤10 Epo mU/ml BL: EPOETIN BETA 2,000 U/OD n = 48 Age, yrs: n (%) Male: Hb BL (g/dl): ≤10 Epo mU/ml BL:	n = 49 Age, yrs: n (%) Male: Hb BL (g/dl): ≤10 Epo mU/ml BL:	Brand: epoetin beta Dose: 2,000 IU/day & 10,000 IU/day Dose adjustment: Duration of epo tx: 24 wks Duration of trial: Follow-up:	SC	Iron: G-CSF: RBCT trigger: NR (Hb incl. criteria level:)	Disease: haem Treatment: chemo, non-plat	HaemR, Hb, RBCT, AE	Y
Rosen, 2003[207] **ROL**	n = 47 Age, yrs: 56 (35–80) n (%) Male: 33 (71) Hb BL (g/dl): <10 g/dl Epo mU/ml BL: NR	n = 43 Age, yrs: 56 (35–80) n (%) Male: 31 (71) Hb BL (g/dl): <10E po mU/ml BL: NR	Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: NR Duration of epo tx: 14 wks + 4 wks continuation Duration of trial: 48 mths Follow-up:	SC	Iron: Y (tx arm only) G-CSF: NR RBCT trigger: Hb <10 g/dl Hb incl. criteria level: ≤16 g/dl)	Disease: solid (head/neck) Treatment: chemo + radio	Hb, patients' RBCT	Y
Ten Bokkel, 1998[47a] **ROL** 3-arm study, only comparison with licensed dose included in current review	n = 42 (analysed 42)[a] Age, yrs: 60.97 n (%) Male: all female Hb BL (g/dl): 12.0 (1.3–12.6)* Epo mU/ml BL: NR	n = 34 (analysed 33) Age, yrs: 58.83 n (%) Male: all female Hb BL (g/dl): 11.8 (10.6–12.5)* Epo mU/ml BL: NR	Brand: epoetin beta Dose: 300 IU/kg TIW[a] Dose adjustment: Y Duration of epo tx: 24 wks Duration of trial: 24 wks Follow-up: NR	SC	Iron: NR G-CSF: No RBCT trigger: Hb <9.7 g/dl (Hb incl. criteria level: <13 g/dl)	Disease: solid (ovary) Treatment: chemo, plat	Patients' RBCT, AE	Y

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
Thatcher, 1999[48a] ROL 3-arm study, only comparison with licensed dose included in current review	n = 44[a] Age, yrs: 58.5 (30–72)* n (%) Male: 29 (66) Hb BL (g/dl): 13.6 (10.9–17.0)* Epo mU/ml BL: NR	n = 44 Age, yrs: 60 (39–74)* n (%) Male: 27 (61.3) Hb BL (g/dl): 13.4 (10.9–16.4)* Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 300 IU/kg TIW[a] Dose adjustment: Y Duration of epo tx: 26 wks Duration of trial: 26 wks Follow-up: NR	SC	Iron: No G-CSF: No RBCT trigger: prn (Hb incl. criteria level: ≥10.5 g/dl)	Disease: solid (SCLC) Treatment: chemo, mixed[d]	Hb. Patients' RBCT, HRQoL, AE	Y
Throuvalas, 2000[208] ROL	n = 28 (analysed 28) Age, yrs: n (%) Male: Hb BL (g/dl): >10 ≤12 Epo mU/ml BL:	n = 27 (analysed 26) Age, yrs: n (%) Male: Hb BL (g/dl): >10 ≤12 Epo mU/ml BL:	Brand: rHuEPO Dose: 50,000 IU QW Dose adjustment: Duration of epo tx: Duration of trial: 6 wks Follow-up:	SC	Iron: G-CSF: RBCT trigger: Hb (Hb incl. criteria level:)	Disease: solid (cervix, bladder) Treatment: chemo (plat) + radio	RBCT	Y
Welch, 1995[209] ROL	n = 15 Age, yrs: NR n (%) Male: NR Hb BL (g/dl): NR Epo mU/ml BL: NR	n = 15 Age, yrs: NR n (%) Male: NR Hb BL (g/dl): NR Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 300 IU/kg TIW Dose adjustment: Duration of epo tx: Duration of trial: 24 wks Follow-up: NR	SC	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: NR)	Disease: solid (ovary) Treatment: chemo, plat	Hb, RBCT, HRQoL, AE	Y
PENTAG REVIEW: 2004 to CURRENT								
Aapro 2008[210] ROL BRAVE Suppl refs: Aapro, 2009	n = 231 Age, yrs: 56 (27–78)* n (%) Male: all female Hb BL g/dl: 11.2 ± 1.2 Epo mU/ml BL: NR	n = 232 Age, yrs: 57.5 (29–83)* n (%) Male: all female Hb BL g/dl: 11.5 ± 1.1 Epo mU/ml BL: NR	Brand: Epoetin beta Dose: 450 IU/kg QW Dose adj.: Y Dur. of epo tx: 24 wks Dur. of trial: 24 wks Follow-up: 18 mths	SC	Iron: Y, oral or i.v. G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: <12.9 g/dl)	Disease: solid (breast) Treatment: chemo: non-plat	HaemR, Hb, RBCT, HRQoL, AE, TR, survival	Y
Aapro 2009[211] Subgroup analysis of Aapro, 2008	n = 231 Age, yrs: 56 (27–78)* n (%) Male: all female Hb BL g/dl: 11.2 ± 1.2 Epo mU/ml BL: NR	n = 232 Age, yrs: 57.5 (29–83)* n (%) Male: all female Hb BL g/dl: 11.5 ± 1.1 Epo mU/ml BL: NR	Brand: Epoetin beta Dose: 450 IU/kg QW Dose adj.: Y Dur. of epo tx: 24 wks Dur. of trial: 24 wks Follow-up: 18 mths	SC	Iron: Y, oral or i.v. G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: <12.9 g/dl)	Disease: solid (breast) Treatment: chemo: non-plat	AE (subgroup analysis, TVEs among patients receiving and not receiving antithromboembolic therapy; hypothesis generating)	N
Berndt, 2005[212] ROL Subgroup	n = 300[k,l] Age, yrs: 60.8 (12.3) (20–91) n (%) Male: 91 (30.3) Hb BL (g/dl): 9.9 (0.9) (6.2–12.2) Epo mU/ml BL: NR		Brand: darbepoetin alfa Dose: 0.5, 1.0, 1.5, 2.25, 4.5, 6.0 & 8.0 µg QW and 3.0, 5.0, 7.0 & 9.0 µg Q2W Dose adjustment: Y, ↓	Head-to-head	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤11 g/dl)	Disease: solid Treatment: chemo, mixed	Analysis explores the impact of fatigue on productivity & caregiver burden	N

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
analysis of Glaspy 2002 (not included in previous HTA)			Duration of epo tx: 12 wks Duration of trial: 12 wks Follow-up: Brand: epoetin alfa Dose: 150 IU/kg TIW & 40,000 IU/QW Dose adjustment: Y[m] Duration of epo tx: 12 wks Duration of trial: 12 wks Follow-up: NR				(although includes licensed doses of intervention under review; results reported are based on pooled data)	
Blohmer, 2011[213] **ROL** NOGGO-AGO	n = 127 Age, yrs: 41 (24–73)* n (%) Male: all female Hb BL (g/dl): NR Epo mU/ml BL: NR	n = 129 Age, yrs: 42 (25–66)* n (%) Male: all female Hb BL (g/dl): NR Epo mU/ml BL: NR	Brand: rHuEPO Dose: 10,000 IU TIW Dose adjustment: Y Duration of epo tx: Unclear Duration of trial: Unclear Follow-up: 3 yrs	No epo	Iron: Y, oral G-CSF: NR RBCT trigger: Hb <9 g/dl (Hb incl. criteria level: NR)	Disease: solid (cervix) Treatment: chemo + radio	Hb, RBCT, HRQoL (ECOG), AE, survival	Y
Cabanillas, 2012[214] **ROL**	n = 55 Age, yrs: 41 ± 16.7 n (%) Male: 33 (58) Hb BL (g/dl): 9 ± 1.5 Epo g/dl BL: 473 ± 570	n = 54 Age, yrs: 42 ± 17.3 n (%) Male: 24 (42) Hb BL (g/dl): 8.9 ± 1.5 Epo mU/ml BL: 326 ± 514	Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: Unclear Duration of trial: Unclear Follow-up: 3 yrs	No epo	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: >10 g/dl)	Disease: haem Treatment: chemo, non-plat	RBCT, HRQoL, AE, TR, survival	N Excluded trials if >80% of participants were diagnosied with an acute leukaemia
Chang, 2005[31] **ROL**	n = 175 Age, yrs: 50.4 (11.1) (27–78) n (%) Male: all female Hb BL (g/dl): 11.2 (0.9) (8.15–12.6)[e] Epo mU/ml BL: NR	n = 175 Age, yrs: 50.1 (10.0) (31–85) n (%) Male: all female Hb BL (g/dl): 11.3 (0.8) (7.8–13.4)[e] Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 weeks Follow-up: NR	SC	Iron: Y, oral, daily (as indicated by transferrin sat.) G-CSF: NR RBCT trigger: Hb <8 g/dl, prn (Hb incl. criteria level: ≤15 g/dl at screening; ≤12 g/dl randomised)	Disease: solid (breast) Treatment: chemo, NR	HaemR[r], Hb, RBCT, HRQoL, AE	Y
Chang, 2004[215] **ROL** Subgroup analysis of Chang 2005 (published online ahead of print 2004)	n = 176 Age, yrs: 50.4 (11.1) (27–78) n (%) Male: all female Hb BL (g/dl): 11.2 (0.9) (8.15–12.6)* Epo mU/ml BL: NR	n = 178 Age, yrs: 50.1 (10.0) (31–85) n (%) Male: all female Hb BL (g/dl): 11.3 (0.8) (7.8–13.4)* Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 weeks Follow-up: NR	SC	Iron: Y, oral, daily (as indicated by transferrin sat.) G-CSF: NR RBCT trigger: Hb <8 g/dl, prn (Hb incl. criteria level: ≤15 g/dl at screening; ≤12 g/dl randomised)	Disease: solid (breast) Treatment: chemo, NR	Analysis of the effect of epoetin alfa on changes in QoL & utility scales at 12 wks	Y

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
Charu, 2007[216] ROL	n = 226 Age, yrs: 71.7 (10.4) n (%) Male: 95 (42) Hb BL (g/dl): 10.1 (0.9) (for n=220) Epo mU/ml BL: NR	n = 59 Age, yrs: 67.2 (12.5) n (%) Male: 23 (39) Hb BL (g/dl): 10.3 (0.9) (for n=55) Epo mU/ml BL: NR	Brand: darbepoetin alfa Dose: 3 µg/kg Q2W Dose adjustment: Y Duration of epo tx: 12 wks Duration of trial: 12 wks[g] Follow-up: NR	No epo	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤11 g/dl)	Disease: Mixed Treatment: chemo, NR	HaemR, Hb, RBCT, HRQoL, AE, # hospitalisations	Y
Christodoulou, 2009[217] ROL	n = 167 Age, yrs: 61 (22–82)* n (%) Male: 88 (53) Hb BL (g/dl): 10.15 ± 0.69 Epo mU/ml BL: NR	n = 170 Age, yrs: 63 (30–89)* n (%) Male: 81 (48) Hb BL (g/dl): 10.30 ± 0.58) Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 10,000 IU TIW Dose adjustment: YDuration of epo tx: Duration of trial: Follow-up: NR	No epo	Iron: Y, oral G-CSF: NRRBCT trigger: Hb <8.5 g/dl prn(Hb incl. criteria level: ≤12 g/dl)	Disease: solid Treatment: chemo, mixed	Hb, RBCT, HRQoL, TR, survival	Y
Engert, 2010[218] RCT GHSG -HD15-EPO	n = 648 Age, yrs: 34 (18–60)* n (%) Male: 402 (62) Hb BL (g/dl): NR Epo mU/ml BL: NR	n = 685 Age, yrs: 34 (18–60)* n (%) Male: 406 (62) Hb BL (g/dl): NR Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: Unclear Duration of trial: Unclear Follow-up: Unclear	PBO	Iron: Y, oral (as indicated by BL transferrin sat. or serum ferritin level) G-CSF: NR RBCT trigger: Hb <8 g/dl (Hb incl. criteria level: NR)	Disease: haem Treatment: chemo, non-plat	Hb, RBCT, HRQoL, AE, survival	Y
Fujisaka, 2011[219] RCT	n = 89 Age, yrs: 67 (40–79)* n (%) Male: 47 (53) Hb BL (g/dl): 9.4 (8.1–11.4)* Epo mU/ml BL: 43 (7.78–577)*	n = 92 Age, yrs: 63.5 (44–79)* n (%) Male: 40 (43) Hb BL (g/dl): 9.3 (7.2–11.4)* Epo mU/ml BL: 43.6 (10.5–320)*	Brand: epoetin beta Dose: 36,000 IU QW Dose adjustment: Y Duration of epo tx: 12 wks Duration of trial: 12 wks Follow-up: 12 mths	PBO	Iron: Y, oral daily (as indicated by transferrin sat). G-CSF: NR RBCT trigger: prn (Hb incl. criteria level: ≤8 / ≤10 g/dl)	Disease: solid (lung or gynae.) Treatment: chemo, plat	Hb, RBCT, HRQoL, AE, survival	Y
Glaspy, 2006[220] ROL active control	DARBEPOETIN ALFA n = 606 Age, yrs: 63.2 (12.4) n (%) Male: 191 (32) Hb BL (g/dl): 10.2 (0.9) Epo mU/ml BL: NR	EPOETIN ALFA n = 603 Age, yrs: 63.7 (11.6) n (%) Male: 222 (37) Hb BL (g/dl): 10.2 (0.9) Epo mU/ml BL: NR	DARBEPOETIN ALFA Brand: darbepoetin alfa Dose: 200 µg Q2W Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 wks Follow-up: NR EPOETIN ALFA Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 wks Follow-up: NR	NA (active control see left)	Iron: NR G-CSF: NR RBCT trigger: Hb >8 g/dl prn (Hb incl. criteria level: ≤11 g/dl)	Disease: solid Treatment: chemo, NR	Hb, RBCT, HRQoL, AE 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[221]	n = 60 (analysed 58) Age, yrs: 48.27 (18–70)	n = 60 (analysed 57) Age, yrs: 48.18 (20–65)	Brand: epoetin beta Dose: 10,000 IU TIW	PBO	Iron: Y, oral 10–15 days before	Disease: solid (cervix) Treatment: chemo (plat)	Hb, RBCT, HRQoL, AE, TR,	Y

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
RCT	n (%) Male: NR Hb BL (g/dl): 10.45 (9.5–11.0) Epo mU/ml BL: NR	n (%) Male: NR Hb BL (g/dl): 10.70 (10.0–12.5) Epo mU/ml BL:	Dose adjustment: NR Duration of epo tx: Unclear Duration of trial: Unclear Follow-up: 24 mths		chemo+radio (unclear whether given in control arm) G-CSF: NR RBCT trigger: Hb ≤10 g/dl (Hb incl. criteria level: 9.5–12.5 g/dl)	+ radio	survival	
Hernandez, 2009[222] RCT	n = 193 Age, yrs: 64.5 (12.1) n (%) Male: 76 (39) Hb BL (g/dl): 10.1 (0.9) Epo mU/ml BL: 90.3 (96.1) (n=186)	n = 193 Age, yrs: 63.6 (12.3) n (%) Male: 76 (39) Hb BL (g/dl): 10.0 (0.9) Epo mU/ml BL: 109.9 (186.4) (n=184)	Brand: darbepoetin alfa Dose: 300 μg/Q3W Dose adjustment: Y Duration of epo tx: 13 wks Duration of trial: 16 wks Follow-up: 29 wks	PBO	Iron: Y, not specified, though based on serum iron, serum ferritin, or transferrin saturation G-CSF: NR RBCT trigger: Hb ≤8 g/dl, or if >8 g/dl & signs of anaemia present (Hb incl. criteria level: <11 g/dl)	Disease: solid & haem? Treatment: chemo, mixed	Hb, RBCT, HRQoL, AE, TR, survival	Y
Leyland-Jones, 2005[223] RCT (BEST)	n = 469 Age, yrs: 55.8 (11.1; 24–83) n (%) Male: all female Hb BL (g/dl): 12.5 (1.8) Epo mU/ml BL: NR	n = 470 Age, yrs: 55.1 (10.5; 30–84) n (%) Male: all female Hb BL (g/dl): 12.5 (1.7) Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 12 mths Duration of trial: 12 mths[g] Follow-up: NR	PBO	Iron: Y, oral (as indicated by transferrin sat.) G-CSF: NR RBCT trigger: prn (Hb incl. criteria level:)	Disease: solid (breast) Treatment: chemo, NR	Hb, RBCT, HRQoL, AE, TR, survival	Y
Milroy, 2011[224] ROL	n = 214 (analysed 189) Age, yrs: 61.6 ± 8.7 (41–82) n (%) Male: 142 (75.1) Hb BL (g/dl): 12.8 ± 1.4 Epo mU/ml BL: NR	n = 191 (analysed 191) Age, yrs: 60.1 ± 9.3 (34–83) n (%) Male: 148 (77.5) Hb BL (g/dl): 12.6 ± 1.6 Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 10,000 IU TIW Dose adjustment: Y Duration of epo tx: 22–28 weeks Duration of trial: 22–28 weeks Follow-up: 6 & 12 mths	SC	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤15 g/dl [males]; ≤14 g/dl [females])	Disease: solid (NSCLC) Treatment: Chemo, plat	HaemR, Hb, RBCT, HRQoL, AE, TR, survival	Y
Nagel, 2011[225] ROL	n = 37 Age, yrs: 61 (41–88) n (%) Male: 29 (77.8) Hb BL (g/dl): NR Epo mU/ml BL: NR	n = 37 Age, yrs: 59 (37–80) n (%) Male: 24 (63.9) Hb BL (g/dl): NR Epo mU/ml BL: NR	Brand: darbepoetin alfa Dose: 300 μg Q2W Dose adjustment: Y Duration of epo tx: up to 28 wks Duration of trial: up to 28 wks Follow-up: 24 mths	SC	Iron: Y, oral G-CSF: Y, pegfilgastrim D4 each C RBCT trigger: prn (Hb incl. criteria level: <12 g/dl; treatment initiated at this point in the	Disease: solid (SCLC) Treatment: Chemo, plat	HRQoL, AE, TR, survival	N Excluded as too many patients in experimental arm did not receive ESAs

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
					intervention group)			
O'Shaugnessy, 2005[226] RCT	n = 47 Age, yrs: 53.3 ± 9.7 n (%) Male: all female Hb BL (g/dl): 12.8 ± 1.0 Epo mU/ml BL: NR	n = 47 Age, yrs: 54.3 ± 12.0 n (%) Male: all female Hb BL (g/dl): 13.0 ± 1.0 Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 12 wks Duration of trial: 16 wks Follow-up: 6 mths	PBO	Iron: Y, not specified but prnG-CSF: NRRBCT trigger: Hb <8 g/dl(Hb incl. criteria level: 9–14 g/dl)	Disease: solid (breast)Treatment: chemo, plat	Hb, cognitive function & mood (EXIT25, CLOX 1 & 2, POMS), HRQoL, AE	Y
Pirker, 2008[227] RCT	n = 298 Age, yrs: n (%) Male: Hb BL (g/dl): Epo mU/ml BL:	n = 298 Age, yrs: n (%) Male: Hb BL (g/dl): Epo mU/ml BL:	Brand: darbepoetin alfa Dose: 300 µg/QW for 4 wks then every 3 wks up to 6 cycles chemo Dose adjustment: Y Duration of epo tx: 13 wks? Duration of trial: 24 wks Follow-up: 12 mths	PBO	Iron: G-CSF: NR RBCT trigger: Hb (Hb incl. criteria level: ≥9 and ≤13 g/dl)	Disease: solid (SCLC) Treatment: chemo, plat	Hb, RBCT, HRQoL, AE, survival, disease progression	Y
Pronzato, 2010[228] ROL EPO-INT-47	n = 107 Age, yrs: 58.3 ± 10.3 (29–76) n (%) Male: all female Hb BL (g/dl): 10.6 Epo mU/ml BL: NR	n = 109 Age, yrs: 54.3 ± 11.6 (27–77) n (%) Male: all female Hb BL (g/dl): 10.8 Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 10,000 IU TIW (5,000 IU/QW if <45 kg) Dose adjustment: Y Duration of epo tx: up to 28 wks Duration of trial: up to 28 wks Follow-up: 6 & 12 mths	SC	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤12 g/dl)	Disease: solid Treatment: chemo, plat	HaemR, Hb, HRQoL, AE, TR, survival	Y
Razzouk, 2006[229h] RCT	n = 111 Age, yrs: 12.4 (3.6) n (%) Male: 63 (56.8) Hb BL (g/dl): 9.8 (1.3) Epo mU/ml BL: NR	n = 111 Age, yrs: 10.8 (4.0) n (%) Male: 58 (52.3) Hb BL (g/dl): 9.5 (1.0) Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 600 IU/kg QW Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 wks Follow-up:	PBO	Iron: Y, oral (as indicated by transferrin sat. or ferritin level) G-CSF: NR RBCT trigger: Hb ≤7 g/dl (Hb incl. criteria level: (<10.5; <11.0, or <12.0 g/dl dependent on age)	Disease: haem Treatment: chemo, NR	Hb, RBCT, HRQoL, AE	Y
Reed, 2005[230] ROL active control Subgroup analysis of Waltzman 2005	n = 274* Age, yrs: 62.4 (11.7) n (%) Male: 93 (34) Hb BL (g/dl): NR Epo mU/ml BL: NR		EPOETIN ALFA Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 wks Follow-up: NR	Head-to-head	Iron: Y, oral, daily or i.v. if contraindicated G-CSF: NR RBCT trigger: Hb (Hb incl. criteria level: ≤11 g/dl)	Disease: solid Treatment: chemo, mixed	Analysis of the patients with a baseline Hb value & at least one post-randomisation Hb value or documentation of	N Compared different ESA products (epoetin vs darbepoetin)

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
			DARBEPOETIN ALFA Brand: darbepoetin alfa Dose: 200 µg Q2W Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 wks Follow-up: NR				RBCT. Patients were dichotomised based on whether they experienced early Hb response, regardless of treatment assignment	
Rosenzweig, 2004[231n] Retrospective analysis, original trial unknown	n = 14 Age, yrs: 55.9 ± 11.7 n (%) Male: all female Hb BL (g/dl): NR Epo mU/ml BL: NR	n = 13 Age, yrs: 53.9 ± 14.20 n (%) Male: all female Hb BL (g/dl): NR Epo mU/ml BL: NR	Brand: rHuEPO Dose: 40,000 IU QW Dose adjustment: NR Duration of epo tx: NR Duration of trial: NR[n] Follow-up: NA	SC	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: <12 g/dl)	Disease: solid (breast) Treatment: chemo, NR	Analysis to determine the efficacy of rHuEPO in reducing cancer-related fatigue & improving QoL & fatigue in patients with metastatic breast cancer experiencing mild anaemia (retrospective review over an 18-mth period)	Y
Savonije, 2006a[232] **RCT** Subgroup analysis of Savonije 2005	n = 211 Age, yrs: 57 ± 11 (20–80) n (%) Male: 117 (55) Hb BL (g/dl): 10.7 ± 1.0 (7.6–13.8) Epo mU/ml BL: NR	n = 104 Age, yrs: 58 ± 10 (27–78) n (%) Male: 61 (59) Hb BL (g/dl): 10.8 ± 10 (8.5–12.7) Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 10,000 IU TIW Dose adjustment: Y Duration of epo tx: Duration of trial: 13.9 wks vs 14.5 wks (mean int. vs control) Follow-up: 12 mths	SC	Iron: Y, oral (as indicated by BL transferrin sat. +/- serum ferritin level) G-CSF: NR RBCT trigger: Hb ≥9.7 g/dl prn (Hb incl. criteria level: ≤12.1 g/dl)	Disease: solid Treatment: Chemo, plat	HRQoL in patients with solid tumours & mild-to-moderate anaemia receiving plat. chemo. relative to population norms	Y
Savonije, 2006b[233] **RCT** Subgroup analysis of Savonije 2005	n = 211 Age, yrs: 57 ± 11 (20–80) n (%) Male: 117 (55) Hb BL (g/dl): 10.7 ± 1.0 (7.6–13.8) Epo mU/ml BL: NR	n = 104 Age, yrs: 58 ± 10 (27–78) n (%) Male: 61 (59) Hb BL (g/dl): 10.8 ± 10 (8.5–12.7) Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 10,000 IU TIW Dose adjustment: Y Duration of epo tx: Duration of trial: 13.9 wks vs 14.5 wks (mean int. vs control) Follow-up: 12 mths	SC	Iron: Y, oral (as indicated by BL transferrin sat. +/- serum ferritin level) G-CSF: NR RBCT trigger: Hb ≥9.7 g/dl prn (Hb incl. criteria level: ≤12.1 g/dl)	Disease: solid Treatment: Chemo, plat	Analyse the effect of BL Hb level on HaemR, Hb, RBCT, & HRQoL	N
Savonije, 2005[234]	n = 211 Age, yrs: 57 ± 11 (20–80) n (%) Male: 117 (55)	n = 104 Age, yrs: 58 ± 10 (27–78) n (%) Male: 61 (59)	Brand: epoetin alfa Dose: 10,000 IU TIW Dose adjustment: Y	SC	Iron: Y, oral (as indicated by BL transferrin sat. +/-	Disease: solid Treatment: Chemo, plat	HaemR, Hb, RBCT, HRQoL, AE, survival (6 &	Y

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
RCT NCT00283465	Hb BL (g/dl): 10.7 ± 1.0 (7.6–13.8) Epo mU/ml BL: NR	Hb BL (g/dl): 10.8 ± 10 (8.5–12.7) Epo mU/ml BL: NR	Duration of epo tx: Duration of trial: 13.9 wks vs 14.5 wks (mean int. vs control) Follow-up: 12 mths		serum ferritin level) G-CSF: NR RBCT trigger: Hb ≥9.7 g/dl prn (Hb incl. criteria level: ≤12.1 g/dl)		12 mths)	
Schwartzberg, 2004[235] **ROL** **active control** Integrated analysis of 3 RCTs incl Senecal, 2005	DARBEPOETIN ALFA n = 157 Age, yrs: 58.7 (11.5) n (%) Male: 23 (15) Hb BL (g/dl): 10.4 (0.8) Epo mU/ml BL: NR	EPOETIN ALFA n = 155 Age, yrs: 61.7 (12.1) n (%) Male: 26 (17) Hb BL (g/dl): 10.4 (0.8) Epo mU/ml BL: NR	DARBEPOETIN ALFA Brand: darbepoetin alfa Dose: 200 µg Q2W Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 19/20 wks Follow-up: NR EPOETIN ALFA Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 19/20 wks Follow-up: NR	Head-to-head	Iron: NRG-CSF: NRRBCT trigger: Hb (Hb incl. criteria level: ≤11 g/dl)	Disease: solid (breast, lung, gynae.)Treatment: chemo, mixed	Hb, RBCT, HRQoL, PSQ, AE Subgroup analysis by BL Hb category <10 g/dl and ≥10 g/dl)	N Excluded as compared ESAs darbepoetin vs epoetin
Senecal, 2005[236] **active control** Also reported in Schwartzberg, 2004	DARBEPOETIN ALFA n = 72 Age, yrs: 53.6 ± 11.4 (35–81) n (%) Male: all female Hb BL (g/dl): 10.5 ± 0.8 Epo mU/ml BL: NR	EPOETIN ALFA n = 69 Age, yrs: 58.4 ± 12.5 (34–81) n (%) Male: all female Hb BL (g/dl): 10.6 ± 0.7 Epo mU/ml BL: NR	DARBEPOETIN ALFA Brand: darbepoetin alfa Dose: 200 µg Q2W Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 19/20 wks Follow-up: NR EPOETIN ALFA Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 19/20 wks Follow-up: NR	Head-to-head	Iron: Y, not specified, per institution standards G-CSF: NR RBCT trigger: Hb <8 g/dl (Hb incl. criteria level: ≤11 g/dl)	Disease: solid (breast) Treatment: chemo, mixed	HaemR, Hb, RBCT, PSQ, AE 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[237] **ROL** GOG-0191; NCT00017004; CAN-NCIC-CX4	n = 57 Age, yrs: 46 (25–77)* n (%) Male: all female Hb BL (g/dl): NR Epo mU/ml BL: NR	n = 52 Age, yrs: 50 (32–78)* n (%) Male: all female Hb BL (g/dl): NR Epo mU/ml BL: NR	Brand: rHuEPO Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: Unclear Duration of trial: Unclear Follow-up: 37 mths (9.8–50.4 mths)*	SC	Iron: G-CSF: NR RBCT trigger: Hb <12 g/dl (as a result of vaginal bleeding, intervention arm) (Hb incl. criteria level: <12 g/dl for	Disease: solid (cervix) Treatment: chemo (plat) + radio	Hb, RBCT, AE (TVEs), survival Trial terminated early with <25% of planned accrual due to concerns with TVEs with	Y

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
					randomisation; <14 g/dl at study entry)		rHuEPO	
Tsuboi, 2009[238] RCT	n = 61 Age, yrs: 61.8 ± 11.9 n (%) Male: 34 (56) Hb BL (g/dl): 10.0 ± 1.0 Epo mU/ml BL: 67.3 ± 72.0	n = 56 Age, yrs: 62.1 ± 9.6 n (%) Male: 33 (59) Hb BL (g/dl): 10.4 ± 1.0 Epo mU/ml BL: 49.1 ± 33.4	Brand: epoetin beta Dose: 36,000 IU QW Dose adjustment: Y Duration of epo tx: 8 wks Duration of trial: 8 wks Follow-up: median follow-up 670 days*	PBO	Iron: Y, oral, if indicated by serum iron sat. or MCV) G-CSF: NR RBCT trigger: prn (Hb incl. criteria level: ≤8.0 and ≤11 g/dl)	Disease: solid (lung) & haem Treatment: chemo, mixed	HaemR, Hb, RBCT, HRQoL, AE, survival[i]	Y
Wagner, 2004[61] ROL[h]	n = 18 Age, yrs: 3.2 (1.2–19.4)* n (%) Male: NR Hb BL (g/dl): 8.85 (6.10–11.20)* Epo mU/ml BL: NR	n = 20 Age, yrs: 3.2 (1.1–7.3)* n (%) Male: NR Hb BL (g/dl): 9.35 (7.00–15.3)* Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 200 IU/kg/day Dose adjustment: Y Duration of epo tx: D6, C1 to 48 hrs before start C2 in subseq cycles given 24 hrs after completion of chemo Duration of trial: Unclear Follow-up: NR	SC	Iron: Y, oral, daily (as indicated by transferrin sat.) G-CSF: 10 µg/kg/OD both tx arms RBCT trigger: Hb ≤8 g/dl (Hb incl. criteria level: NR)	Disease: haem Treatment: chemo, mixed	Hb, RBCT, survival	N Excluded as no usable data for any outcome
Waltzman, 2005[239] ROL **active control**	EPOETIN ALFA n = 178 Age, yrs: 62.1 ± 11.8 n (%) Male: 69 (38.8) Hb BL (g/dl): 10.16 ± 0.749 Epo mU/ml BL: NR	DARBEPOETIN ALFA n = 180 Age, yrs: 63.4 ± 11.8 n (%) Male: 61 (33.9) Hb BL (g/dl): 10.07 ± 0.787 Epo mU/ml BL: NR	EPOETIN ALFA Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 wks Follow-up: DARBEPOETIN ALFA Brand: darbepoetin alfa Dose: 200 µg/Q2W Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 wks Follow-up	Head-to-head	Iron: Y, oral, daily or i.v. if contraindicated G-CSF: NR RBCT trigger: Hb (Hb incl. criteria level: ≤11 g/dl)	Disease: solid Treatment: chemo, mixed	HaemR, Hb, RBCT, HRQoL, AE	N Excluded as ESAs were given in context with surgery, stem cell transplantation
Wilkinson, 2006[240] ROL	n = 114 Age, yrs: 59.1 ± 10.6 (35–87) n (%) Male: all female Hb BL (g/dl): 10.75 ± 0.94 Epo mU/ml BL: NR	n = 59 Age, yrs: 60.3 ± 11.2 (30–79) n (%) Male: all female Hb BL (g/dl): 10.66 ± 0.83 Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 10,000 IU TIW Dose adjustment: Y Duration of epo tx: up to 28 wks Duration of trial: up to 28 wks Follow-up: NR	SC	Iron: Y, oral (as indicated by transferrin sat.) G-CSF: Y, not specified RBCT trigger: Hb <9 g/dl prn (Hb incl. criteria level: ≤12 g/dl)	Disease: solid (ovary) Treatment: chemo, plat	HaemR, Hb, RBCT, HRQoL, AE, TR	Y

Study, year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl in Cochrane 2012, Y/N
Winquist, 2008[241] RCT	n = 26 Age, yrs: 71 (53–87)* n (%) Male: all male Hb BL (g/dl): 104 (73–120)* Epo mU/ml BL: NR	n = 30 Age, yrs: 71 (50–83)* n (%) Male: all male Hb BL (g/dl): 104 (81–120)* Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 40,000 IU TIW Dose adjustment: Y Duration of epo tx: 16 weeks[j] Duration of trial: 16 weeks[j] Follow-up: NA[j]	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤12 g/dl)	Disease: solid (prostate) Treatment: Unclear, NR	Hb, RBCT, HRQoL, AE, survival	Y
Witzig, 2005[242] RCT NCT00003600; CDR0000066673; NCCTG-979253; NCI-P98-0133	n = 174 Age, yrs: 63.6 (11.89) n (%) Male: 75 (45) Hb BL (g/dl): NR Epo mU/ml BL: NR	n = 170 Age, yrs: 63.7 (13.0) n (%) Male: 71 (43) Hb BL (g/dl): NR Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 16 wks Duration of trial: 16 wks Follow-up: 12 mths	PBO	Iron: Y, oral, daily G-CSF: NR RBCT trigger: Hb prn (Hb incl. criteria level: <11.5 g/dl [men]; <10.5 g/dl [women])	Disease: solid & haem Treatment: chemo, mixed	HaemR, Hb, RBCT, HRQoL, AE, TR, survival	Y
Wright, 2007[18] RCT	n = 33 Age, yrs: 68 (47–86)* n (%) Male: 17 (52) Hb BL (g/dl): 103 (72–118) Epo mU/ml BL: NR	n = 37 Age, yrs: 70 (39–87)* n (%) Male: 20 (54) Hb BL (g/dl): 103 (76–120) Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 40,000 IU QW Dose adjustment: Y Duration of epo tx: 12 wks Duration of trial: 12 wks Follow-up: 26 wks +	PBO	Iron: Y, not specified, prn G-CSF: NR RBCT trigger: Hb (Hb incl. criteria level:)	Disease: solid (NSCLC) Treatment: chemo non-plat[m]	Hb, RBCT, HRQoL, AE, survival	Y

Key: ~, approximately; ↓, decrease only; AE, adverse event; BL, baseline; C, cycles; chemo, chemotherapy; D, days; G-CSF, granulocyte colony stimulating factor; GI, gastrointestinal; gynae, gynaecological; HaemR, haematopoietic response; Hb, haemoglobin; HRQoL, health-related quality of life; inc., increase; incl., includ(e/ing); mcv, mean corpuscular volume; mths., months; NR, not reported; OD, once-daily; OS, overall survival; PBO, placebo; plat, platinum-based chemotherapy; prn, pro re nata; as needed; QoL, quality of life; QW, weekly; Q2W, every two weeks; RBCT, red blood cell transfusion; RCT, randomised controlled trial; rHuEPO, recombinant human erythropoietin; ROL, randomised open label; sat., saturation; SC, standard care; SCLC, small-cell lung cancer; TIW, thrice weekly; TR, tumour response; TVEs, thrombovascular events; tx, treatment; wks., weeks; yrs., years

Notes: * indicates median (range) **(a)** Study includes other doses of intervention under review (either dose-response study Hedenus,2002, 2003; Kotasek, 2003; or three-arm trial Ten-Bokkel, 1998; Thatcher, 1999; for licensed dose details see Appendix G); **(b)** Baseline characteristics not reported for epoetin or no epoetin arms of study – Henry 1994; **(c)** BL characteristics and some efficacy outcomes reported for all participants randomised (i.e. for all doses of Darbepoetin alfa [Kotasek 2003]; **(d)** Randomised comparative phase followed by optional open-label treatment phase (12 wks); **(e)** Majority of participants received platinum-based chemotherapy; **(f)** Haematology values were protocol entry deviations; **g** 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 wks); **(h)** Intervention evaluated in a paediatric population; **(i)** A retrospective analysis was performed for survival; **(j)** Trial terminated early due to 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 NSCLC. Both trials underwent underplanned safety analysis because of increase thromboembolism reported in other trials; **(k)** A total of 389 patients in the original RCT. Patients were included in this retrospective analysis if they were randomised, received at least four weeks of study treatment & reported outcomes at BL & at least once after 4 wks of treatment (n=300). 89 patients did not report outcomes at baseline or at least once after 4 wks of treatment; **(l)** 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; **(m)** Eligibility criteria relaxed to exclude only plat-based chemo; **(n)** Trial was halted early by the DSMB due to 28.5% participants developing thromboembolic events

Appendix G: Study & baseline characteristics licensed studies

Study year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl. in Cochrane 2012, Y/N
WILSON AND COLLEAGUES, 2007: PRIMARY STUDIES								
Abels 1993[54] **RCT** Multiple pubs.: *Abels 1996, Henry, 1995; Henry, 1994; Case, 1993*	n = 153/213 (analysed 143/206)[a] Age, yrs: 61.2 ± 13.0 n (%) Male: 102 (47.8) Hb BL g/dl: NR Epo mU/ml BL: 146 ± 260	n = 200 (analysed 135/190) Age, yrs: 62.5 ± 12.3 n (%) Male: 95 (47.5) Hb BL g/dl: NR Epo mU/ml BL: 149 ± 217	Brand: rHuEPO[b] Dose: 150 IU/kg TIW Dose adj.: NR Dur. of epo tx: 12 wks Dur. of trial: 12 wks[c] Follow-up: NR	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤10.5 g/dl)	Disease: haem & solid Treatment: chemo, mixed	HaemR, Hct, RBCT, HRQoL[a], AE[a]	Y
Aravantinos 2003[63] **ROL**	n = 24 Age, yrs: 59 (18–76)* n (%) Male: 2 (8) Hb BL g/dl: 9.8 ± 0.5 Epo mU/ml BL: NR	n = 23 Age, yrs: 64 (23–75)* n (%) Male: 7 (30%) Hb BL g/dl: 9.3 ± 0.8 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y, ↓ prn Dur. of epo tx: Unclear, med. 5 C Dur. of trial: NR Follow-up: NR	SC	Iron: Y, oral, fixed G-CSF: NR RBCT trigger: Hb <9 g/dl (Hb incl. criteria level: <10.5 g/dl)	Disease: solid (incl ovarian) Treatment: chemo, plat	Hb, Hct, patients' RBCT	Y
Boogaerts, 2003[52] **ROL** *(Abstract – Coiffier, 2001 included in Wilson and colleagues review)*	n = 133 Age, yrs: 62 (24–85)* n (%) Male: 46 (35) Hb BL g/dl: 9.0 (5–13)* Epo mU/ml BL: 54 (7–1,650)*	n = 129 Age, yrs: 62 (24–85)* n (%) Male: 52 (40) Hb BL g/dl: 9.2 (5–12)* Epo mU/ml BL: 58 (5–4,300)*	Brand: Epoetin beta Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: NR	SC	Iron: Y, oral (as indicated by transferrin sat. level) G-CSF: NR RBCT trigger: Hb <8.5 g/dl (Hb incl. criteria level: ≤11.0 g/dl)	Disease: haem & solid Treatment: chemo, NR	HaemR, Hb, RBCT, HRQoL, AE	Y
Dammacco 2001[64] **RCT** NCT00270101; CR005911	n = 69 Age, yrs: 67 (43–80)* n (%) Male: 34 (49) Hb BL g/dl: 9.3 ± 1.27 Epo mU/ml BL: 116 (18–5,220)*	n = 76 Age, yrs: 65 (38–89)* n (%) Male: 31 (41) Hb BL g/dl: 9.6 ± 0.95 Epo mU/ml BL: 93 (10–408)*	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: 12 Dur. of trial: 12 wks[c] Follow-up:	PBO	Iron: NR G-CSF: NR RBCT trigger: Hb <8 g/dl (Hb incl. criteria level: <11.0 g/dl)	Disease: haem Treatment: chemo, mixed[d]	HaemR, Hb, RBCT, HRQoL, AE	Y
Del Mastro 1997[65] **ROL**	n = 31 Age, yrs: 54 (31–68)* n (%) Male: NR Hb BL g/dl: 13.0 ± 0.7 Epo mU/ml BL: 21.0 (0–512)*	n = 31 Age, yrs: 56 (29–68)* n (%) Male: NR Hb BL g/dl: 13.1 ± 0.6 Epo mU/ml BL: 25.5 (0–800)*	Brand:rHuEPO[b] Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: 14 wks Dur. of trial: 14 wks Follow-up: 6 mths	SC	Iron: Y, oral iron (as indicated by serum iron, ferritin, & transferrin sat. levels) G-CSF: Y, 5 mcg/kg SC D4-11; C1-5 RBCT trigger: Hb <8 g/dl (Hb incl. criteria level: ≥12.0 g/dl)	Disease: solid (breast) Treatment: chemo, non-plat	Hb, RBCT, HRQoL, AE	Y

Study year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl. in Cochrane 2012, Y/N
Dunphy 1999[66] ROL	n = 15 (analysed 13) Age, yrs: 59 (42–76)* n (%) Male: 12 (92) Hb BL g/dl: 14.1 ± 2.1 Epo mU/ml BL: 8.8 (5.1)	n = 15 (analysed 14) Age, yrs: 67 (32–82)* n (%) Male: 7 (50) Hb BL g/dl: 14.1 ± 1.6 Epo mU/ml BL:7.3 (4.4)	Brand: rHuEPO[b] Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: Unclear, ~6 wks Dur. of trial: Unclear Follow-up: NR	SC	Iron: Y, oral, dailly G-CSF: NR RBCT trigger: Hb <8 g/dl (Hb incl. criteria level: NR)	Disease: solid (incl head & neck, lung) Treatment: chemo, mixed	Hb, RBCT	Y
Hedenus 2002[49] RCT Dose response study, 2 unlicensed doses excluded	n = 22[e] Age, yrs: 69 (20–84) n (%) Male: 14 (64) Hb BL g/dl: 9.4 (1.3) Epo IU/L BL: 69 (12–1,362)*	n = 11 Age, yrs: 63 (25–80) n (%) Male: 2 (18) Hb BL g/dl: 9.5 (1.0) Epo IU/L BL: 45 (12–132)*	Brand: Darbepoetin alfa Dose: 2.25 µg/kg QW[e] Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 16 wks Follow-up: Unclear	PBO	Iron: prn G-CSF: NR RBCT trigger: Hb ≤8 g/dl prn (Hb incl. criteria level: ≤11.0 g/dl)	Disease: haem Treatment: chemo, NR	HaemR, Hb, RBCT, AE	Y
Hedenus 2003[16] RCT Multiple pubs.: *Littlewood, 2006*	n = 176 (analysed 174)[e] Age, yrs: 64.8 (13.8) n (%) Male: 87 (50) Hb BL g/dl: 9.59 (1.22) Epo mU/ml BL: 68.99 (2.3–1,522.7)*	n = 173 (analysed 170) Age, yrs: 64.6 (12.2) n (%) Male:78 (46) Hb BL g/dl: 9.5 (1.21) Epo mU/ml BL: 54.49 (10.9–3,169.1)*	Brand: Darbepoetin alfa Dose: 2.25 µg/kg QW[e] Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 16 wks Follow-up: median ~11 mths	PBO	Iron: prn G-CSF: NR RBCT trigger: Hb ≤8 g/dl prn (Hb incl. criteria level: ≤11.0 g/dl)	Disease: haem Treatment: chemo, NR	HaemR, RBCT, HRQoL, AE	Y
Kotasek 2003[46] RCT Dose response study, 5 unlicensed doses excluded	n = 17/198[a,e] Age, yrs: 58.3 (11.9)[a] n (%) Male: 56 (28)[a] Hb BL g/dl: 9.93 (1.00)[a] Epo mU/ml BL: NR	n = 51 Age, yrs: 56.2 (12.4) n (%) Male:16 (31) Hb BL g/dl: 9.87 (1.12) Epo mU/ml BL: NR	Brand: Darbepoetin alfa Dose: 2.25 µg/kg QW[e] Dose adj.: Y, ↓ Dur. of epo tx: 12 wks Dur. of trial: 12 wks[c] Follow-up: Unclear	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤11.0 g/dl)	Disease: solid (breast, gynae, GI, lung) Treatment: chemo, NR	HaemR, Hb, RBCT, HRQoL[a], AE[a]	Y
Kurz 1997[67] RCT	n = 23 Age, yrs: 54.4 ± 9.7 n (%) Male: NR Hb BL g/dl: 9.88 ± 0.8 Epo mU/ml BL: NR	n = 12 Age, yrs: 52.7 ± 7.5 n (%) Male: NR Hb BL g/dl: 9.85 ± 0.60 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y, Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: NR	PBO	Iron: Y, i.v. iron G-CSF: NR RBCT trigger: Hb <8 g/dl (Hb incl. criteria level: <11.0 g/dl)	Disease: solid (overy, cervix, uterus) Treatment: chemo, mixed[h]	HaemR, RBCT, HRQoL, AE	Y
Littlewood 2001[68] RCT EPO-INT-1 Multiple pubs.: *Aapro, 2004; Bajetta, 2004;*	n = 251 (analysed 244) Age, yrs: 58.3 ± 14.2 n (%) Male: 85 (34) Hb BL g/dl: 9.9 ± 1.1 Epo mU/ml BL: NR	n = 124 (analysed 115) Age, yrs: 59.5 ± 13.9 n (%) Male: 39 (31) Hb BL g/dl: 9.7 ± 1.1 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: up to 28 wks Dur. of trial: up to 28 wks Follow-up: 12-mth[f]	PBO	Iron: Y, oral (or i.v. as indicated by transferrin sat. level) G-CSF: No RBCT trigger: Hb <8 g/dl prn (Hb incl. criteria level: ≤10.5 g/dL or >10.5 but ≤12.0 g/dl after a ≥1.5 g/dl decrease in Hb)	Disease: solid + haem Treatment: chemo, non-plat	HaemR, Hb, RBCT, HRQoL, AE, survival (at 12-mths follow-up)	Y

Study year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl. in Cochrane 2012, Y/N
Patrick, 2003								
Osterborg 2002 **2005, follow-up**[69,70] **RCT**	n = 173 (analysed 170) Age, yrs: 63 (32–86)* n (%) Male: 91 (54) Hb BL g/dl: 9.2 ± 1.1 Epo IU/L BL: 38 (20–72)*	n = 176 (analysed 173) Age, yrs: 64 (28–83)* n (%) Male: 82 (47) Hb BL g/dl: 9.3 ± 1.0 Epo IU/L BL: 41 (21–77)*	Brand: Epoetin beta Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: 16 wks Dur. of trial: up to 16 wks Follow-up: min 17.5 mths both tx grps	PBO	Iron: Y, i.v. (or oral if i.v. precluded) G-CSF: NR RBCT trigger: Hb <8.5 g/dl or inc.in Hb <0.5 g/dl vs BL (Hb incl. criteria level: <10 g/dl[g])	Disease: haem Treatment: chemo, non-plat	HaemR, Hb, RBCT, HRQoL, AE, survival; long-term survival	Y
Silvestris 1995[71] **ROL**	n = 30 (analysed 27) Age, yrs: NR n (%) Male: NR Hb BL g/dl: NR Epo mU/ml BL: NR	n = 24 (analysed 22) Age, yrs: NR n (%) Male: NR Hb BL g/dl: NR Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y, Dur. of epo tx: to 24 wks Dur. of trial: to 24 wks Follow-up: NR	SC	Iron: Y, not specified G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤8 g/dl)	Disease: haem Treatment: chemo, NR	HaemR, HbAE	Y
Ten Bokkel 1998[47] **ROL** Multiple treatment arms, 1 unlicensed dose excluded	n = 46 (analysed 45)[e] Age, yrs: 58.81 n (%) Male: all female Hb BL g/dl: 12.0 (1.3–12.6) Epo mU/ml BL: NR	n = 34 (analysed 33) Age, yrs: 58.83 n (%) Male: all female Hb BL g/dl: 11.8 (10.6–12.5) Epo mU/ml BL: NR	Brand: Epoetin beta Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: 24 wks Dur. of trial: 24 wks Follow-up: NR	SC	Iron: NR G-CSF: NR RBCT trigger: Hb <9.7 g/dl (Hb incl. criteria level:<13 g/dl)	Disease: solid (ovary) Treatment: chemo: plat	Patients' RBCT. AE	Y
Thatcher 1999 **ROL** Multiple treatment arms, 1 unlicensed dose excluded	n = 42[e] Age, yrs: 59 (43–72)* n (%) Male: 26 (61.9) Hb BL g/dl: 13.7 (10.7–16.1) Epo mU/ml BL: NR	n = 44 Age, yrs: 60 (39–74)* n (%) Male: 27 (61.3) Hb BL g/dl: 13.4 (10.9–16.4) Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: 26 wks Dur. of trial: 26 wks Follow-up: NR	SC	Iron: NR G-CSF: NR RBCT trigger: prn (Hb incl. criteria level: ≥10.5 g/dl)	Disease: solid (SCLC) Treatment: chemo: mixed[h]	Hb, Patients' RBCT, HRQoL, AE	Y
Vansteenkiste 2002[72] **RCT** Multiple pubs.: *Vansteenkiste, 2004*	n = 156 Age, yrs: 61.6 (9.2) n (%) Male: 111 (71) Hb BL g/dl: 10.28 (1.08) Epo mU/ml BL: 53.17 (58.87)[i]	n = 158 Age, yrs: 61.3 (8.8) n (%) Male: 116 (73) Hb BL g/dl: 9.93 (1.01) Epo mU/ml BL: 51.10 (71.72)[i]	Brand: Darbepoetin alfa Dose: 2.25 µg/kg QW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: 12 mths	PBO	Iron: NR G-CSF: NR RBCT trigger: Hb ≤8 g/dl (Hb incl. criteria level: ≤11.0 g/dl)	Disease: solid (lung) Treatment: chemo: plat	HaemR, Hb, RBCT (from Wk 5 and Wk 1), HRQoL, AE, disease progression, survival	Y
WILSON AND COLLEAGUES, 2007: MULTIPLE PUBLICATIONS								
Abels, 1996[58] Double-blind	n = 153/213 (analysed 143/206)[a] Age, yrs: 61.2 ± 13.0 n (%) Male: 102 (47.8)	n = 200 (analysed 135/190) Age, yrs: 62.5 ± 12.3 n (%) Male: 95 (47.5) Hb BL g/dl: NR	Brand: rHuEPO[b] Dose: 150 IU/kg TIW Dose adj.: NR Dur. of epo tx: 12 wks	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: ≤10.5	Disease: haem & solid Treatment: chemo, mixed	HaemR, Hct, RBCT, HRQoL[a], AE[a]	Y

Study year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl. in Cochrane 2012, Y/N
data + unified analysis Identified: citation checking Primary study: *Abels 1993*	Hb BL g/dl: NR Epo mU/ml BL: 146 ± 260	Epo mU/ml BL: 149 ± 217	Dur. of trial: 12 wks[c] Follow-up: NR		g/dl)			
Case 1993[55] RCT Primary study: *Abels 1993*	n = 81 (analysed 79) Age, yrs: 64 (27–92)* n (%) Male: 33 (40.7) Hb BL (g/dl): NR Epo mU/ml BL: 95.0 (16–1,262)*	n = 76 (analysed 79) Age, yrs: 64 (30–88)* n (%) Male: 29 (38.1) Hb BL (g/dl): NR Epo mU/ml BL: 93.5 (16–1,734)*	Brand: epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Yes, ↓ prn Dur. of epo tx: NR Dur. of trial: NR Follow-up: NR	SC	Iron: Y, oral iron fixed G-CSF: no RBCT trigger: Hb <9 g/dl (Hb incl. criteria level: <10.5 g/dl)	Disease: solid (incl ovarian) Treatment: chemo, plat	Hb, Hct, patients' RBCT	Y
Henry, 1995[57] ROL Primary study: *Abels 1993*	n=69 (analysed 64) Age, yrs: 58 n (%) Male: 30 (45) Hb BL (g/dl): NR Epo mU/ml BL: NR	n=61 (analysed 65) Age, yrs: 59 n (%) Male: 32 (49) Hb BL (g/dl): NR Epo mU/ml BL: NR	Brand: epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Yes, ↓ prn Dur. of epo tx: 12 wks or until haematocrit =38%−40% Dur. of trial: 12 weeks Follow-up: NR	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: NR)	Disease: haem & solid Treatment: chemo, plat	Hct, RBCT, AE	Y
Henry, 1994[56] ROL Double-blind & open-label extension data Identified: citation checking Primary study: *Abels 1993*	n = 67 (analysed 64) Age, yrs: NR[b] n (%) Male: NR[b] Hb BL (g/dl): NR[b] Epo mU/ml BL: NR[b]	n = 65 (analysed 61) Age, yrs: NR[b] n (%) Male: NR[b] Hb BL (g/dl): NR[b] Epo mU/ml BL: NR[b]	Brand: epoetin alfa Dose: 450 IU/kg QW Dose adjustment: NR Duration of epo tx: 12 wks Duration of trial: NR Follow-up:	SC	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: NR)	Disease: solid & haem Treatment: chemo, plat	HaemR, RBCT, HRQoL, AE	Y
PENTAG REVIEW: STUDY CHARACTERISTICS: PRIMARY STUDIES 2004 to CURRENT								
Grote 2005[73] ROL N93-004	n = 109 Age, yrs: 64.4 (8.7) n (%) Male: 59 (54.1) Hb BL g/dl: 12.8 (1.5) Epo mU/ml BL: NR	n = 115 Age, yrs: 63.2 (8.9) n (%) Male: 64 (55.7) Hb BL g/dl: 13 (1.5) Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: Unclear Dur. of trial: Unclear Follow-up: 3 yrs	PBO	Iron: NR G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: <14.5 g/dl)	Disease: solid (SCLC) Treatment: chemo: plat	Hb, RBCT, AE, TR, survival	Y
Moebus 2013[62]	n = 324 Age, yrs: 50 (29–65)*	n = 319 Age, yrs: 52 (28–67)	Brand: Epoetin alfa Dose: 150 IU/kg TIW	SC	Iron: Y, oral G-CSF: NR	Disease: solid (breast)	Hb, RBCT, HRQoL, AE, survival	N

Study year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl. in Cochrane 2012, Y/N
ROL AGO ETC trial	n (%) Male: all female Hb BL g/dl: 12.4 (9–16)* Epo mU/ml BL: NR	n (%) Male: all female Hb BL g/dl: 12.8 (9–16) Epo mU/ml BL: NR	Dose adj.: Y Dur. of epo tx: 18 wks* Dur. of trial: 18 wks* Follow-up: 10 yr (ongoing)		RBCT trigger: Hb <9 g/dl & investigator discretion (Hb incl. criteria level: NR)	Treatment: chemo: non-plat		However, Moebus 2004, 2007 included
Ray-Coquard 2009[74] **ROL** ELYPSE study	n = 110 Age, yrs: 62.7 (11.6) n (%) Male: 52 (47.3) Hb BL g/dl: 10 (1.2) Epo mU/ml BL: NR	n = 108 Age, yrs: 61.7 (11.6) n (%) Male: 41 (38) Hb BL g/dl: 10 (1.2) Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: 12 mths (95% CI 12–12.4)*	SC	Iron: Y, oral G-CSF: Y RBCT trigger: NR (Hb incl. criteria level: ≤12.0 g/dl)	Disease: solid & haem Treatment: chemo: NR	RBCT, OS, HRQoL, AE	Y
Strauss 2008[75] **RCT** NCT00046969; Roche MO16375; Strauss 2005	n = 34 Age, yrs: 48.8 ± 10.2 n (%) Male: all female Hb BL g/dl: 11.4 (10.8–12.0)* Epo mU/ml BL: NR	n = 40 Age, yrs: 49.2 ± 12.8) n (%) Male: all female Hb BL g/dl: 11.6 (10.9–12.4)* Epo mU/ml BL: NR	Brand: Epoetin beta Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: 6 mths	PBO	Iron: Y, oral or i.v. G-CSF: NR RBCT trigger: ≤8.5 g/dl prn (Hb incl. criteria level: 9–13 g/dl)	Disease: solid (cervix) Treatment: chemo + radio	Hb, RBCT TR, survival, AE	Y
Tjulandin 2010[45] **RCT** ISRCTN09530309	EPOETIN THETA n = 76 Age, yrs: 53.7 ± 10.3 n (%) Male: 30 (39.5) Hb BL g/dl: 9.6 ± 1.1 Epo mU/ml BL: NR EPOETIN BETA n = 73 Age, yrs: 57.3 ± 10.5 n (%) Male: 22 (30.1) Hb BL g/dl: 9.5 ± 0.8 Epo mU/ml BL: NR	n = 74 Age, yrs: 57.3 ± 11.5 n (%) Male: 19 (25.7) Hb BL g/dl: 9.4 ± 1.2 Epo mU/ml BL: NR	Brand: Epoetin beta Dose: 150 IU/kg TIW Dose adj.: Y Brand: Epoetin theta Dose: 20,000 IU/QW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: NR	PBO	Iron: Y, not specified G-CSF: NR RBCT trigger: ≤8.5 g/dL prn (Hb incl. criteria level: ≤11.0 g/dl)	Disease: solid Treatment: chemo: plat	HaemR, Hb, patients' RBCT, units RBCT, HRQoL, AE	Y
Tjulandin 2011[76] **RCT**	n = 95 Age, yrs: 56.9 ± 14.7 n (%) Male: 30 (31.6) Hb BL g/dl: 9.2 ± 1.3 Epo mU/ml BL: NR	n = 91 Age, yrs: 55.8 ± 14.3 n (%) Male: 34 (37.4) Hb BL g/dl: 9.1 ± 1.3 Epo mU/ml BL: NR	Brand: Epoetin theta Dose: 20,000 IU QW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: NR	PBO	Iron: Y, not specified G-CSF: NR RBCT trigger: ≤8.5 g/dL (Hb incl. criteria level: ≤11.0 g/dl)	Disease: solid & haem Treatment: chemo: non-plat	HaemR, Hb, patients' RBCT, units RBCT, HRQoL, AE	Y
Untch 2011a, b[77,78] **RCT**	n = 356 Age, yrs: 48 (23–65)*[a] n (%) Male: NR Hb BL g/dl: 13.64 ± 1.17 Epo mU/ml BL: NR	n = 377 Age, yrs: 48 (23–65)*[a] n (%) Male: NR Hb BL g/dl: 13.61 ± 1.16 Epo mU/ml BL: NR	Brand: Darbepoetin alfa Dose: 4.5 mg/kg Q2W[k] Dose adj.: Y Dur. of epo tx: NR Dur. of trial: NR Follow-up:median 43.5 mths	SC	Iron: Y, oral G-CSF: NR RBCT trigger: NR (Hb incl. criteria level: NR	Disease: solid (breast) Treatment: chemo: non-plat	Hb, pathological response, disease progression, survival, AE	Y

Study year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl. in Cochrane 2012, Y/N
MULTIPLE PUBLICATIONS: PENTAG REVIEW								
Aapro 2004[80] Primary study: *Littlewood, 2001*	n = 251 (analysed 244) Age, yrs: 58.3 ± 14.2 n (%) Male: 85 (34) Hb BL g/dl: 9.9 ± 1.1 Epo mU/ml BL: NR	n = 124 (analysed 115) Age, yrs: 59.5 ± 13.9 n (%) Male: 39 (31) Hb BL g/dl: 9.7 ± 1.1 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: up to 28 wks Dur. of trial: up to 28 wks Follow-up: 12-mth[f]	PBO	Iron: Y, oral or i.v. G-CSF: No RBCT trigger: Hb <8 g/dl prn (Hb incl. criteria level: ≤10.5 g/dL or >10.5 but ≤12.0 g/dl after a ≥1.5 g/dl decrease in Hb)	Disease: solid + haem Treatment: chemo, non-plat	HaemR, Hb, RBCT, HRQoL, AE, survival (at 12-mths follow-up)	N
Bajetta 2004[79] Primary study: *Littlewood, 2001*	SUBGROUP: BREAST POP n = 78 (analysed 75) Age, yrs: 54.6 n (%) Male: 1 (1) Hb BL g/dl: 10.0 ± 1.6 Epo mU/ml BL: NR	SUBGROUP: BREAST POP n = 36 (analysed 35) Age, yrs: 52.9 n (%) Male: all female Hb BL g/dl: 9.9 ± 1.01 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: up to 28 wks Dur. of trial: up to 28 wks Follow-up: 12-mth[f]	PBO	Iron: Y, oral (or i.v. as indicated by transferrin sat. level) G-CSF: No RBCT trigger: Hb <8 g/dl prn (Hb incl. criteria level: ≤10.5 g/dL or >10.5 but ≤12.0 g/dl after a ≥1.5 g/dl decrease in Hb)	Disease: solid + haem Treatment: chemo, non-plat	HaemR, Hb, RBCT, HRQoL, AE (retrospective analysis of breast cancer cohort; trial [Littlewood, 2001])	N
Littlewood 2006[82] Primary study: *Hedenus, 2003*	SUBGROUP: HRQoL SAMPLE n = 303[l] Age, yrs: 64.8 (12.8) n (%) Male: 146 (48.2) Hb BL g/dl: 9.6 (1.2) Epo mU/ml BL: NR		Brand: Darbepoetin alfa Dose: 2.25 µg/kg QW Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: median ~11 mths	PBO	Iron: prn G-CSF: NR RBCT trigger: Hb ≤8 g/dl (Hb incl. criteria level: ≤11.0 g/dl)	Disease: haem Treatment: chemo, NR	HRQoL (alleviating fatigue & effect of fatigue on QoL)	N
Osterborg 2005, follow-up of Osterborg 2002[70] **RCT** Primary study: *Osterborg, 2002*	n = 173 (analysed 170) Age, yrs: 63 (32–86)* n (%) Male: 91 (54) Hb BL g/dl: 9.2 ± 1.1 Epo IU/L BL: 38 (20–72)*	n = 176 (analysed 173) Age, yrs: 64 (28–83)* n (%) Male: 82 (47) Hb BL g/dl: 9.3 ± 1.0 Epo IU/L BL: 41 (21–77)*	Brand: Epoetin beta Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: 16 wks Dur. of trial: up to 16 wks Follow-up: min 17.5 mths both tx grps	PBO	Iron: Y, oral iron, or i.v. iron if transferrin saturation ≤20% G-CSF: No RBCT trigger: Hb <8.5 g/dl or inc.in Hb <0.5 g/dl vs BL (Hb incl. criteria level: <10 g/dl[g])	Disease: haem Treatment: chemo, non-plat	long-term survival	Y
Patrick 2003[60] Primary study: *Littlewood, 2001*	n = 251 (analysed 244) Age, yrs: 58.3 ± 14.2 n (%) Male: 85 (34) Hb BL g/dl: 9.9 ± 1.1 Epo mU/ml BL: NR	n = 124 (analysed 115) Age, yrs: 59.5 ± 13.9 n (%) Male: 39 (31) Hb BL g/dl: 9.7 ± 1.1 Epo mU/ml BL: NR	Brand: Epoetin alfa Dose: 150 IU/kg TIW Dose adj.: Y Dur. of epo tx: up to 28 wks Dur. of trial: up to 28 wks Follow-up: 12-mth[f]	PBO	Iron: Y, oral (or i.v. as indicated by transferrin sat. level) G-CSF: No RBCT trigger: Hb <8 g/dl prn (Hb incl. criteria level: ≤10.5 g/dL or >10.5 but ≤12.0 g/dl after a ≥1.5 g/dl decrease in Hb)	Disease: solid + haem Treatment: chemo, non-plat	HRQoL (minimally important difference in HRQoL)	N
Vansteenkiste 2004[81]	SUBGROUP <10 g/dl n = 51	SUBGROUP <10 g/dl n = 69	Brand: Darbepoetin alfa Dose: 2.25 µg/kg QW	PBO	Iron: No G-CSF: No	Disease: solid (lung) Treatment: chemo:	HaemR, Hb, RBCT (from Wk 5 and Wk 1),	Y

Study year	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Outcomes sought	Incl. in Cochrane 2012, Y/N
Primary study: *Vansteenkiste, 2002*	Age, yrs: 63 (47–76) n (%) Male: 42 (82) Hb BL g/dl: 9.2 (7.4–9.9) Epo mU/ml BL: 50.3 (13.3–739.8) SUBGROUP ≥10 g/dl n = 105 Age, yrs: 62 (39–80) n (%) Male: 69 (66) Hb BL g/dl: 10.8 (10.0–13.6) Epo mU/ml BL: 28.8 (12.0–106.1)	Age, yrs: 60 (42–78) n (%) Male: 52 (75) Hb BL g/dl: 9.2 (6.6–9.9) Epo mU/ml BL: 52.2 (14.3–1,998.6) SUBGROUP ≥10 g/dl n = 89 Age, yrs: 62 (36–76) n (%) Male: 64 (72) Hb BL g/dl: 10.6 (10.0–12.3) Epo mU/ml BL: 30.2 (12.0–109.8)	Dose adj.: Y Dur. of epo tx: 12 wks Dur. of trial: 12 wks Follow-up: 12 mths		RBCT trigger: Hb ≤8 g/dl & prn (Hb incl. criteria level: ≤11.0 g/dl)	plat	HRQoL, AE, disease progression, survival	

Key: ~, approximately; ↓, decrease only; AE, adverse event; BL, baseline; C, cycles; chemo, chemotherapy; D, days; G-CSF, granulocyte colony stimulating factor; GI, gastrointestinal; grps., groups; gynae, gynaecological; HaemR, haematopoietic response; Hb, haemoglobin; HRQoL, health-related quality of life; inc., increase; incl., includ(e/ing); med., median; min., minimum; mths., months; NR, not reported; OS, overall survival; PBO, placebo; plat, platinum-based chemotherapy; prn, pro re nata (as needed); QoL, quality of life; QW, weekly; Q2W, every 2 weeks; RBCT, red blood cell transfusion; rHuEPO, recombinant human erythropoietin; SC, standard care; SCLC, small-cell lung cancer; TIW, thrice weekly; TR, tumour response; TVEs, thrombovascular events; tx, treatment; wks., weeks; yrs., years

Notes: * indicates median (range) **a** BL characteristics /and some efficacy outcomes reported for all participants randomised (i.e. includes participants not receiving chemotherapy [Abels, 1993]); for all doses of Darbepoetin alfa [Kotasek 2003]); for intervention and control combined at randomisation [Untch 2011a,b]); **b** Assumed to be either Epoetin alfa or Epoetin beta based on date of trial and dose administered in the trial; **c** Double-blind phase only; participants given the option to enter 12-week open-label treatment period; **d** Majority of participants received non-platinum chemotherapy; **e** Study includes other doses of intervention under review (either dose-response study Hedenus,2002, 2003; Kotasek, 2003; or three-arm trial Ten-Bokkel, 1998; Thatcher, 1999); **f** Survival based on data collected during 12-mth after study completed by last participant; Reported based on proportion of patients randomised (only available for a proportion of patients randomised; 151 and 145 intervention and control groups respectively); **g** Inclusion criteria for Hb further stratified by serum epo level; **h** Majority of participants received platinum-based chemotherapy; **i** Serum endogenous epo (mU/mL not available for all participants randomised; n= 145 and n= 151 in intervention and control group respectively; **j** Study conducted in paediatric population; **k** Dose administered in study equates to 2.25 µg/kg/QW; **l** Patients evaluated for HRQoL from trial sample (Hedenus 2003), not separated by intervention and control for HRQoL sample

Appendix H: Multiple publications in clinical-effectiveness review

Primary study

Hedenus, M., Adriansson, M., San Miguel, J. *et al* (2003). "Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study." Br J Haematol 122(3): 394-403.

Multiple publications

Littlewood, T. J. K., Joel D.; San Miguel, J. *et al* (2006). "Efficacy of darbepoetin alfa in alleviating fatigue and the effect of fatigue on quality of life in anemic patients with lymphoproliferative malignancies." Journal of Pain & Symptom Management 31: 317-325.

Primary study

Osterborg, A., Brandberg, Y., Molostova, V. *et al* (2002). "Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin Beta, in hematologic malignancies." J Clin Oncol **20**: 2486-2494.

Multiple publications

Osterborg, A. B., Hedenus, Michael (2005). "Impact of epoetin-beta on survival of patients with lymphoproliferative malignancies: long-term follow up of a large randomized study." British Journal of Haematology **129**: 206-209.

Primary study

Vansteenkiste, J., Pirker, R., Massuti, B. *et al* (2002). "Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy." J Natl Cancer Inst 94: 1211-1220.

Multiple publications

Vansteenkiste, J. T., Rossi, G.; Pirker, R. (2004). "Darbepoetin alfa in lung cancer patients on chemotherapy: a retrospective comparison of outcomes in patients with mild versus moderate-to-severe anaemia at baseline." Supportive Care in Cancer 12: 253-262..

Primary study

Littlewood, T. J., Bajetta, E. Nortier, J.W. *et al* (2001). "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 19: 2865-2874.

Multiple publications

Bajetta, E. V., E.; Reinhardt, IU.; Janmohamed, R.; Costa, R. M.; Matulonis, IU. (2004) "Efficacy of epoetin alfa in a retrospective non-stratified subgroup analysis of a breast cancer cohort receiving non-platinum chemotherapy." Tumori, 449-457.

Aapro, M. B., E., Freund, M., Littlewood, T. J. *et al* (2004). "Is there a possible survival benefit to increasing hemoglobin levels with epoetin alfa during chemotherapy?" European Journal of Cancer, Supplement 2: 20-28.

Patrick, D. L., Gagnon, D. D., Zagari, M. J. *et al* (2003). "Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients receiving epoetin alfa." Eur J Cancer 39(3): 335-345.

Primary study

Abels, R. (1993). "Erythropoietin for anaemia in cancer patients." Eur J Cancer 29A Suppl 2: S2-8.

Multiple publications

Case, D. C., Jr., Bukowski, R. M., Carey, R.W. *et al*. (1993). "Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy." J Natl Cancer Inst 85: 801-806.

Henry, D. H. and R. I. Abels (1994). "Recombinant human erythropoietin in the treatment of cancer and chemotherapy-induced anemia: results of double-blind

and open-label follow-up studies." Semin Oncol 21: 21-28.

Henry, D. H., Brooks, B. J. Jr., Case, D. C. Jr. *et al* (1995). "Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy." Cancer J Sci Am 1(4): 252-260.

Abels, R. I., Larholt, K. M., Krantz, K.D. *et al* (1996). "Recombinant Human Erythropoietin (rHuEPO) for the Treatment of the Anemia of Cancer." Oncologist 1(3): 140-150.

Primary study

Untch, M., P., Fasching, A., Konecny, G.E. *et al* (2011). "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." Annals of Oncology 22: 1988-1998.

Multiple publications

Untch, M., P., Fasching, A., Konecny, G.E. *et al* (2011). "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." Annals of Oncology, 1999-2006

Appendix I: Systematic reviews

Table 104. Systematic reviews: study characteristics

Author Year	Title (No. of included studies)	Participants	Intervention	Comparator	Outcomes	Design	Results	Comment
Lawrence, 2004[106]	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. 1 study incl on epo alfa	Various. PBO used in single epo alfa study	Fatigue as determined by HaemR and QoL measures	Variety. Only RCTs included for treatment of CRF	For the epo 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 epo alfa group than the PBO group (2.2 g/dL vs 0.5 g/dL, P< 0.001). Significant differences observed for epo for all 5 cancer and anaemia-specific primary QoL measures (P≤ 0.0048)	Only 1 relevant study involving epo was included in this SR
Bokemeyer, 2007[a,107]	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, transfusion requirement, QoL, OS, QoL	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.	
Ross, 2007[108]	Efficacy and Safety of Erythropoiesis-Stimulating Proteins in MDS: 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 (4 RCTs included for epo vs control)	Significant increase in HaemR (OR, 5.2; CI 2.5-10.8) found for patients receiving epo compared to control. Patients receiving erythropoiesis-stimulating proteins attained a pre-post change (measured using FACT-F) that exceeded minimum clinically important differences.	Only 4 relevant studies (RCTs of epo vs control) were included in this SR

Author Year	Title (No. of included studies)	Participants	Intervention	Comparator	Outcomes	Design	Results	Comment
Wilson, 2007[b1]	A systematic review and economic evaluation of epo alfa, epo beta and darbepo 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 (incl. RBCT)	SC for anaemia (incl. RBCT) alone	HaemR, RBCT, Hb change, HRQoL, tumour response, OS, AEs	RCTs	Epo improves HaemR (defined as an improvement by 2 g dl-1)(RR of 3.4 CI 3-3.8; response rate for epo of 53%). Hb change showed a weighted mean difference of 1.63 g dl -1 (CI 1.46-1.8) in favour of epo. The number of CIA patients receiving RBCT reduced by an estimated 18%. A positive effect was was observed in favour of an improved HRQoL for patients receiving epo	The incidence of side-effects and effects on survival remains highly uncertain. Authors suggest that if there is no impact on survival, it seems highly unlikely that epo would be considered a cost-effective use of healthcare resources
Shehata, 2008[109]	The use of erythropoiesis-stimulating agents in patients with non-myeloid hematological malignancies: a systematic review (22 studies included [17 published reports and 5 abstracts])	Adults with non-myeloid hematological malignancies	ESAs	PBO	RBCT, HRQoL, OS	RCT's	Statistically significant decrease in transfusion requirements. No evidence that the use of ESAs improved survival. Impact on QoL was difficult to assess due to limitations in available studies.	Authors stare that more data is required to confirm improvements in QoL and inferior survival associated with ESA use.
Kvam, 2009[110]	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=2,200; Epo n= 1,207)	Epo alfa, beta; Darb alfa	PBO (in relevant studies)	RBCT, Hb change, transfusion-free survival, HRQOL outcomes and HRQOL influence on clinical decision making (author's statement)	RCTs	Statistically significant decrease in RBCT and rise in Hb levels in patients receiving ESAs. Improvement in HRQOL for Epo beta (1 study); improvement in HRQOL for Darb alfa (1 study); improvement of cancer and anaemic-specific HRQOL domains for epo alfa (1 study)	Only 4 relevant studies were included in this SR. Epo alfa was recommended based on better clinical outcomes and improvement in HRQOL (2 studies). Epo beta was recommended based on improved HRQOL and better clinical outcomes (1 study). Darb alfa was recommended based on better clinical outcomes and less fatigue (1 study). However, average HRQOL benefit of ESA's in these trals appears to be of limited subjective importance, despite HRQOL data being used widely for marketing of ESA's.
Tonelli, 2009[112]	Benefits and harms of erythropoiesis-stimulating	Anaemic adults with cancer	Epo alfa, beta; Darb alfa	No treatment; PBO	Mortality, CV events, HTN,	RCTs	Pooled all-cause mortality during treatment was significantly higher in the group receiving	Use of ESA's resulted in increased risk of

Author Year	Title (No. of included studies)	Participants	Intervention	Comparator	Outcomes	Design	Results	Comment
	agents for anemia related to cancer: a meta-analysis (52 trials included)				HRQoL, RBCT, tumour response		erythropoiesis-stimulating therapy compared to control (RR 1.15. 95% CI 1.03-1.29). Compared with no treatment, use of ESAs led to clinically detectable improvements in disease-specific measures of quality of life. It also reduced the use of blood transfusions (RR 0.64, 95% CI 0.56-0.73)	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)
Bohlius 2010 (results also reported in Bohlius 2009)[c]	Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials (53 studies included)	Paediatric and adult cancer patients	Epo alfa, epo beta, or darb alfa plus RBCT(as necessary)	RBCT alone (as necessary)	Mortality during the active study period, overall survival	RCTs	1,530 patients died during the active study period and 4,993 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, 1.30) and worsened OS (1.06, 1, 1.12), with little heterogeneity between trials. The cHR for mortality during the active period for patients on chemotherapy was 1.10 (0.98-1.24), and 1.04 (0.97, 1.11) for OS. There was little evidence for a difference betwen 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.
Minton, 2010[d113]	Drug therapy for the management of cancer-related fatigue (CRF) (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 epo; 4 relevant studies for darb alfa	A meta-analysis of studies for ESAs showed an effect of ESAs over standard care or PBO for the treatment of CRF. A meta-analysis of studies for darbopoetin studies showed a sma ll but statistically significant difference between darbopoetin and PBO for the treatment of CRF	Authors note increased safety concerns raised regarding ESAs and recommend that it is not used in practice. There was a very high degree of statistical and clinical heterogeneity in the trials.
Grant, 2013[59]	Epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment: comparative effectiveness update (54 studies included)	Anaemic adults undergoing chemotherapy and/or radiation for malignancy	ESAs	Control (various)	OS (on-study and longest available follow-up), PFS, QoL, HaemR, RBCT, tumour response, thromboembolic complications, AEs	RCTs, Obs	In 38 trials, ESA's decreased the risk of transfusion (pooled RR 0.58, CI 0.53, 0.64). In 37 trials, thromboembolic event rates were higher in ESA-treated patients (pooled RR 1.51; CI 1.3, 1.74). In 14 trials reporting quality of life (FACT-fatigue subscale), scores decreased by -0.6 in control arms (CI -6.4, 5.2) and increased by 2.1 in ESA arms (CI -3.9, 8.1). In 37 trials, mortality was increased during the on-study period (pooled HR 1.17; 95% CI, 1.04, 1.31).	Authors conclude that ESAs reduce the need for RBCT and increased 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
Tonia, 2012[e10]	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, tumour response, on-study mortality, OS, AEs	RCTs	Use of ESAs significantly reduces the relative risk of red blood cell transfusion (RR 0.65; CI 0.62, 0.68) Haematological respons was observed more often in participants receiving ESAs (RR 3.93; CI 3.10, 3.71). There was suggestive evidence that ESA's may improve QoL. There was strong evidence that ESAs increase mortality during active study period (HR 1.17. CI 1.06 to 1.29) and some evidence that ESA's decrease OS (HR 1.05; CI 1 to 1.11) Risk of AEs for thromboembolic complications was increased for patients receiving ESA's compared to controls, while HTN and thrombocytopenia/haemorrhage may be increased in patients receiving ESAs compared to controls.	Authors conclude that ESAs reduce the need for RBCT but increase the risk for thromboembolic events and deaths. Authors recommend that the increased risk of death and thromboembolic events should be balanced againstthe potential balance benefits of ESA treatment

Key: AE, adverse event; chemo, chemotherapy; cHR, combined hazard ratio; CI, confidence interval; CIA, cancer induced anaemia; CRF, cancer related fatigue; CV, cardiovascular; darb, darbepoietin; epo, erythropoietin; ESAs, erythropoietin stimulating agents; FACT-F, Functional Assessment of Cancer Therapy – Fatigue; HaemR, haematological response; Hb, haemoglobin; HRQoL, health-related quality of life; HTN, hypertension; incl., includ(e/ing); MM< multiple myeloma; NR, not reported; Obs, observational; OS, overall survival; PFS, progression-free survival; PBO, placebo; QoL, quality of life; RBCT, red blood cell transfusion; RCT, randomised controlled trial; RR, risk ratio; SC, standard care; TR, tumour response

Notes: a This study is an update of the 2004 guidelines by the same author published as Bokemeyer, C.;Aapro, A.; Courdi, J.; et al (2004). "EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer." European journal of cancer 40: 2201-2216[243]; **b** Previous HTA report (TA142)[34] (Wilson and colleagues, 2007); **c** The results of this Cochrane Review are also published in Bohlius, J. S., Kurt; Brillant, C., et al (2009). "Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials.[Erratum appears in Lancet. 2009 Jul 4-2009 Jul 10;374(9683):28]." Lancet 373: 1532-1542[6]; **d** This study is an update of 2008 Cochrane Review: Minton, O.; Richardson, A.; Sharpe, M.; et al. (2008). "Drug therapy for the management of cancer related fatigue." Cochrane Database of Systematic Reviews: CD006704.[111] Also published in Minton, O; Richardson, A; Sharpe, M. et al (2008). "A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue." Journal of the National Cancer Institute 100: 1155-1166[244]; **e** This study is an update of 2006 Cochrane Review: Bohlius J, Wilson J, Seidenfeld J et al. Erythropoietin or Darbepoetin for patients with cancer. Cochrane Database of Systematic Reviews 2006, Issue 3[245]. Also published in Bohlius J, Langensiepen S, Schwarzer G et al. Recombinant human erythropoietin and overall survival in cancer patients: results of a comprehensive meta-analysis. Journal of the National Cancer Institute 2005;97(7):489–98[246]; Bohlius J, Wilson J, Seidenfeld et al.Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9,353 patients. Journal of the National Cancer Institute 2006; 98:708–14[247]; and, Bohlius, J. F.; Langensiepen, S.; Engert, A; et al. (2005). "Effectiveness of erythropoietin in the treatment of patients with malignancies: methods and preliminary results of a Cochrane review." Bailliere's Best Practice in Clinical Haematology 18: 449-454[248]

Table 105. Systematic reviews: PRISMA quality assessment

			Studies										
Section/ topic	**Item**	**Checklist item**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**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** [j]	**P** [p]	**N**	**P** [y]	**P** [ad]	**P** [al]	**P** [ap]	**P** [av]	**P** [ba]
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** [f]	**N**	**P** [k]	**Y** [q]	**P** [t]	**P** [z]	**Y** [ae]	**P** [am]	**P** [aq]	**P** [aw]	**Y**
Methods													
Protocol & 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** [g]	**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** [h]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**P** [ar]	**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** [af]	**Y** [an]	**Y** [as]	**Y** [ax]	**Y** [bb]
Study selection	9	State the process for selecting studies	**N**	**N**	**N**	**Y** [r]	**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** [l]	**Y**	**P** [u]	**N**	**P** [ag]	**Y** [ao]	**P** [at]	**Y** [ay]	**P** [bc]
Data items	11	List and define all variables for which data are sort and any assumptions and simplifications made	**Y**	**N**	**N**	**Y**	**Y**	**N**	**N**	**Y**	**P** [au]	**Y**	**Y**
Risk of bias	12	Describe methods used for assessing risk of bias of individual studies and how this	**N**	**N**	**Y**	**Y**	**Y**	**P** [aa]	**Y** [ah]	**Y**	**Y**	**Y**	**Y**

			Studies										
Section/ topic	**Item**	**Checklist item**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
in individual studies		information is to be used in any data synthesis											
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 done, including measure 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 done, indicating which were pre-specified	**N**	**N**	**Y**	**Y**	**P** [v]	**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 from a flow diagram	**N**	**N**	**N**	**Y**	**N**	**P** [ab]	**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** [ai]	**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** [i]	**N**	**Y**	**Y**	**P** [ac]	**Y** [aj]	**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** [m]	**Y**	**N**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measure of consistency	**N**	**N**	**P** [n]	**Y**	**N**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**
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 done	**N/A**	**N/A**	**Y**	**Y**	**Y** [w]	**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** [0]	**Y**	**Y**	**Y**	**P** [ak]	**Y**	**Y**	**Y**	**P** [bd]
Limitations	25	Discuss limitation at study and outcome level and at review level	**N**	**N**	**N**	**P** [s]	**Y**	**Y**	**Y**	**N**	**Y**	**P** [az]	**N**

			Studies										
Section/ topic	**Item**	**Checklist item**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implication for future research	**Y**	**Y**	**Y**	**Y**	**Y** [x]	**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**

Studies: A Lawrence 2004[106]; B, Bokemeyer, 2007 [a 107] C, Ross, 2007[108]; D, Wilson, 2007[b1]; E, Shehata, 2008[109]; F, Kvam, 2009[110]; G, Tonelli, 2009[112]; H, Bohlius, 2010[c]; I, Minton, 2010[d113]; J, Tonia, 2012[e10]; K, Grant, 2013[59]

Key: Y, present; N, absent; P, partially reported; ?, unclear

Notes: a This study is an update of the 2004 guidelines by the same author published as Bokemeyer, C.;Aapro, A.; Courdi, J.; et al (2004). "EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer." European journal of cancer 40: 2201-2216[243]; **b** Previous HTA report (TA142)[34] (Wilson and colleagues, 2007); **c** The results of this Cochrane Review are also published in Bohlius, J. S., Kurt; Brillant, C., et al (2009). "Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials.[Erratum appears in Lancet. 2009 Jul 4-2009 Jul 10;374(9683):28]." Lancet 373: 1532-1542[6]; **d** This study is an update of 2008 Cochrane Review: Minton, O.; Richardson, A.; Sharpe, M.; et al. (2008). "Drug therapy for the management of cancer related fatigue." Cochrane Database of Systematic Reviews: CD006704.[111] Also published in Minton, O; Richardson, A; Sharpe, M. et al (2008). "A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue." Journal of the National Cancer Institute 100: 1155-1166[244]; **e** This study is an update of 2006 Cochrane Review: Bohlius J, Wilson J, Seidenfeld J et al. Erythropoietin or Darbepoetin for patients with cancer. Cochrane Database of Systematic Reviews 2006, Issue 3[245]. Also published in Bohlius J, Langensiepen S, Schwarzer G et al. Recombinant human erythropoietin and overall survival in cancer patients: results of a comprehensive meta-analysis. Journal of the National Cancer Institute 2005;97(7):489–98[246]; Bohlius J, Wilson J, Seidenfeld et al.Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9,353 patients. Journal of the National Cancer Institute 2006; 98:708–14[247]; and, Bohlius, J. F.; Langensiepen, S.; Engert, A; et al. (2005). "Effectiveness of erythropoietin in the treatment of patients with malignancies: methods and preliminary results of a Cochrane review." Bailliere's Best Practice in Clinical Haematology 18: 449-454[248] **f** Research questions defined in methods section; full PICOS criteria not applicable **g** Full PICOS criteria not applicable **h** No search start date specified **i** Risk of bias assessed using ASCO levels of evidence and grades of recommendation **j** No background, databases, incl/excl criteria, pareticipants, quality appraisal, review implications/limitations or review registration number mentioned in abstract **k** Comparators, main outcome, study design not mentioned in introduction **l** No mention of piloting or processes for obtaining/confirming data **m** Event rates given as percentages rather than frequencies, and only odds ratios provided **n** I^2 values not given in results section **o** Relevance for key groups not addressed **p** No details of quality assessment, study appraisal and synthesis in abstract, with full detaisl presented in methods section **q** PICOS contained in executive summary **r** PRISMA flow diagram in appendix **s** Limitations at review level mentioned **t** Population, intervention and outcome described in abstract, study design in methods section; comparator not defined in either abstract, introduction or methods **u** No mention of piloting or processes for obtaining/confirming data **v** Intention to treat analysis conducted **w** Summary of numbers needed to treat **x** Implications for future research not mentioned **y** Background detailed in introduction. Ojectives specified in abstract but PICOS not appropriate. Data extraction detailed in methods section. Limitations detailed in discussion section. No systematic review registration number **z** Patients, outcomes, and study design detailed in objectives (intervention and comparator not applicable) **aa** Methodological quality was assessed according to a checklist developed for evaluating HRQoL outcomes in clinical trials **ab** Minimum detail provided **ac** Summary of checklist given but no detailed breakdown of criteria **ad** Details online. No systematic review registration number **ae** PICOS covered in abstract and introduction, despite being no defined "objectives" section **af** Details in online appendix **ag** No mention of piloting or processes for obtaining / confirming data **ah** Online (Appendix 4) **ai** Details online **aj** Details online **ak** No assessment/ranking of evidence robustness **al** Data extraction detailed in methods section. No limitations mentioned in abstract, but stated in discussion section. No systematic review registration number **am** Population, intervention and outcome covered in objectives; comparator and study detailed in methods section **an** Online (Appendix A) **ao** No mention of piloting **ap** Objectives in abstract lacking in detail. Elements of PICOS 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 **aq** Population, intervention and comparator covered in objectives. Outcome and study details in methods section **ar** No search start date specified **as** Online appendix **at** No mention of piloting or processes for obtaining / confirming data **au** Broad categories described rather than individual data items **av** Objectives lacking in detail with respect to comparators and studt 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. **aw** Population, intervention and outcome covered in objectives. Comparator and study detailed in methods section. **ax** Details in appendix **ay** No mention of piloting or processes for obtaining/confirming data **az** Limitations at review level **ba** Data sources listed in methods section together with details of study selection criteria, data extraction, synthesis methods, outcomes of interest. Outcomes detailed in executive summary. No systematic review registration number provided **bb** Appendix **bc** No mention of processes for obtaining/confirming data **bd** No consideration of applicability of review's findings

Appendix J: Comparison of search results with the manufacturer submissions

Table 106. Sandoz UK Ltd submission

Haag-Weber, M., K. IU. Eckardt, W. H. Horl, S. D. Roger, A. Vetter and K. Roth (2012). "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 nephrology 77: 8-17.	Comparator (alfa vs alfa); no control
Weigang-Kohler, K. V., Andrea; Thyroff-Friesinger, Ursula (2009). "HX575, recombinant human epoetin alfa, for the treatment of chemotherapy-associated symptomatic anaemia in patients with solid tumours." Onkologie 32: 168-174.	Comparator (alfa vs alfa); no control
Desrame J 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 Sept – 1 Oct 2013.	Abstract only; observational study
Kerkhofs L et al. Use of biosimilar epoetin to increase haemoglobin levels in patients with chemotherapy-induced anemia: real-life clinical experience. Future Oncol 2012; 8: 751–756	Abstract only; retrospective analysis
Lorenz A et al. 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 Sept – 1 Oct 2013	Abstract only; retrospective, matched-cohort analysis
Rodriguez Garzotto A 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 Sept – 1 Oct 2013	Abstract only; study design single centre audit

Table 107. Amgen Ltd submission

Delarue R. Delarue, R. (2012). "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, ECCLU 2012 Lugano Switzerland 82: S12-S13	Abstract only; included in ongoing studies table
Hartmann, J. T. M., B.; Binder, C.; Mergenthaler, H. G.; Rick, O.; Sayer, H. G.; Mayer, F.; Beyer, J.; Lorch, A.; Berdel, W. E.;	Abstract only; included in

Frickhofen, N.; Bokemeyer, C.; Schleicher, J.; Gauler, T. C. (2012). "Addition of darbepoetin alfa to sequential high-dose VIP chemotherapy for patients with advanced metastatic germ cell cancer." 2012 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States 30 (15 SUPPL. 1.)	ongoing studies table
Katsumata, N., Y. Fujiwara, N. Katakami, Y. Nishiwaki, M. Tsuboi, K. Takeda, T. Nakanishi, Y. Ichinose, Y. Kawahara, T. Hotta and N. Saijo (2009). "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, Asia Nagoya Japan 97: 58.	Abstract only; included in ongoing studies table
Nitz IU, Oberhoff C, Reimer T, Schumacher C, Hackmann J, Warm M. Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: a safety analysis from the phase III ARA plus trial. Paper presented at 31st Annual San Antonio Breast Cancer Symposium; 10-14 Dec 2008; San Antonio, USA. Cancer Res 2009;69.	Abstract only; included in ongoing studies table
Suzuki Y, Tokuda Y, Okamoto R, Nakagawa K, Ando K, Iwata H. Randomized, placebo-controlled phase II study of darbepoetin alfa (DA) administered every three weeks (Q3W) in patients with chemotherapy induced anemia (CIA). Paper presented at 34th Congress of the European Society for Medical Oncology (ESMO); 12-16 Sep 2008; Stockholm, Sweden. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2008;19:viii277.	Abstract only; included in ongoing studies table

Appendix K: Ongoing studies

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl 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, London)	UK	80	Phase 3	Active, not recruiting	NA
NCT01444456 / 20101123	Amgen	Assessment of Quality of Life in Patients With Symptomatic Chemotherapy-induced Anaemia	MD, Amgen	Austria, Belgium, France, Germany, Greece, Italy, Netherlands, Poland, Romania	1,264	?	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	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	2,100	Phase 3	Recruiting	NA
NCT00858364 / 20070782	Amgen	Anemia Treatment for Advanced Non-Small Cell Lung Cancer (NSCLC) Patients Receiving Chemotherapy	MD, Amgen	USA, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Croatia, Czech Republic, Germany, Greece, Hong Kong,	3,000	Phase 3	Recruiting	NA

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
				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				
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 4	Recruiting	NA
NCT01795690 / iOM TAn	iOMEDICO AG	Clinical Registry on Anemia-Therapy (TAn-Registry)	?	Germany	1,000	?	Recruiting	NA
STATUS UNKNOWN								
NCT00381836 / 2005-005658-37 / LM: 2612-3148 / Ethical: 20060074 / Data Protection: 2005-41-6015	University of Aarhus and Amgen	Effect of darbepoetin alfa (Aranesp®) on anemia in patients with advanced hormone independent prostate cancer	Michael Borre (Department of Urology, Aarhus University Hospital)	Denmark	140	Phase 3 (anaemia)	Unknown	NA
NCT00400686 / CASE-CCF-5497 / P30CA043703 / CASE-CCF-5497 / ORTHO-CASE-CCF-5497	The Cleveland Clinic	Epoetin alfa in treating anemia in patients undergoing chemotherapy for multiple myeloma	Ronald M. Sobecks (Case Comprehensive Cancer Center)	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 3	Unknown	NA
NCT00039884 / 01/155A	Mirhashemi, Ramin, M.D.	Will Radiation/Chemotherapy Treatment of Cervical Cancer Work Better With Medication That May Improve Anemia?	Mirhashemi, Ramin	USA	64	Phase 2	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	1,234	?	Unknown	NA
NCT00281892 /	German CLL Study Group	Fludarabine and Darbepoetin Alfa in Treating Older Patients With Chronic Lymphocytic Leukemia	Michael Hallek MD (Medizinische Universitaetsklinik I, University	Germany	348	Phase 3	Unknown	-

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
			of Cologne)					
TERMINATED								
NCT00386152 / CR012985 / EPOANE2007	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	A Study Comparing Two Different PROCRIT Doses to a Dose of ARANESP in Anemic Cancer Patients Receiving Chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	USA	235	Phase 2	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 4	Terminated, has results	-
NCT00258440 / CDR0000445450 / OHSU-ONC-03017-LP / OHSU-1616 / OHSU-7754 / ORTHO-ONC-03017-L	OHSU Knight Cancer Institute	Epoetin Alfa in Treating Patients With Anemia Who Are Undergoing Chemotherapy for Cancer	Joseph Bubalo (OHSU Knight Cancer Institute)	USA	7	?	Terminated, has results	-
NCT00989092 / 20000219	Amgen	Darbepoetin Alfa and Anemia of Cancer	Amgen	?	287	Phase 2	Terminated (slow enrollment and change in product development strategy)	-
NCT00254436 / ID00-264	M.D. Anderson Cancer Center	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 (M.D. Anderson Cancer Center)	USA	50	Phase 3	Terminated	-
NCT00246597 / CR002305	Ortho Biotech Products, L.P.	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, L.P.	?	37	Phase 3	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 3	Terminated	-
NCT00306267 / CR10540	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	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, L.L.C	?	61	Phase 2	Terminated	- unlicensed / fixed dose or both*
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 3	Terminated	-

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
NCT00495378 / CR005128	Ortho Biotech Products, L.P.	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, L.P.	?	25	Phase 4	Terminated (25 out of 200 patients enrolled)	- non-randomised study*
COMPLETED								
NCT00117039 / 20030206	Amgen	A Study to Evaluate the Effectiveness of Aranesp® for Cancer Patients with Anaemia	MD Amgen	?	1,500	Phase 4	Completed (results published Boccia 2006 and Boccia 2007)	Identified but excluded as studies non-randomised
NCT00272662 / AFX01-05, 2005-003354-10	Affymax	Study of Subcutaneously Administered Peginesatide in Anemic Cancer Patients Receiving Chemotherapy	Study Director Affymax Inc	Czech Republic, Poland, UK	60	Phase 2	Completed	- non-randomised; dose finding; new ESA*
NCT 00210600 / CR003196	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	Early and Standard Intervention With 120,000 Units of PROCRIT (Epoetin Alfa) Every Three Weeks in Patients Receiving Chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	?	186	Phase 2	Completed (results published, Glaspy 2006)	- unlicensed / fixed dose or both*
NCT00117117 / 20020132	Amgen	A Study to Assess Symptom Burden in Subjects With Nonmyeloid Malignancies Receiving Chemotherapy and Aranesp®	MD Amgen	?	2,423	Phase 4	Completed (results published Gregory 2006 and Gabrilove 2007)	Identified Gabrilove 2007 but not Gregory 2006. However, both non-randomised, single-arm studies
NCT00072059 / ROCHE-NA17101 / UCLA-0303085 / CDR0000335429	Jonsson Comprehensive Cancer Center	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 2	Completed	-
NCT00212862 / CR004561 / ABT-OP-03-02	Ortho Biotech Products, L.P.	Dosing and Outcomes Study of Erythropoietic Stimulating Therapies in Patients With Chemotherapy Induced Anemia (DOSE)	Ortho Biotech Products, L.P.	?	2,130	Phase 4	Completed (results published Larholt 2008)	Not identified as beyond scope of review; an observational cohort study
NCT00270101 / CR005911	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	The Effect of Epoetin Alfa on the Anemia of Patients With Multiple Myeloma	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	?	156	Phase 3	Completed (results published Dammacco 1997)	Not identified as pre-2004 (PenTAG searches 2004-2013)
NCT00158379 / 3002000	North Eastern Germany Society of Gynaecologic	Taxol Carboplatin and Erythropoetin	Jalid Sehouli, Charité Campus Virchow Klinikum	?	105	Phase 2	Completed	- non-randomised

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
	Oncology							study*
NCT00315484 / CR004609	Ortho Biotech Products, L.P.	Hematologic Response of Epoetin Alfa (PROCRIT) Versus Darbepoetin Alfa (ARANESP) in Chemotherapy Induced Anemia	Ortho Biotech Products, L.P.	?	358	Phase 4	Completed (results published Waltzman 2005)	Identified; excluded as unlicensed/fixed dose or both
NCT00540384 / 980291	Amgen	Dose-finding Study of Novel Erythropoiesis Stimulating Protein (NESP) for the Treatment of Anaemia in Subjects With Solid Tumours Receiving Multicycle Chemotherapy	MD Amgen	?	405	Phase 2	Completed (results published Kotasek 2003)	Identified; included treatment arm evaluating at licensed dosage
NCT00344409 / KRN321-SC/05-A54	Kyowa Hakko Kirin Company, Limited	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 3	Completed	-
NCT00144482 / EPO307JP	Chugai Pharmaceutical	A Study of Recombinant Human Erythropoietin in Anemic Cancer Patients Undergoing Chemotherapy	Yoshiharu Ishikura (Chugai Pharmaceutical)	?	122	Phase 3	Completed	- unlicensed / fixed dose or both*
NCT00628043 / EPO316JP	Chugai Pharmaceutical	Clinical Study of Epoetin Beta to Chemotherapy-Induced Anemia (CIA) Patients	Yoshito Suzuki (Chugai Pharmaceutical)	Japan	160	Phase 3	Completed	- unlicensed / fixed dose or both*
NCT00338299 / CR005098	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	Alternate Dosing of PROCRIT (Epoetin Alfa) in Patients With Cancer and Chemotherapy Induced Anemia	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	?	51	Phase 3	Completed (results published Reddy 2006)	Not identified; study was a non-randomised, single arm study
NCT00144495 / EPO308JP	Chugai Pharmaceutical	A Study of Recombinant Human Erythropoietin in Anemic Cancer Patients Undergoing Chemotherapy	Yoshiharu Ishikura (Chugai Pharmaceutical)	?	104	Phase 3	Completed	- non-randomised; unlicensed / fixed dose or both*
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 4	Completed	- non-randomised, single arm; unlicensed / fixed dose*
NCT00035607 / 20010199	Amgen	Chemotherapy Related Anemia	MD Amgen	?	120	Phase 3	Completed (results published Justice 2005)	Identified; excluded as comparison DA vs DA 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 3	Completed	- 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	Incl in PenTAG Review
								bioequivalence study*
NCT00117624 / 20020118	Amgen	A Study of Darbepoetin Alfa for the Treatment of Anemia in Subjects With a Non-Myeloid Malignancy	MD Amgen	?	?	Phase 3	Completed (results published Kotasek 2007)	Identified; excluded as comparison DA vs DA 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 Halle-Wittenberg)	Germany	450	Phase 4	Completed	-
NCT00261313 / 20040137	Amgen	ACCELERATE: Doxorubicin and Cyclophosphamide Followed by Paclitaxel With Pegfilgrastim and Darbepoetin Alfa Support for the Treatment of Women With Breast Cancer	MD Amgen	?	80	Phase 2	Completed	- appears G-CSF not given in both treatment arms*
NCT00148421 / 20030125	Amgen	Study for the Treatment of Anemia in Patients With Non-myeloid Malignancies Receiving Multicycle Chemotherapy	MD Amgen	?	?	Phase 3	Completed (results published Glaspy 2006)	Identified; excluded as unlicensed/fixed dose or both
NCT00401544 / 20060103	Amgen	Darbepoetin Alfa With or Without IV Iron	MD Amgen	?	?	Phase 3	Completed	-
NCT00338416 / CR004612	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	An Efficacy and Safety Study of PROCRIT (Epoetin Alfa) in Cancer Patients Receiving Chemotherapy Every Three Weeks	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	?	115	Phase 2	Completed (results published Montoya 2007)	Not identified; study non-randomised, single arm
NCT00269984 / CR005833	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	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, L.L.C	?	56	Phase 2	Completed	- non-randomised; unlicensed / fixed dose or both*
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 2	Completed	- non-randomised study*
NCT00120705 / 20020167	Amgen	Treatment for Anemic Subjects With Non-Myeloid Malignancies Receiving Chemotherapy	MD Amgen	?	204	Phase 2	Completed (results published Charu 2007)	Identified; excluded unlicensed/fixed dose or both
NCT00364455 *(info*	Janssen-Ortho Inc.,	Impact of Erythropoietin Treatment Versus	?	?	56	Phase 3	Completed	-

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
taken from Source Solution website as record not available on NCT website)	Canada and Ontario Clinical Oncology Group	Placebo on Quality-of-Life in Patients With Advanced Prostate Cancer.						
NCT00135317 /	Amgen	AIM 3: Anemia and Iron Management With Every 3 Week Dosing in Anemic Subjects With Nonmyeloid Malignancies	MD Amgen	?	?	Phase 3	Completed (results published Bastit 2008)	Identified; excluded unlicensed/fixed dose or both
NCT00269997 / CR005839	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	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, L.L.C	?	72	Phase 2	Completed	-
NCT00266617 / CR005845	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	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, L.L.C	?	86	Phase 2	Completed	-
NCT00110955 / 20030232	Amgen	Treatment of Anemia in Subjects With Non-Myeloid Malignancy Receiving Multicycle Chemotherapy	MD Amgen	?	391	Phase 3	Completed (results published Hernandez 2009)	Identified; excluded unlicensed/fixed dose or both
NCT00337948 / CR004615	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	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, L.L.C	?	129	Phase 2	Completed (results published Gregory 2003)	Not identified; non-randomised, single arm study
NCT00255749 / CDR0000449950 / UCLA-0504038 / ORTHO-PR04-27-018	Jonsson Comprehensive Cancer Centre	Epoetin Alfa in Treating Patients With Anemia Who Are Undergoing Chemotherapy for Cancer	John A. Glaspy MD (Jonsson Comprehensive Cancer Center)	USA	89	Phase 2	Completed (results published Glaspy 2009)	Identified; excluded – includes randomized and non-randomised; 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 3	Completed (results published Steensma 2005 abstr and 2006)	Identified; excluded unlicensed/fixed dose or both
NCT00003600 /	North Central Cancer	Epoetin Alfa in Treating Anemia in Patients	Thomas E Witzig MD (Mayo	USA	?	Phase 3	Completed	-

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
CDR0000066673, NCCTG-979253, NCI-P98-0133	Treatment Group	Who Are Receiving Chemotherapy	Clinic)					
NCT00524407 / CR005125	Ortho Biotech Products, L.P.	Effect of Epoetin Alfa on Hemoglobin, Symptom Distress, and Quality of Life in Patients Receiving Chemotherapy	Ortho Biotech Products, L.P.	?	273	Phase 4	Completed (result published Straus 2006)	Identified; excluded unlicensed/fixed dose or both
NCT00261677 / CR002296	Ortho Biotech Products, L.P.	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, L.P.	?	224	Phase 3	Completed (results published Razzouk 2006)	Identified; excluded unlicensed/fixed dose or both (FYI paediatric population)
NCT00036023 / NCT00039247[obsolete] / 20010162	Amgen	Chemotherapy Related Anemia in Patients With Non-Myeloid Malignancies	MD Amgen	?	?	Phase 2	Completed (results published Glaspy 2005)	
NCT00145652 *(info taken from Source Solution website as record not available on NCT website)*	Sundsvall Hospital	Adjuvant I.V. Iron Therapy During Erythropoetin Treatment of Anemic Patients With Lymphoproliferative Disorders	?	?	66	?	Completed	-
NCT00270166 / CR005923	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	The Effect of Epoetin Alfa on the Anemia of Patients With Selected Cancers Receiving Chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	?	201	Phase 3	Completed	-
NCT01626547 / ORHEO	Hospira Inc	Biosimilar RetacritTM (Epoetin Zeta) in the Treatment of Chemotherapy-Induced Symptomatic Anaemia in Haematology and Oncology	?	Germany	240	?	Completed	- non-randomised study*
NCT00121030 / 20020166	Amgen	Treatment for Patients With Gynecological Malignancies Who Suffer From Anemia Due to Chemotherapy	MD Amgen	?	?	Phase 2	Completed (results published Schwartzberg 2004)	Identified; excluded unlicensed/fixed dose or both
NCT00038064 / NCT00046982 [obsolete], 20010101	Amgen	Anemia in Patients With a Non-Myeloid Malignancy	MD Amgen	?	707	Phase 3	Completed	- unlicensed / fixed dose or both*
NCT00120679 / 20020165	Amgen	Treatment for Patients With Non-Small Cell Lung Cancer Who Developed Anemia Due to Chemotherapy	MD Amgen	?	?	Phase 2	Completed (results published Schwartzberg 2004)	
NCT00264108 /	Janssen-Cilag BV	Cost-effectiveness Study of Epoetin Alfa and	Clinical Trials Janssen-Cilag	?	492	Phase 4	Completed	- non-

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
CR002455 / EPOCAN4015		Darbepoetin Alfa in Adult Patients With Cancer Who Have Anemia	BV					randomised; unlicensed/fixed dose or both*
NCT00239239 / 20040232	Amgen	Fractionated Dosing Study: Study to Evaluate Darbepoetin Alfa for the Treatment of Anemia in Subjects With Non-Myeloid Malignancies	MD Amgen	?	44	Phase 3	Completed	- non-randomised; PK study*
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)	USA	109	Phase 2	Completed	- non-randomised*
NCT00120692 / 20020152	Amgen	Treatment for Patients Suffering From Anemia Due to Chemotherapy	MD Amgen	?	?	Phase 2	Completed (results published Senecal 2005)	Identified; excluded unlicensed/fixed dose or both
NCT00119613 / 20010145	Amgen	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	?	600	Phase 3	Completed (results published Pirker 2008)	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)	USA	202-232	Phase 3	Completed	-
NCT00111137 / 20020139	Amgen	Treatment for Patients With Non-Myeloid Malignancies Receiving Chemotherapy	MD Amgen	?	718	Phase 3	Completed	- unlicensed / fixed dose or both*
NCT00022386 / ORTHO-PR-00-27-012 / UCLA-0011004 / CDR0000068811 / ORTHO-PR-01-27-003, NCI-G01-2002	Jonsson Comprehensive Cancer Center 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)	?	2,500	Phase 4	Completed	- non-randomised study*
NCT00017004 / CDR0000068641 /	Gynecologic Oncology Group / National Cancer	Radiation Therapy and Cisplatin With or Without Epoetin Alfa in Treating Patients	Gillian M. Thomas (Odette Cancer Centre at	USA, Canada, Norway, UK	460	Phase 3	Completed	-

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
GOG-0191 / CAN-NCIC-CX4	Institute & NCIC Clinical Trials Group	With Cervical Cancer and Anemia	Sunnybrook); and, Peter S. Craighead (Tom Baker Cancer Centre – Calgary)					
NCT00270127 / CR005917 / EPO-C111-457/EPO-INT-10	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	Epoetin Alfa for Anemia in Patients With Cancer Receiving Non-platinum Chemotherapy	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	?	375	Phase 3	Completed	-
NCT00211133 / CR004414	Johnson & Johnson Pharmaceutical Research & Development, L.L.C	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, L.L.C	?	939	Phase 3	Completed (results published Leyland-Jones 2005)	Identified; excluded unlicensed/fixed dose or both
NCT00284365 / 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 4	Completed (results published Savonije 2005)	Identified; excluded unlicensed/fixed dose or both
NCT00095277 / 20030204	Amgen	Darbepoetin Alfa Administered Once Every 4 Weeks in the Treatment of Subjects With Anemia of Cancer	MD Amgen	?	220	Phase 2	Completed (results published Gordon 2008)	Identified; excluded as patients not receiving chemotherapy
NCT00118638 / 20030231	Amgen	A Study of Darbepoetin Alfa for the Treatment of Anemia in Subjects With Non-Myeloid Malignancy Receiving Multicycle Chemotherapy	MD Amgen	?	705	Phase 3	Completed (results published Canon 2012; Canon 2006; Vansteenkiste 2009)	All identified; excluded Canon 2006 as comparison DA vs DA beyond scope; and, excluded Canon 2012 & Vansteenkiste 2009 as retrospective analyses
NCT00144131 / 20040262	Amgen	Flexibility: A Study to Assess the Impact of Darbepoetin Alfa in Subjects with Non-Myeloid Malignancies With Anemia Due to Chemotherapy	MD Amgen	?	750	Phase 2	Completed (results published Schwartzberg 2010)	Identified; excluded as comparison DA vs DA beyond scope
NCT00091858 / NCT00098696 [obsolete] /	Amgen	Study of Darbepoetin Alfa for the Treatment of Anemia of Cancer	MD Amgen	?	1,000	Phase 3	Completed (results published	Identified; excluded as patients not

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
20010103							Smith 2008)	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 4	Completed (results published Schouwink 2008)	Identified; excluded as comparison EA vs EA beyond scope; & unlicensed/fixed dose or both
NCT00245895 / 03-6503-A	University of Washington / 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 and Science University)	USA	20	Phase 2	Completed	- non-randomised study*
NCT00039247 / 20010162	Amgen	Chemotherapy related anemia in patients with non-myeloid malignancies	MD, Amgen	?		Phase 2	Completed (results published Glaspy 2005)	Identified; excluded as comparison DA vs DA
NCT01099202	M.D. Anderson Cancer Center	Procrit Versus No Procrit in Acute Lymphocytic Leukemia, Lymphoblastic Lymphoma, or Burkitt's Undergoing Induction/Consolidation Chemotherapy	Jorge Cortes (UT MD Anderson Cancer Center)	USA	109		Completed	-
NCT00661999		Darbepoetin Alfa With or Without Iron in Treating Anemia Caused By Chemotherapy in Patients With Cancer	Charles L Loprinzi (Mayo Clinic)	USA	502	Phase 3	Completed	-
NCT01394991 / CR010543 / EPOANE4008	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	A Safety Study of Epoetin Alfa in Patients With Cancer Who Have Chemotherapy-Related Anemia	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	?	504	Phase 4	Completed	-
NCT00236951	Luitpold Pharmaceuticals	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 3	Completed	-
NCT00270049 / CR005905	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	Epoetin Alfa for the Treatment of Anemia Resulting From Chronic Lymphocytic Leukemia	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	?	195	Phase 2	Completed	-
NCT00003341 / 97-125 / MSKCC-97125 / ORTHO-PR-96-27-031 / RPCI-DS-97-38 / NCI-G98-1436	Memorial Sloan-Kettering Cancer Center	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 3	Completed	-
NCT00070382 / CDR0000333213 /	Jonsson Comprehensive Cancer	Darbepoetin Alfa Compared With Epoetin Alfa in Treating Anemia in Patients	John A. Glaspy (MPH Jonsson Comprehensive Cancer	?	14	Phase 3	Completed (published	Identified; excluded

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status	Incl in PenTAG Review
P30CA016042 / UCLA-0306021 / AMGEN-20030125	Center and National Cancer Institute (NCI)	Receiving Chemotherapy for Cancer	Center)				Glaspy 2006)	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	-
Key & notes: ?, not reported / unclear; - unable to match to a publication text; * indicates possible reasons for exclusion based on the information provided in the ClinicalTrials or Controlled Trials databases; DA, darbepoetin alfa; EA, epoetin alfa;								

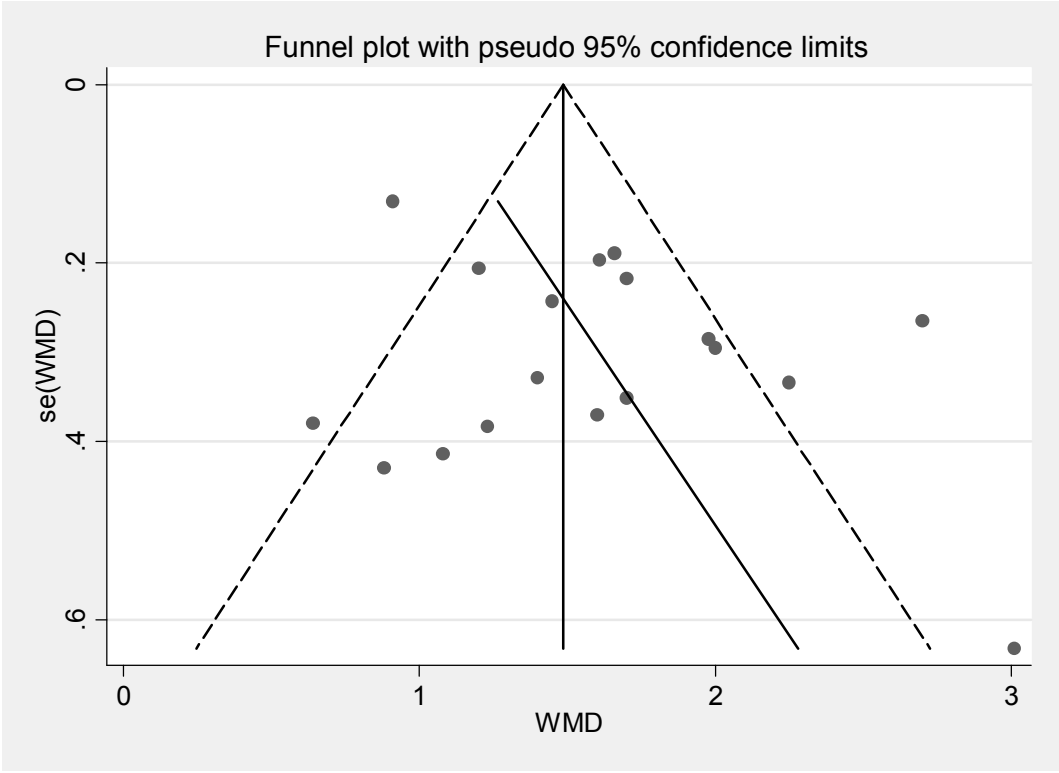
Appendix L: Supplementary analyses

23.1. Anaemia-related outcomes

23.1.1. Hb change

23.1.1.1. Publication bias

Figure 77. Hb change: publication bias, funnel plot

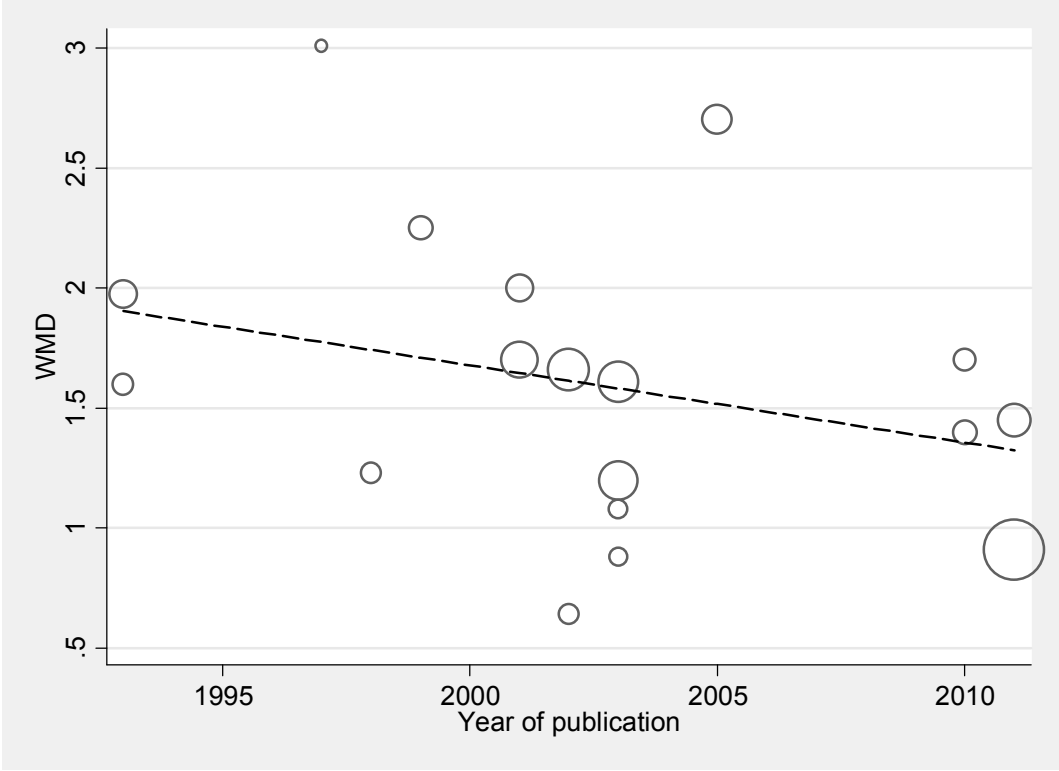


Key: se(WMD): standard error of weighted mean difference; WMD, weighted mean difference

Table 108. Hb change: Egger's test for small study effects

Number of studies 18					**Root MSE 1.952**
Std_Eff	**Coef**	**SE**	**t**	**p>|t|**	**95% CI**
slope	1.002	0.33	3.06	<0.01	0.31, 1.70
bias	2.020	1.28	-1.16	0.13	-0.69, 4.73
Test of H_0 no small-study effects p=0.133					
Key: CI, confidence interval; coef, coefficient; SE, standard error					

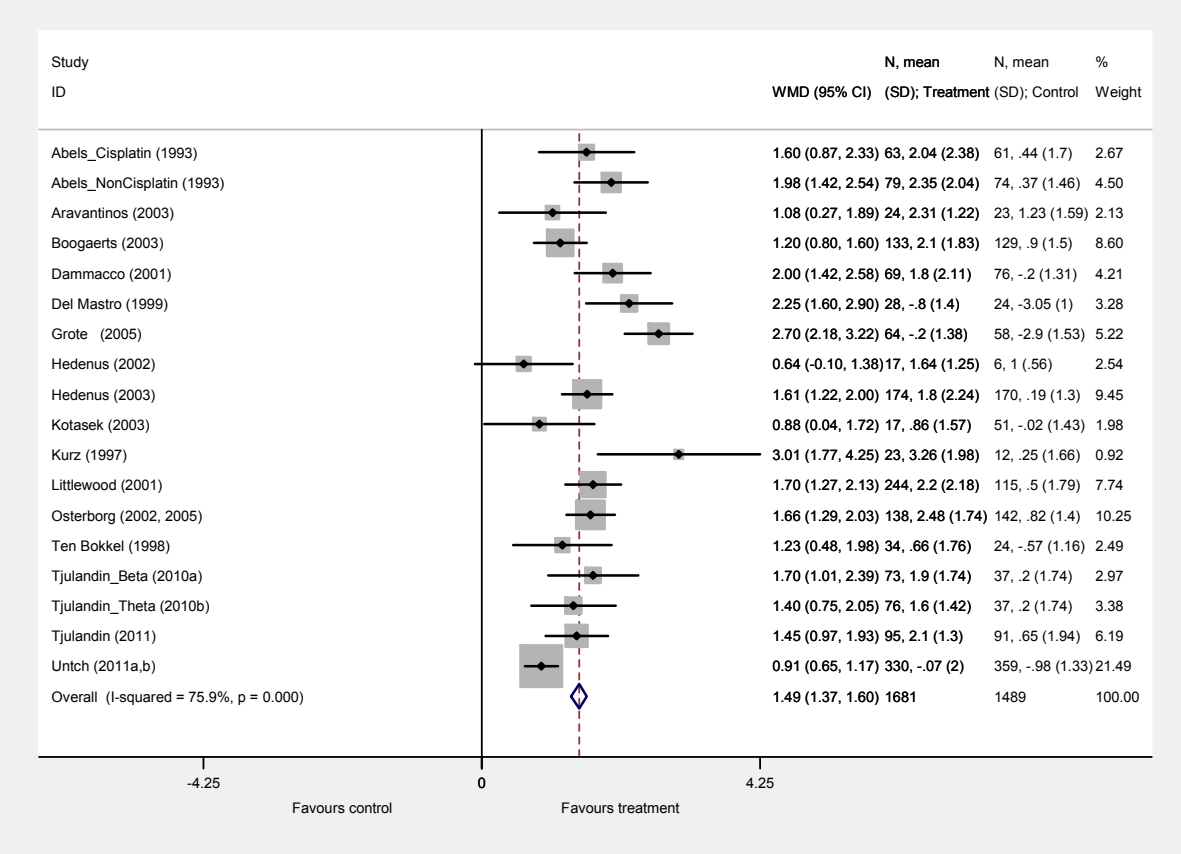
Figure 78. Hb change: Publication bias; meta-regression plot, year of publication as a covariate



Key: se(WMD): standard error of weighted mean difference; WMD, weighted mean difference

23.1.1.2. Fixed effects

Figure 79. Hb change: Forest plot (fixed effects)



Key: CI, confidence intervals; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference
Notes: Fixed effects, Mantel-Haenszel; Studiesl with multiple experimental arm split into subsets in the analysis: **Tjulandin 2010 a, b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

23.1.1.3. Metagression

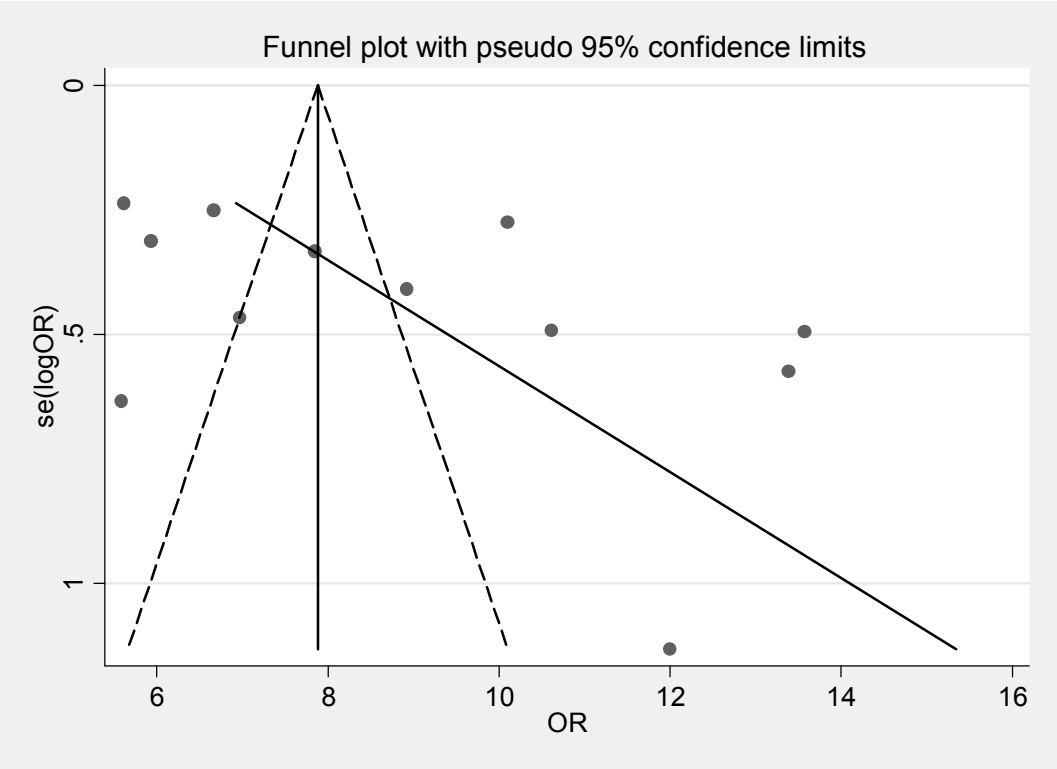
Table 109. Hb change: Results of meta-regression analysis (g/dl)

Variable	Mean difference	Standard error	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
Key: NR, not reported			

23.1.2. Haematological response

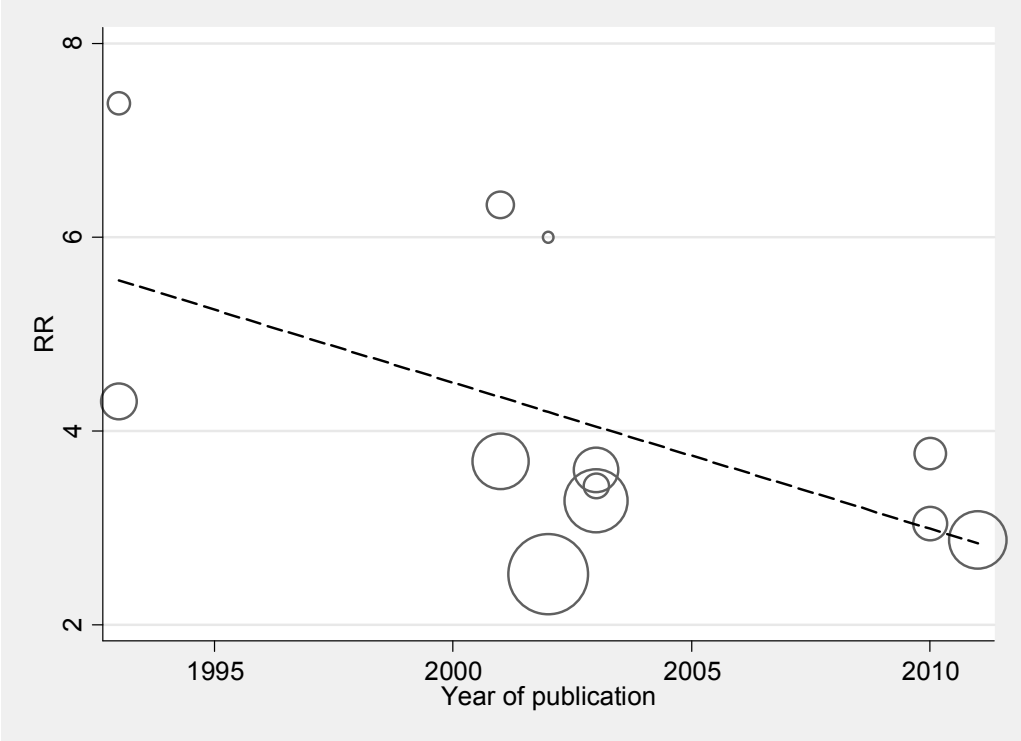
23.1.2.1. Publication bias

Figure 80. HaemR: Publication bias, funnel plot



Key: CI, confidence interval; sqrt: square root; Z, efficient score; V, Z score variance

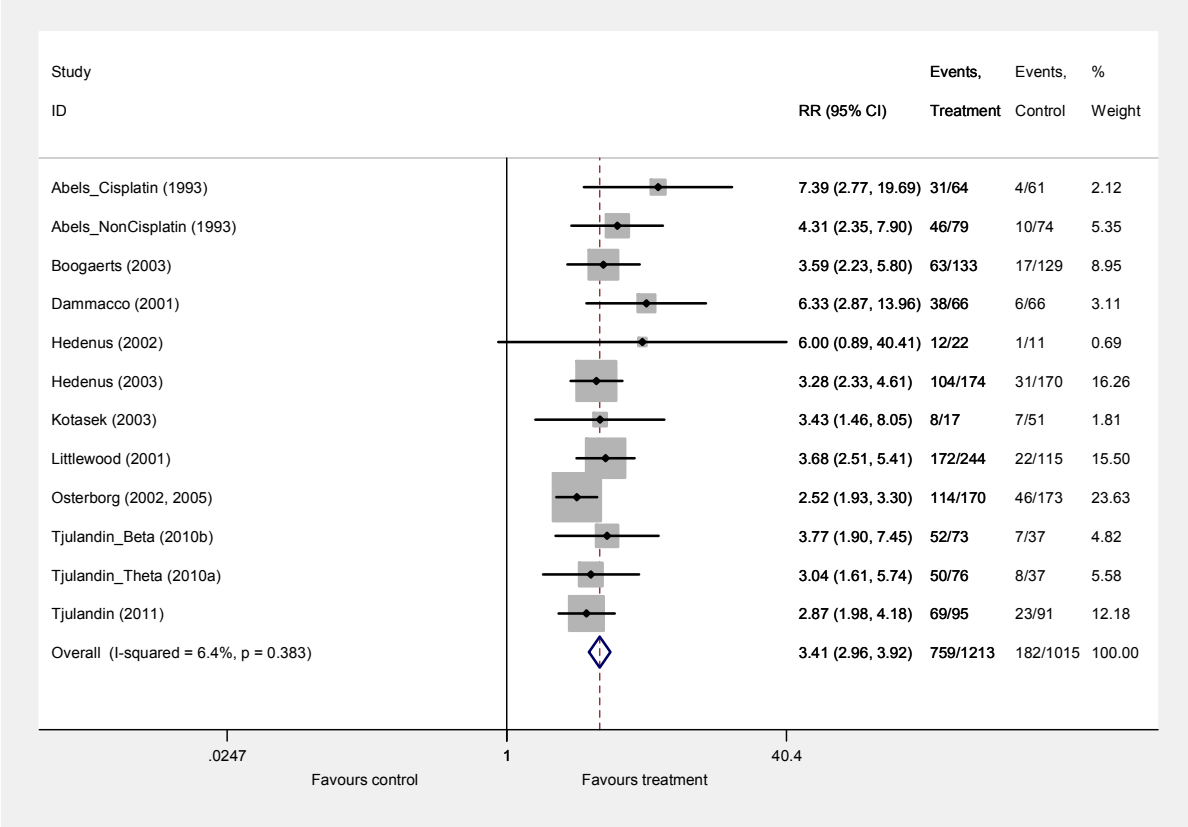
Figure 81. HaemR: Publication bias, meta-regression plot, year of publication as a covariate



Key: RR, risk ratio

23.1.2.2. Fixed effects

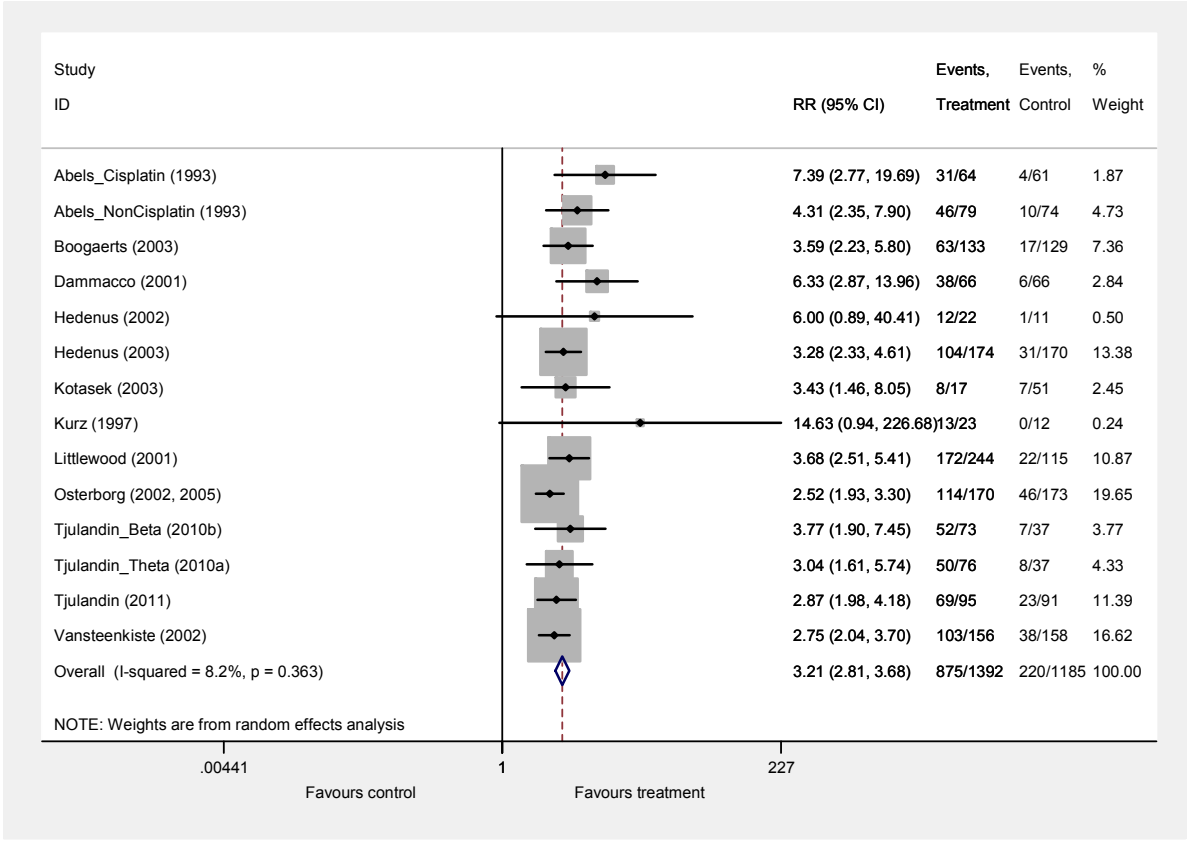
Figure 82. HaemR: Forest plot (fixed effects)



Key: CI, confidence intervals; events, treatment, number of events/ number of participants in treatment group; events, control, number of events/ number of participants in control group; ID, identification; RR, risk ratio
Notes: Fixed effects, Mantel-Haenszel; Studiesl with multiple experimental arm split into subsets in the analysis: **Tjulandin 2010 a, b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

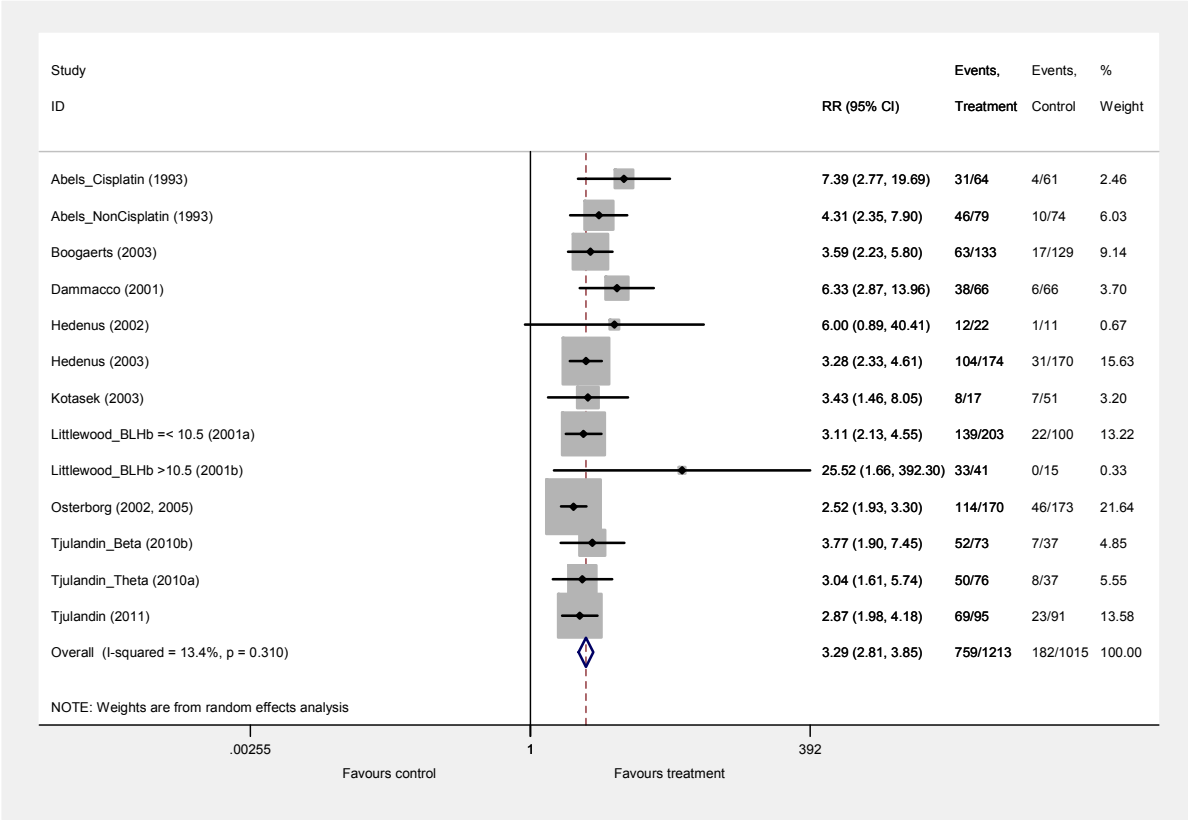
23.1.2.3. Additional analyses

Figure 83. HaemR (including Kurz and colleagues, 1997 and Vansteenkiste and colleagues, 2002): Forest plot (random effects)



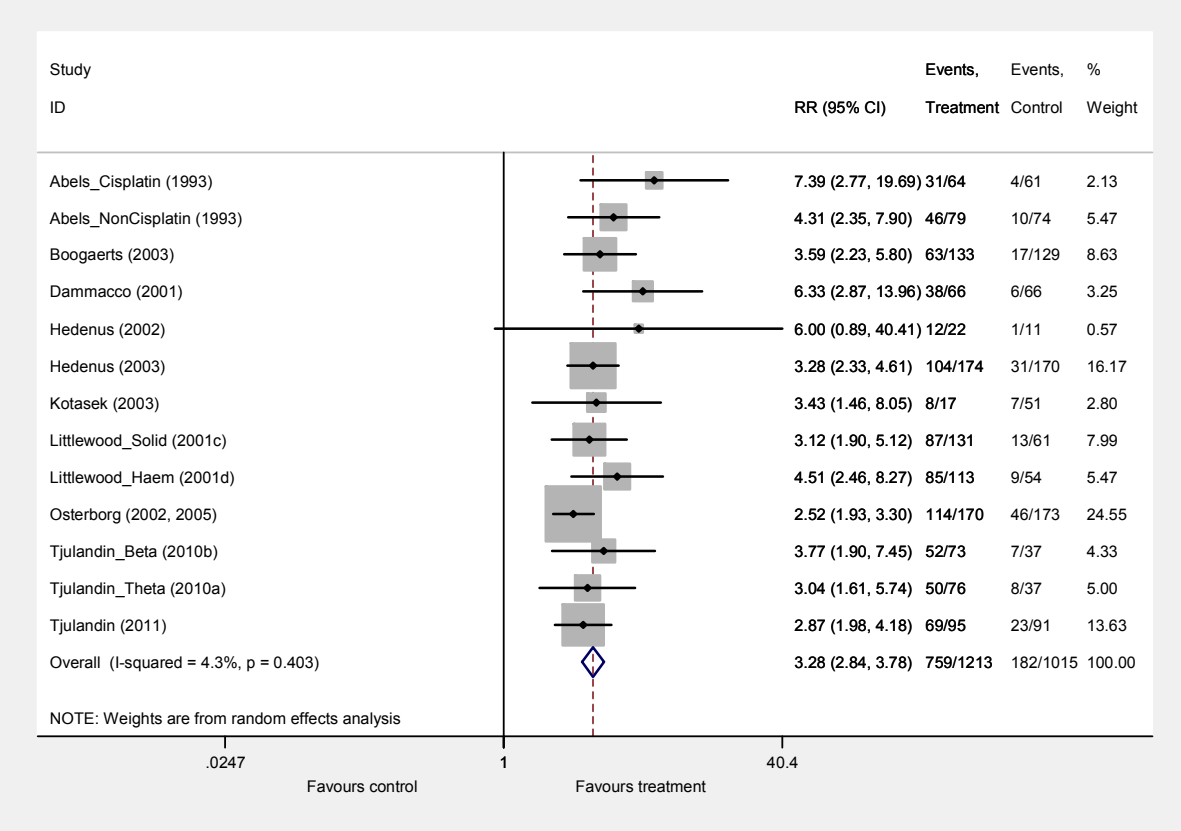
Key: CI, confidence intervals; events, treatment, number of events/ number of participants in treatment group; events, control, number of events/ number of participants in control group; ID, identification; RR, risk ratio
Notes: Random effects, Der-Simonian-Laird; Studiesl with multiple experimental arm split into subsets in the analysis: **Tjulandin 2010 a, b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

Figure 84. HaemR: Random effects meta-analysis using Hb subgroups (Littlewood and colleagues, 2001), forest plot (random effects)



Key: CI, confidence intervals; events, treatment, number of events/ number of participants in treatment group; events, control, number of events/ number of participants in control group; ID, identification; RR, risk ratio
Notes: Random effects, Der-Simonian-Laird; Studiesl with multiple experimental arm split into subsets in the analysis: **Tjulandin 2010 a, b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy; **Littlewood and colleagues, 2001** reports data by baseline Hb ≤10.5 g/dl and >10.5 g/dl

Figure 85. HaemR: Random effects meta-analysis using malignancy subgroups (Littlewood and colleagues, 2001), forest plot (random effects)



Key: CI, confidence intervals; events, treatment, number of events/ number of participants in treatment group; events, control, number of events/ number of participants in control group; ID, identification; RR, risk ratio
Notes: Random effects, Der-Simonian-Laird; Studiesl with multiple experimental arm split into subsets in the analysis: **Tjulandin 2010 a, b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy; **Littlewood and colleagues, 2001** reports data by malignancy type (solid and haematological tumours)

23.1.2.4. Meta-regression

Table 110. HaemR: Results of meta-regression analysis with iron subgroup as a covariate

Variable	RR	Standard error	P-value
Intercept (NR)	5.163	0.497	<0.001
Iron	-2.163	0.626	0.006
Key: NR, not reported; RR, risk ratio			

Table 111. HaemR: Results of meta-regression analysis with Hb baseline levels as a covariate (using Hb subgroup data [Littlewood and colleagues, 2001)

Variable	RR	Standard error	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
Key: NR, not reported; RR, risk ratio			

23.1.3. RBCT

23.1.3.1. Publication bias

Figure 86. RBCT: Publication bias, publication bias, funnel plot

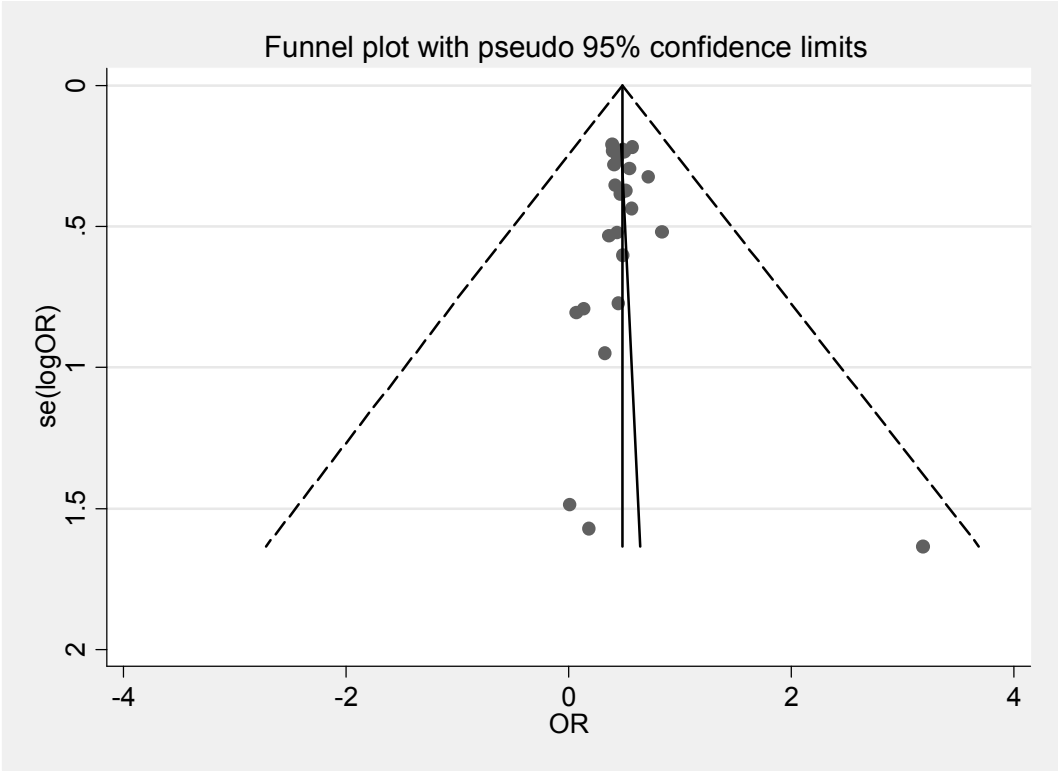
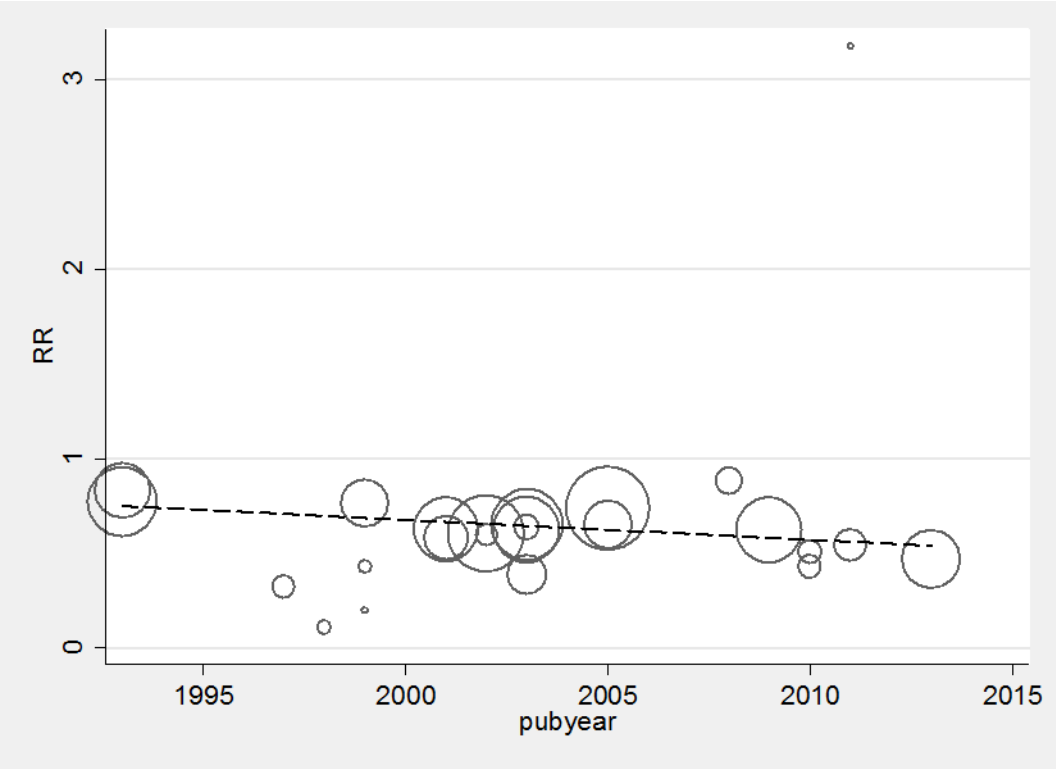


Table 112. RBCT: Harbord's modified test for small study effects

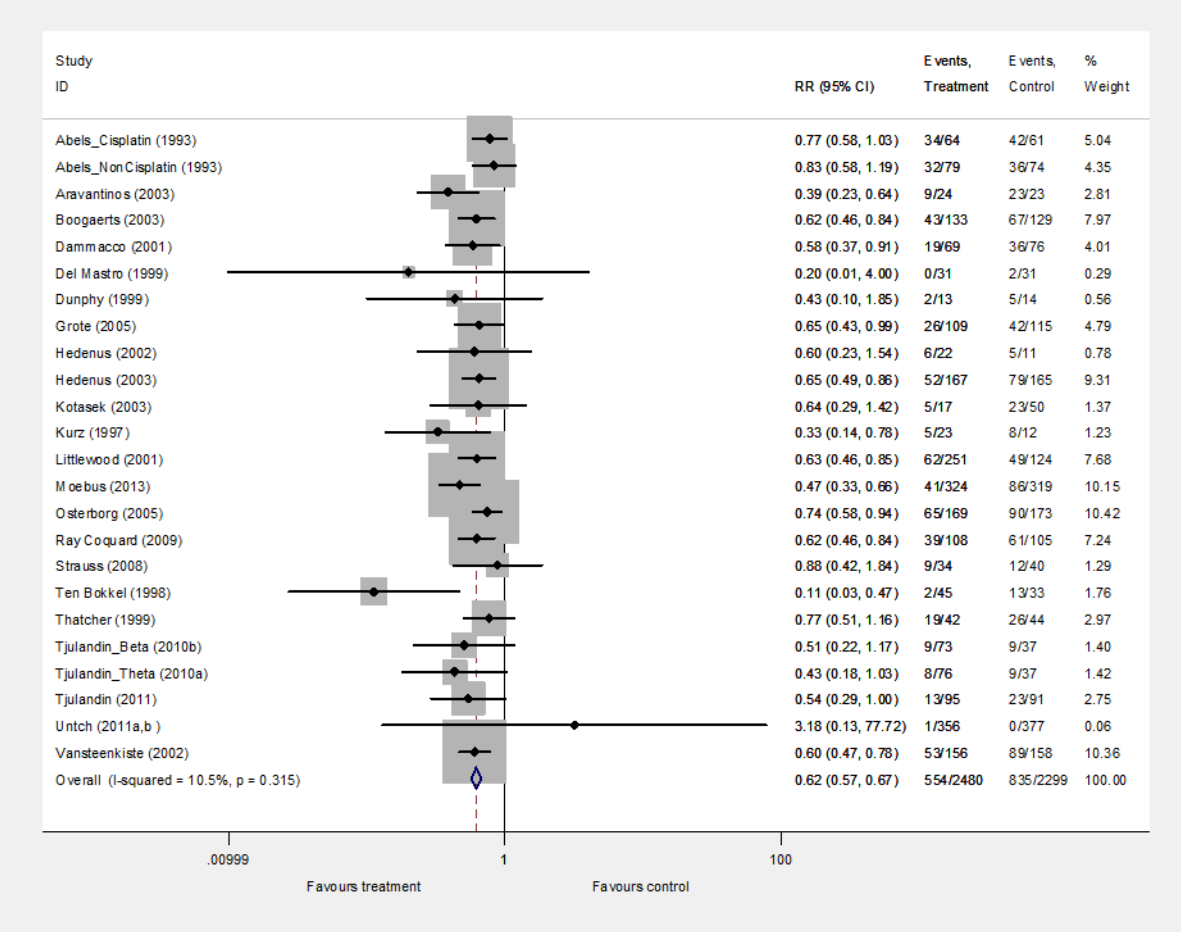
Number of studies 24					**Root MSE – 1.108**
Z/sqrt(V)	**Coef**	**SE**	**t**	**p>|t|**	**95% CI**
sqrt(V)	-0.60	0.17	-3.44	0.002	-0.96, -0.24
bias	-0.62	0.51	-1.22	0.234	-1.68, 0.43
Test of H_0 no small-study effects p=0.234					
Key: CI, confidence interval; coef, coefficient; SE, standard error **Notes:** Regress Z/sqrt(V) on sqrt(V) where Z is efficient score and V is score variance					

Figure 87. RBCT: Publication bias, analysis of year of publication



23.1.3.2. Fixed effects

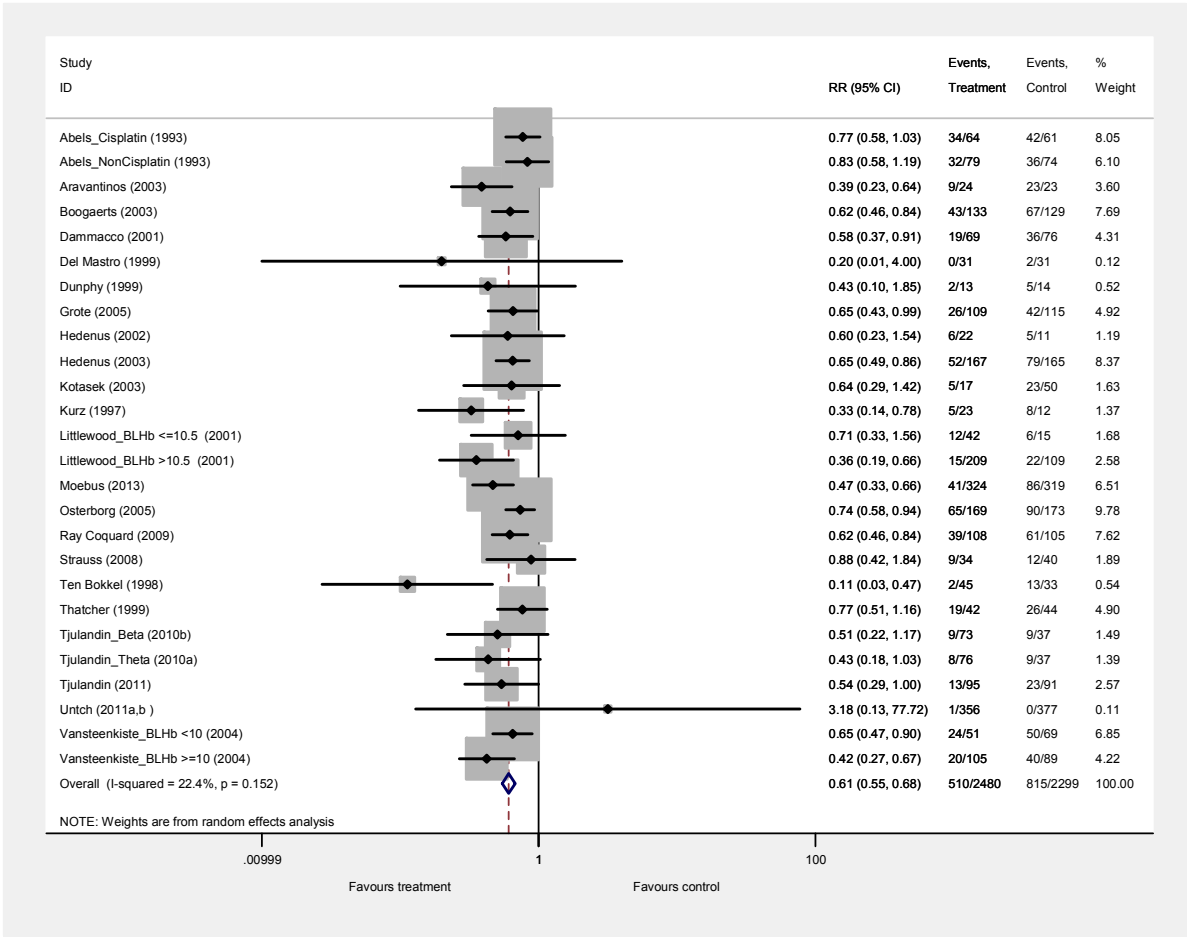
Figure 88. RBCT: Fixed effects meta-analysis



Key: CI, confidence interval; ID, identification; N, number of participants; RR, risk ratio
Notes: **(a)** Mantel-Haenzel pooled RR; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Tjulandin 2010a,b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

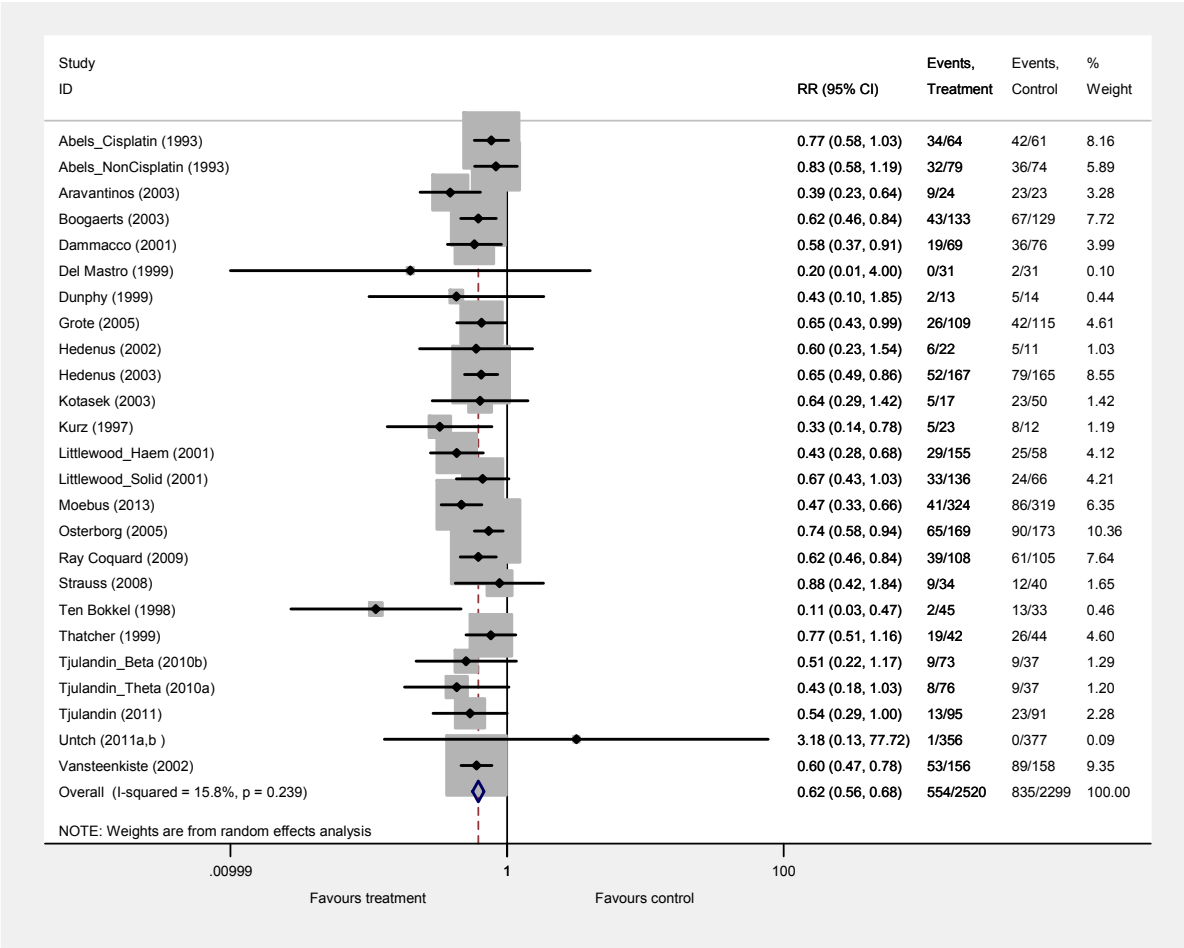
23.1.3.3. Additional analyses

Figure 89. RBCT: Random effects meta-analysis using Hb subgroups (Vanteenkiste and colleagues, 2002 and Littlewood and colleagues, 2001), forest plot (random effects)



Key: CI, confidence interval; ID, identification; N, number of participants; RR, risk ratio
Notes: (a) Random effects, Der Simonian pooled RR; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Tjulandin 2010a,b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

Figure 90 RBCT: Random effects meta-analysis using malignancy subgroups (Littlewood and colleagues, 2001), forest plot (random effects)

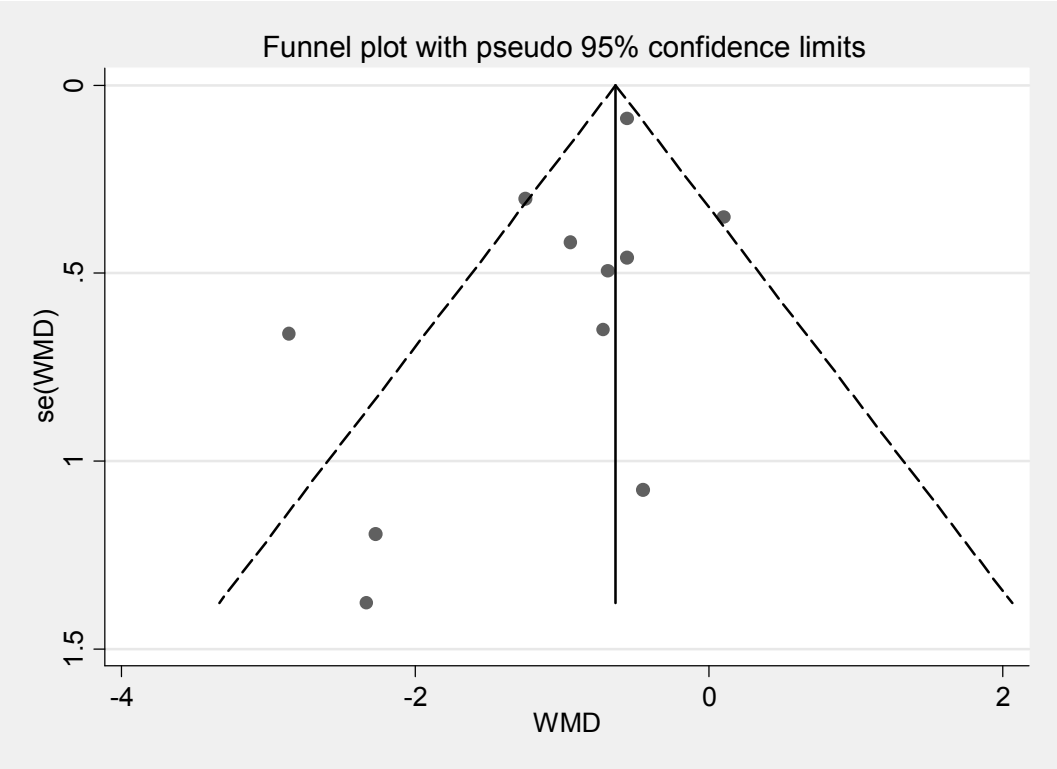


Key: CI, confidence interval; ID, identification; N, number of participants; RR, risk ratio
Notes: (a) Random effects, Der Simonian pooled RR; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Tjulandin 2010a,b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

23.1.4. RBC units transfused

23.1.4.1. Publication bias

Figure 91. RBC units transfused: Publication bias, Egger's test



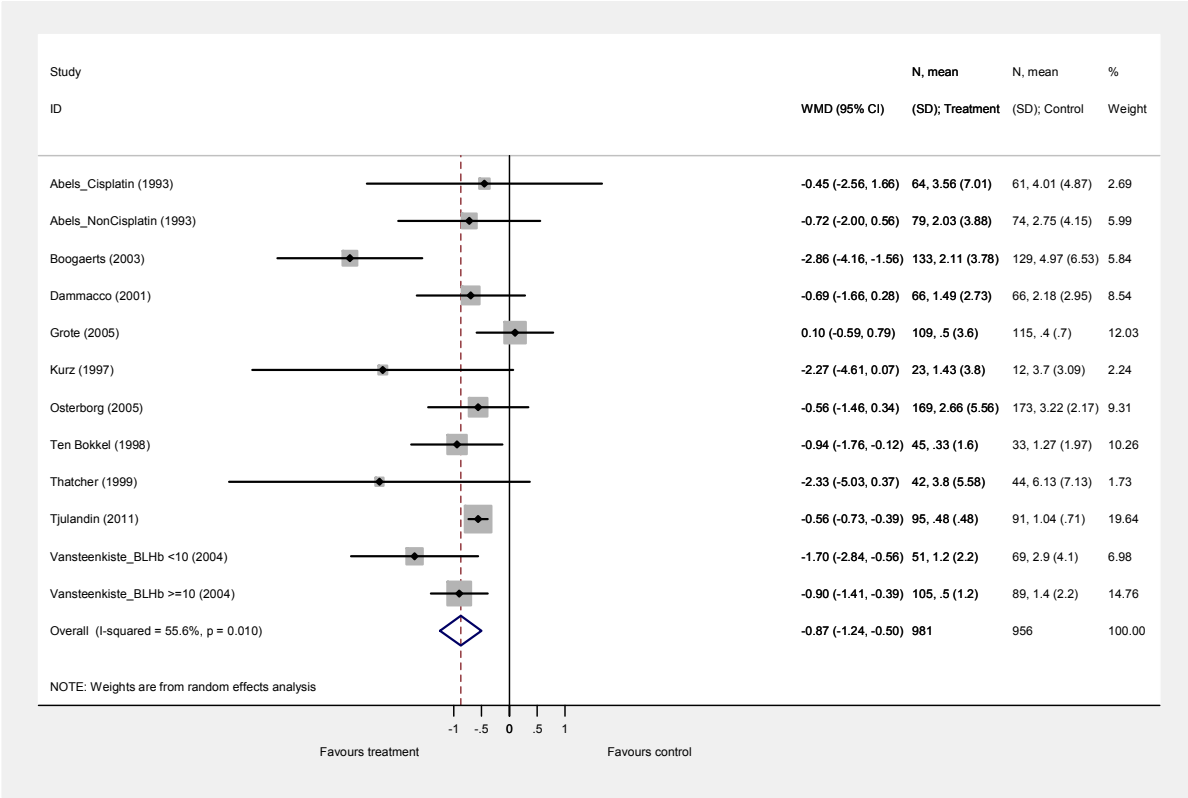
Key: se, standard error; WMD, weighted mean difference

Table 113. RBC units transfused: Egger's test for small study effects

Number of studies 11					**Root MSE – 1.455**
Std_Eff	**Coef**	**SE**	**t**	**p>|t|**	**95% CI**
slope	-0.4604	0.16	-2.96	0.02	-0.81, -0.11
bias	-1.986	0.60	-1.63	0.14	-2.35, 0.38
Test of H_0 no small-study effects p=0.137					
Key: CI, confidence interval; coef, coefficient; SE, standard error					

23.1.4.2. Additional analyses

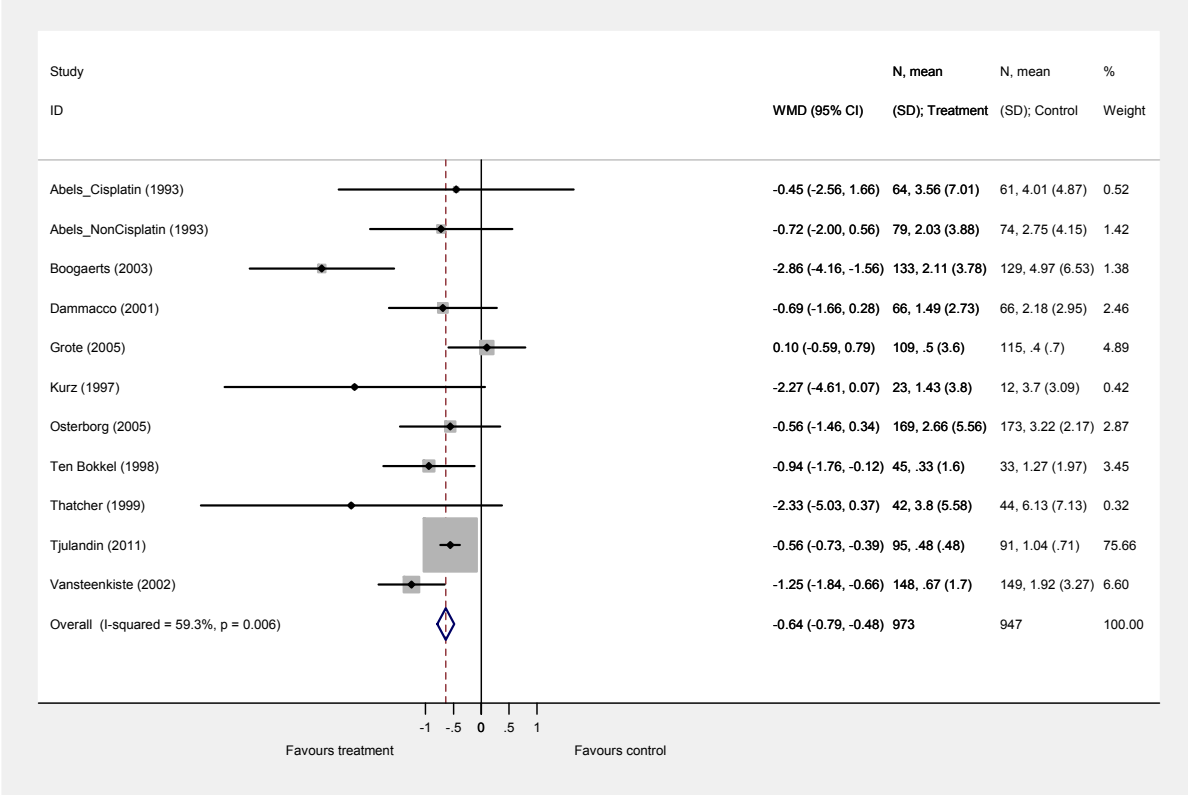
Figure 92. RBC units transfused: Random effects meta-analysis using Hb subgroups (Vanteenkiste and colleagues, 2002), forest plot (random effects)



Key: CI, confidence interval; ID, identification; N, number of events/participants intervention and control; WMD, weighted mean difference
Notes: (a) Random effects (Dersimonian Laird pooled RR); **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

23.1.4.3. Fixed effects

Figure 93. RBC units transfused: Fixed effects



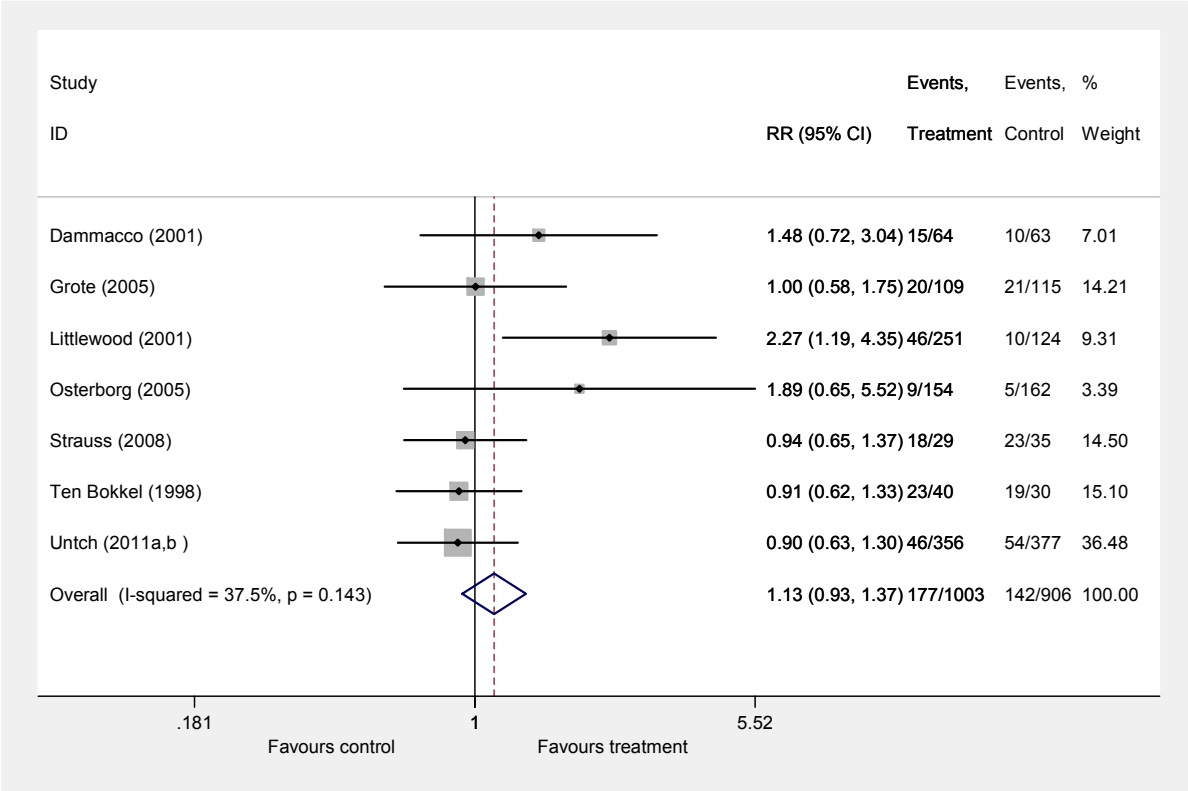
Key: CI, confidence interval; ID, identification; N, number of events/participants intervention and control; WMD, weighted mean difference
Notes: (a) Fixed effects (Mantel-Haenzel pooled RR); **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

23.2. Malignancy-related outcomes

23.2.1. Tumour response

23.2.1.1. Fixed effects

Figure 94. Tumour response: Forest plot (fixed effects)

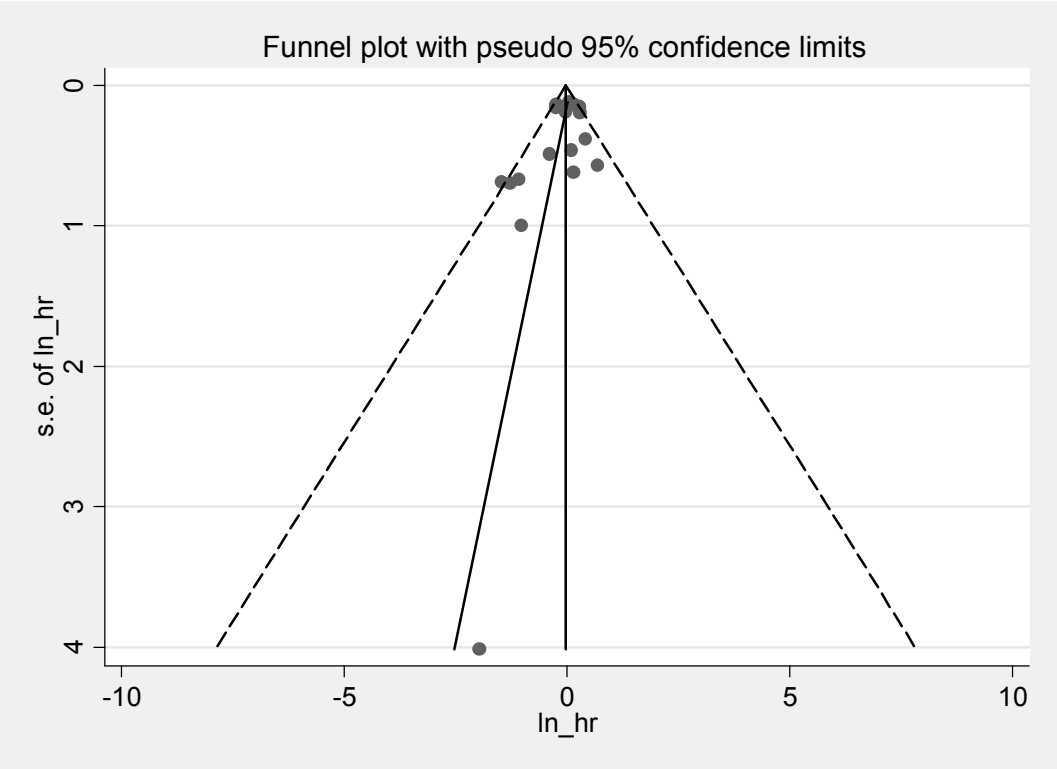


Key: CI, confidence intervals; events, treatment, number of events/ number of participants in treatment group; events, control, number of events/ number of participants in control group; ID, identification; RR, risk ratio
Notes: Fixed effects, Mantel-Haenszel; Studiesl with multiple experimental arm split into subsets in the analysis: **Tjulandin 2010 a, b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

23.2.2. Overall survival

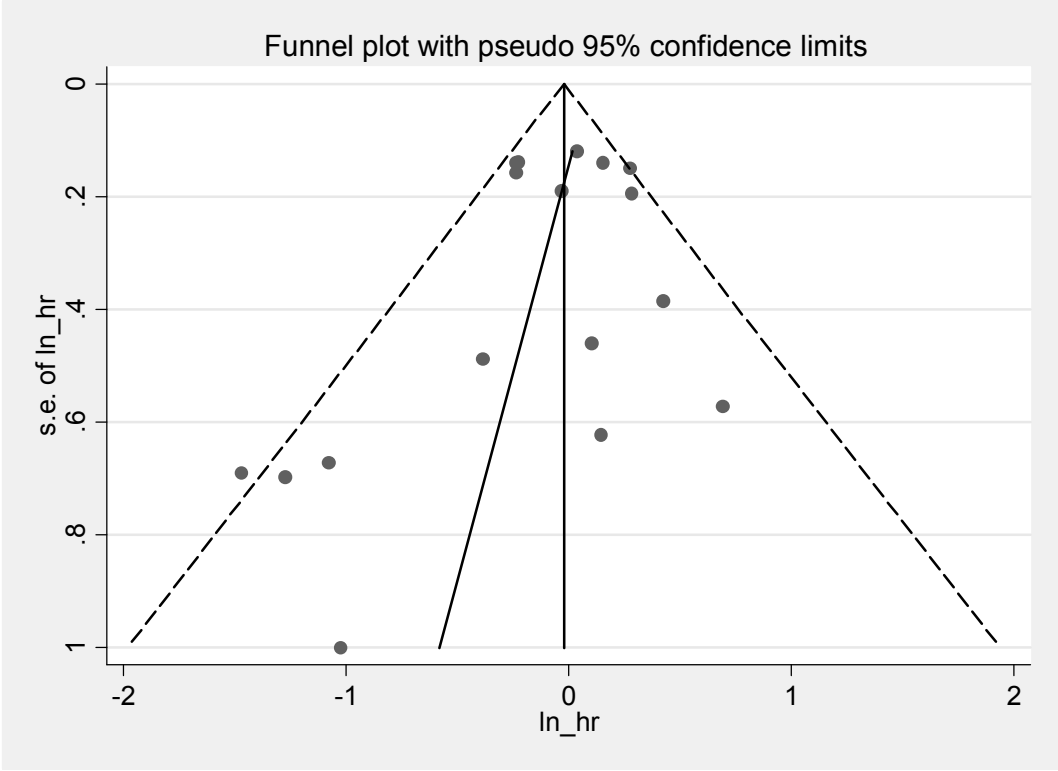
23.2.2.1. Publication bias

Figure 95. Funnel plot: Overall survival



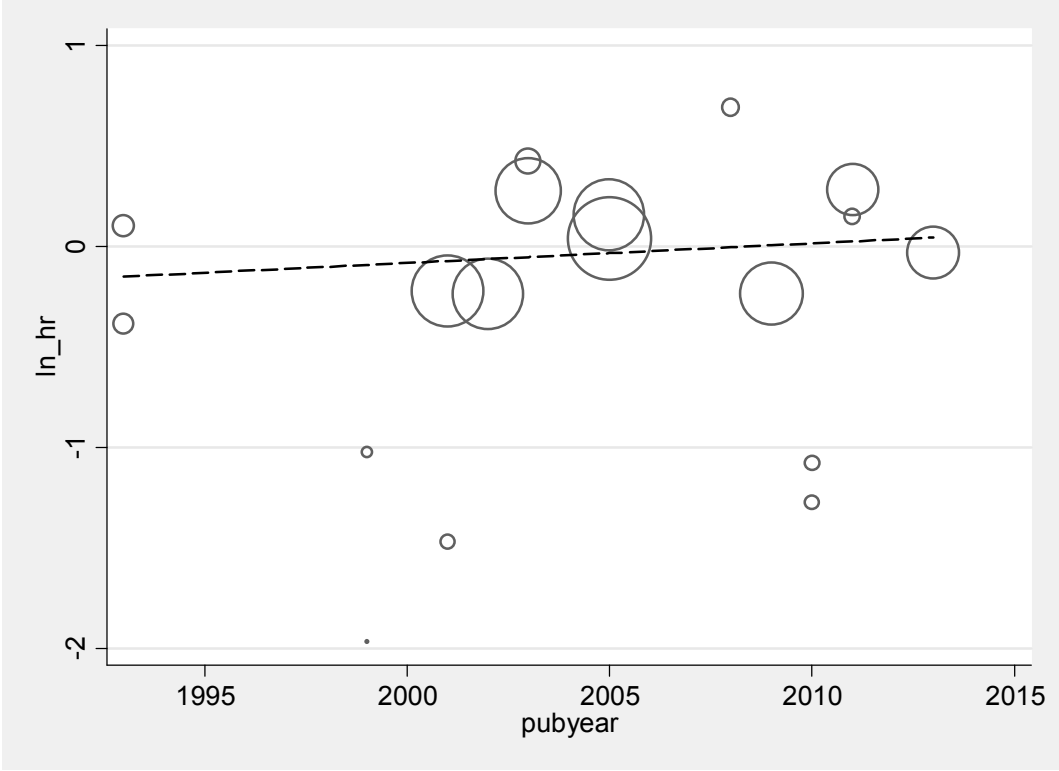
Key: hr, hazard ratio; se, standard error

Figure 96. Funnel plot: Overall survival; excluding Dunphy and colleagues, 1999 trial



Key: hr, hazard ratio; se, standard error

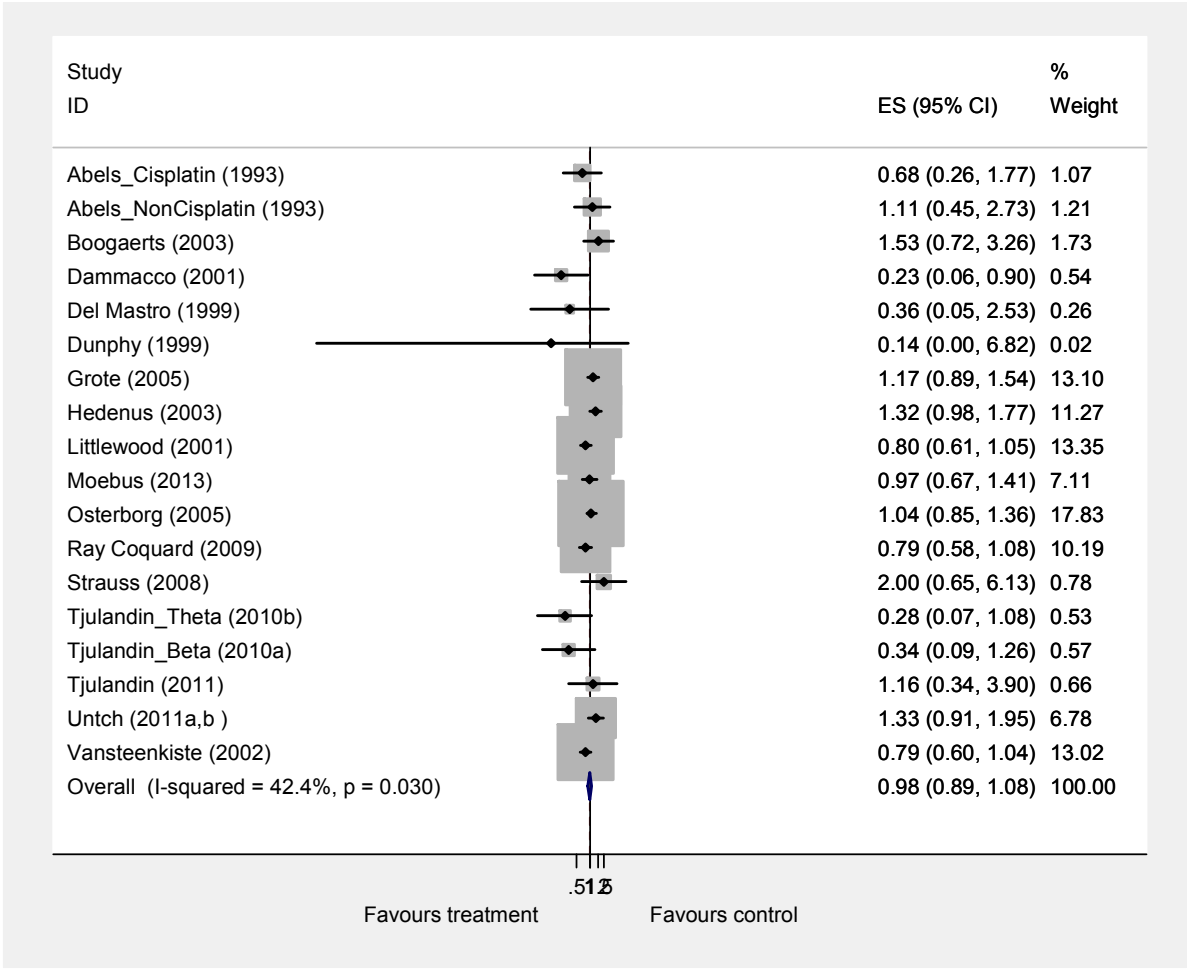
Figure 97. Overall survival: Publication bias, meta-analysis using year of publication as covariate



Key: hr, hazard ratio; pub year, publication year

23.2.2.2. Fixed effects

Figure 98. Overall survival: Fixed effects

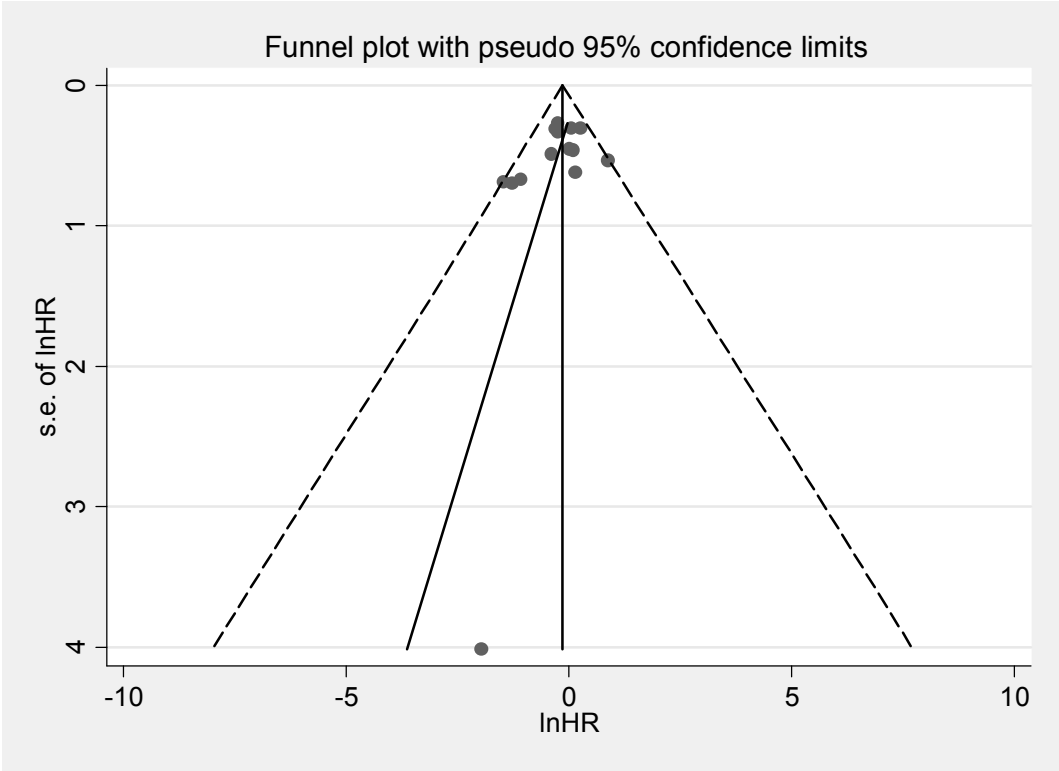


Key: CI, confidence interval; ES effect size; ID, identification
Notes: (a) Fixed effects; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Tjulandin and colleagues, 2010a, b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy; **(c)** Effect sizes reported are hazard ratios; **(d)** IPD data as reported in Tonia and colleagues, 2012 (Cochrane review): Abels and colleagues, 1993; Boogaerts and colleagues, 2003; Dammacco and colleagues, 2001; Grote and colleagues, 2005; Hedenus and colleagues, 2003; Littlewood and colleagues, 2001; Osterborg and colleagues, 2002; Ray-Coquard and colleagues, 2009; Strauss and colleagues, 2008; Vansteenkiste and colleagues, 2002. HRs reported for other trials calculated using other accepted methods.

23.2.3. On-study mortality

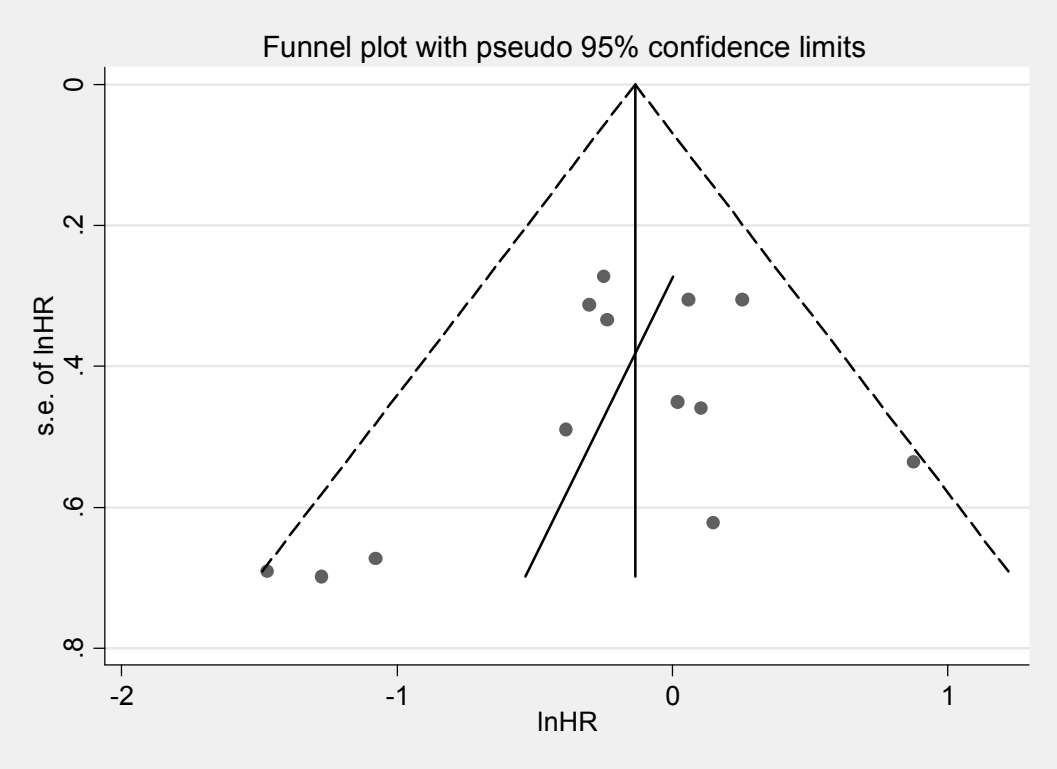
23.2.3.1. Publication bias

Figure 99. Funnel plot: Mortality



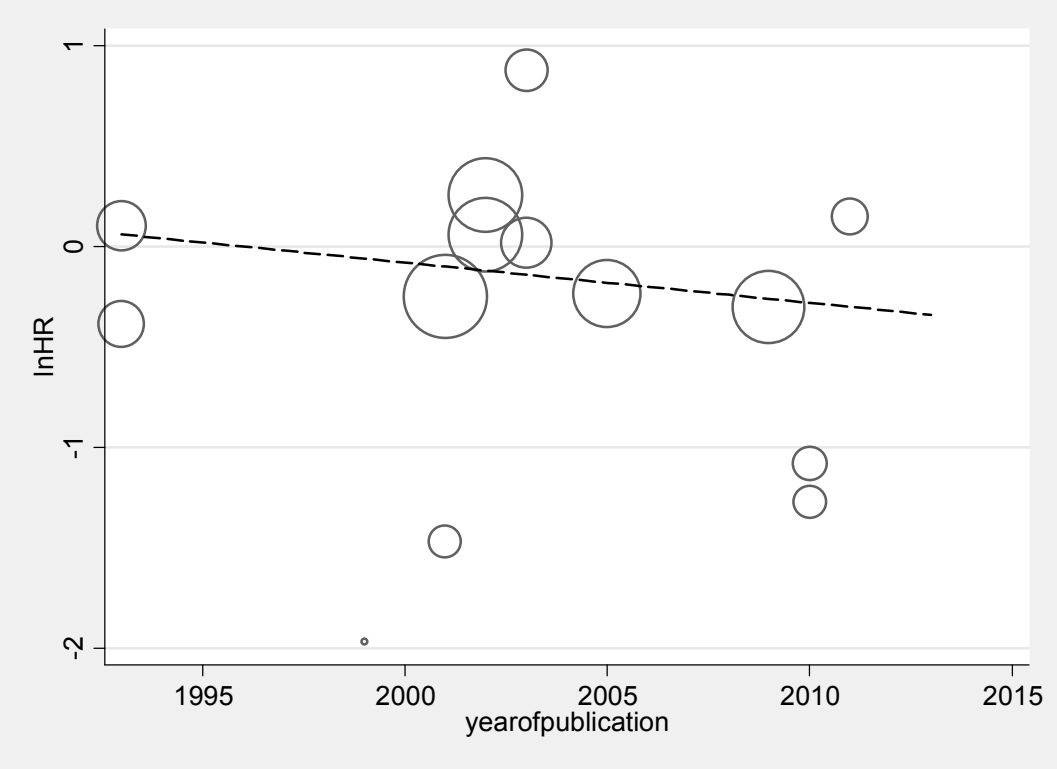
Key: HR, hazard ratio; se, standard error

Figure 100. Funnel plot: Mortality; excluding Dunphy and colleagues, 1999 trial



Key: HR, hazard ratio; se, standard error

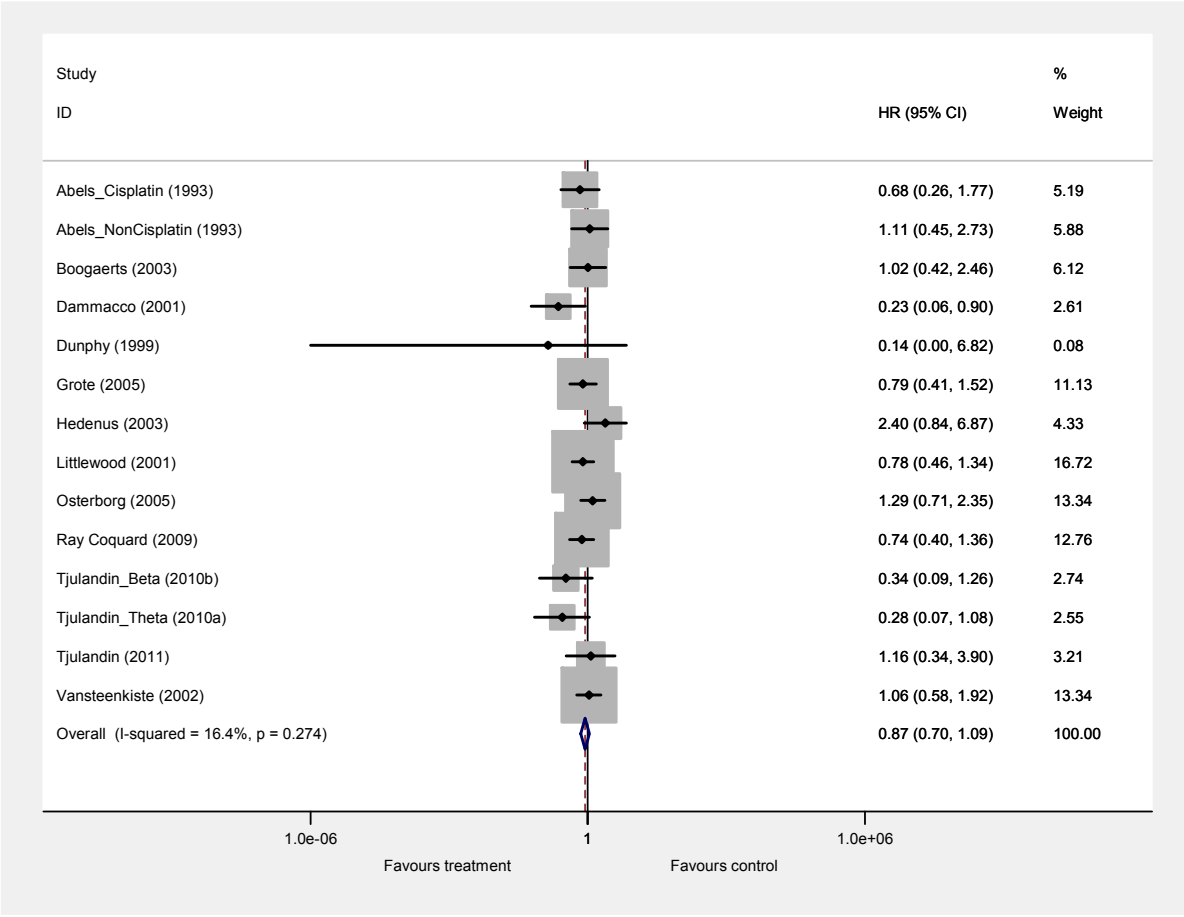
Figure 101. Meta-regression plot: Mortality



Key: HR, hazard ratio.

23.2.3.2. Fixed effects

Figure 102. Forest plot: Mortality (fixed effects)



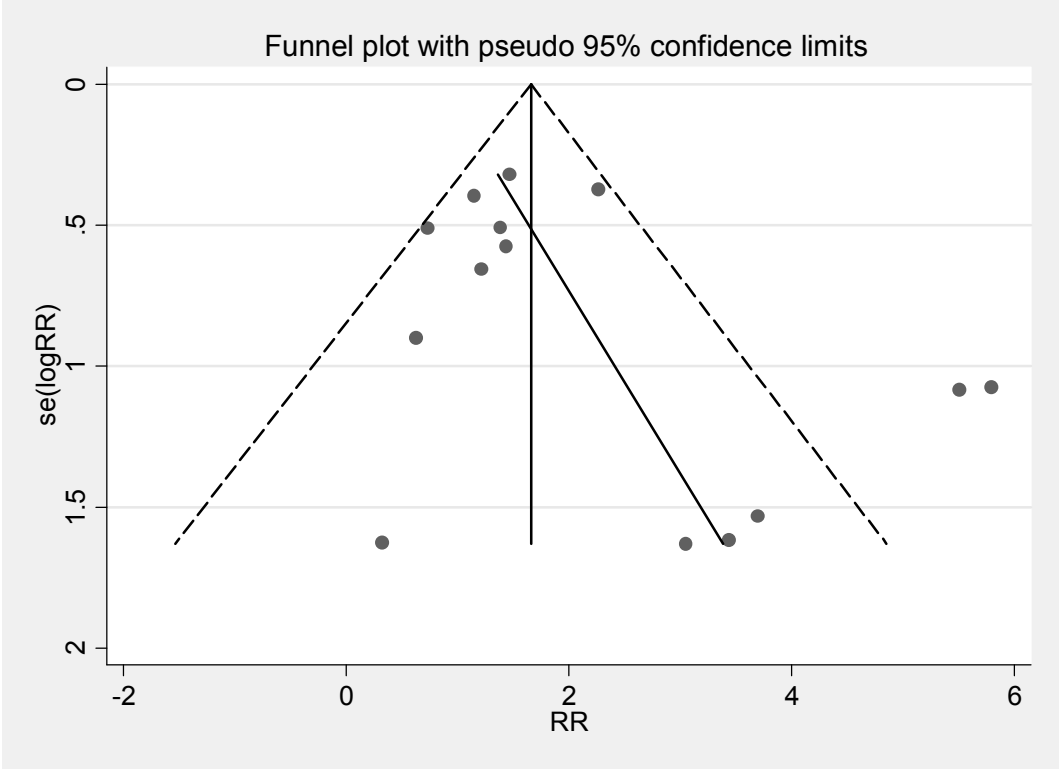
Key: CI, confidence interval; ID, identification; HR, Hazard ratio
Notes: **(a)** Der-Simonian Laird pooled HR; **(b)** Trial with multiple experimental arm split into subsets in the analysis: **Tjulandin and colleagues, 2010a,b** reports data for epoetin theta (2010a) and epoetin beta (2010b) and **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy; **(c)** IPD data as reported in Tonia and colleagues, 2012 (Cochrane review): Abels and colleagues, 1993; Boogaerts and colleagues, 2003; Dammacco and colleagues, 2001; Grote and colleagues, 2005; Hedenus and colleagues, 2003; Littlewood and colleagues, 2001; Osterborg and colleagues, 2002; Ray-Coquard and colleagues, 2009; Vansteenkiste and colleagues, 2002. HRs reported for other trials calculated using other accepted methods.

23.3. Safety-related outcomes

23.3.1. Thromboembolic events

23.3.1.1. Publication bias

Figure 103. Thromboembolic events: Publication bias, funnel plot

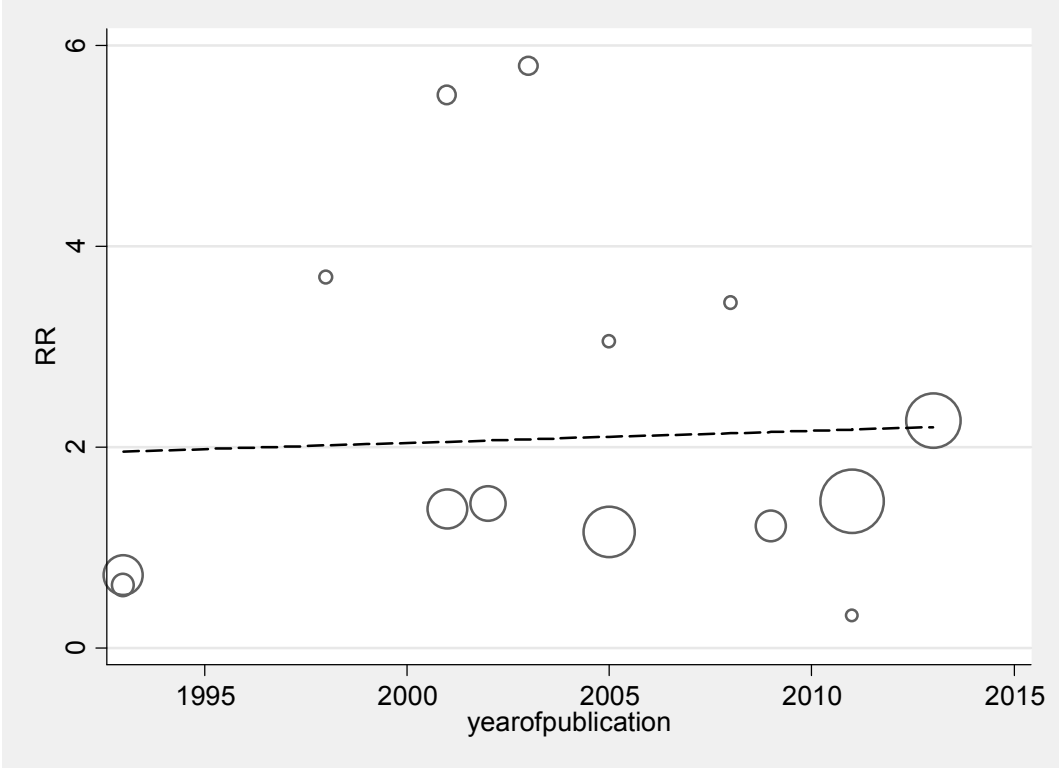


Key: se, standard error; RR, risk ratio

Table 114. Thromboembolic events: Harbord's modified test for small study effects

Number of studies 14					**Root MSE 0.9755**
Z/sqrt(V)	**Coef**	**SE**	**t**	**p>|t|**	**95% CI**
sqrt(V)	0.30	0.33	0.91	0.38	-0.42, 1.03
bias	0.28	0.56	0.63	0.63	-0.94, 1.50
Test of H_0 no small-study effects p=0.627					
Key: CI, confidence interval; coef, coefficient; SE, standard error **Notes:** Regress Z/sqrt(V) on sqrt(V) where Z is efficient score and V is score variance					

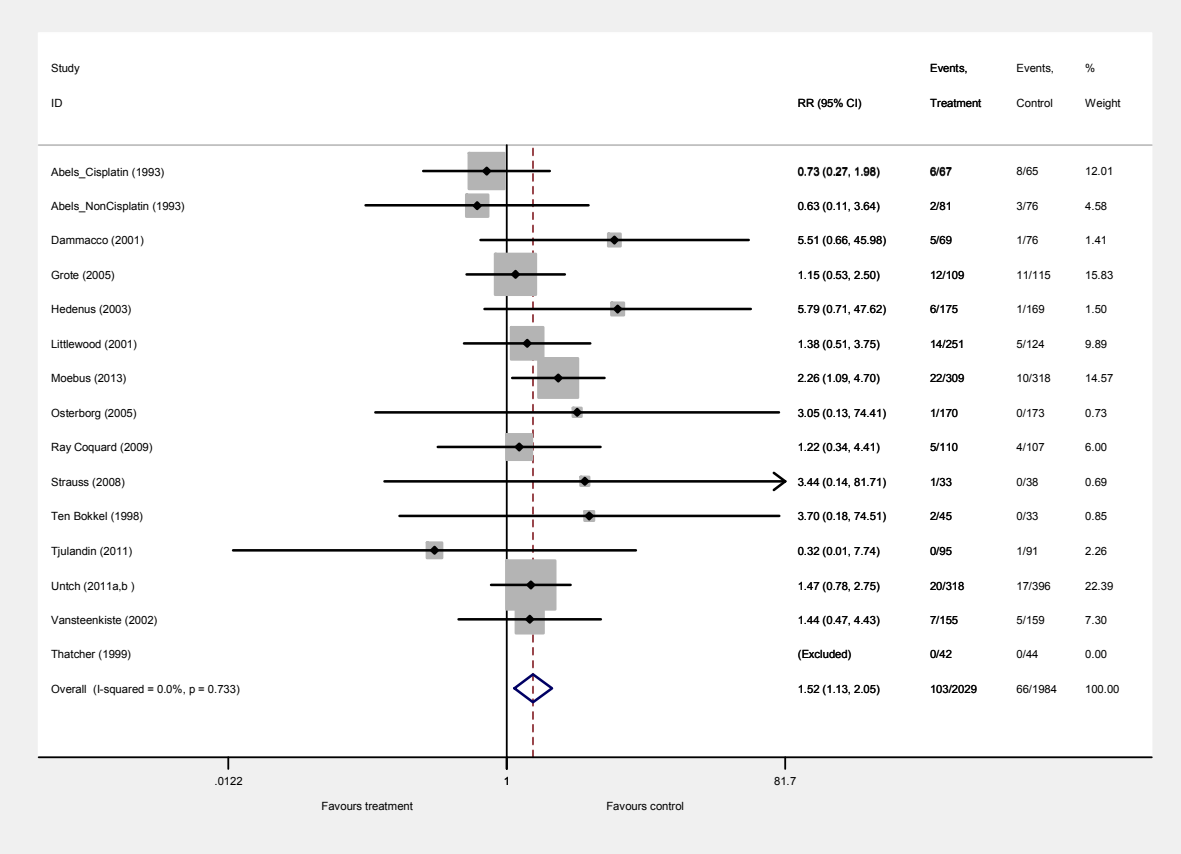
Figure 104. Thromboembolic events: Publication bias (meta-regression plot, year of publication as a covariate)



Key: RR, risk ratio

23.3.1.2. Fixed effects

Figure 105. Thromboembolic events: Overall, Forest plot (fixed effects)

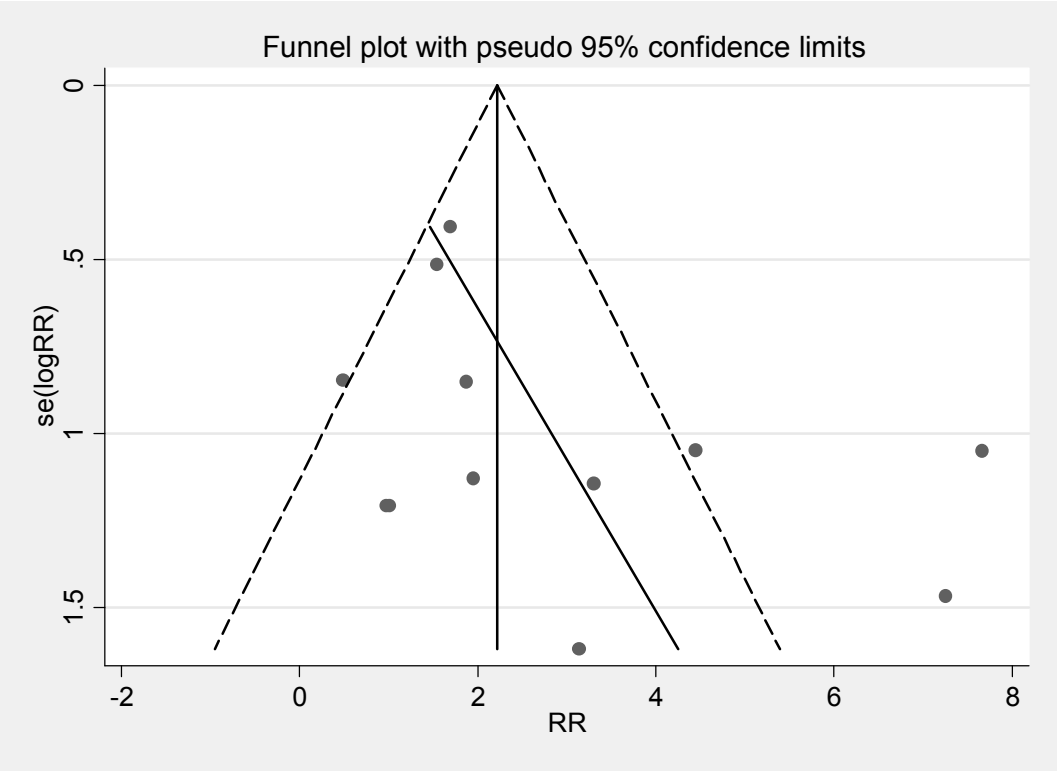


Key: CI, confidence interval; events, treatment, control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: Fixed effects (Mantel-Haenzel); Trial with multiple experimental arm split into subsets in the analysis: **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

23.3.2. Hypertension

23.3.2.1. Publication bias

Figure 106. Hypertension: Forest plot (fixed effects)

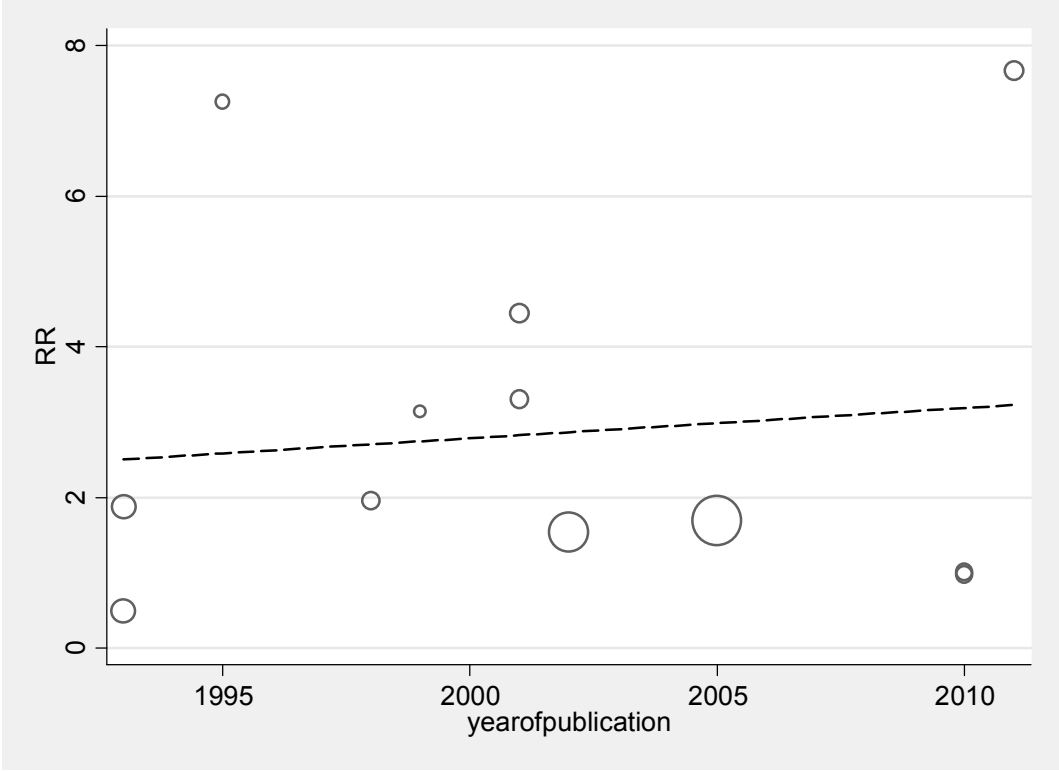


Key: se, standard error; RR, risk ratio

Table 115. HTN: Harbord's modified test for small study effects

Number of studies 12					**Root MSE 0.8809**
Z/sqrt(V)	**Coef**	**SE**	**t**	**p>|t|**	**95% CI**
sqrt(V)	0.49	0.51	0.95	0.364	-0.66, 1.63
bias	0.28	0.68	0.41	0.689	-1.22, 1.79
Test of H_0 no small-study effects p=0.689					
Key: CI, confidence interval; coef, coefficient; SE, standard error **Notes:** Regress Z/sqrt(V) on sqrt(V) where Z is efficient score and V is score variance					

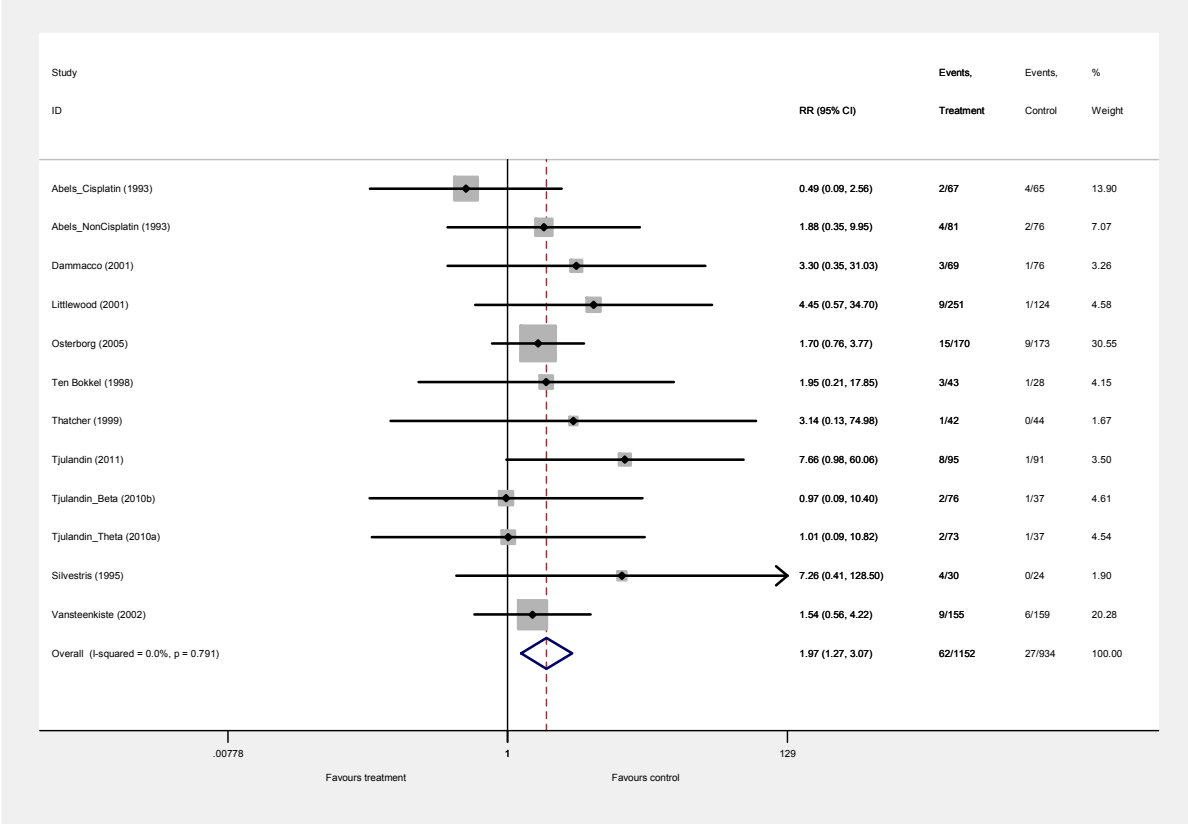
Figure 107. Hypertension: Publication bias (meta-regression plot, year of publication as a covariate)



Key: se, standard error; RR, risk ratio

23.3.2.2. Fixed effects

Figure 108. Hypertension: Overall, Forest plot (fixed effects)

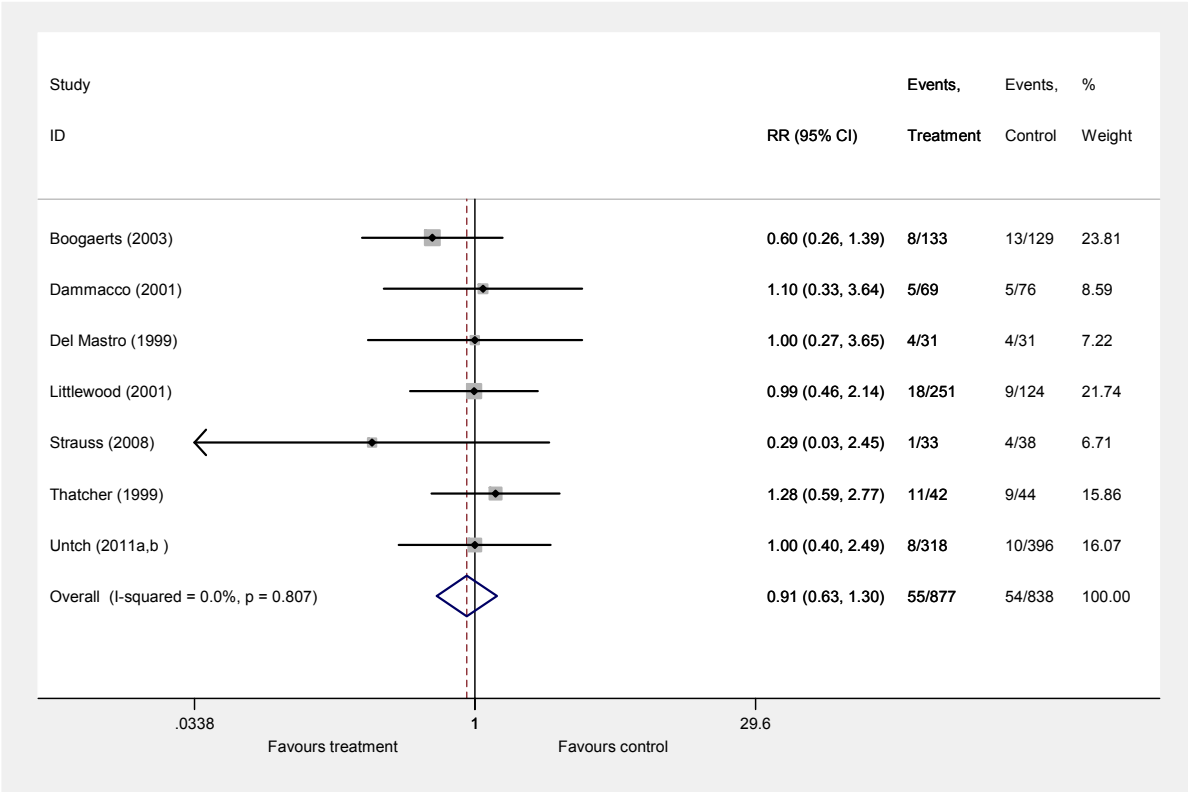


Key: CI, confidence interval; events, treatment, control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: Fixed effects (Mantel-Haenszel); Trial with multiple experimental arm split into subsets in the analysis: **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

23.3.3. Thrombocytopenia/haemorrhage

23.3.3.1. Fixed effects

Figure 109. Thrombocytopenia/haemorrhage: Overall, Forest plot (fixed effects)

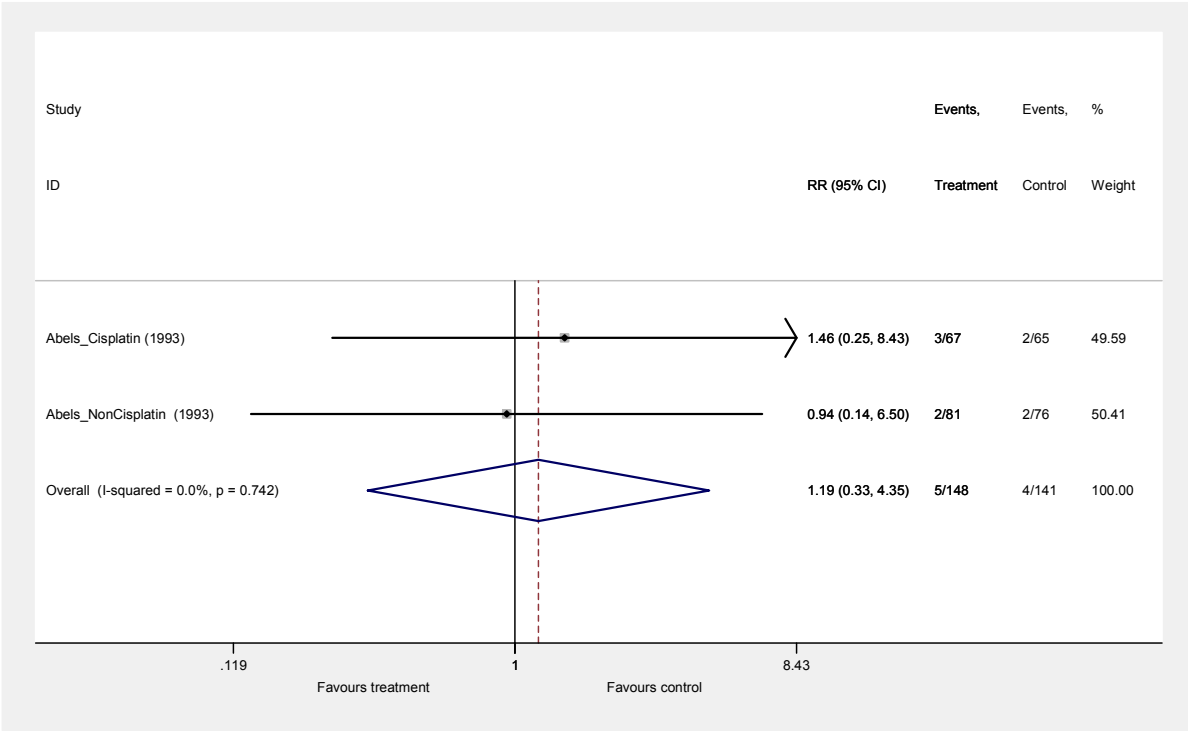


Key: CI, confidence interval; events, treatment, control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: (a) Fixed effects (Mantel-Haenzel)

23.3.4. Seizure

23.3.4.1. Fixed effects

Figure 110. Seizure: Overall, Forest plot (fixed effects)

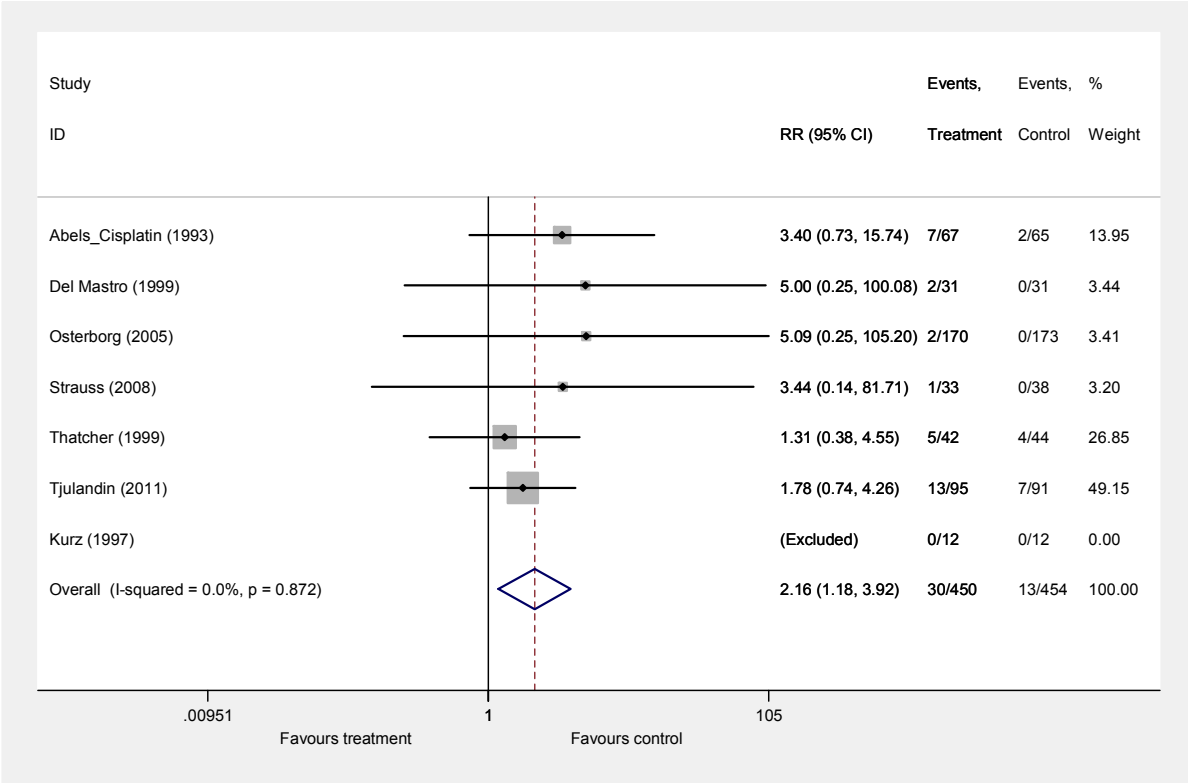


Key: CI, confidence interval; events, treatment, control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: Fixed effects (Mantel-Haenzel); Trial with multiple experimental arm split into subsets in the analysis: **Abels and colleagues 1993** reported data for participants on platinum-based chemotherapy and non-platinum based chemotherapy

23.3.5. Pruritus

23.3.5.1. Fixed effects

Figure 111.Pruritus: overall (fixed effects)



Key: CI, confidence interval; events, treatment, control, number of events/participants in the treatment and control groups; ID, identification; RR, risk ratio
Notes: (a) Fixed effects (Mantel-Haenzel)

23.4. Sensitivity 'close to licence' analyses

Figure 112. 'Close to licence' subgroup analyses using Hb subgroups results from Littlewood and colleagues, 2001 and Vansteenkiste and colleagues, 2002

Licence	Outcome	Trials	ES (95% CI)	I^2
Starting dose criteria met	Hb change[d,e]	18	WMD 1.59 (1.33 − 1.84)	75.9%; p<0.01
	HaemR [a,d,e]	13	RR 3.29 (2.81 − 3.85)	13.4%; p=0.31
	RBCT[b,d,e]	26	RR 0.61 (0.55−0.68)	22.4%; p=0.15
	Units[c,d]	12	WMD -0.87 (-1.24 − -0.50)	55.6%; p=0.01
	Tumour response	7	RR 1.10 (0.86 – 1.41)	37.5%; p=0.14
	Overall survival[d,e]	18	HR 0.97 (0.83 − 1.13)	42.4%; p=0.03
	On study mortality[d,e]	14	HR 0.86 (0.67 − 1.11)	16.4%; p=0.27
	Thromboembolic events[d]	14	RR 1.46 (1.07 − 1.99)	0%; p=0.73
	Hypertension[d,e]	12	RR 1.80 (1.14 − 2.85)	0%; p=0.79
	Thrombocytopenia/ haemorrhage	7	RR 0.93 (0.65 – 1.34)	0%; p=0.81
	Seizures[d]	2	RR 1.19 (0.33 – 4.38)	0%; p=0.74
	Pruritus	6	RR 2.04 (1.11 – 3.75)	0%; p=0.87
Starting dose criteria met and inclusion Hb ≤11 g/dl	Hb change[d,e]	13	WMD 1.52 (1.30 − 1.75)	48.1%; p=0.03
	HaemR [a,d,e]	12	RR 3.20 (2.78 − 3.68)	2.0%; p=0.43
	RBCT[b,d,e]	16	RR 0.64 (0.57 − 0.71)	7.3%; p=0.37
	Units[c,d]	9	WMD -0.99 (-1.41 − -0.56)	56.2%; p=0.02
	Tumour response	2	RR 1.60 (0.88 – 2.90)	0%; p=0.70
	Overall survival[d,e]	10	HR 0.91 (0.70 − 1.20)	51.7%; p=0.03
	On study mortality[d,e]	10	HR 0.89 (0.61 − 1.30)	37.7%; p=0.11
	Thromboembolic events[d]	7	RR 1.29 (0.66 – 2.54)	12.2%; p=0.34
	Hypertension[d,e]	9	RR 1.68 (1.03 – 2.74)	0%; p=0.64
	Thrombocytopenia/ haemorrhage	2	RR 0.73 (0.37 – 1.46)	0%; p=0.41
	Seizures[d]	2	RR 1.19 (0.33 – 4.38)	0%; p=0.74
	Pruritus	3	RR 2.20 (1.05 – 4.58)	0%; p=0.66

Starting dose criteria met and target Hb ≤13 g/dl	Hb change[e]	4	WMD 1.29 (0.90 − 1.67)	61.9%; p=0.05
	HaemR [e]	3	RR 3.06 (2.28 – 4.09)	0%; p=0.79
	RBCT[e]	4	RR 0.52 (0.34 − 0.80)	48.4%; p=0.14
	Units[c]	1	WMD -0.56 (-0.74 − 0.39)	NA
	Tumour response	1	RR 0.90 (0.63 – 1.3)	NA
	Overall survival[e]	4	HR 0.73 (0.32 − 1.64)	61.8%; p=0.05
	On study mortality[e]	3	HR 0.50 (0.20 − 1.23)	29.7%; p=0.24
	Thromboembolic events	2	RR 1.38 (0.75 – 2.57)	0%; p=0.36
	Hypertension[e]	3	RR 2.19 (0.53 – 9.12)	16.8%; p=0.30
	Thrombocytopenia/ haemorrhage	1	RR 1.00 (0.40 – 2.50)	NA
	Seizures	0	NA	NA
	Pruritus	1	RR 1.78 (0.74 – 4.26)	NA
Starting dose criteria met, inclusion Hb ≤11 g/dl et target Hb ≤13 g/dl	Hb change[e]	3	WMD 1.50 (1.16 − 1.83)	0%; p=0.80
	HaemR [e]	3	RR 3.06 (2.28 – 4.09)	0%; p=0.79
	RBCT[e]	3	RR 0.50 (0.33 − 0.77)	0%; p=0.92
	Units[c]	1	WMD -0.56 (-0.74 − 0.39)	NA
	Tumour response	0	NA	NA
	Overall survival[e]	3	HR 0.50 (0.20 − 1.23)	29.7%; p=0.24
	On study mortality[e]	3	HR 0.50 (0.20 − 1.23)	29.7%; p=0.24
	Thromboembolic events	1	RR 0.32 (0.01 – 7.74)	NA
	Hypertension[e]	3	RR 2.19 (0.53 – 9.12)	16.8%; p=0.30
	Thrombocytopenia/ haemorrhage	0	NA	NA
	Seizures	0	NA	NA
	Pruritus	1	RR 1.78 (0.74 – 4.26)	NA

Key: HaemR, haematological response; Hb, haemoglobin; NA, not applicable; RBCT, red blood cell transfusion; Units, units transfused per participant; RR, risk ratio; HR, hazard ratio; WMD, weighted mean difference.
Notes : (a) Using Littlewood and colleagues, 2001 Hb subgroups; (b) Using Littlewood and colleagues, 2001 and Vansteenkinste and colleagues, 2002 Hb subgroups; (c) using Vansteenkinste and colleagues, 2002 Hb subgroups; (d) Abels and colleagues, 1993 reported data for participants on plat-based et non-plat based chemotherapy which we combined; (e) Tjulandin and colleagues, 2010 reported data for erythropoietin beta et theta which were combined.

Appendix M: Supplementary material: HRQoL review

24.1. FACT scales

All scales reproduced in this section reproduced from:
http://www.facit.org/FACITOrg/Questionnaires (copyright © 2010 FACIT.org).

24.1.1. FACT-G Version 4

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	<u>FUNCTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

24.1.2. FACT-An (version 4)

Below is a list of statements that other people with your illness have said are important**.**

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless (“washed out”)	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

24.1.3. FACT-F (Version 4)

Below is a list of statements that other people with your illness have said are important**.**

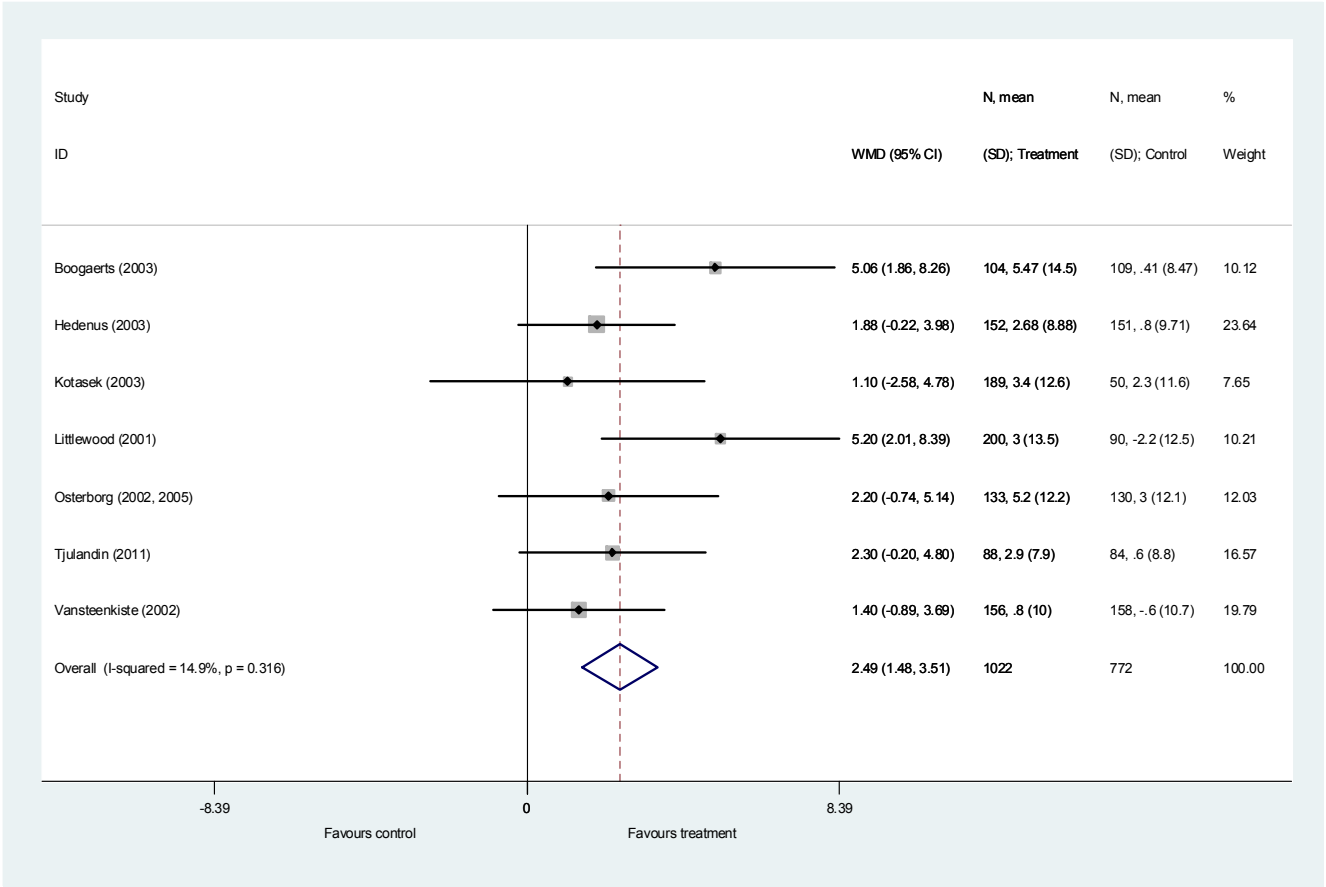
Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

24.2. Meta-analysis: HRQoL

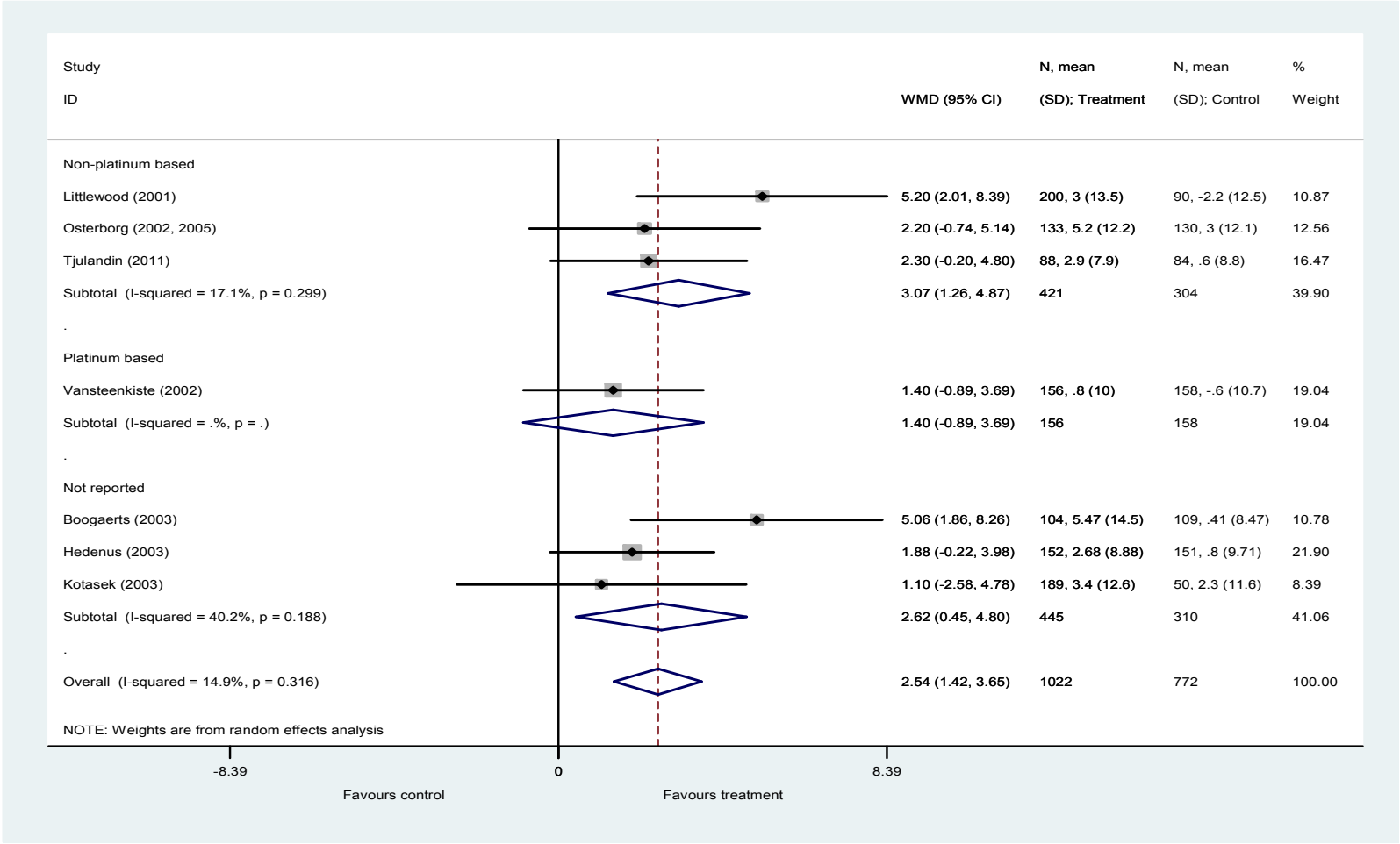
24.2.1. FACT-F: Fixed effects

Figure 113. HRQoL, Change in FACT-F Score: overall (fixed effects)



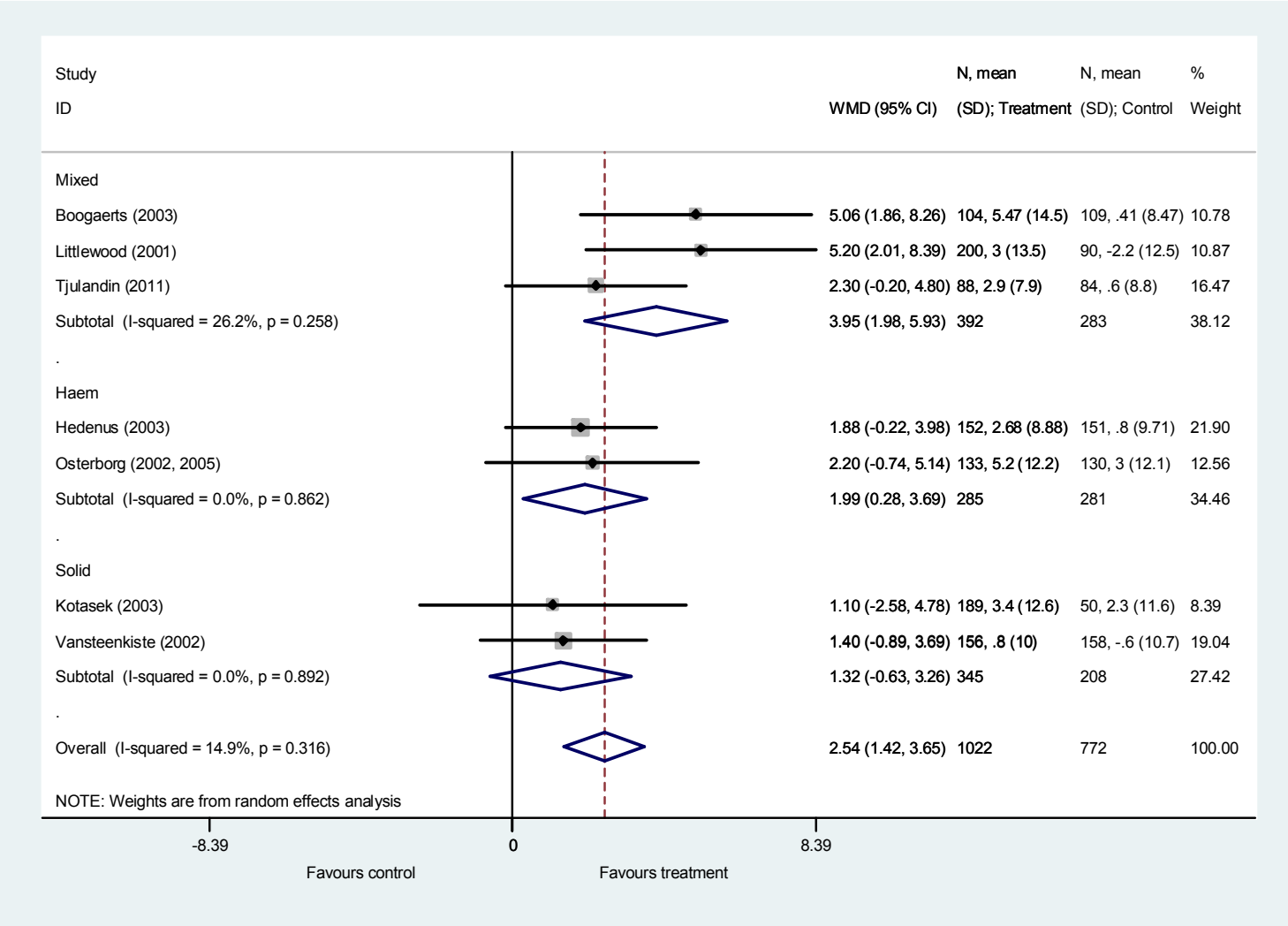
24.2.2. FACT-F: Subgroup analyses

Figure 114. HRQoL: Change in FACT-F by chemotherapy type (random effects)



Key: CI, confidence interval; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference
Notes: a Mantel-Haenzel pooled RR;

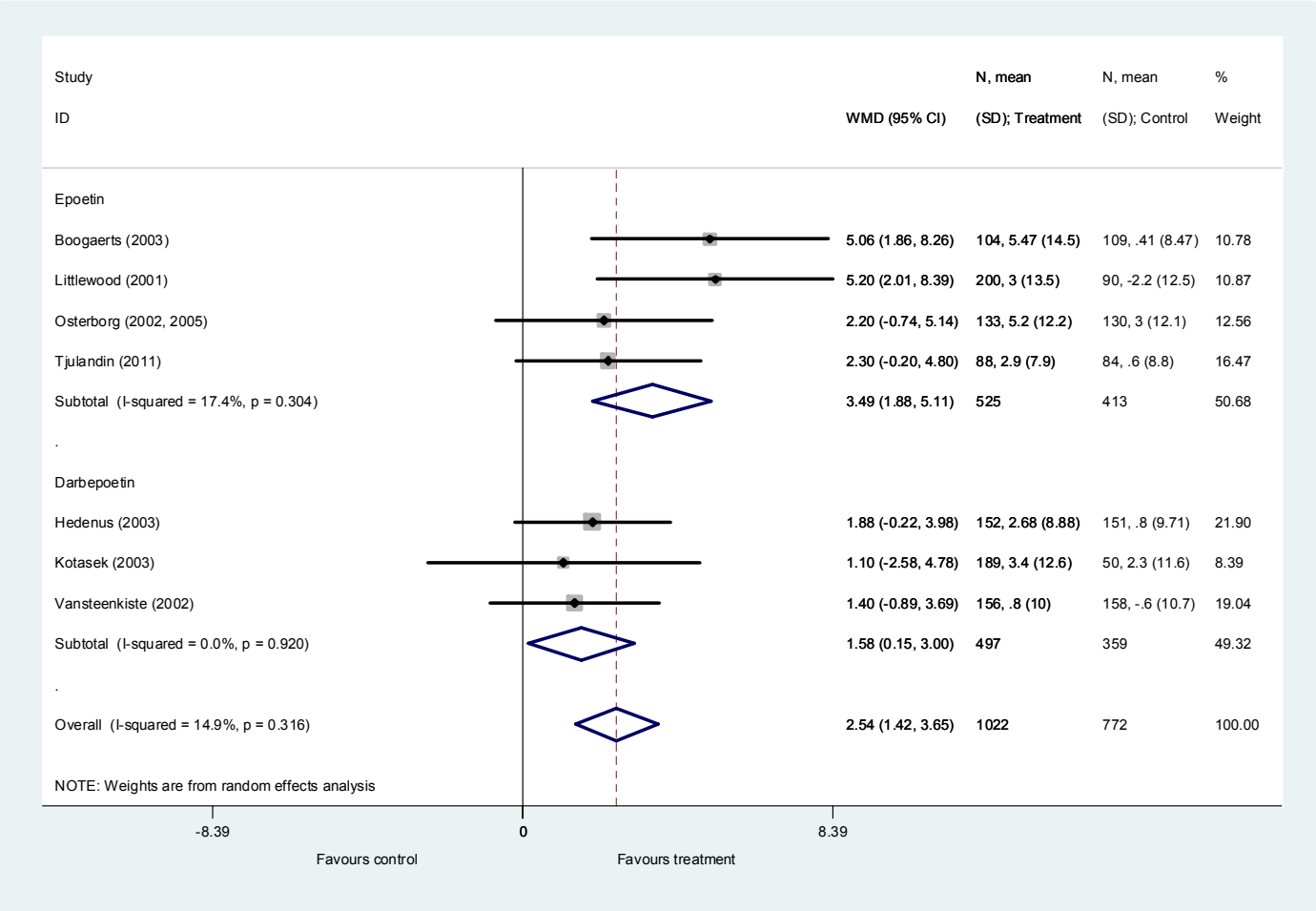
Figure 115. HRQoL: Change in FACT-F by malignancy (random effects)



Key: CI, confidence interval; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference

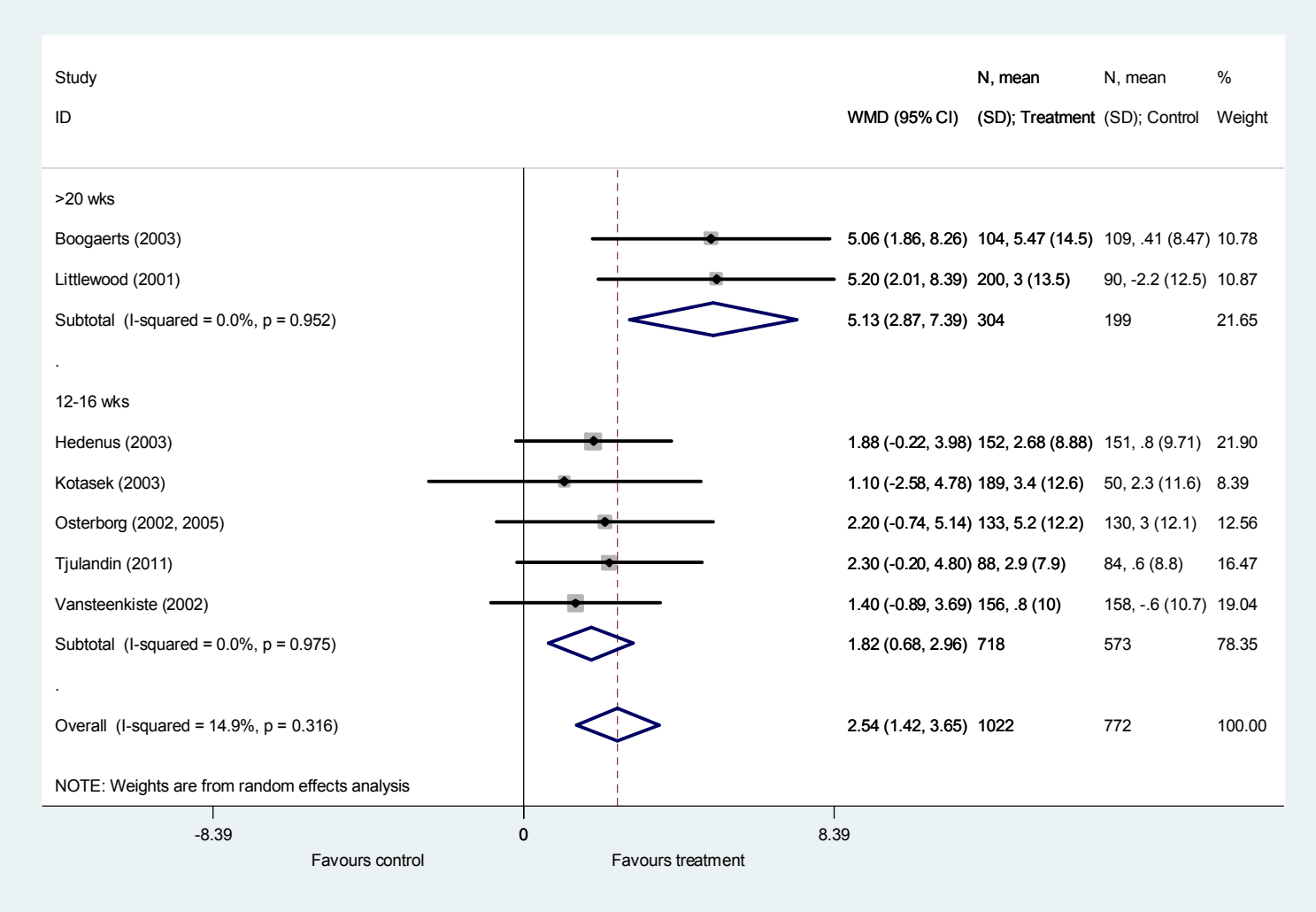
Notes: a Random effects (Der-Simonian–Laird pooled RR)

Figure 116. HRQoL: Change in FACT-F by intervention (random effects)



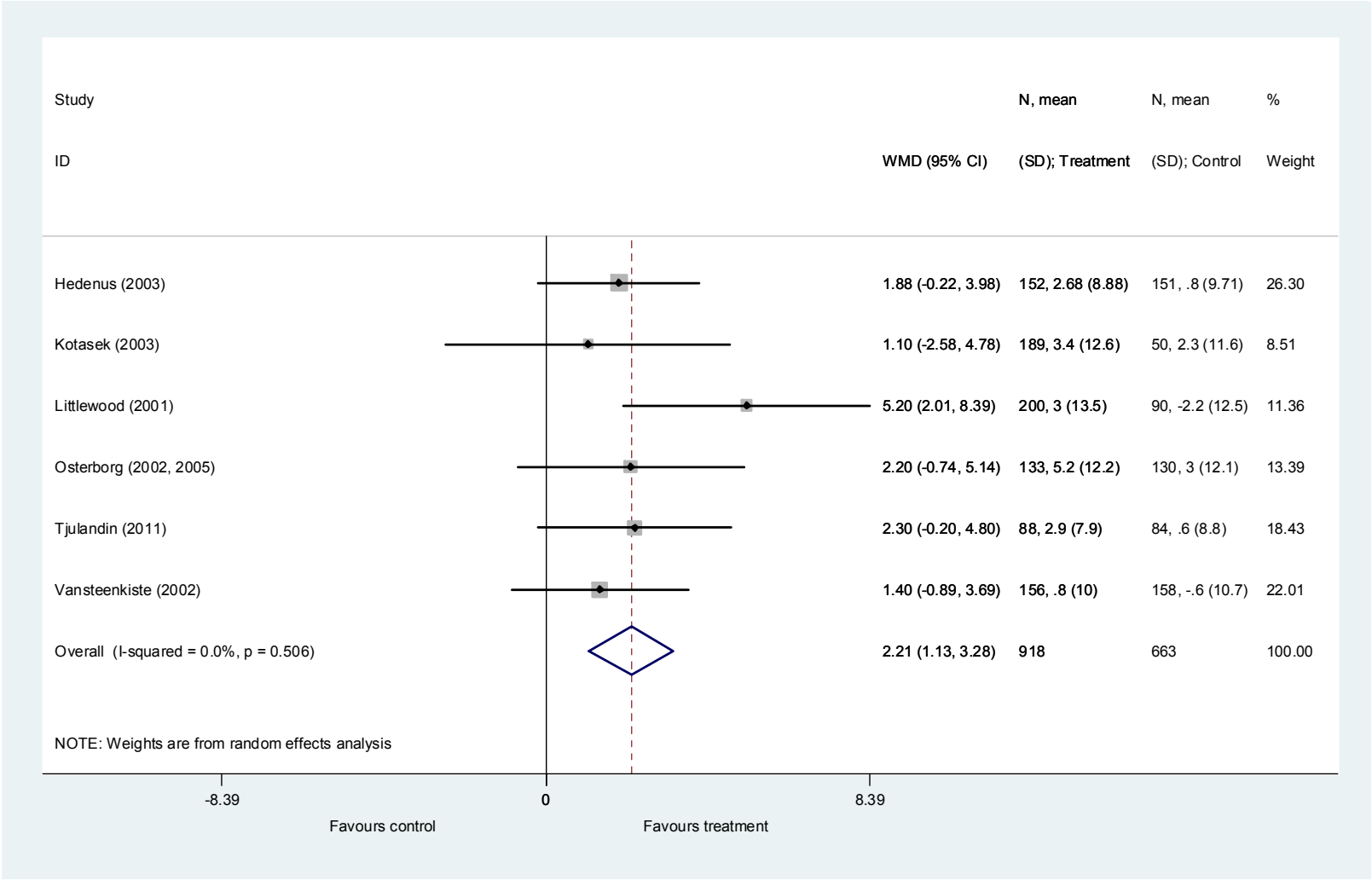
Key: CI, confidence interval; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference
Notes: a Random effects (Der-Simonian–Laird pooled RR)

Figure 117. HRQoL: Change in FACT-F by study duration (random effects)



Key: CI, confidence interval; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference
Notes: a Random effects (Der-Simonian–Laird pooled RR)

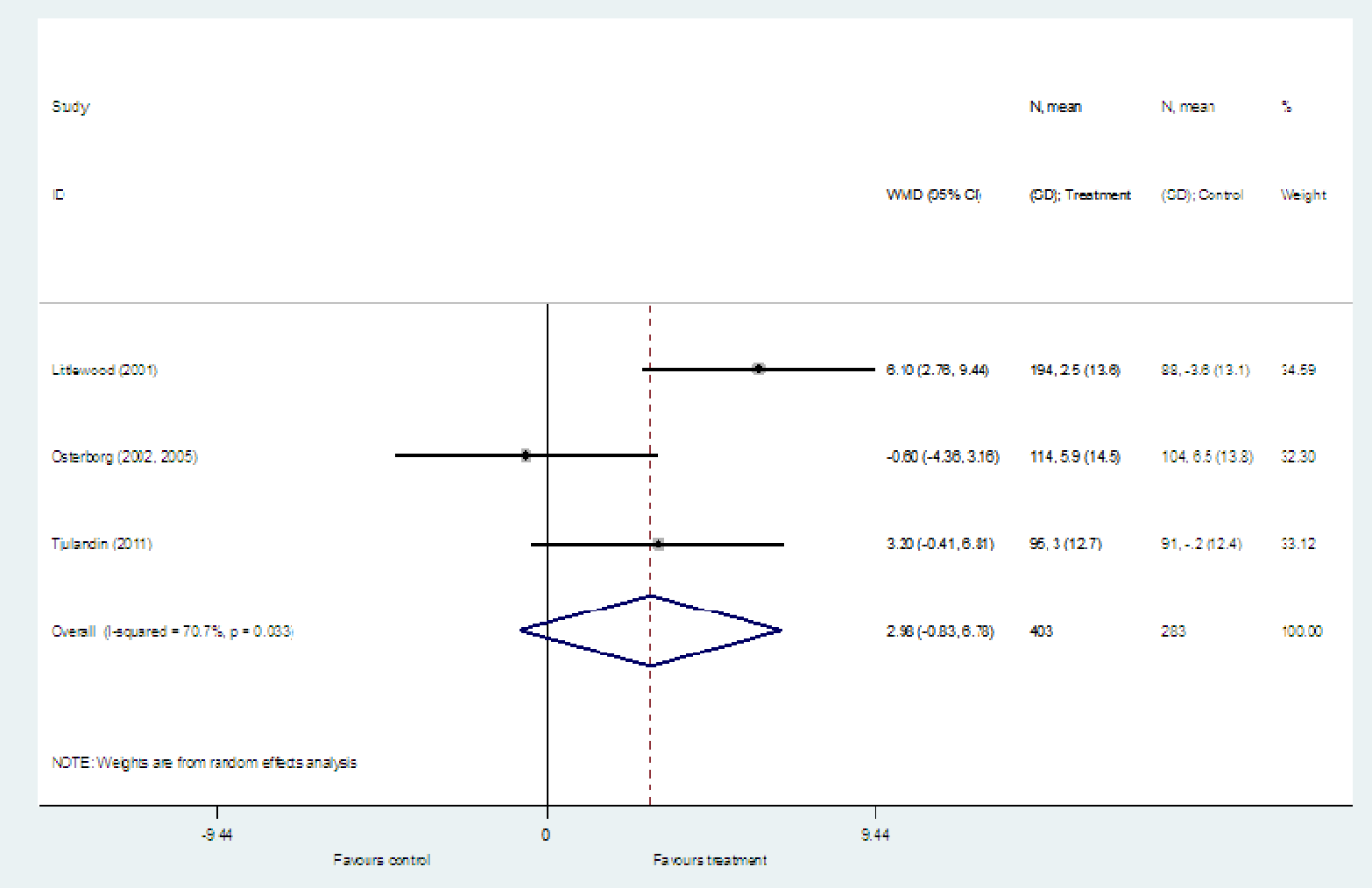
Figure 118. Change in FACT-F with Boogaerts and colleagues (2003) removed



Key: CI, confidence interval; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference
Notes: a Random effects (Der-Simonian–Laird pooled RR)

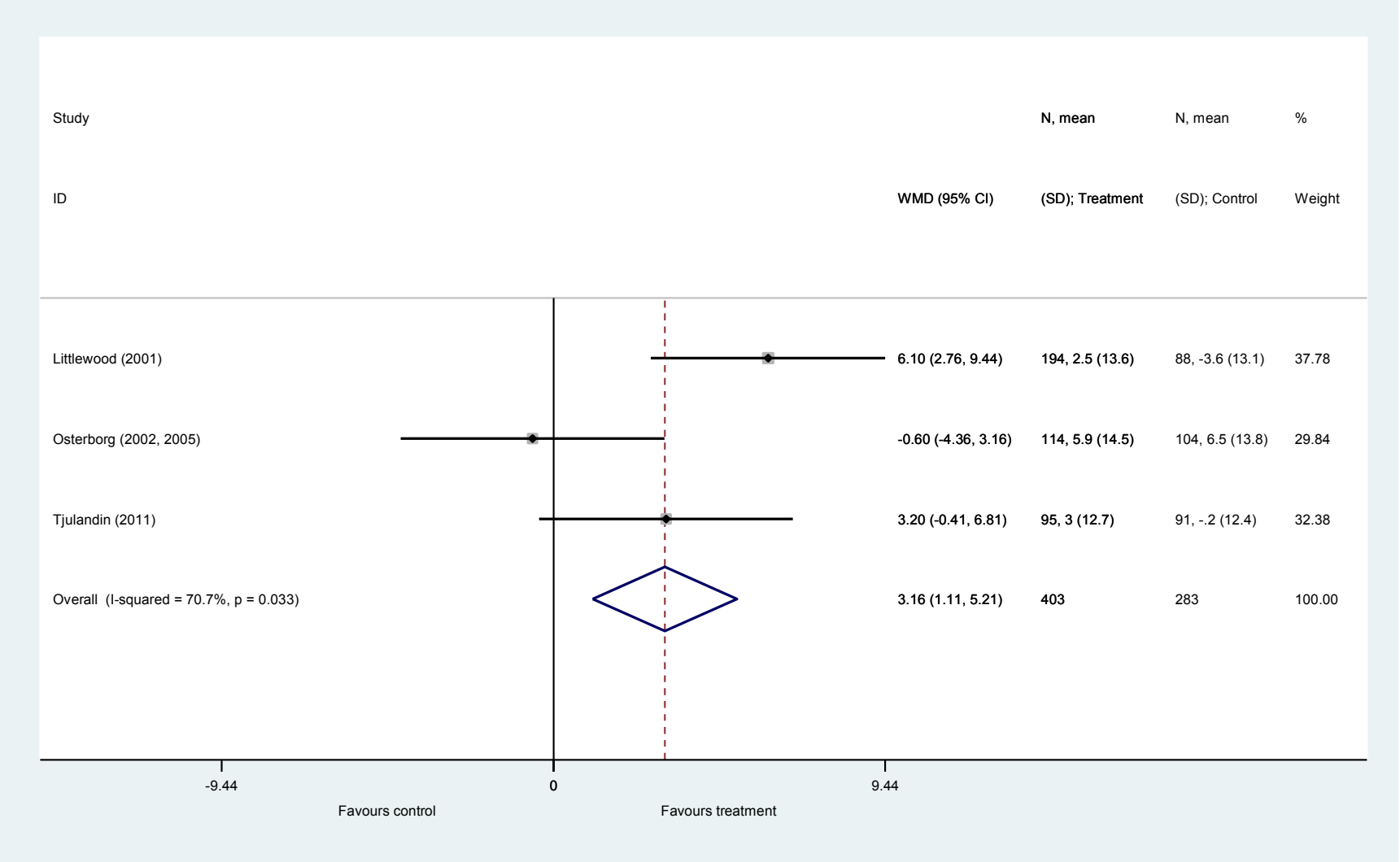
24.2.3. FACT-G

Figure 119. HRQoL: Change in FACT-G: overall (random effects)



Key: CI, confidence interval; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference
Notes: a Random effects (Der-Simonian–Laird pooled WMD)

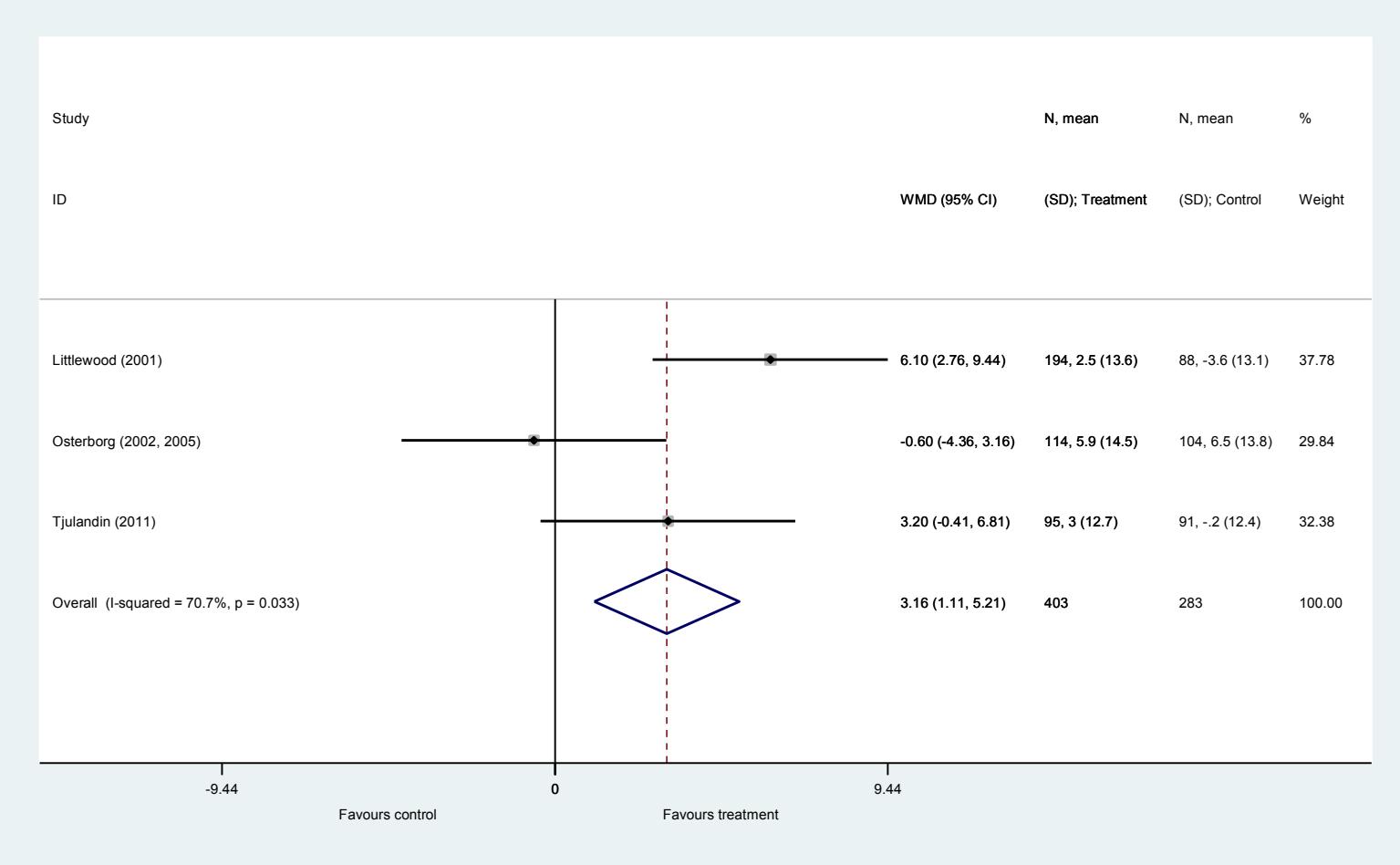
Figure 120. HRQoL: Change in FACT-G: overall (fixed effects)



Key: CI, confidence interval; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference
Notes: a Mantel-Haenzel pooled WMD

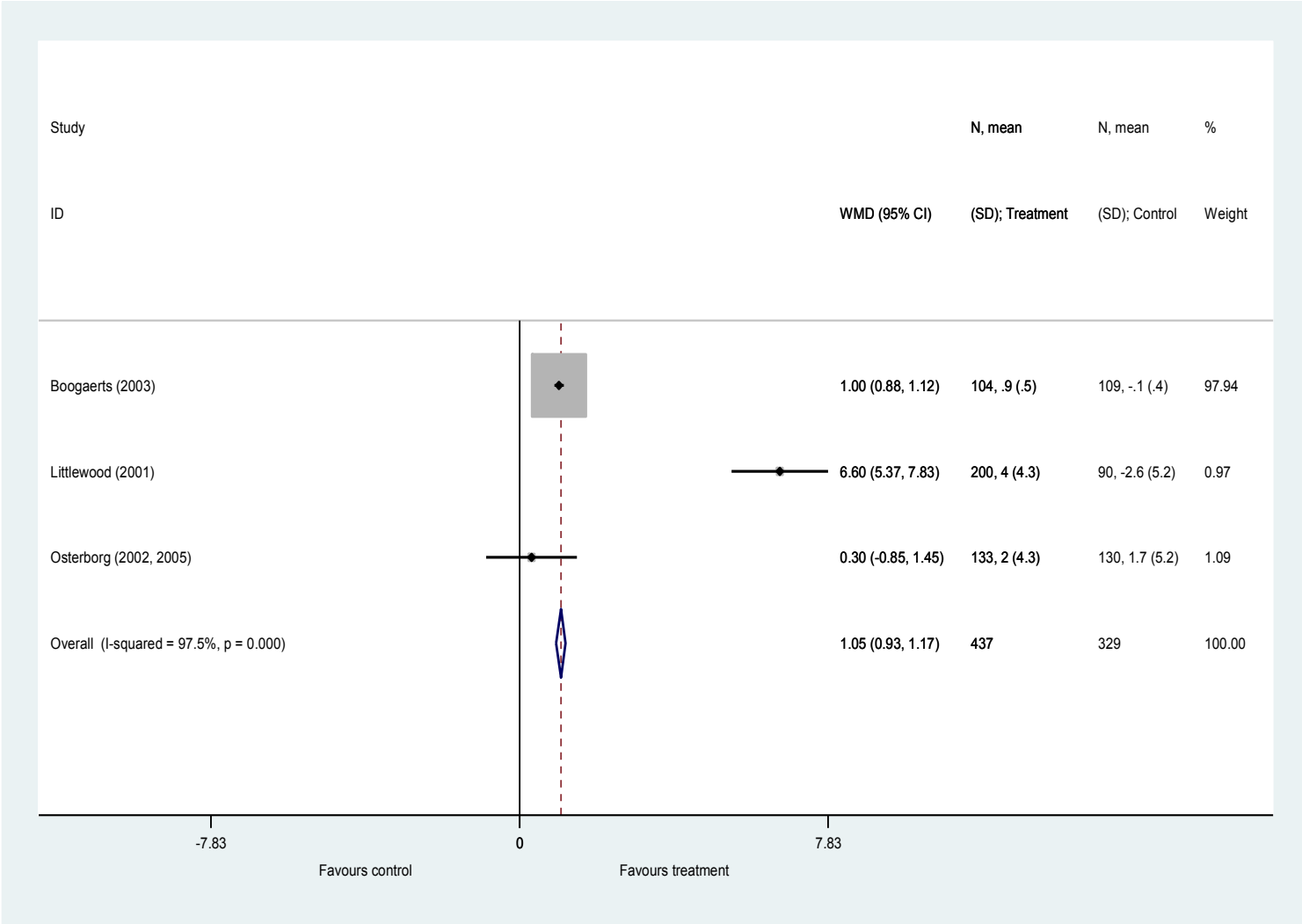
24.2.4. FACT-An

Figure 121. HRQoL: Change in FACT-An overall (fixed effects)



Key: CI, confidence interval; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference
Notes: a Mantel-Haenzel pooled WMD

Figure 122. HRQoL: Change in FACT-An overall (fixed effects)



Key: CI, confidence interval; ID, identification; N, number of participants; SD, standard deviation; WMD, weighted mean difference
Notes: a Mantel-Haenzel pooled WMD

Appendix N: Excluded studies (cost-effectiveness review)

Study	Reason for exclusion	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. Annals of Pharmacotherapy (The). 1997;31:15-22.	Could not be obtained	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. Journal of the Medical Association of Thailand. 2008;91(Suppl 2):S119-S125.	Could not be obtained	
Griggs JJ, Sorbero MES. Cost-utility of erythropoietin in the treatment of cancer-related anemia. Medical Decision Making. 1997;17(4):529.	Could not be obtained	Published pre-2004
Griggs JJ, Blumberg N. Recombinant erythropoietin and blood transfusions in cancer chemotherapy-induced anemia. Anti-Cancer Drugs. 1998;9:925-932.	Could not be obtained	Published pre-2004
Malonne H, editor Cost evaluation of erythropoiesis stimulating agents in the treatment of platinum chemotherapyinduced anaemia. 20th Annual meeting of the Belgian Hematology Society; 2005.	Could not be obtained	
Study design		
Reeder CE. Anemia in cancer and critical care patients: pharmacoeconomic considerations. American Journal of Health-System Pharmacy. 2007 Feb 1;64:S22-7.	Study design	Non-systematic review
Dale DC. The benefits of haematopoietic growth factors in the management of gynaecological oncology. European journal of gynaecological oncology. 2004;25:133-44.	Study design	Expert commentary
Marchetti M, Barosi G. Clinical and economic impact of epoetins in cancer care. Pharmacoeconomics. 2004;22:1029-45.	Study design	Non-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). Journal of Clinical Oncology. 2004 Jul;22:797S-S.	Study design	Cost study, not UK
Steensma DP, Loprinzi CL. Epoetin alfa and darbepoetin alfa go head to head. Journal of Clinical Oncology. 2006;24:2232-6.	Study design	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 Feb;23:357-68.	Study design	Non-systematic review
Herrmann R. Erythropoietin therapy in cancer-related	Study	Non-systematic

anaemia, yes or no? Internal Medicine Journal. 2008;38:749-50.	design	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-S9.	Study design	Non-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 Aug;10:539-54.	Study design	Non-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):S177.	Study design	Cost study, not UK
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 United Kingdom. 2009;145:58.	Population	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 in Health. 2002;5(6):543.	Intervention	Abstract; uses unlicensed Q2W dosing 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 in Health. 2005 May-Jun;8:238.	Outcome	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. 2012 European Association of Hospital Pharmacists, EAHP Congress Milan Italy. 2012;19:202.	Outcome	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 anemia (CIA): A retrospective study. Annals of Oncology. 2006;17:293.	No usable data	Abstract
Grocott R, Metcalfe S, Moodie P. PHARMAC and erythropoietin for cancer patients. N Z Med J. 2006;119:U2039.	No usable data	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	Published pre-2004	Included in Wilson and colleagues

and supportive care: recombinant human erythropoietin as a treatment of cancer-associated anaemia. PharmacoEconomics. 1999;16(5 Pt 1):459-472.		(2007)
Barosi G, Marchetti M, Liberato NL. Cost-effectiveness of recombinant human erythropoietin in the prevention of chemotherapy-induced anaemia. British Journal of Cancer. 1998;78(6):781-787.	Published pre-2004	Included in Wilson and colleagues (2007)
Language (not English)		
Borget I, Chouaid C, Demarteau N, Annemans L, Pujol JL. Cost-effectiveness of darbepoetin a in an every-3-weeks schedule. Bulletin Du Cancer. 2008 Apr;95:465-73.	Language	French language
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA). Epoetin (EPO) for anaemic cancer patients (Structured abstract). Health Technology Assessment Database [Internet]. 2004; (2):[45 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32005000197/frame.html.	Language	Danish language

Appendix O: Multiple publications in cost-effectiveness review

Primary study

I. Borget, P. Tilleul, M. Baud, A. C. Joly, A. Daguenel, and C. Chouaid. Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. *Lung Cancer*:369-376, 2006.

Multiple publications

C. Chouaid, I. Borget, M. Baud, A. C. Joly, A. Daguenel, and P. Tilleul. Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: A Markov analysis. *Lung Cancer* 49:S23, 2005.

I. Borget, P. Tilleul, A. C. Joly, and C. Chouaid. Incremental cost-effectiveness ratio of darbepoetin alfa (Aranesp (R)) in the treatment of chemotherapy-induced anemia in lung cancer patients. *Value Health* 9:A278-A279, 2006.

I. Borget, P. Tilleul, M. Baud, A. C. Joly, and C. Chouaid. Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis. *Pharm World Sci* 29:454, 2007.

Primary study

J. Finek, L. Holubec, A. Wiesnerova, Z. Pav, and L. Dusek. Darbepoetin alfa versus epoetin alfa for treatment of chemotherapy-induced Anemia: A health economic evaluation. *Value Health* 13 (7):A465, 2010.

Multiple publications

J. Finek, L. Holubec, A. Wiesnerova, Z. Pav, and V. Dusek. Darbepoetin alfa versus epoetin alfa for treatment of chemotherapy-induced anemia: A health economic evaluation. *Ann Oncol* 21 (suppl 8):344, 2010.

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. Technology report number 119. 2009. Ottawa, Canadian Agency for Drugs and Technologies in Health.

Multiple publications

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; 116:3224-3232.

Appendix P: Study characteristics, key parameters and results of conference abstracts identified in the cost-effectiveness review

	Szucs, 2001[141]	Cremieux, 2003[142]	Mark, 2003[144]	van Hout, 2004[145]
Evaluation type	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost-consequences analysis	Cost-effectiveness analysis
Modelling used	No	No	No	Yes
Nature of modelling	N/A	N/A	N/A	"Bayesian simulation model"
Perspective	Societal	Societal	Drug cost only	Healthcare[a]
Country (setting)	Multiple (France, Germany, Italy, Sweden and UK)	Not stated (probably USA)	Not stated (probably USA)	UK[a]
Intervention/comparator	**Epo-b TIW:** 150 IU/kg **Standard care**	**Epo-a QW:** 40,000 IU **Darb-a QW:** 2.25 µg/kg	**Epo-a** **Darb-a**	**Epo-a QW:** 150 IU/kg[b] **Darb-a 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 FACT-F FACT-An	Cumulative change in Hb (AUC) Change in FACT-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 (manufacturers of Epo-a)	Ortho Biotec (manufacturers of Epo-a)	Johnson & Johnson (manufacturers of Epo-a)

Key: AUC, area under the curve; Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Epo-b, epoetin beta; FACT-F/An, Functional Assessment of Cancer Therapy - Fatigue/Anemia; Hb, haemoglobin; IU, International Units; QW, once weekly; SF-36 PCS, Short form questionnaire physical component summary; TIW, three times weekly
Notes: (a) Separate analyses were conducted for UK (healthcare), France (healthcare) and US (private health insurance); only UK results 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

	Ben-Hamadi, 2005[146]	Van Bellinghen, 2006[147] }	Esposito, 2007[148]	Van Bellinghen, 2007[149]
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	Healthcare	Societal
Country (setting)	Not stated (probably USA)	France	Italy	Germany
Intervention/comparator	**Epo-a QW:** 40,000 IU **Darb-a QW:** 2.25 µg/kg	**Darb-a Q3W:** 500 µg **Epo-a QW:** European label dose **Epo-b QW:** European label dose	**Darb-a Q3W:** 500 µg **Epo-a QW:** European label dose **Epo-b QW:** European label dose	**Darb-a Q3W:** 500 µg **Epo-a QW:** European label dose **Epo-b 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 (manufacturers of Epo-a)	Amgen (manufacturers of Darb-a)	Amgen (manufacturers of Darb-a)	Amgen (manufacturers of Darb-a)

Key: Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Epo-b, epoetin beta; Hb, haemoglobin; IU, International Units; QW, once weekly; Q3W, once every three weeks

	Finek, 2010[150]	Liwing, 2010[151]	Walter, 2010[152]	Fragoulakis, 2011[143]
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 healthcare)	Healthcare	Healthcare (plus patient transportation)
Country (setting)	Czech Republic (not explicitly stated)	Sweden	Austria	Greece
Intervention/comparator	**Epo-a QW**: 40,000 IU **Darb-a Q3W**: 500 µg	**Epo-a** **Darb-a**	**Darb-a Q3W**: 500 µg **Darb-a QW**: 150 µg **Epo-a QW**: 40,000 IU **Epo-b QW**: 30,000 IU **Epo-b TIW**: 30,000 IU (per week)	**Darb-a Q3W**: 500 µg **Darb-a QW**: 150 µg **Epo-a QW**: 40,000 IU **Epo-b QW**: 30,000 IU **Epo-b 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 RBC transfusions 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 Epo-a)	Amgen (manufacturers of Darb-a)	Genesis Pharma (distributor of Darb-a)

Key: Darb-a, darbepoetin alfa; Epo-a, epoetin alfa; Epo-b, epoetin beta; Hb, haemoglobin; QW, once weekly; Q3W, once every three weeks; TIW, three times weekly; RBC, red blood cell(s)
Notes: (a) Although study is described as cost-minimisation analysis, with similar efficacy for all treatments, in fact treatment responses when calculated are different

Appendix Q: 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 main database searches, resulting in 51 records following deduplication. Two additional records were obtained from DARE, such that 53 records were 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 eligible.

Data extraction was conducted by TS.

The included study by **Michallet and colleagues (2013)**[249] 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.

Michallet and colleagues (2013) is a historically controlled study matching patients receiving ESA therapy with those in the past known not to receive ESA therapy. Not all outcomes were recorded for the control group 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 health-related quality of life compared to baseline, but this was not compared with patients not receiving ESA therapy. The study found that patients receiving ESA therapy had lower transfusion need and no statistically significant difference was found in overall or event-free survival between patients receiving ESA therapy and controls. RBCT costs were lower for patients receiving ESA therapy but these did not sufficiently offset the increased cost due to ESA acquisition/administration.

The tables below show the characteristics, key parameters and results of the study.

	Michallet, 2013
Evaluation type	Cost-consequences analysis
Modelling used	No
Nature of modelling	n/a
Perspective	Healthcare
Country (setting)	France
Intervention/comparator	DA 150 µg QW

	No tx
Population	Patients with anaemia following consolidation chemotherapy for AML
Outcomes considered	HRQoL (FACT-General, FACT-Fatigue, FACT-Anemia) Hb response (CR = Hb >= 12 g/dL; PR = Hb increase >= 2 g/dL) Adverse events Costs Hb levels Transfusion need Survival (overall and event-free)
Time-frame	n/a
Discounting	Not stated
Funding	Not disclosed

Key: AML, acute myeloid leukaemia; CR, complete response; DA, darbepoetin alfa; FACT, Functional Assessment of Cancer Therapy; Hb, haemoglobin; HRQoL, health-related quality of life; PR, partial response; QW, once weekly; tx, treatment
Notes: All data presented for Group 1 (patients with AML treated with chemotherapy); Group 2 (patients having received allogeneic hematopoietic stem cell transplant for any haematological disease) excluded

	Michallet, 2013
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 (overall survival, *P* = 0.77; event-free survival, *P* = 0.57)
Effectiveness (data): QALYs	n/a
QoL/utility (source)	This study
QoL/utility (data)	n/a (Not evaluated for control group)
Costs (source)	This study
Cost year	Not stated

Key: Hb, haemoglobin; HRQoL, health-related quality of life; RBC, red blood cell
Notes: Following outcomes were not evaluated for control group and hence are not shown here: Hb response rate, Hb level, adverse events, HRQoL

	Michallet, 2013
Measure	Costs; transfusion requirement; survival
Cost year; currency	NR; euros (EUR; €)
Base case	ESA cost: DA, €3,904; No tx, €0 RBCT cost: DA, €2,568; No tx, €4,280 **Total cost: DA, €6,472; No tx, €4,280**
Probabilistic results	n/a
Sensitivity analyses	n/a

Key: DA, darbepoetin alfa; ESA, erythropoiesis stimulating agent; NR, not reported; RBCT, red blood cell transfusion; tx, treatment
Notes: Costs presented are *median* costs. Consequences as shown in Key Parameters table

Appendix R: Summary of parameters used in PenTAG cost-effectiveness model

Parameter	Base case (SE)	Subgroup inclusion Hb level ≤ 11.0 g/dL (SE)	Location in report	Wilson value
Overall survival ESA vs. control (HR, SE in log scale)	0.967 (0.079)	0.914 (0.137)	§4.2.6.3.2, p101	1
Overall survival (control arm)	2.670 (1.335)	1.447 (0.723)	§7.1.2.1.8, p277	1.54
Change in Hb from baseline to end of ESA treatment: difference between ESA and control arms	1.59 (0.130)	1.52 (0.115)	§4.2.6.2.1, p75	1.63 (clinical effectiveness review)
Mean number of units transfused in control arm	2.09	2.30	§7.1.2.1.1, p266	2
Mean difference # units RBCs transfused ESA vs. control arm	−0.87 (0.21)	−0.99 (0.22)	§4.2.6.2.4, p91	−1.05
Relative risk of adverse event rates in ESA vs. control arm (reported on natural log scale)				
Thrombotic events	ln(1.46) = 0.378 (0.158)	ln(1.29) = 0.255 (0.344)	§4.2.6.4.1, p110	
Hypertension	ln(1.80) = 0.588 (0.234)	ln(1.68) = 0.519 (0.250)	§4.2.6.4.2, p113	
Thrombocytopenia	ln(0.93) = −0.073 (0.185)	ln(0.73) = −0.315 (0.350)	§4.2.6.4.3, p116	
Probability of adverse event in control arm				0, but 5% SAE on EPO
Thrombotic events	3.3% (0.4%)	3.7% (0.8%)	§7.1.2.3.6, p304	
Hypertension	2.9% (0.5%)	1.8% (1.0%)	§7.1.2.3.6, p304	
Thrombocytopenia	6.4% (0.8%)	2.5% (0.8%)	§7.1.2.3.6, p304	
Baseline Hb level (g/dL)	10.38 (1.59)	9.40 (0.22)	§7.1.2.1.4, p269	9.9 (calculated using reported figures at baseline)
Change in Hb (no ESA) g/dL	−0.155 (1.25)	0.469 (0.41)	§7.1.2.1.5, p271	
Mean diff Hb over time / mean final diff Hb	80.6% (55.0%)	55.5% (12.0%)	§7.1.2.1.6, p273	
Mean age (years)	59.1 (5.3)	60.8 (4.2)	§7.1.2.4.2, p307	Not used
Mean weight (kg)	66.6 (3.3)	66.1 (3.6)	§7.1.2.4.2, p307	Not used
Probability patient is male	0.46		§7.1.2.4.2, p307	
Mean OS (No ESA) (years)	2.670 (1.335)	1.447 (0.724)	§7.1.2.1.8, p277	1.54
Mean weekly ESA dose				
Epoetin alfa (IU)	24,721 (4,944)	24,947 (4,989)	§7.1.2.1.2, p266	
Epoetin beta (IU)	31,138 (6,228)	30,997 (6,199)	§7.1.2.1.2, p266	
Epoetin theta (IU)	22,859 (4,572)	22,810 (4,562)	§7.1.2.1.2, p266	
Epoetin zeta (IU)	24,721 (4,944)	24,947 (4,989)	§7.1.2.1.2, p266	

Parameter		Base case (SE)	Subgroup inclusion Hb level ≤ 11.0 g/dL (SE)	Location in report	Wilson value
Darbepoetin alfa (µg)		141.1 (28.2)	141.2 (28.2)	§7.1.2.1.2, p266	
Number of RBC units per transfusion		2.7 (0.54)		§7.1.2.1.1, p266	
Duration of ESA treatment (weeks)		12			
Normal Hb level (g/dL)		12[a] (0.51)		§7.1.2.1.7, p275	24
Normalisation rate (g/dL per week)		0.2 (0.051)		§7.1.2.1.7, p275	13
Utility increase per Hb level increase (1g/dL)		0.028 (0.006)		§7.1.2.2.5, p296	0.2 (approx)
Long term utility		0.763 (0.183)	0.756 (0.151)	§7.1.2.2.6, p297	0.06
ESA acquisition cost					£276.70 week (inc SAEs)
per 1,000 IU					
Epoetin alfa	Eprex®	£5.53	§7.1.2.3.2, p299	§7.1.2.3.2, p299	
	Binocrit®	£5.09	§7.1.2.3.2, p299	§7.1.2.3.2, p299	
Epoetin beta	NeoRecormon®	£7.01	§7.1.2.3.2, p299	§7.1.2.3.2, p299	
Epoetin theta	Eporatio®	£5.99	§7.1.2.3.2, p299	§7.1.2.3.2, p299	
Epoetin zeta	Retacrit®	£5.66	§7.1.2.3.2, p299	§7.1.2.3.2, p299	
per µg					
Darbepoetin alfa	Aranesp®	£1.47		§7.1.2.3.2, p299	
Dosing schedule of ESA		Once weekly		§7.1.2.3.4, p302	3 times per week
Average cost per ESA administration		£9.13		§7.1.2.3.4, p302	£8.01
Additional blood tests for ESA		4		§7.1.2.3.5, p303	
Cost of blood test		£15.14		§7.1.2.3.5, p303	
Cost of adverse event					£101
Thrombotic events		£1,243 (£249)		§7.1.2.3.6, p304	
Hypertension		£826 (£165)		§7.1.2.3.6, p304	
Thrombocytopenia		£744 (£149)		§7.1.2.3.6, p304	
Unit cost of RBCs		£127 (£25)		§7.1.2.3.7, p305	
Cost of transfusion appointment		£688		§7.1.2.3.8, p305	
Time frame		Lifetime			
Cycle length		NA			
HaemR RR (ESA vs. control)		NA		§7.1.2.1, p258	

Key: §, Section; ESA, erythropoiesis stimulating agent; HaemR, haematological response; Hb, haemoglobin; HR, hazard ratio; IU, international units; NA, not applicable; OS, overall survival; RBC(T), red blood cell (transfusion); RR, relative risk; SE, standard error; SR, systematic review
Notes: a Normalised Hb level equals 12 g/dL or the final Hb level in the ESA arm, whichever is higher

Appendix S: Mean difference in Hb level as a proportion of final difference in Hb 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.

In the case where the parameter is set to 100% this means the average difference in Hb level between the intervention and 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 to apply method being used for each figure.

30.1. Method 1

Measuring tools of Adobe Acrobat X Pro (Adobe Systems, Inc., California, 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 A);
- The (vertical) distance between the intervention arm Hb level curve and control arm Hb level curve at baseline (denoted L_0; positive if baseline Hb higher in intervention arm);
- The (vertical) distance between the intervention arm Hb level curve and control arm Hb level curve at final Hb level measurement (denoted L_1; positive if final Hb higher in intervention arm);
- The (horizontal) distance between times of baseline and final Hb level measurement (denoted W).

The required parameter is then calculated as $(A - L_0 \times W) / [W \times (L_1 - L_0)]$.

30.2. Method 2

An appropriate tool was used to estimate the mean Hb level at each measurement for both intervention and control arms.

The area under each Hb level curve was calculated by summing the areas of trapezoids (denoted $AUC_{Intervention}$ 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 Hb level instantaneously jumped to the final Hb level difference was calculated (denoted $\Delta AUC_{Instantaneous}$).

The required parameter is then calculated as $(\Delta AUC_{Intervention} - \Delta AUC_{Control}) / \Delta AUC_{Instantaneous}$.

30.3. Results

Study	Calculation steps				Result
Method 1	***A***	L_0	L_1	***W***	
Littlewood, 2011	1.00	0.05	0.38	2.42	110%
Grote, 2005	2.39	−0.09	0.24	3.53	232%
Tjulandin, 2010	ET, 1.66 EB, 1.79	ET, 0.00 EB, 0.00	ET, 0.69 EB, 0.78	ET, 3.85 EB, 3.85	ET, 62% EB, 60%
Tjulandin, 2011	2.11	0.11	1.10	3.47	50%
Moebus, 2013	0.69	0.00	0.39	2.29	77%
Method 2	**$\Delta AUC_{Intervention}$**	**$\Delta AUC_{Control}$**	**$\Delta AUC_{Instantaneous}$**		
Silvestris, 1995	46.15	3.04	51.08		84%
Del Mastro, 1997	0.70	−9.35	13.80		73%
Kurz, 1997	20.32	2.26	36.12		50%
Dunphy, 1999	−5.35	−13.00	9.92		77%
Thatcher, 1999	−6.37	−11.03	5.04		92%
Dammacco, 2001	12.37	−0.04	22.15		56%
Hedenus, 2002	9.43	4.11	9.04		59%
Aravantinos, 2003	4.245	3.235	4.32		23%
Boogaerts, 2003	15.98	7.02	13.12		68%
Strauss, 2008	11.80	−6.40	24.00		76%

Key: EB, epoetin beta; ET, epoetin theta

Appendix T: Use of MathMap to construct cumulative hazard and Weibull plots

MathMap [freely available from http://www.complang.tuwien.ac.at/schani/mathmap/] 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 where the result image, *B*, can be based on the input image, *A*, using an arbitrary mathematical backward mapping, i.e., 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 (2001)**. Note that '#' is used to create a comment (non-functioning line) and has been used to 'comment out' a number of statements which 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
```