Draft Comparative Effectiveness Review

Number XX

Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment—Update

U.S. Department of Health and Human Services
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Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment—Update

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Acknowledgments

Technical Expert Panel

Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment—Update

Structured Abstract

Objectives: To update the 2006 systematic review of the comparative benefits and harms of erythropoiesis-stimulating agent (ESA) strategies and non-ESA strategies to manage anemia in patients undergoing chemotherapy or radiation for malignancy (excluding myelodysplastic syndrome and acute leukemia); including the impact of alternative thresholds for initiating treatment and optimal duration of therapy.

Data sources: Literature searches were updated in electronic databases (n=3), conference proceedings (n=3), and FDA transcripts. Multiple sources (n=13) were searched for potential grey literature. A primary source for current survival evidence was a recently published individual patient data meta-analysis. In that meta-analysis, patient data were obtained from investigators for studies enrolling more than 50 patients per arm. Because those data constitute the most currently available, as well as the source for on-study mortality data, we limited inclusion in the current report to similar size studies to avoid potential differential endpoint ascertainment in smaller studies. This contrasts with the previous report that included studies enrolling 10 or more patients per arm. Sensitivity analyses were performed for each outcome including any studies excluded for that reason.

Review methods: Title and abstract screening was performed by one or two (to resolve uncertainty) reviewers; potentially included publications were reviewed in full text. Two or three (to resolve disagreements) reviewers assessed trial quality. Results were abstracted in duplicate and results pooled for outcomes of interest. The balance of benefits and harms was examined in a decision model.

Results: We evaluated evidence from: 5 trials directly comparing darbepoetin to epoetin (pooled N=1,080 patients randomized to darbepoetin, N=989 randomized to epoetin); 40 trials comparing epoetin to control (epoetin N=5,959, control N=5,417); and 7 trials comparing darbepoetin to control (epoetin N=1,654, control N=1,520). Trials varied according to duration; tumor types, cancer therapy, trial quality, iron supplementation, baseline Hb, ESA dosing frequency (and therefore amount per dose), and dose escalation.

ESAs decreased the proportion of patients transfused (pooled RR 0.60; 95 percent CI: 0.55, 0.66; I^2=48 percent; 33 trials) without evidence of meaningful difference between epoetin and darbepoetin. Mortality was increased during the active treatment period (pooled HR 1.16; 95 percent CI: 1.03, 1.31; I^2=0 percent; 37 trials). Thromboembolic event rates were higher in ESA-treated patients (pooled RR 1.50; 95 percent CI: 1.29, 1.75; I^2=0 percent; 34 trials), without difference between epoetin and darbepoetin. In 14 trials reporting total FACT-Fatigue, scores decreased in control arms -0.6 (95 percent CI: -6.5, 5.3; I^2=0 percent) and increased by 2.1 in the

ESA arms (95 percent CI: -3.9, 8.1; I^2=0 percent). Evidence was insufficient to examine immediate treatment versus delayed treatment and no evidence informed optimal duration of therapy. Under circumstances similar to trials, a decision model showed ESA use accompanied by a net loss of life-years.

Conclusions: Since the 2006 review, evidence remains consistent that ESAs reduce the need for transfusions and increase the risk of thromboembolism. The improvement in quality of life FACT-Fatigue scores is small and less than the estimated minimal clinically important difference. Overall, harms appear greater than benefits when ESAs are used to manage anemia in patients undergoing chemotherapy or radiation for malignancy.

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Executive Summary

Background

Anemia, a deficiency in the concentration of hemoglobin-containing red blood cells, is prevalent among cancer patients, depending on the type of malignancy and treatment. Transfusion is one option for treating anemia related to cancer and cancer treatment. Transfusion carries an extremely low risk of infection and other adverse events, including transfusion reactions, alloimmunization, over-transfusion, and immune modulation with theoretically possible adverse effects on tumor growth.[*]

Erythropoietin, a hormone produced in the kidney, is the major regulator of red blood cell production (erythropoiesis). Commercially produced recombinant human erythropoietins have been extensively studied and used clinically for more than a decade to treat anemia in association with various diseases, reducing the need for transfusion. These include epoetin alfa (Epogen®; Procrit®) and epoetin beta (not available in the United States); they have similar clinical efficacy. Darbepoetin alfa (Aranesp®), more recently developed, produces a similar physiologic response and is commercially available in the United States. All erythropoietic-stimulating agents (ESAs) increase the number of red blood cells within about 2 to 3 weeks when given to individuals with functioning erythropoiesis.

The development of intensified antineoplastic therapies has increased the risk for anemia. Initially, adverse effects that could be conclusively attributed to erythropoietin treatment had been reported in very few patients; more recently, randomized controlled trials have reported increased incidence of thrombotic events and reduced survival. This resulted in several pooled analyses of ESA trial data over several years, as well as regulatory actions by the U.S. Food and Drug Administration (FDA). The Blue Cross Blue Shield Association Technology Evaluation Center (TEC), an AHRQ-funded Evidence-based Practice Center, conducted a systematic review of epoetin use in oncology (2001) and a comparative effectiveness review of epoetin and darbepoetin (2006).

This review updates the 2006 Comparative Effectiveness Review of Epoetin and Darbepoetin for managing anemia in patients undergoing cancer treatment. Since that review was completed, further evidence informing some of the Key Questions addressed in that review has become available. In addition and as a result of new evidence, the FDA made several revisions to the approved labeling for ESAs. Based on these new developments, AHRQ concluded that that aspects of the prior review required updating with recently published and presented evidence. This update accordingly addresses only those questions where new evidence has become available. A primary source for current evidence on survival was a recently published individual patient data meta-analysis. In that meta-analysis, patient data were obtained from investigators for studies enrolling more than 50 patients per arm. Because those data constitute the most currently available, as well as the source for on-study mortality data, we limited inclusion in the current report to similar size studies to avoid potential differential endpoint ascertainment in smaller studies. This contrasts with the previous report that included

[*] For example, adverse events that could be definitively attributed to transfusions were not reported in any trial included in this review for adverse event outcomes—9,488 patients randomized to erythropoietic stimulating agents and 6,809 to transfusion strategy.

studies enrolling 10 or more patients per arm. Sensitivity analyses performed for each outcome with data from studies excluded for that reason showed no differing results.

This report addresses the following questions:

1. What are the comparative benefits and harms of erythropoiesis-stimulating agent (ESA) strategies and non-ESA strategies to manage anemia in patients undergoing chemotherapy or radiation for malignancy (excluding myelodysplastic syndrome and acute leukemia)?
2. How do alternative thresholds for initiating treatment compare regarding their effect on the benefits and harms of erythropoietic stimulants?
3. How do different criteria for discontinuing therapy or for optimal duration of therapy compare regarding their effect on the benefits and harms of erythropoietic stimulants?

Conclusions

Comparative Benefits and Harms of ESA and Non-ESA Strategies

Evidence from three groups of trials were summarized and analyzed. Five trials directly compared darbepoetin to epoetin (pooled N=1,080 patients randomized to darbepoetin, N=989 randomized to epoetin); 40 trials compared epoetin to control (pooled N=5,959 randomized to epoetin, N=5,417 to control); and 7 trials compared darbepoetin (pooled N=1,654 randomized to darbepoetin, N=1,520 to control). There was considerable variability among trials (e.g., trial duration, tumor types, cancer therapy, trial quality; iron supplementation, baseline Hb, ESA dosing frequency [and therefore amount per dose], and ESA dose escalation).

Hematologic Response

The evidence does not show any meaningful difference between epoetin and darbepoetin in the proportion of patients receiving transfusion (overall strength of evidence moderate).

The evidence shows that ESAs reduce the proportion of patients receiving transfusions (overall strength of evidence moderate).

Proportion of patients transfused

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Number of trials	5	28	5	33
Patients analyzed	2,005	7,136	1,866	9,002
Pooled RR	1.14	0.60	0.58	0.60
(95% CI)	(0.82, 1.59)	(0.53, 0.67)	(0.51, 0.66)	(0.55, 0.66)
I^2	43%	58%	0%	48%

There is a consistent body of evidence, although somewhat limited by trial quality, that ESAs reduce the probability of transfusion in the setting of cancer treatment. However, these agents do not eliminate the chance of receiving transfusions.

Survival Outcomes

The evidence does not show that ESAs affect survival over the longest available follow-up (overall strength of evidence moderate).

Overall survival

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Number of trials	2	37	7	44
Patients analyzed	1,567	11,145	3,162	14,307
Pooled HR	0.90	1.04	1.04	1.04
(95% CI)	(0.67, 1.20)	(0.97, 1.11)	(0.93, 1.16)	(0.98, 1.10)
I^2	72%	32%	50%	37%

The evidence shows an increase in mortality for the class of ESAs during and shortly following ESA treatment (in this review, referred to as "on-study mortality") (overall strength of evidence moderate).

On-study mortality

	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Number of trials	31	6	37
Patients analyzed	8,859	2,648	11,307
Pooled HR	1.19	1.05	1.16
(95% CI)	(1.04, 1.36)	(0.80, 1.38)	(1.03, 1.31)
I^2	0%	0%	0%

The evidence shows increased mortality risk during the active treatment period not apparent over the longer term including post-treatment follow-up. Pooled hazard ratios not significantly elevated over long-term follow-up but increased during active treatment (on-study period) indicate relative hazards not constant over time, or elevated only during treatment.

Thromboembolic Events

The evidence shows an increased risk of thromboembolic events with ESA treatment (overall strength of evidence moderate), but no clinically meaningful difference between epoetin and darbepoetin in thromboembolic events.

Thromboembolic events

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Number of trials	3	29	5	34
Patients analyzed	1,873	8,905	2,155	11,060
Pooled RR	0.86	1.49	1.55	1.50
(95% CI)	(0.61, 1.21)	(1.25, 1.78)	(1.15, 2.08)	(1.29, 1.75)
I^2	0%	0%	0%	0%

Rates of thromboembolic events were consistently higher in ESA-treated patients. In included trials the number needed to harm was 50 or fewer in 50 percent of trials and 20 or fewer in 21 percent of trials.

Health-Related Quality of Life

Treating to high target hemoglobin levels (greater than 12 g/dL) is accompanied by improved health-related quality of life (HRQoL) scores (e.g., FACT-Fatigue; overall strength of evidence low).

Health-related quality of life

	Epoetin or Darbepoetin vs. Control
Number of trials	14
Patients analyzed	3,643
Mean Difference for Change Fact-Fatigue Score	2.72
(95% CI)	(1.69, 3.74)
I^2	41%

Any clinical significance of the improvement in HRQoL is likely to be small and on average, the difference in change between treatment arms less than the minimal clinically important difference.

Early versus Late ESA Treatment

Evidence from five trials were summarized and analyzed (468 and 465 patients randomized to early [when chemo- or radiotherapy starts] and late [when hemoglobin falls below a defined threshold] ESA treatment, respectively). Hemoglobin thresholds for initiating late treatment ranged from 9 g/dL to 11 g/dL.

The evidence is lacking to determine whether immediate treatment versus delayed treatment produces better outcomes (overall strength of evidence low).

Criteria for Discontinuing Therapy or for Optimal Duration of Therapy

No randomized controlled trials were identified that fulfill the inclusion criteria of this review. Therefore, no results can be provided.

Balance of Potential Benefit and Harm

Under circumstances representative of patients included in these trials, a decision analysis shows ESA use is always accompanied by a net loss of life-years due to increased mortality during the active treatment period. Those patients with the poorest prognosis experience the greatest loss because of a larger increase in absolute risk. Although there may be gain in quality adjusted life for some patients, any improvements in quality of life with use of ESAs is on average less than what is deemed clinically meaningful and offset by shortened length of life.

Remaining Issues

Existing evidence establishes with sufficient certainty that ESA used to manage anemia in patients with cancer is accompanied by increased mortality risk. Whether there are subgroups at higher and lower risk of adverse events and mortality is unclear. An important unanswered question is whether and how dosing practices and overall ESA exposure influence harms. However, the increased risk of mortality raises questions as to whether equipoise exists to justify enrolling patients in clinical trials. Furthermore, examination of observational data collected during the course of usual patient care could be adequate to address unanswered questions. Finally, registry records for all completed studies lacking results or links to them should be appropriately updated; registries should also query investigators when studies are completed and query response posted when results are unavailable in a registry record.

Introduction

This review updates the 2006 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment (1). Since that review was completed, further evidence concerning a number of the Key Questions addressed in that review has become available. In addition and as a result of new evidence, the U.S. Food and Drug Administration (FDA) made several revisions to the approved labeling for erythropoietic-stimulating agents (ESAs). Based on these new developments, AHRQ concluded that that aspects of the prior review required updating with recently published and presented evidence. Importantly, this update accordingly addresses only those questions where new evidence has become available.

The introduction is organized as follows. First, the basic biology of erythropoietin and ESAs is reviewed. We then discuss the significance of anemia and its treatment with ESAs in the setting of cancer therapy. This is followed by a description of previous AHRQ reports and associated collaborations with the Cochrane Hematologic Malignancies Group, who conducted additional evaluations, which provides a brief overview of prior evidence and conclusions. Subsequent changes in FDA-approved labeling are noted and chronicled. We present the scope of this report and Key Questions followed by an overview of the patient populations included, interventions, comparators, and outcomes. The types of studies included in the report are then discussed. Finally, we describe some important complexities presented by the evidence for synthesis, as these complexities directly or indirectly impact much of the analyses, conclusions, and research recommendations.

Background

Erythropoietin

Erythropoietin, a hormone produced in the kidney, is the major regulator of red blood cell production (erythropoiesis). In response to anemia, erythropoietin is synthesized de novo primarily in the kidneys. Erythropoietin binds to specific receptors on the surface of immature erythroid cells in the bone marrow, initiating a signal cascade resulting in the survival of these cells that would otherwise undergo apoptosis (2). Proliferation of erythroid cells may also be a consequence of erythropoietin stimulation. Circulating reticulocytes increase, followed by a more delayed increase in hemoglobin and red blood cell count.

Two commercially produced recombinant human erythropoietins—epoetin alfa (Epogen®; Procrit®) and epoetin beta (the latter not available in the United States)—have been extensively studied and used clinically for more than a decade to treat anemia in association with various diseases; they have similar clinical efficacy (3, 4). Darbepoetin alfa (Aranesp®), more recently developed, produces a similar physiologic response when compared to recombinant human erythropoietin, (5) has been tested in prospective clinical trials, (6-8) and is commercially available in the United States. All ESAs increase the number of red blood cells within about 2 to 3 weeks when given to individuals with functioning erythropoiesis. In addition, erythropoietin has effects on megakaryocytopoiesis (platelet production) and thrombopoiesis possibly related to structural similarities with thrombopoietin (2).

Anemia

Anemia, a deficiency in the concentration of hemoglobin-containing red blood cells, is prevalent among cancer patients. The National Cancer Institute and others classify anemia based on hemoglobin (Hb) values: (9)

- Grade 0, within normal limits, Hb values are 12.0 to 16.0 g/dL for women and 14.0 to 18.0 g/dL for men
- Grade 1, mild (Hb 10 g/dL to normal limits)
- Grade 2, moderate (Hb 8.0 to 10.0 g/dL)
- Grade 3, serious/severe (Hb 6.5 to 7.9 g/dL)
- Grade 4, life threatening (Hb less than 6.5 g/dL).

Anemia and Cancer

The prevalence of anemia varies according to the type of neoplasia and treatment (10). Patients with hematologic malignancies frequently experience anemia. Upon diagnosis, 30 to 40 percent of patients with non-Hodgkin's or Hodgkin’s lymphoma, up to 70 percent of patients with multiple myeloma, and essentially all patients with myelodysplastic syndromes are anemic (11). Although the prevalence of anemia at diagnosis is approximately 40 percent of patients with non-Hodgkin's or Hodgkin’s lymphoma, following 3 to 4 cycles of chemotherapy up to 70 percent of these patients will be anemic (12).

The pathophysiology of tumor anemia is multifactorial. For example, in advanced stages of hematologic malignancies, malignant cells replace most of the normal hematopoietic cells in the bone marrow, leading to progressive anemia. In general, after exclusion of other causes (e.g., iron or vitamin deficiencies, occult bleeding, autoimmune hemolysis, or pure red blood cell aplasia), anemia is typically attributed to “anemia of chronic disease.” It is characterized by a close interaction between the tumor cell population and the immune system, leading to the activation of macrophages and increased expression of various cytokines. This results in insufficient endogenous erythropoietin synthesis, suppressed differentiation of erythroid precursor cells in the bone marrow, and alterations of iron metabolism (13). Anemia of chronic disease is the most common type of anemia in patients with malignant disease, but it can be aggravated by chemo- or radiotherapy. In particular, platinum-based chemotherapy regimens may diminish endogenous erythropoietin production by damaging renal tubular cells (14).

Manifestation and severity of anemia vary considerably among individual cancer patients. Mild to moderate anemia developing over a short time can cause symptoms including headache, palpitations, tachycardia, and shortness of breath. Chronic anemia may result in severe organ damage affecting the cardiovascular system, immune system, lungs, kidneys, muscles, and central nervous system (15). In addition to the physical symptoms, the subjective impact of cancer-related anemia on quality of life (QoL), mental health, and social activities may be substantial. Clinical studies reported correlations between hemoglobin levels and quality of life (16-18).

Anemia may also have be associated with outcomes or have direct effects on the tumor itself. In malignant diseases like Hodgkin’s lymphoma, chronic lymphocytic leukemia, cervical carcinoma, and cancer of the head and neck, anemia is reportedly a prognostic factor (19). There is evidence that anemia, causing tumor hypoxia, might result in a poorer response to radio- or chemotherapy (20). These factors may lead to a higher tumor burden and decrease overall

survival (20-23). Although the prognostic significance of anemia may simply reflect progressive or advanced disease, the observation generated the hypothesis that strategies to diminish cancer-related anemia might alleviate not only anemia-related symptoms and improve quality of life, but also might improve tumor response and extend overall survival time.

Correcting Anemia With Blood Transfusion

Historically, blood transfusion was the treatment of choice for severe cancer-related anemia. The literature reports a degree of anemia appropriate for treatment as hemoglobin concentration below 8 g/dL, while mild-to-moderate cancer-related anemia (hemoglobin level 8-10 g/dL) usually was not treated (24). Although homologous blood transfusion is the fastest method to alleviate symptoms, short and long term risks exist (25). These include transmitting infectious diseases, transfusion reactions, alloimmunization, overtransfusion, and immune modulation with theoretically possible adverse effects on tumor growth (26). The risk of severe infectious complications of blood transfusions are 1:30,000 to 1:250,000 units of blood transfused for Hepatitis B, 1:30,000 to 1:150,000 for Hepatitis C and 1:250,000 to 1:1,000,000 for HIV (27). Emerging infections, such as the West Nile virus epidemic in 2002 in the United States are of concern (28, 29). Still, in decision-analytic models of ESAs, any risk accompanying blood transfusion appears not to meaningfully impact results due to their infrequent occurrence (30, 31).

Pooled Analyses of ESA Treatment Outcomes and Regulatory Actions

The development of intensified antineoplastic therapies has increased the risk for anemia and the need for correction of anemia by blood transfusion or treatment with ESAs. Initially, adverse effects such as hypertension, headaches, and thrombotic events that can be attributed to erythropoietin treatment had been reported in very few patients (32); however, more recently randomized controlled trials have reported increased incidence of thrombotic events (33, 34) and reduced survival (34-36). This resulted in several pooled analyses of ESA trial data over several years, as well as regulatory actions by the U.S. Food and Drug Administration (FDA). Following is a summary of analyses authored, or contributed to, by the Blue Cross and Blue Shield Association Technology Evaluation Center (BCBSA TEC) Evidence-based Practice Center (EPC).

In 2001, the AHRQ-sponsored systematic review “Uses of Epoetin for Anemia in Oncology” was completed (37). The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH), who intended to use the evidence review as the scientific basis for a joint clinical guideline, originally proposed the topic to AHRQ. Members of the ASCO/ASH joint guideline committee participated on the Technical Expert Panel for the systematic review, and subsequently a member of the BCBSA TEC EPC systematic review team participated as an ad hoc member of the guideline panel. It was clear that epoetin given to cancer patients treated with chemotherapy and who became moderately anemic (Hb <10 g/dL) resulted in improved hemoglobin levels and fewer transfusions. A major question at the time was whether initiating epoetin treatment before patients became moderately anemic (i.e., Hb between 10 and 12 g/dL) would result in fewer patients transfused. However, the systematic review concluded that the available evidence was inadequate to answer that question.

The database constructed for the 2001 BCBSA TEC EPC systematic review was shared with the Cochrane Hematologic Malignancies Group with permission from AHRQ; the data provided a starting point for a Cochrane a Review completed in 2004 (38). The results of this review were also consistent with erythropoietin reducing blood transfusions in anemic patients with cancer. Evidence as to whether erythropoietin affected tumor response and overall survival was inconclusive. It was also unclear whether erythropoietin increased the risk of hypertension and thrombotic complications or improved quality of life and fatigue.

In 2006, the BCBSA TEC EPC published a comparative effectiveness review (CER) of epoetin and darbepoetin treatment for anemia related to cancer treatment under the AHRQ contract (1). This review was conducted collaboratively between TEC and the Cochrane Hematologic Malignancies Group.

The 2006 CER found no clinically meaningful difference between epoetin and darbepoetin with regard to hemoglobin response, transfusion reduction, or thromboembolic events. Again, available evidence did not show better transfusion-sparing effects when ESA treatment was initiated before Hb fell to less than 10 g/dL, compared to waiting until it fell below that threshold. When comparing epoetin or darbepoetin to control for thromboembolic events, there was an increase in events associated with ESA use, but variability between control arms of different trials in event rates was high, and several studies targeted higher Hb levels than recommended by product labels at the time. Too few trial results were available to perform a subgroup analysis conforming to label recommendations. Quality of life measures, viewed at the time as one of the most important outcomes of treatment, tended to favor ESA treatment, but variability in the amount of change and potential for bias due to a number of methodologic factors made definitive conclusions difficult. Several trials showed an ESA-associated detriment in survival and others did not. At the time of the review, most of the trials that raised concerns over safety, survival, and tumor response were unpublished. Information about trial design and results was available only from briefings presented to the FDA Oncologic Drugs Advisory Committee, May 4, 2004.[*]

These trials, the 2006 CER, as well as several pooled analyses, led to a series of FDA-directed Physician Alerts and label changes to more stringent dosing recommendations (Table 1). By May 2007, there were data from six randomized trials showing decreased survival (five trials) (34, 39-41) and/or poorer local regional control and progression-free survival (two trials) (33, 42, 43) in the ESA treatment arm. Three trials were stopped early because of adverse events in the treatment arms (33, 39, 42-44). In five of the six trials, the target Hb exceeded 12 g/dL and patients' baseline Hb levels were more than 10 g/dL. Five of the six trials each enrolled patients with a specific tumor type; these were advanced breast, head and neck, lymphoid, or non-small cell lung cancer. The pooled analyses of the BCBSA TEC AHRQ EPC CER and the Cochrane Review were also available, along with other published meta-analyses. The most significant changes to the ESA labels occurred in 2007, and the issue of ESA effect on survival became paramount, with quality of life becoming less important by comparison.

Due to the limitations of pooled analyses from summary measures in published papers, and the inconclusive results regarding the overall effect of ESAs on survival, the Cochrane Hematologic Malignancies Group undertook an analysis of individual patient data (IPD) with TEC Staff participating as members of the IPD Steering Committee. The initial IPD publication

[*] See http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2.htm for May 2004 briefing information and http://www.fda.gov/ohrms/dockets/ac/04/slides/4037s2.htm for slides

(45) and concurrent Cochrane Review, (45) found a significant increase in mortality during active treatment and poorer overall survival will ESA treatment in all cancer patients. The effect was not statistically significant for patients undergoing chemotherapy, but was consistent with an adverse effect. This and other meta-analyses are reviewed in detail later in this report.

Table 1. FDA alerts and actions related to ESA prescribing

Date	Notification Type	Content change
June 2004	Addition of clinical trial results and warning to label	Added descriptions of clinical trial results showing risks for tumor promotion and increased mortality among cancer patients who were receiving ESAs in the treatment of chemotherapy-induced anemia; an additional warning advised physicians of increased thromboembolic event risks with ESAs in the oncology setting.
November 2006	FDA Alert regarding clinical trial results	The "Correction of Hemoglobin and Outcomes in Renal Insufficiency" (CHOIR) study (46) showed that patients treated with an ESA and dosed to a target Hb of 13.5 g/dL were at a significantly increased risk for serious and life-threatening cardiovascular complications, compared to control Hb target of 11.3 g/dL; the alert emphasized then current dosing recommendation that the target Hb not exceed 12 g/dL.
March 2007	New black box warning; updated warnings, and a change to the dosage and administration	Highlights the risk of death and serious cardiovascular events when the Hb target is greater than 12 g/dL and in specific patient categories; recommends avoiding serious cardiovascular and arterial and venous thromboembolic events using the lowest possible ESA dose to reach the lowest Hb level possible to avoid RBC transfusions. Added warnings about increased mortality, cardiovascular events, tumor progression and uncontrolled hypertension. Recommended withholding ESA dose if Hb increase exceeds 12 g/dL or rises by 1g/dL in any 2-week period.
November 2007	Expanded black box warning and more specific dosing language	Revisions warn that data are not sufficient to exclude the possibility of shortened survival and tumor progression in patients with cancer when ESAs are dosed to reach a Hb level between 10 and 12 g/dL. Added information that ESAs caused tumor growth and shortened survival in patients with advanced breast, head and neck, lymphoid, and non-small cell lung cancer when they received a dose that attempted to achieve Hb ≥12 g/dL.
March 2008	Changed black box warning, modified labeling information	Described the results of two additional studies (36, 47) showing increased mortality and more rapid tumor progression in patients with nonadvanced breast and cervical cancers when dosed to target Hb of ≥12 g/dL.
July 2008	Expanded black box warning; dosing language modified	ESAs should not be used in cancer patients receiving chemotherapy if a cure is anticipated. Also included is a statement that ESAs are not to be administered when Hb levels are ≥ 10 g/dL. Language was removed that seemed to imply that it was safe to continue treating patients until their Hb increased to 12 g/dL.
February 2010	Announcement of risk evaluation and mitigation strategy (REMS)	The FDA requires all ESAs to be prescribed and used under the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program, part of a REMS, to ensure safe use of the drugs. ESA manufacturers must ensure that only those hospitals and healthcare professionals who have enrolled and completed training in the ESA APPRISE program will prescribe and dispense ESAs to patients with cancer. The ESA APPRISE program began on March 24, 2010.

Current Guidelines for ESA Use in Cancer Patients

Table 2 summarizes important points of the FDA-approved label information, which is similar for all approved ESAs, (35, 48, 49) and parallel information from joint guidelines for ESA

Table 2. ESA prescribing information and guidelines

	FDA-approved full prescribing information (similar for all approved ESAs) (49-51)	**American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update (2010) (52, 53)**	**NCCN Guidelines, Cancer and Chemotherapy-Induced Anemia (V 2.2011) (54)**
ESAs are indicated for:	The treatment of anemia due to the effect of concomitantly administered chemotherapy	ESAs are a recommended treatment option for patients with chemotherapy-associated anemia; red blood cell transfusion may also be an option. ESAs are also a treatment option for patients with lower risk myelodysplastic syndrome (MDS) who are not undergoing concurrent chemotherapy. "Although the FDA label now limits the indication for ESA use to patients receiving chemotherapy for palliative intent . . . determining the treatment intent requires clinical judgment of an individual patient's circumstances."	• Patients undergoing palliative treatment or myelosuppressive chemotherapy without curative intent may be treated with ESAs using FDA-approved indications/dosing/dosing adjustments OR may be treated with red blood cell transfusions per provided guidelines. • Patients with anemia due to myelosuppressive chemotherapy should be assessed for risk of adverse events due to anemia, and need for initial transfusion.
ESAs are NOT indicated for:	• Use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy; • Use in patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of ESAs on progression-free and overall survival; • The treatment of anemia in cancer patients due to other factors.	• Clinicians should consider other correctable causes of anemia before considering ESA therapy • Recommends against using ESAs to treat anemia associated with malignancy in patients (excepting those with lower risk MDS) who are not receiving concurrent myelosuppressive chemotherapy.	ESA treatment is not recommended when patients are treated with myelosuppressive chemotherapy with curative intent.

Table 2. ESA prescribing information and guidelines (continued)

	FDA-approved full prescribing information (similar for all approved ESAs) (49-51)	**American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update (2010) (52, 53)**	**NCCN Guidelines, Cancer and Chemotherapy-Induced Anemia (V 2.2011)** (54)
ESA treatment symptom outcomes	ESA use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.	Evidence does not conclusively show that ESA use leads to improved quality of life as can be perceived and valued by patients; recommends that the goal of ESA use should be to avoid transfusions.	Not discussed.
Risk evaluation and mitigation strategy (REMS)	Prescribers and hospitals must enroll in and comply with the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe Use of ESAs) Oncology Program, part of a REMS, to prescribe and/or dispense ESAs to patients with cancer.	Notes requirement	Notes requirement
Hb levels for ESA initiation	ESA therapy should not be initiated at Hb levels ≥10 g/dL.	Recommended when Hb level has decreased to <10 g/dL. Whether or not to initiate treatment when Hb is between 10 and 12 g/dL should be determined by clinical judgment, consideration of ESA risks and benefits (transfusion avoidance) and patient preferences. Transfusion is also an option.	If Hb is <11 g/dL or >2 g/dL below baseline, an evaluation for possible causes of anemia is suggested. If a cause is not identified, then anemia due to myelosuppressive chemotherapy is considered.
Span of ESA treatment	ESA therapy should be discontinued following the completion of a chemotherapy course.	Recommends discontinuing ESA treatment when chemotherapy concludes, per FDA guidelines.	Physicians are advised not to administer ESAs outside the treatment period of cancer-related chemotherapy.

Table 2. ESA prescribing information and guidelines (continued)

	FDA-approved full prescribing information (similar for all approved ESAs) (49-51)	**American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update (2010) (52, 53)**	**NCCN Guidelines, Cancer and Chemotherapy-Induced Anemia (V 2.2011)** (54)
ESA dosing modifications	• Starting ESA dose should be reduced by 25% when Hb reaches a level needed to avoid transfusion or increases >1 g/dL in any 2-week period. • ESA dose should be withheld if Hb exceeds a level needed to avoid transfusion. (Restart at 25% below the previous dose when the Hb approaches a level where transfusions may be required.) • Starting ESA dose may be increased (per specific product label) if response after 4 weeks is not satisfactory to achieve and maintain the lowest Hb level sufficient to avoid RBC transfusion. • ESA should be discontinued if after 8 weeks of therapy there is no response as measured by Hb levels or if transfusions are still required.	Recommends ESA starting doses and dose adjustments follow FDA guidelines, noting that alternative doses and schedules have not improved medical outcomes. Refers to product label directing clinicians to use the lowest possible ESA dose (i.e., minimize ESA exposure) to reach the lowest hemoglobin level sufficient to avoid RBC transfusions.	Dosing and titration directions for epoetin-alfa and darbepoetin-alfa are reproduced from the FDA-approved labels
Hb target	None given ("level needed to avoid transfusion")	Hb can be raised to the lowest hemoglobin level needed to avoid RBC transfusions. An optimal target Hb cannot be determined from the available evidence.	No Hb target is mentioned; notes that the risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to a target Hb <12 g/dL.
Iron	Prior to and during ESA therapy, should be evaluated. Virtually all patients will eventually require supplemental iron.	Iron studies at baseline and periodically during treatment may be valuable to minimize the need for ESA treatment, maximize improvement of symptoms, or determine the reason for failure to respond.	Iron studies and supplementation of functional iron deficiency are recommended for patients treated with ESAs.

Table 2. ESA prescribing information and guidelines (continued)

	FDA-approved full prescribing information (similar for all approved ESAs) (49-51)	**American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update (2010) (52, 53)**	**NCCN Guidelines, Cancer and Chemotherapy-Induced Anemia (V 2.2011)** (54)
Thromboembolic risk	Black box warning notes the increased risk for thromboembolic events in clinical studies administering ESAs to a Hb target of 13 g/dL and above.	Caution is urged in the use of these agents with patients judged to be at high risk for thromboembolic events, and regarding ESA use together with therapies that increase risk of thromboembolic events.	Patients with previous risk factors for thrombosis may be at higher risk when administered ESAs and should undergo risk assessment; the risk of ESA-associated thrombosis is independent of Hb levels.
Response to treatment	If the patient fails to respond or to maintain a response to doses within the recommended dosing range after 8 weeks of therapy, ESA treatment should be discontinued and other etiologies of anemia should be considered and evaluated.	If a patient does not respond to ESAs after 6 to 8 weeks, despite a dose increase, ESA therapy should be discontinued and the clinician should investigate possible underlying tumor progression, iron deficiency, or other causes of the anemia.	ESA therapy should be discontinued if a patient shows no response despite iron supplementation after 8-9 weeks of treatment.

use prepared by the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) (52, 53), and from the National Comprehensive Cancer Network (NCCN) Guidelines for Cancer and Chemotherapy-Induced Anemia (54).

Key Questions and Rationale for Update

The Southern California EPC reviewed a sample of literature published through 2008 and obtained four expert opinions regarding the need to update conclusions for each key question (55) included in the 2006 CER (56). The consistency and strength of the evidence and expert opinion supporting recommendations to update specific key questions were evaluated by the EPC together with more recent evidence. Based on that appraisal, the three key questions (KQ) listed below were judged relevant and are the questions addressed in this CER and illustrated in the analytic framework (Figure 1).

KQ1: What are the comparative benefits and harms of erythropoiesis stimulating agent (ESA) strategies and non-ESA strategies to manage anemia in patients undergoing chemotherapy or radiation for malignancy (excluding myelodysplastic syndrome and acute leukemia)?

Outcomes of interest include overall survival (on study and longest available follow-up), progression-free survival, quality of life, hematologic responses, transfusions, tumor response to therapy, thromboembolic complications, and other adverse events. Specific comparisons to be included are:

1. Epoetin alfa or beta versus no ESA;
2. Darbepoetin versus no ESA;
3. Epoetin alfa or beta or darbepoetin versus no ESA; and
4. Epoetin alfa or beta versus darbepoetin.

KQ2: How do alternative thresholds for initiating treatment compare as regards their effect on the benefits and harms of erythropoietic stimulants?

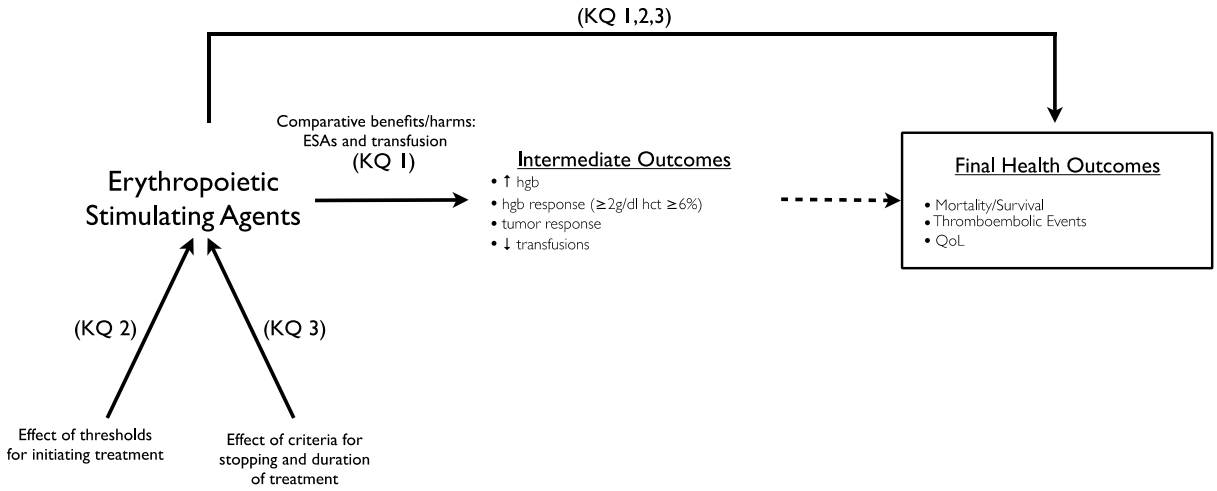
Evidence is limited to directly comparative data from randomized controlled trials. Outcomes of interest to include: hematologic response (change in hemoglobin or hematocrit), proportion of patients transfused, quality of life, survival (overall and progression-free), and adverse effects.

KQ3: How do different criteria for discontinuing therapy or for optimal duration of therapy compare as regards their effect on the benefits and harms of erythropoietic stimulants?

Evidence is limited to directly comparative data from randomized controlled trials. Outcomes of interest to include: hematologic response (change in hemoglobin or hematocrit),

proportion of patients transfused, quality of life, survival (overall and progression-free), and adverse effects.

Figure 1. Analytic framework for effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment—update



A brief summary of the rationale applied to updating key questions from the 2006 CER follows.

The 2006 CER revealed safety concerns for the erythropoietic stimulants as a class. The evidence showed a significant risk for thromboembolic events with ESA use, and suggested that ESAs stimulated tumor progression and that they had an adverse effect on overall survival. Moreover, these safety concerns could not be narrowly attributed to use of ESAs to achieve high hemoglobin (Hb) targets, but might also be associated with usual use according to the label at the time.

In 2007, the FDA issued warnings and labeling changes consistent with the safety concerns that we raised in the 2006 CER. As noted in the rationale for an updated review (55), the "CER may need updating based on new data presented to the FDA and difference in expert opinion."

The 2006 findings on quality of life were not judged to require updating (55). The EPC agreed in substance and noted that the FDA has stated that there is insufficient evidence to support claims of improved quality of life with use of ESAs. However, it was judged important that issues surrounding quality of life be at least qualitatively addressed, and quantitatively examined for the most important and commonly ascertained outcome—fatigue. The principles of critical appraisal of use and interpretation of disease-specific quality of life instruments that were raised in the 2006 CER should continue to be accessible to users of the 2010 Update. Moreover, these points should be tied to the Guidance for measurement of patient-reported outcomes that was issued by the FDA in 2008.

Issues raised in the 2006 CER were broader than a comparison of epoetin and darbepoetin, and were more fundamentally a question of approaches to managing anemia of cancer treatment. Thus for the 2010 Update, the proposed key questions were modified accordingly. Most notably, Key Question 1 was been modified from "What are the comparative efficacy and safety of epoetin (alfa or beta) and darbepoetin?" to "What are the comparative benefits and harms of

erythropoiesis-stimulating (ESA) strategies and non-ESA strategies to manage anemia in patients undergoing chemotherapy or radiation for malignancy?"

An update of Key Question 2 was not recommended (55)—"How do alternative dosing strategies affect the comparative efficacy and safety of epoetin (alfa or beta) and darbepoetin?" and the TEC EPC concurred. It is not included in our 2010 Update Key Questions.

Key Question 3, "How do alternative thresholds for initiating treatment or alternative criteria for discontinuing therapy or the duration of therapy affect the comparative efficacy and safety of epoetin (alfa or beta) and darbepoetin?" was judged needing updating as indicated by FDA changes to labeling and expert opinion (55). Accordingly, the question is included in the 2010 Update.

Finally, an update of Key Question 4 was not suggested (55), "Are any patient characteristics at baseline or early hematologic changes useful to select patients or to predict responses to treatment with erythropoietin?" This recommendation was based on expert opinion that referred to patient treatment characteristics and FDA labeling. However, the TEC EPC judged that updating this question would be of little value. The literature reviewed in the 2006 CER was related to single or multifactorial algorithmic predictive testing. None was promising, and the literature has no bearing on the FDA changes to labeling, which are closely tied to the evidence for Key Question 1. This question was not included in the update.

Table 3 reviews the current ESA approval status and approved starting dose.

Table 3. ESAs, approval status, and approved starting dose

ESA	Approval Status U.S.	Approval Status European Union	Approved Dose
Epoetin alfa	EPOGEN® (Amgen)	Eprex® (Janssen-Cilag)	Epoetin alfa preparations are formulated for intravenous (IV) or subcutaneous (SC) administration. The recommended adult starting dose is 150 Units/kg SC 3 times per week or 40,000 Units SC weekly. Dose may be modified depending on Hb response.
	PROCRIT® (Ortho Biotech)		
Darbepoetin alfa	Aranesp® (Amgen)	Aranesp® (Amgen)	Aranesp® is formulated for IV or SC administration. The recommended initial adult dose is either 2.25 mcg/kg SC weekly or 500 mcg SC every 3 weeks. Dose may be modified depending on Hb response.
Epoetin beta	Not approved for use in the U.S.*	NeoRecormon® (Hoffmann-La Roche)	NeoRecormon® is formulated for IV or SC administration. The recommended initial dose is 30,000 IU per week given as one injection per week or in divided doses 3 to 7 times per week. Dose may be modified depending on Hb response.

*See also Background. While not approved in U.S., effects are considered exchangeable with epoetin alfa.

Methods

This report updates the 2006 "Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment." The current chapter describes the search strategies used to identify literature; criteria and methods for selecting eligible articles; methods for data abstraction, quality assessment, and evidence synthesis; and, finally, the process for technical expert advice and peer review. General and specific guidance from the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews was used throughout to advise review conduct (57).

A Technical Expert Panel (TEP) provided consultation for the development phase of the systematic review. The draft report was reviewed by __ external reviewers, including invited clinical experts and stakeholders. Revisions were made to the draft report based on reviewers' comments.

Search Strategies

The search for randomized controlled trials published subsequent to the 2006 Report was updated through electronic searching of the Cochrane Central Register of Controlled Trials Register (CENTRAL, 03/2005 to 11/2009), MEDLINE® (03/2005 to 10/2009), and EMBASE (03/2005 to 10/2009). Electronic searching also included the conference proceedings of the American Society of Clinical Oncology (03/2005 to 10/2009), European Society of Medical Oncology (03/2005 to 10/2009), and American Society of Hematology (03/2005 to 10/2009).

A separate search for *comparative* observational studies, primarily to augment the evidence on adverse events, was conducted in MEDLINE® only. A separate search for published meta-analyses and individual patient data analyses addressing outcomes of ESA treatment was conducted in PubMed and Cochrane databases in March 2010.

Literature searches were updated prior to finalizing the report to determine if any new studies were published that may potentially impact the review. New studies were evaluated against inclusion/exclusion criteria in the same manner as all other studies.

TEP members were invited to provide additional studies. Studies suggested by stakeholders during the public review period were also evaluated against inclusion/exclusion criteria in the same manner as all other studies. In addition, we received the following materials from the Scientific Resource Center:

1. A search of the grey literature included following sources: regulatory information, clinical trial registries (completed trials only), abstracts and conference papers, grants and federally funded research, and other miscellaneous sources.
2. Scientific information packets submitted by Amgen and Centocor Ortho Biotech, Inc.

All search results were compiled into an EndNote® reference manager database with exclusion of duplicates.

Additional details on these materials and results of our review are provided in the Results chapter. Search strategies are detailed in Appendix A.

Grey Literature

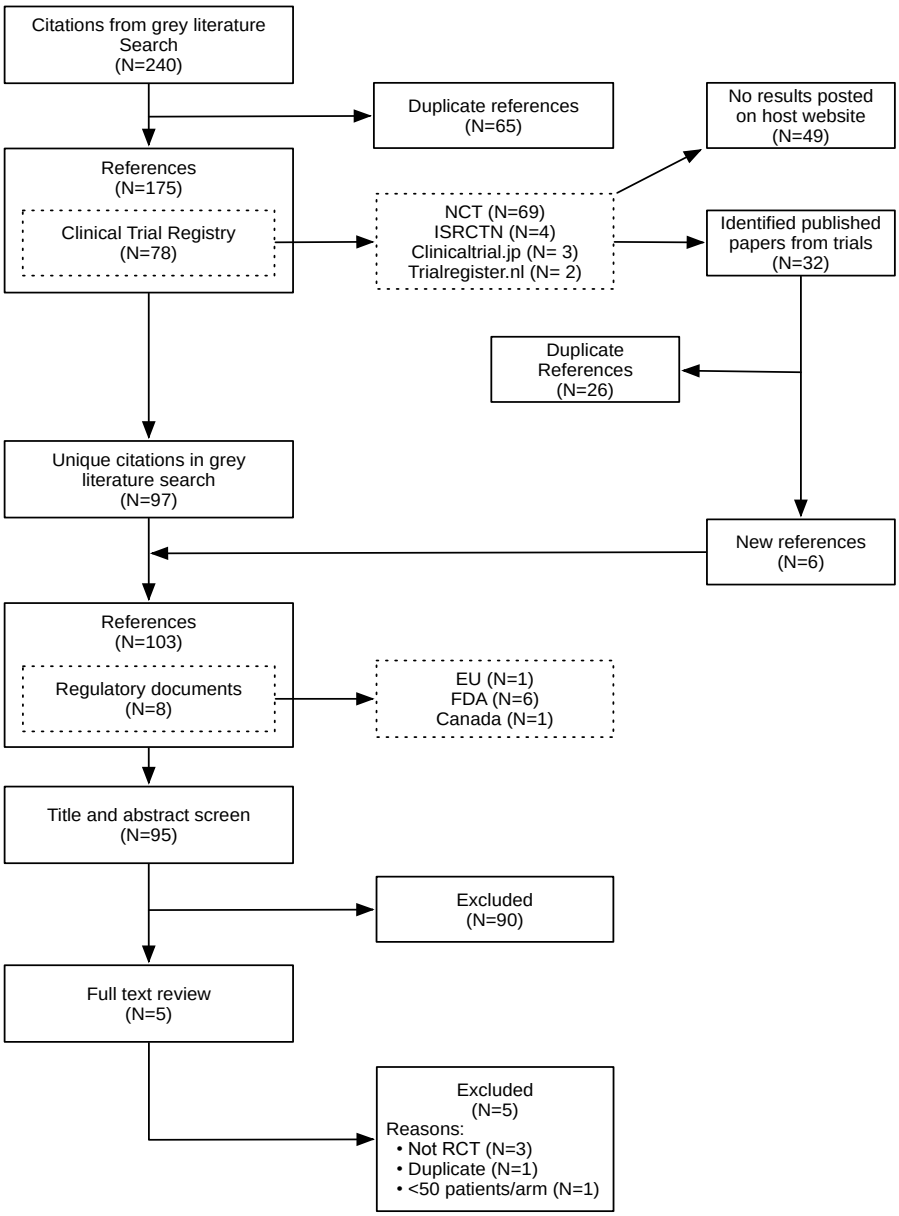
The Scientific Resource Center for the AHRQ Effective Health Care Program conducted a search of the following grey literature sources in support of this review:

1. Regulatory Information
    a. FDA
    b. Health Canada
    c. Authorized Medicines for EU
2. Clinical Trial Registries (completed trials only)
    a. ClinicalTrials.gov
    b. Current Controlled Trials
    c. Clinical Study Results
    d. WHO Clinical Trials
3. Abstracts and Conference Papers
    a. Conference Papers Index
    b. Scopus
4. Grants and Federally Funded Research
    a. NIH RePORTER (a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions)
    b. HSRPROJ (a database providing access to ongoing grants and contracts in health services research)
5. Other Miscellaneous Sources
    a. Hayes, Inc. Health Technology Assessment
    b. NY Academy of Medicine's Grey Literature Report

These sources were searched using sensitive searches similar to the searches in bibliographic databases. Citations for published articles linked to trials registered at ClinicalTrials.gov were included.

We evaluated the results of the grey literature search with results summarized in Figure 2. Twenty-six literature citations were already included in our reference database. Fifty-six references were reviewed at the abstract or summary level, in duplicate, and were excluded according to our study protocol. Seven references were retrieved in full and all were excluded (or had already been included) according to our study protocol. Thus, no new references were added to our review as a result of the grey literature search. We were unable to identify results, publications, or reports from 49 trial registry entries noted as completed trials (no results, citations, or links to results were listed in the trial registry entries).

Figure 2. PRISMA diagram for identified grey literature



Scientific Information Packets

Industry stakeholders were invited to submit the following types of information for possible inclusion as evidence:

- A current product label;
- Published randomized controlled trials and observational studies relevant to the clinical outcomes; and
- Unpublished randomized controlled trials and observational studies relevant to the clinical outcomes.

In response, scientific information packets (SIPs) were received from Centocor Ortho Biotech, Inc. and Amgen. Disposition of the material can be found in Figure 3. In addition to product labels, the submissions consisted of either published references or listings of clinical trials; no unpublished data were provided by either company.

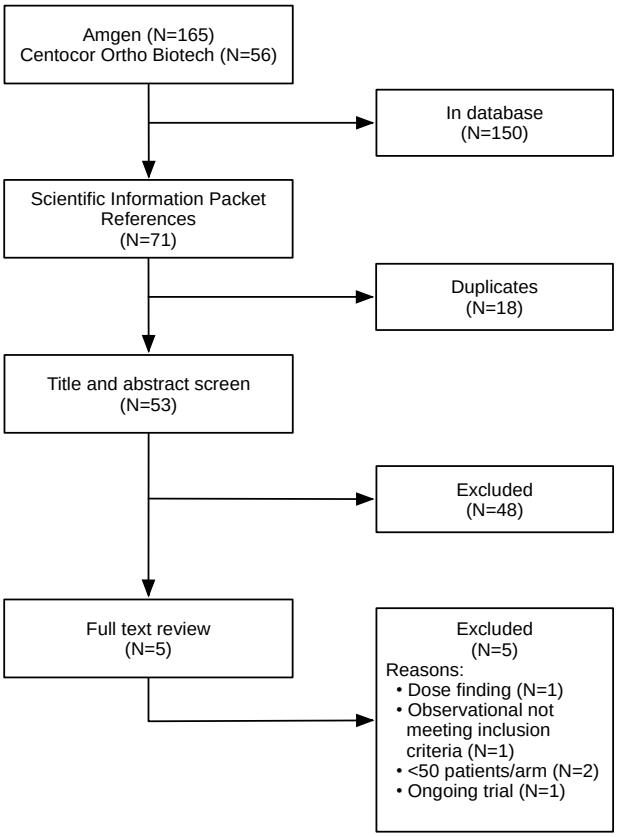
Product Labels

All submitted product labels, which included labels for countries other than the United States, were reviewed for clinical studies that were not included in our search. No new studies were found.

References

Centocor Ortho Biotech, Inc. submitted 56 citations and Amgen submitted 165. These were first compared to our database excluding duplicates. Of the 71 remaining references, 18 were duplicates. One reviewer reviewed abstracts for the 53 outstanding references; 10 were identified for full review, and the remainder were excluded as not relevant or already were addressed in our review. A second reviewer evaluated the 10 studies in full; all were excluded.

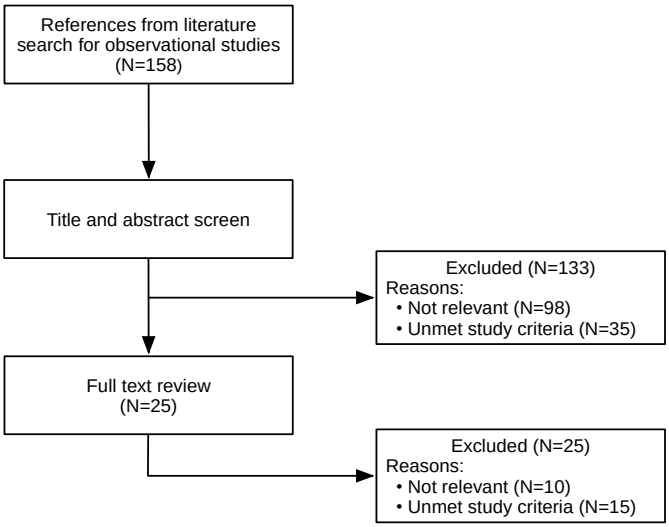
Figure 3. PRISMA diagram for scientific information packets



Observational Studies

We identified 158 observational studies in the MEDLINE® search. Disposition of the studies according to selection criteria is shown in Figure 4.

Figure 4. PRISMA diagram for observational studies



Trials

Sources and disposition for identified trials are shown in Figure 5 and Figure 6.

Figure 5. PRISMA diagram for identified trials—Key Questions

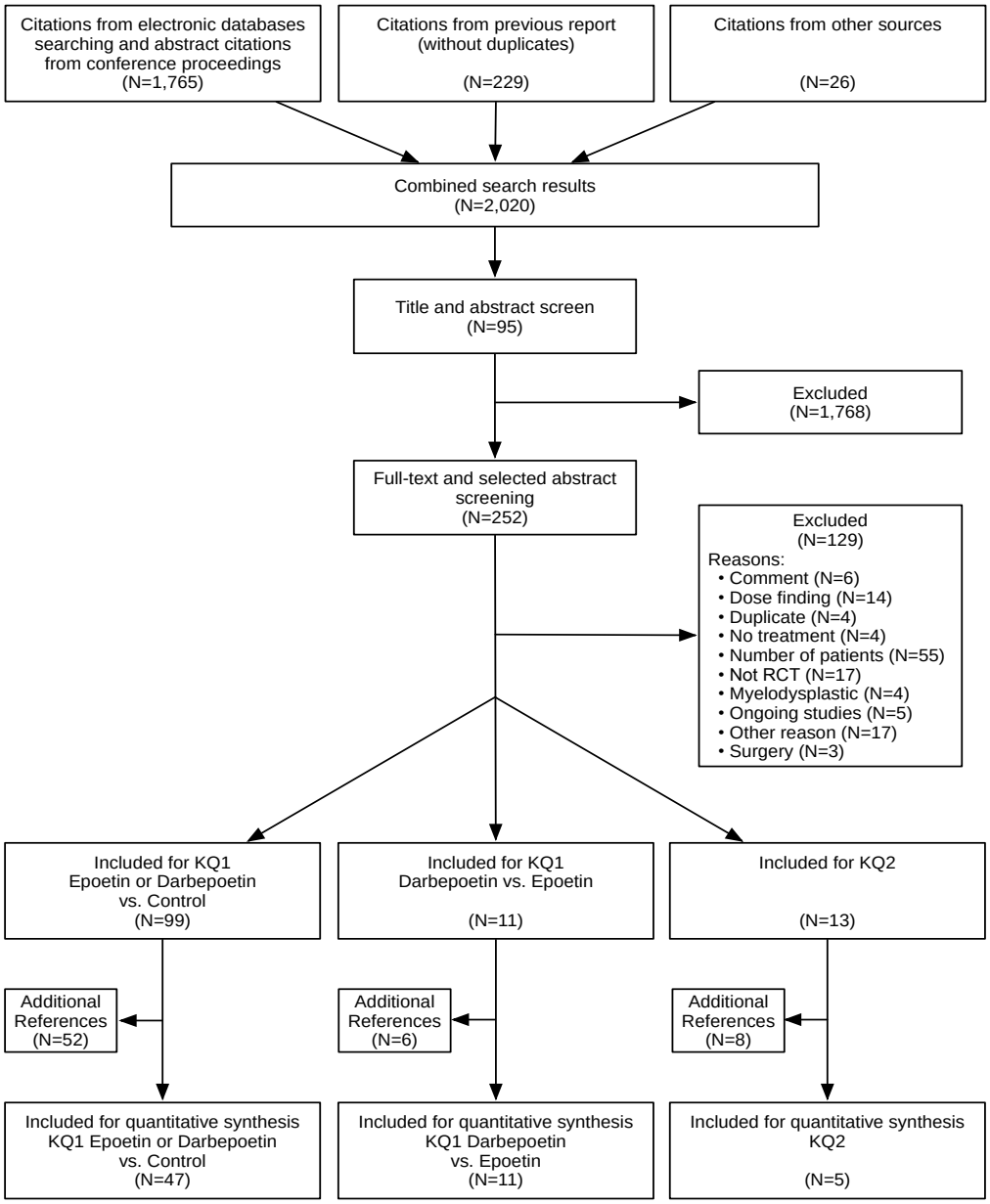
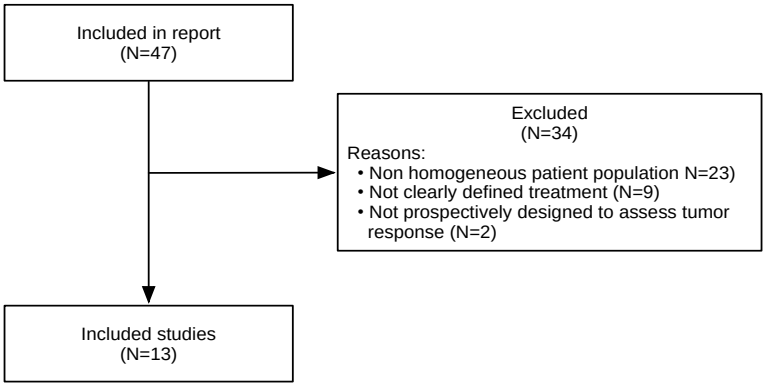


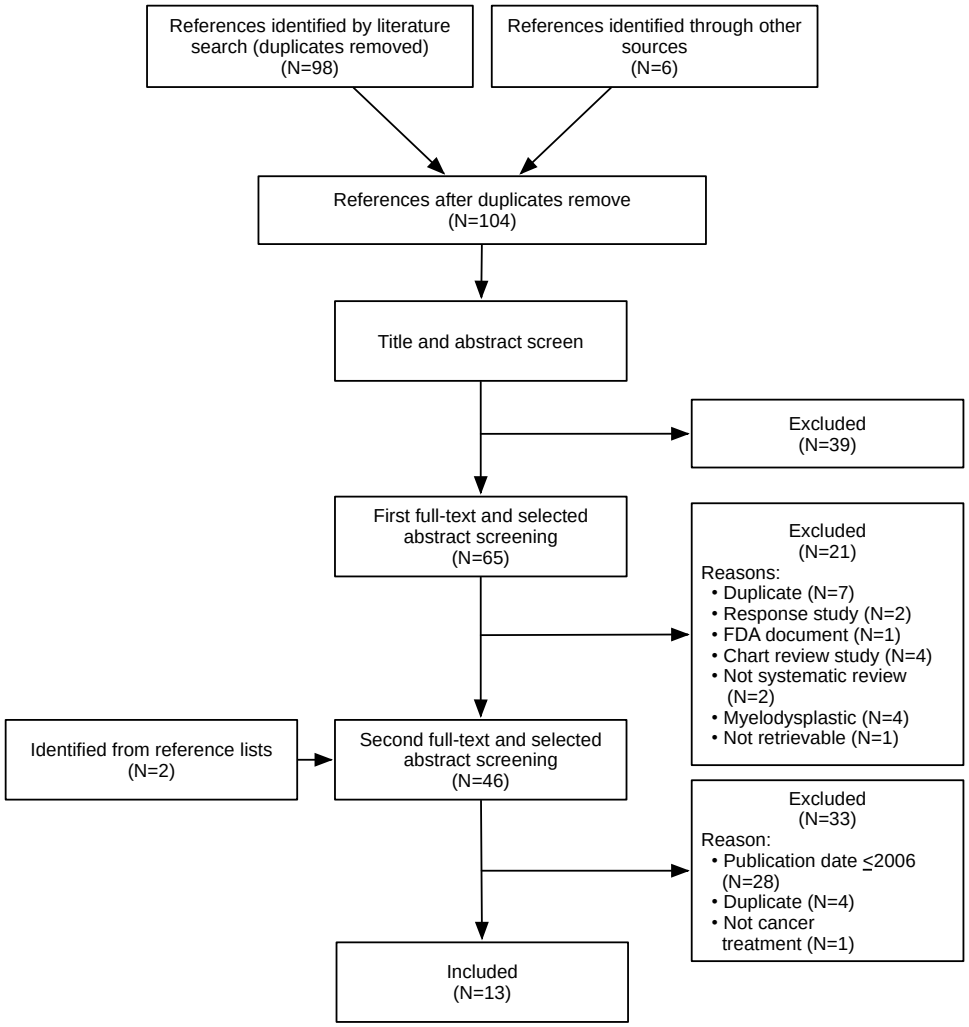
Figure 6. PRISMA diagram for identified trials—Key Question 1, tumor progression



Meta-Analyses

Figure 7 outlines the identification of meta-analyses and systematic reviews.

Figure 7. PRISMA diagram for meta-analyses



Study Selection Criteria

Study selection criteria were drafted and described in detail for randomized controlled trials and meta-analyses in Table 4. A primary source for current survival evidence was a recently published individual patient data meta-analysis (58). In that meta-analysis, patient data were obtained from investigators for studies enrolling more than 50 patients per arm. Because those data constitute the most currently available, as well as the source for on-study mortality data, we limited inclusion in the current report to similar size studies to avoid potential differential endpoint ascertainment in smaller studies. This contrasts with the previous report that included studies enrolling 10 or more patients per arm. Sensitivity analyses were performed for each outcome including any studies excluded for that reason. Inclusion criteria for observational studies were as in Table 4 except for "Types of studies." Exclusion criteria were also the same except that studies enrolling fewer than 250 patients were excluded.

Table 4. Inclusion/exclusion criteria for randomized controlled trials; and study-level and individual patient data meta-analyses

	Inclusion criteria	**Exclusion criteria**
Types of studies	Randomized controlled clinical trials. For studies where the specific randomization method is unclear, but the study is described as "randomized," retain and categorize as "randomization unclear."	Trials with inadequate allocation concealment, e.g. where patients were allocated by alternation, the use of case record numbers, dates of birth or day of week, and any other procedure that is transparent before allocation, such as an open list of random numbers. Trials with unclear allocation concealment were retained.
	Study-level and individual patient data meta-analyses.	Trials with 50 or fewer randomized participants per study arm for studies of adults; 10 or fewer participants per study arm in pediatric samples.
	Studies in European languages such as German, French, and Spanish; no effort will be made to translate languages such as Chinese or Arabic.	Ongoing studies and interim analyses.
Sources of evidence	Full text publications.	
	Meeting abstract publications, PowerPoint presentations, or posters.	
	Supplementary data communicated by primary authors of included trials or studies.	
	Data presented at the ODAC, FDA hearings on May 10, 2007 and March 13, 2008. These data will be taken from the official FDA report and documents submitted by pharmaceutical companies and posted on the FDA's Web site. These documents include both reports and power point presentations and are publicly available.	

Table 4. Inclusion/exclusion criteria for randomized controlled trials; and study-level and individual patient data meta-analyses (continued)

	Inclusion criteria	**Exclusion criteria**
Types of participants	Only participants diagnosed with malignant disease, using clinical or histological/cytological criteria, regardless of type or stage of the disease or previous therapy.	Studies of patients with a malignant disease NOT undergoing anticancer therapy.
	Only participants who are anemic or at risk for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease.	Studies of high-dose myeloablative chemotherapy regimens followed by bone marrow or peripheral blood stem cell transplantation.
	Patients of any/all ages.	Studies using erythropoietin for short-term preoperative treatment to correct anemia or to support collection of autologous blood prior to cancer surgery for use during or after surgery.
		Studies in which patients received surgical treatment while being administered ESA.
		Studies on patients with myelodysplastic syndrome or acute leukemia.
Types of interventions	Trials on the use of erythropoietin plus chemotherapy and/or radiotherapy and red blood cell transfusions if necessary, compared with identical anticancer therapy and red blood cell transfusions if necessary (alone or with placebo) will be included.	
	Dose adaptation of erythropoietin depending on hematologic response allowed.	
	Concomitant supportive treatments, e.g., granulocyte colony-stimulating factors (G-CSF), must be given equally in all study arms or any differential effect of supportive treatments on outcomes ascertainable, EXCEPT studies where iron was given only in the ESA arm. These studies will be included and sensitivity analyses conducted with vs. without them.	

Table 4. Inclusion/exclusion criteria for randomized controlled trials; and study-level and individual patient data meta-analyses (continued)

	Inclusion criteria	Exclusion criteria
Types of outcome measures	Hematologic response: proportion of patients with an increase in hemoglobin level of 2 g/dl or more, or increase in hematocrit of 6 points or more, independent of blood transfusions.	
	Proportion of patients receiving red blood cell transfusions.	
	Quality of Life data will be only abstracted from studies employing a validated instrument, such as SF-36; EORTC Quality of life Questionnaire (QLQ-C30); Functional Assessment of Cancer Therapy (FACT, including G-General; F-Fatigue; An-Anemia. Sample size and extent of missing data will be extracted.	LASA, VAS, and CLAS scales will be excluded
	Tumor response will only be evaluated in studies that were prospectively designed to assess tumor response, i.e., studies with a homogeneous patient population undergoing a predefined anticancer therapy, with predefined criteria when and how tumor response will be assessed and a clear definition of tumor response.	
	Overall survival, disease-free, and progression-free survival.	
	Adverse effects limited to thromboembolic events, hypertension, rash and similar symptoms, seizures, rEPO antibodies, and transfusion adverse events.	

Randomized Controlled Trial Selection

One reviewer screened titles and abstracts of trials identified from the above sources against the inclusion/exclusion criteria. If this could not be done satisfactorily from the title and abstract, a full text version was obtained for review. We evaluated studies that appeared to meet the inclusion criteria in the initial screening with an eligibility form containing the following questions:

1. Is the study described as randomized?
2. Did the participants in the study have a previously treated or untreated malignant disease?
3. Were the participants anemic or at risk for anemia from chemotherapy and/or radiotherapy?
4. Was one group given epoetin (alfa or beta) or darbepoetin subcutaneously or intravenously for at least four weeks?
5. Did the control group receive the same care (e.g., chemotherapy and supportive therapies) with or without placebo, or is any differential effect of supportive treatments on outcomes ascertainable? (Note exception for iron supplementation; see Criteria for Considering Studies, Types of Interventions.)
6. Did the study document one of the relevant outcome measures?

Eligible trials met all of the criteria listed above. Disagreements between the reviewers were resolved by discussion. Duplicate studies were identified and data extracted from the most recent

publication. However, if there were additional data in one of the older publications, these were extracted as well. Full-text versions of all eligible studies were obtained for quality assessment and data extraction.

Observational Study Selection

A first reviewer screened titles and abstracts of identified studies from the above sources against the eligibility criteria. If the first reviewer was unable to categorize the study, it was screened by a second reviewer and inclusion/exclusion status established by consensus. If this could not be done satisfactorily from the title and abstract, a full-text version was obtained for review. Eligible studies met the following criteria:

1. Is the study described as nonrandomized?
2. Were there more than 250 subjects?
3. Did the participants in the study have a previously treated or untreated malignant disease?
4. Were the participants anemic or at risk for anemia from chemotherapy and/or radiotherapy?
5. Was epoetin (alfa or beta) or darbepoetin given subcutaneously or intravenously for at least 4 weeks?
6. Did the study document one of the relevant outcome measures (benefit or harm)?
7. In the study analyses was one of the following techniques used to examine causal effects: 1) appropriate propensity score approaches, 2) instrumental variable methods, 3) inverse probability weighting, or 4) G-estimation techniques to take into account potential bias.

Study and Independent Patient-Level Meta-Analysis Selection

Both study- and patient-level meta-analyses examining benefits or harms of ESA treatment were included. Progression-free or disease-free survival study-level results from industry-funded meta-analyses were also be included if the original study was designed to evaluate that outcome.

Assessment of Methodologic Quality

Quality Assessment of Included Randomized Clinical Trials

Two reviewers evaluated the full text articles included in the review for study quality. Any discordance was discussed with the project group until consensus was obtained. We used a modification of the The Cochrane Collaboration's tool for assessing risk of bias (The Cochrane Handbook, Table 8.5.a (59)) containing the following questions:

1. Was allocation truly random?
2. Was the treatment allocation concealed?
3. Were study participants blinded (masked) to the treatment they received?
4. Were study clinicians blinded (masked) to the treatment received by individual study participants?
5. Were the number of patient withdrawals, dropouts, and those lost to follow-up in each group stated in the main publication?

6. Did the analysis include an intention-to-treat analysis? That is, did the analysis include all patients randomized according to their randomized assignment?
7. Were the participant characteristics similar at baseline in the study groups compared?

For health-related quality of life studies (HRQoL), we also evaluated whether patients were blinded towards their Hb levels when HRQoL questionnaires were completed. For studies for which there were several reports/analyses, we used our best judgment for accurately and efficiently assessing quality (study level was the default).

Trials were excluded from the analysis if they were not truly randomized or had inadequately concealed allocation. Studies that met all criteria listed below were included in the group of higher quality trials for purposes of sensitivity analysis.

1. The study was a randomized controlled trial (see details under Criteria for Study Selection).
2. The study was double blind.
3. At least one of the following conditions was true: Less than 10 percent of subjects within each study arm were excluded from the analysis and the percentage of subjects excluded from analysis in each arm was less than 2:1; or less than 5 percent of subjects were excluded in each study arm.

Quality Assessment of Published Meta-Analyses

AMSTAR (Assessment of Multiple Systematic Reviews) is a validated instrument used for quality assessment of meta-analyses (60). While the instrument has been validated with study-level meta-analyses, 9 of the 11 elements apply directly and the remaining 2 elements indirectly to individual patient meta-analyses. Accordingly, the instrument was applied to all meta-analyses.

Quality Assessment of Observational Studies

No quality assessment of observational studies was conducted (no studies met inclusion criteria).

Data Extraction

One reviewer performed data extraction for the review using a standardized data extraction form modified slightly from the previous systematic review (Appendix B), including the types of items listed below. An independent reviewer checked abstracted data.

For randomized controlled clinical trials, the following were abstracted:

1. General information: title, authors, source, contact address, year of publication, duplicate publications, setting, funding.
2. Trial characteristics: design, method of randomization, concealment of allocation, blinding of patients and clinicians.
3. Patients: sampling, exclusion criteria, sample size, baseline characteristics, similarity of groups at baseline, diagnostic criteria, withdrawals, losses to follow up.

4. Interventions: placebo use, dose, dosing regimen, duration, route, red blood cell (RBC) transfusion trigger, co-medications with dose, route and timing. Outcomes as specified previously.
5. Analytical methods

Any disagreements at any stage were resolved by discussion and consensus.

Discrepant Data

For trials published in multiple articles, reports or presentations, we extracted the most recent or most comprehensive data. The data of any trial taken from different sources were compared. If data from different sources were discrepant, data were selected for analysis using the following rules:

1. We used the most complete data sets (i.e., those with the largest sample size), or data with consistently defined outcomes across trials.
2. If different results were available from the same trial, i.e. "intention-to-treat" and "as treated" analyses, we use the intention-to-treat based data for analysis and explored the influence of alternative results in sensitivity analyses if appropriate.

Other Issues

If a trial only reported the overall number of randomized patients but failed to report the number of patients per study arm, we assigned 50 percent of the study patients to each of the study arms. For updating reports that were already included in the previous review, the focus was on variables important to the analyses, rather than on a global update.

Trial-level evidence tables were created in Microsoft Excel® and Word®. For summary evidence tables, a dataset of trial characteristics was constructed in Excel, summaries table data calculated and formatted in R (R Core Development Team, 2010) (61), then exported to Excel®. Templates similar to the 2006 report were used. One reviewer performed primary data entry into the Excel® evidence tables, and a second performed accuracy checks.

PRISMA (62) or PRISMA-like diagrams were constructed for each Key Question and other applicable searches (meta-analyses, observational studies, grey literature, scientific information packets).

Rating the Body of Evidence

We used information from the AHRQ EPC Methods Guide for Comparative Effectiveness Reviews (63) to rate the strength of the overall body of evidence. The EPC method is largely based on the system developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (64). The EPC method explicitly addresses the following domains: risk of bias, consistency, directness, and precision. Additional domains are added where appropriate; we also considered strength of association and publication bias. We identified five key outcomes as the most clinically important for rating: proportion transfused, overall survival, on-study mortality, thromboembolic events, and health-related quality of life (FACT-Fatigue).

Strength of evidence is classified into the following four grades:

1. High: High confidence that the evidence reflects the true effect. Further research is very unlikely to change confidence in the estimate of effect.

2. Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change confidence in the estimate of effect and may change the estimate.
3. Low: Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
4. Insufficient: Evidence either is unavailable or does not permit a conclusion.

Grading the Evidence

Two reviewers (MG and MP) with primary roles in the report developed consensus for each outcome and comparison as follows. First, domains and associated criteria were reviewed with AHRQ guidance (65). The two reviewers jointly rated domains and rated quality of evidence for each outcome and comparison. Agreement was achieved by discussion and consensus.

Data Analysis

When study-level outcome data were available from multiple trials (three or more), results were pooled in meta-analyses. Survival outcomes were pooled using two approaches. First, hazard ratios (HR) were combined in fixed effects models using Peto's method (66) for observed and expected events with accompanying variance estimate (67, 68). Second, event rates were pooled in Bayesian hierarchical. Noninformative priors were specified in these models. To obtain relative risks, the approach outlined by Warn et al. (69) was adopted. A Bayesian model was also used to examine the association between baseline risk (as reflected by control group mortality rate) and relative risk; the model accounts for the inherent correlation between relative effect and baseline risk (70). For all other meta-analyses, random effects models were fitted and relative risks reported. While values of I^2 were reported throughout, in many instances its magnitude does not correctly or appropriately reflect statistical heterogeneity due to the low event rates in individual trials and accompanying imprecision (71). Accordingly and as noted in the results section, I^2 cannot be used under such circumstances as an adequate representation of statistical heterogeneity. Between-study heterogeneity was explored as appropriate in sensitivity analyses examining subgroups through meta-regressions.

Hazard ratios for time to event data were calculated based on individual patient data (IPD) when available from Bohlius et al. (2009). If IPD data were not available, no efforts were made to obtain it and the HR calculated from published reports. When direct comparative data were not available, qualitative indirect comparisons were performed, and quantitative indirect comparisons explored when feasible. Recognizing limitations, indications of possible publication bias were explored in funnel plots. Funnel plots were inspected, but noted only if there was a suggestion of publication bias. Forest plots were included when judged informative.

Subgroup analyses were performed including the following factors, if feasible and appropriate:

- Hemoglobin at study entry (e.g., continuous and hemoglobin level <10 g/dL versus 10-12 g/dL versus >12 g/dL)
- Achieved hemoglobin (e.g., continuous and hemoglobin level 10-11 g/dL versus 11-12 g/dL versus >12 g/dL)
- Difference between target and achieved hemoglobin
- Solid tumors versus hematologic malignancies versus mixed (studies including both solid tumors and hematologic malignancies)

- Type of treatment given (platinum-based chemotherapy versus chemotherapy without platinum; chemotherapy alone versus chemotherapy plus radiotherapy versus radiotherapy alone)
- Radiotherapy versus chemotherapy versus radio-chemotherapy
- Planned iron supplementation (e.g., fixed versus as necessary versus none)
- Planned duration of erythropoietin or darbepoetin treatment
- Erythropoietin versus darbepoetin
- For overall survival additionally: duration of follow up
- Study quality (high- versus low-quality studies)
- Source of data (full-text publications versus abstract publications versus unreported data versus data presented at FDA hearing versus data from published IPD meta-analyses; source for data for a given study could differ between outcomes, e.g., survival data taken from FDA hearing, transfusion data taken from publication)

While the protocol included potential categorizations of covariates, to obtain sufficient precision (i.e., avoid strata with few trials) we conducted subgroup analyses with covariates dichotomized into the most clinically relevant categories in meta-regressions. Additionally, there was evidence of substantial clinical heterogeneity between trials—design, tumor type, baseline and target Hb, chemotherapy, dosing, escalation and de-escalation rules, iron supplementation, and length of follow-up, to name a few. Under these conditions, any subgroup findings require cautious interpretation and may be problematic. Accordingly, subgroup results were explored but not generally discussed at length. Finally, potential ecological bias further limits subgroup interpretation (e.g., for hemoglobin).

Software

Analyses were performed using RevMan (72), R (73-76), and OpenBUGS (77).

Decision Analysis

To examine the balance of potential benefit and harms, a decision model was developed and used to quantify life-years and quality-adjusted life years for ESA and non-ESA strategies. Utilities accompanying the two alive health states included in the model (9 g/dL and 11 g/dL) were estimated using those obtained using time trade-off (2 studies) and EQ-5D (2 studies) reported in other technology assessments (78, 79). Midpoints were assigned to reported Hb range for the reported utilities and included in a hierarchical model (with study as group) to estimate the two utility values used here. Over a 1-year time horizon (for the base case and other likely conditions), life years and quality-adjusted life years were calculated for a cohort of 1,000 patients undergoing 12 weeks of ESA treatment and presumed to be at increased risk of mortality through 16 weeks. A 4-week cycle (without mid-cycle correction) was used. Other relevant features of the model are described in Chapter 4. Calculations were performed using Excel®.

Results

Key Question 1

What are the comparative benefits and harms of erythropoiesis-stimulating agent (ESA) strategies and non-ESA strategies to manage anemia in patients undergoing chemotherapy or radiation for malignancy (excluding myelodysplastic syndrome and acute leukemia)? Outcomes of interest include overall survival (on study and longest available follow-up), progression free survival, quality of life, hematologic responses, transfusions, tumor response to therapy, thromboembolic complications, and other adverse events. Specific comparisons to be included are:

1. Epoetin alfa or beta versus no ESA;
2. Darbepoetin versus no ESA;
3. Epoetin alfa or beta or darbepoetin versus no ESA; and
4. Epoetin alfa or beta versus darbepoetin.

Organization of Results for Key Question 1

First, an overview of results for all outcomes is presented (Table 5 though Table 13). A detailed tabular listing of trials reporting one or more outcomes is then provided (Table 14); the reader is referred there for specific trials included in each pooled result. Next, for each outcome and comparison, characteristics of included trials are summarized and results detailed. Changes in trials included compared to the previous review are outlined (Appendix Table E1). When relevant, sensitivity analyses were performed to account for any trials excluded here, but included in the 2006 review. Quality of life and survival outcomes play central roles in understanding relative benefit and harms, and contain some differences from the prior report; each section accordingly includes discussion of methodologic underpinnings and considerations. In addition to meta-analyses of survival outcomes, relevant published meta-analytical results are appraised and reviewed.

Overview of Evidence and Findings for KQ1

Evidence from three groups of trials were summarized and analyzed (for complete study details, refer to Appendix C). Five trials compared darbepoetin to epoetin (pooled N=1,080 randomized to darbepoetin, N=989 to epoetin); 40 trials compared epoetin to control (pooled N=5,959 randomized to epoetin, N=5,417 to control)[*];and 7 trials compared darbepoetin (pooled N=1,654 randomized to darbepoetin, N=1,520 to control). Trials characteristics differed with respect to: primary and secondary endpoints, reported outcomes, types of malignancies, baseline Hb, duration, treatment protocols (e.g., frequency of administration and amount, and iron supplementation), publication type, and quality ratings (Table 15). Reported target Hb levels ranged from 11.5 g/dL to 14 g/dL (mean 12.6 g/dL), but was in only one trial lower than 12 g/dL and in two trials higher than 13 g/dL. Three trials comparing epoetin to control (N=286 total) enrolled pediatric patients (80-82).

[*] There were 11,536 patients randomized, but 160 were not evaluated and so were not included in any pooling.

Major findings are summarized in Table 5 though Table 13.

Table 5. Overview: hematologic response

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Number of trials	2	16	2	18
Patients analyzed	464	3,862	593	4,455
Pooled RR	0.73	3.5	3.3	3.4
(95% CI)	(0.61, 0.87)	(2.7, 4.4)	(2.4, 4.4)	(2.8, 4.2)
I^2	0%	78%	0%	68%

Table 6. Overview: proportion transfused

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Number of trials	5	28	5	33
Patients analyzed	2,005	7,136	1,866	9,002
Pooled RR	1.14	0.60	0.58	0.60
(95% CI)	(0.82, 1.59)	(0.54, 0.67)	(0.51, 0.66)	(0.55, 0.66)
I^2	43%	58%	0%	48%

Table 7. Overview: overall survival

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Number of trials	2	37	7	44
Patients analyzed	1,567	11,145	3,162	14,307
Pooled HR	0.90	1.04[a]	1.04	1.04[ab]
(95% CI)	(0.67, 1.20)	(0.97, 1.11)	(0.93, 1.16)	(0.98, 1.10)
I^2	72%	32%	50%	37%

[a] Excluding the single trial enrolling pediatric patients did not alter the estimate
[b] Estimate in Bayesian random effects model of 1.01 (95% CrI: 0.96, 1.06)

Table 8. Overview: on-study mortality

	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Number of trials	31	6	37
Patients analyzed	8,859	2,648	11,307
Pooled HR	1.19[a]	1.05[b]	1.16[c]
(95% CI)	(1.04, 1.36)	(0.80, 1.38)	(1.03, 1.31)
I^2	0%	0%	0%

[a] Estimate in Bayesian random effects model of 1.16 (95% CrI: 1.01, 1.33)
[b] Estimate in Bayesian random effects model of 1.11 (95% CrI: 0.77, 1.61)
[c] Estimate in Bayesian random effects model of 1.15 (95% CrI: 1.01, 1.29)

Table 9. Overview: progression-free survival

21 trials reported some outcome related to disease progression; 3 reported significant differences in disease-free or progression-free survival, one trial in favor of epoetin and two in favor of control

Table 10. Overview: thromboembolic events

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Number of trials	3	29	5	34
Patients analyzed	1,873	8,905	2,155	11,060
Pooled RR	0.86	1.49	1.55	1.50
(95% CI)	(0.61, 1.21)	(1.25, 1.78)	(1.15, 2.08)	(1.29, 1.75)
I^2	0%	0%	0%	0%

Table 11. Overview: health-related quality of life

	Epoetin or Darbepoetin vs. Control
Number of trials	14
Patients analyzed	3,643
Mean Difference for Change Fact Fatigue Score	2.72
(95% CI)	(1.69, 3.74)
I^2	41%

Table 12. Overview: tumor response and progression

	Epoetin or Darbepoetin vs. Control
Number of trials	13
Patients	5,034
Tumor Response or Progression	No evidence of an association with ESAs; results not pooled due to heterogeneous outcome definitions

Table 13. Overview: other adverse events

	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Hypertension			
Number of trials	12	3	15
Patients analyzed	2,538	1,297	3,835
Pooled relative risk	1.59	1.31	1.46
(95% CI)	(1.01, 2.53)	(0.79, 2.18)	(1.04, 2.05)
I^2	0%	0%	0%
Thrombocytopenia/Hemorrhage			
Number of trials	9	1	10
Patients analyzed	1,798	301	2,395
Pooled relative risk	1.02	1.55	1.16
(95% CI)	(0.78, 1.33)	(1.07, 2.26)	(0.91, 1.48)
I^2	0%	N/A	8%
Rash			
Number of trials	2	–	–
Patients analyzed	1,043	–	–
Pooled relative risk	1.86	–	–
(95% CI)	(0.82, 4.23)	–	–
I^2	9%	–	–
Seizures			
Number of trials	3	2	5
Patients analyzed	604	983	1,587
Pooled relative risk	1.49	0.88	0.93
(95% CI)	(1.45, 4.87)	(0.14, 5.41)	(0.43, 2.04)
I^2	0%	54%	0%

Table 14. Trials contributing evidence to specific outcomes and comparisons

Medication	Study	Hematologic Response	Transfusion Rates	Overall Survival	On Study Mortality	Progression Free Survival	Tumor Response	Thromboembolic Events	QoL FACT-Fatigue	Adverse Events HTN	Adverse Events Thrombocytopenia	Adverse Events Rash	Adverse Events Seizure	Full Text	Abstract	FDA Documents	IPD[a]
Epoetin beta	Aapro 2008	•	•	•	•	•		•						◦			◦
Epoetin	Antonadou 2001			•		•									◦		
Epoetin alfa	Bamias 2003	•	•	•	•			•		•	•			◦			
Epoetin alfa	Blohmer 2004		•	•			•	•							◦	◦	
Epoetin beta	Boogaerts 2003, Coiffier 2001	•	•	•	•				•		•			◦			◦
Epoetin alfa	Case 1993	•	•	•	•			•		•			•	◦		◦	◦
Epoetin alfa	Chang 2005	•	•	•	•			•	•					◦			◦
Epoetin alfa	Christodoulou 2009, Janinis 2003		•	•					•					◦			
Epoetin alfa	Dammacco 2001	•	•	•	•			•		•	•			◦		◦	◦
Epoetin alfa	Debus 2006			•	•		•	•								◦	◦
Epoetin alfa	Engert 2009, Engert 2010			•		•	•	•						◦	◦		
Epoetin alfa	EPO-INT-1			•	•			•							◦	◦	◦
Epoetin alfa	EPO-INT-3		•	•	•			•								◦	◦
Epoetin alfa	Goss 2005, EPO-CAN-15		•	•	•	•	•	•			•				◦	◦	◦
Epoetin alfa	Grote 2005, N03-004		•	•	•	•		•						◦		◦	◦
Epoetin beta	Gupta 2009		•	•			•	•			•	•		◦			
Epoetin beta	Henke 2003			•	•	•	•	•						◦		◦	◦
Epoetin alfa	Henry 1995	•	•	•	•			•		•		•	•	◦		◦	◦
Epoetin alfa	Hoskin 2009, EPO-GBR-7			•	•		•	•	•	•				◦		◦	◦
Epoetin alfa	Iconomou 2003	•	•						•	•				◦			
Epoetin alfa	Leyland-Jones 2005; Leyland-Jones 2003		•	•	•	•		•						◦		◦	◦
Epoetin alfa	Littlewood 2001	•	•	•	•			•	•	•	•			◦		◦	◦
Epoetin alfa	Machtay 2007, Machtay 2004			•	•	•	•	•						◦			◦
Epoetin alfa	Moebus 2007		•	•	•	•	•	•						◦		◦	◦
Epoetin alfa	Milroy 2003			•	•										◦		◦
Epoetin beta	ML17620	•		•	•										◦		
Epoetin beta	Oberhoff 1998	•	•	•	•									◦			◦

Medication	Study	Hematologic Response	Transfusion Rates	Overall Survival	On Study Mortality	Progression Free Survival	Tumor Response	Thromboembolic Events	QoL FACT-Fatigue	Adverse Events HTN	Adverse Events Thrombocytopenia	Adverse Events Rash	Adverse Events Seizure	Full Text	Abstract	FDA Documents	IPD[a]
Epoetin beta	Osterborg 2002, Osterborg 2005	•	•	•	•	•		•	•	•		•		◦			◦
Epoetin alfa	Porter 1996		•														
Epoetin alfa	Pronzato 2002			•	•										◦		◦
Epoetin alfa	Ray-Coquard 2009		•	•	•	•		•						◦			◦
Epoetin alfa	Razzouk 2006; Razzouk 2004	•	•	•	•			•		•				◦			◦
Epoetin alfa	Rose 1994	•	•	•	•			•		•					◦	◦	◦
Epoetin alfa	Savonije 2005; Savonije 2004	•	•	•	•			•	•	•	•		•	◦			◦
Epoetin alfa	Thomas 2002		•	•	•										◦		◦
Epoetin alfa	Thomas 2008, GOG-0191			•	•	•	•	•						◦		◦	◦
Epoetin beta	Tsuboi 2009		•	•				•	•	•	•	•		◦			
Epoetin alfa	Wagner 2004						•							◦			
Epoetin alfa	Wilkinson 2006		•	•	•	•		•		•				◦			◦
Epoetin alfa	Witzig 2005	•	•	•	•	•		•	•		•	•		◦		◦	◦
Darbepoetin alfa	Hedenus 2003	•	•	•	•			•	•					◦		◦	◦
Darbepoetin alfa	Hernandez 2009		•	•	•			•		•			•	◦			◦
Darbepoetin alfa	Kotasek 2003	•	•	•	•				•					◦			◦
Darbepoetin alfa	Overgaard 2009			•		•		•							◦		
Darbepoetin alfa	Pirker 2008		•	•	•	•		•	•	•	•		•	◦			◦
Darbepoetin alfa	Untch 2008			•	•	•									◦		◦
Darbepoetin alfa	Vansteenkiste 2002		•	•	•			•	•	•				◦		◦	◦
Epoetin/Darbepoetin	Glaspy 2002	•	•														
Epoetin/Darbepoetin	Glaspy 2006, Glaspy 2005	•	•	•													
Epoetin/Darbepoetin	Kotsori 2006		•														
Epoetin/Darbepoetin	Schwartzberg 2004	•	•				•										
Epoetin/Darbepoetin	Waltzman 2005	•	•	•			•										

[a] Data for overall and on-study mortality from Bohlius et al. (58).

Table 15. Summary characteristics of the 52 trials included in Key Question 1

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Trials	5	40	7	47
Patients				
Treatment	1,016	5,837	1,646	7,483
Comparator	989	5,293	1,516	6,809
Mean Age Range[a]				
Treatment	57.8-63.7	3.2-68.3	49-64.8	3.2-68.3
Comparator	58.7-63.4	3.2-68.1	48-64.6	3.2-68.1
Trial Quality n (%)				
High	0 (0)	16 (40)	5 (71.4)	21 (44.7)
Low	5 (100)	24 (60)	2 (28.6)	26 (55.3)
Treatment Modality n (%)				
Chemotherapy	5 (100)	30 (75)	6 (85.7)	36 (76.6)
Includes Platinum	3 (60)	24 (60)	4 (57.1)	28 (59.6)
Radiotherapy	0 (0)	4 (10)	1 (14.3)	5 (10.6)
Chemoradiotherapy	0 (0)	6 (15)	0 (0)	6 (12.8)
Dose Escalation n (%)				
Allowed	0 (0)	16 (40)	2 (28.6)	18 (38.3)
Not allowed	5 (100)	19 (47.5)	4 (57.1)	23 (48.9)
Unknown	0 (0)	5 (12.5)	1 (14.3)	6 (12.8)
Iron n (%)				
As necessary	0 (0)	27 (67.5)	5 (71.4)	32 (68.1)
Other including fixed	1 (20)	10 (25)	2 (28.6)	12 (25.5)
Not reported	4 (80)	3 (7.5)	0 (0)	3 (6.4)
Tumor Type n (%)				
Solid	4 (80)	26 (65)	5 (71.4)	31 (66)
Mixed	1 (20)	8 (20)	1 (14.3)	9 (19.1)
Hematologic	0 (0)	4 (10)	1 (14.3)	5 (10.6)
Baseline Hb g/dL	9.9-10.4	8.8-13.7	9.5-14	8.8-14
Therapy Duration (weeks)	8-16	4-52	9-23	4-52

[a] Average of reported means or medians

KQ1 Hematologic Response

Hematologic response was defined as the proportion of patients demonstrating a hemoglobin increase ≥2 g/dL. In the 20 included trials, baseline hemoglobin levels ranged from 9.0 to 11.5 g/dL (mean 10.0 g/dL). Data from the seven trials using different definitions of hematologic response are reported in Appendix Tables C7–C9, but were not pooled. Table 16 summarizes characteristics of included trials.

Table 16. Summary of characteristics for trials included in analysis of hematologic response

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Trials	2	16	2	18
Patients				
Treatment	236	2,092	372	2,464
Comparator	228	1,770	221	1,991
Mean Age Range[a]				
Treatment	57.8-62.1	12.4-68.3	58.3-64.8	12.4-68.3
Comparator	61.9-63.4	10.8-68.1	56.2-64.6	10.8-68.1
Trial Quality n (%)				
High	0 (0)	8 (50)	2 (100)	8 (44.4)
Low	2 (100)	8 (50)	0 (0)	10 (55.6)
Treatment Modality n (%)				
Chemotherapy	2 (100)	16 (100)	2 (100)	18 (100)
Includes Platinum	1 (50)	9 (56.2)	1 (50)	10 (55.6)
Radiotherapy	0 (0)	0 (0)	0 (0)	0 (0)
Chemoradiotherapy	0 (0)	0 (0)	0 (0)	0 (0)
Dose Escalation n (%)				
Allowed	0 (0)	6 (37.5)	1 (50)	7 (38.9)
Not allowed	2 (100)	8 (50)	1 (50)	9 (50)
Unknown	0 (0)	2 (12.5)	0 (0)	2 (11.1)
Iron n (%)				
As necessary	0 (0)	12 (75)	2 (100)	14 (77.8)
Other including fixed	1 (50)	3 (18.8)	0 (0)	3 (16.7)
Not reported	1 (50)	1 (6.2)	0 (0)	1 (5.6)
Tumor Type n (%)				
Solid	2 (100)	7 (43.8)	1 (50)	8 (44.4)
Mixed	0 (0)	5 (31.2)	0 (0)	5 (27.8)
Hematologic	0 (0)	3 (18.8)	1 (50)	4 (22.2)
Baseline Hb g/dL	9.9-10.16	9-11.5	9.5-9.9	9-11.5
Therapy Duration (weeks)	12-14	12-28	12	12-28

[a] Average of reported means or medians

Darbepoetin versus Epoetin. Two trials (83, 84) compared hematologic response rates as defined in this review between patients randomized to darbepoetin or epoetin (Appendix Table C9). Both trials were unblinded and judged of poor quality. Glaspy et al. (85) and Waltzman et al. (86) used different dose adjustments in the darbepoetin and epoetin arms; three trials (Table 17) initiated darbepoetin at a dose of 200 mcg every 2 weeks and epoetin at 40,000 IU/week (83, 86, 87). No trial included a control arm. Only Waltzman et al. (86) described any supplemental iron administration. Study results are summarized in Table 17.

Table 17. Study characteristics and results of trials directly comparing hb response rates for darbepoetin versus epoetin

Trial	Darbepoetin	Epoetin	Response ≥2 g/dL	Response Rate Darbepoetin N (%)	Response Rate Epoetin N (%)	RR (95% CI)
	200 mcg once per 2 weeks	40,000 IU once weekly				
Waltzman 2005[a,b]	177	175	yes	74 (41.8)	101 (57.7)	0.72 (0.58, 0.90)
Glaspy 2006	606	603	no[c]	463 (76.4)	487 (80.8)	0.95 (0.89, 1.00)
Schwartzberg 2004	157	155	no[d]	109 (69.4)	112 (72.3)	0.96 (0.83, 1.11)
	Other Doses	Other Doses				
Glaspy 2002 A[a,e]	59	53	yes	31 (52.5)	38 (71.7)	0.73 (0.55, 0.98)

[a] Arms differed in dose adjustment for inadequate response.
[b] Waltzman 2005 patients with <1 g/dL Hb rise from baseline had 1.5-fold dose increase at week 6 if randomized to darbepoetin (from 200 to 300 mcg q2W), but at week 4 if randomized to epoetin (from 40,000 to 60,000 IU/week).
[c] Glaspy 2006 defined response as reaching Hb >11 g/dL and remaining between 11 and 13 g/dL, results from Glaspy 2005 abstract darbepoetin 90.3% (95% CI: 87.5%, 93.1%), epoetin 95.5% (95% CI: 93.6%, 97.4%).
[d] Schwartzberg 2004 defined response as reaching Hb >12 g/dL or increasing by 2 g/dL from baseline to end of study.
[e] Glaspy 2002A compared arms given 2.25 mcg/kg darbepoetin QW versus epoetin alfa 150 IU/kg TIW (arm d); dose increase for inadequate Hb response only permitted for epoetin arm. (Results derived from a figure and were calculated from the percentages reported; randomization of the darbepoetin arms was not clearly stated.)

Results. Fewer patients randomized to darbepoetin experienced ≥2 g/dL improvement in Hb in the two trials employing the response definition—pooled RR 0.73 (95 percent CI: 0.61, 0.87; I^2=0 percent). For all four trials, using response definitions from each trial, the pooled RR of response comparing darbepoetin to epoetin was 0.88 (95 percent CI: 0.77, 1.00; I^2=65 percent).

Hematologic response of ≥2 g/dL increase, or as variously defined in the trials, was less frequent in the darbepoetin-treated arms. However, the trials and results are accompanied by clinical variability owing to differing doses and dosing adjustment strategies, both between trials and arms. Accounting for any influence of dose-adjustment strategy (a time-varying treatment induced by Hb as a time-varying confounder) requires analytical methods not applied in any trial (88). These results are not consistent with differences between drugs in achieving hematologic response.

Changes from 2006 review. Two trials from the previous review were excluded, three trials included unchanged (two with a different definition of response and not pooled), and one new trial identified (Appendix Table E1). Table 18 compares current results to sensitivity analysis with two excluded trials.

Table 18. Hematologic response results darbepoetin versus epoetin—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Darbepoetin vs. Epoetin N	Control N	RR (95% CI)	I^2
Current	2	236	228	0.73 (0.61, 0.87)	0%
Current & Excluded	4	999	986	0.88 (0.77, 1.00)	65%
2006 review	NR	NR	NR	NR	NR

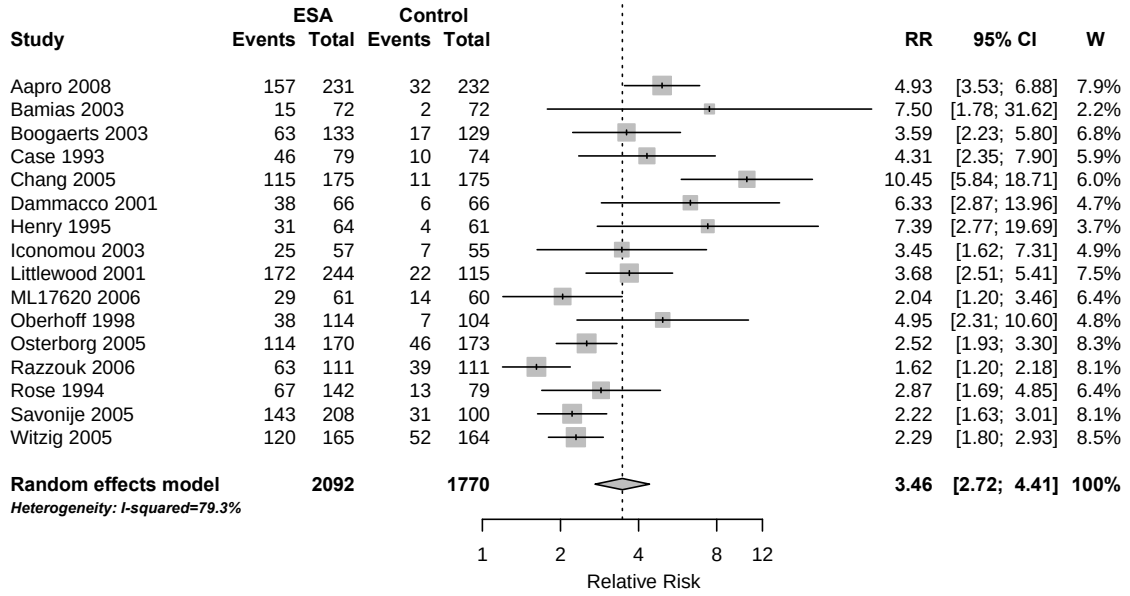
NR—not reported

Epoetin versus Control. Sixteen trials (Table 14) compared hematologic response rates (≥2 g/dL) between patients randomized to epoetin (N=3,862) or control (N=1,770). Trial characteristics varied as summarized in Table 16, including antineoplastic therapies and dose escalation. Eight trials were judged of low quality due primarily to lack of blinding. Individual trial characteristics are detailed in Appendix Table C7.

Results. More patients randomized to epoetin experienced ≥2 g/dL Hb improvement compared to control—pooled RR 3.5 (95 percent CI: 2.7, 4.4; I^2=78 percent). Heterogeneity (Figure 8) was consistent with the varied trial characteristics. In meta-regressions trial quality, blinding, baseline Hb, or iron use did not meaningfully account for the heterogeneity (e.g., decreasing I^2 or was a significant covariate). Five trials employed different response definitions (results summarized in Appendix Table C10) (89-93).

Hematologic response ≥2 g/dL was more frequent in the epoetin treated than control arms of included trials. While heterogeneity accompanied the pooled estimates, trials consistently demonstrated higher response rates with epoetin. These results are consistent with superiority of epoetin to a transfusion strategy achieving a ≥2 g/dL hematologic response.

Figure 8. Forest plot—hematologic response epoetin versus control



Changes from 2006 review. Two trials from the previous review were excluded, 12 trials were included unchanged, data were updated for one trial, and three new trials were identified (Appendix Table E1). Table 19 compares current results with the 2006 review and sensitivity analysis with the excluded trials.

Table 19. Hematologic response results epoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Epoetin N	Control N	RR (95% CI)	I^2
Current	16	2,092	1,770	3.5 (2.7, 4.5)	79%
Current & Excluded	18	2,244	1,848	3.5 (2.7, 4.5)	78%
2006 review	15	1,844	1,449	3.4 (3.0, 3.9)	66%

Darbepoetin versus Control. Two trials (Table 14) compared hematologic response rates (≥2 g/dL) between patients randomized to darbepoetin (N=372) or control (N=221). Kotasek et al. (94) examined six doses. Except for dosing, characteristics of the two trials were generally similar (Table 20).

Results. More patients randomized to darbepoetin experienced ≥2 g/dL improvement in Hb compared to control—pooled RR 3.3 (95 percent CI: 2.4, 4.6; I^2=0 percent). Outcomes from two trials (95, 96) defining response differently (Appendix Table C11) were consistent with a similar clinical effect improving Hb for darbepoetin compared to control.

Changes from 2006 review. One trial from the previous review was excluded, two trials were included unchanged, and no new trials were identified (Appendix Table E1). Table 25 shows similar current results with the 2006 review and sensitivity analysis with the excluded trial.

Table 20. Hematologic response results darbepoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Darbepoetin N	Control N	RR (95% CI)	I^2
Current	2	372	221	3.28 (2.41, 4.45)	0%
Current & Excluded	3	427	232	3.33 (2.46, 4.51)	0%
2006 review	3	427	232	3.36 (2.48, 4.56)	0%

KQ1 Proportion Transfused

Transfusion risk was examined as the proportion of patients transfused at least once during the trial.

Darbepoetin versus Epoetin. Five trials (83, 85-87, 97) compared transfusion risk between patients randomized to darbepoetin or epoetin. All trials were unblinded and judged of poor quality. Schwartzberg et al. (87) randomized patients with breast, lung, and gynecologic tumors independently; results were reported separately and accordingly pooled. Glaspy et al. (85) evaluated multiple darbepoetin doses in a dose-finding study, and results for 2.25 mcg/kg every week were included in the main analysis; sensitivity analyses performed including all results were not different. No trial included a control arm. Trial characteristics are summarized in Table 21 and detailed in Appendix Tables C1–6.

Table 21. Summary of characteristics for trials included in analysis of proportion transfused

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Trials	5	28	5	33
Patients				
Treatment	1,016	3,790	1,002	4,792
Comparator	989	3,346	864	4,210
Mean Age Range[a]				
Treatment	57.8-63.7	12.4-68.3	58.3-64.8	12.4-68.3
Comparator	58.7-63.4	10.8-68.1	56.2-64.6	10.8-68.1
Trial Quality n (%)				
High	0 (0)	13 (46.4)	5 (100)	18 (54.5)
Low	5 (100)	15 (53.6)	0 (0)	15 (45.5)
Treatment Modality n (%)				
Chemotherapy	5 (100)	24 (85.7)	5 (100)	29 (87.9)
Includes Platinum	3 (60)	17 (60.7)	4 (80)	21 (63.6)
Radiotherapy	0 (0)	0 (0)	0 (0)	0 (0)
Chemoradiotherapy	0 (0)	4 (14.3)	0 (0)	4 (12.1)
Dose Escalation				
Allowed	0 (0)	12 (42.9)	1 (20)	13 (39.4)
Not allowed	5 (100)	14 (50)	4 (80)	18 (54.5)
Unknown	0 (0)	2 (7.1)	0 (0)	2 (6.1)
Iron n (%)				
As necessary	0 (0)	20 (71.4)	4 (80)	24 (72.7)
Other including fixed	1 (20)	7 (25)	1 (20)	8 (24.2)
Not reported	4 (80)	1 (3.6)	0 (0)	1 (3)
Tumor Type n (%)				
Solid	4 (80)	15 (53.6)	3 (60)	18 (54.5)
Mixed	1 (20)	8 (28.6)	1 (20)	9 (27.3)
Hematologic	0 (0)	3 (10.7)	1 (20)	4 (12.1)
Baseline Hb g/dL	9.9-10.4	9-13.5	9.5-12.03	9-13.5
Therapy Duration (weeks)	8-16	7-52	12-19	7-52

[a] Average of reported means or medians

Results. More patients randomized to darbepoetin received one or more transfusions—pooled RR 1.1 (95 percent CI: 0.82, 1.6; I^2=43 percent); including all comparisons from Glaspy et al. (85) yielded a similar estimate—RR 1.1 (95 percent CI: 0.82, 1.5; I^2=35 percent). Similar to results for hemoglobin response, analytical methods applied in these trials did not account for dose-adjustment strategies. Results are consistent with no difference between agents in risk for transfusion.

Changes from 2006 review. One trial from the previous review was excluded, three trials were included unchanged, data were updated for one trial, and one new trial was identified (Appendix Table E1). Table 22 compares current results with the 2006 review and sensitivity analysis with the excluded trial.

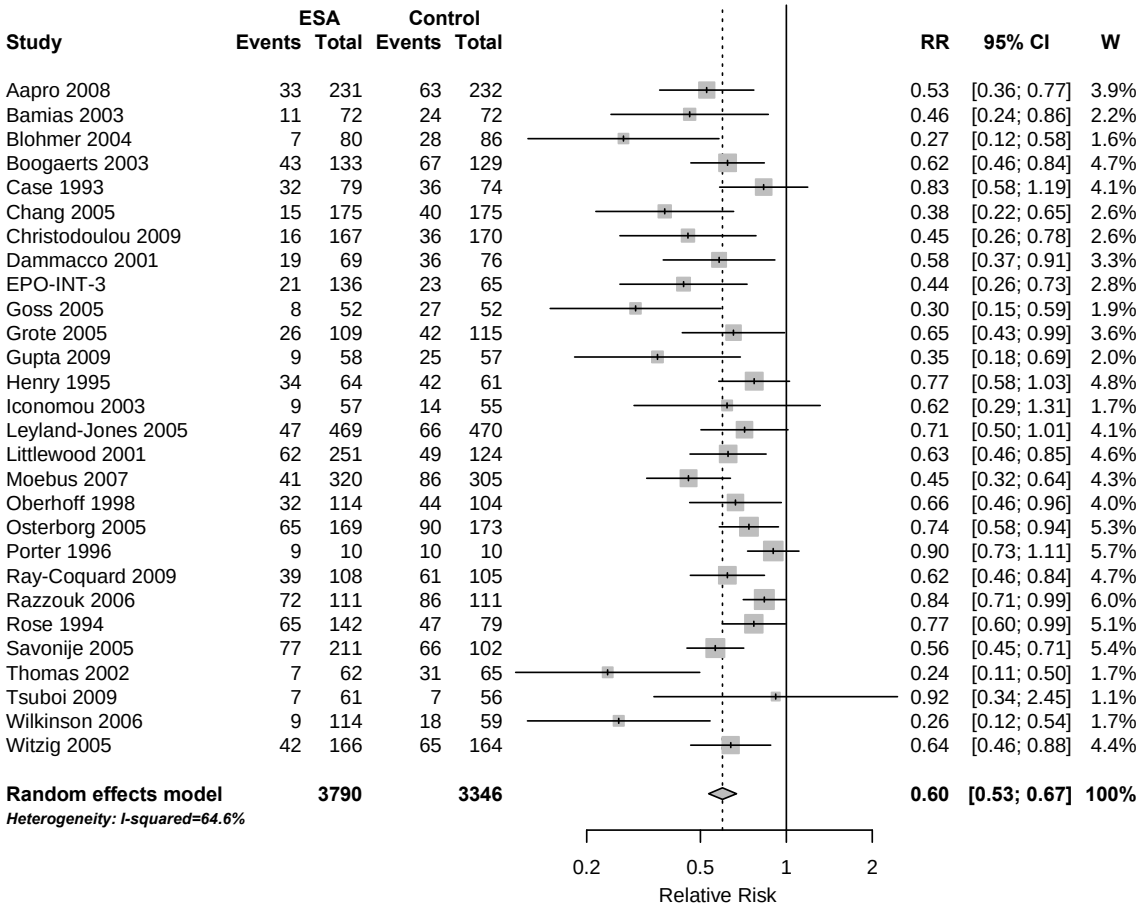
Table 22. Proportion receiving ≥1 transfusion darbepoetin versus epoetin—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Darbepoetin N	Epoetin N	RR (95% CI)	I^2
Current	5	1,016	989	1.14 (0.82, 1.59)	43%
Current & Excluded	6	1,041	1,014	1.16 (0.85, 1.56)	34%
2006 review	6	1,169	989	1.10 (0.93, 1.29)	43%

Epoetin versus Control. Twenty-eight trials comparing transfusion between patients randomized to epoetin (N=3,790) or control (N=3,346) were included (Table 14). Half the trials were unblinded and 15 were judged to be low quality. Trial characteristics varied in other respects, including chemotherapeutic agents, dose adjustment protocols, and transfusion triggers (mean 8.3 g/dL, as high as 10 g/dL, nine trials including physician discretion).

Results. Fewer patients randomized to epoetin received one or more transfusions—pooled RR 0.60 (95 percent CI: 0.53, 0.67; I^2=58 percent). Heterogeneity displayed in the forest plot (Figure 9) is consistent with varied trial characteristics. The results are consistent with superiority of epoetin over a transfusion strategy for avoiding transfusion. The data do not allow estimating the number of transfusions avoided.

Figure 9. Forest plot ≥1 transfusion: epoetin versus control



Changes from 2006 review. Eighteen trials from the previous review were excluded, 14 trials were included unchanged, data were updated for two trials, and 12 new trials were identified (Appendix Table E1). Table 23 compares current results with the 2006 review and sensitivity analysis with excluded trials—all are similar.

Table 23. Proportion receiving ≥1 transfusion: epoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Epoetin N	Control N	RR (95% CI)	I^2
Current	28	3,790	3,346	0.59 (0.53, 0.67)	62%
Current & Excluded	46	4,584	3,940	0.57 (0.51, 0.63)	67%
2006 review	34	2,859	2,351	0.63 (0.59, 0.67)	63%

Darbepoetin versus Control. Five trials comparing transfusion between patients randomized to darbepoetin (N=1,866) or control (N=864) were included (Table 14). Kotasek et al. (94) examined six doses. While the trials were blinded and judged to be high quality, other characteristics varied. Transfusion triggers were specified as 8 g/dL in three trials (also allowing physician discretion) but not reported in the others.

Results. Fewer patients randomized to darbepoetin received one or more transfusions—pooled RR 0.58 (95 percent CI: 0.51, 0.66; I^2=0 percent).

Changes from 2006 review: One trial was excluded, three trials were included unchanged, and two new trials were identified (Appendix Table E1). Table 24 compares current results with the 2006 review and sensitivity analysis with the excluded trial.

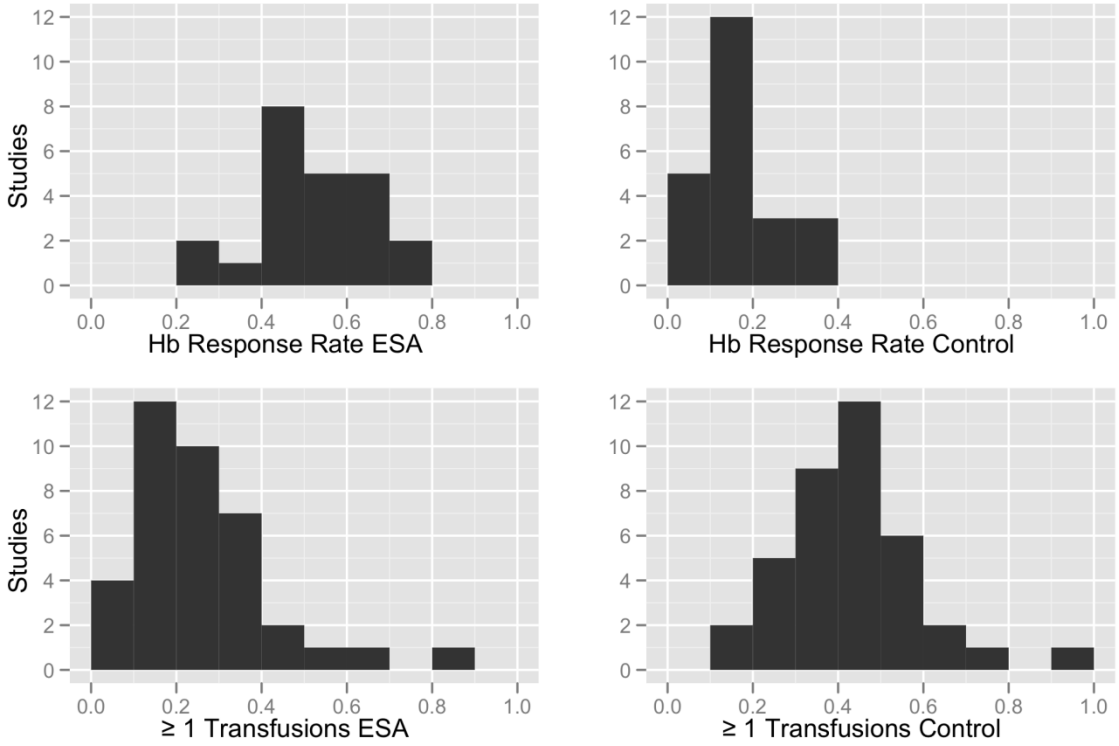
Table 24. Proportion receiving ≥1 transfusion: darbepoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Epoetin N	Control N	RR (95% CI)	I^2
Current	5	1,002	864	0.58 (0.51, 0.66)	0%
Current & Excluded	6	1,057	875	0.58 (0.51, 0.66)	0%
2006 review	4	566	384	0.61 (0.52, 0.72)	0%

Hematologic Outcomes—Class of Erythropoietic-Stimulating Agents. Considering all ESA trials, pooled effects indicate that these agents improve Hb (pooled RR 3.4; 95 percent CI: 2.8, 4.2; I^2=68 percent; 18 trials) and result in fewer transfusions (pooled RR 0.60; 95 percent CI: 0.55, 0.66; I^2=48 percent; 33 trials). The consistency of these corresponding relationships is illustrated in Figure 10. Still, these agents decrease but do not eliminate the risk of receiving transfusions.

The pooled proportions receiving ≥1 transfusion with ESA treatment was 0.25 (95 percent CI: 0.21, 0.30; I^2=92 percent) compared to control of 0.43 (95 percent CI; 0.38, 0.49; I^2=93 percent); respective pooled proportions experiencing Hb response were 0.54 (95 percent CI: 0.48, 0.60; I^2=87 percent) 0.16 (95 percent CI: 0.12, 0.21; I^2=82 percent).

Figure 10. Hb response rates and proportions receiving ≥1 transfusion in treated and control arms of included trials (18 trials of Hb response; 33 trials of transfusion risk)



Finally, while these results are highly consistent, they are based on a clinically heterogeneous collection of trials. To explore that heterogeneity, we examined trial characteristics that might modify pooled estimates for transfusion risk (Table 25). Only transfusion risk was examined, both for its clinical relevance and because just over half the trials reported Hb response. The proportion receiving ≥1 transfusion estimates varied by baseline Hb, trial quality, blinding, use of platinum-based chemotherapy, and iron administration. In a model including all these covariates, each modified the effect. These results are consistent with a notion that physician judgment influenced transfusion policies in these trials and probably more so in unblinded ones.

Table 25. Relative risks from single covariate meta-regressions—transfusion risk

Covariate	RR (95% CI)	p-value
Dose Escalation		
Yes	0.59 (0.50, 0.69)	0.70
No	0.61 (0.47, 0.79)	
Iron		
All other	0.49 (0.42, 0.58)	0.005
As necessary	0.60 (0.50, 0.84)	
Platinum-Base Chemotherapy		
Yes	0.68 (0.61, 0.77)	0.007
No	0.55 (0.45, 0.67)	
Baseline Hb		
>10 g/dL	0.72 (0.66, 0.79)	<.0001
≤10 g/dL	0.50 (0.42, 0.60)	
Study Duration		
≤12 weeks	0.69 (0.52, 0.93)	0.30
>12 weeks	0.63 (0.44, 0.89)	
Trial Quality		
Low	0.53 (0.46, 0.61)	0.025
High	0.65 (0.52, 0.82)	
Blinding		
Yes	0.67 (0.61, 0.74)	<.0001
No	0.50 (0.41, 0.61)	

Evidence GRADE. The evidence shows a class effect for ESAs reducing the proportion of patients receiving transfusions (overall strength of evidence moderate, Table 26).

Table 26. Risk of transfusion: ESA versus control (GRADE evidence table)

Trials (N)	Subjects (N)	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results RR (95% CI); I^2
33	9,002	Medium trial quality: high-18; low-15	Consistent	Direct	Precise	0.60 (0.55, 0.66); 48%

The evidence does not show any meaningful difference between epoetin and darbepoetin in the proportion of patients receiving transfusion (overall strength of evidence moderate, Table 27).

Table 27. Risk of transfusion: darbepoetin versus epoetin (GRADE evidence table)

Trials (N)	Subjects (N)	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results RR (95% CI); I^2
5 Darbepoetin vs. Epoetin	2,005	Medium trial quality high-0; low-5	Consistent	Direct/ Indirect[a]	Precise	1.14 (0.82, 1.59); 43%
28 Epoetin vs. Control	7,136	Medium trial quality: high-13; low-15	Consistent	Direct	Precise	0.59 (0.53, 0.67); 62%
5 Darbepoetin vs. Control	1,866	High trial quality: high-5; low-0	Consistent	Direct	Precise	0.58 (0.51, 0.66); 0%

[a] 5 trials and 2,005 participants direct evidence; similar effect magnitudes for darbepoetin vs. control and epoetin vs. control in table constitute indirect evidence

Survival Outcomes

We evaluated survival from two perspectives—"overall survival" and "on-study mortality." Overall survival was defined as survival over the longest available follow-up; on-study mortality as mortality ascertained during, and up to 1 month following, ESA treatment. Although important, limitations accompany the overall survival outcome: 1) fewer than half the trials included an overall survival endpoint and detailed a survival analyses; 2) over the longer term during post-treatment follow-up, many nonrandom interventions affect survival (i.e., causing a bias to the null or no difference); 3) adverse consequences of ESAs are biologically most plausible during the active treatment period or soon thereafter—not well after treatment is stopped; and 4) different trial durations introduce issues for pooling (discussed below). Mortality during the active study period is therefore of primary interest because it represents a biologically plausible causal effect and less prone to limitations accompanying overall survival.

There are issues to consider when pooling survival results: trials of varying lengths of follow-up; different underlying mortality risks; and some trials lacking deaths in one or both treatment arms. To address these issues, this section is organized as follows. First, sources and important aspects of the evidence are detailed. Next, the approaches to pooling trial results and exploring potential subgroup effects are outlined. Finally, details of included trials and results for overall survival and on-study mortality are presented. Because there are considerably fewer darbepoetin than epoetin trials, pooled results restricted to darbepoetin are necessarily imprecise. Given consistent magnitude of effects and pharmacologic basis for treating ESAs as a class, our focus here as throughout this report is on the class effect.

Overall survival data were abstracted for the longest available follow-up reported—updated or obtained from Bohlius et al. (58) for 27 trials (see Table 14). On-study mortality data were taken primarily from a published individual patient data meta-analysis (58) where on-study mortality was defined "as death from any cause between date of randomization and 28 days after the end of the active study phase." For trials not included in Bohlius et al. (58), data were abstracted as outlined by Parmar et al. (67). Deaths in three trials (98-100) were estimated from the published Kaplan-Meier curves.

There are three methodologic issues to consider when pooling trial survival and mortality results. First, while study duration and active treatment periods varied, combining estimates assumes that follow-up duration did not affect relative effects. This, essentially a proportional

hazards assumption, is unverifiable. Furthermore, if as indicated in other meta-analyses, mortality is increased during the on-study period (58, 101) but not over the long term, then the assumption of constant relative effect (proportional hazards) over longest follow-up may not hold. Second, it can be difficult to examine the relationship between underlying mortality rate or baseline risk (i.e., control arms) and relative risk of mortality with ESA use. The relationship is of interest because current labeling recommends avoiding ESA use in patients undergoing chemotherapy with curative intent—that is, patients with low underlying mortality rates. Examining the relationship between underlying mortality rates and relative effects can be problematic due to their inherent correlation (control mortality rate is used to calculate relative effect). Third, the absence of events in some trial arms, as occurs in these data, can be problematic in standard meta-analyses (102).

Because of these issues yet fundamental importance of mortality effects, these data were analyzed using two approaches. First, from calculated observed and expected events with accompanying variance (67), the pooled hazard ratio was obtained using the Peto method[*] (103). The approach includes trials without events in one arm, but is a fixed-effects estimate. Therefore, the main results were also pooled in Bayesian hierarchical (random-effects) models. This Bayesian approach models events directly (not relative effects) and so appropriately incorporates trials lacking events in one arm. To obtain relative risks (as opposed to odds ratios), we used the approach outlined by Warn et al. (69). The Bayesian model was also used to examine the relationship between underlying risk (control group mortality rate) and relative risk; it appropriately accounts for correlation between relative effect and underlying risk (70). Noninformative priors were specified in these models which were fitted using OpenBUGS (77). Finally, reported or estimated 12- to 16-week mortality rates in the control arms were used to represent underlying mortality risk. Because the most common trial duration was 12 weeks, for those trials longer or shorter we estimated 12-week mortality in the control arm using the relationship between rate, probability, and time (104).

KQ1 Overall Survival

Trials included in overall survival analyses are listed in Table 14 and summary characteristics shown in Table 28. Trials varied in quality, use of iron, tumor types, cancer treatment, baseline Hb, and duration. One trial enrolled pediatric patients (81).

[*] The same method was used in the 2006 review.

Table 28. Summary of characteristics for trials included in analysis of overall survival

	Darbepoetin vs. Epoetin	Epoetin vs. Control[a]	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Trials	2	37	7	44
Patients				
Treatment	791	5,840	1,646	7,486
Comparator	776	5,305	1,516	6,821
Mean Age Range[b]				
Treatment	62.1-63.7	12.4-68.3	49-64.8	12.4-68.3
Comparator	63.2-63.4	10.8-68.1	48-64.6	10.8-68.1
Trial Quality n (%)				
High	0 (0)	16 (43.2)	5 (71.4)	21 (47.7)
Low	2 (100)	21 (56.8)	2 (28.6)	23 (52.3)
Treatment Modality n (%)				
Chemotherapy	2 (100)	28 (75.7)	6 (85.7)	34 (77.3)
Includes Platinum	2 (100)	22 (59.5)	4 (57.1)	26 (59.1)
Radiotherapy	0 (0)	4 (10.8)	1 (14.3)	5 (11.4)
Chemoradiotherapy	0 (0)	5 (13.5)	0 (0)	5 (11.4)
Dose Escalation n (%)				
Allowed	0 (0)	16 (43.2)	2 (28.6)	18 (40.9)
Not allowed	2 (100)	16 (43.2)	4 (57.1)	20 (45.5)
Unknown	0 (0)	5 (13.5)	1 (14.3)	6 (13.6)
Iron n (%)				
As necessary	0 (0)	25 (67.6)	5 (71.4)	30 (68.2)
Other including fixed	1 (50)	9 (24.3)	2 (28.6)	11 (25)
Not reported	1 (50)	3 (8.1)	0 (0)	3 (6.8)
Tumor Type n (%)				
Solid	1 (50)	23 (62.2)	5 (71.4)	28 (63.6)
Mixed	1 (50)	8 (21.6)	1 (14.3)	9 (20.5)
Hematologic	0 (0)	4 (10.8)	1 (14.3)	5 (11.4)
Baseline Hb g/dL	10.1-10.2	9-13.7	9.5-14	9-14
Therapy Duration (weeks)	14-16	4-52	9-23	4-52

[a] Includes one trial of only pediatric patients
[b] Of reported means or medians

Darbepoetin versus Epoetin. Two trials reported overall survival for participants randomized to darbepoetin or epoetin (83, 86). The trials differed in tumor type, although they were otherwise generally similar and judged to be of low quality (Table 28).

Results. Neither trial reported a survival difference; no difference was noted when the trial results were combined—HR 0.90 (95 percent CI: 0.67, 1.20; I^2=72 percent).

Changes from 2006 review. One new trial was identified (Appendix Table E1). Table 29 compares current results with the single trial in the 2006 review.

Table 29. Overall survival darbepoetin versus epoetin—current report and 2006 review

	Trials	Epoetin N	Darbepoetin N	HR (95% CI)	I^2
Current	2	776	791	0.90 (0.67, 1.20)	72%
2006 review	1	180	178	1.34 (0.84, 2.16)	N/A

N/A—not applicable

Epoetin versus Control. Thirty-seven trials (Table 14) reported overall survival in patients randomized to epoetin treatment (N=5,840) or control (N=5,305). Trial characteristics varied considerably as summarized in Table 28 and detailed in Appendix Table C1. One trial included pediatric patients (81); 10 trials included only women with gynecologic and/or breast cancers.

Results. There was no detectable increased risk accompanying epoetin use—HR 1.04 (95 percent CI: 0.97, 1.11; I^2=32 percent). The relative hazard excluding the single trial in pediatric patients was unchanged.

Changes from 2006 review: Thirteen trials were excluded, 1 trial was included unchanged, data were updated for 21 trials, and 15 new trials were identified (Appendix Table E1). Table 30 compares current results with the 2006 review and sensitivity analysis with the excluded trials.

Table 30. Overall survival epoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Epoetin N	Control N	HR (95% CI)	I^2
Current	37	5,840	5,305	1.04 (0.97, 1.11)	32%
Current & Excluded	50	6,467	5,694	1.03 (0.97, 1.10)	27%
2006 review	35	3,825	3,093	1.11 (1.00, 1.22)	48%

Darbepoetin versus Control. Overall survival was reported in seven trials (Table 14) for patients randomized to darbepoetin treatment (N=1,646) or control (N=1,516). Similar to epoetin trials, characteristics varied (Table 28), none included pediatric patients and one included only women with breast cancer (36). Five trials were designed for long-term follow-up of at least 12 months (96, 105-108).

Results. Similar to epoetin, there was no detectable increased relative risk in darbepoetin treated patients—pooled HR 1.04 (95 percent CI: 0.93, 1.16; I^2=50 percent).

Changes from 2006 review. One trial from the previous review was excluded, three trials were included unchanged, and four new trials were identified (Appendix Table E1). Table 31 compares current results with the 2006 review and sensitivity analysis with the excluded trials.

Table 31. Overall survival darbepoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Darbepoetin N	Control N	HR (95% CI)	I^2
Current	7	1,646	1,516	1.04 (0.93, 1.16)	50%
Current & Excluded	8	1,701	1,571	1.04 (0.93, 1.16)	50%
2006 review	4	583	390	0.96 (0.78, 1.17)	72%

Evidence Regarding the Class of Erythropoietic-Stimulating Agents. Combined results from the 44 trials of either ESA versus control were similar—pooled HR 1.04 (95 percent CI: 0.98,

1.10; I^2=34 percent). However, this result was obtained from a clinically heterogeneous set of trials, so we explored trial characteristics that might modify pooled estimates (Table 32). Because the Peto method of combining hazard ratios is not easily amenable to including covariates, meta regressions were performed in random-effects models and so point estimates are not precisely comparable. Nonetheless, there is no indication that any of the characteristics modifies the pooled estimate.

Table 32. Relative risks from single covariate meta-regressions—overall survival epoetin or darbepoetin versus control

Characteristic	RR (95% CI)	p-value
Dose Escalation		
Yes	1.00 (0.94, 1.06)	0.97
No	1.00 (0.90, 1.10)	
Iron		
All other	0.96 (0.89, 1.03)	0.07
As necessary	1.04 (0.93, 1.17)	
Platinum-Base Chemotherapy		
Yes	1.05 (0.98, 1.12)	0.12
No	0.97 (0.87, 1.09)	
Baseline Hb b		
>10 g/dL	0.97 (0.89, 1.07)	0.30
≤10 g/dL	1.03 (0.90, 1.19)	
Study Duration		
≤12 weeks	0.98 (0.84, 1.14)	0.67
>12 weeks	1.00 (0.83, 1.19)	
Trial Quality		
Low	1.00 (0.93, 1.07)	0.71
High	1.02 (0.90, 1.14)	
Blinding		
Yes	1.02 (0.95, 1.09)	0.71
No	1.00 (0.86, 1.12)	

Changes from 2006 review: Fourteen trials from the previous review were excluded, four trials were included unchanged, results for 21 trials were updated, and 19 new trials were identified (Appendix Table E1). Table 33 compares current results with the 2006 review and sensitivity analysis with excluded trials.

Table 33. Overall survival epoetin or darbepoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Epoetin or Darbepoetin N	Control N	RR (95% CI)	I^2
Current	44	7,486	6,821	1.04 (0.98, 1.10)	37%
Current & Excluded	58	8,113	7,210	1.03 (0.98, 1.09)	61%
2006 review	39	4,408	3,483	1.08 (0.98, 1.18)	13%

In summary, we did not detect an association between ESA use and survival over the longest available follow-up. There were no meaningful differences from the 2006 effect estimate. Estimates for overall pooled relative effect using different methods were indistinguishable—Peto (fixed-effects), HR 1.04 (95 percent CI: 0.98, 1.10); Bayesian (random-effects), RR 1.01 (95 percent CI: 0.96, 1.06).

Evidence GRADE. The evidence does not show an effect of the class of ESAs on survival over the longest available follow-up—including both during and following ESA treatment (overall strength of evidence moderate, Table 34).

Table 34. Overall survival ESA versus control (GRADE evidence table)

Trials (N)	Subjects (N)	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results RR (95% CI); I^2
44	14,307	Medium[a] trial quality high-21; low-23	Consistent	Direct	Precise	1.04 (0.98, 1.10); 37%

[a] Fewer than half of trials included survival as a primary or secondary outcome; no trial was powered to detect a survival difference.

KQ1 On-Study Mortality

On-study mortality was unavailable in the 2006 review. The individual patient data meta-analysis of Bohlius et al. (58) allowed evaluating on-study mortality. Trials included in these analyses and data source for each trial are listed in Table 14; summary characteristics are shown in Table 35.

Table 35. Summary of characteristics for trials included in analysis of on-study mortality

	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Trials	31	6	37
Patients			
Treatment	4,603	1,391	5,994
Comparator	4,056	1,257	5,313
Mean Age Range[a]			
Treatment	12.4-68.3	49-64.8	12.4-68.3
Comparator	10.8-68.1	48-64.6	10.8-68.1
Trial Quality n (%)			
High	14 (45.2)	5 (83.3)	19 (51.4)
Low	17 (54.8)	1 (16.7)	18 (48.6)
Treatment Modality n (%)			
Chemotherapy	25 (80.6)	6 (100)	31 (83.8)
Includes Platinum	18 (58.1)	4 (66.7)	22 (59.5)
Radiotherapy	3 (9.7)	0 (0)	3 (8.1)
Chemoradiotherapy	3 (9.7)	0 (0)	3 (8.1)
Dose Escalation n (%)			
Allowed	12 (38.7)	2 (33.3)	14 (37.8)
Not allowed	15 (48.4)	4 (66.7)	19 (51.4)
Unknown	4 (12.9)	0 (0)	4 (10.8)
Iron n (%)			
As necessary	24 (77.4)	4 (66.7)	28 (75.7)
Other including fixed	5 (16.1)	2 (33.3)	7 (18.9)
Not reported	2 (6.5)	0 (0)	2 (5.4)
Tumor Type n (%)			
Solid	19 (61.3)	4 (66.7)	23 (62.2)
Mixed	7 (22.6)	1 (16.7)	8 (21.6)
Hematologic	3 (9.7)	1 (16.7)	4 (10.8)
Baseline Hb g/dL	9-13.7	9.5-14	9-14
Therapy Duration (weeks)	4-52	12-23	4-52

[a] Of reported means or medians

Darbepoetin versus Epoetin. No trials reported on study mortality.

Epoetin versus Control. Thirty-one trials (Table 14) reported on-study mortality in patients randomized to epoetin (N=4,603) or control (N=4,056). Trial characteristics varied (Table 35) and are detailed in Appendix Table C1. One trial enrolled pediatric patients (81); eight trials enrolled only women with gynecologic or breast cancers.

Results. The pooled hazard ratio was consistent with an increased risk of mortality during the on-study period—HR 1.19 (95 percent CI: 1.04, 1.36; I^2=0 percent); Bayesian random effects RR of 1.16 (95 percent CrI: 1.01, 1.33). Including six trials where on-study mortality was not reported at the end of the active study period, but estimated from Kaplan-Meier curves (98-100, 109) or from overall survival (110, 111) yielded a pooled HR of 1.14 (95 percent CI: 1.01, 1.26; I^2=0 percent). Excluding the single trial enrolling pediatric patients did not alter the estimated relative effect.

Changes from 2006 review: On-study mortality was not examined in the 2006 review.

Darbepoetin versus Control. Six trials (Table 14) reported on-study mortality in patients randomized to darbepoetin (N=1,391) or control (N=1,257). The characteristics of included trials (Table 35) were less varied than epoetin trials (detailed in Appendix Table C2). None enrolled pediatric patients; one trial enrolled only women with gynecologic or breast cancers (108); no patients in the trial died in the active treatment period.

Results. The pooled hazard ratio during the on-study period was 1.05 (95 percent CI: 0.80, 1.38; I^2=0 percent); Bayesian random effects RR of 1.11 (95 percent CrI: 0.77, 1.61). While the small number of trials (five contributing to the effect estimate) limits inferences, the result magnitude is consistent with an increased risk of mortality during the active treatment period.

Changes from 2006 review: On-study mortality was not examined.

Evidence Regarding the Class of Erythropoietic-Stimulating Agents. Given the basis for considering these agents as a class and evidence consistent with increased mortality during the active treatment period, all trial results were combined for analysis with three aims: 1) estimate overall pooled effect, 2) examine potential subgroup differences, and 3) explore any relationship between relative and underlying mortality risk (i.e., on-study mortality in the control arms).

Pooling on-study mortality from the 37 trials* yielded an estimated hazard ratio of 1.16 (95 percent CI: 1.03, 1.31; I^2=0 percent) (Figure 11) and Bayesian random effects RR of 1.15 (95 percent CrI: 1.01, 1.29). I^2, while zero percent, should not be interpreted as a lack of heterogeneity (71) because it depends on within-study precision, which in these trials is exceedingly low. Considered as a whole and displayed in Table 36, the estimates are consistent with an association between ESA treatment and increased mortality during the active treatment period. A limitation of these data is the uncertainty (wide confidence intervals) accompanying individual trial results, as none were designed or powered to detect even a lower limit for increased mortality risk during the active treatment period. To illustrate, a trial with an anticipated 10 percent mortality rate in the control arm would require just over 13,000 patients randomized 1:1 to treatment or control to detect a 15 percent relative increase in mortality with 80 percent power and α=0.05.†

Table 36. All pooled results for on-study mortality

	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. control
Number of trials	31	6	37
Patients analyzed	8,859	2,648	11,307
Pooled HR (95% CI)[a]	1.19 (1.04, 1.36)	1.05 (0.80, 1.38)	1.16 (1.03, 1.31)
Pooled RR (95% CrI)[b]	1.16 (1.01, 1.33)	1.11 (0.77, 1.61)	1.15 (1.01, 1.29)

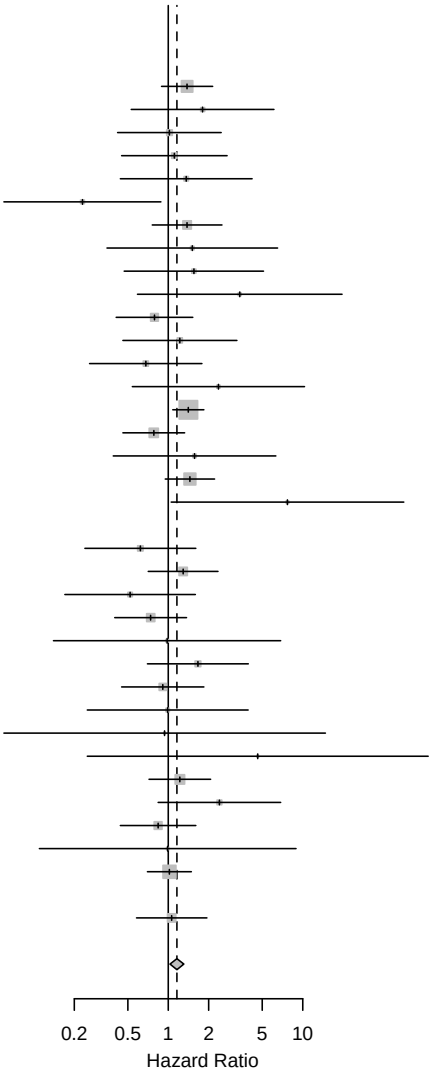
[a] Peto fixed effect
[b] Bayesian random effects

* Hazard ratio for the longest-available follow-up for these 37 trials was 1.05 (95% CI: 0.98, 1.11) or consistent with the estimate in the previous section for the 44 trials analyzed.
† Obtained from a sample size estimate for proportions assuming complete follow-up.

Figure 11. Forest plot of trials pooled to estimate on-study mortality

Study	ESA Events	ESA Total	Control Events	Control Total	HR (Peto)	95% CI	W
Aapro 2008 IPD	47	231	35	232	1.38	[0.89; 2.14]	7.4%
Bamias 2003	7	72	4	72	1.80	[0.53; 6.11]	0.9%
Boogaerts 2003 IPD	10	132	10	127	1.02	[0.42; 2.48]	1.8%
Case 1993 IPD	10	81	9	76	1.11	[0.45; 2.74]	1.7%
Chang 2005 IPD	7	176	5	178	1.36	[0.44; 4.20]	1.1%
Dammacco 2001 IPD	1	69	7	76	0.23	[0.06; 0.88]	0.8%
Debus 2006 IPD	26	195	18	190	1.38	[0.76; 2.51]	4.0%
EPO-INT-1 IPD	6	165	2	81	1.51	[0.35; 6.51]	0.7%
EPO-INT-3 IPD	9	135	3	65	1.55	[0.47; 5.11]	1.0%
Goss 2005 IPD	4	52	1	52	3.40	[0.59; 19.59]	0.5%
Grote 2005 IPD	16	109	21	115	0.79	[0.41; 1.52]	3.3%
Henke 2003 IPD	9	180	7	171	1.22	[0.46; 3.24]	1.5%
Henry 1995 IPD	7	67	10	65	0.68	[0.26; 1.78]	1.5%
Hoskin 2009 IPD	5	151	2	149	2.36	[0.54; 10.31]	0.6%
Leyland-Jones 2005 IPD	121	469	91	470	1.41	[1.08; 1.84]	19.3%
Littlewood 2001 IPD	40	251	22	124	0.78	[0.46; 1.32]	4.8%
Machtay 2007 IPD	5	77	3	71	1.57	[0.39; 6.32]	0.7%
Milroy 2003 IPD	51	214	38	210	1.45	[0.95; 2.21]	7.9%
ML17620 2006	4	61	0	60	7.70	[1.05; 56.46]	0.4%
Moebus 2007 IPD	0	324	0	319			0.0%
Oberhoff 1998 IPD	9	116	10	111	0.62	[0.24; 1.60]	1.6%
Osterborg 2002 IPD	24	173	19	176	1.29	[0.71; 2.34]	3.9%
Pronzato 2002 IPD	4	110	8	113	0.52	[0.17; 1.59]	1.1%
Ray-Coquard 2009 IPD	18	110	23	108	0.74	[0.40; 1.37]	3.7%
Razzouk 2006	2	112	2	110	0.98	[0.14; 6.86]	0.4%
Rose 1994 IPD	16	142	6	79	1.66	[0.70; 3.94]	1.9%
Savonije 2005 IPD	24	211	13	104	0.91	[0.45; 1.84]	2.9%
Thomas 2002 IPD	4	65	4	65	0.99	[0.25; 3.92]	0.7%
Thomas 2008 IPD	1	58	1	56	0.94	[0.06; 14.73]	0.2%
Wilkinson 2006 IPD	2	121	0	61	4.63	[0.25; 85.74]	0.2%
Witzig 2005 IPD	31	174	25	170	1.22	[0.72; 2.07]	5.1%
Hedenus 2003 IPD	10	176	4	173	2.40	[0.84; 6.86]	1.3%
Hernandez 2009 IPD	17	196	20	195	0.84	[0.44; 1.60]	3.4%
Kotasek 2003 IPD	4	208	1	51	0.99	[0.11; 8.91]	0.3%
Pirker 2008 IPD	53	299	51	301	1.02	[0.70; 1.49]	9.6%
Untch 2008 IPD	0	353	0	376			0.0%
Vansteenkiste 2002 IPD	23	159	21	161	1.06	[0.58; 1.94]	3.9%
Fixed effect model		**5994**		**5313**	**1.16**	**[1.03; 1.31]**	**100%**

Heterogeneity: I-squared=0%



Subgroup differences were explored in meta-regressions. The Peto method of combining hazard ratios is not readily amenable to including covariates, so meta-regressions were performed using a random-effects model so that estimates are not precisely comparable. The lack of effect modification by any study characteristic (Table 37) is consistent with the wide confidence intervals among trials. However, given the magnitude of effects, lack of precision, and trial variability, meaningful differences would not be expected.

Table 37. Relative risks from single covariate meta-regressions—overall survival epoetin or darbepoetin versus control

Characteristic	RR (95% CI)	p value
Dose Escalation		
Yes	1.17 (0.98, 1.40)	0.92
No	1.16 (0.86, 1.55)	
Iron		
All other	1.16 (0.93, 1.46)	0.92
As necessary	1.15 (0.81, 1.62)	
Platinum-Base Chemotherapy		
Yes	1.21 (1.04, 1.42)	0.36
No	1.09 (0.84, 1.43)	
Baseline Hb[b]		
>10 g/dL	1.02 (0.83, 1.25)	0.16
≤10 g/dL	1.21 (0.88, 1.68)	
Study Duration		
≤12 weeks	0.95 (0.62, 1.46)	0.37
>12 weeks	1.06 (0.65, 1.75)	
Trial Quality		
Low	1.17 (0.98, 1.41)	0.79
High	1.14 (0.85, 1.53)	
Blinding		
Yes	1.14 (0.99, 1.30)	0.79
No	1.17 (0.90, 1.53)	

Finally, we explored the relationship of underlying mortality rates to increased risk accompanying ESA treatment. The single trial of pediatric patients was excluded from these analyses. Figure 12 plots the 12-week mortality rate in the control arms (either reported for 12-week trials or estimated for trials of different length) against the logarithm[*] of on-study relative risk of mortality. The depiction is consistent with a higher relative risk in trials with lower control arm mortality rates. Moreover, when included in a model (70), control arm mortality modified the relative effect (p=0.003). Table 38 displays the estimated relative risks according to approximate quartiles of mortality rate in control patients, as well as for a trial with very low (1 percent) control arm on-study mortality. These results are consistent with higher relative risks in trials enrolling patients at lower risk of mortality during the active treatment period.

[*] The log(RR) is a linear variable while RR is not.

Figure 12. Plot of control arm mortality rate during active treatment and relative risk plotted on a logarithmic scale (excludes trials with no control arm deaths)

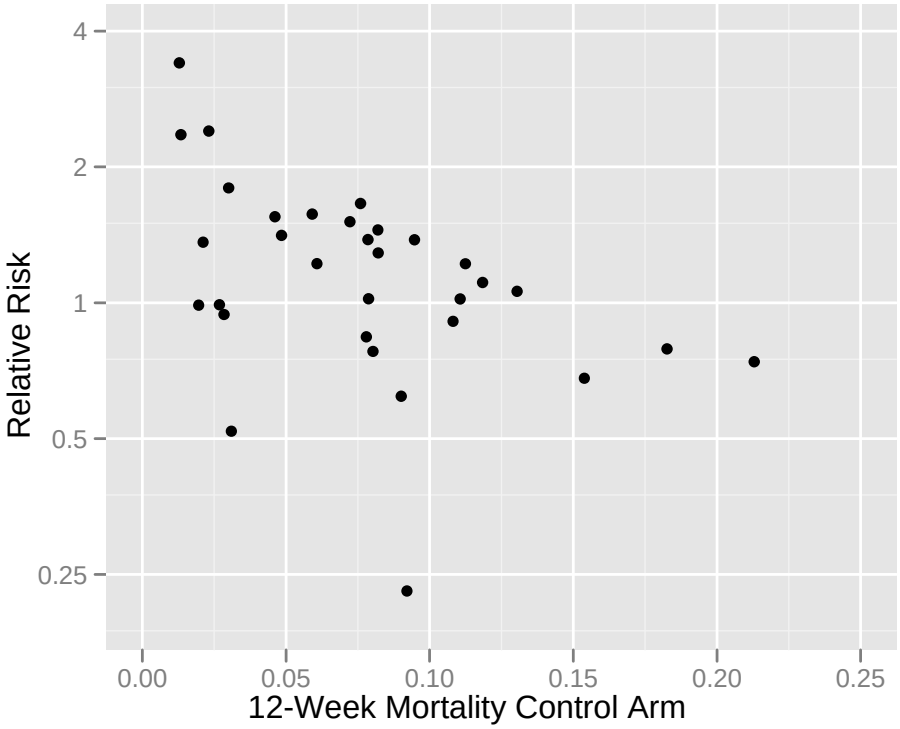


Table 38. Relationship between 12-week mortality rate in control arm and relative risk

Control Arm 12-Week Mortality	RR	95% CrI[a]
1.0%	1.59	(1.23, 2.02)
3.0%	1.46	(1.19, 1.78)
7.5%	1.22	(1.07, 1.38)
10.0%	1.10	(0.97, 1.24)[a]

[a] The credible interval overlapping with 1.0 should not be interpreted as lack of increased risk. The analysis in this collection of trials lacks sufficient power to support conclusions other than a modification of effect by underlying risk or prognosis.

Summary of Overall Survival and On-Study Mortality Results. For ESAs, the body of evidence shows increased mortality risk during the active treatment period that is not seen over the longer term, including follow-up after active treatment. The increased risk is consistent with a biologically plausible effect. While overall or longer-term pooled relative hazards (or risks) were not increased, the on-study results indicate that relative hazards are not constant over time and therefore obscured in the long-term estimates.[*] As pointed out previously, a constant hazard ratio (proportional hazards) was assumed, yet appears inconsistent with these results. The informative result is therefore that mortality risk is increased during the duration of ESA therapy.

[*] The on-study results are hidden within the long-term estimates.

Evidence GRADE. The evidence (Table 39) shows an increase in mortality for the class of ESAs during and shortly following ESA treatment (on-study) (overall strength of evidence moderate).

Table 39. On-study mortality ESA versus control (GRADE evidence table)

Trials (N)	Subjects (N)	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results HR (95% CI); I^2
37	11,307	Medium[a] trial quality: high-19; low-18	Inconsistent	Direct	Precise	1.16 (1.03, 1.31); 0%

Meta-Analyses of Survival Outcomes

To further scrutinize the consistency of the survival and on-study mortality results, we evaluated meta-analyses of ESA versus control in patients undergoing cancer treatment (also reporting results for thromboembolic complications). Only meta-analyses including trials published following and not associated with our previous review were included to be able to compare results with this update. Our literature search for meta-analyses resulted in 104 citations, of which 46 were classified as meta-analyses and of which 13 were selected for full review based on the abstract (112-126). We included meta-analyses that:

1. evaluated survival,
2. excluded trials of patients with myelodysplastic syndrome, and
3. analyzed a subgroup of trials in which patients received concurrent chemo/radio-therapy.

Table 40 shows the 13 published meta-analyses that were reviewed in full, included, or excluded (with reasons for exclusion). Appendix Table F1 lists the trials included in the four meta-analyses appraised in our assessment.

Quality Assessment. We evaluated the methodologic quality of the meta-analyses using AMSTAR (60), a measurement instrument for the "assessment of multiple systematic reviews" (Table 41). For each AMSTAR domain (question), the instrument provides detail on desirable information to include or methods to be used. Table 41 provides a brief summary of our assessment of each study for each question (desired answers are indicated in brackets after the question in the first column). AMSTAR does not provide a summary score; however, based on the results, Bohlius et al. (112) appears to be the highest quality review and additionally is a patient-level meta-analysis. Ludwig et al. (127) is limited than the other reviews in that it is focused solely on darbepoetin trials in patients with chemotherapy-induced anemia, but is a patient-level meta-analysis.

Results. For overall survival using longest available follow-up, only Bennett et al. (128) found significantly poorer survival with ESA use—HR 1.10 (95 percent CI: 1.01,1.20; I^2=20 percent; 45 trials). Both Bohlius et al. (2009) and Ludwig et al. (101) pooled trial results for the on-study or active treatment period only and found increased risks of mortality. In Bohlius et al. (2009), including a much larger number of trials, the risk of on-study mortality was increased in the chemotherapy trials—HR 1.10 (95 percent CI: 0.98, 1.24; I^2=0 percent; 38 trials); and for all trials a HR of 1.17 (95 percent CI: 1.06, 1.30; I^2=0 percent; 53 trials) (Table 42). Ludwig et al.

(101), including individual patient data from six darbepoetin trials, found an increased risk of mortality during the on-study period of similar magnitude—HR 1.11 (95 percent CI: 0.84, 1.47; I^2 NR).

(As anticipated from previous reviews, estimates of relative effect of ESAs for thromboembolic events ranged from 1.5 to 1.6. No effect was found for disease progression.)

Table 40. Included and excluded published meta-analyses

Meta-analysis	Perioperative, myeloablative procedures excluded? (Required=Yes)	Limited by cancer type? (Required=No)	Other
Included:			
Bennett 2008	Yes	No	
Bohlius 2009	Yes	No	
Glaspy 2010	Yes	No	
Ludwig 2009	Yes	No	
Excluded:			
Shehata 2007		Yes	
Aapro 2008/2009	No		
Lambin 2009		Yes	
Tonelli 2009	No		
Kimel 2008			Included only trials reporting HRQoL
Gascon 2008			Review of other meta-analyses
Cornes 2007			Review of cost-effectiveness studies
Minton 2008			Limited to fatigue outcomes
Ray 2008			Guidelines based on systematic review and expert judgment

Table 41. AMSTAR quality evaluation of meta-analyses

	Glaspy 2010	Bohlius 2009	Bennett 2008	Ludwig 2009
AMSTAR Component				
A priori design provided? [Yes]	Not reported	Yes	Not reported	Not reported
Duplicate study selection/data abstraction? [Yes]	Not reported	Yes	Yes	Not reported
Comprehensive literature search? [Yes]	Yes	Yes	Yes	No
Publication status used as inclusion criterion? [No]	No	No	No	No
List of included and excluded trials provided? [Yes]	Yes - included only	Yes - included list in publication; excluded list in Cochrane review authored by same group	Yes - included only	Yes - included only
Characteristics of included trials provided? [Yes]	Yes - minimal	Yes	Yes	Yes
Quality of included trials assessed? [Yes]	No	Yes	Only with regard to prospective evaluation of outcomes of interest	No
Quality of included trials used in formulating conclusions? [Yes]	No	Yes	Yes	No
Methods used to combine study findings appropriate? [Yes]	Yes	Yes	Yes	Yes
Publication bias assessed? [Yes]	No	Yes	Yes	No
Conflict of interest stated? [Yes]	No	Yes - 7 of 23 authors received honoraria, travel grants, or research funding from ESA suppliers; 1 author conducts systematic reviews of health technology for the Blue Cross and Blue Shield Association	Yes - 2 of 21 authors were consultants and/or received research funding from an ESA supplier	Yes - all authors reported employment, stock ownership, consulting, honoraria, and/or research funding from an ESA supplier

Table 42. Overall survival, thromboembolic events, and disease progression meta-analysis results by study

	Glaspy 2010	Bohlius 2009	Bennett 2008	Ludwig 2009
Analysis methods	ORs were generated using the Comprehensive Meta-Analysis (V2) software and random-effects models; intention-to-treat (ITT) and modified-ITT approaches (only patients who received study drug were analyzed) were used; sensitivity analyses were carried out on 20 chemotherapy trials with long-term follow-up (46 months) “to address concerns regarding use of OR as a point estimate.” For sensitivity analyses, patient-level data from 16 of the 20 trials were obtained.	Authors calculated log hazard ratios with log-rank test and Cox regression for each study and combined these in fixed-effects and random-effects meta-analyses (2-stage method). Also calculated Cox regression models stratified by study (1-stage fixed-effects method). Trials with no events in both groups did not contribute. All analyses were by intention-to-treat	Pooled RR, HR using random-effects models; "When mortality events were not available, HRs were calculated by using the inverse variance method to pool HRs. When VTE events were not available, a correction factor (0.5) was used to compute the RRs. "	Kaplan-Meier survival curves were created for overall survival, progression-free survival, and disease progression; all included long-term follow-up data. Effect of ESAs was characterized using Cox proportional hazards models stratified by study protocol.
Overall				
Trials	60	53	51	6
Patients	15,323	13933	13,611	2,122
Chemotherapy and/or radiotherapy				
Trials	51	53	45	
Patients	13,422	13933	11,522	
Chemotherapy +/- radiotherapy	includes chemo-radiotherapy	no chemo-radiotherapy		includes chemo-radiotherapy
Trials	47	38		6
Patients	12,108	10,441		2,122
Radiotherapy alone				
Trials	4	3	3	
Patients	1,314	799	1,173	

Table 42. Overall survival, thromboembolic events, and disease progression meta-analysis results by study (continued)

	Glaspy 2010	Bohlius 2009	Bennett 2008	Ludwig 2009
No Treatment				
Trials	9	5	6	
Patients	1,901	1690	2,089	
Results Reported According to Follow-up				
On-study or active treatment	No	Yes	No	Yes
Long- or mixed-term follow-up	Yes	Yes	Yes	Yes
Meta-Analysis Results				
Overall Survival				
Long- or Mixed-Term Pooled Effect (HR or **OR**):				
Chemotherapy and/or radiotherapy	NR	NR	1.09 (0.99, 1.19); I^2=21%	
Chemotherapy +/- Radiotherapy	**1.03 (0.93, 1.13)**; I^2=1%	1.04 (0.97, 1.11); I^2=5%	NR	0.97 (0.85, 1.10); I^2 NR
Radiotherapy Only	**1.18 (0.95, 1.47)**; I^2 NR	NR	NR	-
All Trials	**1.06 (0.97, 1.15)**; I^2=0%	1.06 (1.00, 1.12); I^2=7%	1.10 (1.01, 1.20); I^2=20%	

Table 42. Overall survival, thromboembolic events, and disease progression meta-analysis results by study (continued)

	Glaspy 2010	Bohlius 2009	Bennett 2008	Ludwig 2009
On-Study or Active Treatment Pooled Effect (HR or **OR**):				
Chemotherapy and/or Radiotherapy		NR		
Chemotherapy +/- Radiotherapy		1.10 (0.98, 1.24); I^2=0%		1.11 (0.84, 1.47); I^2 NR
Radiotherapy only		NR		
All trials		1.17 (1.06, 1.30); I^2=0%		
Thromboembolic events				
N trials included	44		38	6
Total N patients	13,196		8172	2,122
(HR or **OR**)	**1.48 (1.28, 1.72)**		1.57 (1.31, 1.87)	1.57 (1.10, 2.26)
	all reporting			
	1.48 (1.27, 1.72)			
	chemotherapy only			
Disease progression				
N trials included	26			6
Total N patients	9646			2,122
(HR or **OR**)	**1.01 (0.90, 1.14)**			0.92 (0.82, 1.03)
	all reporting			
	0.95 (0.85, 1.06)			
	chemotherapy only			

KQ1 Progression-Free Survival

Twenty trials reported results related to tumor progression (34, 36, 47, 129-144); few trials included progression free survival as a primary outcome. Trials and results are briefly summarized in Appendix Table G1.

Tumor progression was reported variably as a hazard ratio or a risk ratio for progression-free survival, as disease-free survival, as time to progression, or as the proportion of patients with tumor progression. Only a minority of trials defined how disease progression was measured in the published report. Where definitions were provided, they were not always consistent across trials. In light of such varied and insufficient reporting, combining results was not possible.

Of the 20 trials, only three reported significant differences in disease-free or progression-free survival, one trial in favor of epoetin (130) and two in favor of control. Thus, these results do not add important information to the discussion of ESA outcomes.

KQ1 Thromboembolic Events

Ascertainment of thromboembolic events differed considerably across trials. Definitions either varied or in a majority of trials unstated (Appendix Tables C24 and C25). Given lack of uniformity, any of the following reported events were included: thrombosis, transient ischemic attack, stroke, pulmonary embolism, or myocardial infarction. There were also discrepancies in different data sources for the same trials (Appendix Tables C26 and C27). When there were discrepancies, the most complete data reporting absolute event rates was used or, alternatively, data with the most consistent definitions across trials and absolute event rates were included (similar to the 2006 review). Accordingly, much of the thromboembolic event data were obtained from the 2004 FDA ODAC hearings.

Trials included in these analyses and data source are listed in Table 14; summary characteristics are shown in Table 43.

Table 43. Summary of characteristics for trials included in analysis of thromboembolic events

	Darbepoetin vs. Epoetin	Epoetin vs. Control	Darbepoetin vs. Control	Epoetin or Darbepoetin vs. Control
Trials	3	29	5	34
Patients				
Treatment	945	4,712	1,080	5,792
Comparator	928	4,193	1,075	5,268
Mean Age Range[a]				
Treatment	61.7-63.7	12.4-68.3	60.6-64.8	12.4-68.3
Comparator	58.7-63.4	10.8-68.1	61.3-64.6	10.8-68.1
Trial Quality n (%)				
High	0 (0)	16 (55.2)	4 (80)	20 (58.8)
Low	3 (100)	13 (44.8)	1 (20)	14 (41.2)
Treatment Modality n (%)				
Chemotherapy	3 (100)	21 (72.4)	4 (80)	25 (73.5)
Includes Platinum	3 (100)	16 (55.2)	3 (60)	19 (55.9)
Radiotherapy	0 (0)	3 (10.3)	1 (20)	4 (11.8)
Chemoradiotherapy	0 (0)	5 (17.2)	0 (0)	5 (14.7)
Dose Escalation n (%)				
Allowed	0 (0)	13 (44.8)	0 (0)	13 (38.2)
Not allowed	3 (100)	15 (51.7)	4 (80)	19 (55.9)
Unknown	0 (0)	1 (3.4)	1 (20)	2 (5.9)
Iron n (%)				
As necessary	0 (0)	19 (65.5)	4 (80)	23 (67.6)
Other including fixed	1 (33.3)	7 (24.1)	1 (20)	8 (23.5)
Not reported	2 (66.7)	3 (10.3)	0 (0)	3 (8.8)
Tumor Type n (%)				
Solid	2 (66.7)	17 (58.6)	3 (60)	20 (58.8)
Mixed	1 (33.3)	7 (24.1)	1 (20)	8 (23.5)
Hematologic	0 (0)	4 (13.8)	1 (20)	5 (14.7)
Baseline Hb g/dL	10.07-10.4	9.1-13.7	9.5-13	9.1-13.7
Therapy Duration (weeks)	14-16	4-52	9-19	4-52

[a] Of reported means or medians

Darbepoetin versus Epoetin. Three trials reported thromboembolic event rates for participants randomized to darbepoetin or epoetin (83, 86, 87). The trials differed in tumor type and iron supplementation (Table 43).

Results. The pooled relative risk from the three trials showed no difference between agents—RR 0.86 (95 percent CI: 0.61, 1.21; I^2=0 percent). Absolute event rates ranged from 1.3 percent to 11.4 percent.

Changes from 2006 review. There were no changes from the 2006 review.

Epoetin versus Control. Twenty-nine trials (Table 14) reported thromboembolic event rates in patients randomized to epoetin (N=4,712) or control (N=4,193). Trial characteristics varied, summarized in Table 43. One trial included pediatric patients (81) and nine trials included only women with gynecologic and/or breast cancers.

Results. The pooled relative risk indicated an increased risk of thromboembolic events in epoetin treated patients—RR 1.49 (95 percent CI: 1.25, 1.78: I^2=0 percent). Absolute event rates

in the epoetin and control arms ranged from zero percent to 30.8 percent, and zero percent to 12.3 percent, respectively.

Changes from 2006 review. Ten trials from the previous review were excluded, 13 trials included unchanged, data were updated for seven trials, and nine new trials were identified (Appendix Table E1). Table 44 compares current results with the 2006 review and sensitivity analysis with excluded trials showing similar results.

Table 44. Thromboembolic events: epoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Epoetin N	Control N	RR (95% CI)	I^2
Current	29	4,712	4,193	1.49 (1.25, 1.78)	0%
Current & Excluded	39	5,180	4,497	1.53 (1.28, 1.82)	0%
2006 review	30	3,355	2,737	1.69 (1.36, 2.10)	0%

Darbepoetin versus Control. Five trials (Table 14) reported thromboembolic event rates in patients randomized to darbepoetin (N=1,080) or control (N=1.075). Trial characteristics varied somewhat (Table 43). In one trial, radiotherapy was the sole treatment modality (106).

Results. There was evidence for an increased risk of thromboembolic events with darbepoetin—pooled RR 1.55 (95 percent CI: 1.15, 2.08; I^2=0 percent). Absolute event rates in the darbepoetin and control arms ranged from 2.7 percent to 21.6 percent and 0.6 percent to 14.5 percent respectively.

Changes from 2006 review. One trial from the previous review was included unchanged and four new trials were identified (Appendix Table E1). Table 45 compares current results and those from the single trial included in the 2006 review.

Table 45. Thromboembolic events: darbepoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Darbepoetin N	Control N	RR (95% CI)	I^2
Current	5	1080	1075	1.55 (1.15, 2.08)	0%
2006 review	1	155	159	1.44 (0.47, 4.43)	N/A

N/A not applicable

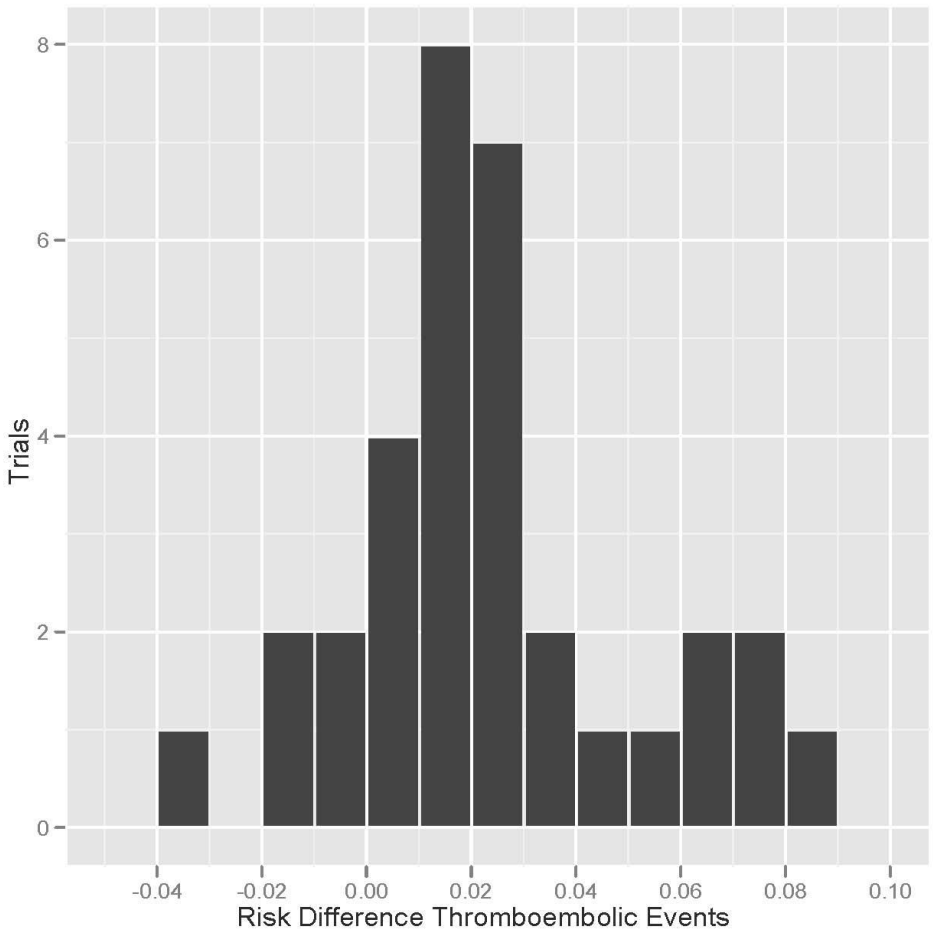
Evidence Regarding the Class of Erythropoietic-Stimulating Agents. Combining results from the 34 trials of epoetin or darbepoetin versus control yielded an association between treatment and thromboembolic events—pooled RR 1.50 (95 percent CI: 1.29, 1.75; I^2=0 percent). Absolute events rates ranged from 0 percent to 30.8 in treatment arms (pooled 7.2 percent) and from zero percent to 14.5 percent in control arms (pooled 4.8 percent); risk differences ranged from -3.4 percent to 26.9 percent. Figure 13 displays the distribution of absolute risk differences showing that in almost all trials thromboembolic event rates accompanying ESA treatment exceeded, often substantially, control arm rates.

Changes from 2006 review. Ten trials from the previous review were excluded, 14 included unchanged, data were updated for seven trials, and 13 new trials were identified (Appendix Table E1). Table 46 shows similar results for the current and 2006 reviews as well as sensitivity analysis with the excluded trials.

Table 46. Thromboembolic Events: epoetin or darbepoetin versus control—current report, current with trials excluded but in 2006 review, and 2006 review

	Trials	Epoetin or Darbepoetin N	Control N	RR (95% CI)	I^2
Current	34	5,792	5,268	1.50 (1.29, 1.75)	0%
Current & Excluded	44	6,260	5,572	1.53 (1.32, 1.78)	0%
2006 review	31	3,510	2,896	1.68 (1.36, 2.08)	0%

Figure 13. Distribution of risk differences in thromboembolic event rates—ESA versus control (a single outlier trial with a risk difference of 0.27 is not shown)



Evidence GRADE. The evidence shows an increased risk of thromboembolic events with ESA treatment (overall strength of evidence moderate), but no clinically meaningful difference between epoetin and darbepoetin in thromboembolic events (Table 47).

Table 47. Thromboembolic events: ESA versus control (GRADE evidence table)

Trials (N)	Subjects (N)	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results RR (95% CI); I^2
341	11,060	Medium[a] trial quality high-20; low-14	Consistent	Direct	Precise	1.50 (1.29, 1.75); 0%

[a] Due to lack of consistent endpoint ascertainment across trials.

KQ1 Health-Related Quality of Life

Quality of life is a general concept that is often inclusive of all aspects of life that impact on a person's well-being. A more specific term, health-related quality of life (HRQoL), describes aspects of quality of life directly related to individual health and distinguishes these from experiences less directly related to the individual and more dependent on social and political trends (145). The FDA includes quality of life measures that support labeling claims, but avoids the use of "quality of life" terminology, preferring "patient reported outcomes" (PRO) for this particular purpose. A PRO is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by anyone" (146). During product development, a PRO instrument intended to measure the patient's experience can support a labeling claim if it can be shown to reliably measure the claimed concept in the patient population enrolled in the clinical trial.

Measuring HRQoL in clinical trials can be particularly helpful for eventual patient management when the symptoms of a condition are many and varied, and when the treatment of interest is expected to have little if any impact on survival but a positive impact on HRQoL. Note that only controlled trials can support causal inferences about the effects of a particular treatment on quality of life (147). Potentially confounding factors (e.g., changes in disease status) that may affect both direct treatment outcome and quality of life are distributed randomly and equally among trial arms and do not affect the results.

Instruments designed to measure change in HRQoL may be general or specific to the disease under study. Global instruments are intended for use across various disease populations, and permit comparison of HRQoL outcomes among interventions and diseases. Global instruments, however, may be insensitive and fail to detect small but clinically important changes. Disease or condition-specific instruments address this problem, but may be limited by their narrow range of applicability. Thus, global and specific instruments are often used together. Researchers measuring the impact of anemia symptoms due to cancer therapy, and the treatment of anemia have used a variety of HRQoL instruments. In fact, one of the difficulties in attempting pooled analysis of results in this area has been lack of consensus on one or a very few validated instruments for use in clinical trials.

The FDA presupposes that use of a PRO as a clinical trial endpoint in order to support labeling claims is based on use of an instrument that has been "adequately developed and validated" (146). Validation of a fully developed questionnaire consists of studies that address the following elements, where patients meet the criteria for the type of study intervention (148):

- Reproducibility: repeated administration to stable patients produces the same result;

- Responsiveness: in stable patients administered a relevant intervention of known efficacy, the questionnaire should show sufficiently large improvement in HRQoL relative to the variability shown by stable patients;
- Construct validity: the questionnaire behaves in relation to other measures as expected if it was really measuring the intended domains of HRQoL.

In addition to using a validated instrument, the logistics of questionnaire administration should be handled to minimize the impact on the integrity of the quality of life assessment. Feedback from the investigator, treating physician, or staff that affects the patient's sense of well-being is a potential source of bias. Ideally, the instrument should be administered prior to discussions with health care providers as to treatment response, adverse events, or other information (e.g., Hb level) that could affect patients' responses to the quality of life questionnaire. The study protocol should detail the time intervals for administering the instrument as well as training for staff or for the patient if the instrument is self-administered.

As noted, trials of ESAs reporting HRQoL outcomes have used a variety of instruments, some of them not validated. However, many of the more recent trials have used a validated, multi-dimensional instrument, The Functional Assessment of Cancer-Anemia (FACT-An) (149), or one of its subscales. The core of the FACT-An is the Functional Assessment of Cancer Therapy—General (FACT-G), which contains 27 questions that can generate subscale scores regarding physical, functional, emotional, and social well-being (150). Data from 1,172 cancer patients who answered the FACT-G questionnaire indicated that fatigue was the symptom most often reported (73 percent). As a result, two additional subscales assess fatigue and anemia. The FACT-Fatigue (FACT-F) consists of a fatigue-specific subscale of 13 items that was added to the FACT-G; the FACT-Anemia (FACT-An) adds to the FACT-F seven nonfatigue items relevant to anemia in cancer patients. For details and references regarding instrument validation, the reader is referred to the Functional Assessment of Chronic Illness Therapy Web site.[*] Other well-validated global instruments that have been used, sometimes in conjunction with the FACT-An or a subscale, include the Short Form (36) Health Survey (SF-36) and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30).

HRQoL results have been evaluated in different ways and often incompletely reported (e.g., baseline scores, absolute values, and measures of result dispersion may be missing), making it difficult to pool results across trials. Analysis should compare change from baseline between study and control arms from randomized controlled trials to adequately control for placebo response. Other factors may need to be considered in the analysis. For example, in the previous systematic reviews conducted by TEC, only trials with average baseline Hb less than 10 mg/dL reported statistically significant HRQoL results using FACT-An or subscales whereas trials of patients with higher average baseline Hb were not significant for this outcome.

Missing data is an important issue that can impact interpretation of HRQoL results. First, when, as is common in ESA trials HRQoL is a secondary outcome, not all patients in the trial may be administered questionnaires. Often missing from the trial report is a description of the HRQoL subset and evaluation of potential for selection bias. Second, among those followed for HRQoL, nonrandom missing data can result in serious bias. For example, patients with missing questionnaires may be the sickest patients or those least responsive to therapy; failure to respond to specific items in a questionnaire also raises concerns. Trial protocols should include a detailed

[*] http://facit.org/validity/validation_articles.aspx

plan for preventing missing data, investigating the pattern and mechanism of missing data, and addressing missing data in the analysis using acceptable methods and sensitivity analyses.

Statistically significant HRQoL results are often reported without additional discussion. However, statistically significant improvements in HRQoL measures in an ESA treated clinical trial population compared to control may not be clinically perceived by an individual patient as an improvement. For example, Clement et al. (151) evaluated randomized controlled trials of ESA therapy in patients with anemia associated with chronic kidney disease that reported HRQoL results from a validated questionnaire (SF-36). The authors found that treating to attain Hb >12 g/dL resulted in small, statistically significant, but not clinically meaningful changes in HRQoL. That is, on average, patients would not be able to perceive the improvement.

Given that ESA treatment is intended to improve individual patient management, it is important to determine whether the patient is able to notice the difference measured by the HRQoL instrument. In recognition of the importance of clinical significance, the FDA (146) encourages sponsors to "avoid proposing [PRO] labeling claims based on statistical significance alone." Rather, results should ideally be compared to the minimal clinically important difference (MCID), the smallest difference in score in the domain of interest that patients perceive as beneficial and which would lead to a change in patient management (152). Modifications to this definition have addressed deterioration, such that harmful differences, which may be perceived on a different scale (153), are also considered (154). While the concept is appealing, MCID estimation is not simple, and estimates may vary depending on patient population, disease severity, and clinical study context (154, 155).

MCID estimation relies on anchor-based approaches, reviewed in a number of publications (154-157). Briefly, a well-understood external indicator (anchor) such as a laboratory measure, clinician rating, or patient-based global rating is used to categorize patients by degree of change from baseline in the anchor (e.g., none, small positive, large positive, small negative, large negative). The groups characterized as a little better or a little worse are the minimal change groups, and the change in the PRO in these groups is a measure of the MCID. Anchors should be selected for important qualities: change in the anchor should be clinically interpretable; and there should be a strong relationship between the anchor and the PRO measure. Use of multiple anchors is recommended for MCID estimation, and an MCID range, rather than a point estimate, is recommended to accommodate variability in the estimate as well as variability in the patient population and clinical scenario (154, 155, 158). Similarly, use of the lowest possible estimate is not recommended as some scores may be falsely included as meaningful; rather, a slightly higher cutoff may be more appropriate (159).

Distribution-based methods, which rely on instrument score statistical distributions, may be used to supplement anchor-based MCID estimates but are not recommended as sole MCID estimation methods. These include defining MCID as one half of a standard deviation of a given HRQoL instrument based on a large review of studies by Norman et al. (160). Standard error of measurement (161, 162) has also been proposed as a measure of MCID. Cohen et al. (163) suggested 0.2, 0.5, and 0.8 standardized effects representing small, moderate, and large changes but in the context of power calculations. Such estimates are not always generalizable; in a review of studies using the FACT-G questionnaire (164), the authors found that use of Cohen's thresholds resulted in at times overestimation and in other cases underestimation of an observed effect, concluding that "general rules for effect sizes may be too simplistic."

Comparison of the mean difference in the PRO between study arms to the MCID should enable determination of clinical significance. However, and particularly when there are several HRQoL domains and results are close to the MCID, overall clinical significance may not be so clear. In addition to reporting data related to the mean difference, it is also helpful to report the difference between study arms in the proportion of patients achieving an improvement greater than the MCID as well as deterioration greater than the MCID. "Adding those differences in proportion yields a risk difference that one can convert to a number needed to treat (NNT)" (156), a result that is intuitively easy to understand.

Both anchor- and distribution-based methods have been used to estimate MCID for FACT-An and subscales in cancer patients treated with epoetin. Two follow-up studies (165, 166) used change in Hb as an anchor; only Patrick et al. (166) reported correlations of 0.26 (FACT-G) and 0.29 (FACT-fatigue subscale) between QoL scale and a Hb increase of 1 g/dL, similar to correlations reported in other trials (167, 168). Neither study provided information on how to interpret change in Hb. Cella et al. (165) also used ECOG and Karnofsky performance scores as anchors. They did not report on the correlation of either performance scores with FACT scales, or on interpreting change in performance score. That these changes are closely linked to the physical aspects of QoL in epoetin and darbepoetin-treated patients is supported by data from an unrelated study of chemotherapy in patients with lung cancer, where baseline ECOG performance score was strongly correlated with the EORTC QLQ C-30 scales at -0.52 (physical function), -0.63 (global health status), and 0.52 (fatigue) (169). EORTC QLQ C-30 and FACT-G physical and functional domain scores have shown good correlation (170, 171).

In these studies, patients were separated only into "improved," "unchanged/stable," or "worsened" categories, with no identification of groups with only small improvement or small decline. Using simple differences between stable and improved groups, Patrick et al. (166) estimated MCIDs at 2.5 for FACT-G and 4.2 for FACT-Fatigue. Cella et al. (165) reported between-group changes for the FACT-Fatigue subscale as 0.2-8.8 score units and for the FACT-G Total as 1.9-9.9. Using Cohen's recommendation of 0.2 as a "small" effect size to set MCID lower limits and point estimates, the authors reported MCIDs of 3 and 4 for FACT-Fatigue and FACT-G, respectively. While this study appropriately uses different anchors to accumulate between-group change data, it uses a distribution-based method to choose the actual MCID estimate, rather than identifying groups with perceived small changes in the anchor to determine the corresponding range of changes in FACT scores. Nevertheless, these MCID estimates have become widely reported in the literature.

Trials that convert health outcomes into a common result, such as quality-adjusted life years (QALYs) or cost (cost-utility and cost-benefit), cannot use the HRQoL results from measures such as FACT scales. Rather, preference (utility)-based measures are required (172); their main purpose is to measure the "utility" of health states (that is, the preferences people have for different health states along a continuum extending from death to full health) in a way suitable for use in economic evaluation studies.

No ESA trials have reported HRQoL outcomes using utility-based measures. The scales used by instruments such as FACT scales may have minima and maxima that fall well within the conceptual range of utility-based measures, making conversion difficult. Such conversion has been attempted in other types of studies, and requires ad hoc assignment of reported health-status data categories to corresponding values on a standard health utility measure. However, the process has not been found uniform across studies or reliable within a single study (173). As an alternative, Ossa et al. (174) used FACT-An to develop descriptions of health states related to

anemia and the associated Hb levels, and time tradeoff methods to determine utility values for the different states. Finally, Wilson et al. (79) published utility values by Hb level from ESA manufacturer submissions and used them to model cost per QALY.

Quality of Life Outcomes.

Summary of Trials. For this review, we included trials reporting health-related quality of life (HRQoL) evidence as change from baseline to final follow-up in each study arm, and change in treatment arm(s) compared to that in the control arm. Ideally, trials would also report the percentage of patients in each study arm that achieved a prespecified clinically meaningful improvement but few did. We also required trials to use a validated instrument; scales and subscales reported by included trials are described in Table 48. Trials reporting only linear analogue self-assessment (LASA) or visual analog scales (VAS) were excluded.

Twenty-six trials reported HRQoL results meeting the above criteria:

- 9,410 randomized patients (4,929 ESA; 4,481 control); number evaluated for HRQoL likely to be less
- 21 trials of epoetin (7,497 randomized; 3,894 epoetin, 3,603 control)
- 5 trials of darbepoetin (1,913 randomized; 1,035 epoetin, 878 control)
- 1 study of epoetin that reported a statistically significant difference in the total FACT-Anemia scale favoring ESA, but did not report data for inclusion in the evidence analysis (175)

Objective of the Evidence Evaluation. The most commonly reported HRQoL instrument was the FACT-Fatigue subscale, with 14 trials of ESA versus no ESA reporting sufficient data for quantitative analysis (Table 48). The next most commonly reported instrument was the FACT-G and the FACT nonfatigue anemia subscale in six trials each. In view of the limited number of trials using the same instrument, and recommendations of Shekelle et al. (55) that the 2006 evaluation of quality of life did not need updating (see Introduction), it was decided to limit the goals of the HRQoL evidence analysis and conduct a focused, quantitative evaluation of results from trials reporting data for the FACT-Fatigue subscale. The comparison is that for KQ1: epoetin (alfa or beta) or darbepoetin versus placebo/no treatment.

Table 48. Description of the scales and subscales evaluated in trials included in this review

FACT instrument or subscale	#Trials reporting	Type of instru-ment	Domains addressed (#questions)	Range of scale (highest=most favorable)
FACT-fatigue subscale	17 (14 with complete data)	Symptom-specific	Fatigue-specific questions from the anemia-specific questions of FACT-An (13)	0-52
FACT non-fatigue anemia subscale	6	Symptom-specific	Questions from the anemia-specific questions of FACT-An that are not part of the FACT-fatigue subscale (7)	0-28
FACT-G(eneral)	6	General	Physical well-being (7) Social/family well-being (7) Emotional well-being (6) Functional well-being (7)	0-108
FACT-An(emia)	5	Symptom-specific	Includes FACT-G, all domains (27)[a] Anemia-specific symptoms (20)	0-188
SF-36 Physical Summary Component (PCS) score	2	General	Physical Functioning (10) Role Physical (4) Bodily Pain (2) (these scales contribute most to PSC scoring)	Transformed to have a mean of 50 and SD of 10 in the US population
European Organization for Research and Treatment of Cancer QLQ-C30 core questionnaire	2	General	5 functional domains 3 symptom scales single items for symptoms 2 global items (30)	Transformed to 0-100
SF-36 Mental Summary Component (MCS) score	1	General	Vitality (4) Social functioning (2) Role-emotional (3) Mental health (5)	Transformed to have a mean of 50 and SD of 10 in the US population
Nottingham Health Profile	1	General	Part I, 38 questions in 6 subareas: • energy level (3) • pain (8) • emotional reaction (9) • sleep (5) • social isolation (5) • physical abilities (8) Part II, 7 life areas affected (7)	Part I:0-100 Part II: 0-7
Symptom Distress Scale	1	General	nausea frequency, nausea severity, appetite, insomnia, pain frequency, pain severity, fatigue, bowel pattern, concentration, appearance, breathing, outlook, and cough (13)	Transformed to 0-100
PedsQL-GCS	1	General	physical functioning (8) emotional functioning (5) social functioning (5) school functioning (5)	Transformed to 0-100
PedsQL 3.0 Cancer Module	1	Symptom-specific	Pain and hurt (2) Nausea (5) Procedural anxiety (3) Treatment anxiety (3) Worry (3) Cognitive problems (5) Perceived physical appearance (3) Communication (3)	Transformed to 0-100

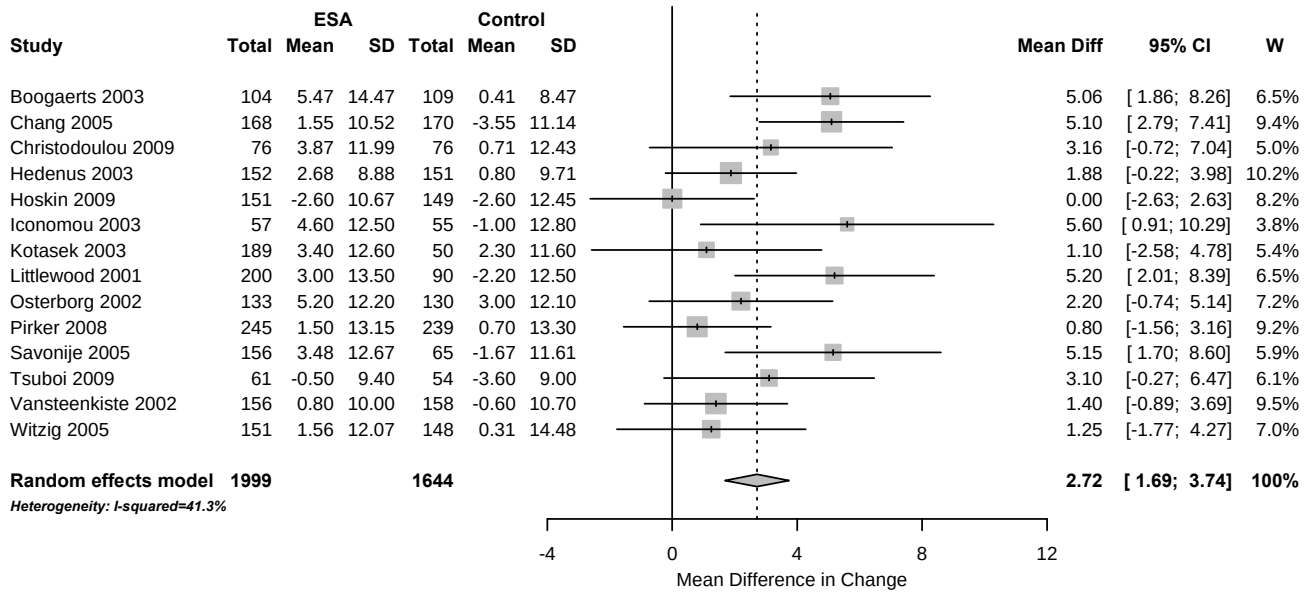
[a] While FACT-Anemia incorporates FACT-G, it was not classified as a general instrument since the results could be dominated by either the general FACT-G or the symptom-specific subscales.

Data Analysis. The FACT-Fatigue subscale was evaluated in 17 trials; ESA treatment was found to statistically improve fatigue in seven trials (Table 48). Nine trials reported no statistically significant differences between ESA treatment and control arms. One trial reported results only by change in Hb (176). Three trials did not report sufficient results for inclusion in a meta-analysis (34, 140, 177). Thus, 14 trials were included in a meta-analysis—3,643 participants (1,999 ESA; 1,644 control).

Trial quality varied and only five of 14 identified HRQoL as a primary outcome (Table 48); up to 55 percent enrolled patients were not evaluable for HRQoL in study arms. Blinding to treatment and patient blinding to Hb value prior to HRQoL questionnaire administration was inconsistent. All trials administered ESA to achieve Hb values greater than 12 g/dL in the treatment arms, higher than currently recommended. Few trials adjusted their analyses for the baseline value of the FACT-Fatigue; only eight reported baseline FACT-Fatigue results, so that it was not possible to adjust for this variable in the meta-regressions.

Vote-counting analysis (Table 50) found that no trial result favored the control arm. The mean difference between treatment arms was zero in one study, but never negative. The pooled post-test difference in change was 2.72 (95 percent CI: 1.69, 3.74; I^2=41 percent) in favor of ESA treatment (Figure 14). The pooled mean change in the ESA arms was +2.1 (95 percent CI: -3.9, 8.1; I^2=0 percent), while in control arms -0.6 (95 percent CI: -6.5, 5.3; I^2=0 percent).

Figure 14. Forest plot—difference in change for FACT-Fatigue



Conclusions

ESA treatment with epoetin or darbepoetin to high Hb target values (>12 g/dL) was accompanied by higher HRQoL scores compared to transfusion as needed, as measured by the FACT-Fatigue subscale, in nearly all reporting trials (Table 51). Such vote-counting results suggest that ESA treatment may at least attenuate the decline seen in non-ESA treatment arms.

The pooled end-of-treatment difference between study arms favored of ESA treatment. The pooled mean change in the treatment arm and the pooled mean difference in change between study arms are less than 3, the generally accepted minimal clinically important difference estimated by Cella et al. (165). However, the pooled mean difference between study arms (2.7) is the same as the lowest of the reported estimates of the MCID (165). In summarizing their data from anchor-based measures, Cella et al. (165) accepted only mean differences that corresponded to a Cohen's effect size of at least 0.2 (see Introduction: Health-related Quality of Life). The effect size for the mean difference calculated in the meta-analysis is 0.23 and for the change in the ESA treatment arm alone is 0.21. Thus, while statistically significant, the clinical significance of the FACT-Fatigue difference between ESA treatment and no ESA treatment is likely to be small referent to the MCID.

This analysis has several limitations. First are those noted in the general QoL discussion with using MCID estimates as final arbiters of significant results, particularly here where results are nearly equal to the value of the estimated MCID. Other FACT scores were not analyzed due to insufficient data. In addition, FACT-Fatigue scores were reported in only a subset of included trials in this overall review, were not primary outcomes in most reporting studies, and were not reported for the vast majority of patients. Moreover, the conditions in which ESAs were administered (i.e. target values >12 g/dL) are not consistent with current practice. Thus, results may not be generalizable. However, they represent the current best estimate of HRQoL benefits, which would need to be considered along with the potential harms of treatment for each patient.

Changes from 2006 review: Eight trials from the previous review were included unchanged and six new trials were included (Appendix Table E1).

Evidence GRADE. Treating to high target Hb levels (≥12 g/dL) is accompanied by improved health-related quality of life (HRQoL) scores (e.g., FACT-Fatigue); any clinical significance of the improvement is likely to be small (overall strength of evidence low) (Table 49).

Table 49. HRQoL: ESA versus control (GRADE evidence table)

Trials (N)	Subjects (N)	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results Mean Difference Change in FACT-Fatigue Score (95% CI); I^2
14	3,643	High trial quality: high-2; low-12	Consistent	Direct	Precise	2.72 (1.69, 3.74); 41%

Table 50. Vote-counting results for trials reporting FACT-Fatigue subscale

Study	ESA	Evaluable for QoL N	Enrolled not evaluable %	Blinded	Significantly pro-tx	Not Significant	Significantly pro-control
Boogaerts 2003	Epo	213	19	**No**	•		
Chang 2005	Epo	338	3	**No**	•		
Christodoulou 2009	Epo	153	55	**No**		•	
Hedenus 2003	Epo	303	13	**Yes**	•[a]		
Hernandez 2009	Darb	315	19	**Yes**		•	
Hoskin 2009	Epo	NR	NR	**No**		•	
Iconomou 2003	Epo	112	8	**No**	•		
Kotasek 2003	Darb	249	2	**Yes**	**(NR)**	**(NR)**	**(NR)**
Leyland-Jones 2005	Epo	NR	NR	**Yes**		•	
Littlewood 2001	Epo	290	23	**Yes**	•		
Osterborg 2002	Epo	263	23	**Yes**		•	
Pirker 2008	Darb	484	19	**Yes**			
Savonije 2005	Epo	221	30	**No**	•		
Tsuboi 2009	Epo	117	4	**Yes**		•	
Vansteenkiste 2002	Darb	255	20	**Yes**	•		
Wilkinson 2006	Epo	NR	NR	**No**		•	
Witzig 2005	Epo	299	13	**Yes**		•	

[a] Significant after adjusting for baseline fatigue score

Table 51. FACT-Fatigue subscale, trials comparing ESA to placebo or no treatment

Study (ESA)	1°/2° out-come	N, ESA (% not eval-uated)	N, Ctl (% not eval-uated)	Blinding to treat-ment/ Patient blinded to Hb	ESA duration /Trial follow-up for QoL (weeks)	Base-line Hb (g/dL)	Hb Target (g/dL)	ESA Baseline FACT-F Mean (SD)	Ctl Base-line FACT-F Mean (SD)	Adjusted for baseline QoL/Hb in reported analysis	ESA Mean Change (SD)	ESA Ef-fect size	Ctl Mean Change (SD)	Ctl Ef-fect size	Mean Diff (95% CI)	Diff Effect size
Boogaerts 2003 (Epo)	1	133 (22)	129 (16)	N/Y	12/12	<10	12-14	27 (12)	31 (11)	N/N	5.47 (14.47)	0.38	0.41 (8.47)	0.05	5.06 (1.86, 8.26)	0.43
Chang 2005 (Epo)	1	175 (4)	175 (3)	N/Y	16/12	10-12	14	NR	NR	Y/N	1.55 (10.52)	0.15	-3.55 (11.14)	-0.32	5.1 (2.79, 7.41)	0.47
Christodou-lou 2009 (Epo)	1	167 (54)	170 (55)	N/NR	NR/26	10-12	>12	33 (12) non-plat; 32 (11) plat	32 (12) non-plat; 27(13) plat	Y/Y (>or ≤10.5)	3.87 (11.99)	0.32	0.71 (12.43)	0.06	3.16 (-0.72, 7.04)	0.26
Hedenus 2003 (Darb)	2	176 (14)	173 (13)	Y/Y	12/12	≤10	13-14 F	NR	NR	Stratified analysis/ N	2.68 (8.88)	0.30	0.8 (9.71)	0.08	1.88 (-0.22, 3.98)	0.20
Hoskin 2009 (Epo)	2	151 (0)	149 (0)	N/NR	12/2	>12	>12	NR	NR	N/N	-2.6 (10.67)	-0.24	-2.6 (12.45)	-0.21	0 (-2.63, 2.63)	0.00
Iconomou 2003 (Epo)	1	61 (7)	61 (10)	N/NR	12/12	10-12	NR	22 (12)	23 (11)	N/N	4.6 (12.5)	0.37	-1 (12.8)	-0.08	5.6 (0.91, 10.29)	0.44
Kotasek 2003 (Darb)	2	208 (5)	51 (0)	Y/NR	12/10	<10	13-14 F	27 (12)	27 (12)	N/N	3.4 (12.6)	0.27	2.3 (11.6)	0.20	1.1 (-2.58, 4.78)	0.09
Littlewood 2001 (Epo)	2	251 (23)	124 (29)	Y/NR	28/ 4 to 24	<10	<15	NR	NR	N/N	3 (13.5)	0.22	-2.2 (12.5)	-0.18	5.2 (2.01, 8.39)	0.40
Osterborg 2002 (Epo)	2	170 (38)	173 (40)	Y/Y	16/16	<10	13-14	29 (11)	29 (11)	Y/N	5.2 (12.2)	0.43	3 (12.1)	0.25	2.2 (-0.74, 5.14)	0.18
Pirker 2008 (Darb)	2	299 (18)	301 (21)	Y/NR	19/19	10-12	13-14	31 (11)	31 (11)	Y/N	1.5 (13.15)	0.11	0.7 (13.3)	0.05	0.8 (-1.56, 3.16)	0.06
Savonije 2005 (Epo)	2	211 (26)	104 (38)	N/NR	1414	10-12	13-14	NR	NR	N/N	3.48 (12.67)	0.27	-1.67 (11.61)	-0.14	5.15 (1.70, 8.60)	0.42

Study (ESA)	1°/2° out-come	N, ESA (% not eval-uated)	N, Ctl (% not eval-uated)	Blinding to treat-ment/ Patient blinded to Hb	ESA duration /Trial follow-up for QoL (weeks)	Base-line Hb (g/dL)	Hb Target (g/dL)	ESA Baseline FACT-F Mean (SD)	Ctl Base-line FACT-F Mean (SD)	Adjusted for baseline QoL/Hb in reported analysis	ESA Mean Change (SD)	ESA Ef-fect size	Ctl Mean Change (SD)	Ctl Ef-fect size	Mean Diff (95% CI)	Diff Effect size
Tsuboi 2009 (Epo)	2	63 (3)	59 (5)	Y/NR	8/8	10-12	<14	36 (10)	34 (10)	Stratified analysis/ Hb change influenced QoL change	-0.5 (9.4)	-0.05	-3.6 (9)	-0.40	3.1 (-0.27, 6.47)	0.34
Vansteen-kiste 2002 (Darb)	2	156 (19)	158 (19)	Y/Y	12/52	10-12	13-14 F	NR	NR	N/N	0.8 (10)	0.08	-0.6 (10.7)	-0.06	1.4 (-0.89, 3.69)	0.14
Witzig 2005 (Epo)	1	174 (13)	170 (13)	Y/Y	16/16	<=10	13-15	26 (11)	28 (12)	N/N	1.56 (12.07)	0.13	0.31 (14.48)	0.02	1.25 (-1.77, 4.27)	0.09
Pooled											**2.08** (95% CI: -3.90, 8.07)	**0.17**	**-0.59** (95% CI: -6.47, 5.28)	**-0.06**	**2.72** (95% CI: 1.69, 3.74)	**0.23**

KQ1 Tumor Response and Progression

Different possible effects of erythropoietic stimulants on tumor response and progression have been posited. One is that through better tumor oxygenation, ESAs might improve chemotherapeutic agents' cytocidal effects or enhanced the effect of radiation therapy (178). However, overall and on-study survival results would be inconsistent with any potential beneficial effect. On the other hand, stimulation of erythropoietin receptors on neoplastic cells (179, 180) could result in more rapid tumor growth.

To evaluate any effect of erythropoietic stimulants on tumor response and progression required trials with specific and homogeneous characteristics. Accordingly, we included only those that met the following criteria:

1. enrolled a homogeneous population including patients with similar tumor types and when clinically appropriate at the same stage; or trial results were stratified by tumor type and stage,
2. participants were given a predefined and uniform anticancer therapy; or trial results were stratified by anticancer therapy, and
3. trial was designed to prospectively assess tumor response or control, reporting either as a primary or secondary outcome

Thirteen trials (11 epoetin, two darbepoetin) meeting these criteria were included. Because definitions of tumor response or progression varied, results were not pooled. Table 52 details characteristics of the 13 trials listing the variety of outcome measures assessed related to tumor progression and response. Results from those trials reporting tumor response outcomes are shown in Table 53. There was no evidence of an association between tumor response for any of the definitions and ESA use. Results for other tumor outcomes are listed in Table 54. While some relative effects differ from unity (both greater and less than), results were inconsistent across trials.

Changes from 2006 review. Three trials from the previous review were excluded, eight trials were included unchanged, and eight new trials were identified (Appendix Table E1).

Table 52. Characteristics of trials reporting tumor response or duration-related outcomes

Study Characteristic	Blohmer 2004	Debus 2006	Engert 2009	Goss 2005	Gupta 2009	Henke 2003	Hoskin 2009
Drug	Epoetin	Epoetin	Epoetin	Epoetin	Epoetin	Epoetin	Epoetin
Control N	129	190	648	53	60	171	149
ESA N	128	195	655	53	60	180	151
Malignancy	cervical (high risk)	NSCLC, stage IIIA/B, primarily inoperable	advanced HD	limited disease SCLC	cervical cancer (stage IIB-IIIB)	advanced (stage III , IV) head and neck	head and neck, stage I-IV
Treatment	Pt chemo + radio Tx	cisplatinum w/sequential chemo-radiotherapy	chemotherapy, without platinum	Pt chemo + radio Tx	Pt chemo + radio Tx	radiotherapy	radiotherapy
Duration	46	NR	NR	16-24	NR	NR	40 days
Outcome	RFS	TR	TR, FFTF, PFS	tumor control, PFS	DFS	PFS, tumor progression	local DFS, tumor response
Assessed	229 weeks	NR (planned 2 years)	NR	NR	2 years (survival)	≈2 years	12 weeks
ESA dose	3 x 10,000 IU/wk	40,000 IU/wk	40,000 IU/wk	40,000 IU/wk	3 x 10,000 IU/wk	3 x 300 IU/kg/wk	if Hb <12.5 then 3 x 10,000 IU (25% of patients) if Hb >12.5 then 3 x 4,000 IU (75% of patients) sc
ESA duration (weeks)	27	12	22-24	12-24	7	7-9	12
Baseline Hb (control/ESA)	11.8/12.0 g/dL	NR	12.3/12.2 g/dL	13.5/13.5 g/dL	10.7/10.4 g/ dL	11.8/11.7 g/dL	13.7/13.4 g/dL
Hb target	13-14 g/dL	13-14 g/dL	14 g/dL	16 g/dL	NR	14 g/dL,women 15 g/dL,men	15 g/dL
Re-start if Hb less than	NR	12 g/dL	NR	<14 g/dL	NR	14 g/dL,women 15 g/dL,men	14.5 g/dL

Table 52. Characteristics of trials reporting tumor response or duration-related outcomes (continued)

Study Characteristic	Machtay 2007	Moebus 2007	Thomas 2008	Wagner 2004	Overgaard 2009	Untch 2008
Drug	Epoetin	Epoetin	Epoetin	Epoetin	Darbepoetin	Darbepoetin
Control N	71	325	55	20	262	377
ESA N	77	333	58	18	260	356
Malignancy	head and neck nonmetastatic, not resected	breast cancer	cervix carcinoma	neuroblastoma	head and neck cancer	breast cancer
Treatment	radiotherapy	chemotherapy, without platinum	radio-chemotherapy	chemotherapy	radiotherapy	chemotherapy without platinum
Duration	NR	NR	8	111 days	NR	3 years
Outcome	locoregional failure rate, locoregional PFS, CR	DFS, local relapse	PFS, local tumor control	PFS, tumor response	locoregional control, DFS	RFS, pathological complete response
Assessed	2 and 3 years	5 years	3 years	5 years	5 years	3 years
ESA dose	1x 40,000 IU/wk	3 x 150 IU/kg/wk	1 x 40,000 IU/wk	7 x 200 IU/kg	150 mcg QW	300 mcg Q4W, after 4 weeks changed to Q3W
ESA duration (weeks)	8-9	≈18	6-9	12-6	8-10	21-25
Baseline Hb (control/ESA)	12.1/12.0 g/dL	12.8/12.4 g/dL	10.9/10.6 g/dL	9.4/8.8 g/dL	≈13/≈13 g/dL	14/14 g/dL
Hb target	14 g/dLwomen 16 g/dLmen	14 g/dL	14 g/dL	13 g/dL	15.5 g/dL	14g/dL
Re-start if Hb less than	12.5g/dLwomen 13.5 g/dLmen	NR	13 g/dL	13g/dL	NR	13g/dL

Abbreviations: FFTF—freedom from treatment failure; PFS—progression free survival; DFS—disease free survival; TR—treatment response; RFS—relapse free survival; Pt-platinum

Table 53. Tumor response outcomes—epoetin or darbepoetin versus control

Study ID	Drug	Outcome Reported	Response definition	Intervention (events/total)	Control (events/total)	RR (95% CI) Calculated[a]
Blohmer 2004	Epoetin	overall response rate	NR	48/52	42/52	0.88 (0.75, 1.02)
Engert 2009	Epoetin	complete response	CR/CRu	619/648	614/655	0.98 (0.96, 1.01)
Engert 2009	Epoetin	partial response	NR	10/648	11/655	1.09 (0.47, 2.54)
Goss 2005	Epoetin	overall response 6 wks post chemo	CR + PR	48/52	42/52	0.88 (0.75, 1.02)
Gupta 2009	Epoetin	overall response rate at 1 month	NR	56/58	53/57	0.96 (0.88, 1.05)
Hoskin 2009	Epoetin	tumor response	CR+PR	149/151	148/149	1.01 (0.98, 1.03)
Wagner 2004	Epoetin	tumor response	CR+PR	12/17	12/18	0.94 (0.60, 1.48)
Untch 2008	Darbepoetin	pathological complete remission	w w/o noninvasive residual	77/356	94/377	1.15 (0.89, 1.50)

[a] From event rates in tables.

Abbreviations: NR—not reported; CR—complete response; CRu—unconfirmed complete response; PR—partial response

Table 54. Other tumor outcomes—epoetin or darbepoetin

Author	Drug	Outcome	ESA Events/sample size	Control Events/sample size	Relative Risk **Hazard Ratio** (95% CI)
Blohmer 2004	Epoetin	relapse-free survival	21/124	32/128	0.67 (0.38, 1.17)
Blohmer 2004	Epoetin	relapse-free survival at 229 weeks	19/113	31/116	NR
Engert 2009	Epoetin	freedom from treatment failure	n/644	n/641	**0.9** (0.6-1.2)
Goss 2005	Epoetin	median time to progression	15.8m	16.5m	NR
Goss 2005	Epoetin	time to progression	NR	NR	NR
Gupta 2009	Epoetin	2-year DFS	36/58	34/57	0.96 (0.72, 1.29)[a]
Henke 2003 Stratum I	Epoetin	locoregional tumor progression or death	47/102	41/94	0.95 (0.69, 1.29)[a]
Henke 2003 Stratum II	Epoetin	locoregional tumor progression or death	30/39	16/38	0.55 (0.36, 0.83)[a]
Henke 2003 Stratum III	Epoetin	locoregional tumor progression or death	39/39	35/39	0.90 (0.81, 1.00)[a]
Henke 2003	Epoetin	locoregional tumor progression	65/180	49/171	1.69 (1.16, 2.47)
Henke 2003	Epoetin	locoregional PFS	116/180	92/171	1.62 (1.22, 2.14)
Hoskin 2009	Epoetin	median duration local DFS	85/151, 31.5 mo	84/149, 35.4 mo	1.04 (0.77, 1.41)
Hoskin 2009	Epoetin	median DFS	87/151, 30.1 mo	85/149, 35.4 mo	1.06 (0.79, 1.43)
Hoskin 2009	Epoetin	time to local disease recurrence	NR	NR	0.94 (0.64, 1.38)
Machtay 2007	Epoetin	locoregional failure	31/72	27/69	0.91 (0.61, 1.35)[a]
Machtay 2007	Epoetin	2-year locoregional failure	29/72	25/69	0.90 (0.59, 1.37)[a]
Machtay 2007	Epoetin	3-year locoregional failure	32/72	25/69	1.20 (0.72, 2.02)
Machtay 2007	Epoetin	2-year locoregional PFS	36/72	40/69	1.16 (0.85, 1.57)[a]
Machtay 2007	Epoetin	3-year locoregional PFS	33/72	36/69	1.19 (0.76, 1.86)
Moebus 2007	Epoetin	56m DFS	70.70%	72%	NR
Moebus 2007	Epoetin	62m DFS	240/333	231/325	0.99 (0.90, 1.09)[a]
Thomas 2008	Epoetin	3-year PFS	23/57	18/52	0.86 (0.53, 1.40)[a]
Thomas 2008	Epoetin	3-year PFS	59%	62%	1.06 (0.58, 1.91)
Thomas 2008	Epoetin	recurrence (local+distant)	19/57	13/52	0.75 (0.41, 1.36) [a]
Wagner 2004	Epoetin	PFS	38.9%±11.5%	25.0%±8.8%	NR
Overgaard 2009	Darbepoetin	5-year locoregional control	135/255	171/259	1.51 (1.05, 2.17)
Overgaard 2009	Darbepoetin	5-year DFS	84/255	119/259	1.52 (1.07, 2.16)
Overgaard 2009	Darbepoetin	locoregional tumor control	143/255	179/260	0.81 (0.71, 0.93)
Overgaard 2009	Darbepoetin	locoregional PFS	130/255	174/260	0.52 (0.36, 0.74)
Untch 2008	Darbepoetin	3-year PFS	260/356	298/377	1.33 (0.99, 1.79)

[a] Calculated from events abstracted

Author	Comments
Blohmer 2004	KM analysis p=0.0831, trend favoring ESA group. Info from Amgen ODAC 2008. total n for each group calculated based on reported 17% and 25% in Amgen ODAC 2008, total n =250
Blohmer 2004	abstract 2004
Engert 2009	slide presentation
Goss 2005	Amgen ODAC 2008
Goss 2005	abstract, “no significant difference”
Gupta 2009	numbers calculated from reported 62% and 60% respectively in full-text
Henke 2003 Stratum I	Kaplan Meier estimate, median locoregional progression-free survival in days: EPO: 1,049d, control 1,152d, p=0.9
Henke 2003 Stratum II	Kaplan Meier estimate, median locoregional progression-free survival in days: EPO 377d, control 1,791d p=0.001
Henke 2003 Stratum III	Kaplan Meier estimate, median locoregional progression-free survival in days: EPO 141d, control 207d, p=0.006
Henke 2003	full text publication, ITT population, adjusted for stratum and American Joint Committee on Cancer stage. 115 and 122 patients were censored. Kaplan Meier estimate, median EPO 280 days vs. control not reached , p=0.09). Tumor progression was assumed when tumor size increased more than 25%.
Henke 2003	full text and FDA 2007. ITT population, adjusted for stratum and American Joint Committee on Cancer Stage, 79 and 64 pts respectively were censored. Kaplan Meier estimate, median locoregional PFS in days, EPO 406d, control 745 d, p=0.04
Hoskin 2009	full-text publication and Amgen ODAC 2008
Hoskin 2009	full-text publication
Hoskin 2009	full-text publication
Machtay 2007	numbers reported in figure 1, full-text publication
Machtay 2007	numbers calculated from reported 40% and 36% in full-text publication
Machtay 2007	numbers calculated from reported 44% and 36% in full-text publication and Amgen ODAC 2008
Machtay 2007	numbers calculated from reported 50% and 58% in full-text publication
Machtay 2007	numbers calculated from reported 46.5% and 51.5% in full-text publication and Amgen ODAC 2008
Moebus 2007	Amgen ODAC 2008. n per group not reported. Total n=643
Moebus 2007	numbers calculated from reported 72% and 71% respectively in abstract publication
Thomas 2008	full text publication, figure 1
Thomas 2008	KM estimates from Amgen ODAC 2008. N per group not reported. Total n=114
Thomas 2008	full-text publication
Wagner 2004	probability of PFS at five years
Overgaard 2009	numbers calculated from reported 53% and 66% in slide presentation ASCO 2009
Overgaard 2009	numbers calculated from reported 33% and 46% in ASCO slide presentation
Overgaard 2009	from Cochrane review 2009 (Lambin et al.)
Overgaard 2009	from Cochrane review 2009
Untch 2008	numbers calculated from reported 73% and 79% in Amgen ODAC 2008. Interim data

KQ1 Other Adverse Events

Non-thromboembolic adverse events reported included hypertension, thrombocytopenia and/or hemorrhage, rash, and seizures. Data from trials on the development of potentially neutralizing antibodies to ESAs were also reviewed. Adverse events that could be definitively attributed to transfusions were not reported in any trial.

Darbepoetin versus Epoetin. Three trials ascertained antibody levels to both drugs (83, 86, 87); Glaspy et al. (85) assessed antibodies for only darbepoetin, but none were detected. There were no data reported on hypertension, thrombocytopenia and/or hemorrhage, rash, or seizure.

Changes from 2006 report: One trial was excluded; two were included unchanged; data were updated for one trial; and one new trial was identified (Appendix Table E1).

Epoetin versus Control.

Hypertension

Thirteen trials (Table 14) reported hypertension incidence (epoetin N=1,552; control N=1,207) (Appendix Table C30). Only one trial included a definition for hypertension. Incidences ranged from zero to 56 percent and zero to 60 percent in epoetin and control arms respectively. Because one trial (181) reported clearly outlier incidence rates (56 percent and 60 percent versus the next highest of 9 percent) the trial was excluded from pooling. In the remaining 12 trials, the pooled relative risk was consistent with an increased risk of hypertension accompanying ESA treatment.

Thrombocytopenia and/or Hemorrhage

Nine trials (Table 14) reported incidence of thrombocytopenia and/or hemorrhage (epoetin N=1,018; control N=780) (Appendix Table C32). The pooled relative risk did not suggest an association (Table 55).

Rash

Five trials (Table 14) reported that the incidence of rash (epoetin N=525; control N=518) (Appendix Table C34) was more common in the epoetin arms (Table 55).

Seizures

Three trials (Table 14) reported that seizure incidence (epoetin N=359; control N=245) (Appendix Table C35) was higher in the epoetin arms (Table 55).

Table 55. Pooled relative risks and other adverse event rates—epoetin versus control

Outcome	Trials	Epoetin N	Control N	RR (95% CI)	I^2	Incidence Epoetin (95% CI)	Incidence Control (95% CI)
Hypertension	12	1,410	1,128	1.59 (1.01, 2.53)	0%	4.0% (2.9, 5.4)	2.4% (1.4, 3.7)
Thrombocytopenia and/or Hemorrhage	9	1,018	780	1.02 (0.78, 1.33)	0%	9.3% (4.1, 16.1)	7.9% (2.6, 15.6)
Rash	5	525	518	1.86 (0.82, 4.23)	9%	3.0% (0.5, 7.6)	2.0% (0.3, 5.0)
Seizures	3	359	245	1.49 (1.45, 4.87)	0%	2.8% (1.4, 1.7)	1.8% (0.2, 5.3)

Antibodies

Five trials ascertained antibody levels (111, 182-185) (epoetin N=498 [461 tested for antibodies]; control N=480 [445 tested for antibodies]). In only Henry et al. (1995) were antibodies detected (2 patients of 26 tested in each trial arm) (Appendix Table C37).

Changes from 2006 review are shown in Table 56 and detailed in (Appendix Table E1).

Table 56. Changes in trials from 2006 review—adverse events epoetin versus control

	Trials Excluded	Trials Unchanged	Trials Updated	New Trials
Hypertension	9	7	0	6
Thrombocytopenia/Hemorrhage	4	3	0	6
Rash	5	1	0	4
Seizures	1	2	0	1
Antibodies	2	4	0	1

Darbepoetin versus Control.

Hypertension

Three trials (Table 14) reported hypertension incidence (darbepoetin N=650; control N=547) (Appendix Table C31) but none included a definition of hypertension. Incidence rates ranged from 3.1 percent to 6.0 percent and 2.1 percent to 5.1 percent in darbepoetin and control arms, respectively.

Thrombocytopenia and/or Hemorrhage

One trial (Table 14) reported incidence of thrombocytopenia and/or hemorrhage (darbepoetin N=301; control N=296) (Appendix Table C33). Incidence was high in both arms and relative risk elevated in with darbepoetin (Table 57).

Rash

No trials comparing darbepoetin with control reported incidence of rash.

Seizures

Two trials (Table 14) reported seizure incidences of 1.3 percent and 1.6 percent in the darbepoetin and 0.5 percent and 3.0 percent in the control arms, respectively (Appendix Table C36) (Table 57).

Table 57. Pooled relative risks and other adverse event rates—darbepoetin versus control

Outcome	Trials	Darbepoetin N	Control N	RR (95% CI)	I^2	Incidence Darbepoetin (95% CI)	Incidence Darbepoetin (95% CI)
Hypertension	3	650	647	1.31 (0.79, 2.18)	0%	5.2% (3.5, 7.2)	3.9% (2.3, 5.9)
Thrombocytopenia and/or Hemorrhage	1	301	296	1.55 (1.07, 2.26)	N/A	19.9% (15.8, 24.5)	12.8% (9.5, 17.1)
Rash	–	–	–	–	–	–	–
Seizures	2	495	488	0.88 (0.14, 5.41)	54%	1.6% (0.7, 2.9)	1.8% (0.2, 5.0)

Antibodies

Five trials ascertained antibody levels (94, 95, 105, 107, 186) (darbepoetin N=1,038 [972 tested for antibodies]; control N=881 [812 tested for antibodies]) but none were detected (Appendix Table C38).

Changes from the 2006 review are shown in Table 58 and detailed in Appendix Table E1.

Table 58. Changes in trials from 2006 review—adverse events darbepoetin versus control

	Trials Excluded	Trials Unchanged	Trials Updated	New Trials
Hypertension	0	0	0	0
Thrombocytopenia/Hemorrhage	0	0	0	1
Rash	0	0	0	0
Seizures	0	0	0	0
Antibodies	0	1	1	1

Evidence Regarding the Class of Erythropoietic-Stimulating Agents. Pooled results and incidence rates for epoetin and darbepoetin are shown in Table 59. These adverse events were generally more frequent with ESA use although the magnitude of difference was difficult to ascertain given the lack of standard definitions and limited trial data. There is no evidence to indicate antibodies to these agents develop during treatment for anemia related to cancer therapy.

Table 59. Pooled relative risks and other adverse event rates—epoetin or darbepoetin versus control

Outcome	Trials	ESA N	Control N	RR (95% CI)	I^2	Incidence ESA (95% CI)	Incidence Control (95% CI)
Hypertension	15[a]	2,060	1,775	1.46 (1.04, 2.05)	0%	4.3% (3.3, 5.5)	2.8% (1.8, 3.9)
Thrombocytopenia and/or Hemorrhage	10	1,319	1,076	1.16 (0.91, 1.48)	8%	10.4% (5.1, 17.2)	8.4% (3.6, 14.9)
Rash	5	525	518	1.86 (0.82, 4.23)	9%	3.0% (0.5, 7.6)	2.0% (0.3, 5.0)
Seizures	5	854	733	0.93 (0.43, 2.04)	0%	2.1% (1.2, 3.1)	1.8% (0.6, 3.7)

[a] Excludes one trial judged an outlier

Key Question 2

How do alternative thresholds for initiating treatment compare regarding their effect on the benefits and harms of erythropoietic stimulants? Evidence is limited to directly comparative data from randomized controlled trials. Outcomes of interest include: hematologic response (change in hemoglobin or hematocrit), proportion of patients transfused, quality of life, survival (overall and progression-free), and adverse effects.

Overview of Evidence and Findings for KQ2

Five trials were included (187-191) — a total of 468 patients were randomized to the early intervention and 465 to the late intervention (delay until Hb ≤9-11 g/dL). All included trials were open-label, and thus quality was rated low. All trials were limited to adult patients.

The key question pertains to the class of erythropoietin-stimulating agents; accordingly, results from all trials using epoetin and darbepoetin were combined. Among the five included trials, three used the same threshold for initiating treatment in the late arm (188-190). For purposes of meta-analysis by outcome, all trials reporting a specific outcome were combined (except for hematologic response, see following); and the three trials with the same treatment initiation threshold were combined in a separate analysis, where appropriate. Major findings are summarized in Table 60 to Table 64.

Table 60. Overview: hematologic response, early versus late ESA

	ESA Early vs. Late Response = Hb Increase ≥2g/dL
Number of studies	1 (189)
Patients analyzed	180
Pooled relative risk	1.09
(95% CI)	(0.60, 1.97)
I^2	N/A

Table 61. Overview: transfusion rates, early versus late ESA

	ESA Early vs. Late All Trials	**ESA Early vs. Late Same ESA Initiation Threshold**
Number of studies	5	3[a]
Patients analyzed	908	520
Pooled relative risk	0.73	0.74
(95% CI)	(0.56, 0.96)	(0.52, 1.04)
I^2	0%	0%

[a](188-190)

Table 62. Overview: thromboembolic events, early versus late ESA

	ESA Early vs. Late All Trials	ESA Early vs. Late Same ESA Initiation Threshold
Number of studies	5	3[a]
Patients analyzed	908	524
Pooled relative risk	1.61	1.57
(95% CI)	(0.85, 3.05)	(0.71, 3.46)
I^2	58%	61%

[a](188-190)

Table 63. Overview: on-study survival, early versus late ESA

	ESA Early vs. Late All Trials	ESA Early vs. Late Same ESA Initiation Threshold
Number of studies	3	2[a]
Patients analyzed	438	319
Pooled relative risk	1.28	1.40
(95% CI)	(0.62, 2.64)	(0.64, 3.04)
I^2	0%	0%

[a](188, 190)

Table 64. Overview: overall survival, early versus late ESA

Parameter	ESA Early vs. Late All Trials	ESA Early vs. Late Same ESA Initiation Threshold
Number of studies	4	3
Patients analyzed	793	524
Pooled relative risk	0.95	0.95
(95% CI)	(0.77, 1.17)	(0.77, 1.18)
I^2	0%	0%

[a](188-190)

Detailed Analysis

Characteristics of Included Trials. Each trial compared immediate treatment with ESA to treatment delayed until Hb level decreased to, or below, a prespecified threshold. Characteristics of the five included trials are summarized in Table 65. All enrolled adult patients being treated with chemotherapy; two administered chemotherapy regimens including platinum (188, 190) while one did not report this information clearly (189). Hb level for patient eligibility was ≤12 g/dL in four trials; Crawford et al. (188) enrolled patients with baseline Hb less than 15 g/dL. As noted, three trials use a threshold of Hb ≤10 g/dL for the delayed treatment arm (188-190) while Straus et al. (187) used a threshold Hb ≤9 g/dL and Glaspy et al. (191) Hb ≤11 g/dL to start ESA treatment. Glaspy et al. (2009) also administered epoetin every 3 weeks while the other three studies using epoetin weekly. Charu et al. (2007) and Straus et al. (2006) did not supplement with iron, whereas the other three trials did. Only Schouwink et al. (2008) reported information on a transfusion trigger, giving transfusion as necessary with the recommendation not to transfuse if Hb greater than 9.7 g/dL.

Table 65. Characteristics of the five included studies, early versus late ESA

Study	Malignancy	Total Patients (N), Patients randomized	ESA	Treat-ment duration (weeks)	ESA Early (E)	ESA Late (L) (% Treated)	Hb level for eligibility to enter trial Baseline Hb Early (E), Late (L)
Charu 2007	solid and hematologic tumors	N=204 E: 102 L: 102	Darb	22	300 µg Q3W	Observation until Hb **≤10 g/dL** then start treatment 300 µg Q3W (63%)	≥ 10.5 g/dL but ≤ 12.0 g/dL; E: 11.1, L: 11.2
Crawford 2007	solid tumors (lung)	N=216 E: 109 L: 107	Epo	16	40,000 IU QW	Observation until Hb **≤10 g/dL** then start treatment 40,000 IU QW (46%)	≥ 11.0 g/dL to < 15 g/dL; E: 13.1, L: 13.0
Schouwink 2008	solid tumors (lung, ovary, and breast)	N=110 E: 54 L: 54	Epo	24	40,000 IU QW	Observation until Hb **≤10 g/dL** then start treatment 40,000 IU QW (61%)	> 10.0 g/dL to ≤ 12.0 g/dL E: 11.2, L: 11.2
Straus 2006	hematologic tumors	N=269 E: 135 L: 134	Epo	16	40,000 IU QW	Observation until Hb **≤9 g/dL** after 2nd chemotherapy cycle, then start treatment: 40,000 IU QW (19.4%)	≥ 10.0 g/dL to ≤ 12.0 g/dL E: 11.1, L: 11.2
Glaspy 2009	solid or hematologic tumors	N=136 E: 68 L: 68	Epo	16	120,000 Q3W	Observation until Hb **<11 g/dL** then start treatment 120,000 IU Q3W (75%)	≥ 11.0 g/dL to ≤ 12.0 g/dL E: 11.5, L: 11.5

Hematologic response. Four trials compared hematologic response rates of patients randomized to early or late treatment (187-189, 191). Of these, only Charu et al. (2007) reported Hb responses as defined in this review (Hb increase ≥2 g/dL); the other trials were not included in the analysis of hematologic response. In Charu et al., (2007) nearly 20 percent of early and 30 percent of late randomized patients were not evaluated. Of those assessed, Hb responses were reported for 19 of 94 patients (20.2 percent) in the early arm treated at a mean Hb of 11.1 g/dL and for 16 of 86 patients (18.6 percent) in the arm delayed to a threshold of 10 g/dL (Table 60; RR 1.09; 95 percent CI: 0.60, 1.97) or no detectable difference.

Transfusion rates. All five trials reported effects on transfusion. Trials differed in treatment duration, iron supplementation, chemotherapy, and baseline Hb. Results from the five trials and from the three using the same late arm Hb threshold for initiating ESA treatment (188-190) were pooled with nearly the same results (Table 61; for all trials, RR 0.73; 95 percent CI: 0.56, 0.96; I^2=0 percent). Accordingly, results favor early ESA treatment.

Thromboembolic Events. All five trials reported thromboembolic event rates. Trials differed in treatment duration, iron supplementation, chemotherapy, and baseline. All five trials and the three trials using the same late arm Hb threshold for initiating ESA treatment (188-190); pooled

results favored late ESA treatment (Table 62; all trials, RR 1.61; 95 percent CI: 0.85, 3.05; I^2=58 percent).

Individual trial results for this outcome varied considerably. For example, Glaspy et al. (2009) and Crawford et al. (2007) found no difference between early and late ESA initiation. In contrast, Straus et al., (2006) obtained a RR of 3.72 (95 percent CI (1.27, 10.92), favoring late ESA. The threshold for late initiation in this trial was the lowest at less than 9 g/dL and baseline Hb 11.1 g/dL for the early treatment arm. Consequently, only 19 percent of late patients were treated with ESA. In addition, patients had hematologic malignancies and were being treated with chemotherapy, a population in which risk of thromboembolic complications may be elevated. Thus, late ESA initiation, a low threshold, and overall much lower population exposure in the late intervention arm likely resulted in many fewer events.

Survival. Three trials reported on-study mortality (188, 190, 191); two of these used similar ESA initiation thresholds (188, 190). Results were similar whether two or three trials were pooled (Table 63; for all trials, the pooled RR was 1.28 (95 percent CI: 0.62, 2.64; I^2=0 percent) favoring late ESA but was not significant.

Four trials reported overall survival (187-190); three trials used the same late ESA initiation threshold (188-190) but observation duration varied among the trials—from 40 months in Crawford et al. (2007) to the on-study time (187) of 20 weeks. There was no evidence of difference in pooled relative effects comparing risk of early to late initiation for the three trials: RR 0.95 (95 percent CI: 0.77, 1.17; I^2=0 percent).

Quality of Life. Of the five trials, only one (192) reported no QoL results. Where possible, we focus on FACT-Fatigue subscale results, as in Key Question 1.

In Charu et al. (2007) the change in FACT-Fatigue scores from baseline were reported according to the change in Hb from baseline to end of treatment. We calculated the weighted mean change in FACT-F for the early intervention group and for the late intervention group separately (for calculation see Methods). The mean FACT-Fatigue changes from baseline to end of treatment (week 22) were 0.7 ± 12.9 (n=94) and 0.6 ± 14.2 (n=86) in the early and late groups respectively; less than the MCID of 3 (165).

Crawford et al. (2007) noted that "[i]n the immediate epoetin alfa group, FACT-An subscale scores declined significantly from baseline to study end with a mean change of -7.7 and a p-value of 0.0187." No data were reported for the delayed intervention group, thus no comparative conclusions can be drawn.

Glaspy et al. reported FACT-Fatigue at baseline in the early and late treatment arms of 33.5 ± 13.2 and 27.8 ± 12.0, and at last visit of 32.0 ± 13.2 and 30.4 ± 11.7 respectively; a decrease in the early group of -1.5 and increase in delayed of +2.6.

Straus et al. (193) found an increase of 1.45 for FACT-Fatigue subscale results in the early intervention arm and a decrease of -1.68 in the delayed intervention arm; clinically not significant changes.

Overall there is little evidence to support a clinically meaningful improvement in QoL using either early or late ESA treatment initiation.

Other Outcomes. There was insufficient evidence to report other adverse events or tumor progression.

Changes from 2006 review. Three trials included in the previous review published as abstracts were included as full text (193-195) and two new trials were included (192, 196).

KQ2 Discussion and Conclusions

Five trials compared early to late ESA intervention when Hb level decreased below a pre-specified threshold. These trials were unblinded and lacked placebo arms, and thus were evaluated as low quality, potentially subject to bias. Absence of information on a transfusion trigger further complicates interpretation. The evidence base is small and may not be reliable.

Hematologic response and transfusion rates favored early ESA treatment, in keeping with the established hematologic outcomes of ESA treatment, but the estimate was only just significant for transfusion. In contrast, thromboembolic event outcomes favored late treatment, which also exposed fewer patients to treatment, also in keeping with the known increased risk for thromboembolic events with increased ESA exposure, but results were not significant. On-study survival outcomes favored delayed treatment as well, but were not significant. The quality of life evidence, evaluating the FACT-Fatigue subscale in four trials and FACT-An in a fifth, was inconsistent and did not support a clinically meaningful improvement in either study arm.

In short, the strength of the evidence base is low to determine whether immediate or treatment delayed to when Hb falls below a prespecified threshold results in different outcomes. Nor is evidence sufficient to identify a preferred Hb threshold, among three tested, for initiating ESA treatment.

Evidence GRADE for Central Outcomes. The evidence is lacking to determine whether immediate treatment versus delayed treatment produces better transfusion outcomes or fewer thromboembolic events (overall strength of evidence low) (Table 66 and Table 67).

Table 66. Transfusions: early versus late ESA (GRADE evidence table)

Trials (N)	Subjects (N)	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results RR (95% CI); I^2
5	908	High trial quality: high-0; low-5	Consistent	Direct	Precise	0.73 (0.56, 0.96); 0%

Table 67. Thromboembolic events: early versus late ESA (GRADE evidence table)

Trials (N)	Subjects (N)	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results RR (95% CI); I^2
5	908	High trial quality: high-0; low-5	Consistent	Direct	Imprecise	1.61 (0.85, 3.05); 58%

Key Question 3

How do different criteria for discontinuing therapy or for optimal duration of therapy compare regarding their effect on the benefits and harms of erythropoietic stimulants? Evidence is limited to directly comparative data from randomized controlled trials. Outcomes of interest include: hematologic response (change in Hb or hematocrit), proportion of patients transfused, quality of life, overall and progression-free survival, and other adverse effects.

No randomized controlled trials were identified that fulfill the inclusion criteria of this review. Therefore, no results can be provided.

Decision Analysis

The direct benefits of ESA treatment are increased Hb and lesser risk of transfusion. The greatest potential harm is mortality. While there is uncertainty in the magnitude and clinical importance of measured improvements in quality of life with alleviation of anemia (higher Hb), utilities (values between 0 and 1, the extremes representing death and perfect health, respectively) corresponding to Hb levels have been examined in cancer patients (79). A central question in the decision to administer ESAs is the tradeoff between higher Hb and its potential benefit with the relative increase in mortality; the balance of benefit and harm. Incorporating results from this systematic review into a decision model examining that balance is accordingly an important element of the evidence synthesis. For that purpose, we have organized this section as follows. First, the basic model and base case are outlined. Second, results are presented. Third, results are presented from analyses with relative risk varied with baseline risk. Finally, potential implications and limitations are noted. Results are presented for both quality adjusted life-years and life-years in a hypothetical cohort of 1,000 similar patients. While transfusions are not without risk, as noted by others (78) the frequency of adverse transfusion events is too low to be included here. This is supported by our review for reported adverse events attributed to transfusions in the included trials and by review of summary articles on the topic (197-202).

Model

The model structure is shown in Figure 15 and includes three health states—patients at a baseline Hb of 9 g/dL, an achieved Hb of 11 g/dL through either ESA or transfusion, and death. A 12-week course of chemotherapy and ESA treatment is assumed (the most common scenario in included trials) and patients are followed one year. If an ESA is used, we assumed that it is administered for 12 weeks and any increase in mortality persists through week 16 (58). From week 16 through week 52 we assumed similar mortality and Hb levels in patients initially treated with an ESA or transfusion strategy—consistent with the evidence and with biology. Utilities derived from 3 studies, corresponding to Hb levels of 9 and 11 g/dL were assigned (0.61 and 0.70 respectively). Hb levels for treatment were chosen to approximate current guidance.

To illustrate the above mentioned assumptions, consider a hypothetical patient undergoing a 12-week course of chemotherapy with an initial Hb of 9 g/dL, who receives and responds to administered ESA and survives 52 weeks. The patient begins with a Hb of 9 g/dL, which by week 4 is 11 g/dL, and quality of life or utility improved from 0.61 to 0.70; we assume they spend the entire 4 weeks with a Hb of 11 g/dL (response typically is seen in 2 to 4 weeks) as they do the entire 52 weeks. If the patient does not respond, they remain with a Hb of 9 g/dL but following chemotherapy (week 16 on) their Hb is assumed to improve to 11 g/dL. For the purposes of modeling, a 4-week cycle length was used.

Figure 15. Structure of Decision Model

For the all patients, the risk of mortality is incorporated as follows: during the first 16 weeks or on-study period the underlying mortality rate is that without ESA treatment. In the base case (Table 68), the approximate median of these studies or 7.5% is used; results are also estimated for approximate quartiles of on-study mortality 3 percent, 7.5 percent, 10percent and a low-risk population with a 1 percent rate. Based on the on-study mortality results, those receiving ESAs have a 15% relative increased risk of mortality during the first 16 weeks but not thereafter. We assume that following the on-study period the annual mortality rate would be 5 percent.

Table 68. Base Case Parameters for Decision Model—1-Year Time Horizon

Baseline Hb (g/dL)	9
Achieved Hb (g/dL) during therapy (weeks 0-16)	11
Hb (g/dL) following therapy (weeks 20-52)	11
Response rates (proportion achieving 11 g/dL Hb)	
ESA	54%
Control (transfusion only)	16%
On-study control mortality rate	7.5%
Mortality relative risk on-study with ESA use	1.15
Annual mortality rate weeks 20 to 52 all patients	5%
Utilities	
Hb 9 g/dL	0.61
Hb 11 g/dL	0.70
Dead	0

Results

Results for different underlying mortality rates (i.e., prognosis) are displayed in Table 69 for a hypothetical cohort of 1,000 patients. Assuming relative risk does not vary with underlying mortality risk, over 1 year, an ESA strategy results in either more or similar quality-adjusted life-years, but fewer years of life. The trade-off is worse in patients with a poorer baseline prognosis.

Table 69. Quality-adjusted and life-years gained or lost over a 1-year period in a hypothetical cohort of 1,000 patients

On-Study Mortality Rate Controls	QALYs ESA	QALYs Control	Difference (+ESA better -ESA worse)	Life Years ESA	Life Years Control	Difference (+ESA better -ESA worse)
1.0%	671.5	662.2	+9.3	973.5	975.3	-1.7
3.0%	653.5	646.6	+6.9	947.4	952.4	-5.1
7.5%	614.3	612.5	+1.8	890.5	902.7	-12.1
10.0%	593.3	594.2	-0.8	860.1	875.9	-15.8

When relative mortality risks were varied with underlying risk, again life-years were always lost. Differences in quality adjusted life years varied with some losing over a 1-year time horizon. Varying the annual mortality rates following the on-study period to 10% or 20% changed the magnitude of differences (Appendix Tables H1 and H2) but life-years were always lost.

Table 70. Quality-adjusted and life-years gained or lost over a 1-year period in a hypothetical cohort of 1,000 patients; relative risk varies with underlying risk

On-Study Mortality Rate Controls	QALYs ESA	QALYs Control	Difference (+ESA better -ESA worse)	Life Years ESA	Life Years Control	Difference (+ESA better -ESA worse)
1.0%	668.0	662.2	+5.8	968.5	975.3	-6.8
3.0%	646.3	646.6	-0.3	937.0	952.4	-15.6
7.5%	610.4	612.5	-2.1	884.9	902.7	-17.8
10.0%	596.9	594.2	+2.8	865.4	875.9	-10.5

Limitations

The limitation of the current Markov model used for this analysis is that it is a basic representation of circumstances that are otherwise complex—for example, dose, escalation strategies, cancer therapies. However, the assumptions used for this model are consistent with natural history of and evidence surrounding anemia accompanying cancer treatment. Consequences of thromboembolic events were not included in the model; however, doing so would favor a transfusion strategy. Additionally, the estimates of utilities used in the model may not necessarily be precise though they were based on the findings of four independent studies. Finally, we did not perform a probabilistic sensitivity analysis. The reason for not doing so was that the results of this systematic review are consistent with other meta-analyses. On-study mortality is increased while long-term mortality is not. A probabilistic analysis is not required to examine the tradeoffs.

Implications

Using a base case scenario close to current guidance for ESA use and estimates from this systematic review, these results clarify the tradeoffs accompanying ESA use. Depending on underlying mortality risk or prognosis, there can be gains in quality-adjusted years. But as noted in the results previously, any improvements in quality of life with use of ESAs are on average less than what is deemed clinically meaningful. Finally, there is always a net loss of life-years that will be greatest for patients with the poorest prognoses.

Discussion

Previous systematic reviews have shown erythropoietic-stimulating agents to have comparable hematologic effects and comparable harms. These results, together with the biochemical and pharmacologic similarities of the different agents, are consistent with consideration of ESAs as a class. The body of evidence included here is substantial and adequate to provide sufficient certainty to confirm or fully address the most important questions regarding the effects of these drugs: 1) their effect on Hb levels and transfusions, 2) impact on HRQoL, and 3) adverse consequences including thromboembolic events and mortality.

The collection of included trials was clinically heterogeneous. Nevertheless, there is convincing evidence that ESAs can improve Hb in the setting of cancer treatment, and when successful, result in a commensurate reduction in the risk of transfusion. In slightly more than half, but not all patients, ESAs improve Hb and help avoid transfusion. ESAs reduce the proportion of patients transfused by approximately 40 percent but do not eliminate it—25 percent of patients receiving ESAs in the trials reviewed here required ≥1 transfusion.

Whether, and by what magnitude, ESA use in anemia related to cancer treatment might improve quality of life has been the focus of considerable study. The evidence found through systematic search in this update, and documented in the previous report, is consistent. In the most relevant domain of fatigue, better scores on a well-validated instrument such as FACT-Fatigue accompany the higher Hb levels achieved with ESA use. In contrast, patients randomized to a transfusion strategy experience, on average, a small decline in FACT-Fatigue score. The magnitude of mean difference in change between the two groups was less than the reported minimal clinically important difference; the difference in fatigue experienced by patients, is on average, less than clinically meaningful.

The increased incidence of thromboembolic events and mortality during ESA treatment that has been noted in this report has also been reported by several others, and is consistent with a biologically plausible causal effect of these agents. The relative and absolute increases in thromboembolic events allow a high degree of certainty regarding the magnitude of effect.

The consistent increase in pooled on-study mortality accompanying ESA treatment found in systematic reviews is convincing of a causal effect. The higher relative risk estimate during the on-study period reported by Bohlius et al. (2009), including all trials regardless of cancer treatment, and therefore patients with longer ESA exposure, also supports a causal effect. Although the magnitude of the on-study mortality risk on average is not large, the increase in risk alters the balance of benefit and harm.

Much of the evidence included here was obtained under treatment protocols not currently used—for example, higher baseline and target Hb levels. While it is possible that adverse event rates might be somewhat different with lower baseline and target Hb levels, we found little difference in effect when baseline Hb was less than, or exceeded 10 g/dL. This result is similar to the more convincing individual patient data meta-analysis (45). While some uncertainty remains, given that the adverse consequences are life threatening, the current evidence does not suggest that by following new guidelines, adverse event rates and relative effects will be substantially different.

Some outcomes and aspects of this evidence are accompanied by important uncertainty. First, whether ESAs enhance tumor progression remains unanswered in this review. The evidence surrounding tumor progression is heterogeneous and insufficient to support conclusions. Evidence examining progression-free survival is similarly varied and limited.

Likely the most salient uncertainty pertains to possible subgroups at highest risk of mortality and/or thromboembolic events. We were unable to effectively address those questions with the data included in this review; nor does individual trial data address those questions. There are clues that lack of response to ESAs (203) and dose escalation might be associated with mortality higher than with standard dosing in responders. This notion is also supported by data obtained in other settings. Among patients with end-stage renal disease managed with hemodialysis and ESA treatment; in these patients, the epoetin dose required to attain defined hematocrit values has been reported to be an independent predictor of total mortality (204). Similar results have been reported in diabetics with chronic kidney disease not on dialysis (205). However, for cancer patients, detailed patient-level data unavailable even in individual patient data meta-analyses are necessary.

Finally, the most important concern regarding ESAs in the setting of cancer therapy is the balance of potential benefits and harms. Using circumstances representative of patients included in these trials as the base case in a decision analysis, ESA use is always accompanied by a net loss in life-years. Furthermore, patients with the worst prognosis experience the greatest loss. Although there is gain in quality-adjusted life for some patients, any improvement in quality of life with use of ESAs is on average less than what is deemed clinically meaningful and offset by shortened length of life.

Future Research

Given the current state of evidence, unanswered questions, and balance of benefit and harms, how should future research be considered? Given the magnitude of relative mortality increase and underlying mortality rates in this patient population, it is clear that attempts to reduce uncertainty in relative risk of mortality through clinical trials would require very large samples. The confidence and credible intervals for the estimated relative increase in mortality span a range values—the true relative increase in risk could be higher or lower than 1.15 estimated here. Still these data do establish with sufficient certainty that mortality rates increase. Questions are therefore raised regarding equipoise in pursuing some “true ” relative risk in further clinical trials.

At the same time these agents will continue to be used in for reasons beyond the scope of this review—for example, patient preference, availability of blood, possible emergence of infectious agents in the blood supply. It is therefore important to address whether there are patient subgroups with low risk of harm and how dosing practices influence harms. Unfortunately, these questions present complexities not addressed even in the most carefully designed trials. The fundamental complexity concerns time-varying treatment and confounding—ESA dose is typically varied depending on the Hb level achieved. It is well known that traditional analytical approaches fail to correctly estimate treatment effects under these conditions (88). Accordingly, it is highly unlikely that any future meta-analysis or systematic review will be able to inform these questions.

However, there is a compelling rationale to examine observational data (e.g., carefully conducted registries) using methods appropriate to these questions—whether there is a subgroup and dosing strategy accompanied by some lower risk. A large registry with precise information on dose (amount, frequency, duration, escalation), Hb (baseline, and all recorded values preferably at times specified protocol), and outcomes (including but not limited to thromboembolism, myocardial infarction, death including underlying and contributory causes) would provide the best opportunity to examine these questions. The Dosing and Outcomes Study

of Erythropoiesis-Stimulating Therapies (DOSE) is one example (206). While deriving conclusions from appropriate analytical methods—inverse probability weighting, G-methods, and marginal structural models—requires some assumptions for inference, they are the approaches most able to address unanswered questions.

Lastly, we found many registered completed trials without clearly or readily identified results. The goals of trial registration fall short when results from completed trials are difficult to identify. This situation requires rectifying with clearly identifying results within trial registries.

In summary, a large collection of trials examining ESA use in patients undergoing cancer treatment provides evidence sufficient to conclude that Hb levels are improved and transfusions avoided together with higher rates of thromboembolic events and mortality. Whether there are subgroups at higher and lower risk of adverse events and mortality is unclear. Future research to address the unanswered questions should be limited to examination of observational data collected during the course of usual patient care.

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Appendix A

Search Strategies

Randomized Controlled Trial Search Strategy: PubMed/MEDLINE®

#97	Search **#90 NOT #96**	664
#96	Search **#94 NOT #92**	455958
#94	Search **"Animals"[Mesh]** Limits: **Entrez Date from 2005/03/11 to 2009/10/22**	2477346
#92	Search **"Humans"[Mesh]** Limits: **Entrez Date from 2005/03/11 to 2009/10/22**	2021388
#90	Search **#64 AND #84** Limits: **Entrez Date from 2005/03/11 to 2009/10/22**	717
#89	Search **#64 AND #84**	2133
#84	Search **#70 OR #73 OR #74 OR #77 OR #82 OR #83**	4817344
#83	Search **control OR controlled OR controls OR prospectiv* OR volunteer***	3143028
#82	Search **(("Research Design"[Mesh] OR "Comparative Study "[Publication Type]) OR "Evaluation Studies "[Publication Type]) OR "Follow-Up Studies"[Mesh]**	2021817
#77	Search **"Placebos"[Mesh] OR placebo* OR random***	672908
#74	Search **(singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)**	150424
#73	Search **("Clinical Trial "[Publication Type] OR "Clinical Trials as Topic"[Mesh]) OR "clinical trial"**	735975
#70	Search **((("Randomized Controlled Trial "[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh])) OR "Controlled Clinical Trial "[Publication Type]) OR "Random Allocation"[Mesh]) OR "Double-Blind Method"[Mesh]**	460955
#64	Search **#63 AND #62**	5655
#63	Search **#58 OR #59**	22990
#62	Search **"Neoplasms"[Mesh] OR "Carcinoma"[Mesh] OR malignan* OR cancer OR cancers OR cancerous OR oncolog* OR myelodysplas* OR tumor OR tumors OR tumour* OR neoplas* OR carcinom***	2658404
#59	Search **erythropoietin OR epoetin* OR eprex OR neorecormon OR aranesp OR procrit OR darbepoetin OR CERA OR "C.E.R.A."**	22990
#58	Search **((("Erythropoietin, Recombinant"[Mesh] OR "Erythropoietin"[Mesh] OR "continuous erythropoietin receptor activator "[Substance Name])) OR ("Epoetin Alfa"[Mesh] OR "epoetin beta "[Substance Name])) OR "darbepoetin alfa "[Substance Name]**	17551

Randomized Controlled Trial Search Strategy: EMBASE

#7 #5 AND #6	850
#6 [embase]/lim NOT [medline]/lim AND [2005-2010]/py	1,318,658
#5 #3 AND #4	2,107
#4 'randomized controlled trial'/exp OR 'randomised controlled trial'/exp OR 'controlled clinical trial'/exp OR 'random allocation'/exp OR 'double-blind method'/exp OR 'single-blind method'/exp OR 'clinical trial'/exp OR (singl* OR doubl* OR trebl* OR tripl* AND (mask* OR blind*)) OR placebo* OR random* OR 'research design'/exp OR 'comparative study'/exp OR 'evaluation studies'/exp OR 'follow-up studies'/exp OR 'control'/exp OR controlled OR controls OR prospectiv* OR volunteer* AND [2005-2010]/py	1,959,179
#3 #1 AND #2	3,171
#2 'neoplasms'/exp OR 'carcinoma'/exp OR malignan* OR 'cancer'/exp OR 'cancers'/exp OR cancerous OR oncolog* OR myelodysplas* OR 'tumor'/exp OR tumors OR tumour* OR neoplas* AND [2005-2010]/py	606,635
#1 'erythropoietin, recombinant'/exp OR 'erythropoietin'/exp OR 'epoetin alfa'/exp OR 'epoetin beta'/exp OR 'epoetin'/exp OR 'eprex'/exp OR 'neorecormon'/exp OR 'aranesp'/exp OR 'procrit'/exp OR 'continuous erythropoietin receptor activator'/exp OR 'cera'/exp OR 'c.e.r.a.' OR 'darbepoetin'/exp OR 'darbepoetin alfa'/exp AND [2005-2010]/py	9,914

Observational Study Search Strategy: PubMed/MEDLINE®

#4	Search **#1 AND #2 AND #3**	158
#3	Search **("Neoplasms"[Mesh] OR "Carcinoma"[Mesh] OR malignan* OR cancer OR cancers OR cancerous OR oncolog* OR myelodysplas* OR tumor OR tumors OR tumour* OR neoplas* OR carcinom*)**	2741885
#2	Search **AND ("Erythropoietin, Recombinant"[Mesh] OR "Erythropoietin"[Mesh] OR "continuous erythropoietin receptor activator "[Substance Name] OR ("Epoetin Alfa"[Mesh] OR "epoetin beta "[Substance Name] OR "darbepoetin alfa "[Substance Name] OR erythropoietin OR epoetin* OR eprex OR neorecormon OR aranesp OR procrit OR darbepoetin OR CERA OR "C.E.R.A.")**	23621
#1	Search **Retrospective Studies[MH]**	344634

Note: search results were the same using **("observational/descriptive studies"[MH]) OR "retrospective studies"[MH]** for #1

Meta-analysis Search Strategy: PubMed/MEDLINE®

Hits: 61

#1 AND #2 AND #3

#1 neoplasms (mesh) OR cancer OR cancer*
#2 darbepoetin OR darbepo* OR epoetin OR epoetin* OR erythropoie*
#3 meta-analysis OR meta-analys* OR “meta-analysis” (publication type)

Meta-analysis Search Strategy: Cochrane

Hits: 273

#2 (epoetin OR epoetin* OR darbepoetin OR darbepo* OR ESA or erythropoie*)

AND

#1 (cancer OR cancer* OR neoplasms)

Appendix B: Data Forms

Study eligibility form

Date:

first author, year:

Reviewer:

TYPE OF STUDY 1. Is the study described as randomised? NB: Answer 'no' if the study is in cross over or quasi randomised design	Yes ⇩ Unclear ⇩ Go to Next question No ⇩ **Exclude**
PARTICIPANTS IN THE STUDY 2. Did the participants in the study have a previous treated or untreated malignant disease?	Yes ⇩ Unclear ⇩ Go to Next question No ⇩ **Exclude**
3. Were the participants anaemic or at risk for anaemia from chemotherapy and/or radiotherapy or their malignant disease?	Yes ⇩ Unclear ⇩ Go to Next question No ⇩ **Exclude**
INTERVENTIONS IN THE STUDY 4. Was one group given Epoetin alpha or Epoetin beta subcutaneously or intravenously (not per os) in a dose of at least 300U /kg /week for at least four weeks?	Yes ⇩ Unclear ⇩ Go to Next question No ⇩ **Exclude**
5. Did the control group receive the same care (eg chemotherapy and supportive therapies) with or without placebo?	Yes ⇩ Unclear ⇩ Go to Next question No ⇩ **Exclude**

OUTCOMES IN THE STUDY	Yes	Unclear	No
6. Did the study document haematologic response? ***Or*** Did the study document number of patients or red blood cell units transfused? **Or** Did the study document Quality of life?	⇩	⇩	⇩
	Go to Next question		**Exclude**

Final Decision	**Include**	**Unclear**	**Exclude**
1x 'no' ⇒ **exlude** 1x 'unclear' ⇒ **unclear**			

Study validity form

First author, year:

Date:
Reviewer:

TREATMENT ALLOCATION			
1. Was allocation truly random? Yes: random numbers, coin toss, shuffle etc No: for patient number, date of birth, alternate Unclear: if the method of randomisation was not stated or unclear	Yes	No	Unclear
2. Was the treatment allocation concealed? Yes: central allocation at trials office or pharmacy, sequentially numbered or coded vials, other methods where the trialist allocating treatment could not be aware of the treatment Inadequate: allocation was alternate (by patient, day of the week, admission on ward, etc) or based on information, such as date of birth, already known to the trialist) Unclear: insufficient information given	Yes	inadequate	Unclear
SIMILARITY OF GROUPS			
3.Were the patients characteristics at baseline similar in all groups?	Yes	No	Unclear
IMPLEMENTATION OF MASKING			
4. Was the treatment allocation masked from the participants? (either stated explicitly, or an identical placebo is used)	Yes	No	Unclear
5. Was the treatment allocation masked from the clinicians?	Yes	No	Unclear
COMPLETENESS OF THE TRIAL			
6. Were the number of withdrawals, drop outs and lost to follow up in each group stated? NB: Yes, if there have not been any drop outs or lost to follow up	Yes	No	Unclear
7. Did the analysis include an intention-to-treat analysis **OR WERE LESS THAN 10% OF PATIENTS EXCLUDED?**	Yes	No	Unclear

Data Extraction Main Review – revised 21-11-04

Extractor initials: Date:

Section 1: Paper details

Section 1. Paper details.

Paper title:	
Ref manager number and initials:	
First Author:	
Authors contact address (if available)	
Publication year	
Full text article or only published as an abstract	
Number of trials included in this paper: (if more than one, complete separate extraction forms for each, and add letters A, B, C, etc to the paper name)	
Papers of other trials with which this may link: (if other papers report further results of this trial, incorporate them onto this form, and note what has been here)	
Trial design: Singlecentre or multicentre	
Source of participants (inpatients or outpatients)	
Method of recruitment:	
Dates for recruitment:	
Funding: pharmaceutical or not (give details);	
In industry submission?	
In IPD- Cochrane Review? If yes is it an included study, an excluded study or ongoing trial?	

Aim of study:

Details of comparisons evaluated in this trial:

	X = yes	comments
Epoetin versus placebo		
Epoetin versus no treatment		
Epo versus standard care		
Epo versus administration		
Epo versus brand		
Epo versus dose		
	x = yes	comments
Epoetin plus RBC Transfusions in all arms		
Epoetin plus iron suppl. in all arms		
Epoetin plus G-CSF in all arms		
Epoetin plus other		

Eligibility criteria – describe in text box below:

Exclusion criteria - describe in box below:

How was epo deficiency derived? ie tested for epo or diagnosed by elimination of other causes of anaemia?

Staging evaluation:

Histology/Cytology Yes or no
Describe

Was compliance assessed?
If so describe:

Section 2: Outcomes sought

Outcomes	
Primary	
Secondary	
QoL	

Describe statistics used:

Any power calculations and if so for what?

Time periods of surveillance – describe

Maximum duration of surveillance:

Notes:
Dichotomous data: N/n: number of events/total number of patients
Continuous data: N/n/SD: treatment mean of outcome parameter/total number of patients in group/treatment standard deviation of outcome parameter.

Section 3. Intervention

	Intervention	Control	comments
	Group 1[n=] (%)	Group [n=](%)	
Intervention/control			
Epo Dose IU/kg			
Epo dose frequency			
Epo dose per week IU/kg			
Duration of epo treatment (weeks)			
Dosing regimen*$			
Route (s.c or iv)			
RBC transfusion trigger ? if so what ?			
iron supplementation? if so describe			

***Dosing regimen:**
Fixed (F): all patients were given continuously the same dose of Epoetin
Decreasing (D): patients with a defined response were given a reduced amount of Epoetin
Increasing (I): patients showing no response within a specified period of time were given an increased dose of Epoetin
Notes: e.g. *describe dosing regime:*

1. Chemotherapy:

Chemotherapy regime describe:

Cycles repeated (days):

Times:

Adjustments:

Notes:

(if stated add the number of pts on each chemo regime)

{describe}		Intervention {}	Control {}	comments
Please give numbers and percentages		Group 1 [n=] (%)	Group [n=] (%)	Group 2 [n=] (%)
Chemo agents (list) ↓	Dose/route/time schedule			

2. Radiotherapy:

Radiotherapy regimen

Radiation repeated every days

Times:

Adjustments:

Notes:

(if stated add the number of pts on each chemo regime)

{describe}		Intervention {}	Control {}	comments
Please give numbers and percentages		Group 1 [n=] (%)	Group [n=] (%)	
Radiotherapy regime (list) ↓	Dose/route/time schedule			

Section 4. Results - Patient Characteristics

Comment: number of patients evaluated usually varies in each outcome

Number of patients recruited for this study:	
Number of patients randomised:	
Number of patients evaluated:	
Number of patients recruited for QoL:	
Number of patients evaluated in QoL	

{}	Intervention {} Group 1 [n=] (%)	Control {} Group [n=] (%)	comments
Total Patients randomised			
Total Patients evaluated			
Total Patients not evaluated			
Exclusions Reasons:			
Withdrawals reasons:			
Lost to follow up reasons:			

Were the withdrawals and losses to follow up less than 10% of the study population?:

Characteristics at baseline: *Comment: this was designed to fit also studies with several treatment arms add extra columns if need be.*

{describe}	Intervention {}	Control {}	comments
Please give numbers and percentages	Group 1 [n=] (%)	Group [n=] (%)	
Age (state if mean; median; range)			
Gender M / F	/	/	/
Disease category- Solid or haem			
List diseases ↓			

Disease Stage			
I			
II			
{describe}	Intervention {}	Control {}	comments
III			
IV			
Bone Marrow Involvement			
Performance status			
(Karnofsky, etc 0			
1			
2			
3			
4			
No. with previous epo therapy (describe if details given)			
No. with previous transfusion			
n = transfusion at baseline (give Hb value for pts with previous transfusion)			
Hb baseline (all patients)			
Hb baseline (no prior transfusion/n patients)			
Hematocrit baseline			
serum EPO, no. pts tested			
serum EPO baseline			
serum iron baseline			
serum ferritin baseline			

Are these characteristics roughly balanced between the groups?:

Section 4. Results – Outcomes

Maximum duration of surveillance:
Describe surveillance: ie time on epo, time after trial stopped

dichotomous data: N/n : number of events/total number of patients in group
continuous data: N/n/SD : treatment mean of outcome parameter/ total number of patients in group/treatment standard deviation of outcome parameter

Haematologic response:

	Definition
complete response	
partial response	
no response	

{describe}	Intervention {}	Control {}	comments
	Group 1 [n=] (%)	Group [n=] (%)	
overall response			
complete response			
partial response			
no response			

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Haemoglobin:

{describe}	Intervention {}	Control {}	comments
	Group 1 [n=] (%)	Group [n=] (%)	
Hb (g/dl) Baseline			
Hb (g/dl) Finish of epo therapy*(put time point in brackets)*			
Hb (g/dl) Endpoint *(put time point in brackets)*			
Hb change *(g/dl) if stated in the paper (put time point in brackets)* {SD}			
Other time points			

Data extracted from which text, table, figure?

Expert statistical attention needed?
Notes:

Haematocrit:

{describe}	Intervention {}	Control {}	comments
	Group 1 [n=] (%)	Group [n=] (%)	
Hematocrit Baseline			
Hematocrit Finish of epo therapy*(put time point in brackets)*			
Hematocrit Endpoint *(put time point in brackets)*			
Hematocrit Change if stated in the paper *(put time point in brackets)* {SD}			
Other time points			

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Transfusion:

{describe}	Intervention {}	Control {}	comments
	Group 1 [n=] (%)	Group [n=] (%)	
Number of Patients transfused			
Number of RBC-units transfused			
Number of RBC-units transfused per patient			
Number of RBC-units			

transfused/patient/4weeks			

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Quality of Life / Performance status

Quality of life outcomes? if so refer paper to Jayne and Susan

{describe}	Intervention {}	Control {}	p-value	comments
	Group 1 [n=] (%)	Group [n=] (%)		
QoL Baseline				
FACT G – 27 items				
Domain 1				
Domain 2				
Domain 3				
Domain 4				
FACT F – 13 items				
QOL Score - endpoint				
FACT G – 27 items				
Domain 1				
Domain 2				
Domain 3				
Domain 4				
FACT F – 13 items				
QOL Score - overall				
FACT G – 27 items				
Domain 1				
Domain 2				
Domain 3				
Domain 4				
FACT F – 13 items				
Performance				
Score				
Endpoint				
Performance				
Score				

Change				

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Tumour response

Reported?:

	Definition
CR **complete response**	
PR **partial response**	
NR **no response**	
When was tumour response assessed, ie at end of study, at n weeks?	
How was tumour response assessed? clinical exam, radiotherapy, computer tomography, other?	

{describe}	Intervention {} Group 1 [n=] (%)	Control {} Group [n=] (%)	Comments, p-value
CR			
PR			
NR			

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Mortality

Reported?:

{describe} **Cause of death**	Intervention {} Group 1 [n=] (%)	Control {} Group [n=] (%)	Comments, p-value

Data extracted from which text, table, figure?
Expert statistical attention needed? Notes:

Adverse events:

document during which period the adverse events occurred: during study period, after completion of study

{describe}	Intervention {}	Control {}	Comments, p-value
	Group 1 [n=] (%)	Group [n=] (%)	
Hypertension (definition)			
Rash/Irritation			
Pruritis			
Mortality			
Thrombotic Event (Definition)			
Seizure			
Haemorrhage/Thrombopenia			
Fatigue: Definition:			
EPO Antibodies			

Other adverse events:

{describe}	Intervention {} Group 1 [n=] (%)	Control {} Group [n=] (%)	Comments, p-value

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Survival

Reported?:

Main results	**HR**	**CI**	**p**	**Comments (inc details)**
Unadjusted (logrank or M-H)				
Stratified				
Cox model				

Other data	**Group 1**	**Group 2**	**Total**	**Comments (inc details)**
Number of events				
Number analysed				
Median survival				
Follow-up (min/max/median)				
Proportions alive at t				
Kaplan Meier curves?				
Other survival curves?				

Summary data estimates				
Method	**O-E**	**V**	**Favours...**	**Comments (inc details)**

*complete one sheet for each comparison between groups

Comments

Data Extraction – AHRQ 2009 Update

Author, Date: _____ Reviewer, Date: _____ Source: _____

ADDITIONAL DATA: (x = yes/100% , nr = not reported, 'number'%)

Age of the Patients:

(mean/median, SD, range: ESA: …… ……control: ……..……)

	only children (<18 J)		> 68% children (<18 J)
	adults (≥ 18 J), explain:		
	only elderly (≥ 65 J)		> 68% elderly
	only non-elderly adults (≥ 18 J but ≤ 65 J)		> 68% non-elderly
	other, explain:		

Gender:

male only	female only	both

Type of Chemotherapy

	platinum-based (100% of the study population received platinum-based ct)
	platinum-based (> 70% of the study population received platinum-based ct)
	both (less than 70% platinum-containing)
	both (no numbers given)
	without platinum (all patients)
	other, explain:

Hb- target (see ‘dosing regimen’), **Hb-target defined as Hb level when ESA had to be stopped**

<10 g/dl	10 – 12 g/dl	>12 g/dl

Quality Assessment

a. The study was a randomized controlled trial (‘Yes’ if stated to be randomized)
b. The study was double-blind (‘Yes’ if a placebo is used)
c. Less than 10% of subjects within each study arm were excluded from the analysis and the percentage of subjects excluded from analysis in each arm was less than 2:1; or less than 5% of subjects were excluded in each study arm.

High Quality: A and B and C	Low Quality: At least one not fulfilled

Hypertension

Is a Definition of Hypertension reported in the date extraction? If not, please note there.

Transfusion Data

Are the transfusion data reported in the data extraction including (a) and excluding (b) the first 4 weeks of ESA treatment? If not, please note there (data for (a) and/or (b) or “not reported” or “unclear”)

TRIAL SELECTION FORM FOR **AHRQ 2009**

Reviewer: Date:

TO INCLUDE*	KQ1 a,b,c	KQ1 d	KQ2	KQ3	QoL
SURE					
UNSURE					
TO EXCLUDE**					
CONFIRMED					

Reason for exclusion**	nrct	allo	ong	none	mbt	ept	surg	nop	msl	ora	eqol	dup

REF ID					
First author and year of publication					
Connex to trial - No ongoing interim? => ex - Duplicate publication? => ex					
Source of evidence	Full text	Abstract	FDA	Personal	Other (specify)

Key Questions

Question 1

1. What are the comparative benefits and harms of erythropoiesis stimulating (ESA) strategies and non-erythropoiesis stimulating (ESA) strategies to manage anemia in patients undergoing chemotherapy or radiation for malignancy (excluding myelodysplastic syndrome)? Outcomes of interest include overall survival (longest available follow-up), progression-free survival, quality of life, hematologic responses, transfusions, tumor response to therapy, thromboembolic complications, and other adverse events. Specific comparisons to be included are:

a. Epoetin* versus no ESA;
b. Darbepoetin versus no ESA;
c. Epoetin* or darbepoetin versus no ESA; and
d. Epoetin* versus darbepoetin.
*alpha or beta

Question 2

How do alternative thresholds for initiating treatment compare as regards their affect on the benefits and harms of erythropoietic stimulants? Evidence is limited to directly comparative data from randomized controlled trials. Outcomes of interest to include: hematologic response (change in hemoglobin or hematocrit), proportion of patients transfused, quality of life, survival (overall and progression free) and adverse effects.

Question 3

How do different criteria for discontinuing therapy or for optimal duration of therapy compare as regards their affect on the benefits and harms of erythropoietic stimulants? Evidence is limited to directly comparative data from randomized controlled trials. Outcomes of interest to include: hematologic response (change in hemoglobin or hematocrit), proportion of patients transfused, quality of life, survival (overall and progression free) and adverse effects.

Appendix C: Evidence Tables

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I UPDATE 2009/2010**

Study author	n randomized	n random-ized in experi-mental arm	n random -ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Aapro 2008	463	231	232	epoetin beta	1 x 30,000 IU/wk sc	fixed	24	decreasing: if Hb increased > 2 g/dL between two visits, dose reduced. Stopped if Hb >15 g/dl, restarted when Hb ≤13 g/dl	as necessary	at discretion of physician	OS, PFS, tumor response, RBCT, Hb safety, QoL
Antonadou 2001	401	190 evaluated	195 evaluate d	epoetin	5 x 10,000 IU/wk sc	fixed	5 -6	NR	fix	NR	Hb, local tumor control, safety, DFS, OS
Bamias 2003	144	72	72	epoetin alfa	3 x 10,000 IU/wk sc	fixed	21 to 24 wks (duration of chemo), categorized as >20	decreasing: if Hb increased by 2 g/dl dose reduced to 75%, stopping: if Hb > 15 g/dL epo stopped and resumed at 75% dose when Hb <13g/dl	NR	at discretion of physician	RBCT, Hb, predictors of response, QoL in a subset of centers
Blohmer 2004	257	128	129	epoetin alfa	3 x 10,000 IU/wk sc	fixed	4 cycles of chemotherapy each 3 weeks plus radiotherapy plus additional 2 weeks approx. 27 weeks, categorized as >20	decreasing: if Hb reached 13 g/dL dose reduced to 66%. Increasing: if baseline Hb < 10.5 g/dL ESA 10,000 6 times weekly, stopping: if Hb > 14 g/dL epo stopped	in ESA arm fixed, not in control arm	in controls if Hb < 9 g/dL	RFS, Hb, RBCT, QoL, safety
Boogaerts 2003, Coiffier 2001	262	133	129	epoetin beta	3 x 150 IU/kg/wk sc	weight	12	increasing: if Hb increase <0.5 g/dL within 3-4 wks or <1 g/dL within 6-8 wks dose increased to 300 IU/kg. Decreasing: if Hb increase >2 g/dL within 4 wks dose reduced by 50%. If Hb >14 g/dL stopped and reinstated at 50% if Hb <12 g/dL	as necessary	Hb <8.5 g/dL	QoL, Hb, RBCT, safety
Case 1993	157	81	76	epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	decreasing: if Hct 38% was reached dose could be reduced to maintain Hct level	as necessary	at discretion of physician	Hb, RBCT, QoL, AE

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I** (cont'd)

Study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Chang 2005	354	176	178	epoetin alfa	1 x 40,000 IU/wk sc	fixed	16, max 28, categorized as 16 wks	increasing: if at the end of week 4 or 6 Hb had decreased > 2 g/dl dose increased to 60,000 IU, decreasing: If Hb > 14 g/dl stopped until ≤12g/dl, then restart with 75%, iff Hb increased > 2 g/dl per month dose reduced by 25%	as necessary	Hb < 8 g/dL or discretion of physician	QoL, Hb, RBCT, safety
Christodoulou 2009, Janinis 2003	399	167 evaluated	170 evaluated	epoetin alfa	3 x 10,000 IU/wk sc	fixed	with concurrent chemotherapy, minimum 12 weeks	decreasing: if Hb > 14 g/dl stopped until ≤12g/dl, then restart with 66%, i.e. 10.000 IU given twice a week.	fix	Hb < 8.5 g/dL or discretion of physician	QoL, RBCT, Hb
Dammacco 2001	145	69	76	epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	increasing: if Hb had not increased >1g/dL by week 4, dose doubled to 300IU/kg tiw, decreasing: if Hb increased by 2g/dL within a 4 week period, EPO reduced by 25%, if Hb >14g/dL withheld until Hb<12g/dL then reinitiated at 25% lower dose	as necessary	Hb < 8 g/dL or discretion of physician	Hb, RBCT, QoL, AE
Debus 2006	385	195	190	epoetin alfa	1 x 40,000 IU/wk sc	fixed	during chemotherapy and radiotherapy, approx. 12 weeks	stopped at 14 g/dL and reinstated at 12 g/dL, in 11/2003 reduced to 13 g/dL.	handled differently	NR	OS, TR, QoL, Hb, RBCT, safety, tolerance to EPO

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I** (cont'd)

Study author	**n random-ized**	**n random-ized in experi-mental arm**	**n random-ized in control arm**	**Drug**	**Dose**	**Weight based or fix**	**Duration of study drug medication (weeks)**	**Dose adjustment**	**Iron**	**Transfusion trigger**	**Primary and secondary outcomes of the study**
Engert 2009	1379, evaluated 1303	648	655	epoetin alfa	1 x 40,000 IU/wk sc	fixed	22-24	Hb target initially 13 g/dL, after protocol amendment 14 g/dL	NR	NR	QoL, Hb, OS, FFTF, PSF, TVE, RBCT, safety
EPO-INT-1	246	165	81	epoetin alfa	a: 3 x 150 (n=85); b: 3 x 300 IU/kg (n=80) sc	weight	1 month post chemotherapy, categorized as unclear	increasing: if reticulocyte after 4 weeks < 40,000 double dose (for 150 arm), stopping: if Hb > 14 g/dL stop until Hb < 12.5 g/dL then restart at 75%	as necessary	NR	tumor response, survival, disease progression, TVEs
EPO-INT-3	201	136	65	epoetin alfa	3 x 150-300 IU/kg sc	weight	12	increasing: if reticulocyte after 4 weeks < 40,000 double dose, stopping: if Hb > 14 g/dL (w) or > 16 g/dL (m) stop until Hb < 12 g/dL (w) or 14 g/dL (m) then restart at 75%	as necessary	NR	RBCT,Hb, QoL

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I** (cont'd)

Study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Goss 2005, EPO-CAN-15	106	53	53	epoetin alfa	1 x 40,000 IU/wk sc	fixed	approximately 12-24, categorized as > 20	target 14 – 16 g/dL	as necessary	NR	local tumor control, progression free survival, overall survival, Hb, RBCT, QoL, safety, median survival
Grote 2005, N03-004	224	109	115	epoetin alfa	3 x 150 IU/kg/wk sc	weight	12 (assumed as drug given during 3 x 3 wks chemo plus 3 wks)	decreasing: dose withheld if Hb >16 g/dL and restarted at 50% if Hb <14 g/dL	as necessary [10]	NR	tumor response, overall survival, Hb, transfusion rate
Gupta 2009	120	60	60	epoetin beta	3 x 10,000 IU/wk sc	fixed	7 (assumed, drug started 10-15 days before 5 weeks of chemoradiotherapy)	NR	fix	if Hb < 10 g/dL	Hb, QoL, OS

[10] Information taken from Bohlius 2009 Cochrane Review

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I** (cont'd)

Study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Henke 2003	351	180	171	epoetin beta	3 x 300 IU/kg/wk sc	weight	7-9, median duration of epo tx: 42.5 days	stopping: stop if Hb level >14g/dL (women) or 15g/dL (men), or if Hb increase >2g/dL/wk, resumed if Hb fell below target	as necessary	NR	locoregional progression free survival, survival, Hb, AE, tumor progression
Henry 1995	132	67	65	epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	decreasing: if Hct 38% was reached drug stopped until Hct < 38%	as necessary	at discretion of physician (result: epo Hct 24.7%, control Hct 25.45)	Hb, RBCT, QoL, AE
Hoskin 2009, EPO-GBR-7	301 (one patient randomly assigned but no data collected)	151	149	epoetin alfa	if hb < 12.5 then 3 x 10,000 IU (25% of patients) ; if hb > 12.5 then 3 x 4,000 IU (75% of patients) sc	adjusted	12	titration: to achieve and maintain Hb 12.5 g/dl to 15 g/dl, initiate at Hb level 15g/dL.; iff Hb > 15 g/dL drug withheld and restarted at Hb 14.5 at 50% dose.; if Hb below 12.5 g/d at week 4 dose increased to 120,000 IU per week.	fix	NR	local disease free survival, OS, tumor response, AE, QoL
Iconomou 2003	122	61	61	epoetin alfa	3 x 10,000 IU/wk sc	fixed	12	increasing: if Hb increase < 1 g/dL dose increased to 3 x 20,000 IU; decreasing: if Hb increased >2g/dL dose reduced by 25%	fix	Hb 7.5 g/dL or discretion of physician	QoL, Hb change, RBCTs in an outpatients oncology setting

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I** (cont'd)

Study author	n random-ized	n random-ized in experimental arm	n random-ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Leyland-Jones 2005; Leyland-Jones 2003	939	469	470	epoetin alfa	1x 40,000 IU/wk sc	fixed	median duration 52 weeks	increasing: if Hb increase <10.5 g/dL after 4 wks drug increased to 60,000 IU/wk, decreasing: if Hb level >14 g/dL or increase > 2 g/dL drug withheld	as necessary	NR	survival, QoL, hematological effects, transfusions, time to progression, AE, tumor response
Littlewood 2001	375	251	124	epoetin alfa	3 x 150 IU/kg/wk sc	weight	28	stopping: if Hb level increased to >15 g/dL drug was stopped and restarted if Hb 12 g/dL	as necessary	Hb < 8 g/dL or clinical symptoms	Hb, RBCT, QoL, AE, after protocol amendment also survival
Machtay 2007, Machtay 2004	148	77	71	epoetin alfa	1x 40,000 IU/wk sc	fixed	approx. 8-9	decreasing: if Hb $\geq$ 16 g/dL (men) or >14 g/dL (women) drug stopped, if Hb <13.5 g/dL (men) or <12.5 d/dL (women) dosing resumed at a dose reduction of 30,000 IU, increasing: if Hb did not increase >1g/dL after 4 weeks, dose increased to 60,000 IU/week	handled differently	NR	local regional failure rate, local regional progression free survival, overall survival, Hb , toxicity, patterns of failure

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I** (cont'd)

Study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Moebus 2007	658	333	325	epoetin alfa	3 x 150 IU/kg/wk sc	weight	approx. 18	NR, target Hb 12.5 to 13 g/dL, stopping rule from IPD review Hb 14 g/dL	handled differently	NR	DFS, OS, relapse free survival, anemia, RBCT, toxicity, Hb, local relapse, QoL
Milroy 2003	425	214 evaluated	210 evaluated	epoetin alfa	3 x 10,000 IU/wk sc	fixed	28	start if Hb ≤ 13 g/dL (men) or Hb ≤ 12 g/dL (women), drug stopped at Hb 15 g/dL (men) and 14 g/dL (women)	as necessary	NR	QoL, Hb, RBCT, survival
ML17620	121	Assume 61	Assume 60	epoetin beta	3 x 150 IU/kg/wk sc	weight	12	NR	as necessary	as necessary	Hb, RBCT, safety, iron
Oberhoff 1998	218	114	104	epoetin beta	7 x 5,000IU/wk sc	fixed	12	target ceiling 14 g/dL	as necessary	discretion of physician	Hb, RBCT, AE

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I** (cont'd)

Study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Osterborg 2002, Osterborg 2005	349	173	176	epoetin beta	3 x 150 IU/kg/wk sc	weight	16	increasing: if no signs of response within 4 weeks, dose increased to 300; decreasing: if Hb increase >2 g/dL per 4 weeks dose reduced by 50%; iIf Hb level >14 g/dL study drug was stopped, if Hb level <13 g/dL reinstated at 50%	as necessary	Hb < 8.5 g/dL or medically indicated	Hb, RBCT, AE, QoL, OS, transfusion free survival, Hb response
Porter 1996	24	10 evaluated	10 evaluated	epoetin alfa	3 x 150 IU/kg/wk sc	weight	16	increasing: if Hb < 11.5 g/dL at week 4 increase by 50 IU/kg, decreasing: if Hb ≥ 15 g/dL reduce by 50 IU/kg, stopping: if Hb > 16.5 g/dL stop until Hb < 11.5 g/dL.	as necessary	Hb < 8.0 g/dL or medically indicated	RBCT
Pronzato 2002	223	110	113	epoetin alfa	if body weight > 45 kg 3 x 10,000 IU	adjusted	approximately 28 weeks (duration of chemotherapy plus 4 weeks)	drug withheld if Hb > 14 g/dL	as necessary	NR	QoL, RBCT, Hb, tumor response
Ray-Coquard 2009	218	110	108	epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	decreasing: if Hb increased >2g/dL in a month, EPO decreased to 75%, increasing: if after 4 weeks Hb<10.5 g/dl with <1g/dL decrease in the previous 4w and reticulocyte count <40,000 EPO 60,000/week. Hb ceiling from IPD review: 14 g/dL	as necessary	NR	RBCT, OS, safety, Hb, DFS, QoL, time to disease progression

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I** (cont'd)

Study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Razzouk 2006; Razzouk 2004	224	113	111	epoetin alfa	1 x 600 IU/kg/wk U IV	weight	16	increasing: if Hb increase <1 g/dL within 4 wks drug increased to 900 IU/kg, maximal 60,000 IU iv qw; decreasing: if Hb > 15 g/dL drug withheld, restarted if Hb < 13 g/dL with 25% dose reduction	as necessary	Hb < 7 g/dL	Hb, QoL, RBCT, safety, vital signs
Rose 1994	221	142	79	epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	epoetin alfa dose titrated to maintain Hct between 38%-40%	as necessary	NR	HR, RBCT, QoL, safety
Savonije 2005; Savonije 2004	315	211	104	epoetin alfa	3 x 10,000 IU/wk sc	fixed	until end of chemotherapy, mean treatment duration 14 weeks	increasing: if Hb increase <1 g/dL and Hb < 12.1 g/d after 4 wks drug increased to 20,000 IU tiw; decreasing: if Hb > 14 g/dL drug withheld until Hb < 13 g/dL, resumed at 10,000 IU twice weekly; if Hb > 2 g/dL in 4 weeks drug reduced to 10,000 IU twice weekly	handled differently	discretion of physician, to be avoided if Hb > 9.7 g/dl	Hb, RBCT, survival, safety, QoL
Thomas 2002	130	65	65	epoetin alfa	if body weight > 45 kg 3 x 10,000 IU qw sc, if body weight < 45 kg 3 x 5,000 IU qw sc	adjusted	28	drug stopped if Hb > 14 g/dL	as necessary	at discretion of physician	Hb, QoL, RBCT, tumor response, survival, safety

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part I** (cont'd)

Study author	**n random-ized**	**n random-ized in experi-mental arm**	**n random-ized in control arm**	**Drug**	**Dose**	**Weight based or fix**	**Duration of study drug medication (weeks)**	**Dose adjustment**	**Iron**	**Transfusion trigger**	**Primary and secondary outcomes of the study**
Thomas 2008, GOG-0191	113	58	55	epoetin alfa	1 x 40,000 IU/wk sc	fixed	during radiochemotherapy, approx. 6-9 weeks	titration to maintain >13 g/dl, initiate at Hb level 12 g/dl, stop if Hb > 14 g/dL for 2 weeks or more, reinstate if Hb < 13 g/dL at same dose	as necessary	in ESA arm in Hb < 12 g/dL, in control arm recommended	Hb, survival, progression free survival, local tumor control, quality of life
Tsuboi 2009	122	63	59	epoetin beta	1 x 36,000 IU/wk sc	fixed	8	stopping: if Hb level ≥14 g/dL drug stopped	as necessary	at discretion of physician	Hb, RBCT, survival (retrospective), QoL
Wagner 2004	38	18	20	epoetin alfa (plus G-CSF in both study arms)	7 x 200 IU/kg sc	weight	assumed category 12-16	Ii Hb <10g/dL EPO administered daily, if Hb >10 g/dL Epo administered 3 times/week, iIf Hb>13g/dL EPO withheld until Hb<13g/dL	as necessary	Hb < 8 g/dL or medically indicated	RBCT, safety
Wilkinson 2006	182	121	61	epoetin alfa	3 x 10,000 IU/wk sc if body weight > 45 kg, otherwise 3 x 5,000 IU/wk sc	adjusted	max 28 weeks	increasing: if Hb increase < 1 g/dL or reticulcytes not >40,000 at 4 weeks dose doubled, stopping: if Hb > 14 g/dL ESA stopped and restarted at Hb 12 g/dL with 25-50% dose reduction, decreasing: if Hb increase > 2 g/dL/4weeks dose reduced by 25-50%	as necessary	Hb < 9 g/dL	Hb, RBCT, tumor response, safety, QoL
Witzig 2005	344	174	170	epoetin alfa	1 x 40,000 IU/wk sc	fixed	16	increasing: if Hb increase < 1 g/dL after 4 weeks or patients required RBCT, dose increased to 60,000 IU; if Hb level >15g/dL for two weeks, drug stopped and restarted with 75% when Hb <13 g/dl	fix	at discretion of physician	RBCT, Hb, response predictors, survival, tumor response, QoL

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part II updated 2009/2010**

Study author	n random-ized	Cancer details	Cancer category	Therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	Age; EPO arm, as reported (mean, SD) range if not reported otherwise	Age; control arm, as reported (mean or median, SD), range	Age category (children, adults, elderly (>65)
Aapro 2008	463	breast cancer (stage IV)	solid	chemotherapy without platinum	Hb < 12.9 g/dL	11.5 (SD 1.1)	11.2 (SD 1.2)	10-12	median 56 (range 27-78)	median 57.5 (range 29-83)	adults
Antonadou 2001	401	pelvic tumors	solid	radiotherapy	NR	9.8 (+/- 0.1)	10.1 (+/- 0.6)	10	58.6 (+/- 5)	56 (+/- 6.1)	adults
Bamias 2003	144	ovarian, NSCLC, SCLC, other	solid	platinum based chemotherapy	Hb <13 g/dL	11.5 (95% CI 11.1, 11.9)	11.5 (95% CI 11.2, 11.8)	10-12	median 60 (range 18-77)	62 (19-80)	adults
Blohmer 2004	257	cervical cancer	Solid	platinum based radiochemotherapy	NR	12.0 (+/- 1.3)	11.8 (+/- 1.3)	10-12	41.3 (+/-9)	43.4 (+/-9.7)	adults
Boogaerts 2003, Coiffier 2001	262	MM, NHL, CLL, ovarian, bone, GI, respiratory, other	mixed	chemotherapy, platinum & non platinum, details not reported but interpreted as such as some solid cancers which are usually treated with platinum are included	Hb ≤11 g/dl	median 9.0 (range 5-13)	median 9.2 (range 5-12)	10	median 62 (range 24-68)	median 62 (range 24-85)	adults
Case 1993	157	solid and hematological tumors	mixed	chemotherapy without platinum	Hb ≤10.5 g/dl	9.29 (SD 1.14)	9.57 (SD 1.04)	10	median 64 (range 27-92)	median 64 (range 30-88)	adults
Chang 2005	354	breast cancer, stage I-IV	solid	chemotherapy without platinum	Hb <12g/dL	11.2 (SD 0.9)	11.3 (SD 0.8)	10-12	50.4 (SD 11.1)	50.1 (SD 10)	adults

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part II** (cont'd)

Study author	n random-ized	Cancer details	Cancer category	Therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	Age; EPO arm, as reported (mean, SD) range if not reported otherwise	Age; control arm, as reported (mean or median, SD), range	Age category (children, adults, elderly (>65)
Christoudoulou 2009, Janinis 2003	399	solid tumors	solid	chemotherapy, platinum & non platinum (38% received platinum)	Hb ≤12.0 g/dL	10.15 (+/- SD 0.69)	10.30 (+/- SD 0.58)	10-12	median 61 (range 22 – 82)	median 63 (range 30 – 89)	adults
Dammacco 2001	145	MM	hematological	chemotherapy, platinum & non platinum, no numbers reported	Hb ≤11 g/dl	9.3 (SD 1.27)	9.6 (SD 0.95)	10	median 67.3 range 43.0-80.4	median 65.0 range 38.2-88.9	adults
Debus 2006	385	NSCLC, stage IIIA/B, primarily inoperable	solid	cisplatinum containing sequential chemoradiotherapy	NR	NR	NR	NR	NR	NR	adults
Engert 2009	1379	advanced HD	hematological	chemotherapy without platinum	NR	median 12.19 (SD 1.97)[11]	median 12.34 (SD 1.97) [2]	12	median 35 (range 18-60)	median 34 (range 18-60)	adults
EPO-INT-1	246	ovarian	solid	NR, categorized as platinum-based chemotherapy	Hb ≤ 11 g/dl	NR	NR	NR (no assumption possible)	NR	NR	adults
EPO-INT-3	201	breast cancer, NHL, MM, ovarian cancer, SCLC, other	mixed	chemotherapy, platinum (27%) and non platinum (73%)	Hb ≤ 12 g/dl	NR	NR	NR (no assumption possible)	NR	NR	adults
Goss 2005, EPO-CAN-15	106	limited disease SCLC	solid	platinum based chemotherapy plus radiotherapy, categorized as radiochemotherapy	NR	13.5 g/dL	13.5 g/dL	12	NR	NR	adults
Grote 2005	224	SCLC, limited and extended disease	solid	platinum based chemotherapy	Hb ≤14 g/dl	12.8 (SD 1.5)	13.0 (SD 1.5)	12	64.4 (SD 8.7)	63.2 (SD 8.9)	adults
Gupta 2009	120	Cervical cancer (stage IIB-IIIB)	solid	Platinum based chemotherapy plus radiotherapy, categorized as radiochemotherapy	Hb 10-11 g/dL	10.45 (range 9.5-11.0)	10.70 (range 10.0 – 12.5)	10-12	48.27 (range 18-70)	48.18 (range 20-65)	adults

[11] Median and SD estimated from graph, see Hb table

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part II** (cont'd)

Study author	n random-ized	Cancer details	Cancer category	Therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	Age; EPO arm, as reported (mean, SD) range if not reported otherwise	Age; control arm, as reported (mean or median, SD), range	Age category (children, adults, elderly (>65)
Henke 2003	351	advanced (stage III , IV) head and neck	solid	radiotherapy after surgical resection, 22% (78/351) of patients radiotherapy only	<13 g/dL (men), <12 g/dL (women)	median 11.7 (range 8.5 –14.4)	median 11.8 (range 6.9 – 14.6)	10-12	median 58 (range 25-81)	median 57 (range 36-87)	adults
Henry 1995	132	solid and hematological tumors	mixed	platinum based chemotherapy	Hb ≤10.5 g/dl	9.68 (SD 1.28)	9.27 (SD 1.49)	10	60 (20-84)	60 (34-83)	adults
Hoskin 2009, EPO-GBR-7	301	head and neck, stage I-IV	solid	radiotherapy	Hb ≤15 g/dl	13.4 (range 9.3 – 15.5)	13.7 (range 8.9 – 16.7)	12	60 (range 37 – 88)	58 (range 35 - 84)	adults
Iconomou 2003	122	lung, breast, colorectal, ovarian, unknown primary, kidney, stomach, other	solid	chemotherapy, platinum & non platinum (51/122 (42%) received platinum)	Hb ≤11.0g/dL	10.1 (+/- SD 0.6)	10.1 (+/- SD 0.4)	10-12	60.6 (SD 10.7)	62.6 (SD 10.3)	adults
Leyland-Jones 2005	939	metastatic breast cancer	solid	chemotherapy, no details reported, categorized as chemotherapy without platinum	Hb of any level. No upper or lower limit for inclusion	12.5 (SD 1.8)	12.5 (SD 1.7)	12	55.8 (SD 11.13)	55.1 (SD 10.49)	adults
Littlewood 2001	375	NHL, MM, breast, HD, CLL, GI, other	mixed	chemotherapy without platinum	Hb ≤10.5 g/dl OR 10.5-12 AND decrease of ≥1.5 g/dL per cycle	9.9 (SD 1.13)	9.7 (SD 1.13)	10	58.3 (SD 14.8), range 18.7-84.9	59.5 (SD 13.9), range 21.1-88.6	adults
Machtay 2007, Machtay 2004	148	head and neck non-metastatic, not resected	solid	radiotherapy, advanced stages received in addition platinum based chemotherapy, categorized as radiotherapy	Hb 9-13.5 g/dL (men), 9-12.5 g/dL (women)	median 12.0 (range 9.2 – 13.5)	median 12.1 (range 9.0 – 13.5)	12	median 64 (range 24–90)	median 61 (range 42–86)	adults

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part II** (cont'd)

Study author	n random-ized	Cancer details	Cancer category	Therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	Age; EPO arm, as reported (mean, SD) range if not reported otherwise	Age; control arm, as reported (mean or median, SD), range	Age category (children, adults, elderly (>65)
Milroy 2003	425	NSCLC, stage IIIB/IV	solid	platinum based chemotherapy	Hb ≤15 g/dL (men), Hb ≤14 g/dL (women),	12.8	12.8	12	NR	NR	adults
ML17620	121	solid tumors	Solid	platinum based chemotherapy	anemia	NR	NR	NR (no assumption possible)	NR	NR	adults
Moebus 2007	658	breast cancer	solid	chemotherapy without platinum	NR	median 12.4	median 12.8	12	median 51	median 51	adults
Oberhoff 1998	218	solid tumours; ovarian, breast, lung, GU, GI, other	solid	chemotherapy, platinum (56%) & non platinum	Hb ≤11 g/dl OR ≤13 g/dl AND decrease of ≥1.5 g/dL per CT cycle	9.65 (SD 1.10)	9.75 (SD 1.09)	10	median 53, range 20-77	56, range 19-73	adults
Osterborg 2002, Osterborg 2005	349	MM, NHL, CLL	hematological	chemotherapy presumably without platinum	Hb ≤10 g/dl	9.2 (SD 1.1)	9.3 (SD 1.0)	10	63 (32-86)	64 (28-83)	adults
Porter 1996	24	sarcoma	Solid	chemotherapy without platinum, some patients received also radiotherapy during study (n=10)	Hb < 10.5 g/dL	median 9.7 (range 7.7-10.8)	median 9.4 (range 8.2-10.1)	10	median 14 (range 5-17)	median 13 (range 5-16)	children

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part II** (cont'd)

Study author	n random-ized	Cancer details	Cancer category	Therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	Age; EPO arm, as reported (mean, SD) range if not reported otherwise	Age; control arm, as reported (mean or median, SD), range	Age category (children, adults, elderly (>65)
Pronzato 2002	223	breast cancer, stage I-IV	solid	chemotherapy not reported, assumed without platinum	NR	10.7	10.8	10-12	53.3	54.2	adults
Ray-Coquard 2009	218	carcinoma, sarcoma, lymphoma, other	mixed	chemotherapy 'unclear'	Hb <12 g/dl	10 (1.2)	10 (1.2)	10-12	62.7 (SD 11.6)	61.7 (11.6)	adults
Razzouk 2006	224	solid tumours, Hodgkin's disease, non-Hodgkin's disease, ALL	mixed	chemotherapy 'unclear'	Hb ≤10.5 g/dl if aged 5-12, Hb ≤11 g/dl for girls aged > 12, Hb ≤12 for boys aged > 12	9.8 (SD 1.3)	9.5 (SD 1.0)	10	12.4 (SD 3.6)	10.8 (SD 4.0)	children
Rose 1994	221	CLL, stage III, IV	hematological	in the IPD review < 70% received chemotherapy, categorized as "other"	Hct ≤32%	9.1 (1.3)	9.3 (1.2)	10	68.3 (SD 10)	68.1 (9.3)	adults
Savonije 2005; Savonije 2004	315	solid tumors	solid	platinum based chemotherapy	Hb <12.1 g/dL	10.7 (SD 1.0)	10.8 (SD 1.0)	10-12	57.0 (SD 11.0)	58.0 (SD 10.0)	adults

Appendix Table C1. **KQ1: epoetin versus control, study characteristics, Part II** (cont'd)

Study author	n random-ized	Cancer details	Cancer category	Therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	Age; EPO arm, as reported (mean, SD) range if not reported otherwise	Age; control arm, as reported (mean or median, SD), range	Age category (children, adults, elderly (>65)
Thomas 2002	130	"cancer patients"	unclear	chemotherapy, platinum and non platinum based, proportion of patients unclear	Hb < 12g/dL	10.59 (SD 1.05)	10.59 (SD 1.05)	10-12	NR	NR	adults
Thomas 2008, GOG-0191	113	cervix carcinoma	solid	platinum based chemotherapy plus radiotherapy, categorized as radiochemotherapy	Hb ≤14 g/dl	10.55 (SD 1.98)[12]	10.91 (SD 1.35)[2]	10-12	median 46 (range 25-77)	median 50 (range 32-78)	adults
Tsuboi 2009	122	lung cancer, lymphoma	mixed	chemotherapy, for some patients platinum based, no numbers given	Hb < 8 g/dL	10.0 (SD 1.0)	10.4 (SD 1.0)	10-12	61.8 (11.9)	62.1 (9.6)	adults
Wagner 2004	38	neuroblastoma	solid	chemotherapy	NR	median 8.85 (range 6.1-11.2)	median 9.35 (range 7.0-15.3)	10	median 3.2 (range 1.2-19.4)	median 3.2 (range 1.1-7.3)	children
Wilkinson 2006	182	ovarian cancer (stage I-IV)	solid	platinum based chemotherapy	Hb ≤12 g/dl	10.75 (SD 0.94)	10.66 (SD 0.83)	10-12	59.1 (SD 10.6)	60.3 (SD 11.2)	adults
Witzig 2005	344	lung cancer, breast cancer, other cancers, active incurable advanced stage	unclear	chemotherapy, platinum & non platinum, 56/330 (17%) received platinum	Hb ≤11.5 g/dl (men), Hb ≤10.5 g/dl (women)	9.5 , range 6.0-11.4	9.4 , range 6.9-11.4	10	63.6 (SD 11.89)	63.7 (SD 13.00)	adults

[12] SD estimated from graph, see Hb table

Appendix Table C2. **KQ1: darbepoetin versus control, study characteristics, Part I**

Study author	n randomized	n random-ized in experi-mental arm	n random-ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Hedenus 2003	349	176	173	darbepoetin alfa	2.25 µg/kg/ qw sc	weight	12	increasing: if Hb increase <1.0 g/dL within 4 wks of treatment dose was doubled; decreasing: if Hb increase >15 g/dL (men) or >14g/dL (women) drug stopped until Hb <13 g/dL and reinstated at 50%	as necessary	Hb < 8g/dL or discretion of physician	Hb response, transfusion, Hb change, QoL
Hernandez 2009	391	196	195	darbepoetin alfa	300 µg Q3W sc	fixed	16	increasing: if Hb < 9 g/dL at week 4 or < 10 g/dL at week 7 and Hb increase < 1 g/dL compared to baseline increase to 500 µg Q3W; decreasing: if Hb increased >1g/dL per 2 weeks dose reduced.;stopping: if Hb > 13 g/dL drug stopped until Hb ≤ 12 g/dL	as necessary	Hb ≤ 8 g/dL or discretion of physician	RBCT, QoL, Hb
Kotasek 2003 a,b,c,d,e,f	259	208	51	darbepoetin alfa	a: 4.5 µg/kg Q3W, b:6.75 µg/kg Q3W, c: 9 µg/kg Q3W, d:12 µg/kg Q3W, e:13.5 µg/kg Q3W, f:15 µg/kg Q3W sc	weight	12	increasing not allowed, decreasing: if Hb increased >15 g/dL (men) or >14 g/dl (women) drug stopped and reinstated at a lower dose level if Hb <13 g/dL	as necessary	NR	safety, antibodies, Hb, RBCT, QoL, darbepoetin concentration in blood

Appendix Table C2. **KQ1: darbepoetin versus control, study characteristics, Part I** (cont'd)

Study author	n randomized	n random-ized in experi-mental arm	n random-ized in control arm	Drug	Dose	Weight based or fix	Duration of study drug medication (weeks)	Dose adjustment	Iron	Transfusion trigger	Primary and secondary outcomes of the study
Overgaard 2009	522	260	262	darbepoetin alfa	150 µg QW sc	fixed	8-10	Hb target: 15.5 g/dL	as necessary	NR	loco regional control, OS, Hb, safety, DFS
Pirker 2008	600	299	301	darbepoetin alfa	300 µg Q4W, after 4 weeks changed to Q3W sc	weight	until end of chemotherapy, categorized as > 20 weeks	increasing: if Hb < 11 g/dL drug given QW, stopping: if Hb ≥ 14 g/dL study drug was stopped and restarted if Hb <13 g/dL	as necessary	NR	Hb, OS, RBCT, safety, disease progression, QoL
Untch 2008	733	356	377	darbepoetin alfa	4.5 µg/kg Q2W sc	weight	during chemotherapy, approximately 21-25	Hb target 13 g/dL	handled differently	Not reported	DFS, OS, success of surgery, tumor response, safety
Vansteenkiste 2002	320	159	161	darbepoetin alfa	2.25 mcg/kg qw sc	weight	12	increasing: if Hb increase < 1 g/dL within 6 wks dose doubled to 4.5 µg/kg/wk, decreasing: If Hb >15 g/dl (men) or >14 g/dl (women) drug stopped, reinstated at 50% if Hb <13 g/dl	as necessary	Hb < 8g/dL or at discretion of physician	transfusion, number of RBCTs, Hb response, AE, overall survival, progression free survival, QoL, hospitalization, antibody formation

Appendix Table C2. **KQ1: darbepoetin versus control, study characteristics, Part II**

Study author	n random-ized	Cancer details	Cancer category	Therapy	Hb eligibility criteria	Hb baseline EPO arm [mean g/dl (SD)]	control arm mean baseline HB (SD)	Hb category	Age; darbepo arm, as reported (mean, SD) range if not reported otherwise	Age; control arm, as reported (mean or median, SD), range	Age category (children, adults, elderly (>65)
Hedenus 2003	349	lymphoma: HD, NHL, MM	hematological	NR, assumed to be chemotherapy without platinum	Hb ≤11.0 g/dL	9.59 (SD 1.22)	9.50 (SD 1.21)	10	64.8 (SD 13.8)	64.6 (SD 12.2)	adults
Hernandez 2009	391	lung, gynecological, other solid and hematological malignancies	mixed	chemotherapy, platinum & non platinum (140/386 (36%) received platinum)	Hb < 11 g/dl	10.1 (0.9)	10.0 (0.9)	10-12	64.5 (12.1)	63.6 (12.3)	adults
Kotasek 2003 a,b,c,d,e,f	259	breast, gyne, gastrointestinal, lung, other	solid	chemotherapy, not reported if with or without platinum, interpreted as some patients receiving platinum as some of solid cancers included are usually treated with platinum	Hb ≤11.0 g/dL	9.93 (SD 1.0)	9.87 (SD 1.12)	10	58.3 (SD 11.9)	56.2 (SD 12.4)	adults
Overgaard 2009	522	head and neck cancer	solid	radiotherapy	Hb < 14.5 g/dL	approx. 13 g/dL	approx. 13 g/dL	12	NR	NR	adults

Appendix Table C2. **KQ1: darbepoetin versus control, study characteristics, Part II** (cont'd)

Study author	n random-ized	Cancer details	Cancer category	Therapy	Hb eligibility criteria	Hb baseline EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	Age; darbepo arm, as reported (mean, SD) range if not reported otherwise	Age; control arm, as reported (mean or median, SD), range	Age category (children, adults, elderly (>65)
Pirker 2008	600	extensive stage SCLC	solid	platinum based chemotherapy	Hb >9 and ≤ 13 g/dL	12.03 (1.07)	11.86 (1.03)	10-12	60.6 (9.2)	61.3 (8.3)	adults
Untch 2008	733	breast cancer	solid	chemotherapy without platinum	NR	median 14.0 (range 9-17)	median 14.0 (range 9-17)	12	median 49 (range 23-65)	median 48 (range 23-65)	adults
Vansteenkiste 2002	320	SCLC, and non-SCLC	solid	platinum based chemotherapy	Hb ≤11.0 g/dL	10.28 (SD 1.08)	9.93 (SD 1.01)	10-12	61.6 (SD 9.2)	61.3 (SD 8.8)	adults

Appendix Table C3. **KQ1: darbepoetin versus control, study characteristics, Part I**

study author	# randomized	design	drug	Darbepoetin dose per week	Epoetin dose per week	weight based or fix	duration of medication (weeks)	Dose adjustment Darbepoetin	Dose adjustment Epoetin	iron	transfu-sion trigger	primary and secondary outcomes of the study
Glaspy 2002, Part A	269	sequential dose finding study	Darbepoetin versus epoetin alfa	a: 0.5; b: 1.0; c: 1.5; d: 2.25; e: 4.5; f: 6.0 and g: 8.0 µg/kg qw	150 IU/kg tiw	darb weight based, epo weight based	12	no dose adjustment	Increasing: if Hb increase < 1.0 g/dL at wk 8 EPO increased to 300 IU/kg tiw	NR	NR	safety, Hb response, Hb levels, RBCT, QoL
Glaspy 2006	1,220	phase 3, non-inferiority trial	Darbepoetin versus epoetin alfa	1 x 200 µg q2w	40,000 IU qw	darb fixed, epo fixed	16	dose escalation permitted at wk 5 if the Hb increase < 1 g/dL.; withheld if Hb > 13 g/dL at any time, and reinstated at 75% of the previously administered dose after Hb to ≤ 12 g/dL	dose escalation permitted at wk 5 if the Hb increase < 1 g/dL.; withheld if Hb > 13 g/dL at any time, and reinstated at 75% of the previously administered dose after Hb to ≤ 12 g/dL Rules changed from a mandatory requirement to physician decision	NR	Hb ≤ 8 g/dL	RBCT, safety, Hb response, QoL
Schwartzberg 2004, a-c	318	to validate patient questionnaire	Darbepoetin versus epoetin alfa	200 µg q2w	40,000 IU qw	darb fixed, epo fixed	16	Increasing: if Hb increase ≤ 1.0 g/dL at wk 4 Darb increased to 300 µg q2w; Stopping: drug was withheld if Hb level > 13.0 g/dL and reinstated at the previous dose if Hb ≤ 13 g/dL.	Increasing: if Hb increase ≤ 1.0 g/dL at wk 4 EPO increased to 60,000 IU qw; Stopping: drug was withheld if Hb level > 13.0 g/dL and reinstated at the previous dose if Hb ≤ 13 g/dL.	NR	NR	validate patient satisfaction questionnaire, efficacy (Hb, Hct, RBCT), safety

Appendix Table C3. **KQ1: darbepoetin versus control, study characteristics, Part I** (cont'd)

study author	# randomized	design	drug	Darbepoetin dose per week	Epoetin dose per week	weight based or fix	duration of medication (weeks)	Dose adjustment Darbepoetin	Dose adjustment Epoetin	iron	transfu-sion trigger	primary and secondary outcomes of the study
Waltzman 2005	358	effectiveness study to compare Hb response rates	Darbepoetin versus epoetin alfa	200 µg q2w	40,000 IU qw	darb fixed, epo fixed	12 to 16	Increasing: if Hb increase < 1.0 g/dL at wk 6 Darb increased to 300 µg q2w; Decreasing: if Hb rise > 1.0 g/dL in 2 wks dose decreased by 25%; Stopping: drug was withheld if Hb level > 13.0 g/dL resumed at 25% dose reduction when Hb < 12 g/dL.	Increasing: if Hb increase < 1.0 g/dL at wk 4 EPO increased to 60,000 IU qw; Decreasing: if Hb rise > 1.0 g/dL in 2 wks dose decreased by 25%; Stopping: drug was withheld if Hb level > 13.0 g/dL, resumed at 25% dose reduction when Hb < 12 g/dL.	325 mg/d oral in each arm, i.v if not tolerated	NR	Hb response, RBCTs, QoL, safety
Kotsori 2006	110	NR	Darbepoetin versus epoetin	150 µg qw	10,000 IU tiw	darb fixed, epo fixed	8	If no response after 4 weeks dose was doubled	If no response after 4 weeks dose was doubled	NR	NR	Hb increase, QoL assessment using FACT-An scale, transfusion

Appendix Table C3. **KQ1: darbepoetin versus epoetin, study characteristics, Part II**

study author	n randomized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb baseline Darb arm [mean g/dl (SD)]	Hb baseline EPO arm [mean g/dl (SD)]	Hb category *Target*	Age Darb arm [mean (SD)] if not stated otherwise	Age EPO arm [mean (SD)] if not stated otherwise	age category (children , adults, elderly (>65)
Glaspy 2002, Part A	269	Breast, GI, lung, other	solid	chemotherapy	Hb ≤ 11 g/dL	9.91 (SD 0.94)	10.02 (SD 0.88)	> 12 *14 for women 15 for men*	61.9 (SD 11.9)	57.8 (SD 14.5)	adults
Glaspy 2006	1220	lung, breast, GI, gyne, lymphoproliferative (7.5%), other cancers	solid or hematological	chemotherapy, some (42%) platinum-based	Hb ≤11 g/dL	10.18 (SD 0.90)	10.21 (SD 0.89)	> 12 *13*	63.2 (SD 12.4)	63.7 (SD 11.6)	adults
Schwartzberg 2004, a-c	318	a: breast cancer, b: lung cancer (stage IIIb, IV), c: gynecological cancers	solid	chemotherapy, some platinum-based (41%)	Hb ≤ 11 g/dL	10.4 (SD 0.8)	10.4 (SD 0.8)	> 12 *13*	58.7 (SD 11.5)	61.7 (SD 12.1)	adults
Waltzman 2005	358	lung, breast	solid	chemotherapy, some platinum-based (40.5%)	Hb ≤ 11 g/dL	10.07 (SD 0.79)	10.16 (SD 0.75)	> 12 *13*	63.4 (SD 11.8)	62.1 (SD 11.8)	adults
Kotsori 2006	110	Non hematological tumors	solid	unclear	Hb ≤ 11 g/dL	10.26 (SD 0.81)	10.11(SD 0.94)	NR	NR	NR	NR

Appendix Table C4. **KQ1: epoetin versus control, study quality UPDATE 2009/2010**

Study author	Random publication	Random MDQ	Random IPD	Allocation publication	Allocation MDQ	Allocation IPD	Blinding	Placebo	ITT or 10%	Similar	High or low quality	Publication
Aapro 2008	unclear	NA	unclear	adequate	NA	adequate	no	no placebo	yes, unclear for QoL	yes	low	full text, IPD
Antonadou 2001	unclear	NA	NA	unclear	NA	NA	no	no placebo	unclear	yes	low	abstract, poster
Bamias 2003	unclear	NA	NA	unclear	NA	NA	no	no placebo	yes, exception QoL	control group had statistically significant lower EPO levels at baseline (EPO: 24.8 (16.6-37), control: 12.5 (8.7-18), mU/ml, geometric mean, p=0.012)	low	full text publication
Blohmer 2004	unclear	yes	NA	unclear	adequate	NA	no	no placebo	yes, except RBCT, OS,; unclear for TVE	Yes	low	abstract, slides, ODAC, MDQ
Boogaerts 2003, Coiffier 2001	unclear	yes	unclear	unclear	adequate	adequate	no	no placebo	yes, except QoL	more patients in control (80%) had CT before study compared to EPO (68%), p=0.025	low	full text publication, abstract publication, ODAC documents, MDQ, IPD
Case 1993	yes	yes	yes	unclear	adequate	unclear	double	placebo	yes	yes, no details for cancer stage available	high	full text publication, ODAC documents, MDQ, IPD
Chang 2005	unclear	NA	unclear	unclear	NA	adequate	no	no placebo	yes	patients with metastatic disease appear to have lower baseline and significantly higher level of serum ferritin, more cycles of chemotherapy were given in the epo arm (mean 5.0 vs 4.6, p=0.058)	low	full text publication, IPD

NA: not available, MDQ: missing data questionnaire for Cochrane Review 2004, IPD: individual patient data analysis from Bohlius et al 2009, ITT: intention to treat; ODAC: Oncologic Drug Advisory Committee

Appendix Table C4. **KQ1: epoetin versus control, study quality UPDATE 2009/2010, continued**

Study author	Random publication	Random MDQ	Random IPD	Allocation publication	Allocation MDQ	Allocation IPD	Blinding	Placebo	ITT or 10%	Similar	High or low quality	Publication
Christodoulou 2009, Janinis 2003	yes	NA	NA	adequate	NA	NA	no	no placebo	more than 10% excluded	yes	low	full text, abstract
Dammacco 2001	unclear	yes	unclear	unclear	unclear	unclear	double	placebo	yes, exception: Hb response	yes	high, low for Hb response	full text publication, ODAC documents, MDQ, IPD
Debus 2006; EPO-GER-22	unclear	NA	unclear	unclear	NA	unclear	no	no placebo	yes, except QoL;unclear for TVE	unclear	low	abstract, IPD
Engert 2009	unclear	NA	NA	unclear	NA	NA	double	placebo	yes, except QoL	unclear	high, low for QoL	abstract, slides, ODAC documents
EPO-INT-1	unclear	NA	unclear	unclear	NA	unclear	double	placebo	yes	unclear	high	ODAC documents, IPD
EPO-INT-3	unclear	NA	unclear	unclear	NA	adequate	double	placebo	yes	unclear	high	ODAC documents, IPD, online publication

Appendix Table C4. **KQ1: epoetin versus control, study quality UPDATE 2009/2010, continued**

Study author	Random publication	Random MDQ	Random IPD	Allocation publication	Allocation MDQ	Allocation IPD	Blinding	Placebo	ITT or 10%	Similar	High or low quality	Publication
Goss 2005, EPO-CAN-15	unclear	NA	yes	unclear	NA	adequate	double	Placebo	yes	unclear	high	abstract, ODAC documents, IPD
Grote 2005	unclear	NA	yes	unclear	NA	unclear	double	placebo	yes	slightly higher proportion of patients in the EPO arm had extensive SCLC than in the placebo arm (66% vs 59%)	high	full text publication, ODAC documents, IPD
Gupta 2009	unclear	NA	NA	Unclear (“drawing sealed envelopes”)	NA	NA	no	no placebo	yes	yes	low	full text
Henke 2003	unclear	NA	unclear	unclear	NA	adequate	double	Placebo	yes	more smokers (66% vs 53%) in the EPO group; more stage IV patients in the EPO hypopharynx subgroup (85% vs 70%)	high	full text publication, ODAC documents, IPD
Henry 1995	yes	yes	yes	unclear	adequate	unclear	double	Placebo	yes	yes, no details for cancer stage available	high	full text publication, MDQ, ODAC documents, IPD
Hoskin 2009, EPO-GBR-7	unclear	NA	unclear	unclear	NA	unclear	no	no placebo	yes, not TVE, unclear for QoL	Well balanced, more subjects in the EPO arm had tumor stage IV (39% vs 36%)	low	full text, ODAC documents, IPD
Iconomou 2003	unclear	NA	NA	yes (was performed by a telephone call to the registry of the department of medicine)	NA	NA	no	no placebo	yes, unclear for QoL	yes (“Univariate analyses revealed no 27significant differences at baseline between groups for any of the demographic and clinical characteristics […].”)	low	full text publication

Appendix Table C4. **KQ1: epoetin versus control study quality** (cont'd)

Study author	Random publication	Random MDQ	Random IPD	Allocation publication	Allocation MDQ	Allocation IPD	Blinding	Placebo	ITT or 10%	Similar	High or low quality	Publication
Leyland-Jones 2005	unclear	NA	adequate	unclear	NA	adequate	double	placebo	yes, unclear for QoL	EPO patients were more likely to have adverse factors such as advanced age, lower performance status, greater extent of disease at baseline, and more risk factors for TVEs (based on retrospective chart review)	high, unclear for QoL	full text publication, ODAC documents, IPD
Littlewood 2001	unclear	yes	yes	unclear	unclear	adequate	double	placebo	yes, except for QoL	Fewer previously transfused patients at baseline in the ESA arm compared to controls (28% vs 36%)	high, except for QoL	full text publication, MDQ, ODAC documents, IPD
Machtay 2007, Machtay 2004	unclear	NA	unclear	adequate	NA	adequate	no	no placebo	yes	More current smoker in ESA arm (57% vs 48%), more Zubrod performance score 0 in ESA arm (51.5% vs 46.5%)	low	abstract, ODAC documents, full text, IPD
Milroy 2003	unclear	NA	unclear	adequate	NA	adequate	no	no placebo	yes, unclear for QoL	unclear	low	abstracts, ODAC documents, IPD
ML17620	unclear	NA	unclear	unclear	NA	unclear	no	no placebo	OS and Hb unclear	unclear	low	online document
Moebus 2007	unclear	NA	yes	unclear	NA	adequate	no	no placebo	yes, not for TVE	unclear	low	abstracts, ODAC documents, IPD

Appendix Table C4. **KQ1: epoetin versus control study quality** (cont'd)

Study author	Random publication	Random MDQ	Random IPD	Allocation publication	Allocation MDQ	Allocation IPD	Blinding	Placebo	ITT or 10%	Similar	High or low quality	Publication
Oberhoff 1998	unclear	yes	unclear	unclear	adequate	adequate	no	no placebo	yes	yes	low	full text publication, MDQ, ODAC documents, IPD
Osterborg 2002, Osterborg 2005	unclear	yes	unclear	unclear	adequate	adequate	double	placebo	yes, except for QoL	yes	high, low for QoL	full text publication, MDQ, ODAC documents, IPD
Porter 1996	yes	NA	NA	unclear	NA	NA	double	placebo	no, more than 10% excluded	yes	low	full text
Pronzato 2002	unclear	NA	unclear	unclear	NA	adequate	No	no placebo	yes , except for QoL	unclear	low	abstract, IPD
Ray-Coquard 2009	unclear	NA	yes	adequate	NA	adequate	No	no placebo	yes, except for QoL	unclear	low	full text, IPD
Razzouk 2006, Razzouk 2004	unclear	NA	yes	unclear	NA	adequate	double	placebo	yes	unclear	high	full text, IPD
Rose 1994	yes	yes	yes	unclear	unclear	unclear	double	placebo	yes	yes	high	abstract, MDQ, ODAC documents, IPD
Savonije 2005	yes	NA	unclear	adequate	NA	adequate	no	no placebo	yes, except for QoL	significantly more patients with metastatic disease and higher ECOG score in EPO group	low	abstract, full text, IPD
Thomas 2002	unclear	NA	unclear	unclear	NA	adequate	no	no placebo	yes	yes ("At baseline, groups balanced for Hb, demographics, CT and disease related variables.")	low	abstract, IPD

Appendix Table C4. **KQ1: epoetin versus control study quality** (cont'd)

Study author	Random publication	Random MDQ	Random IPD	Allocation publication	Allocation MDQ	Allocation IPD	Blinding	Placebo	ITT or 10%	Similar	High or low quality	Publication
Thomas 2008, GOG-0191	yes	NA	unclear	adequate	NA	adequate	no	no placebo	yes	in ESA arm more patients aged < 45 (ESA 49% vs control 27%), in control more patients with PS 0 (ESA 65% vs control 77%), more control patients have FIGO IIB (ESA 65% vs control 75%)	Low	ODAC documents, full text, abstract, IPD
Tsuboi 2009	unclear	NA	NA	adequate	NA	NA	double	placebo	yes	yes	high	full text
Wagner 2004	unclear	NA	NA	unclear	NA	NA	no	no	yes	unclear	low	full text
Wilkinson 2006	unclear	NA	unclear	unclear	NA	unclear	no	no placebo	yes, unclear for QoL	yes	low	full text, ODAC documents, IPD
Witzig 2005	unclear	NA	adequate	unclear	NA	adequate	double	placebo	yes, except for QoL	yes	high, low for QoL	full text publication, ODAC documents, IPD

Appendix Table C5. **KQ1: darbepoetin versus control, study quality UPDATE 2009/2010**

Study author	Random publication	Random MDQ	Random IPD	Allocation publication	Allocation MDQ	Allocation IPD	Blinding	Placebo	ITT or 10%	Similar	High or low quality	Publication
Hedenus 2003	unclear	NA	unclear	yes (central randomization service)	NA	adequate	double	placebo	yes, except for QoL, unclear for TVE	more patients with indolent lymphoma were randomized to placebo and more patients with higher stage of disease were randomized to Aranesp	high, low for QoL, unclear for TVE	full text publication, ODAC documents, IPD
Hernandez 2009	unclear	NA	unclear	unclear	NA	adequate	double	placebo	yes, except for QoL	Epo baseline levels were higher in placebo group, disease stage more advanced in placebo group (stage IV ESA 30%, placebo 43%)	high, low for QoL	full text, ODAC documents, IPD
Kotasek 2003 a,b,c,d,e,f	unclear	NA	unclear	unclear	NA	adequate	double	placebo	yes, not for transfusion	slightly higher proportion of patients in the 12 µg group had breast cancer (61%) compared with the other groups, which ranged from 15 to 38%. The 12 µg group had also a slightly higher mean Hb at baseline (10.4 g/d, compared with the other groups (9.7 to 10.2).	high, low for transfusion	full text publication, IPD, ODAC documents
Overgaard 2009	yes	Na	NA	unclear	NA	NA	No	no placebo	yes	yes	low	abstract, ODAC documents, protocol
Pirker 2008	unclear	NA	unclear	adequate	NA	adequate	double	placebo	yes, except for QoL	yes	high, low for QoL	full text publication, ODAC documents, IPD
Untch 2008	unclear	NA	unclear	unclear	NA	unclear	no	no placebo	yes	yes	low	abstract, ODAC documents, IPD
Vansteenkiste 2002	unclear	NA	unclear	adequate	NA	adequate	double	placebo	yes, except for QoL	yes	high, low for QoL	full text publication, ODAC documents, IPD

Appendix Table C6. **KQ1: darbepoetin versus epoetin, study quality**

study author	random	allocation	blinding	placebo	ITT or 10%	similar baseline characteristics	high or low quality	publication
Glaspy 2002, Part A	unclear	unclear	no	no placebo	ITT or 10%	yes	low	full text
Glaspy 2006	unclear	yes	no	no placebo	ITT or 10%, not for QoL	yes	low	full text
Schwartzberg 2004	unclear	unclear	no	no placebo	ITT or 10%	yes	low	full text
Waltzman 2005	unclear	unclear	no	no placebo	ITT or 10%, more pts excluded for QoL	yes	low	full text
Kotsori 2006	unclear	NR	NR	no placebo	NR	NR	low	abstract

Appendix Table C7. **KQ1 Outcome I. hematologic response: evidence table epoetin versus control UPDATED 2009/2010**

Study author	Hb response definition	Epo n	Epo N	Proportion (%)	Control n	Control N	Proportion (%)	Comments
Hb at baseline < 10 g/dL								
Boogaerts 2003	Hb increase of 2 g/dL during the treatment phase without transfusion requirements after the initial 4 treatment weeks	63	133	47.37%	17	129	13.18%	data were included in Cochrane Review 2004 as Coiffier 2001
Case 1993	Hct increase of 6% from baseline independent of transfusion	46	79	58.23%	10	74	13.51%	Hct definition
Dammacco 2001	Hb increase of 2 g/dL independent of transfusion	38	66	57.58%	6	66	9.09%	
Henry 1995	Hct increase of 6% from baseline independent of transfusion	31	64	48.44%	4	61	6.56%	Hct definition
Littlewood 2001	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	172	244	70.49%	22	115	19.13%	efficacy population: patients on study at least 28 days
Oberhoff 1998	Hb increase of 2 g/dL independent of transfusion	38	114	33.33%	7	104	6.73%	at week 12, data submitted for Cochrane Review
Osterborg 2002	Hb increase of 2 g/dL independent of transfusion within 6 weeks	114	170	67.06%	46	173	26.59%	at end of week 16
Razzouk 2006	Hb increase at any time after 4 weeks independent of red blood cell transfusions	63	111	56.76%	39	111	35.14%	
Rose 1994	Hb Hct increase of ≥ 6% of Hct unrelated to transfusion	67	142	47.18%	13	79	16.46%	Hct definitions, data submitted for Cochrane Review
Witzig 2004	Hb increase of 2 g/dL from baseline	120	165	72.73%	52	164	31.71%	unclear if independent of transfusion

Appendix Table C7. **KQ1 Outcome I. hematologic response: evidence table epoetin versus control** UPDATED (cont'd)

Study author	Hb response definition	Epo n	Epo N	Proportion (%)	Control n	Control N	Proportion (%)	Comments
Hb at baseline 10 to 12 g/dL								
Aapro 2008	Hb increase of 2 g/dL from baseline without transfusions in the previous 6 weeks	157	231	67.97%	32	232	13.79%	
Bamias 2003	Hb increase of 2 g/dl	15	72	20.83%	2	72	2.78%	unclear if independent of transfusion
Chang 2005	Hb increase of 2 g/dl independent of transfusion in the previous 28 days	115	175	65.71%	11	175	6.29%	Hb response was evaluated retrospectively
Iconomou 2003	Hb increase of 2 g/dl	25	57	43.86%	7	55	12.73%	after 12 wks of treatment, unclear if independent of transfusion
Savonije 2005	Hb increase of 2 g/dl independent of transfusion in the previous 28 days	143	208	68.75%	31	100	31.00%	
Hb at baseline not reported								
ML17620	Hb increase of 2 g/dL without transfusions in the previous 6 weeks	29	61	47.54%	14	60	23.33%	

Appendix Table C8. **KQ1 Outcome I. hematologic response: darbepoetin versus control, updated, no new studies or information 2009/2010**

Study Author	Darbepo n	Darbepo N	Proportion (%)	Control n	Control N	Proportion (%)	Hb definition	Comment
Hedenus 2003	104	174	59.77%	31	170	18.24%	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	Derived using Kaplan-Meier method (darb arm response 60%, N=174, control response 18%. N=170)
Kotasek 2003a	8	32	25.00%	7	51	13.73%		Derived using Kaplan-Meier method; arm a: 24%, N=32, control 14%, N=51
Kotasek 2003b	8	17	47.06%				increase Hb 2 g/dL from baseline during 12 week study in the absence of RBCT in the previous 28 days	c: 50%, N=17
Kotasek 2003c	23	46	50.00%					b: 48%, N=46
Kotasek 2003d	17	28	60.71%					d: 62%, N=28
Kotasek 2003e	20	35	57.14%					e: 58%, N=35
Kotasek 2003f	20	40	50.00%					f: 50%, N=40

Appendix Table C9. **KQ1d Outcome I. Hematologic response: darbepoetin versus epoetin**

study author	Hb response definition	Hb response assessed at week	Darb (n)	Darb (N)	Percentage (%)	EPO (n)	EPO (N)	Percentage (%)	Comments
Hb at baseline 10-12 g/dL									
Waltzman 2005	Hb increase of > 2 g/dL at week 17	17	74	177	41.81%	101	175	57.71%	based on patients who received at least 1 dose of study drug and had at least 1 postbaseline hb or transfusion, p=0.004 (logistic regression model adjusted for CT)
Hb at baseline <10 g/dL									
Glaspy 2002 Part A	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	12	31	59	52.5%	38	53	71.7%	dosage: 2.25 µg/kg arm d

Appendix Table C10. **KQ1 Outcome I. Hematologic response studies omitted from meta-analysis: epoetin versus control, updated 2009/2010**

Study author	**Hb response definition**	**Hb response, comments**	**Hb response n EPO**	**Hb response n control**
Henke 2003	Hb target level reached (women: Hb ≥14 g/dL, men Hb ≥15 g/dL)		148/180 (82%)	26/171 (15%)
Thomas 2002	Hb increase 2 g/dL or reaching Hb > 14 g/dL		42/62 (67%)	17/65 (26%)
Thomas 2008	Hb ≥ 12g/dL		41/57 (71.9%)	6/52 (11.5%)
Tsuboi 2009	Hb ≥ 12g/dL and Hb < 12 g/dL at baseline		29/59 (9.649.2%)	5/52 (9.6%)
Wilkinson 2006	Hb increase ≥ 1 g/dL independent of transfusion within the preceeding 4 weeks		87/112 (77.7%)	19/59 (32.32%)

Appendix Table C11. **KQ1 Outcome I. Hematologic response study omitted from meta-analysis: darbepoetin versus control, updated 2009/2010**

Study author	Hb response definition	Hb response, comments	Hb response n EPO	Hb response n control
Hernandez 2009	Hb $\geq$ 11 g/dL	not in MA, absolute numbers were derived using Kaplan-Meier method, darb 88%, N=193, control 49%, N=193	170/193 (88%)	95/193 (49%)
Vansteenkiste 2002	Hematological response as defined by Hb increase 2 g/dL OR target Hb 12g/dL	not in MA, absolute numbers were derived using Kaplan-Meier method, darb 66%, N=156, control 24%, N=158	103/156 (66.3%)	38/158 (24.05%)

Appendix Table C12. **KQ1 Outcome I. Hematologic response studies omitted from meta-analysis: darbepoetin versus epoetin**

study author	Hb response definition	response assessed at week	Darb (n)	Darb (N)	Proportion (%)	EPO (n)	EPO (N)	Proportion (%)	Comments
Schwartzberg 2004	Hb increase of ≥ 2 g/dL OR Hb level ≥12 g/dL		108	157	68.79%	112	155	72.26%	definition did not meet our criteria, percentages reported
Glaspy 2006	achieving Hb target ≥ 11 g/dL		463	606	80%	487	603	86%	

Appendix Table C13. **KQ1 Outcome I. Hematologic response subgroup analysis: epoetin versus control; no additional information**

Study	**Subgroups prospectively** stratified for	**Epo n/N (%)**	**Control n/N (%)**	**p-value**
Littlewood 2001	Overall efficacy population	172/244 (70.5%)	22/115 (19.1%)	<0.001
	solid tumors	87/131 (66.4%)	13/61 (21%)	NR
	hematological tumors	85/113 (75.22%)	9/543 (16.6%)	NR
	Hb ≤ 10.5	139/293 (47.4%)	22/100 (22%)	NR
	Hb > 10.5	33/41 (80.5%)	0/15 (0%)	NR
Osterborg 2002	All	114/170 (67%)	46/173 (27%)	<0.001
	MM	44/58 (76%)	17/58 (29%)	<0.001
	NHL	33/53 (62%)	12/49 (24%)	<0.001

Appendix Table C14. **KQ1 Outcome I. Hematologic response subgroup analysis: darbepoetin versus control; no additional information**

Study	**Subgroups prospectively stratified for**	**Darbepo n/N (%)**	**Control n/N (%)**	**p-value**
Hedenus 2003	lymphoma	64% (55/86)	13% (11/84)	<0.001
	myeloma	56% (49/88)	22% (20/86)	<0.001

Appendix Table C15. **KQ1 Outcome I. Hematologic response subgroup analysis: darbepoetin versus epoetin**

Study	Subgroups prospectively stratified for	Darb n/N (%)	Epo n/N (%)	p-value
Schwartzberg 2004	Overall population	108/157 (69%)	112/155 (72%)	NR
	Breast cancer	63/72 (88%)	56/69 (81%)	NR
	Lung cancer	25/51 (49%)	30/51 (59%)	NR
	Gynecological cancers	21/34 (62%)	26/35 (74%)	NR
	Hb < 10.5	21/38 (55%)	18/38 (47%)	NR
	Hb ≥ 10.5	88/119 (74%)	94/117 (80%)	NR

Appendix Table C16. **KQ1 Outcome II. Transfusion: epoetin versus control, updated 2009/2010**

Study ID	Treatment n	Treatment N	Proportion (%)	Control n	Control N	Proportion (%)	First 4 weeks included in analysis?	Comments
Baseline Hb below < 10g/dL								
Boogaerts 2003	43	133	32.33	67	129	51.94	included	
Case 1993	*32*	*79*	*40.51*	*36*	*74*	*48.65*	*included*	*data submitted for original Cochrane Review*
Dammacco 2001	19	69	27.54	36	76	47.37	excluded	
Henry 1995	34	64	53.13	42	61	68.85	included	
Littlewood 2001	62	251	24.70	49	124	39.52	included	
Oberhoff 1998	*32*	*114*	*28.07*	*44*	*104*	*42.31*	*included*	*data submitted for original Cochrane Review*
Osterborg 2002	*65*	*169*	*38.46*	*90*	*173*	*52.02*	*included*	*data submitted for original Cochrane Review*
Porter 1996	*9*	*10*	*90.00*	*10*	*10*	*100.00*	unclear	
Razzouk 2006	72	111	64.86	86	111	77.48	included	
Rose 1994	*65*	*142*	*45.77*	*47*	*79*	*59.49*	*included*	*data submitted for original Cochrane Review*
Witzig 2004	42	166	25.30	65	164	39.63	included	

Appendix Table C16. **KQ1 Outcome II. Transfusion: epoetin versus control (cont'd) updated 2009/2010**

Study ID	Treatment n	Treatment N	Proportion (%)	Control n	Control N	Proportion (%)	First 4 weeks included in analysis?	Comments
Baseline Hb 10-12g/dL								
Aapro 2008	33	231	14.29	63	232	27.16	unclear	
Bamias 2003	11	72	15.28	24	72	33.33	included	
Blohmer 2004	7	80	8.75	28	86	32.56	unclear	
Chang 2005	15	175	8.57	40	175	22.86	unclear	
Christodoulou 2009	16	167	9.5758	36	170	21.18	unclear	
Gupta 2009	9	58	15.52	25	57	43.86	unclear	
Iconomou 2003	9	57	15.79	14	55	25.45	included	
Ray-Coquard 2009	39	108	36.11	61	105	58.10	unclear	
Savonije 2005	77	211	36.49	66	102	64.71	included	
Thomas 2002	7	62	11.29	31	65	47.69	unclear	
Tsuboi 2009	7	61	11.48	7	56	12.50	included	
Wilkinson 2006	9	114	7.89	18	59	30.51	excluded	
Baseline Hb 12g/dL								
Goss 2005	8	52	15.38	27	52	51.92	unclear	
Grote 2005	26	109	23.85	42	115	36.52	included	
Leyland-Jones 2005	47	469	10.02	66	470	14.04	unclear	
Moebus 2007	41	320	12.81	86	305	28.20	unclear	
Baseline not reported								
EPO-INT-3 J%&J 2004	21	136	15.44	23	65	35.38	excluded	

Appendix Table C17. **KQ1 Outcome II. Transfusion: darbepoetin versus control, updated 2009/2010**

Study ID	Dosage	Treatment n	Treatment N	Proportion (%)	Control n	Control N	Proportion (%)	First 4 weeks included in analysis?	Comments
Baseline Hb below < 10g/dL									
Hedenus 2003	2.25 µg/kg/qw	52	167	31.14%	79	165	47.88	excluded	derived from K-M estimates, arm a: 31%(95% CI 24-38), N=167; 48% (95% CI 41%-56%), N=165
Kotasek 2003a	4.5 µg/kg Q3W	8	30	26.67%	23	50	46%	excluded	arm a: 25% (9%-41%), N=30; control 46% (32%-61%), N=50
Kotasek 2003b	6.75 µg/kg Q3W	5	17	29.41%					arm b: 28% (7%-51%), N=17
Kotasek 2003c	9.0 µg/kg Q3W	12	41	29.27%					arm c: 30% (16%-44%), N=41
Kotasek 2003d	12.0 µg/kg Q3W	7	27	25.93%					arm d: 26% (7.5%-41%), N=27
Kotasek 2003e	13.5 µg/kg Q3W	9	35	25.71%					arm e: 27% (11%-40%), N=35
Kotasek 2003f	15 µg/kg Q3W	7	38	18.42%					arm f: 19% (6%-32%), N=38

Appendix Table C17. **KQ1 Outcome II. Transfusion: darbepoetin versus control, updated 2009/2010, continued**

Study ID	Dosage	Treatment n	Treatment N	Proportion (%)	Control n	Control N	Proportion (%)	First 4 weeks included in analysis?	Comments
Baseline Hb 10-12g/dL									
Hernandez 2009	300 µg Q3W	58	193	30.05	91	193	47.15	included	
Pirker 2008	300 µg Q4W, after 4 weeks changed to Q3W sc	52	298	17.45	116	298	38.93	unclear	
Vansteen._FDA report	2.25 µg/kg qw	53	156	33.97%	89	158	56.33	included	

Appendix Table C18. **KQ1 Outcome II. Transfusion: darbepoetin versus epoetin**

Study ID	Darbepoetin (n)	Darbepoetin (N)	Percentage (%)	Epoetin (n)	Epoetin (N)	Percentage (%)	Weeks included	Comments
Baseline Hb below < 10g/dL								
Glaspy 2002 Part A, c (1.5 µg/kg/qw)	9	35	25.71%	12	53	22.64%	5-13	K-M percentages reported, c: 26% 95% CI (9; 43), EPO 23% 95% CI (10; 36)
Glaspy 2002 Part A, d* (2.25 µg/kg/qw)	**8**	**59**	**13.56%**	**see above**	**see above**	**see above**	**see above**	**d: 13% 95% CI (4; 23)**
Glaspy 2002 Part A, e (4.5 µg/kg/qw)	2	29	6.90%	see above	see above	see above	see above	e: 6% 95% CI (2; 30)
Baseline Hb below 10-12 g/dL								
Schwartzberg 2004 a (breast cancer)	4	72	5.56%	11	69	15.94%	1-16	percentages reported (a: 6% vs 16%, b: 27% vs 18%, c: 21% vs 17%)
Schwartzberg 2004 b (lung cancer)	14	51	27.45%	9	51	17.65%		
Schwartzberg 2004 c (gynecological)	7	34	20.59%	6	35	17.14%		
Glaspy 2006	157	582	26.98%	126	571	22.07%	1- 17	K-M percentages reported, darb: 27%, EPO 22%
Waltzman 2005	29	163	17.79%	20	155	12.90%	5 to end of treatment period (wk 17)	p=0.2936 logistic regression, adjusted for CT
Kotsori 2006	9	55	16.4%	3	55	5.5%	NR	assumed 1:1 randomization

*Glaspy 2002 A d is the arm used as main results for the meta-analysis. The arms c and e were applied for sensitivity analysis.

Appendix Table C19. **KQ1 Outcome II. Transfusion studies omitted from meta-analysis: epoetin versus control, updated 2009/2010**

Study ID	Treatment n	Treatment N	Treatment Percentage	Control n	Control N	Control Percentage	First 4 weeks included in analysis?	Comment
Thomas 2008	34	57	59.65%	29	52	55.77%	unclear	

Appendix Table C20. **KQ1 Outcome II. Transfusion studies omitted from meta-analysis: darbepoetin versus control updated**

Study ID	Treatment n	Treatment N	Treatment Percentage	Control n	Control N	Control Percentage	First 4 weeks included in analysis?	Comment
Vansteenkiste 2002	40	148	27.03%	77	149	51.68%	excluding first 4 weeks, counting week 5 to end of treatment	Based on K-M estimates. Darb: 27% (20% to 35%), N=148, control: 52% (44% to 66%), N=149, Difference of 25% (95% CI 14% to 36%) was statistically significant, p<0.001.

Appendix Table C21. **KQ1 Outcome II. Transfusion subgroup analysis: epoetin versus control updated**

Study	Subgroups prospectively stratified for	Epo n/N (%)	Control n/N (%)	p-value	comments
Razzouk 2004	All patients	72/111 (35%)	85/111 (23%)	p=0.0536	p value refers to proportion NOT transfused
	ALL (n=75)	26/40 (65.0%)	22/35 (62.9%)		
Witzig 2004Aapro 2008	All patients	42/166 (25.3%)63/232 (27.0%)	65/164 (39.6%)33/231 (14.0%)	p=0.005	
	mild anemia (Baseline Hb > 9<11 g/dL)	19%20/ 232 (8.6%)	29%39/231 (16.9%)		
	severe anemia (Basline Hb < 9>11 g/dL)	40%	62%		
Chang 2005	All patients	15/175 (8.6%)	40/175 (22.9%)	p<0.0001	
	Adjuvant	10/175 (7.2%)	30/175 (22.1%)	NR	
	Metastatic	5/175 (14.7%)	10/175 (26.3%)	NR	
	Baseline Hb <11 g/dL	11/175 (20.4%)	20/175 (38.5%)	NR	
	Baseline HB≥11 g/dL	4/175 (3.4%)	20/175 (16.4%)	NR	
Hernandez 2009	Study period	22/99 (22.2%)	48/116 (41.4%)	p=0.008	
	First 4 weeks excluded	58/193 (30.1%)	91/193 (47.2%)	p=0.003	
	Per protocol analysis set, first 4 weeks excluded	44/181 (24.3%)	76/185 (41.1%)	p<0.001	To account for protocol deviations, the primary endpoint was also examined using an alternate analysis set (per-protocol analysis set)
Savonije 2005	Study period	77/211 (36%)	66 /102 (65%)	p<0.001	
	First 4 weeks excluded	49/211 (23%)	53/102 (52%)	p<0.001	
Tsuboi 2009	Study period	7/61 (11.5%)	7/56 (12.5%)	p=0.856	
	First 4 weeks excluded	5/61 (8.2%)	7/56 (12.5%)	p=0.443	
Witzig 2005	All patients	42/166 (25.3%)	65/164 (39.6%)	p=0.005	
	mild anemia (Hb > 9 g/dL)	32/166 (19.2%)	48/164 (29.3%)	NR	Numbers derived from percentages 19% and 29% respectively
	severe anemia (Hb < 9 g/dL)	66/166 (39.8%)	102/164 (62.2%)	NR	Numbers derived from percentages 40% and 62% respectively
Witzig 2005	All patients	39/154 (25.3%)	60/151 (39.7%)	NR	
	Baseline serum Epo level low (<44 U/ml)	8/44 (18.2%)	18/57 (31.6%)	NR	
	Baseline serum Epo level mid (44-86 U/ml)	14/56 (25.0%)	19/47 (40.4%)	NR	
	Baseline serum Epo level high (>86 U/ml)	17/54 (31.5%`)	23/47 (48.9%)	NR	

Appendix Table C22. **KQ1 Outcome II. Transfusion subgroup analysis: darbepoetin versus control updated**

Study	Subgroups prospectively stratified for	Epo % (n/N)	Control % (n/N)	p-value	Comments
Hedenus 2003					
excluding first 4 weeks	lymphoma	27%	49%	0.002	
	myeloma	35%	48%	0.042	
including first 4 weeks	lymphoma	NR	NR	0.011	
	myeloma	NR	NR	0.018	
Hernandez 2009	Study period	22/99 (22.2%)	48/116 (41.4%)	p=0.008	Numbers were calculated using percentages given in a figure
	First 4 weeks excluded	58/193 (30.1%)	91/193 (47.2%)	p=0.003	Numbers were calculated using percentages given in a figure
	Per protocol analysis set, first 4 weeks excluded (To account for protocol deviations, the primary endpoint was also examined using an alternate analysis set)	44/181 (24.3%)	76/185 (41.1%)	p<0.001	Numbers were calculated using percentages given in a figure

Appendix Table C23. **KQ1 Outcome II. Transfusion subgroup analysis: darbepoetin versus epoetin**

Study	Subgroups prospectively stratified for	Darbepoetin (n)	Darbepoetin (N)	Proportion (%)	Epoetin (n)	Epoetin (N)	Proportion (%)	Comments
Schwartzberg 2004	**Overall**	25	157	15.92%	26	155	16.77%	weeks 1 to 16, percentages reported
	Hb < 10 g/dL	8	38	21.05%	16	38	42.11%	
	Hb ≥ 10 g/dL	17	119	14.29%	10	117	8.54%	

Appendix Table C24. **KQ1 Outcome VI. Thromboembolic complications: epoetin versus control, definition for thromboembolic events as defined in journal publications**

Study	Predefined definition	TE recorded	Other information reported
Aapro 2008	No	Yes	Serious TE versus non serious
Bamias 2003	Yes for all adverse events: "Death or any event requiring specific treatment, admission to hospital or a life-threatening event was reported as serious adverse event".	Yes	
Case 1993	No	Yes	
Chang 2005	No	Yes	TE attribution to epoetin reported
Engert 2009	No	Yes	
Henke 2003	Vascular disorders were hypertension, hemorrhage, venous thrombosis and pulmonary embolism, and cerebrovascular disorders	Yes, including hypertension	Relation to study drug reported
Henry 1995	No	Yes	
Hoskin 2009	No	Yes	Clinically relevant TE reported
Leyland-Jones 2005	TVEs were compiled by medical monitors at Johnson & Johnson Pharmaceutical Research Division, based on WHO Adverse Reaction Terms 97 Q4.	Yes	Fatal TE reported. Relation to study drug reported.
Littlewood 2001	Thrombotic or possible thrombotic event	Yes	
Machtay 2007	No	Yes	Relation to study drug reported
Osterborg 2002	No	Yes	
Ray-Coquard 2009	Thrombovascular events were compiled by medical monitor, on the basis of WHO Adverse Reaction Terms 97 Q4. No systematic specific exam was carried out to evaluate the risk; only reported events and/ or abnormal results of tests ordered by investigators were taken into account.	Yes	
Razzouk 2006	Thrombotic vascular events (intravenous thrombus, chest pain, edema, thrombosis, disseminated intravascular coagulation, cerebral infarction and pulmonary thrombosis) were summarized by seriousness and clinical relevance.	Yes	Seriousness, resolution and relation to study drug reported
Savonije 2005	Adverse events recorded regardless of their relationship to the drug and rated as mild, moderate or severe	Yes	Relation of TE to study drug reported
Thomas 2008	No	Yes	Associated grade, time of incidence, treatment attribution, patient's baseline traits and hemoglobin levels at time of TE incident reported.

TE: thromboembolic events, TVE: thrombovascular events

Appendix Table C24. **KQ1 Outcome VI. Thromboembolic complications: epoetin versus control, definition for thromboembolic events as defined in journal publications, continued**

Tsuboi 2009	Safety was assessed by National Cancer Institute- Common Toxicity Criteria, vers. 2	Yes	Relation to treatment reported
Study	**Predefined definition**	**TE recorded**	**Other information reported**
Wilkinson 2006	No	Yes	Information about whether TE led to death and whether patients recovered from TE
Witzig 2005	No	Yes	Grade of TE and relation to drug reported. Relation to Hb change recorded.

TE: thromboembolic events, TVE: thrombovascular events

Appendix Table C25. **KQ1 Outcome VI. Thromboembolic complications: darbepoetin versus control, definition for thromboembolic events as defined in journal publications**

Study	**Predefined definition**	**TE recorded**	**Other information reported**
Hernandez 2009	No	Yes	Adverse events were grouped by primary system organ class and preferred term within primary system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 9.0). The frequency and percentage distributions of adverse events to study drug were summarized. Relation to study drug reported.
Overgaard 2009	No	No	In abstract only cardiovascular adverse events are reported.
Pirker 2008	No	Yes	Relation to treatment reported
Vansteenkiste 2002	No	Yes	

TE: thromboembolic events

Appendix Table C26. **KQ1 Outcome VI. Thromboembolism data sources: epoetin versus control, updated 2009/2010**

Note: J&J 2007: definition for TVEs: clinically relevant if no otherwise specified, Amgen 2008: no definition given, FDA reports: no consistent definition used
Highlighted in yellow are the data that were included in the meta-analysis for the AHRQ 2009/2010 update

Study	**Full text/abstract**		**FDA report 2004 if not otherwise indicated**		**J&J report**		**Other reports, as indicated**		**Investigator meta-analysis**
	EPO event/sample size	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	
Aapro 2008 BRAVE	29/231 (13%)	13/231 (6%)	13% FDA 2007	6% FDA 2007	All 13%, serious 4%, J&J 2007	All 6%, serious 3%, J&J 2007	-	-	OR 2.41 (95% CI 1.22;4.76) Glaspy 2010, n not reported
Bamias 2003	0/72	1/72	-	-	-	-	-	-	OR 0.33 (95% CI 0.01;8.20), Glaspy 2010, n not reported
Blohmer 2004 AGO/NOGGO	-	-	-	-	2/119 (2%) J&J 2004 2% J&J 2007	3/122 (2%) J&J 2004 2% J&J 2007, n=241	-	-	OR 0.34 (95% CI 0.03;3.30), Glaspy 2010, n not reported
Case Mixed non-cisplatin	4/81	4/76	-	-	2/81 (2%) J&J 2004 2% J&J 2007	3/76 (4%) J&J 2004 4% J&J 2007, n=157	4% Amgen 2008	4% Amgen 2008, n=157	OR 0.94 (95% CI 0.23;3.88), Glaspy 2010, n not reported
Chang 2005 EPO-CAN-17	19/176[13]	14/178	TVE 20.5%, DVT 6.3%, FDA 2007	TVE 16.9%, DVT 0.06%, n=354, FDA 2007	11% J&J 2007	8% J&J 2007, n=354	-	-	OR 1.27 (95% CI 0.74;2.17), Glaspy 2010, n not reported

[13] Chang 2005: for the previous AHRQ 2006 report we used the following data for ESA and control: 19/175 and 14/175. Based on the publication Chang 2005 data were corrected as outlined in the table above.

Appendix Table C26. **KQ1 Outcome VI. Thromboembolism data sources: epoetin versus control, continued**

Study	Full text/abstract		FDA report 2004 if not otherwise indicated		J&J report		Other reports, as indicated		Investigator meta-analysis
	EPO event/sample size	Control event/sample size	EPO event/sample size	Control event/sample size	EPO event/sample size	Control event/sample size	EPO event/sample size	Control event/sample size	
Dammacco 2001 EPO-INT-2	-	-	-	-	5/69 (7%) J&J 2004 7% J&J 2007	1/76 (1%) J&J 2004 1% J&J 2007, n=145	4% Amgen 2008	0% Amgen 2008, n=145	OR 5.86 (95% CI 0.67;51.46), Glaspy 2010, n not reported
Debus 2006 EPO-GER-22	-	-	TVE 17.7% , total TVE 26 (23%), FDA 2007	TVE 8.5% , total TVE 11 (9.4%), 230 of 389 patients evaluated, FDA 2007	20% J&J 2007	12% J&J 2007, n=383	-	-	OR 1.44 (95% CI 0.81;2.56), Glaspy 2010, n not reported
Engert 2009	45/645	44/644	NC	NC	NC	NC	NC	NC	OR 1.48 (95% CI 0.74;2.96), Glaspy 2010, n not reported
EPO-INT-1	-	-	-	-	3/164 (2%) J&J 2004 2% J&J 2007	1/80 (1%) J&J 2004 1% J&J 2007, n=244	2% Amgen 2008 slides	0% Amgen 2008 slides, n=246	OR 1.47 (95% CI 0.15;14.38), Glaspy 2010, n not reported
EPO-INT-3	-	-	-	-	8/135 (6%) J&J 2004 6% J&J 2007	1/65 (2%) J&J 2004 2% J&J 2007. n=200	6% Amgen 2008	0% Amgen 2008, n=201	OR 4.03 (95% CI 0.49;32.94), Glaspy 2010, n not reported
Goss 2005, EPO-CAN-15	-	-	18/53 FDA 2004 OR 7.73 FDA 2007	3/53 FDA 2004	16/52 (31%) J&J 2004 31% J&J 2007	2/52 (4%) J&J 2004 4% J&J 2007, n=104	-	-	OR 9.40 (95% CI 2.58;34.34), Glaspy 2010, n not reported
Grote 2005, N93-004	12/109 (11.0%)	11/115 (9.6%),clinically relevant	All events 24/109 FDA 2004, calculated from reported 22%	All events 26/115 FDA 2004, calculated from reported 23%	12/109 (11%) J&J 2004 11% J&J 2007	11/115 (10%) J&J 2004 10% J&J 2007, n=224	-	-	OR 0.97 (95% CI 0.52;1.81), Glaspy 2010, n not reported
Gupta 2009	0/57 grade 1-4, 0/57 grade 3-4	0/59 grade 1-4, 0/59 grade 3-4	-	-	-	-	-	-	NR

Appendix Table C26. **KQ1 Outcome VI. Thromboembolism data sources: epoetin versus control, continued**

Study	**Full text/abstract**		**FDA report 2004 if not otherwise indicated**		**J&J report**		**Other reports, as indicated**		**Investigator meta-analysis**
	EPO event/sample size	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	
Henke ENHANCE	20/180 (including hypertension), calculated from reported 11%	9/171 (including hypertension), calculated from reported 5%	-	-	-	-	10 (5.6%) assumed 180 Roche 2004	6 (3.5%), assumed 171 Roche 2004	OR 1.62 (95% CI 0.57;4.55), Glaspy 2010, n not reported
Henry Mixed cisplatin	6/67	2/65			6/67 (9%) J&J 2004 9% J&J 2007	8/65 (12%) J&J 2004 12% J&J 2007, n=132	10% Amgen 2008	6% Amgen 2008, n=132	OR 0.70 (95% CI 0.23;2.14), Glaspy 2010, n not reported
Hoskin 2009, GBR-07	3/133	2/149	5 (3%), FDA 2004 3% FDA 2007	1 (1%), FDA 2004 1% FDA 2007	4/133 (3%) J&J 2004 3% J&J 2007	2/149 (1%) J&J 2004 1% J&J 2007, n=282	5 (3%)	2 (1%), Amgen 2007	OR 1.70 (95% CI 0.28;10.31), Glaspy 2010, n not reported
Littlewood 2001 EPO-INT-10	17/251 (7%)	8/124 (6%)	-		14/251 (6%) J&J 2004 6% J&J 2007	5/124 (4%) J&J 2004 4% J&J 2007, n=375	4% Amgen 2008	4% Amgen 2008, n=375	OR 1.05 (95% CI 0.44;2.51), Glaspy 2010, n not reported
Leyland-Jones EPO-INT-76	16% / 469 overall TVE, fatal TVE: 6, fatal TVE within 4 months: 5	14% / 470 overall TVE, fatal TVE: 2, fatal TVE within 4 months: 1	2.3% FDA 2004	1.4% FDA 2004	36/448 (8%) J&J 2004 8% J&J 2007	25/456 J&J (5%) 2004 5% J&J 2007, n=904	-	-	OR 1.17 (95% CI 0.81;1.67), Glaspy 2010, n not reported
Machtay RTOG-99-03	1/67, **slides: 2/71 (≥Grade 3),** publication 6/72 (Grade 1-5); 2/72 (≥Grade 3)	0/68, **slides: 0/70 (≥Grade 3),** publication 2/68 (Grade 1-5); 0/68 (≥Grade 3)	-	-	1/67 (1%) J&J 2004 1% J&J 2007	0/68 (0%) J&J 2004 0% J&J 2007, n=135	-	-	OR 6.72 (95% CI 0.34;132.38), Glaspy 2010, n not reported
Moebus 2007 EPO-GER-7	-	-	3.0% FDA 2007	1.7% FDA 2007, n=593	3.0%, 9/305, J&J 2007	1.7%, 5/288, J&J 2007			OR 1.86 (95% CI 1.12;3.11), Glaspy 2010, n not reported

Appendix Table C26. **KQ1 Outcome VI. Thromboembolism data sources: epoetin versus control, continued**

Study	**Full text/abstract**		**FDA report 2004 if not otherwise indicated**		**J&J report**		**Other reports, as indicated**		**Investigator meta-analysis**
	EPO event/sample size	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	
Osterborg 2002 MF4467	1/170 (P.E.)	0/173 (P.E.)	-	-	-	-	-	-	OR 3.07 (95% CI 0.12;75.91), Glaspy 2010, n not reported
Ray-Coquard 2009	4.5% (calculated 5/110)	3.7% (calculated 4/107)	-	-	-	-	-	-	NR
Razzouk 2006 PR-99-11-034/044	6/112 clinically relevant, any TVE 25/112 (calculated from reported 22.3%)	2/110 clinically relevant, 25/110 any TVE (calculated from reported 22.7%)	-	-	-	-	7% Amgen 2008	2% Amgen 2008, n=224	OR 0.98 (95% CI 0.52;1.83), Glaspy 2010, n not reported
Rose 1994 J89-040	-	-	-	-	9/142 (6%) J&J 2004 6% J&J 2007	2/79 (3%) J&J 2004 3% J&J 2007, n=221	3% Amgen 2008	1% Amgen 2008, n=221	NR
Savonije 2004, Savonije 2005 PRI/EPO-NED-17	9/211 (2004); 7/211 (3.3%), 2005)	1/104 (2004); 1/104 (1%, 2005)	-	-	-	-	5% Amgen 2008	1% Amgen 2008, n=315	OR 3.53 (95% CI 0.43;29.11), Glaspy 2010, n not reported
Thomas 2008; GOG-191	11/57	4/52	**9/58** FDA 2004	**3/55** FDA 2004	10/58 (17%) J&J 2004 17% J&J 2007	5/55 (9%) J&J 2004 9% J&J 2007, n=113	10/58, 17%, Amgen 2007 19%, Amgen 2008	5/55, 9%, Amgen 2007 9%, n=114 Amgen 2008	OR 2.87 (95% CI 0.85;9.66), Glaspy 2010, n not reported
Tsuboi 2009, Watanabe 2006	1/62	0/58	**-**	**-**	-	-	-	-	NR
Wilkinson 2006 INT-45	10/121 (8.3%)	1/60 (1.7%)	**-**	**-**	-	-	-	-	OR 5.32 (95% CI 0.66;42.54), Glaspy 2010, n not reported
Witzig 2005 PR98-27-008	8/168 (5%), grade 3-4	5/165 (3%), grade 3-4	-	-	9/168 (5%) J&J 2004 5% J&J 2007	6/165 (4%) J&J 2004 4% J&J 2007, n=233	5% Amgen 2008	4% Amgen 2008, n=344	OR 1.60 (95% CI 0.51;5.00), Glaspy 2010, n not reported

Appendix Table C27. **KQ1 Outcome VI. Thromboembolism data sources: darbepoetin versus control**

Study	**Full text/abstract**		**FDA report 2004 if not otherwise indicated**		**J&J report**		**Other reports, as indicated**		**Investigator meta-analysis**
	EPO event/sample size	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	
Hedenus 2003 20000161	-	-	3.4% FDA 2007, calculated 6/175	0.6% FDA 2007, calculated 1/169	-	-	-	-	OR 2.00 (95% CI 0.73;5.46), Glaspy 2010, n not reported
Hernandez 2009, Taylor 2005 20030232	16/194 (8%)	11/192 (6%)	7.1% FDA 2007	3.6%, n=391 FDA 2007	-	-	-	-	OR 1.48 (95% CI 0.67;3.28), Glaspy 2010, n not reported
Kotasek 2003 9802911	-	-	-	-	-	-	-	-	OR 1.03 (95% CI 0.40;2.68), Glaspy 2010, n not reported
Overgaard 2009 DAHANCA-10, SE-2002-9001	7/255 (3%), calculated from reported 3%	3/259 (1%), calculated from reported 1%	-	-	-	-	-	-	NR
Pirker 2008 20010145	65/301 (22%)	43/296 (15%)	-	-	-	-	-	-	OR 1.77 (95% CI 0.92;3.42), Glaspy 2010, n not reported
Untch 2008 DE20010033	NR	NR	NR	NR	NR	NR	NR	NR	OR 1.92 (95% CI 0.91;4.05), Glaspy 2010, n not reported
Vansteenkiste 2002 980297	7/155 (5%)	5/159 (3%)	5/155 FDA 2007	5/159 FDA 2007	-	-	-	-	OR 1.46 (95% CI 0.45;4.69), Glaspy 2010, n not reported

Appendix Table C28. **KQ1 Outcome VI. Thromboembolic complications: epoetin versus control, updated 2009/2010**

Study ID						
Hb </= 10 g/dL	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
Case J&J 2004	2	81	2.47%	3	76	3.95%
Dammacco 2001 J&J 2004	5	69	7.25%	1	76	1.32%
Henry 1995 J&J 2004	6	67	8.96%	8	65	12.31%
Littlewood 2001 J&J 2004	14	251	5.58%	5	124	4.03%
Osterborg 2002	1	170	0.59%	0	173	0.00%
Razzouk 2006	6	112	5.36%	2	110	1.82%
Rose 1994 J&J 2004	9	142	6.34%	2	79	2.53%
Witzig 2005 J&J 2004	9	168	5.36%	6	165	3.64%
Hb 10 to 12 g/dL	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
Aapro 2008	29	231	12.55%	13	231	5.63%
Bamias 2003	0	72	0.00%	1	72	1.39%
Blohmer 2004 J&J 2004	2	119	1.68%	3	122	2.46%
Chang 2005	19	176	10.80%	14	178	7.87%
Gupta 2005	0	57	0.00%	0	59	0.00%
Henke 2003 Roche 2004	10	180	5.56%	6	171	3.51%
Ray-Coquard 2009	5	110	4.55%	4	107	3.74%
Savonije 2005	7	211	3.32%	1	104	0.96%
Thomas 2008 J&J 2004	10	58	17.24%	5	55	9.09%
Tsuboi 2009	1	62	1.61%	0	58	0.00%
Wilkinson 2006	10	121	8.26%	1	60	1.67%

Appendix Table C28. **KQ1 Outcome VI. Thromboembolic complications: epoetin versus control (cont'd)**

Study ID						
Hb > 12 g/dL	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
Engert 2009	45	645	6.98%	44	644	6.83%
Goss 2005 J&J 2004	16	52	30.77%	2	52	3.85%
Grote 2005 J&J 2004	12	109	11.01%	11	115	9.57%
Hoskin 2009 J%J 2004	4	133	3.01%	2	149	1.34%
Leyland-Jones 2005 J&J 2004	36	448	8.04%	25	456	5.48%
Machtay 2007	2	72	2.78%	0	68	0.00%
Moebus 2007 J%J 2007	9	305	2.95%	5	288	1.74%
unclear	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
Debus 2006 J&J 2007	38	192	19.79%	23	191	12.04%
EPO-INT-1 J&J 2004	3	164	1.83%	1	80	1.25%
EPO-INT-3 J&J 2004	8	135	5.93%	1	65	1.54%

Appendix Table C29. **KQ1 Outcome VI. Thromboembolic complications: darbepoetin versus control**

Study ID						
Hb <10 g/dL	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
Hedenus 2003 FDA 2007	6	175	3.43%	1	169	0.59%
Hb 10-12 g/dL	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
Hernandez 2009	16	194	8.25%	11	192	5.73%
Pirker 2008	65	301	21.59%	43	296	14.53%
Vansteenkiste 2002	7	155	4.52%	5	159	3.14%
Hb > 12 g/dL	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
Overgaard 2009	7	255	2.75%	3	259	1.16%

Appendix Table C30. **KQ1 Outcome VII. Other adverse events -- hypertension: epoetin versus control, evidence table and definition for hypertension**

Study ID	Treatment n	Treatment N	Percentage	Control n	Control N	Percentage	Definition of Hypertension
Bamias 2003	2	72	2.78%	0	72	0.00%	not reported or available from detailed results
Case 1993	4	81	4.94%	2	76	2.63%	not reported or available from detailed results
Dammacco 2001	3	69	4.35%	1	76	1.32%	not reported or available from detailed results
Henry 1995	2	67	2.99%	4	65	6.15%	not reported or available from detailed results
Hoskin 2009	5	133	3.76%	5	149	3.36%	not reported or available from detailed results
Iconomou 2003	0	61	0.00%	0	61	0.00%	not reported or available from detailed results
Littlewood 2001	9	251	3.59%	1	124	0.81%	not reported or available from detailed results
Österborg 2002	15	170	8.82%	9	173	5.20%	not reported or available from detailed results
Razzouk 2006	2	112	1.79%	1	110	0.91%	not reported or available from detailed results
Rose 1994	*80*	*142*	*60.56%*	*47*	*79*	*63.29%*	systolic >140 mm Hg; from trial sponsor's clinical study report
Savonije 2005	7	211	3.32%	3	104	2.88%	not reported or available from detailed results
Tsuboi 2009	4	62	6.45%	2	58	3.45%	not reported or available from detailed results
Wilkinson 2006	3	121	2.48%	0	60	0.00%	not reported or available from detailed results
Alternative data							
Dammacco 2001	43	69	62.32%	36	76	47.37%	systolic >150 mmHg or diastolic >100 mmHg; data from trial sponsor's clinical study report
Rose 1994	6	142	4.23%	3	79	3.80%	diastolic >95 mmHg; data from trial sponsor's clinical study report

Appendix Table C31. **KQ1 Outcome VII. Other adverse events -- hypertension: darbepoetin versus control, evidence table and definition for hypertension**

Study ID	Treatment n	Treatment N	Percentage	Control n	Control N	Percentage	Definition of Hypertension
Hernandez 2009	6	194	3.09%	4	192	2.08%	not reported or available from detailed results
Pirker 2008	18	301	5.98%	15	296	5.07%	not reported or available from detailed results
Vansteenkiste 2002	9	155	5.81%	6	159	3.77%	not reported or available from detailed results

Appendix Table C32. **KQ1 Outcome VII. Other adverse events -- thrombocytopenia: epoetin versus control, updated 2009/2010**

Study ID	Treatment n	Treatment N	Percentage (%)	Control n	Control N	Percentage (%)
Bamias 2003	2	72	2.78%	0	72	0.00%
Boogaerts 2003	8	133	6.02%	13	129	10.08%
Dammacco 2001	5	69	7.25%	5	76	6.58%
Goss 2005	1	52	1.92%	0	52	0.00%
Gupta 2009	0	0	-	0	0	-
Littlewood 2001	18	251	7.17%	9	124	7.26%
Savonije 2005	22	211	10.43%	6	104	5.77%
Tsuboi 2009	31	62	50.00%	28	58	48.28%
Witzig 2005	7	168	4.17%	10	165	6.06%

Appendix Table C33. **KQ1 Outcome VII. Other adverse events -- thrombocytopenia: darbepoetin versus control, ahrq 2009/2010**

Study ID	Treatment n	Treatment N	Percentage (%)	Control n	Control N	Percentage (%)
Pirker 2008	60	301	19.93%	38	296	12.84%

Appendix Table C34. **KQ1 Outcome VII. Other adverse events -- rash: epoetin versus control**

Study ID	Treatment n	Treatment N	Percentage (%)	Control n	Control N	Percentage (%)
Gupta 2009	0	58	0.00%	0	57	0.00%
Henry 1995	7	67	10.45%	2	65	3.08%
Osterborg 2002	2	170	1.18%	0	173	0.00%
Tsuboi 2009	0	62	0.00%	2	58	3.45%
Witzig 2005	12	168	7.14%	7	165	4.24%

Appendix Table C35. **KQ1 Outcome VII. Other adverse events -- seizures: epoetin versus control**

Study ID	Treatment n	Treatment N	Percentage (%)	Control n	Control N	Percentage (%)
Case 1993	2	81	2.47%	2	76	2.63%
Henry 1995	3	67	4.48%	2	65	3.08%
Savonije 2005	4	211	1.90%	0	104	0.00%

Appendix Table C36. **KQ1 Outcome VII. Other adverse events -- seizures: darbepoetin versus control**

Study ID	Treatment n	Treatment N	Percentage (%)	Control n	Control N	Percentage (%)
Hernandez 2009	3	194	1.55%	1	192	0.52%
Pirker 2008	4	301	1.33%	9	296	3.04%

Appendix Table C37. **KQ1 Outcome VI. Antibodies: epoetin versus control, AHRQ 2009/2010**

Study ID	Antibodies Reported	Numbers	Comments
Aapro 2008	Not reported		
Antonadou 2001	Not reported		
Bamias 2003	Not reported		
Blohmer 2004	Not reported		
Boogaerts 2003	Not reported		
Case 1993	Yes		Serum samples for the determination of antibodies against rHuEPO were obtained at entry and after completion of the study's 12-week double blind phase or when a patient prematurely withdrew from the study.
Chang 2005	Not reported		
Christodoulou 2009	Not reported		
Dammacco 2001	Not reported		
Debus 2006	Not reported		
Engert 2009	Not reported		
EPO INT-1	Not reported		
EPO INT-3	Not reported		
Goss 2005	Not reported		
Grote 2005	Not reported		
Gupta 2009	Not reported		
Henke 2003	Not reported		
Henry 1995	Yes	Evaluated: 60 (30/30). Negative: 56 (28/28). Positive: 4 (2/2)	Assays for anti-r-HuEPO antibodies before and after therapy were done on **56** patients (28 in each group) and none had a positive titer to the r-HuEPO. Four patients (2 r-HuEPO, 2 placebo) had a positive titer both before and during the study, suggesting a reaction to the albumin containing vehicle.
Hoskin 2009	Not reported		
Iconomou 2003	Not reported		

Appendix Table C37. **KQ1 Outcome VI. Antibodies: epoetin versus control, AHRQ 2009/2010, continued**

Study ID	Antibodies Reported	Numbers	Comments
Leyland-Jones 2005	Not reported		
Littlewood 2001	Not reported		
Machtay 2007	Not reported		
Moebus 2007	Not reported		
Milroy 2003	Not reported		
ML17620	Not reported		
Oberhoff 1998	Yes		Anti-EPO antibodies were measured at baseline and at the end of the controlled treatment phase. No anti-bodies against rhEPO developed during therapy in the study.
Osterborg 2002	Yes		No antibodies to erythropoietin were detected in any patient.
Porter 1996	Not reported		
Pronzato 2002	Not reported		
Ray-Coquard 2009	Not reported		
Razzouk 2006	Not reported		
Rose 1994	Not reported		
Savonije 2005	Not reported		
Thomas 2002	Not reported		
Thomas 2008	Not reported		
Tsuboi 2009	Yes		Anti-erythropoietin antibodies were masured by enzyme-linked immunosorbent assay and radioimmunoprecipitation assay and compared with the data of the last observation. Detection by either method was judged as positive. No anti-erythropoietin antibodies were reported
Wagner 2004	Not repored		
Wilkinson 2006	Not repoted		
Witzig 2005	Not reported		

Appendix Table C38. **KQ1 Outcome VI. Antibodies: darbepoetin versus control, AHRQ 2009/2010**

Study ID	Antibodies Reported	Numbers	Comments
Hedenus 2003	Yes		Use of three validated assays to evaluate antibody formation. No evidence for neutralizing antibodies to darbepoetin alfa was detected for any patient.
Hernandez 2009	Yes	Evaluated pre and post treatment: 340 (171/169)	Screening for presence before study drug administration, at week 10 and at the end of treatment phase. No neutralizing ant-darbepoetin alfa antibodies were detected in this study population (185 and 191 patients tested at screening in the placebo and darbepoetin alfa groups respectively and 169 and 171 during the treatment period, respectively.
Kotasek 2003	Yes		No neutralizing antibodies to darbepoetin alfa were detected
Overgaard 2009	Not reported		
Pirker 2008	Yes	Evaluated pre and post treatment: 516. No information for number of evaluated patients per arm. Assumed 258/258.	Across both treatment groups 574 patients (96%) had a predose antibody result and 516 patients (86%) had one or more postdose results. No sample tested positive for neutrilizing antibodies to darbepoetin alfa.
Untch 2008	Not reported		
Vansteekiste 2002	Yes	Reporting just n of serum samples and not n of evaluated patients	No anti-darbepoetin alfa antibodies were detected in 1054 serum samples (531 serum samples from patients in the darbepoetin alfa group and 523 serum samples from patients in the placebo group) tested during the study and no clinical sequelae indicative of antibody formation have been observed during the follow up period.

Appendix Table C39. **KQ2: Study characteristics, Part I**

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fixed	Maximum duration of ESA medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
Charu 2007	204 E: 102 L: 102	Darbepoetin alfa	300 µg Q3W	Observation until **Hb≤ 10** g/dl then start treatment 300µg Q3W	Fixed	up to 22	Increase to 500µg /Dose- . for Early: if Hb <10g/dL; for Late: if Hb <9 g/dL or if after 2 consecutives doses of DA Hb <10 g/dL Withheld if Hb >13 g/dL	NR	NR	Full text Abstract Charu 2004	proportions with: Hb drop below 10 g/dl by week 12; Hb drop during therapy; RBC transfused during therapy; also, mean Hb over time; mean change in FACT-Fatigue subscale score; proportion maintaining Hb 11.0 to 13.0 (target)
Straus 2006	269 E: 135 L: 134	Epoetin alfa	40,000 IU QW	Observation until Hb≤9 g/dl after 2nd chemotherapy cycle, then start treatment: 40,000 IU QW [26 pt (19.4%)]	Fixed	16	Increased to 60,000 in either group if after 4w of Epo treatment Hb I≤1g/dl Withheld if Hb >15 g/dl on 2 consecutive evaluations. If Hb subsequently decreased to <13 g/dl treatment was resumed	NR	NR	Full text Abstract Straus 2003	Hb response; RBC transfusions, tumor response; QoL; Safety Health Care utilization Work / Productivity

Appendix Table C39. **KQ2: Study characteristics, Part I (cont'd)**

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fixed	Maximum duration of ESA medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
Crawford 2007	216 E: 109 L: 107	Epoetin alfa	40,000 IU QW	Observation until **Hb≤ 10** g/dl, then start treatment at 40,000 IU QW (46% of controls had Hb<10 g/dL and received late epoetin)	Fixed	16	Increased to 60,000 IU QW if ≥2 g/dL Hb decrease; dose withheld if Hb >15 g/dL twice consecutively; re-start with dose decreased by 20,000 IU weekly when Hb ≤13 g/dL	as needed (ferritin <100 ng/mL or Tsat<20%)	NR	Full text Abstract (Crawford 2003)	Hb changes over time; proportion transfused; RBC units/patient; QoL changes with Fact-An, Fact-G, Fact-L, LASA; tumor size; survival; adverse events Safety and efficacy
Glaspy 2009	136 E: 68, L: 68	Epoetin alfa	120,000 U Q3W	Observation until Hb <11 g/dl then start treatment 120,000 IU Q3W	Fix	16 weeks	**D** if Hb >12.0 g/dl or I by >1.5 g/dl in 3w: D from 120,000 to 80,000U q3w, 80,000 to 60,000 Uq3w, 60,000 to 40,000 Uq3w **b**: If Hb still >13.0 g/dl withheld of epo. **I: a:**if Hb dropped by ≥1 g/dl after dose reduction, the previous dose of epo was restarted. **B**: If Hb <10.0 g/dl after at least 1 dose of epo q3w, patient treated with epo 40,000U qw. If Hb not risen by ≥ 1 g/dl after 4 wks at this dose, epo dose increased to 60,000 U qw. If Hb still not increased by ≥ 1 g/dl from baseline after 4 wks at 60,000qw, the patient was considered to have failed qw therapy	325 mg orally	Predefined for each site per local transfusion policy	Full text	Mean proportion of haemoglobin values within the target range (11.0-13.0 g/dl) among randomized patients. Maintenance of all weekly Hb values during epoetin-α treatment between 11.0-13.0 g/dl, beginning at week 1 in the early intervention group and once Hb was ≥ 11.0 g/dl in the standard intervention. Transfusion Adverse events QoL

Appendix Table C39. **KQ2: Study characteristics, Part I (cont'd)**

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fixed	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
Schouwink 2008	110 E: 54, L: 54	Epoetin alfa	40,000 UI weekly	when **Hb ≤10** g/dl 40,000 UI weekly	fixed	24	When Hb >13 g/dl, epo withdrawn and resumed at 40,000 IU QW when Hb < 12 g/dl. If Hb did not increase > 1 g/dl within the 4 first weeks of treatment, dose increase to 80,000 IU QW	All patients received oral iron 3 times daily	As necessary with the recommendation not to transfuse if Hb > 9.7 g/dl	Full text	Mean change in Hb after weeks ¾, 8/9, and 12, and at the end of treatment survival safety r-EPO antibodies

Appendix Table C39. **KQ2: Study characteristics, Part II**

study author	n randomized	cancer details	cancer category	therapy	Hb eligibility criteria [g/dl]	Hb baseline Early [mean g/dl (SD)]	Hb baseline Late arm [mean g/dl (SD)]	Hb cate-gory *Hb target*	Age Early arm [mean (SD)] if not stated otherwise	Age Late arm [mean (SD)] if not stated otherwise	age category (children adults elders (>65)
Charu 2007	204	Breast; Lung; GiT; Genitourinary; hematologic; Gyne; Other	Mixed	chemotherapy	≥10.5 g/dl and ≤12.0 g/dl	11.1 (SD 0.7)	11.2 (SD 0.6)	>12 *>13*	63.2 (SD 10.9)	63.7 (SD 12.2)	Adults
Straus 2006	269	NHL; MM ; Hodgkin; CL	Hematological	chemotherapy with cycles week (1;2;3;4)	Hb > 10 g/dl and Hb ≤12.0 g/dl	11.1(SE 0.7)	11.2 (SE 0.7)	>12 *15*	59.0 (SD14.0)	60,5 (SD14,9)	Adults
Crawford 2007	216	Lung cancer (non-small cell)	Solid	chemotherapy with platinum, 78-80% of each arm	Hb ≥11 g/dL and <15 g/dL	13.1 (SD 1.0)	13,0 (SD 1,2)	>12 *>15*	62,3 (SD 11.0)	62.7 (SD 10.6)	Adults
Glaspy 2009	136	Breast; GiTl; Lung; Hematologic; Gyne; Other	Mixed	Chemotherapy	Hb ≥11.0 g/dl - ≤12.0 g/dl	11.5 (0.3)	11.5 (0.4)	12 *12*	60.5 (12.8)	61.3 (15.4)	Adults
Schouwink 2008	110	NSCLC, SCLC, Ovary, Colon, breast, bladder, other	Solid	chemotherapy with and without platinum	>10 g/dl and ≤12 g/dl	11.2 (0.8)	11.2 (0.7)	>12 *>13*	60.0 (10.8)	61.7 (12.3)	Adults

Appendix Table C40. **KQ2: study quality**

study author	random	allocation	blinding	placebo	ITT or 10%	similar characteristics at baseline	high or low quality
Charu 2007	yes	unclear	no	no placebo	ITT	yes	low
Straus 2006	yes	NR	no	no placebo	ITT	yes	low
Crawford 2007	unclear	unclear	no	no placebo	ITT	ECOG performance status 0-1: 95.3% in early arm, 80% in delayed arm 2: 5.7% in early arm, 20.0% in delayed arm Race: Caucasian 68.9% in early arm, 81.9% in delayed arm	low
Schouwink 2008	unclear	unclear	no	no placebo	ITT	yes	low
Glaspy 2009	yes: Computer-generated randomization schedule The randomization was balanced using randomly permuted blocks.	no	no	no placebo	ITT	yes	low

Appendix Table C41. **KQ2. Hematologic response**

study author	Hb response definition	Early (n)	Early (N)	Percentage (%)	Late (n)	Late (N)	Percentage (%)	Comments
Charu 2007	Hb Increase ≥ 2 g/dl	19	94	20,2	16	86	18,6	Data presented by Charu-2004

Appendix Table C42. **KQ2: Study not included for hematologic response**

study author	Hb response definition	Early	Late	Comments
Straus 2006	Hb increase ≥ 2 g/dL OR Hb increase Hb ≥ 12 g/dl	70,4% (95 Pt)	25,4% (34 Pt)	P < 0,001 (ITT)
Crawford 2007	Proportion maintaining Hb ≥10 g/dL	82% calculated	56% calculated	Reported is the proportion of patients with Hb decrease <10 g/dL. Therefore the following calculation was done: early arm 100%-18%=82%, late arm 100%-44%=56%
Glaspy 2009	Maintaining all Hb values between 11.0 and 13.0 g/dL during treatment with epoetin- α q3w alone	49 (72%)	28 (68%)	
Schouwink 2008	NR	NR	NR	

Appendix Table C42. **KQ2: Transfusion**

Study ID	time of measurement	Intervention (n)	Intervention (N)	Percentage (%)	Control (n)	Control(N)	Percentage (%)	Comments
Charu 2007	12 weeks	14	99	14% (CI 7;20)	22	102	22% (CI 13;30)	P=0.18 calculated
Charu 2007	22 weeks	17	99	17,2% (CI 9-25)	27	102	26,5% (CI 16-35)	P=0,12 calculated
Straus 2006	16 weeks	24	135	17,8%	35	134	26,1	P=0,11 reported
Crawford 2007	16 weeks	12	106	11,3%	19	105	18.1	P=0.17 calculated
Glaspy 2009	16 weeks	6	68	8.8%	4	51	7.8%	P=0.23 calculated
Schouwink 2008	24 weeks	15	54	28%	15	54	28%	P=1.00 calculated

Appendix Table C43. **KQ2: Thrombotic events**

Study ID	Intervention Early n	Intervention Early N	Percentage (%)	Control Late n	Control Late N	Percentage (%)	Definition of TE	Comments
Charu 2007	16	99	16.2%	7	102	6.9%	Cardiovascular and thromboembolic events	
Straus 2006	15	135	11.1%	4	134	3.0%	Thrombovascular events	
Crawford 2007	13	108	12.0%	16	107	15.0%	Any thrombovascular events	safety population n=215 correspond to the randomized population
Glaspy 2009	6	68	8.8%	6	51	11.8%	Thrombovascular events	
Schouwink 2008	10	54	18.5%	4	54	7.4%		pulmonary embolism, thrombosis and superficial venous phenomena pooled together

Appendix Table C44. **KQ2: QoL data from Straus et al. 2006**

Straus 2006	**Baseline Immediate**	**Change Immediate**	**Baseline Delayed**	**Change Delayed**	**p-value between groups**	**comments**
FACT-G						
- FACT –G Physical well being	20.9 (n=117)	1.0 (n=119)	20.9 (n=113)	- 0.33 (n=113)	0.007	Baseline from poster Straus 2003
- FACT –G Functional well being	17.6 (n=118)	0.43 (n=119)	18.3 (n=114)	- 1.03 (n=113)	0. 024	Baseline from poster Straus 2003
- FACT -G Emotional	NR	0.64 (n=119)	NR	0.03 (n=113)	0.360	
- FACT -G Social	NR	- 0.43 (n=119)	NR	- 0.67 (n=113)	0.840	
FACT – anemia subscale						
- FACT – fatigue subscale	34.0 (n=118)	1.45 (n=119)	34.3 (n=112)	- 1.68 (n=113)	0.005	Baseline from poster Straus 2003
- FACT – F Non-fatigue	NR	0.54 (n=119)	NR	- 0.03 (n=113)	0.078	
- Total of FACT anemia subscale	55.0 (n=118)	1.92 (n=119)	55.2 (n=112)	- 1.71 (n=113)	0.008	Baseline from poster Straus 2003
- Total of FACT anemia (FACT- General + anemia subscale; 47)	NR	3.84 (m=119)	NR	- 4.37 (n=113)	0.003	

Appendix Table C45. **KQ2: QoL data from Charu 2007**

Rearden 2004	**Baseline Immediate**	**Change (week 22) Immediate**	**Baseline Delayed**	**Change (week 22) Delayed**	**comments**
- FACT – fatigue subscale		n=94		n=86	
	NR	0.7 ± 12.9	NR	0.6 ± 14.2	mean ± SD calculated from results reported in a figure

Appendix Table C46. **KQ2: QoL data from Glaspy 2009**

Glaspy 2009	Baseline Immediate	Last visit (week) Immediate	Baseline Delayed:	Last visit (week) Delayed	comments
- FACT – fatigue subscale	33.5 ± 13.2	32.0 ± 13.2	27.8 ± 12.0	30.4 ± 11.7	

Schouwink 2008: no QoL reported.
Crawford 2007: FACT-An mean change from baseline in the early intervention group was of -7.7. No data is reported for the late intervention group. BFI (Brief Fatigue Inventory) mean change from baseline in the early intervention group was of -3.2 and of -3.3 in the late intervention group.

Appendix Table C47. **KQ2: On study mortality**

Study ID	time of measurement	Intervention Early (n)	Intervention Early(N)	Percentage (%)	Control Late(n)	Control Late (N)	Percentage (%)	Comments
Crawford 2007	16 weeks	6	106	5.7%	5	105	4.8%	
Schouwink 2008	16 weeks	8	54	14.8%	5	54	9.3%	
Glaspy 2009	16 weeks	2	68	2.9%	2	51	3.9%	

Appendix Table C48. **KQ2: Overall survival***

Study ID	time of measurement	Intervention Early (n)	Intervention Early(N)	Percentage (%)	Control Late(n)	Control Late (N)	Percentage (%)	Comments
Crawford 2007 b	40 months	11	108	10.2%	14	107	13.1%	safety population n=215 correspond to the randomized population
Schouwink 2008 b	24 weeks	39	54	72.2%	40	54	74.1%	
Straus 2006	20 weeks	3	135	2.2%	4	134	3.0%	on study + 30d none of the late Epo group's death received Epo
Charu 2007	up to 26 weeks	6	99	6.1%	7	102	6.9%	on study or within 30d of end of study

*Overall survival is defined as on study mortality + follow up

Appendix D: Excluded Studies

Excluded at the level of full-text paper or abstract if not published as full text
Abbreviations/key to reasons for exclusion

▪ nrct	**N**o **R**andomized-**C**ontrolled **T**rial
▪ allo	Trials with inadequate **allo**cation concealment, e.g. where patients were allocated by alternation, the use of case record numbers, dates of birth or day of week, and any other procedure that is transparent before allocation, such as an open list of random numbers
▪ ong	**Ongoing** studies and interim analyses
▪ none	Studies of patients with a malignant disease **NOT** undergoing anticancer-therapy
▪ mbt	Studies of high-dose **M**yeloablative chemotherapy regimens followed by bone marrow or peripheral **B**lood stem cell **T**ransplantation
▪ ept	Studies using **E**rythropoietin for short-term **P**reoperative **T**reatment to correct anemia or to support collection of autologous blood prior to cancer surgery for administration during or after surgery
▪ surg	Studies in which patients received **surgical** treatment while being administered ESA
▪ nop	**N**umber **O**f **P**atients: Trials with 50 or fewer randomized (≤) participants per study arm for studies of adults; 10 or fewer (≤) participants per study arm in paediatric samples
▪ msl	Studies on patients with **M**yelodysplastic **S**yndrome or acute **L**eukaemia
▪ ora	**O**ther **R**easons or **A**nemia, such as hemolysis, iron deficiency and occult bleeding, should have been excluded
▪ eqol	**Q**uality **o**f **l**ife using LASA, VAS and CLAS scales are **e**xcluded
▪ dup	**Du**plicate **P**ublication
▪ other reasons	Study objective than comparison of erythropoiesis-stimulating products or comparison to control; different drug used than epoetin alfa, beta or darbepoetin; different randomization than defined for this review.
▪ add reference	Additional reference
▪ comment	?
▪ dose-finding	?

List of excluded studies:

1. Abdelrazik N, Fouda M. Once weekly recombinant human erythropoietin treatment for cancer-induced anemia in children with acute lymphoblastic leukemia receiving maintenance chemotherapy: a randomized case-controlled study. Hematology 2007; 12(6): 533-541.
   Notes: KQ1 a-c: msl.

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   Notes: KQ1 a-c: none.

3. Alexopoulos CG, Kotsori, AA. A randomized comparison of rHuEPO with darbepoetin for cancer related anemia [abstract]. Ann Oncol 2004;15(Suppl 3);<page no>.
Notes: KQ1 d: nop.

4. Anonymous. High-dose erythropoietin linked to longer survival in patients with MM and anemia. Oncol Rep 2005;(FALL): 91.
Notes: KQ1 a-c: nrct.

5. Anonymous. Epoetin alfa shows greater increase in hemoglobin levels than darbepoetin alfa. Oncol Rep 2005;(FALL): 122-123.
Notes: KQ1 a-c: other reasons.

6. Aravantinos G, Linardou H, Makridaki D et al. Recombinant human erythropoietin for platinum-based chemotherapy-induced anaemia: A single-centre randomised study. Journal of BUON 2003; 8(2): 127-132.
Notes: KQ1 a-c: nop.

7. Arcasoy, MO. Erythropoiesis-stimulating agents in cancer. J Clin Oncol 2008; 26(18): 3097-3098.
Notes: KQ1 a-c: comment.

8. Auerbach M, Ballard H, Trout JR et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol 2004; 22(7): 1301-1307.
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Notes: KQ1 a-c: nrct.

11. Becker G, Momm F, Xander C et al. Religious belief as a coping strategy: an explorative trial in patients irradiated for head-and-neck cancer. Strahlenther Onkol 2006; 182(5): 270-276.
Notes: KQ1 a-c: other reasons.

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Notes: KQ2: other reasons.

14. Blayney D, Fesen M, Mirtsching BC et al. Every-2-week darbepoetin alfa improves hemoglobin in anemic patients with cancer undergoing chemotherapy: A stratified analysis by tumor type. Blood 2003; 102 (11):.
Notes: KQ1 a-c: other reasons.

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16. Bradbury J. Less-frequent erythropoietin for cancer-associated anaemia. Lancet Oncol 2006; 7(4): 286.
    Notes: KQ1 a-c: nrct.

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    Notes: KQ1 a-c: other reasons.

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    Notes: KQ1 a-c: dose-finding.

21. Carabantes, FJ, Benavides, M, Trujillo, R et al. Epoetin alfa in the prevention of anemia in cancer patients undergoing platinum-based chemotherapy (CT). A prospective randomized study [Abstract]. Proceedings of ASCO 1999; #2303.
    Notes: KQ1 a-c: nop.

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    Notes: KQ1 a-c: comment.

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    Notes: KQ1 a-c: nrct.

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Notes: KQ1 a-c: none.

28. Charu V, Belani CP, Gill AN et al. Efficacy and safety of every-2-week darbepoetin alfa in patients with anemia of cancer: a controlled, randomized, open-label phase II trial. Oncologist 2007; 12(6): 727-737.
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29. Charu, V, Moyo, V, Luo, D et al. Erythroid response to epoetin alfa (epo) 120,000 units (u) every three weeks (q3w) initiated early or at a standard threshold in chemotherapy-induced anemia (CIA) [Abstract]. Blood (ASH Annual Meeting Abstracts) 2007; 110(11): 3770.
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Notes: KQ1 a-c: comment.

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38. EPO-GER-20. EPO-GER-20. in Bohlius,J. 2009: Erythropoietin or Darbepoetin for patients with cancer - meta-analysis based on individual patient data
Notes: KQ1 a-c: nop.

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Notes KQ1 d: nop.

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Notes: KQ1 d: dup.

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Notes: KQ1 a-c: none.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: nrct.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: msl.

52. Henke M, Guttenberger R, Barke A et al. Erythropoietin for patients undergoing radiotherapy: a pilot study. Radiother Oncol 1999; 50(2): 185-190.
Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: msl.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: other reasons.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: surg.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: other reasons.

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Notes: KQ1 a-c: other reasons.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nrct.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: other reasons.

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Notes: KQ1 a-c: surg.

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Notes: KQ1 a-c: nrct.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: nrct.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: dup.

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Notes: KQ1 a-c: nop.

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Notes: KQ2: other reasons.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nrct.

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Notes: KQ1 d: dup.

121. Waxman IM. Epoeitin alfa use in children undergoing myelosuppressive chemotherapy [14]. J Clin Oncol. 2007; 25(7): 919.
Notes: KQ1 a-c: comment.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: nop.

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Notes: KQ1 a-c: comment.

127. Yurut-Caloglu V, Caloglu M. Treatment of anemia by recombinant human erythropoietin in cancer patients undergoing radiotherapy. Asia Pac J Clin Oncol 2008; 4(4): 199-207.
Notes: KQ1 a-c: nrct.

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Notes: KQ1 a-c: dose-finding.

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Notes: KQ1 a-c: other reasons.

APPENDIX E

Appendix Table E1. Changes in Trials Included in Current and 2006 Reviews

			Hematologic Response
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	2	Glaspy 2003, Alexopoulos 2004
	Included unchanged	3	Glaspy 2002, Schwartzberg 2004, Waltzman 2005
	Data updated	0	
	New data	1	Glaspy 2006
	Total Studies Included	4	
Epoetin vs. Control	**Excluded**	2	Cazzola 1995, Osterborg 1996
	Included unchanged	12	Bamias 2003, Boogaerts 2003, Case 1993, Chang 2005, Dammacco 2001, Henry 1995, Iconomou 2003, Littlewood 2001, Oberhoff 1998, Osterborg 2002, Rose 1994, Witzig 2005
	Data updated	1	
	New data	3	Razzouk 2006, Aapro 2008, ML17620
	Total Studies Included	16	
Darbepoetin vs. Control	**Excluded**	1	Hedenus 2002
	Included unchanged	2	Hedenus 2003, Kotasek 2003
	Data updated	0	
	New data	0	
	Total Studies Included	2	

Appendix Table E1. Changes in Trials Included in Current and 2006 Reviews (continued)

			Transfusion Rates
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	1	Alexopoulos 2004
	Included unchanged	2	Glaspy 2002, Schwartzberg 2004
	Data updated	2	Glaspy 2005 → Glaspy 2006, Waltzman 2005 → Waltzman 2005
	New data	1	Kotsori 2006
	Total Studies Included	5	
Epoetin vs. Control	**Excluded**	18	Aravantinos 2003 , Carabantes 1999, Cascinu 1994, Cazzola 1995, Del Mastro 1997, Dunphy 1999, Henze 2002, Huddart 2002, Kunikane 2001, Kurz 1997, Osterborg 1996, Quirt 1996, Ten Bokkel Huinink 1998, Thatcher 1999, Throuvalas 2000, Vadhan-Raj 2004, Welch 1995, Wurnig 1996
	Included unchanged	13	Bamias 2003, Boogaerts 2003, Case 1993, Chang 2005, Dammacco 2001, Henry 1995, Iconomou 2003, Littlewood 2001, Oberhoff 1998, Osterborg 2002, Thomas 2002, Rose 1994, Witzig 2005
	Data updated	3	Razzouk 2004 → Razzouk 2006, Janinis 2003→ Christodoulou 2009, Savonije 2004→Savonije 2005
	New data	12	Aapro 2008, Blohmer 2004, EPO-INT-3, Goss 2005, Grote 2005, Gupta 2009, Leyland-Jones 2005, Moebus 2007, Porter 1996, Ray-Coquard 2009, Tsuboi 2009, Wilkinson 2006
	Total Studies Included	28	
Darbepoetin vs. Control	**Excluded**	1	Hedenus 2002
	Included unchanged	3	Hedenus 2003, Kotasek 2003, Vansteenkiste 2002
	Data updated	0	
	New data	2	Hernandez 2009, Pirker 2008
	Total Studies Included	5	

Appendix Table E1. Changes in Trials Included in Current and 2006 Reviews (continued)

			Overall Survival
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	0	
	Included unchanged	0	
	Data updated	2	Glaspy 2005 → Glaspy 2006, Waltzman 2005 → Waltzman 2005
	New data	0	
	Total Studies Included	2	
Epoetin vs. Control	**Excluded**	13	Cascinu 1994, Cazzola 1995, Del Mastro 1997, Dunphy 1999, EPO-CAN-20, Kurz 1997, O'Shaughnessy 2005, Osterborg 1996, P-174, ten Bokkel 1998, Thatcher 1999, Throuvalas 2000, Vadhan-Raj 2004
	Included unchanged	1	Bamias 2003
	Data updated	21	Case 1993 → Case 1993 IPD, Chang 2005 → Chang 2005 IPD, Coiffier 2001 → Boogaerts 2003 IPD, Dammacco 2001 → Dammacco 2001 IPD, Henke 2003 → Henke 2003 IPD, Henry 1995 → Henry 1995 IPD, Leyland-Jones 2003 → Leyland-Jones 2005 IPD, Littlewood 2001 → Littlewood 2001 IPD, Machtay 2004 → Machtay 2007, Oberhoff 1998 → Oberhoff 1998 IPD, Osterborg 2005 → Osterborg 2002 IPD, Rose 1994 → Rose 1994 IPD, Savonije 2004 → Savonije 2005 IPD, Witzig 2005 → Witzig 2005 IPD, EPO-CAN-15 → Goss 2005 IPD, EPO GBR-07 → Hoskin 2009 IPD, GOG-191 → Thomas 2008, N93004 2004 → Grote 2005 IPD, INT-1 → EPO-INT-1IPD, INT-3 → EPO-INT-3 IPD
	New data	15	Aapro 2008 IPD, Pronzato 2002 IPD, Ray-Coquard 2009 IPD, Thomas 2002 IPD, Wilkinson 2006 IPD, Milroy 2003 IPD, Moebus 2007 IPD, Debus 2006 IPD, Antonadou 2001, Blohmer 2004, Christodoulou 2009, Gupta 2009, Tsuboi 2009, Engert 2009, ML17620
	Total Studies Included	37	
Darbepoetin vs. Control	**Excluded**	1	Hedenus 2002
	Included unchanged	3	Hedenus 2003, Kotasek 2003, Vansteenkiste 2002
	Data updated	0	
	New data	4	Hernandez 2009, Pirker 2008, Overgaard 2009, Untch 2008
	Total Studies Included	7	

Appendix Table E1. Changes in Trials Included in Current and 2006 reviews (continued)

			Thromboembolic Events
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	0	
	Included unchanged	1	Schwartzberg 2004
	Data updated	2	Glaspy 2005 → Glaspy 2006, Waltzman 2005 → Waltzman 2005
	New data	0	
	Total Studies Included	3	
Epoetin vs. Control	**Excluded**	10	Cascinu 1994, Osterborg 1996, P-174, Rosenzweig 2004, Ten Bokkel 1998, Thatcher 1999, Throuvalas 2000, Vadhan-Raj 2004, Welch 1995, EPO-CAN-20
	Included unchanged	13	Bamias 2003, Case J&J 2004, Chang 2005, Dammacco J&J 2004, EPO-INT-1 J&J 2004, EPO-INT-3 J&J 2004, Henke Roche 2004, Henry J&J 2004, Leyland-Jones J&J 2004, Littlewood J&J 2004, Osterborg 2002, Rose J&J 2004, Witzig J&J 2004
	Data updated	7	EPO-CAN-15 → Goss 2005, N93004 2004 → Grote 2005, EPO-GBR-07 → Hoskin 2009, GOG 191 → Thomas 2008, Machtay 2004 → Machtay 2007, Savonije 2004→ Savonije 2005, Razzouk 2004 → Razzouk 2006
	New data	9	Aapro 2008, Blohmer 2004, J&J 2004, Debus 2006, J&J 2007, Engert 2009; Gupta 2009, Moebus 2007, Ray-Coquard 2009, Tsuboi 2009, Wilkinson 2006
	Total Studies Included	29	
Darbepoetin vs. Control	**Excluded**		
	Included unchanged	1	Vansteenkiste 2002
	Data updated		
	New data	4	Hedenus 2003, Hernandez 2009, Pirker 2008, Overgaard 2009
	Total Studies Included	5	

Appendix Table E1. Changes in Trials Included in Current and 2006 reviews (continued)

			QoL FACT-Fatigue (Complete Data)
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	0	
	Included unchanged	0	
	Data updated	1	Glaspy 2005 → Glaspy 2006
	New data	0	
	Total Studies Included	1	
Epoetin vs. Control	**Excluded**	0	
	Included unchanged	7	Boogaerts 2003, Chang 2005, Hedenus 2003, Iconomou 2003, Littlewood 2001, Osterborg 2002, Witzig 2005
	Data updated	0	
	New data	4	Christodoulou 2009, Hoskin 2009, Savonije 2005, Tsuboi 2009
	Total Studies Included	13	
Darbepoetin vs. Control	**Excluded**	0	
	Included unchanged	1	Vansteenkiste 2002
	Data updated	0	
	New data	2	Kotasek 2003, Pirker 2008
	Total Studies Included	4	

			Tumor Response
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	0	
	Included unchanged	0	
	Data updated	0	
	New data	0	
	Total Studies Included	0	
Epoetin vs. Control	**Excluded**	3	Throuvalas 2000, N93004 2004, Vadhan-Raj 2004
	Included unchanged	1	Henke 2003
	Data updated	4	EPO-CAN-15 → Goss 2005, EPO-GBR-07 → Hoskin 2009, GOG 191 → Thomas 2008, Machtay 2004 → Machtay 2007
	New data	6	Blohmer 2004, Debus 2006, Engert 2009, Gupta 2009, , Moebus 2007, Wagner 2004
	Total Studies Included	11	
Darbepoetin vs. Control	**Excluded**	0	
	Included unchanged	0	
	Data updated	0	
	New data	2	Overgaard 2009, Untch 2008
	Total Studies Included	2	

Appendix Table E1. Changes in Trials Included in Current and 2006 reviews (continued)

			ADE (Hypertension)
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	0	
	Included unchanged	0	
	Data updated	0	
	New data	0	
	Total Studies Included	0	
Epoetin vs. Control	**Excluded**	9	Cascinu 1994, Kunikane 2001, Osterborg 1996, Rosenzweig 2004, Silvestris 1995, Ten Bokkel Huinink 1998, Thatcher 1999, Welch 1995
	Included unchanged	7	Bamias 2003, Case 1993, Dammaccco 2001, Henry 1995, Iconomou 2003, Littlewood 2001, Rose 1994
	Data updated	0	
	New data	6	Hoskin 2009, Osterborg 2002, Razzouk 2006, Savonije 2005, Wilkinson 2006, Tsuboi 2009
	Total Studies Included	13	
Darbepoetin vs. Control	**Excluded**	0	
	Included unchanged	1	Vansteenkiste 2002
	Data updated	0	
	New data	2	Hernandez 2009, Pirker 2008
	Total Studies Included	3	

			ADE (Thrombocytp/Hemorrh)
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	0	
	Included unchanged	0	
	Data updated	0	
	New data	1	Pirker 2008
	Total Studies Included	1	
Epoetin vs. Control	**Excluded**	4	Cascinu 1994, Del Mastro 1997, Kunikane 2001, Thatcher 1999
	Included unchanged	3	Bamias 2003, Boogaerts 2003, Dammacco 2001
	Data updated	0	
	New data	6	Goss 2005, Gupta 2009, Littlewood 2001, Savonije 2005, Tsuboi 2009, Witzig 2005
	Total Studies Included	9	
Darbepoetin vs. Control	**Excluded**	0	
	Included unchanged	0	
	Data updated	0	
	New data	1	Pirker 2008
	Total Studies Included	1	

Appendix Table E1. Changes in Trials Included in Current and 2006 reviews (continued)

			ADE (Rash)
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	0	
	Included unchanged	0	
	Data updated	0	
	New data	0	
	Total Studies Included	0	
Epoetin vs. Control	**Excluded**	5	Del Mastro 1997, Kurz 1997, Osterborg 1996, Thatcher 1999, Welch 1995
	Included unchanged	1	Henry 1995
	Data updated	0	
	New data	4	Gupta 2009, Osterborg 2002, Tsuboi 2009, Witzig 2005
	Total Studies Included	5	
Darbepoetin vs. Control	**Excluded**	0	
	Included unchanged	0	
	Data updated	0	
	New data	0	
	Total Studies Included	0	

			ADE (Seizure)
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	1	Glaspy 2003
	Included unchanged	0	
	Data updated	0	
	New data	0	
	Total Studies Included	0	
Epoetin vs. Control	**Excluded**	1	Cascinu 1994
	Included unchanged	2	Case 1993, Henry 1995
	Data updated	0	
	New data	1	Savonije 2005
	Total Studies Included	3	
Darbepoetin vs. Control	**Excluded**	0	
	Included unchanged	0	
	Data updated	0	
	New data	2	Hernandez 2009, Pirker 2008
	Total Studies Included	2	

Appendix Table E1. Changes in Trials Included in Current and 2006 reviews (continued)

			ADE (Antibodies)
		Trials	**Study**
Darbepoetin vs. Epoetin	**Excluded**	1	Glaspy 2003
	Included unchanged	2	Schwartzberg 2004, Glaspy 2002
	Data updated	1	Glaspy 2005 → Glaspy 2006
	New data	1	Waltzman 2005
	Total Studies Included	4	
Epoetin vs. Control	**Excluded**	2	Thatcher 1999, Ten Bokkel 1998
	Included unchanged	4	Chang 2005, Henry 1995, Oberhoff 1998, Osterborg 2002
	Data updated	0	
	New data	1	Tsuboi 2009
	Total Studies Included	5	
Darbepoetin vs. Control	**Excluded**	0	
	Included unchanged	1	Vansteenkiste 2002
	Data updated	0	
	New data	4	Hedenus 2003, Hernandez 2009, Kotasek 2003, Pirker 2008
	Total Studies Included	5	

Appendix F

Appendix Table F1. ESA Trials Included In Published Meta-Analyses Evaluated In This Review

	Publi-cation status	ESA	Glaspy 2010	Bohlius 2009	Bennett 2008	Ludwig 2009
Number of included studies			**60**	**53**	**51**	**7**
Sample size exclusions?			None	Yes[a]	None	None
Individual patient data meta-analysis?			No	Yes	No	Yes
Trials included in meta-analysis:						
Aapro 2008	full	epo-b	•	•		
Abels 1993	full	epo-a	•	•	•	
Bamias 2003	full	epo-a	•		•	
Blohmer 2003/4	abs	epo-a	•		•	
Boogaerts 2003 (Coiffier 2001)	full	epo-b	•	•	•	
Cascinu 1994	full	epo-a	•			
Case 1993	full	epo-a	•	•	•	
Cazzola 1995	full	epo-b	•	•	•	
Chang 2005 (EPO-CAN-17)	full	epo-a	•	•	•	
Charu 2007	full	darb	•	•	•	
Dammacco 2001	full	epo-a	•	•	•	
Debus 2007	abs	epo-a	•	•	•	
Del Mastro 1997	full	epo-?	•		•	
Dunphy 1999	full	epo-?	•		•	
Engert 2007	unpub	epo-a	•			
EPO-CAN-203	unpub	epo-a	•			
EPO-CAN-303	unpub	epo-a	•			
EPO-GER-20	unpub	epo-a		•		
OBE/EPO-INT-03	unpub	epo-a		•		
Gordon 2006	abs	darb	•	•	•	
Goss 2005 (EPO-CAN-15)	abs	epo-a	•	•	•	
Grote 2005 (N93-004)	full	epo-a	•	•	•	
Hedenus 2002	full	darb	•			•
Hedenus 2003	full	darb	•	•	•	•
Henke 2003	full	epo-b	•	•	•	
Henry 1995	full	epo-a	•	•	•	
Huddart 2002	abs	epo-a		•		
Kotasek 2002	abs	darb		•		•
Kotasek 2003	full	darb	•	•	•	•
Kurz 1997	full	epo-a	•			
Leyland-Jones 2005	full	epo-a	•	•	•	
Littlewood 2001	full	epo-a	•	•	•	
Machtay 2007	full	epo-a	•	•	•	
Milroy 2003	abs	epo-a	•	•		
Moebus 2007	abs	epo-a	•	•	•	

Appendix Table F1. ESA Trials Included in Published Meta-Analyses Evaluated in this Review (continued)

	Publi-cation status	ESA	Glaspy 2010	Bohlius 2009	Bennett 2008	Ludwig 2009
Mystakidou 2005	full	epo-a	•		•	
Oberhoff 1998	full	epo-b	•	•	•	
ODAC 2004, INT-1	unpub	epo-a	•	•	•	
ODAC 2004, INT-3	unpub	epo-a	•	•	•	
ODAC 2004, EPO-GBR-07 (Hoskin 2004)	unpub	epo-a	•	•	•	
ODAC 2004, P-174 (Pangalis 1995)	unpub	epoa	•	•	•	
O'Shaughnessy 2005	full	epo-a	•	•	•	
Osterborg 1996	full	epo-b	•	•	•	
Osterborg 2002/2005	full	epo-b	•	•	•	
Overgaard 2007 (ended early)	abs	darb	•		•	
Pirker 2008 (Amgen DA 145)	full	darb	•	•	•	•
Prozanto 2002	abs	epo-a	•	•		
Quirt 1996	abs	epo-a		•		
Ray-Coquard 2006	abs	epo-a		•		
Razzouk 2004/2006 (all patients)	abs/full	epo-a	•		•	
Razzouk 2006 (NHL/solid tumors only)	full	epo-a		•		
Rose 1994	abs	epo-a	•	•	•	
Savonije 2005	full	epo-a	•	•	•	
Smith 2003	full	darb	•		•	
Smith 2008 (Glaspy 2007)	full	darb	•	•	•	
Strauss 2008	full	epo-b	•	•	•	
Taylor 2005	abs	darb	•	•	•	•
Ten Bokkel Huinink 1998	full	epo-b	•	•	•	
Thatcher 1999	full	epo-a	•	•	•	
Thomas 2002	abs	epo-a		•		
Thomas 2008 (GOG-191)	full	epo-a	•	•	•	
Throuvalas 2000	abs	epo-?	•		•	
Untch 2008 (PREPARE)	abs	darb	•	•	•	
Vadhan-Raj 2004	abs	epo-a	•	•	•	
Vansteenkiste 2002	full	darb	•	•	•	•
Wilkinson 2006	full	epo-a	•	•	•	
Witzig 2005	full	epo-a	•	•	•	
Wright 2007 (EPO-CAN-20)	full	epo-a	•	•	•	

[a]Excluded RCTs with <100 patients or analyses based on <50 patients

Appendix G

Appendix Table G1. Summary of Trials Reporting Results Related to Tumor Progression

	ESA	Progression-Free Survival	Disease-Free survival	Time to Progression	Proportion of Patients with Progressive Disease
Aapro 2008	epo	Metastatic breast cancer; No definition of progression; HR=1.07; 95% CI, 0.89 to 1.30; P=0.448 at 18 mo. (treatment = 24 wk)			
Antonadou 2001	epo		Pelvic malignancies receiving RT; No definition of DFS; 4-yr DFS 85.3% (epo) vs. 67.2%, p=0.0008		
Engert 2010	epo				Hodgkin's Lymphoma; No definition of progression; Proportion with progression or relapse (8.3% epo vs. 7.8%), proportion with progressive disease (2.9% epo vs. 1.9%)
EPO-INT-1	epo			Ovarian cancer; no definition of progression; 16% (epo) vs. 15%	
Goss 2005, EPO-CAN-15	epo			Limited disease SCLC on chemoRx; no definition of progression; TTP, p=0.83	
Grote 2005, N03-004	epo				SCLC on chemo; 14.7% (epo) vs. 12.2% ; PD defined as (1) >25% increase in the size of at least one measurable malignant lesion or >25% increase in the estimated size of any assessable but nonmeasurable lesion; or (2) >25% increase in the estimated extent of assessable disease or >25% increase in the estimated extent of unmeasurable disease; or (3) development of a new malignant lesion.

Henke 2003	epo	**Locoregional** PFS; Tumour progression was assumed when tumour size increased by >25%; RR=1·69 (1·16–2·47, p=0·007)			
Hoskin 2009, EPO-GBR-7	epo		H&N Ca on radiotx; **Local** tumor recurrence was assessed clinically, and radiologically; HR=1.04; 95% CI, 0.77 to 1.41		
Leyland-Jones 2005	epo				Metastatic breast cancer on chemo; tumor response assessed by WHO criteria; 27% (epo) vs 22%
Machtay 2007	epo	H&N Ca on radiotx ± chemo; Local–regional failure was defined as the failure to obtain a complete response after definitive radiotherapy, or the reappearance of local and/or regional head-and-neck cancer after a complete response; biopsy confirmation was not required if there was convincing clinical/ radiographic evidence of local–regional persistence/recurrence in the opinion of the treating oncologist(s). **Locoregional** PFS, multi-variate HR 1.26 (95% CI, 0.80–1.99)			
Moebus 2007	epo		High risk breast cancer on chemo; no definition of DFS; 5-year DFS 72% (epo) vs. 71% (p=0.86)		
Osterborg 2005	epo				B-CLL, NHL, MM; No definition of disease progression; 18% (epo) vs 23%
Ray-Coquard 2009	epo			solid or hematologic tumors on chemo; no definition of disease progression; median PFS (epo) 5.0 months (95% CI: 4.3–6.6) vs 4.4 months	

				(95% CI: 3.8–5.2)	
Thomas 2008, GOG-0191	epo				Cervical cancer on chemoradiotx; Progression was defined as > 50% increase in the cross-product of the existing primary tumor relative to the smallest cross-product from all previous exams; 58% (epo) vs. 65% at 3 years
Wilkinson 2006	epo				ovarian cancer on chemo; no definition of disease progression; 11% (epo) vs 2%, P=0.425)
Witzig 2005	epo				incurable cancer on chemo; no definition of disease progression; 33% (epo) vs 29% (p=0.86)
Overgaard 2009	darb	H&N on chemo; no definition of disease progression; RR: 1.47 (1.14-1.94)	RR: 1.32 (1.04-1.68)		
Pirker 2008	darb	Extensive stage SCLC on chemo; disease progression defined by modified Response Evaluation Criteria in Solid Tumors; HR=1.02, (0.86 to 1.21)			
Untch 2008	darb				breast cancer on chemo; no definition of disease progression; 27% (darb) vs 21%
Vansteenkiste 2002	darb			Lung cancer on chemo; no definition of disease progression; median duration 22 weeks (95% CI 18 to 31 weeks, darb) vs 20 weeks (95% CI 17 to 23)	

Appendix H: Decision Model Mortality Rate Tables

Appendix Decision Table H1. 10% Annual Morality Rate Following On-Study Period

On-Study Mortality Rate Controls	QALYs ESA	QALYs Control	Difference (+ESA better -ESA worse)		Life Years ESA	Life Years Control	Difference (+ESA better -ESA worse)
1.0%	662.5	653.3	+9.3		960.8	962.5	-1.7
3.0%	644.8	637.9	+6.9		935.0	940.0	-5.0
7.5%	606.2	604.3	+1.9		879.0	891.0	-11.9
10.0%	585.6	586.3	-0.7		849.1	864.6	-15.5

Appendix Decision Table H2. 20% Annual Morality Rate Following On-Study Period

On-Study Mortality Rate Controls	QALYs ESA	QALYs Control	Difference (+ESA better -ESA worse)		Life Years ESA	Life Years Control	Difference (+ESA better -ESA worse)
1.0%	645.2	635.9	+9.3		936.2	937.8	-1.7
3.0%	628.0	621.0	+7.0		911.1	916.0	-4.9
7.5%	590.6	588.4	+2.1		856.8	868.4	-11.6
10.0%	570.5	570.9	-0.4		827.7	842.8	-15.1