*Evidence-based Practice Center Systematic Review Protocol*

# Project Title: Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment–An Update to the 2006 Report

## I. Background and Objectives for the Systematic Review

### Objective

Shekelle et al.[1] reviewed a sample of literature published through 2008 and obtained four expert opinions regarding the need to update conclusions for each key question included in the 2006 Comparative Effectiveness Review (CER) of the erythropoietin stimulating agents (ESA) epoetin and darbepoetin.[2] The consistency and strength of the evidence and expert opinion supporting recommendations to update specific key questions were evaluated by the Southern California Evidence-based Practice Center (EPC). Based on that appraisal, three key questions (see Section II) were judged relevant.

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 raised in the 2006 CER. As noted by Shekelle et al.,[1] the "CER may need updating based on new data presented to the FDA and difference in expert opinion."

Shekelle et al. recommend that the 2006 findings on quality of life do not need to be updated. The EPC agreed in substance, noting that the FDA stated there is insufficient evidence to support claims of improved quality of life with ESA use. However, we believe it important that quality of life evidence be at least qualitatively reviewed and that the principles of critical appraisal of use and interpretation of disease-specific quality of life instruments that were raised in the 2006 CER continue to be accessible in the 2010 Update. Moreover, these points should be tied to the Guidance for measurement of patient-reported outcomes issued by the FDA in 2008.

The 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, the overall objective of this comparative

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effectiveness review is to systematically update the previous CER and synthesize the available evidence on the outcomes of epoetin (alpha or beta) or darbepoetin treatment (compared to no treatment, to placebo, or to each other) in patients being treated for a malignancy with myelosuppressive chemotherapy and/or radiation.

Two forms of recombinant human erythropoietin—epoetin alfa and epoetin beta (the latter not commercially available in the United States)—have been extensively studied and used clinically for more than a decade to treat various anemias; they have similar clinical efficacy.[3,4] In a recent review of safety concerns associated with recombinant human erythropoietins, a U.S. Food and Drug Administration (FDA) briefing document[5] noted that "…the biochemical differences between various erythropoietin products are not associated with marked differences in the pharmacodynamic properties of the different products when used at recommended doses, thus effects observed with these non-US-licensed products may also be associated with the U.S. licensed product." For this reason, both forms of epoetin will be evaluated in this review.

This update will not address epoetin delta [Dynepo]. Dynepo had been approved in Europe for the treatment of symptomatic anemia associated with chronic renal failure in adult patients and has been studied almost entirely in this population. In February 2009, the manufacturer elected to withdraw the product from the market for commercial reasons and it is now discontinued. This update will also not address the third-generation molecule, Continuous Erythropoietin Receptor Activator (CERA), which has a different method of action, and has been studied very little in patients with cancer.

## Clinical Summary

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: [6]

- Grade 0, within normal limits, hemoglobin 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).

The prevalence of anemia varies according to the type of neoplasia.[7] Patients with hematological malignancies frequently experience anemia. At diagnosis, 30 to 40% of patents with non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HD), up to 70% of patients with multiple myeloma, and essentially all with myelodysplastic syndromes are anemic.[8] The type of cytocidal or cytostatic treatment also influences the degree of anemia. For patients with lymphoma, anemia is present in approximately

40% of patients at diagnosis; following 3 to 4 cycles of chemotherapy up to 70% of the patients will be anemic.[9]

The pathophysiology of tumor anemia is multi-factorial. In advanced stages of hematological malignancies bone marrow involvement with malignant cells often leads to progressive anemia. After exclusion of other causes, e.g. iron or vitamin deficiencies, occult bleeding, autoimmune hemolysis or pure red blood cell aplasia, anemia can be related 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, especially Interferon-g, Interleukin-1 and tumor necrosis factor. This is followed by insufficient endogenous erythropoietin synthesis, suppressed differentiation of erythroid precursor cells in the bone marrow, and alterations of iron metabolism.[10] Anemia of chronic disease is the most common type in patients with malignant disease, though it is often aggravated by chemo- or radiotherapy. In particular, platinum-based chemotherapy regimens may diminish endogenous erythropoietin production by damaging renal tubular cells.[11]

Manifestations and severity of anemia vary considerably among individual patients. Mild to moderate anemia can cause typical 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 the central nervous system.[12] 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.[13-15]

Another aspect of anemia in patients with malignant disease is the possible effect on the tumor itself. For malignant diseases like HD, chronic lymphocytic leukemia (CLL), cervical carcinoma and cancer of the head and neck, anemia is reportedly a prognostic factor.[16] There is evidence that anemia, causing increased tumor hypoxia, might result in a poorer response to radio- or chemotherapy.[17] These factors may lead to a higher tumor burden and decrease overall survival.[17-20] Although the prognostic significance of anemia may simply reflect progressive or advanced disease, the observations 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. Randomized controlled trials examining this hypothesis have generated conflicting evidence including improved disease free survival and worse tumor control and survival.[21, 22]

Historically, blood transfusion was the conventional treatment of choice for severe cancer-related anemia. The literature reports a critical degree of anemia as hemoglobin concentration below 8 g/dl, while mild-to-moderate anemia (hemoglobin level 8-10 g/dl) usually has been left untreated.[23] Although homologous blood transfusion is the fastest method to alleviate symptoms, short and long term risks exist.[24] Potential complications associated with blood transfusion include transmitting infectious diseases, transfusion reactions, alloimmunization, over-transfusion, and

immune modulation with theoretically possible adverse effects on tumor growth.[25] 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.[26] Emerging infections, such as the West Nile virus epidemic in 2002 in the US are of concern.[27,28] However, in decision-analytic models of erythropoietic stimulating agents, the risk of blood transfusion appears not to meaningfully impact results.[29,30]

The development of intensified anti-neoplastic therapies has increased the risk for blood transfusion, prompting oncologists to weigh the advantages and disadvantages of this treatment. Recombinant human erythropoietin is a treatment option for cancer-related anemia. Two forms of recombinant human erythropoietin (EPO), epoetin-alpha and beta, are available for the treatment of anemia, both with similar clinical efficacy.[31,32] Recently a novel long-acting erythropoietin preparation has been developed: novel-erythropoiesis stimulating protein (NESP) or darbepoetin-alpha. Darbepoetin-alpha produces a similar physiologic response when compared to recombinant human erythropoietin[33] and has already been tested in prospective clinical trials.[34-36] Erythropoietin was first approved for the treatment of anemia in chronic kidney failure. In 1990, erythropoietin was introduced in a cancer therapy regimen for patients with multiple myeloma.[37] Adverse effects such as hypertension, headaches and thrombotic events that can be conclusively attributed to erythropoietin treatment had been reported in very few patients,[38] however, recently published randomized controlled trials reported increased incidences of thrombotic events.[21,22]

## FDA Status, Indications, and Warnings for Use of ESAs

Epoetin alfa

*Treatment of Anemia in Cancer Patients on Chemotherapy*

EPOGEN® [PROCRIT®[1]] is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies receiving chemotherapy for a minimum of 2 months. Studies to determine whether EPOGEN® [PROCRIT®] increases mortality or decreases progression-free/recurrence-free survival are ongoing.

- EPOGEN® [PROCRIT®] is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- EPOGEN® [PROCRIT®] is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of EPOGEN® on progression-free and overall survival (see WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence).

[1] Labeled indications are the same for both EPOGEN and PROCRIT.

- EPOGEN® [PROCRIT®] is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding (see PRECAUTIONS: Lack or Loss of Response).
- EPOGEN® [PROCRIT®] use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

Darbepoetin

*Anemia with Non-Myeloid Malignancies Due to Chemotherapy*

Aranesp® is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies. Studies to determine whether Aranesp® increases mortality or decreases progression-free/recurrence-free survival are ongoing.

- Aranesp® is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- Aranesp® is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of Aranesp® on progression-free and overall survival (see WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence).
- Aranesp® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

FDA label warnings: (Epoetin and Darbepoetin)

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR EVENTS, THROMBOEMBOLIC EVENTS, STROKE and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE

Cancer:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.
- Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense

EPOGEN® (Epoetin alfa) to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance.

- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

## Prior Evidence Analyses and Guidelines

Erythropoietin appears to reduce transfusion requirements in patients with malignancy undergoing chemotherapy. At the same time, evidence is consistent with an increased risk of thromboembolic events and mortality. Although there are fewer transfusions, the balance of benefits and harms and whether there is a net clinical benefit accrued from erythropoietic stimulants in this setting are of considerable consequence. These concerns are reflected in recent changes to FDA labeling intended to minimize harms of these agents including a target hemoglobin no greater than 12 g/dl and avoiding use in the setting of curative intent for the malignancy being treated.

There are several evidence-based guidelines assessing the efficacy of erythropoietin for treating patients with solid tumors receiving chemotherapy and summarizing evidence for reduced transfusion requirements. The most comprehensive is the guideline of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH).[39] The evidence base for this review derived from a collection of systematic reviews, most prominently one commissioned by the Agency for Health Care Research and Quality (AHRQ) and conducted by the Blue Cross and Blue Shield Association's Technology Evaluation Center Evidence-based Practice Center (BCBSA EPC)[2] and another conducted by Cochrane Collaboration.[40] Highlighting concerns over benefits and harms, no fewer than three meta-analyses have appeared in 2009. In an individual patient data meta-analysis of 13,933 patients in 53 trials treated with epoetin alfa or beta and darbepoetin alpha, Bohlius et al. found a 17% relative increase in mortality during the active study period.[41] In contrast, Ludwig et al. analyzed individual patient data from 2,122 patients in 6 trials receiving darbepoetin alpha finding no relative increase in mortality.[42] Finally, examining study level data from 52 trials Tonelli et al.[43] reported results consistent with the large individual patient data meta-analysis.[41]

Despite many trials, systematic reviews and meta-analyses, a number of uncertainties surrounding erythropoiesis-stimulating agents persist. Most fundamental is the balance of potential benefits (QoL, fewer transfusions) and harms (increased mortality, thromboembolic events) and how treatment strategies (thresholds for

initiation, therapy duration) might affect that balance. Moreover, both recombinant erythropoietin and darbepoetin alpha are costly. Accordingly, a systematic update addressing uncertainties in the body of evidence is timely.

## *II. The Key Questions*

Following the public posting of the key questions, several comments were received and discussed. A summary of relevant comments and our responses follow each key question; general comments applying to all key questions and responses are listed after the last key question.

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 and/or radiation for malignancy (excluding myelodysplastic syndrome and acute leukemia)? Specific comparisons to be included are:

a. Epoetin (alfa or beta) versus no ESA;

b. Darbepoetin versus no ESA;

c. Epoetin (alfa or beta) or darbepoetin versus no ESA; and

d. Epoetin (alfa or beta) versus darbepoetin.

| **Question 1 Comment** | **EPC Response** |
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| It is important to include the comparative effectiveness (including potential harms) of non-ESA therapies such as transfusions in the considerations of anemia management for patients with cancer. It is hoped that the studies available to inform these outcomes include information on other adverse events that are related to transfusions; if these studies are not available, this fact should be acknowledged in the published report. | Adverse events related to transfusions reported in included studies will be incorporated in the review. As noted in the previous report, transfusion-related adverse events are uncommon. As suggested, availability of evidence will be acknowledged in the report. |
| Suggest reframing the question by limiting evidence to comparative data from randomized controlled trials (RCTs) or meta-analyses of RCTs, which allow for a comparison of efficacy and safety within the context of equivalent populations, dosing, and health outcomes. Because RCT data encompass both the analysis of prespecified endpoints as well as post-hoc retrospective analyses, both approaches can be used to evaluate the evidence. Data from observational research, while informative, are less internally valid than RCT data and results are typically only | Given the focus on comparative benefits and harms, KQ1 allows for inclusion of observational studies after applying clearly defined and rigorous selection criteria. |

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| considered reliable if consistent with results demonstrated within RCTs. The existence of multiple confounding factors in observational studies may also limit interpretation of these data, particularly considering the complex nature of ESA use in cancer patients with anemia undergoing chemotherapy. | |

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.

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.

| **Question 2/Question 3 Comment** | **EPC Response** |
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| Although determining how alternative thresholds (KQ2) for initiating treatment compare regarding their effect on the benefits and harms of erythropoietic stimulants is important, it is not clear how well this can be addressed using the available literature and the confounding information from other factors including gradually increasing ESA use at higher initiation thresholds over time, coincident with increasing vigilance for survival and other adverse events over time, and changing indications for ESA use. A more important (or adjunctive) analysis to perform, in keeping with some of the data available from the renal ESA literature, may be to consider the dose density/intensity of the ESA, particularly in those recipients who do not initially respond to ESA with a hemoglobin (Hb) increase. One might hypothesize that the Hb at initiation, or the achieved Hb, may matter less than the intensity of exposure to ESA (concentration and duration) with regard to adverse events, particularly in non-respondents or slow respondents. | KQs 2 and 3 were included as advised by content experts during the assessment of the need to update the prior report. We concur with the importance of examining any possible relationship of dose/dosing with outcomes and will make efforts to do so with the available evidence. While other primary data sources might provide further insights, data on ESA exposure available at the study level may lack specificity when data are available. Such analyses are likely best be done at the patient level, which is outside the scope of this project. |
| This question (KQ3) and the available data have been specifically considered and addressed by the FDA. Therefore, it is unclear why AHRQ would consider this at this time. | |

| General Comments | EPC Response |
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| Overall, there is concern that an updated literature-based systematic review or meta-analysis will not provide data to address the important questions that remain about ESA use. Rather, new analyses are needed. The most important question facing oncologists and their patients regarding ESA strategies is whether everyone with chemotherapy-induced anemia is equally at risk for the potential harms and is equally likely to experience the potential benefits. Updating a literature-based systematic review and meta-analysis would not provide data to address this information need. A meta-analysis would only be able to refine already published point estimates and confidence intervals for ESA treatment effects, without addressing the most pressing clinical questions concerning the use of these agents, in particular, clinical and biological classifiers of risk and benefit. Instead, we would hope that the next generation of data analyses could contribute substantially to resolving current uncertainties | While the KQs may not directly address the issues raised, the current report will address the current state of evidence and examine as explicitly as possible the important tradeoffs encountered with ESA use. We intend that many of the issues raised will be examined by including a decision-analytic evaluation of the benefit/risk balance--e.g., life-years and quality-adjusted life years gained or lost. We believe this approach will add perspective to some of these critical questions. We also appreciate that other research, and suggestions offered are important. However, any primary data collection would be beyond the scope of this report. |
| ESAs were developed and approved with the goal of avoiding transfusions, and not as an anemia treatment compared with transfusions. Treatments should only be compared when employed to achieve the same clinical or Hb outcome. Therefore, comparisons of ESAs and transfusions to treat anemia to different Hb levels are not valid comparisons and conclusions about their relative efficacy or safety are not possible | While ESA- and non-ESA strategies (transfusion) to treat chemotherapy induced anemia may have different effects on Hb, comparative effectiveness is intended to examine differing strategies for managing the same condition. In comparative effectiveness research it is expected that different treatments will have different outcomes including benefits and harms. |
| Recommend identifying specific Hb and/or symptom cutoffs that will be used in the evaluation. There is value in using both prespecified endpoints from RCTs, as well as post-hoc retrospective analyses of RCT data and therefore, both approaches are recommended to evaluate the evidence. Further, analyses of efficacy and safety are suggested, either assessed per the approved prescribing information (per label) or as experimental approaches to achieve higher than the approved Hb levels. | While cutoffs for analysis are important as suggested, they will be informed by content experts and current practice. Specification of cutoffs would not be consistent with the objectives of the current project. A goal is to include the largest body of literature to allow exploring important parameters and outcomes. |
| Suggest specifically defining the criteria that will be considered for evaluating therapy discontinuation and optimal duration and clarifying how they will be prespecified. | Given the evidence under consideration, our concern is that prespecificiation could unnecessarily restrict the evidence base. |
| The ESAs are indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to concomitantly administered chemotherapy. ESAs are not indicated for patients receiving radiation therapy unless concomitant chemotherapy is administered. | To be consistent with the previous reports, the current systematic review will include patients undergoing chemotherapy or radiation for cancer. A sensitivity analysis will be included to evaluate any effect of radiation-only studies on the results |
| Consideration should also be given to evaluate the potential impact of the Hb threshold for ESA initiation on overall blood utilization (e.g. number of units transfused). | Based on prior reports, the evidence base on number of transfused units has been sparse. While the question is an important it would be potentially addressed by new research. |

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| I wonder if having some information related to patient age and sex would be useful, i.e., safer in pediatric patients and women vs. geriatric patients and men, etc. | Previous systematic reviews were unable to effectively examine these subgroups using study-level data. Given the extent of new evidence, addressing differential benefits and harms according to these subgroups was judged unlikely to yield different results. |

## Important refinement points regarding all key questions:

- **Population(s):**
  Patients experiencing or at risk of anemia due to chemotherapy and/or radiation treatment for malignancy are included. Patients with myelodysplastic syndrome or patients with acute leukemia who have anemia due to bone marrow ablation and stem cell transplantation are excluded.
- **Interventions:**
  Studies of using the following ESAs will be included:

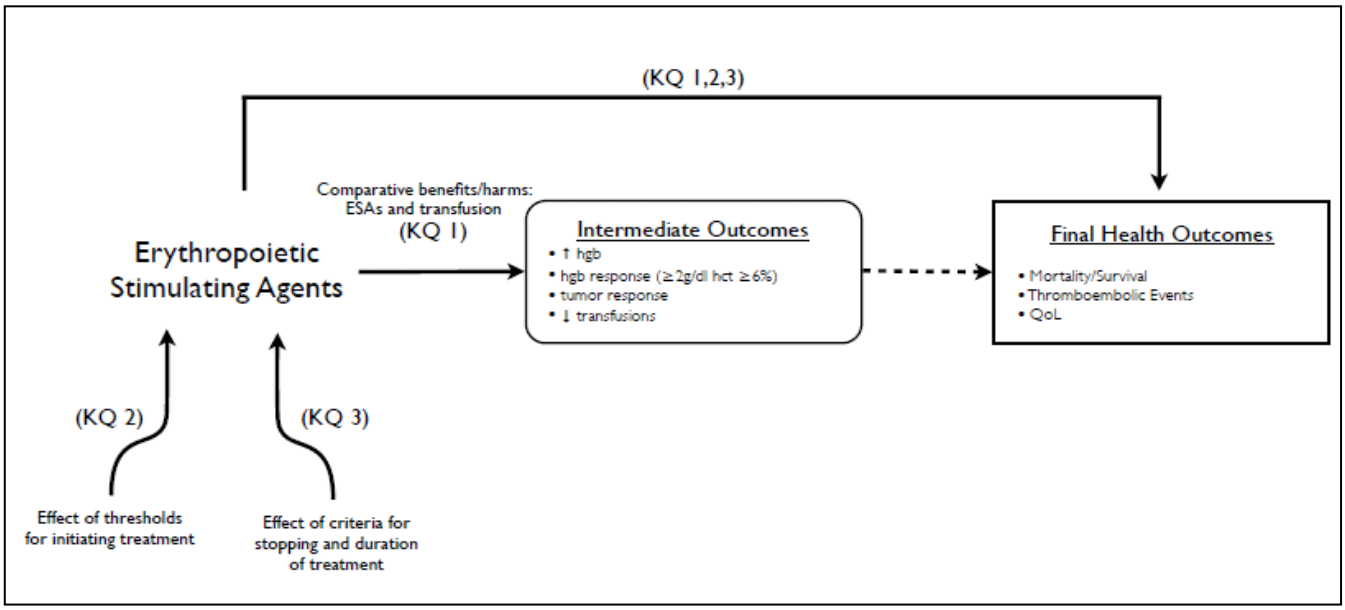
| ESA | Approval Status U.S. | Approval Status European Union | Approved Dose |
|---|---|---|---|
| Epoetin alfa | EPOGEN® (Amgen); PROCRIT® (Ortho Biotech) | Eprex® (Janssen-Cilag) | Epoetin alfa preparations are formulated for intravenous (IV) or subcutaneous (SC) administration. The recommended adult 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. |
| 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 and Objectives. While not approved in U.S. effects are considered exchangeable with Epoetin alfa.

- **Comparators:**
  Placebo and/or usual care, which includes red blood cell transfusions if necessary.
- **Outcomes:**
  Final health outcomes:
  - overall survival (on-study and longest available follow-up)
  - progression free survival
  - quality of life
  - thromboembolic complications
  - other adverse events including those related to red blood cell transfusion

  Intermediate outcomes:
  - hematologic responses
  - transfusions
  - tumor response to therapy
- **Timing:**
  All durations of follow-up will be included.
- **Settings:**
  All settings will be included.

## *III. Analytic Framework*




## *IV. Methods*

### A. Criteria for Inclusion/Exclusion of Studies in the Review

**Inclusion/exclusion criteria for randomized controlled trials:**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Types of studies | Randomized controlled clinical trials.<br><br>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. |
| | 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, Spanish; no effort will be made to translate languages such as Chinese or Arabic. | Ongoing studies and interim analyses. |
| Sources of | Full text publications. | |

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| evidence | 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. | |
| 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 hematological 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. | |

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| Types of outcome measures | Hematological 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. | |

Inclusion criteria for observational studies are as above except for "Types of studies." Exclusion criteria are also the same except that studies enrolling less than 250 patients will be excluded.

## B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

We will update the randomized controlled trial literature from the previous review through: (1) electronic searching of the Cochrane Central Register of Controlled Trials Register (CENTRAL, 03/2005 to 09/2009), MEDLINE (03/2005 to 09/2009), and EMBASE (03/2005 to 09/2009). Electronic searching will also include the conference proceedings of the American Society of Clinical Oncology (03/2005 to 09/2009), European Society of Medical Oncology (03/2005 to 08/2009), American Society of Hematology (03/2005 to 09/2009). A separate search for observational studies, primarily although not exclusively to augment the evidence on adverse events, will be conducted in MEDLINE only. Results will be compiled into a reference manager database with exclusion of duplicates. The search strategies are shown in the Appendix (Section XI).

The literature searches will be updated prior to finalizing a draft of the review to determine if any new studies have been published that may potentially impact the review. New studies will be evaluated against inclusion/exclusion criteria in the same manner as all other studies.

Similarly, any additional data recommended during public and peer review of the draft document will also be evaluated against inclusion/exclusion criteria in the same manner as all other studies.

## C. Data Abstraction and Data Management

**Randomized controlled trial selection:**

One reviewer will screen titles and abstracts of trials identified from the above sources for the eligibility criteria stated previously. If this cannot be done satisfactorily from the title and abstract, we will obtain a full text version for assessment. We will assess studies that appear to meet the inclusion criteria in the initial screening for eligibility 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 (alpha 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?

For trials to be eligible, studies must meet all of the criteria stated above. Any disagreements between the reviewers will be resolved by discussion. Duplicate studies will be identified and data will be extracted from the most recent publication. Full text versions of all eligible studies will be obtained for quality assessment and data extraction.

**Observational Study Selection:**

When trial evidence is insufficient, observational data will be searched. One reviewer will screen titles and abstracts of identified studies from the above sources for the eligibility criteria below. If this cannot be done satisfactorily from the title and abstract, we will obtain a full text version for assessment. Eligible studies will include those suitable to address questions not informed by trials.

1. Is the study described as non-randomized?

2. Are there more than 250 subjects?

4. Did the participants in the study have a previously treated or untreated malignant disease?

5. Were the participants anemic or at risk for anemia from chemotherapy and/or radiotherapy?

6. Was epoetin (alfa or beta) or darbepoetin given subcutaneously or intravenously for at least four weeks?

7. Did the study document one of the relevant outcome measures (benefit or harm)?

8. 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:**

Results from study- and patient-level meta-analysis will be included (e.g., Bohlius et al[41]). Progression-free or disease-free survival study-level results from industry-funded meta-analyses will also be included if the original study was designed to evaluate that outcome.

**Data Abstraction:**

One reviewer will perform data extraction for the review using a standardized data extraction form modified slightly from the previous systematic review, including the types of items listed below. A second reviewer will independently fact-check the data.

For randomized controlled clinical trials:

- General information: title, authors, source, contact address, year of publication, duplicate publications, setting, funding.
- Trial characteristics: design, method of randomization, concealment of allocation, blinding of patients and clinicians.
- Patients: sampling, exclusion criteria, sample size, baseline characteristics, similarity of groups at baseline, diagnostic criteria, withdrawals, losses to follow up.
- Interventions: placebo use, dose, dosing regimen, duration, route, RBC transfusion trigger, co-medications with dose, route and timing. Outcomes as specified above.
- Analytical methods

Disagreements at any stage will be resolved by discussion and consensus.

Discrepant data: For studies published in multiple articles, reports or presentations, we will extract the most recent or most comprehensive data. The data of any study taken from different sources will be compared. If data from different sources are discrepant, data will be selected for analysis using the following rules:

- We will use the most complete data sets (i.e., those with the largest sample size), or data with consistently defined outcomes across trials.
- If different results are available from the same study, i.e. "intention-to-treat" and "as treated" analyses, we will use the intention-to-treat based data for a base-case analysis and explore the influence of alternative results in sensitivity analyses.

Handling of incompletely reported numbers: If a study only reports the overall number of randomized patients but fails to report the number of patients per study arm we will assign 50 percent of the study patients to each of the study arms.

For updating reports that were already included in the previous systematic review, the focus will be on variables that are important to the analyses, rather than on a global update.

**Evidence Tables:**

We will create evidence tables in Microsoft Excel and summary evidence tables in Microsoft Word using templates from the prior systematic review. One reviewer will perform primary data abstraction of all data elements into the Excel evidence tables, and a second reviewer will perform accuracy checks. Relevant extracted data will be summarized in Word evidence tables.

**PRISMA:**

A PRISMA diagram[44] will be constructed for each Key Question.

Assessment of Applicability:

Applicability of findings in this review will be assessed within the EPICOT framework (Evidence, Population, Intervention, Comparison, Outcome, Time stamp)[45]. Selected studies will be assessed for relevance against target populations, interventions of interest and outcomes of interest.

## D. Assessment of Methodological Quality of Individual Studies

Two reviewers will assess the full text articles eligible for the review on quality. Any discordance will be discussed with the rest of the group until consensus is obtained. Because of the problematic use of quality summary scores,[46,47] we will use a quality assessment form designed for the topic of this review,[48] 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?

8. For QoL studies it will in addition be assessed whether patients were blinded towards their Hb levels when QoL questionnaires were completed.

Note: for studies for which there are several reports/analyses, we will use our best judgment for accurately and efficiently assessing quality (study level will be the default).

Trials will be excluded from the analysis if they are not truly randomized or have inadequately concealed allocation.

Trials will be grouped into higher quality and low quality trials by the following criteria. Studies that meet all criteria will be included in the group of higher quality trials for purposes of sensitivity analysis.[2]

1. The study was a randomized controlled trial (see details under Criteria for Considering Studies).

2. The study was double-blind.

3. At least one of the following conditions was true: 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.

**Quality Assessment of Meta-Analysis:**

AMSTAR is a validated tool used for quality assessment of meta-analyses.[49] While the tool has been validated with study-level meta-analyses, 9 of the 11 tool

[2] "Excluded from the analysis" refers to all patients who were randomized in the study but were not included in the analysis of results. Subjects excluded from the analysis are those not included in the results for any reason, including: withdrawn after randomization, lost to follow-up, or with missing data. A study will be classified as double-blind if stated as such in the publication without further description of the method of blinding and if the study used a placebo. If a placebo was used, but there is no mention of double blinding, the study will be classified as single-blinded. If a placebo was not used, or if there was no mention that a placebo was used, or if it was stated that the study was unblinded, the study will be classified as unblinded. The other quality criteria will be used for descriptive purposes only but not for sensitivity analysis.

elements apply directly and the remaining 2 elements indirectly to individual patient meta-analyses. Accordingly, the tool will be applied to all meta-analyses.

NOTE: No quality assessment of observational (adverse effects) studies will be conducted.

## E. Data Synthesis

When study-level outcome data are available from multiple trials (3 or more), aggregate data meta-analyses will be conducted. If IPD meta-analytical results are available for specific outcomes, aggregate data meta-analyses will be performed if appropriate study-level results are available. A random effects model will be assumed for all meta-analyses. For binary data, the relative risk will be used as a measure of treatment effect. If the relative effect is independent of baseline risk (control rate), numbers needed to treat (NNT) and numbers needed to harm (NNH) will be calculated as appropriate. Time to event data, e.g., overall survival, will be calculated as hazard ratios (HR) based on individual patient data (IPD) if available from previous work. If IPD data are not available no efforts will be made to obtain it and the HR will be calculated from published reports, using methods described by Parmar et al.[50] from binary mortality data. Between-study heterogeneity will be evaluated by examining measures of between-study variability (e.g., $tau^2$, $I^2$) and explored as indicated using subgroup analyses and meta-regression. When direct comparative data are not available, qualitative indirect comparisons will be carried out, and quantitative indirect comparisons explored when feasible. Recognizing limitations,[51] indications of possible publication bias will be examined in funnel plots.

When there are zero events in one trial arm, or in both arms not attributable to lack of ascertainment, pooling will be performed using methods described by Warn et al.[52] and Vandermeer et al.[53] Analyses will be performed using R.[54-56]

Subgroup analyses may include the following factors, if feasible and appropriate:

- Hemoglobin at study entry (continuous and hemoglobin level < 10 g/dl versus 10-12 g/dl versus >12 g/dl)
- Achieved hemoglobin (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 hematological malignancies versus mixed (studies including both solid tumors and hematological 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

- Iron supplementation (fixed versus as necessary versus none)
- 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)

## F. Grading the Evidence for Each Key Question

We will use the system for rating the strength of the overall body of evidence developed by the GRADE Working Group.[57] The GRADE system explicitly addresses the following domains: risk of bias, consistency, directness, precision, strength of association, and publication bias. Quality of evidence is classified into the following 4 categories:

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Insufficient: Any estimate of effect is very uncertain

## *V. References*

1. Shekelle P, Newberry S, Maglione M, et al. Evaluation of the need to update comparative effectiveness reviews. Rockville, MD: Agency for Healthcare Research and Quality; October 2009. Available at: www.effectivehealthcare.ahrq.gov/ehc/products/125/331/2009_0923UpdatingReports.pdf .
2. Seidenfeld J, Piper M, Bohlius J, et al. Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment. Comparative Effectiveness Review No. 3. (Prepared by Blue Cross and Blue Shield Association Evidence-based Practice Center under Contract No. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality, May 2006. AHRQ Publication No. 06-EHC008-1. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm .
3. Halstenson CE, Macres M, Katz SA, et al. Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. *Clin Pharmacol Ther* 1991;50(6):702-12.
4. Storring PL, Tiplady RJ, Gaines Das RE, et al. Epoetin alfa and beta differ in their erythropoietin isoform compositions and biological properties. *Br J Haematol* 1998;100(1):79-89.
5. Food and Drug Administration Oncologic Drugs Advisory Committee. May 4, 2004, Meeting Briefing Information (available at: www.fda/gov/ohrms/docktes/ac/04/briefing/4037b2.h ). Last accessed, June 7, 2010.
6. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst* 1999;91(19): 1616-34.
7. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *Am J Med* 2004;116 Suppl 7A:11S-26S.
8. Garton JP, Gertz MA, Witzig TE, et al. Epoetin alfa for the treatment of the anemia of multiple myeloma. A prospective, randomized, placebo-controlled, double-blind trial. *Arch Intern Med* 1995;155(19): 2069-74.
9. Samol J, Littlewood TJ. The efficacy of rHuEPO in cancer-related anaemia. *Br J Haematol* 2003;121(1): 3-11.
10. Ludwig H, Fritz E. Anemia in cancer patients. *Semin Oncol* 1998;25(3 Suppl 7): 2-6.
11. Wood PA, Hrushesky WJ. Cisplatin-associated anemia: an erythropoietin deficiency syndrome. *J Clin Invest* 1995;95(4): 1650-9.
12. Ludwig H, Strasser K. Symptomatology of anemia. *Semin Oncol* 2001;28(2 Suppl 8): 7-14.

13. Leitgeb C, Pecherstorfer M, Fritz E, et al. Quality of life in chronic anemia of cancer during treatment with recombinant human erythropoietin. *Cancer* 1994;73(10): 2535-42.
14. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol* 1998;25(3 Suppl 7): 43-6.
15. Thomas ML. Impact of anemia and fatigue on quality of life in cancer patients: a brief review." *Med Oncol* 1998;15 Suppl 1: S3-7.
16. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med* 1998;339(21): 1506-14.
17. Vaupel P, Hockel M. Blood supply, oxygenation status and metabolic micromilieu of breast cancers: characterization and therapeutic relevance." *Int J Oncol* 2000;17(5): 869-79.
18. Knocke TH, Weitmann HD, Feldmann HJ, et al. Intratumoral pO2-measurements as predictive assay in the treatment of carcinoma of the uterine cervix. *Radiother Oncol* 1999;53(2): 99-104.
19. Grau C, Overgaard J. Significance of hemoglobin concentration for treatment outcome. Blood Perfusion and Microenvironment of Human Tumors. Molls M, Vaupel P, eds. New York, Springer; 2000 p101-12.
20. Glaser CM, Millesi W, Kornek GV, et al. Impact of hemoglobin level and use of recombinant erythropoietin on efficacy of preoperative chemoradiation therapy for squamous cell carcinoma of the oral cavity and oropharynx. *Int J Radiat Oncol Biol Phys* 2001;50(3): 705-15.
21. Henke M, Laszig R, Rübe C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial." *Lancet* 2003;362(9392): 1255-60.
22. Leyland-Jones B. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol* 2003;4(8): 459-60.
23. Koeller JM. Clinical guidelines for the treatment of cancer-related anemia. *Pharmacotherapy* 1998;18(1): 156-69.
24. Engert A. Recombinant human erythropoietin as an alternative to blood transfusion in cancer-related anaemia. *Dis Manage Health Outcomes* 2000;8(5): 259-272.
25. Landers DF, Hill GE, Wong KC, et al. Blood transfusion-induced immunomodulation. *Anesth Analg* 1996;82(1): 187-204.
26. Goodnough LT. Risks of blood transfusion. *Anesthesiol Clin North America* 2005;23(2): 241-52.
27. Biggerstaff BJ, Petersen LR. Estimated risk of West Nile virus transmission through blood transfusion during an epidemic in Queens, New York City. *Transfusion* 2002;42(8): 1019-26.

28. Allain JP (2003). Transfusion risks of yesterday and of today. *Transfus Clin Biol* 2003;10(1): 1-5.
29. Barosi G, Marchetti M, Liberato NL. Cost-effectiveness of recombinant human erythropoietin in the prevention of chemotherapy-induced anaemia. *Br J Cancer* 1998;78(6): 781-7.
30. Cremieux PY, Finkelstein SN, Berndt ER, et al. Cost effectiveness, quality-adjusted life-years and supportive care. Recombinant human erythropoietin as a treatment of cancer-associated anaemia." *Pharmacoeconomics* 1999;16(5 Pt 1): 459-72.
31. Halstenson CE, Macres M, Katz SA, et al. Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. *Clin Pharmacol Ther* 1991;50(6): 702-12.
32. Storring PL, Tiplady RJ, Gaines Das RE, et al. Epoetin alfa and beta differ in their erythropoietin isoform compositions and biological properties. *Br J Haematol* 1998;100(1): 79-89.
33. Joy MS. Darbepoetin alfa: a novel erythropoiesis-stimulating protein. *Ann Pharmacother* 2002;36(7-8): 1183-92.
34. Hedenus M, Hansen S, Taylor K, et al. Randomized, dose-finding study of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies. *Br J Haematol* 2002;119(1): 79-86.
35. Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy." *J Natl Cancer Inst* 2002;94(16): 1211-20.
36. Glaspy JA, Jadeja JS, Justice G, et al. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease." *Cancer* 2003;97(5): 1312-20.
37. Ludwig H., Fritz E, Kotzmann H, et al. Erythropoietin treatment of anemia associated with multiple myeloma." *N Engl J Med* 1990;322(24): 1693-9.
38. Beguin Y. A risk-benefit assessment of epoetin in the management of anaemia associated with cancer. *Drug Saf* 1998;19(4): 269-82.
39. Rizzo JD, Somerfield MR, Hagerty KL, et al. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol* 2008;26(1): 132-49.
40. Bohlius J, Schmidlin K, Corinne Brillant, et al. Erythropoietin or Darbepoetin for patients with cancer--meta-analysis based on individual patient data. *Cochrane Database Syst Rev* 2009;(3): CD007303.
41. Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet* 2009;373(9674): 1532-42.

42. Ludwig H, Crawford J, Osterborg A, et al. Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. *J Clin Oncol* 2009;27(17): 2838-47.

43. Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. *CMAJ* 2009;180(11): E62-71.

44. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *Ann Intern Med* 2009;51:W-65–W-94.

45. Brown P, Brunnhuber K, Chalkidou K, et al. How to formulate research recommendations. *BMJ* 2006;333(7572): 804-6.

46. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273(5): 408-12.

47. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;282(11): 1054-60.

48. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org .

49. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;15:7-10.

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

51. Lau J, Ioannidis JP, Terrin N, et al. The case of the misleading funnel plot. *BMJ* 2006;333(7568): 597-600.

52. Warn DE, Thompson SG, Spiegelhalter DJ. Bayesian random effects meta-analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales. *Stat Med* 2002;21(11):1601-23.

53. Vandermeer B, Bialy L, Hooton N, et al. Meta-analyses of safety data: a comparison of exact versus asymptotic methods. *Stat Methods Med Res* 2009;18(4): 421-32.

54. Schwarzer G. 2010. meta: Meta-Analysis, R package version 1.5-0.

55. R Development Core Team. 2010. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. http://www.R-project.org

56. Viechtbauer V. 2010. metafor: Meta-Analysis Package for R. R package version 1.1-0.

57. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328(7454): 1490.

## *VI. Definition of Terms*

(Defined as needed in text.)

## *VII. Summary of Protocol Amendments*

(None.)

## *VIII. Review of Key Questions*

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

## *IX. Technical Expert Panel (TEP)*

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

## *X. Peer Review*

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

**It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.**

# *XI. Appendix*

## Search strategy for randomized controlled trials:

#97 Search **#90 NOT #96**

#96 Search **#94 NOT #92**

#94 Search **"Animals"[Mesh]** Limits: **Entrez Date from 2005/03/11 to 2009/10/22**

#92 Search **"Humans"[Mesh]** Limits: **Entrez Date from 2005/03/11 to 2009/10/22**

#90 Search **#64 AND #84** Limits: **Entrez Date from 2005/03/11 to 2009/10/22**

#89 Search **#64 AND #84**

#84 Search **#70 OR #73 OR #74 OR #77 OR #82 OR #83**

#83 Search **control OR controlled OR controls OR prospectiv* OR volunteer***

#82 Search **(("Research Design"[Mesh] OR "Comparative Study "[Publication Type]) OR "Evaluation Studies "[Publication Type]) OR "Follow-Up Studies"[Mesh]**

#77 Search **"Placebos"[Mesh] OR placebo* OR random***

#74 Search **(singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)**

#73 Search **("Clinical Trial "[Publication Type] OR "Clinical Trials as Topic"[Mesh]) OR "clinical trial"**

#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]**

#64 Search **#63 AND #62**

#63 Search **#58 OR #59**

#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***

#59 Search **erythropoietin OR epoetin* OR eprex OR neorecormon OR aranesp OR procrit OR darbepoetin OR CERA OR "C.E.R.A."**

#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]**

## Search strategy for observational studies:

Retrospective Studies[MH] 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.")

AND

("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*)

AND

("adverse effects "[Subheading] OR "poisoning "[Subheading] OR "toxicity "[Subheading] OR "chemically induced "[Subheading] OR "contraindications "[Subheading] OR "complications "[Subheading] OR “adverse effect*” OR “adverse drug reaction*” OR “side effect*” OR “toxic effect*” OR “adverse event*” OR “complication*”)