



April 30, 2010

**2010**

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RE: Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment—An Update to the 2006 Report

To Whom it May Concern:

The American Society of Hematology (ASH) appreciates the opportunity to comment on the Agency for Healthcare Research and Quality (AHRQ) key questions for the 2010 update of the 2006 report on Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment.

ASH represents over 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases such as leukemia, lymphoma, anemia and thrombosis. Below, please find ASH's comments on the key questions AHRQ will use to assist in updating its 2006 report on Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment.

**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)?**

AHRQ has indicated that 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. Additionally, 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.

ASH strongly believes 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. ASH is hopeful 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.

**Key Question 2: How do alternative thresholds for initiating treatment compare regarding their effect on the benefits and harms of erythropoietic stimulants?**

AHRQ has indicated that it will be seeking evidence 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.

Although ASH believes determining how alternative thresholds 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. ASH questions whether a more important (or adjunctive) analysis to perform, in keeping with some of the data available from the renal ESA literature, is to consider the dose density/intensity of the ESA, particularly in those recipients who do not initially respond to ESA with a hemoglobin increase. One might hypothesize that the hemoglobin at initiation, or the achieved hemoglobin, 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.

**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?**

ASH has no specific comments concerning Key Question 3, except that the suggestions provided above for Key Question 2 and any findings of these analyses may inform the Evidence-based Practice Center's recommendations regarding discontinuation of therapy, particularly in those who are non-respondents if they are indeed at increased risk.

Additionally, it is perhaps noteworthy that these documents regarding statement of work do not overtly acknowledge the limitations of our current understanding of the reasons why cancer patients treated with ESAs may be at increased risk of harm, and the Key Questions appear to fall short of actually tackling this critical issue. The fundamental question of whether particular treatment settings or treatment plans explain the risk, and hence may be avoided, is high in clinicians and patients minds. An answer may not be achievable with the current clinical trials that have been completed, but should be considered carefully. If it cannot be addressed, ASH believes the issue should be discussed in the report.

Again, ASH appreciates the opportunity to submit these comments. If you have any questions or require any additional information, please contact ASH Senior Manager of Policy and Practice Carol Schwartz at [cschwartz@hematology.org](mailto:cschwartz@hematology.org) or 202-776-0544.

Sincerely,

A handwritten signature in black ink that reads "Lawrence A. Solberg, Jr." The signature is written in a cursive style with a large initial 'L'.

Lawrence A. Solberg, Jr., MD, PhD  
Chair, Committee on Practice