DRAFT

Anemia of chronic kidney disease: Patient informed consent for anemia treatment

3b Measure Justification

Importance

- ◆ *High Impact Aspect of Health Care*
  - ○ **Demonstrated high impact aspect**

  1a1.1 Select from the following all that apply:
    - ▪ *Affects large numbers*
    - ▪ *A leading cause of morbidity/mortality*
    - ▪ *Frequently performed procedure*
    - ▪ *High resource use*
    - ▪ ***Patient/societal consequences of poor quality***

The risks associated with aggressive treatment of anemia of CKD with ESAs have been documented with increased frequency over the last several years. Recently published KDIGO Anemia Management Guidelines as well as updated FDA package insert information for ESAs highlight this evolving understanding of these risks.

Given the highlighted risks associated with aggressive anemia management with ESAs, the net benefit of ESA treatment of anemia of CKD has been questioned, particularly in patients identified as being at higher risk for development of complications (ESA resistant, high risk for thromboembolic events, active malignancy).

Careful evaluation of the alternative treatment options available, risks and potential benefits of ESA treatment of anemia in patients with CKD should be made prior to initiation of ESAs or if dose escalation is contemplated.

  - ○ **Summary of evidence of high impact**

  1a3. Provide epidemiological or resource use data

ESAs are used to treat the anemia of CKD in the vast majority of dialysis-dependent CKD patients. Therefore, minimizing the risks associated with their use will impact morbidity and mortality risk in the entire population of over 400,000 chronic dialysis patients in the United States. In addition, ESAs account for several billion dollars in Medicare spending annually. Careful consideration of alternative treatments of CKD anemia and more judicious use of ESAs in this population will result in conservation of limited healthcare resources.

  - ○ **Citations**

  1a.4. Provide citations for the evidence described above

- FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease.
  http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm
- Highlights of prescribing information: Epogen (epoetin alfa)
  http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103234Orig1s5166_103234Orig1s5266lbl.pdf
- Highlights of prescribing information: Aranesp (darbepoetin alfa)
  http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103951Orig1s5173_103951Orig1s5258lbl.pdfKidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney inter., Suppl. 2012; 2: 279–335.
- U.S. Renal Data System, USRDS 2012 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2012.

◆ *Opportunity for Improvement*
  o **Briefly explain the benefits envisioned by use of this measure**
  1b.1. (Quality improvement anticipated)

This measure will facilitate increased awareness on the part of both patients and dialysis providers of the risks associated with ESA use. In addition, it will contribute to the recalibration of hemoglobin targeting by providers in this healthcare environment, to reduce overuse of ESAs in the treatment of chronic dialysis patients. In addition, the measure will help to educate and engage patients in important risk/benefit decisions regarding the anemia management strategy used in their care.

  o **Summary of data demonstrating performance gap**
  1b.2. (Variation or overall less than optimal performance across providers)

According to the USRDS 2012 Annual Report, the average achieved hemoglobin in ESA-treated chronic dialysis patient in the US was 11.27 gm/dL, with over 20% of patients with achieved hemoglobin greater than 12 gm/dL

  o **Citations**
  1b.3. Provide citations for the evidence described above

U.S. Renal Data System, USRDS 2012 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2012

  o **Summary of data on disparities by population group**
  1b.4.Summarize evidence found that demonstrates any disparities. Describe groups in which disparities exist.
  N/A

  o **Citations**
  1b.5. Provide citations for the evidence described above
  N/A

◆ *Evidence to Support Measure Focus*

   ○ **Structure-process-outcome relationship**

1c.1. Briefly state the measure focus (for example, health outcome, intermediate clinical outcome, process, structure) Then, identify the appropriate links (for example, structure-process-health outcome, process-health outcome, intermediate clinical outcome-health outcome)

This is a process measure. The link to health outcome is process-intermediate clinical outcome-health outcome. The evidence that aggressive treatment of CKD anemia, defined as targeting higher hemoglobins even if high dose ESA use is required has been associated with increased morbidity and mortality in clinical trials. Whether the poorer outcomes are directly related to higher ESA doses or are mediated by higher achieved hemoglobin remains controversial.

   ○ **Type of evidence**

      ▪ *1c.2. Describe the type of evidence, selecting from the following list all that apply:*

      ▪ *Clinical practice guideline*

      ▪ *Selected individual studies (rather than entire body of evidence)*

      ▪ *Systematic review of body of evidence (other than within guideline development)*
        Other (state type of evidence)

Randomized controlled trials, observational studies, Clinical practice guidelines.

   ○ **Directness of evidence to the specified measure**

1c.4. State the central topic, population, and outcomes addressed in the body of evidence and identify any differences from the measure focus and measure target population.

Randomized controlled trials include the Normal Hematocrit Trial in dialysis-requiring CKD patients, the CHOIR and CREATE Trials in patients with advanced CKD not requiring dialysis and the TREAT Study in non-dialysis requiring diabetic CKD patients. Observational studies suggesting association with higher achieved hemoglobin and/or higher dose ESA use with increased mortality include studies using the clinical database of one large US dialysis organization as well as studies evaluating Medicare administrative and claim data.

   ○ **Quantity of studies in the body of evidence**

1c.5. Total number of studies, not articles
Seven

   ○ **Quality of body of evidence**

1c.6. Summarize the certainty or confidence in the estimates of benefits and harms to patients across studies in the body of evidence resulting from study factors. Please address:

     a) *Study design/flaws*

     b) *Directness/indirectness of the evidence to this measure (for example, interventions, comparisons, outcomes assessed, population included in the evidence)*
       Imprecision/wide confidence intervals due to few patients or events)

	Normal Hematocrit Study (NHS) (N = 1265)	CHOIR (N = 1432)	TREAT (N = 4038)
Time Period of Trial	1993 to 1996	2003 to 2006	2004 to 2009
Population	CKD patients on hemodialysis with coexisting CHF or CAD, hematocrit 30 ± 3% on epoetin alfa	CKD patients not on dialysis with hemoglobin < 11 g/dL not previously administered epoetin alfa	CKD patients not on dialysis with type II diabetes, hemoglobin ≤ 11 g/dL
Hemoglobin Target; Higher vs. Lower (g/dL)	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. ≥ 9.0
Median (Q1, Q3) Achieved Hemoglobin level (g/dL)	12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)	13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)	12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)
Primary Endpoint	All-cause mortality or non-fatal MI	All-cause mortality, MI, hospitalization for CHF, or stroke	All-cause mortality, MI, myocardial ischemia, heart failure, and stroke
Hazard Ratio or Relative Risk (95% CI)	1.28 (1.06 - 1.56)	1.34 (1.03 - 1.74)	1.05 (0.94 - 1.17)
Adverse Outcome for Higher Target Group	All-cause mortality	All-cause mortality	Stroke
Hazard Ratio or Relative Risk (95% CI)	1.27 (1.04 - 1.54)	1.48 (0.97 - 2.27)	1.92 (1.38 - 2.68)

- o **Consistency of results across studies**

1c7. Summarize the consistency of the magnitude and direction of the effect across studies

See above table. Of note, both NHS and CHOIR were terminated early by Data Safety Oversight Committees. In addition, the results of the smaller CREATE Trial, although of marginal statistical significance, were directionally similar to the CHOIR results.

The three observational studies cited provide similar overall results, particularly supporting the observation that higher ESA dose is associated with increased mortality. In addition, two of three studies also identified increased mortality in patients treated to achieved hemoglobin above 12.5-13 gm/dl.

- o **Net benefit**

1c8. Provide estimates of effect for benefit/outcome, identify harms addressed and estimates of effect, and net benefit---benefit over harms across studies. Please include results of business/social/economic case for the measure.
N/A

- o **Grading of strength/quality of the body of evidence**

1c9, 1c10. 1c11, 1c13, 1c14. Please address:

- *Indicate if the body of evidence has been graded*
- *If the body of evidence was graded, identify the entity that graded the evidence including balance of representation and any disclosures regarding bias*
- *System used for grading the body of evidence*
- *Grade assigned to the body of evidence*
  Summary of controversy/contradictory evidence

The interventional trials noted above were included in the graded literature review for KDIGO Guideline development.

o **Citation**

1c15. Provide citations for the evidence described above

- Besarab A, Bolton WK, Browne JK, et al. "The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin." *The New England journal of medicine* (1998) 339:584-90. PMID: 9718377

- Singh AK, Szczech L, Tang KL, et al. "Correction of anemia with epoetin alfa in chronic kidney disease." *The New England journal of medicine* (2006) 355:2085-98. PMID: 17108343

- Drüeke TB, Locatelli F, Clyne N, et al. "Normalization of hemoglobin level in patients with chronic kidney disease and anemia." *The New England journal of medicine* (2006) 355:2071-84. PMID: 17108342

- Pfeffer MA, Burdmann EA, Chen CY, et al. "A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease." *The New England journal of medicine* (2009) 361:2019-32. PMID: 19880844

- Regidor DL, Kopple JD, Kovesdy CP, et al. "Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients." *Journal of the American Society of Nephrology : JASN* (2006) 17:1181-91. PMID: 16565261

- Zhang Y, Thamer M, Stefanik K, et al. "Epoetin requirements predict mortality in hemodialysis patients." *American journal of kidney diseases : the official journal of the National Kidney Foundation* (2004) 44:866-76. PMID: 15492953

- Messana J M, Chuang C, Turenne M, Wheeler J, Turner J, Sleeman K, Tedeschi P, Hirth R: Association of quarterly average achieved hematocrit with mortality in dialysis patients: a time-dependent comorbidity-adjusted model. American Journal of Kidney Diseases 53(3):503-12, 2009.

o **Guideline recommendation**

1c16. Quote verbatim, the specific guideline recommendation (Including guideline number and/or page number)

KDIGO Anemia Guidelines 2012: Guideline 3.2: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (1B)

KDIGO Anemia Guidelines 2012: Guideline 3.3: We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome— (1B), a history of stroke (1B), or a history of malignancy (2C)

o   **Citation**

1c17. Provide citations for the clinical practice guideline quoted above

Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney inter., Suppl. 2012; 2: 279–335.

o   **URL**

1c18. National Guideline Clearinghouse or other URL

http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf

o   **Grading of strength of recommendation**

1c191 1c21, 1c23. Please address:

- *Has the recommendation been graded? yes*
- *System used for grading the strength of guideline recommendation (USPSTF, GRADE, etc.) Grade assigned to the recommendation*
  Grading system (1- We recommend, 2- We suggest) combined with a 4 category quality of evidence grading (A, B, C, D).

o   **Rationale for using this guideline over others**

1c24. If multiple guidelines exist, describe why the guideline cited was chosen. Factors may include rigor of guideline development, widespread acceptance and use, etc.

KDIGO Clinical Practice Guidelines for Anemia in Chronic Kidney Disease are the most recently published guidelines. In addition, they were developed by an international consortium of dialysis organizations using rigorous literature review and systematic grading methodology.

o   **Overall assessment of the body of evidence**

1c25, 1c26, 1c.27. Based on the NQF descriptions for rating the evidence, what was your assessment of the following attributes of the body of evidence?

- *Quantity*
- *Quality*
- *Consistency*

The Guidelines used to support this measure development were graded 1B and 2C. The guideline to use ESAs with caution and to balance the risks against benefits is strongly supported by evidence from both clinical and observational trials, some of which are cited above. KDIGO evaluators rated the strength of this recommendation as "1B", supporting our belief that the measure submitted is well supported by the available evidence.

Reliability and Validity – Scientific Acceptability of Measure Properties

This measure is intended to evaluate facility provision of informed consent regarding the risks and benefits of ESA therapy and blood transfusion. The need to balance these risks and benefits is indicated by recent clinical trial results, KDIGO anemia management guidelines, and updated FDA package insert information for ESAs. These recent developments provide face validity for a measure that assesses whether these discussions with patients regarding potential risks and benefits of treatment options have occurred. No data are currently available to assess the reliability or validity of this measure. It is anticipated that facility performance of this essential function

can be captured using data that will need to be collected through CROWNWeb. Future assessments of the reliability and validity of this measure will include analyses of the association of this process measure with other anemia-related processes of care and outcomes.

◆ *Reliability Testing*
  ○ **Data sample**
  2a2.1.Describe the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included
  N/A

  ○ **Analytic methods**
  2b2.2 .Describe method of validity testing and rationale; if face validity, describe systematic assessment
  N/A

  ○ **Testing results**
  2a2.3. Provide reliability statistics and assessment of adequacy in the context of norms for the test conducted
  N/A

◆ *Validity Testing*
  ○ **Data sample**
  2b2.1. Describe the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included

  ○ **Analytic method**
  2b2.2 .Describe method of validity testing and rationale; if face validity, describe systematic assessment
  N/A

  ○ **Testing results**
  2b2.3. (Provide statistical results and assessment of adequacy in the context of norms for the test conducted; if face validity, describe results of systematic assessment)
  N/A

◆ *Exclusions*
  ○ **Data sample for analysis of exclusions**
  2b3.1.Describe the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included
  N/A

    ○ **Analytic method**

2b3.2. Describe type of analysis and rationale for examining exclusions, including exclusion related to patient preference

N/A

    ○ **Results**

2b3.3. Provide statistical results for analysis of exclusions (for example, frequency, variability, sensitivity analyses)

N/A

◆ *Risk Adjustment Strategy*

    ○ **Data/ sample**

2b4.1. Describe the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included. Delete row if measure is not risk adjusted.

N/A

    ○ **Analytic method**

2b4.2. Describe methods and rationale for development and testing of risk model or risk stratification including selection of factors/variables

N/A

    ○ **Testing results**

2b4.3. Statistical risk model: Provide quantitative assessment of relative contribution of model risk factors; risk model performance metrics including cross-validation discrimination and calibration statistics, calibration curve and risk decile plot, and assessment of adequacy in the context of norms for risk models. Risk stratification: Provide quantitative assessment of relationship of risk factors to the outcome and differences in outcomes among the strata. Delete row if measure is not risk adjusted.

N/A

    ○ **Rationale for no adjustment**

2b4.4. If outcome or resource use measure is not risk adjusted, provide rationale and analyses to justify lack of adjustment. The three rows above may be deleted if this field is used. Delete row if measure is risk adjusted or if this is a process measure.

N/A

◆ *Identification of Meaningful Differences in Performance*

    ○ **Data/ sample**

2b5.1 Describe the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included

N/A

- o **Analytic method**

2b5.2. Describe methods and rationale to identify statistically significant and practically/meaningfully differences in performance

N/A

- o **Testing results**

2b5.3. Results-Provide measure performance results/scores (for example, distribution by quartile, mean, median, SD, etc.); identification of statistically significant and meaningfully differences in performance

N/A

- ◆ *Comparability of Multiple Data Sources/Methods*
  - o **Data/ sample**

2b6.1. Describe the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included

N/A

- o **Analytic method**

2b6.2. Describe methods and rationale for testing comparability of scores produced by the different data sources specified in the measure

N/A

- o **Testing results**

2b6.3. Provide statistical results (for example, correlation statistics, and comparison of rankings) and assessment of adequacy in the context of norms for the test conducted

N/A

- ◆ *Disparities in Care*
  - o **Stratification**

2c.1. If measure is stratified for disparities, provide stratified results (scores by stratified categories/cohorts)

N/A

- o **Rationale for no stratification**

2c.2. If disparities have been reported/identified, but measure is not specified to detect disparities, please explain.

N/A

- o **Supplemental information**

2.1. Supplemental testing methodology information: If additional information if available, please indicate where this information can be found: appendix, attachment, or URL

N/A

Usability

◆ *Public Reporting*
  ○ **Meaningful, understandable and useful**
  3a.1. Use in public reporting---disclosure of performance results to the public at large (If used in a public reporting program, provide name of program(s), locations, Web page URL(s). If not publicly reported in a national or community program, state the reason and plans to achieve public reporting, potential reporting programs or commitments, and timeline, for example, within 3 years of endorsement)
  N/A

  3a.2. Provide a rationale for why the measure performance results are meaningful, understandable, and useful for public reporting. If usefulness was demonstrated (for example, focus, group, cognitive testing) describe the data, method and results.

◆ *Quality Improvement*
  ○ **Meaningful, understandable and useful**
  3b.1. Use in QI (If used in quality improvement program, provide name of program(s), locations, Web page URL(s))
  3b.2. Provide a rationale for why the measure performance results are meaningful, understandable, and useful for quality improvement. If usefulness was demonstrated (for example, QI, initiative) describe the data, method and results
  N/A

  ○ **Other accountability uses**
  3.2. Use for other accountability functions (payment, certification, accreditation) (If used in a public accountability program, provide name of program(s), locations, Web page URL(s)). This row may be deleted if not applicable.
  N/A

Feasibility

◆ *How the data elements needed to compute measure score are generated*
  4a.1. How are the data elements needed to compute measure scores generated? State all that apply. Data used in the measure are:

- o *Generated by and used by health care personnel during the provision of care (for example, blood pressure, lab value, medical condition)*
  Coded by someone other than person obtaining original information (for example, DRG, ICD-9 codes on claims)
- o *Abstracted from a record by someone other than person obtaining original information (for example, chart abstraction for quality measure or registry) Other*

Fields for submitting the attestation could be added to Medicare claims or CROWNWeb (to be generated and used by healthcare personnel during the provision of care). It is not currently built into any data collection system.

- ◆ ***Electronic availability***
  4b.1. Are the data elements needed for the measure as specified available electronically (elements that are needed to compute measure scores are in defined, computer-readable fields)?

  - o *ALL data elements in electronic health records (EHRs)*
  - o *ALL data elements in electronic claims*
  - o *ALL data elements are in a combination of electronic sources (describe)*
  - o *Some data elements are in electronic sources (describe)*
    - ▪ *No data elements are in electronic sources*

  No data elements are in electronic sources at this time.

- ◆ ***Susceptibility to inaccuracies, errors, or unintended consequences***
  4c.1. Identify susceptibility to inaccuracies, errors, or unintended consequences of measurement identified during testing and/or operational use and strategies to prevent, minimize, or detect. If audited, provide results.
  N/A

- ◆ ***Data collection strategy***
  4d.1. Describe what you have learned/modified as a result of testing and/or operational use of the measure regarding data collection, availability of data, missing data, timing and frequency of data collection, sampling, patient confidentiality, time and cost of data collection, other feasibility/implementation issues (for example fees for use of proprietary measures)
  N/A

Related Measures

- ◆ ***Harmonization***
  5a.1. If this measure has EITHER the same measure focus OR the same target population as NQF-endorsed measure(s): Are the measure specifications completely harmonized? Is so, describe.

  N/A

- ◆ ***Similar measures***
  5b.1. If this measure has both the same measure focus and the same target population as NQF-endorsed measure(s) or other measures in current use, describe why this measure is superior to existing measures (for

example, a more valid or efficient way to measure quality); OR, provide a rationale for the additive value of developing and endorsing an additional measure. (Provide analyses when possible.)

N/A