

## Reducing versus Discontinuing Erythropoietin at High Hemoglobin Levels

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### ABSTRACT

A 2006 change in Medicare policy allowed reimbursement for erythropoietin (EPO) in dialysis patients whose most recent hemoglobin exceeded 13 g/dl. We investigated the effects of a change in dosing algorithm implemented in response to this policy, in which EPO dosages were reduced instead of temporarily discontinued for hemoglobin levels  $\geq 13$  g/dl. Among 1688 individuals in 18 hemodialysis units, the reduction protocol resulted in more hemoglobin levels  $\geq 13$  g/dl ( $P < 0.0001$ ), fewer levels between 11 and 12.9 g/dl ( $P \leq 0.004$ ), no difference in the proportion of levels  $< 11$  g/dl, and more EPO administered per session ( $P < 0.0001$ ) than the discontinuation protocol. In view of the expense of erythropoiesis stimulating agents and the uncertainty of the safety of using EPO to achieve high hemoglobin targets, this study suggests that discontinuation, rather than reduction, of EPO treatment is appropriate when hemoglobin reaches 13 g/dl in hemodialysis patients.

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Since its introduction, recombinant erythropoietin (EPO) has been a mainstay of dialysis care, decreasing transfusion requirements and improving health-related quality of life.<sup>1–3</sup> Accordingly, anemia management became a quality indicator for the ESRD program, with a corresponding rise in utilization of erythropoiesis-stimulating agents (ESAs).<sup>4</sup> These medications are Medicare's largest single pharmaceutical expense, costing about \$2 billion in 2004, and they represent a critical source of dialysis provider revenue.<sup>5</sup>

The 1997 National Kidney Foundation Dialysis Outcome Quality Initiative recommended target hemoglobin levels of 11 to 12 g/dl for dialysis patients, and the first update to these guidelines in 2000 maintained this recommendation.<sup>6,7</sup> Subsequent literature emphasized the difficulty of keeping individual patients' hemoglobin values within a 1 g/dl range and reported that hemoglobin variability occurring with discontinuation and re-initiation of ESAs may be associated with worse outcomes.<sup>8,9</sup> Therefore, revised 2006 guidelines recommended a

minimum hemoglobin target of 11g/dl without specifying a maximum target level.<sup>10</sup> Although these guidelines were further revised in 2007 to include an upper target hemoglobin level of 12 g/dl, the optimal ESA dosing when targets are exceeded remains unknown.<sup>11</sup> Responding to potential risks associated with hemoglobin variability, the Centers for Medicare and Medicaid Services (CMS) implemented a new EPO Monitoring Policy on April 3, 2006, allowing continued EPO dosing at hemoglobin levels  $\geq 13$  g/dl, and mandating a 25% reduction in total ESA dose for patients exceeding this level.<sup>12</sup>

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Our study assesses the effects of a treatment algorithm change at Dialysis Clinic, Inc. (DCI) on EPO use and hemoglobin concentrations after the April 2006 CMS guideline change. In response to escalating demands on physician and nurse time, inconsistency in application of EPO protocols, and increasingly complex EPO reimbursement guidelines, DCI initiated a computer-assisted EPO dosing protocol in 2004. A revised protocol was implemented on May 1, 2006, in response to the CMS policy change. For this analysis, we examined data from dialysis units that used the computerized protocol by October 1, 2005, to evaluate the effect of reducing rather than discontinuing EPO at higher hemoglobin levels.

## RESULTS

During the 14-mo study period, 1688 individuals received hemodialysis in units using the protocols. Baseline characteristics are presented in Table 1. Hemoglobin was measured for 15,695 patient-months with mean monthly hemoglobin levels of  $11.8 \pm 1.4$  g/dl. Median monthly EPO dose was 43,300 (IQR, 19,600 to 88,400) units, equating to 3300 (IQR, 1500–6800) units per hemodialysis session.

The mean hemoglobin value was  $11.8 \pm 1.3$  g/dl for patients on the discontinuation protocol and  $11.9 \pm 1.4$  g/dl for patients on the reduction protocol ( $P < 0.0001$ ). There was no

significant difference between protocols in the proportion of individuals falling into the  $<10$  g/dl or the 10 to 10.9 g/dl groups. The number of values in the 11 to 11.9 g/dl and 12 to 12.9 g/dl hemoglobin groups was significantly greater for individuals on the discontinuation protocol ( $P = 0.004$  and  $P < 0.0001$ , respectively), whereas the number of values  $\geq 13$  g/dl was significantly greater for the reduction protocol ( $P < 0.0001$ ) (Figure 1).

The median EPO dose per treatment on the discontinuation protocol from November 2005 to March 2006 was 3219 (IQR, 1500 to 6348) units, whereas the median EPO dose on the reduction protocol from June 2006 to October 2006 was 3477 (IQR, 1569 to 7262) units ( $P < 0.0001$ ). There were 10,725 records with EPO doses in the month preceding hemoglobin measurements. Figure 2 shows EPO dose and the corresponding next month's hemoglobin level. Compared with the discontinuation protocol, EPO use in the reduction protocol was significantly greater in the month that preceded hemoglobin levels of 12 to 12.9 g/dl and  $\geq 13$  g/dl ( $P < 0.001$  and  $P < 0.0001$ , respectively).

### Sensitivity Analysis

In paired analysis of 822 patients having data for all 14 mo, mean hemoglobin level was  $11.8 \pm 0.6$  g/dl for the 5 mo on the discontinuation protocol and  $11.9 \pm 0.7$  g/dl for the reduction protocol ( $P < 0.001$ ). Median per session EPO use was 4343

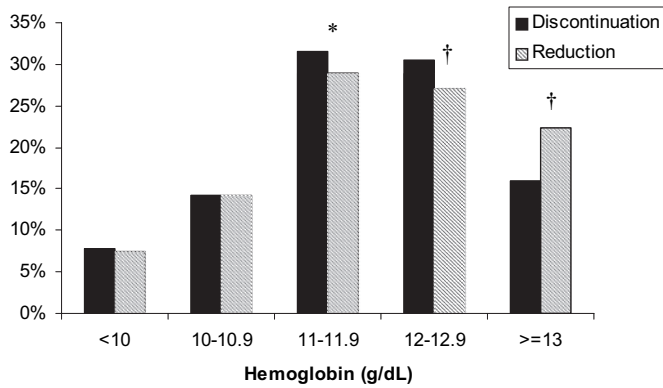
**Table 1.** Baseline characteristics of DCI patients in the discontinuation and reduction protocols

	Discontinuation (n = 1127)	Reduction (n = 1147)	USRDS (n = 309,269)	P Value
Age, yr (n, %)				0.99
<20	7 (0.6)	6 (0.5)	1354 (0.4)	
20 to 44	151 (13.4)	153 (13.3)	44,740 (14.5)	
45 to 64	419 (37.8)	427 (37.2)	123,024 (39.8)	
65 to 74	257 (22.8)	254 (22.1)	71,744 (23.2)	
$\geq 75$	293 (26.0)	307 (26.8)	68,406 (22.1)	
Mean (SD)	$62.9 \pm 15.6$	$63.1 \pm 15.6$	—	0.66
Race				0.95
white	673 (59.7)	683 (59.6)	169,127 (54.7)	
African American	357 (31.7)	361 (31.5)	117,151 (37.9)	
other	97 (8.7)	103 (8.9)	22,991 (7.4)	
Sex				0.42
female	495 (44.0)	523 (45.6)	141,362 (45.7)	
male	631 (56.0)	623 (54.4)	167,846 (54.3)	
Etiology				0.99
diabetes	479 (42.5)	490 (42.7)	132,954 (43.0)	
hypertension	265 (23.5)	271 (23.6)	88,218 (28.5)	
glomerulonephritis	179 (15.9)	180 (15.7)	34,218 (11.1)	
other	204 (18.1)	206 (18.0)	53,879 (17.4)	
Dialysis duration	27.3 (10.2 to 57.7)	29.4 (12.8 to 59.9)	—	0.06
Estimated dry weight (kg)	$78.0 \pm 22.2$	$78.9 \pm 23.0$	—	0.44
Kt/V	$1.63 \pm 0.39$	$1.65 \pm 0.51$	—	0.37

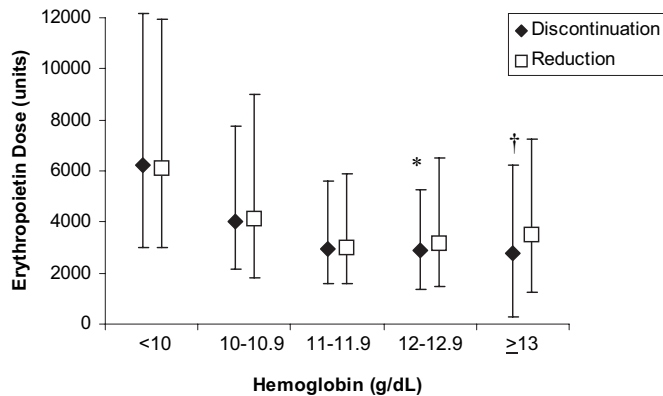
Age is in years, dialysis duration in months and estimated dry weight. GN, glomerular nephropathy; Kt/V, .

Demographic data for the discontinuation protocol are for individuals present on December 1, 2005, and for the reduction protocol are for individuals present on July 1, 2006. Estimated dry weight and Kt/V are for November 2005 and June 2006 because this corresponds with earliest EPO administration data used in this study. US Renal Data System (USRDS) data is from prevalent hemodialysis patients in 2004.<sup>26</sup>

All comparisons are between the discontinuation and reduction protocols. *P* values were calculated with *t* tests for means, the Mann-Whitney-Wilcoxon test was used for medians, and the Cochran-Mantel-Haenszel statistic was used for ordinal data.

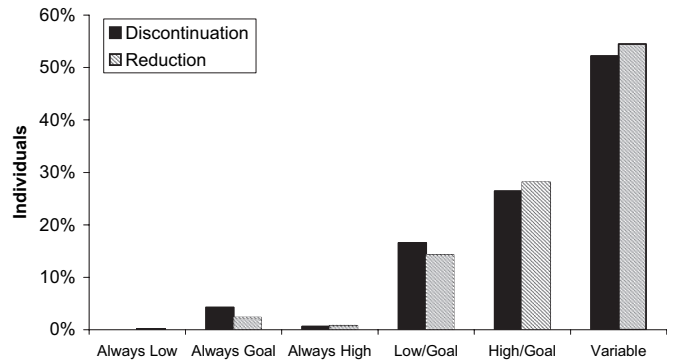


**Figure 1.** The distribution of hemoglobin measurements by protocol. The Discontinuation protocol guided dosing decisions influencing hemoglobin measurements made from December 2005 to April 2006. The Reduction protocol guided dosing decisions influencing hemoglobin measurements made from July 2006 to November 2006. \* $P = 0.004$ , † $P < 0.0001$  for differences between protocols. For other differences,  $P > 0.20$ .



**Figure 2.** Median intravenous erythropoietin dose per hemodialysis treatment stratified by hemoglobin value at the beginning of the following month. Error bars present the interquartile range. \* $P < 0.001$ ; † $P < 0.0001$ . For other differences,  $P > 0.20$ .

(IQR, 2967 to 6363) units on the discontinuation protocol and 4672 (IQR, 3109 to 6740) units on the reduction protocol ( $P = 0.02$ ). The number of values  $\geq 13$  g/dl was significantly greater for the reduction protocol ( $n = 648$  (15.8%) versus 896 (21.8%);  $P < 0.0001$ ) with no significant difference in the number of measurements falling into the  $<10$  and 10 to 10.9 g/dl groups. This was confirmed when comparing the frequency of hemoglobin  $\geq 13$  g/dl between the discontinuation and reduction protocols one month at a time, for which  $P$  values were 0.03,  $<0.001$ ,  $<0.001$ , 0.01, and  $<0.001$ ; there was no month during which the frequency of hemoglobin  $<10$  and 10 to 10.9 g/dl differed between protocols ( $P > 0.20$  for all). Finally, when hemoglobin variability was examined, most individuals in both protocols had highly variable levels during the 5-mo periods, and overall differences in cycling between the discontinuation and reduction protocols were minimal (Figure 3).



**Figure 3.** The frequency of hemoglobin cycling patterns by protocol over 5 mo. All comparisons between protocols were nonsignificant ( $P > 0.20$ ) except for the Always Goal group, for which  $P = 0.04$ . Always Low: hemoglobin  $<11$  g/dl during all 5 mo; Always Goal: hemoglobin from 11 to 12.4 g/dl during all 5 mo; Always High: hemoglobin  $\geq 12.5$  g/dl; Low/Goal: hemoglobin  $<12.5$  g/dl during all 5 mo; High/Goal: hemoglobin  $\geq 11$  g/dl during all 5 mo; Variable: hemoglobin values both  $<11$  g/dl and  $\geq 12.5$  g/dl.

**DISCUSSION**

Although the Medicare ESRD program spends \$2 billion a year on EPO, physicians, investigators, administrators, and legislators struggle to define its optimal use.<sup>13</sup> In this study we demonstrate that, after implementing a protocol change that resulted in continuation of EPO at higher hemoglobin levels, there was an increase in the number of individuals with higher hemoglobin levels but no significant reduction in the frequency of very low hemoglobin ( $<10$  g/dl) and low hemoglobin (10 to 10.9 g/dl) levels. This lack of benefit was accompanied by significantly greater EPO use. Therefore, this study supports more aggressive reduction in EPO administration in response to high hemoglobin levels than is currently required by CMS reimbursement guidelines.

This study assumes clinical importance in light of several trials suggesting that harm may be associated with higher hemoglobin targets. In hemodialysis patients, Besarab *et al.* showed that hemodialysis patients randomized to a higher hemoglobin target had increased mortality; that study was halted before statistical significance was achieved.<sup>14</sup> More recently, two trials in stage 4 chronic kidney disease showed either harm or no benefit to targeting a hemoglobin level of 13 to 15 g/dl.<sup>15,16</sup> Although administration of recombinant human EPO has been associated with nonhematologic complications including hypertension, the mechanisms of adverse outcomes among patients receiving ESAs to target high hemoglobin levels remain undefined; it is not even clear whether the ESA or the higher hemoglobin level itself is responsible.<sup>14,17-19</sup>

The 2006 Kidney Disease Outcomes Quality Initiative (KDOQI) anemia management guidelines and CMS reimbursement policy were motivated in large part by concern about hemoglobin variability and therefore focus on avoidance of low hemoglobin levels. Fishbane and Berns demonstrated

that 90% of stable dialysis patients experience significant hemoglobin cycling in any given year, defined by a sustained change of  $\geq 1.5$  g/dl in hemoglobin level for a minimum of 8 wk; the majority of patients cycled 3 to 4 times each year.<sup>9</sup> Ebben *et al.* demonstrated that 40% of individuals had highly variable hemoglobin levels over a 6-mo period and showed an association between hemoglobin variability and adverse events.<sup>8</sup>

Accordingly, the 2006 KDOQI anemia guidelines recommended a minimum hemoglobin target of 11 g/dl without specifying a maximum target.<sup>10</sup> Changes in CMS reimbursement mirrored the KDOQI guidelines. Before April 2006, CMS recommended a threshold hematocrit value of 37.5% (equivalent to a hemoglobin level of 12.5 g/dl) for monitoring proper EPO usage, focusing compliance efforts on practitioners with an atypical number of patients with a 90-d rolling average hematocrit level above this threshold.<sup>20</sup> Therefore, many dialysis providers, including DCI, would discontinue EPO when hemoglobin rose to 13 g/dl, a policy that theoretically could result in cycling. On April 3, 2006, CMS changed its policy, increasing the hemoglobin level at which they would monitor EPO usage to 13 g/dl on a single measurement and mandating a 25% reduction in ESA dose for patients whose latest hemoglobin exceeded that level. The changes in hemoglobin levels and EPO usage seen on the reduction protocol discussed in this manuscript reflect these policy changes.

Ofsthun and Lazarus evaluated the impact of this CMS policy change within Fresenius Medical Care, the largest dialysis provider in the United States.<sup>21</sup> They found that the revised CMS policy was associated with a slight reduction in the proportion of patients with hemoglobin  $> 13$  g/dl, while the proportion with hemoglobin  $< 11$  g/dl was increased. It should be noted that mean EPO dose and hemoglobin levels at Fresenius units historically have been higher than at DCI units, and, when compared with other national dialysis providers, DCI-affiliated units were more likely to reduce EPO dose when patients' hemoglobin levels were between 12 and 13 g/dl and tended to have a higher proportion of individuals within the hemoglobin target range of 11 to 12 g/dl.<sup>22</sup> A recent manuscript by Thamer *et al.* presents similar findings from November to December 2004, demonstrating lower EPO use and fewer hematocrit levels  $\geq 39\%$  in DCI when compared with for-profit dialysis providers.<sup>23</sup> These findings suggest that anemia management practice patterns at DCI-affiliated units may differ from practice patterns at units affiliated with other national providers and provide a plausible explanation for the different results.

Our study has several limitations. We utilize only hemoglobin and EPO data and do not adjust for demographics or comorbid conditions. However, although comorbid conditions certainly affect EPO responsiveness, current EPO algorithms account for only hemoglobin and EPO dose. Therefore, our study represents clinical practice. Furthermore, we did not utilize mixed models for this study, but neither do current clinical performance measures, which compare the proportion of di-

alysis unit patients falling into a target range on a month-to-month basis without regard to the prior month's or the next month's hemoglobin levels.<sup>24</sup> We were not able to evaluate patient-level deviations from the protocol, but overall deviation occurred for approximately 10% of protocol-generated orders for both protocols, and any discrepancies in deviation rates would probably bias toward the null hypothesis that there is no difference between protocols. We did not have data on EPO administered outside of the dialysis unit, in particular during hospitalizations. However, we attempted to adjust for this by normalizing EPO administration to 13 sessions per month. Finally, we did not examine patient subsets; it is possible that there are groups of patients for whom the discontinuation protocol might reduce the proportion of hemoglobin values below the target range.

Our study also has several notable strengths. Comparing the same clinics during two different periods allows us to use the clinics as their own controls. We have no reason to presume that the proportion of incident and prevalent patients would have changed between the two periods. Furthermore, in sensitivity analysis, we use paired comparisons among prevalent hemodialysis patients to examine the effect of different protocols on subsequent hemoglobin levels. The results are remarkably consistent, supporting our primary analyses. Finally, DCI's use of computerized decision support protocols allows examination of the effects of algorithm changes on anemia treatment in hemodialysis with minimal confounding by individual physician practices.

In evaluating anemia management data in October 2006, DCI's Quality Management Committee noted that, after implementation of the reduction protocol, the proportion of patients with hemoglobin  $\geq 13$  g/dl had risen substantially. On December 1, 2006, the reduction protocol was terminated and replaced by a modification of the discontinuation protocol. This analysis supports that decision, and DCI's detection of the changes and response after only 7 mo on the reduction protocol demonstrate the feasibility and importance of continued monitoring of hemodialysis care indicators.<sup>4</sup>

In conclusion, we found that reducing rather than discontinuing EPO supplementation at hemoglobin  $\geq 13$  g/dl was associated with a significantly greater proportion of hemodialysis patients at high hemoglobin levels, had no effect on the proportion of individuals with lower hemoglobin levels, and was associated with increased EPO use. In view of the expense of ESAs and the uncertainty about the safety of using EPO to achieve high hemoglobin targets, this study suggests that discontinuation rather than reduction of EPO treatment of hemodialysis patients is appropriate when hemoglobin reaches 13 g/dl.

## CONCISE METHODS

### Subjects

All patients receiving chronic hemodialysis in the 18 units active on the computerized protocol as of October 2005 were eligible for anal-

**Table 2.** DCI units on computerized protocol as of October 1, 2005

Location	Patients Treated (Oct 2005)	Patients Treated (Nov 2006)
Lafayette, GA	34	39
Boston, MA	96	97
Concord, MA	53	47
Belton, MO	41	45
Boonville, MO	24	27
Clinton, MO	32	39
Columbia, MO	109	80
Kansas City, MO	113	121
Kansas City, MO (Rockhill)	134	130
Lee's Summit, MO	37	37
Sedalia, MO	61	65
Carson City, NV	67	68
Elko, NV	17	31
Auburn, NY	40	46
Oswego, NY	45	47
Syracuse, NY	134	131
Pittsburgh, PA (North Borough)	22	28
Pittsburgh, PA (North Hills)	51	47

ysis (Table 2). Five months of individual patient hemoglobin data were analyzed, from December 2005 to April 2006, allowing for a minimum 2-mo period on the discontinuation protocol for the dialysis unit before analysis. All 18 units switched to the reduction protocol on May 1, 2006. Data from 5 mo (July 2006 to November 2006) were analyzed, again allowing for a 2-mo period on protocol before analysis. Because the prior month's EPO dose is reflected in the next month's hemoglobin level, data on EPO administration from November 2005 to March 2006 were used to evaluate the discontinuation protocol and data from June 2006 to October 2006 were used to evaluate the reduction protocol.

Individuals with >3 consecutive months with hemoglobin between 10.5 g/dl and 12.5 g/dl who had not received EPO (*n* = 10) were excluded because of the likelihood that these individuals were receiving another ESA or were receiving an ESA outside the dialysis unit.

**Hemoglobin Measurement**

Frequency of hemoglobin measurement was at the discretion of the individual dialysis unit. Within DCI, hemoglobin is generally measured once to twice monthly, although, in patients not receiving EPO, hemoglobin level is assessed weekly or biweekly to facilitate timely re-initiation of EPO. The first hemoglobin level of each month was

used to define an individual patient's hemoglobin level for the entire month. Nearly 97% of hemoglobin levels were measured at DCI's central laboratory in Nashville, Tennessee. The remainder were measured at local laboratories and electronically transferred to the medical information system.

**EPO Dosing**

In 2004, DCI initiated a computerized EPO dosing algorithm (Appendix 1). The revised algorithm was implemented on May 1, 2006 (Appendix 2). Units could elect to use the computerized protocol or could dose EPO manually or pursuant to local paper-based protocols. The computerized protocol provides EPO orders that are subsequently reviewed by a nurse and electronically signed by a physician. Although the physician could alter the order, deviation occurred infrequently. Iron was dosed at the discretion of the treating physician.

The protocols most notably differed in the response to a hemoglobin concentration  $\geq 13$  g/dl. The discontinuation protocol discontinued EPO when the hemoglobin reached 13 g/dl, whereas the reduction protocol reduced the EPO dose by 25% to 75% over the course of a month for sustained hemoglobin values  $\geq 13$  g/dl (Table 3).

All patients in units using the computerized protocol received erythropoietin alfa (Epogen, Amgen Inc, Thousand Oaks, CA) by intravenous administration during the dialysis session. The dose of administered EPO was recorded in the medical information system for each patient at the time of each treatment. Because only EPO administered in the outpatient setting would be noted in the electronic medical information system, we quantified EPO administration as the sum of the amount given over the month divided by the number of doses. To standardize to a monthly dose, this value was multiplied by 13. This approach is similar to that used by DCI to determine appropriate 25% reductions for individuals who have missed a significant number of dialysis sessions in a given month.

**Statistical Analysis**

This study was conducted as part of DCI's quality improvement efforts to assess the effects of alterations in protocol on hemoglobin levels and EPO use. Mean hemoglobin levels were compared by discontinuation *versus* reduction protocol using a *t* test. Hemoglobin was then stratified by predefined levels: <10 g/dl, 10 to 10.9 g/dl, 11 to 11.9 g/dl, 12 to 12.9 g/dl and  $\geq 13$  g/dl. The number of individuals' measurements falling within a hemoglobin group was compared using  $\chi^2$  tests. All testing is 2-sided. As EPO dosage is not normally distributed, EPO data are presented as median (interquartile range). EPO levels were compared across groups using the Mann-Whitney-Wilcoxon test.

**Table 3.** Critical elements in the discontinuation and reduction protocols that changed as a result of CMS regulations implemented on April 1, 2006

Discontinuation Protocol	Reduction Protocol
When Hgb $\geq 13$ g/dl, discontinue EPO	When Hgb >13 g/dl, decrease EPO immediately by 25%.
• Resume EPO with a 25% dose reduction when Hgb reaches <12.5 g/dl	• If the last Hgb of the prior month $\geq 13$ g/dl, decrease EPO by 75% on the 1st of the next month.
	When Hgb $\geq 15$ g/dl, discontinue EPO.
	• Resume when Hgb <13 g/dl with a 25% dose reduction.
Maximum EPO dose = 900 units/kg per wk	Maximum EPO dose = 500,000 units/month and 900 units/kg per wk

In sensitivity analyses, we examined only individuals for whom hemoglobin was measured during all 14 mo. This was analyzed using a paired *t* test for the mean hemoglobin level over each 5-mo period and the Wilcoxon Signed Rank test for median per session EPO dose. Using weighted kappa coefficients, we compared the frequency of results within hemoglobin groups using the discontinuation and reduction protocols. Then, in the same manner, we compared the distribution of hemoglobin groups month by month, such that distributions for December 2005 were compared with July 2006, January 2006 with August 2006, February 2006 with September 2006, March 2006 with October 2006, and April 2006 with November 2006. Finally, to examine hemoglobin cycling by protocol, we used the classification described by Ebben *et al.* to define six variability groups: “always low” had hemoglobin <11 g/dl during all 5 mo on protocol; “always goal” had hemoglobin of 11 to 12.4 g/dl; “always high” had hemoglobin  $\geq$ 12.5 g/dl; “low/goal” had hemoglobin <12.5 g/dl; “high/goal” had hemoglobin  $\geq$ 11 g/dl; and “variable” had hemoglobin values both <11 g/dl and  $\geq$ 12.5 g/dl.<sup>8</sup> Using weighted kappa coefficients, we compared these groups between protocols. All testing was 2-sided. SAS version 9.1 (Cary, NC) was used for analyses.

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## Appendix 1

Discontinuation anemia management protocol used as a basis for computerized decision support before May 1, 2006. DCI uses calculated hematocrit (HCT) values in the protocol; these are derived by multiplying the measured hemoglobin by 3.

1. EPO doses are based on estimated dry weight.
2. The protocol will change the EPO dose no more often than every 4 wk, except in the following cases:
  - a. Discontinue EPO when the calculated Hct is  $\geq$ 39%.
  - b. Increase the EPO dose when the calculated Hct is <33% and the previous dose change was a reduction in EPO.

- c. Decrease the EPO dose when the calculated Hct is >37.4% and the previous dose change was an increase in EPO.
3. If the calculated Hct is  $\geq$ 39%, then discontinue EPO and check the calculated Hct weekly. Resume EPO at 25% less than the previous dose as soon as the calculated Hct is  $\geq$ 37.4%.
4. For established patients who have had no EPO order within the last 3 mo and have calculated Hct <33%, start EPO 375 units/kg per wk; for Hct 33 to 35.9%, start EPO 225 units/kg per wk; for Hct 36 to 37.4%, start EPO 150 units/kg per wk.
5. For new patients without EPO orders who have calculated Hct <33%, start EPO 375 units/kg per wk; for patients who have calculated Hct 33 to 35.9%, start EPO 225 units/kg per wk; for patients who have calculated Hct >35.9%, start no EPO, but check calculated Hct every 2 wk.
6. The weekly doses described in (4) and (5) will be equally divided for intravenous dosing at each HD treatment.
7. Increase EPO dose by protocol to a maximum dose of 900 units/kg per wk.
8. For patients who have an EPO order and the order was not changed with the last 4 wk or cases described in (2):
  - a. If calculated Hct <28%, then increase EPO 50% but not less than 375 units/kg per wk.
  - b. If calculated Hct between 28 to 29.9%, then increase EPO 50%.
  - c. If calculated Hct between 30 to 32.9%, then increase EPO 20%.
  - d. If calculated Hct between 33 to 35.9% and Hct decreased 1.5% or more since last dose change, then increase EPO 10%.
  - e. If calculated Hct is between 33 to 35.9% and Hct increased/decreased <1.5% since last dose change, then do not change EPO dose.
  - f. If calculated Hct is between 33 to 35.4% and Hct increased 1.5% or more since last dose, change then do not change EPO dose.
  - g. If calculated Hct is between 35.5 to 35.9% and Hct increased 1.5% or more since last dose change, then decrease EPO 10%.
  - h. If calculated Hct is between 36 to 37.4% and Hct decreased 1.5% or more since last dose change, then do not change EPO dose.
  - i. If calculated Hct is between 36 to 37.4% and Hct increased/decreased <1.5% since last dose change, then decrease EPO 10%.
  - j. If calculated Hct is between 36 to 37.4% and Hct increased 1.5% or more since last dose change, then decrease EPO 20%.
  - k. If calculated Hct is between 37.5 to 38.9% and Hct decreased 1.5% or more since last dose change, then decrease EPO 10%.
  - l. If calculated Hct is between 37.5 to 38.9% and Hct in-

creased/decreased <1.5% since last dose change, then decrease EPO 20%.

- m. If calculated Hct is between 37.5 to 38.9% and Hct increased 1.5% or more since last dose change, then decrease EPO 20%.
- n. If calculated Hct is  $\geq 39\%$ , then stop EPO and check calculated Hct weekly.

## Appendix 2

Revised anemia management protocol used as a basis for computerized decision support May 1 to November 30, 2006. DCI uses calculated hematocrit (HCT) values in the protocol; these are derived by multiplying the measured hemoglobin by 3.

1. EPO doses are based on estimated dry weight.
2. Increase EPO dose by protocol to a maximum dose of 900 units/kg per wk and a maximum dose of 500,000 units/mo.
3. The protocol will change the EPO dose no more often than every 4 wk, except in the following cases:
  - a. On the 1st of the month there will be additional EPO dose decrease for patients with last calculated Hct for the previous month of  $>39\%$ . The rules for this decrease are described in (9) below.
  - b. Increase the EPO dose when the calculated Hct is  $<33\%$  and the previous dose change was a reduction in EPO.
  - c. Decrease the EPO dose when the calculated Hct is  $>37.4\%$  and the previous dose change was an increase in EPO.
4. For established patients who have had no EPO order within the last 3 mo and have calculated Hct  $<33\%$ , start EPO 375 units/kg per wk; for Hct 33 to 35.9% start EPO 225 units/kg per wk; for Hct 36 to 37.4% start EPO 150 units/kg per wk.
5. For new patients without EPO orders who have calculated Hct  $<33\%$ , start EPO 375 units/kg per wk; for patients who have calculated Hct 33 to 35.9%, start EPO 225 units/kg per wk; for patients who have calculated Hct  $>35.9\%$ , start no EPO.
6. The weekly doses described in (4) and (5) will be equally divided for intravenous dosing at each HD treatment.
7. For patients who have an EPO order and the order was not changed with the last 4 wk or cases described in (3):
  - a. If calculated Hct is  $<30\%$ , then increase EPO 50% but not  $<375$  units/kg per wk.
  - b. If calculated Hct is between 30 to 32.9%, then increase EPO 25%.
  - c. If calculated Hct is between 33 to 35.9% and Hct decreased 1.5% or more since last dose change then increase EPO 10%.
  - d. If calculated Hct is between 33 to 35.9% and Hct increased/decreased less than 1.5% since last dose change then do not change EPO dose.
  - e. If calculated Hct is between 33 to 35.9% and Hct in-

creased 1.5% or more since last dose change, then do not change EPO dose.

- f. If calculated Hct is between 36 to 37.4% and Hct decreased 1.5% or more since last dose change, then do not change EPO dose.
- g. If calculated Hct is between 36 to 37.4% and Hct increased/decreased  $<1.5\%$  since last dose change, then decrease EPO 10%.
- h. If calculated Hct is between 36 to 37.4% and Hct increased 1.5% or more since last dose change, then decrease EPO 20%.
- i. If calculated Hct is between 37.5 to 39% and Hct decreased 1.5% or more since last dose change, then decrease EPO 10%.
- j. If calculated Hct is between 37.5 to 39% and Hct increased/decreased  $<1.5\%$  since last dose change, then decrease EPO 20%.
- k. If calculated Hct is between 37.5 to 39% and Hct increased 1.5% or more since last dose change, then decrease EPO 20%.
- l. If calculated Hct is  $>39\%$ , then decrease EPO 25%. Check calculated Hct periodically based on physician preference.
- 8. Discontinue EPO dose when calculated Hct is  $\geq 45\%$  or at a level identified by the clinic's medical director. Check calculated Hct weekly. If patient's calculated Hct falls below 39% within 3 mo, start EPO dose at 25% less than the previous dose.
- 9. On the 1st of the month for patients whose calculated Hct for the previous month was  $>39\%$ , decrease monthly EPO to 75% of the previous month dose.
- 10. All EPO dose decreases will be rounded down to the nearest 100 units. All EPO dose increases will be rounded up to the nearest 100 units. Dose will not be decreased below 400 units.

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