NOV 5 2009

TO: Charlene Frizzera
Acting Administrator
Centers for Medicare & Medicaid Services

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration

FROM: Stuart Wright /S/
Deputy Inspector General
for Evaluation and Inspections

SUBJECT: Memorandum Report: "Renal Dialysis Facilities' Dosage Protocols for Administering Erythropoiesis-Stimulating Agents," OEI-03-09-00010

This memorandum report presents the results of our review to (1) determine the extent to which Medicare-certified dialysis facilities have protocols for administering erythropoiesis-stimulating agents (ESAs), (2) determine the extent to which facilities' protocols are consistent with the boxed warning and selected guidelines on ESAs' labels, and (3) determine the extent to which facilities' protocols conform with Medicare's benefit policy for ESAs and payment monitoring policy for ESA claims.

While they are not required to do so, dialysis facilities may develop their own protocols for administering ESAs to patients with chronic kidney failure. The protocols may define target hemoglobin levels and dosage instructions for administering ESAs. When physicians approve the protocols for specific patients, the patients' target hemoglobin levels and ESA dosages are based on the protocols.

According to the boxed warning on ESAs' labels, maintaining higher rather than lower hemoglobin levels in a patient with chronic kidney failure can adversely affect the patient's health and increase the risk of death. Specifically, the boxed warning states that providers should administer ESAs "to achieve and maintain hemoglobin levels within the range of 10 to 12 grams per deciliter (g/dL)." The Medicare benefit policy for ESAs reflects the target hemoglobin range specified in the boxed warning. A separate Medicare policy for monitoring ESA payments states that the Centers for Medicare & Medicaid Services (CMS) will reduce reported dosages upon which ESA claims are paid when patients' hemoglobin levels exceed 13g/dL.

We conducted this review in response to a request from Chairman Fortney Pete Stark of the Subcommittee on Health, Committee on Ways and Means, U.S. House of Representatives. Some members of Congress have raised concerns that dialysis facilities' protocols for administering ESAs may not be consistent with the current boxed warning for these drugs.

We found that most Medicare-certified dialysis facilities had protocols in place for administering ESAs, but only 56 percent of facilities' protocols explicitly state a target hemoglobin range. We could not determine whether the remaining 44 percent of protocols were consistent with the boxed warning and Medicare's benefit policy because they do not specify a target hemoglobin range. Of the protocols that state a target hemoglobin range, 94 percent are consistent with the boxed warning and the Medicare benefit policy for ESAs because the upper limit of the stated target range is equal to or less than 12 g/dL.

In addition, our review of protocols to determine whether they are consistent with selected guidelines on ESAs' labels revealed that some protocols contain information that differs from labeling guidelines regarding starting doses, dose adjustments, and withholding ESA doses. Finally, all of the protocols that include a target hemoglobin range or level at which to increase ESA doses conform with CMS's monitoring policy for ESA claims.

BACKGROUND

End Stage Renal Disease

Chronic kidney failure is the gradual loss of kidney function. When chronic kidney failure progresses, it may eventually lead to end stage renal disease (ESRD). ESRD is a permanent kidney impairment that requires either a regular course of dialysis or a kidney transplant. Generally, patients with ESRD are entitled to Medicare benefits regardless of their age.[1] CMS covers an estimated 400,000 beneficiaries with ESRD and spends about $8.1 billion annually for ESRD services, including dialysis and related supplies, equipment, and drugs.[2]

According to the National Kidney Foundation, dialysis is a treatment for ESRD patients that functions in place of healthy kidneys. Dialysis removes waste, salt, and extra water from the body; keeps a safe level of certain chemicals in the blood; and helps to control blood pressure.[3] Dialysis facilities provide outpatient dialysis to ESRD patients. Dialysis facilities must be certified in order to receive Medicare reimbursement.[4] A dialysis facility may be a freestanding unit or be located in a hospital.[5] As of October 2008, there were 5,113 Medicare-certified

[1] Section 226A of the Social Security Act; 42 CFR § 406.13.
[2] "Payment, Safety, and Quality Issues in Treatment of Patients With End-Stage Renal Disease: Hearing Before U.S. House Committee on Ways and Means Subcommittee on Health," 109th Congress, 2007. Statement of Leslie Norwalk, Acting Administrator, CMS.
[3] National Kidney Foundation, "Dialysis." Available online at http://www.kidney.org/atoz/atozItem.cfm?id=39. Accessed on May 11, 2009.
[4] 42 CFR §§ 405.2102 and 488.60.
[5] 42 CFR § 405.2102; CMS, "Medicare Benefit Policy Manual," Pub. No. 100-02, ch. 11, § 10.B.

dialysis facilities in the United States. Eighty-one percent of these facilities (4,120) were for-profit entities, while 19 percent (993) were nonprofit entities.

Anemia

Nearly all patients with ESRD have anemia, which may begin to develop in the early stages of chronic kidney failure. Healthy kidneys produce a hormone that stimulates bone marrow to produce the proper number of red blood cells. Diseased kidneys often do not produce sufficient amounts of this hormone, which results in fewer red blood cells and the development of anemia. Tests that measure patients' hemoglobin (a protein made by red blood cells) and hematocrit (the proportion of red blood cells in whole blood) can be used to monitor anemia.

Erythropoeisis-Stimulating Agents

ESAs are prescription drugs that increase the number of red blood cells in patients suffering from anemia. For ESRD patients, ESAs are typically administered during dialysis treatments by intravenous or subcutaneous injection. After an ESA dose is administered or a dose adjustment is made, it may take several weeks for a patient's hemoglobin level to change significantly. Epoetin alfa (marketed under the names Epogen and Procrit) and darbepoetin alfa (marketed under the name Aranesp) are the two ESAs approved by FDA for the treatment of anemia associated with chronic kidney failure.

ESAs are covered under the Medicare Part B benefit for ESRD patients.[6] CMS currently pays dialysis facilities a composite rate for most dialysis services, including labor costs, related supplies, and certain drugs.[7] However, the composite rate does not include ESAs and other specific drugs. Dialysis facilities bill separately for these drugs.[8] [9] Payments for ESAs account for over 60 percent of separately billable drugs, and over 25 percent of total Medicare spending on ESRD services annually.[10]

Protocols for Administering ESAs

While not required, dialysis facilities may develop their own protocols for administering ESAs to ESRD patients. The protocols may define target hemoglobin levels and dosage instructions for ESAs. For dialysis facilities with protocols in place for administering ESAs, physicians may approve the protocols as patients' standing orders.

When physicians approve the protocols for specific patients, the patients' target hemoglobin levels and ESA dosages are based on the protocols. Anemia managers, frequently nurses

[6] CMS, "Medicare Benefit Policy Manual," § 90.
[7] CMS, "Medicare Benefit Policy Manual," § 30.
[8] CMS, "Medicare Claims Processing Manual," Pub. No. 100-04, ch. 8, § 60.4 (epoetin alfa) and § 60.7 (darbepoetin alfa).
[9] Pursuant to section 153(b) of the Medicare Improvements for Patients and Providers Act of 2008 (P.L. No. 110-275), CMS is required to implement a fully bundled payment system for ESRD services by January 1, 2011. The new bundled payment will include reimbursement for both ESAs and services currently included in the composite rate.
[10] Norwalk, loc. cit.

employed by dialysis facilities, oversee patients' anemia management. These practitioners may make dosage changes based on the protocols without new orders from physicians.

For facilities with protocols, physicians may still choose not to approve the protocols and instead may write individual ESA orders for their patients. For dialysis facilities that do not have protocols for administering ESAs, physicians must write individual orders for ESAs.

FDA's Requirements for Labeling of ESAs

FDA determines whether new drugs are safe, effective, and should be approved for marketing in the United States. Once a drug is approved, FDA conducts postmarket surveillance and risk assessment to identify adverse reactions and safety risks that did not appear during clinical trials before drug approval.

Clinical trials conducted after ESAs were approved have provided new safety information on the use of these drugs to treat anemia in patients with chronic kidney failure. Results of studies conducted in 1996 and 2006 showed that patients with chronic kidney failure were at increased risk for serious cardiovascular complications when ESAs were administered to target higher, rather than lower, hemoglobin levels. These complications included stroke, heart attack, heart failure, and death.

FDA's Cardiovascular and Renal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee met in September 2007 to discuss the risks and benefits of ESAs when used to treat anemia due to chronic kidney failure.[11] Although the committees did not reach consensus in recommending a specific target hemoglobin level, many members at the meeting recommended a target range of 10 to 12 g/dL or a specific target within that range.

Boxed Warning. Based on the results of clinical trials and input from the FDA advisory committees, FDA required the manufacturer of ESAs to revise the labeling for ESAs and add a boxed warning. The warning information is placed prominently at the top of the labeling and is enclosed in a box. A boxed warning is the strongest warning for an FDA-approved product. It is used to highlight warning information that is especially important to the prescriber, including an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug. It is also used to highlight a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug.

The current boxed warning on ESA labels for patients with chronic kidney failure states:

> Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower

[11] FDA establishes advisory committees to obtain independent, expert advice on products regulated by FDA, including drugs.

> hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.[12]

The ESAs' labels contain other information, including guidelines for selecting the starting dose and adjusting subsequent dosages for patients with chronic kidney failure.

Medicare Policies for ESAs

According to Chapter 11 of the Medicare Benefit Policy Manual, ESAs are covered under Part B for ESRD patients suffering from anemia. The benefit policy states that "ESRD patients who have been receiving [ESA] therapy should have a hematocrit between 30 and 36." This hematocrit range is equivalent to a hemoglobin between 10 and 12 g/dL.

Effective January 1, 2008, CMS modified its policy for monitoring ESA claims and payments in response to emerging scientific data and the boxed warning on ESAs' labels. Dialysis facilities are required to report patient hemoglobin or hematocrit levels on all ESA claims.[13] CMS's monitoring policy is based on these reported hemoglobin or hematocrit levels and establishes a threshold at which CMS reduces the reported ESA dosage upon which an ESA claim is paid.[14]

For all patients whose hemoglobin levels exceed 13 g/dL for less than 3 months and for whom a reduction in the ESA dosage has not been reported, CMS will pay only for a dosage which represents a 25-percent reduction of the dosage reported on the claim.[15] For ESA claims with reported hemoglobin levels that exceed 13 g/dL for 3 or more consecutive months, CMS will pay for a dosage that represents a 50-percent reduction from the dosage reported on a claim.[16]

METHODOLOGY

Scope

We reviewed current protocols for administering ESAs from a stratified random sample of Medicare-certified dialysis facilities. We compared information contained in these protocols to (1) the boxed warning and selected dosage guidelines on ESAs' labels, and (2) Medicare's benefit policy for ESAs and monitoring policy for ESA claims. We did not review Medicare claims for ESAs. We did not collect ESRD patients' records to review documentation, such as physician orders, that may support ESA claims.

---

[12] FDA, "Information on Erythropoeisis-Stimulating Agents Epoetin alfa (marketed as Procrit, Epogen) and Darbepoetin alfa (marketed as Aranesp)." Available online at http://www.fda.gov/cder/drug/infopage/RHE/default.htm. Accessed on June 3, 2009.

[13] CMS, "Medicare Claims Processing Manual," §§ 60.4 (epoetin alfa) and 60.7 (darbepoetin alfa).

[14] Although CMS's monitoring policy refers to both hemoglobin and hematocrit levels, and each of these measures will be applied during the study as appropriate, hereinafter, we will refer only to hemoglobin levels.

[15] CMS, "Medicare Claims Processing Manual," loc. cit.

[16] Ibid.

Sample Design

We selected a stratified random sample of 400 dialysis facilities from CMS's October 2008 Dialysis Facility Compare database, which contains all Medicare-certified dialysis facilities.[17] The total number of facilities in the sample was reduced from 400 to 399 because one facility responded that it is an inpatient hospital unit that does not provide outpatient dialysis services.

As shown in Table 1, we stratified the population of dialysis facilities by profit status to ensure that our sample would contain a sufficient number of both for-profit and nonprofit facilities.

Table 1: Sample of Dialysis Facilities

Stratum	Description of Stratum	Facilities in Population	Facilities in Sample	Responding Facilities
1	For-profit dialysis facilities	4,120	200	190
2	Nonprofit dialysis facilities	993	199	176
Total		**5,113**	**399**	**366**

Source: Office of Inspector General (OIG) sample design and CMS Dialysis Facility Compare Database, October 2008.

Data Collection

We obtained business name and address information for each dialysis facility in the sample from the Dialysis Facility Compare database. In January 2009, we requested by mail the sample facilities' protocols for administering ESAs. We asked all facilities to complete a one-page request form indicating whether they have a protocol in place and providing general information about the characteristics of the facility. We received responses to our request from 366 of 399 sample dialysis facilities—a 92-percent response rate.

Some facilities did not have protocols in place. Fourteen facilities in our sample had more than one ESA protocol in place at the time of our request. These 14 facilities submitted multiple protocols for administering ESAs. For example, a facility may have a protocol in place for the administration of epoetin alfa, in addition to a separate protocol for the administration of darbepoetin alfa.

We received a total of 357 protocols from the 366 responding facilities. Eighty-four percent of protocols were specific to epoetin alfa and 16 percent were specific to darbepoetin alfa.

We created a structured data collection instrument to guide our review of each ESA protocol we received from sample facilities. We collected information on the type of ESA protocol, target hemoglobin levels presented in the protocol, and starting dose and dose adjustment information presented in the protocol.

[17] "Medicare Dialysis Facility Compare Database." Available online at http://www.medicare.gov/Download/DownloadDB.asp. Accessed on December 18, 2008.

Data Analysis

We determined the number of dialysis facilities that have ESA protocols in place. We analyzed the protocol review data to determine the percentage of protocols that are consistent with the boxed warning on ESA labels and the Medicare benefit policy for ESAs. The boxed warning and benefit policy specify that the target hemoglobin level for patients with chronic kidney failure should be in the range of 10 to 12 g/dL. We reviewed protocols to determine whether they specified an explicit target hemoglobin range. Of protocols that specified an explicit target range, we considered those in which the upper limit of the range was equal to or less than 12 g/dL to be consistent with both the boxed warning and the benefit policy.[18] We used the upper limit of the target range to determine consistency because the boxed warning on ESA labels states that health risks increase with higher hemoglobin levels.

We analyzed the protocol review data regarding starting doses and dose adjustments.[19] We compared this information to selected dosage and administration guidelines on the FDA-approved labeling for ESAs. The selected guidelines are presented in Table 2.

Table 2: Selected ESA Dosage and Administration Guidelines for Patients With Chronic Kidney Failure

Starting Dose Guidelines
Epoetin alfa starting dose for adults is 50 to 100 units per kilogram, 3 times per week.
Darbepoetin alfa starting dose for adults is 0.45 micrograms per kilogram, weekly.
Dose Adjustment Guidelines
Increase epoetin alfa dose when hemoglobin level is less than 10 g/dL.
Decrease epoetin alfa and darbepoetin alfa dose when hemoglobin approaches 12 g/dL.
Withhold epoetin alfa and darbepoetin alfa dose when hemoglobin continues to rise after a dose decrease.

Source: Epogen, Procrit, and Aranesp labels, approved by FDA on November 19, 2008.

We also determined whether dialysis facilities' protocols conform with the hemoglobin threshold specified in CMS's monitoring policy for ESA claims. We considered protocols with target hemoglobin levels that do not exceed 13 g/dL to conform with the monitoring policy. In addition, we compared protocol review data regarding dose increases to the monitoring policy.

Facilities that responded to our request for ESA protocols indicated their profit status, whether the facility is part of a chain, whether the facility is hospital-based or freestanding, and the size of the facility (number of dialysis stations). We examined whether the percentage of protocols

[18] Three protocols specified a single target hemoglobin level, rather than a target range. We considered the target hemoglobin level to be the upper limit of the target range for these protocols.

[19] Some ESA protocols include starting dose information that we cannot compare to the guidelines on the ESAs' labels. Therefore, we did not include these protocols in our starting dose analysis. For example, some protocols include starting dose amounts, but do not specify how many times per week the dose should be administered.

that are consistent with the boxed warning differs based on dialysis facilities' self-reported characteristics. We tested for statistically significant differences.

We used SUDAAN software to produce weighted estimates of protocol review data percentages. These estimates reflect our stratified sample design and are provided in Appendix A. The results of our statistical significance tests are provided in Appendix B.

Standards

This study was conducted in accordance with the "Quality Standards for Inspections" approved by the Council of the Inspectors General on Integrity and Efficiency.

RESULTS

Ninety-Three Percent of Medicare-Certified Dialysis Facilities Had Protocols in Place for Administering ESAs, But Only 56 Percent of the Protocols Explicitly State a Target Hemoglobin Range

Based on responses we received from the Medicare-certified dialysis facilities in our sample, we estimate that 93 percent of all facilities had protocols in place for administering ESAs at the time of our request. Seven percent of facilities did not have ESA protocols in place. Point estimates and confidence intervals for all statistics presented in the findings of this memorandum report are provided in Appendix A.

Table 3 displays selected types of information included in the protocols for administering ESAs, such as target hemoglobin range and dosage and administration guidelines. Fifty-six percent of protocols include a target hemoglobin range and ESA starting dose information. More than 90 percent of protocols include information about when to increase, decrease, and withhold ESA doses.

Table 3: Selected Types of Information Included in ESA Protocols

Type of Information	Percentage of Protocols That Include This Information	Percentage of Protocols That Do Not Include This Information
Target hemoglobin range	56%	44%
Starting dose instructions	56%	44%
Specific hemoglobin level at which to increase dose (epoetin alfa protocols only)	95%	5%
Specific hemoglobin level at which to decrease dose	91%	9%
Specific hemoglobin level at which to withhold dose	95%	5%

Source: OIG analysis of dialysis facilities' protocols for administering ESAs, 2009.

Ninety-Four Percent of Protocols That Include a Target Hemoglobin Range Are Consistent With the Boxed Warning on ESAs' Labels and the Medicare Benefit Policy for ESAs

The boxed warning on ESA labels states that providers should administer the drugs to "achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL" for patients with chronic kidney failure.[20] The Medicare benefit policy for ESAs reflects the target hemoglobin range specified in the boxed warning. Fifty-six percent of protocols explicitly state a target hemoglobin range. We could not determine whether the remaining 44 percent of protocols in our review are consistent with the boxed warning or Medicare benefit policy because they do not specify a target hemoglobin range.

Of protocols that include a target hemoglobin range, 94 percent are consistent with the boxed warning on the FDA-approved labels and the Medicare benefit policy for ESAs. These protocols include a target hemoglobin range in which the upper limit of the target range is equal to or less than 12 g/dL. For the remaining 6 percent of protocols that include a target hemoglobin range, the upper limit of the target range exceeds 12 g/dL. The upper limits in these protocols range from 12.1 g/dL to 13 g/dL with a median of 12.5 g/dL.

More chain facilities are consistent with the warning than nonchain facilities. We detected no statistically significant difference between the percentage of protocols that are consistent with the boxed warning based on facilities' profit status, whether the facility is freestanding or hospital-based, or on facility size. However, we detected a statistically significant difference at the 95-percent confidence level based on whether the facility is part of a chain. Protocols from chain facilities are more likely to be consistent with the boxed warning than protocols from nonchain facilities. Specifically, 97 percent of protocols from chain facilities are consistent with the warning, compared to 87 percent of protocols from nonchain facilities.

For protocols that specify a target hemoglobin range, the lower limit of the target range is typically 11 g/dL. The lower limit of the target range is equal to 10 g/dL for only 16 percent of protocols that include a target hemoglobin range. The remaining 84 percent of protocols include a target hemoglobin range with a lower limit that is greater than 10 g/dL. Almost all of these protocols (97 percent) report a lower limit of 11 g/dL. The lower limit of the hemoglobin target range for these protocols exceeds the lower limit of the target range on the boxed warning and in the Medicare benefit policy. However, it is consistent with a March 2007 National Kidney Foundation clinical practice recommendation that, for patients "with chronic kidney disease receiving ESA therapy, the selected hemoglobin target should generally be in the range of 11 to 12 g/dL."[21]

[20] FDA, "Information on Erythropoeisis-Stimulating Agents," loc. cit.

[21] National Kidney Foundation, "Kidney Disease Outcomes Quality Initiatives Guidelines." Available online at http://www.kidney.org/professionals/KDOQI/guidelines_anemia/cpr21message.htm. Accessed on May 11, 2009.

Some Dialysis Facilities' Protocols Contain Information That Differs From Selected Guidelines on ESAs' Labels

The percentage of dialysis facilities' protocols that addressed each of the selected ESA dosage and administration guidelines ranged from 56 percent to 95 percent. However, some of these protocols include information that differs from the guidelines outlined on the FDA-approved labels for ESAs.

Sixteen percent of protocols that include instructions regarding starting doses instruct providers to administer a higher starting dose than is recommended. The FDA-approved epoetin alfa label states that the starting dose for adults should be 50 to 100 units per kilogram, three times per week. The FDA-approved darbepoetin alfa label states that the starting dose for adults should be 0.45 micrograms per kilogram, once per week. As shown in Table 3, 56 percent of protocols include instructions regarding starting doses. Of these protocols, 16 percent instruct providers to administer a higher maximum starting dose than is recommended on ESAs' labels. All but two of these protocols are specific to epoetin alfa. The maximum starting doses for these epoetin alfa protocols range from 125 to 200 units per kilogram, three times per week.

Ninety-four percent of protocols that specify a hemoglobin level at which to increase patients' dosages instruct providers to increase dosages when hemoglobin levels are already within the target range on the boxed warning. The FDA-approved label for epoetin alfa states that providers should increase the dose if a patient's hemoglobin level falls below 10 g/dL.[22] Ninety-five percent of epoetin alfa protocols specify a hemoglobin level at which to increase patients' dosages. Of these protocols, 94 percent instruct providers to increase the dose when a patient's hemoglobin level is within the recommended target range of 10 to 12 g/dL. Most of these protocols instruct providers to increase the dose when a patient's hemoglobin level is within the range of 11 to 12 g/dL.

For 62 percent of the epoetin alfa protocols that specify a hemoglobin level at which to increase patients' dosages, providers are also instructed to ensure that additional conditions are met before increasing the dose. For example, some protocols instruct providers to increase the dose when a patient's hemoglobin level is equal to 12 g/dL, but only if the patient's hemoglobin level is decreasing over time. Other protocols instruct providers to increase the dose when a patient's hemoglobin level is 12 g/dL, but the patient's hemoglobin level must be decreasing over time and the previous dose must have been below a specified amount.

More than 40 percent of protocols that specify a hemoglobin level at which to decrease patients' ESA dosages do not instruct providers to decrease dosages until hemoglobin levels are 12 g/dL or higher. The FDA-approved labels for ESAs state that providers should reduce the ESA dose if a patient's hemoglobin level is "approaching 12 g/dL." Ninety-one percent of protocols specify a hemoglobin level at which to decrease patients' ESA dosages. Of these protocols, 43 percent do not instruct providers to decrease a patient's ESA dose until the patient's hemoglobin level is 12 g/dL or higher. The remaining 57 percent of protocols that specify a

[22] The darbepoetin alfa label does not include this guideline for increasing patients' ESA dosages.

hemoglobin level at which to decrease patients' ESA dosages instruct providers to reduce the ESA dose when a patient's hemoglobin level is less than 12 g/dL.

Ninety percent of protocols that specify a hemoglobin level at which to withhold patients' ESA dosages do not instruct providers to withhold dosages until hemoglobin levels are 13 g/dL or higher. ESAs' labels state that the dose "should be temporarily withheld" if the dose has been reduced because a patient's hemoglobin level is approaching 12 g/dL and the hemoglobin level continues to increase despite the dose reduction. Ninety-five percent of protocols specify a hemoglobin level at which to withhold patients' ESA dosages. Of these protocols, 81 percent do not instruct providers to withhold the dose until a patient's hemoglobin level is in the range of 13 to 13.4 g/dL. Whether the dose is withheld depends on additional conditions for two-thirds of these protocols. For example, many protocols that instruct providers to withhold ESA doses when hemoglobin levels are greater than 13 g/dL state that hemoglobin must exceed 13 g/dL for 3 or more consecutive months before withholding the dose.

An additional 9 percent of dialysis facilities' protocols that specify a hemoglobin level at which to withhold patients' ESA doses do not instruct providers to withhold the dose until a patient's hemoglobin level is 13.5 to 15 g/dL.

All Protocols That Include a Target Hemoglobin Range or Level at Which To Increase the Dose Conform With CMS's Monitoring Policy for ESA Claims

CMS initiates its ESA payment monitoring policy when the hemoglobin level reported on an ESA claim exceeds 13 g/dL. For hemoglobin levels that exceed 13 g/dL for less than 3 months, CMS instructs providers to report ESA dose reductions. If providers do not report dose reductions, CMS will pay only for a dosage which represents a 25-percent reduction of the dosage reported on the claim. For claims that report hemoglobin levels that exceed 13 g/dL for 3 or more consecutive months, CMS reimburses providers for an ESA dose that represents a 50-percent reduction of the dose reported on the claim.[23]

None of the dialysis facilities' protocols that include a target hemoglobin range report a target range that exceeds 13 g/dL. Six percent of protocols include a target range with an upper limit that is between 12.1 and 13 g/dL. For the epoetin alfa protocols that specify a hemoglobin level at which to increase patients' ESA dosages, no protocol instructs providers to increase the dose when a patient's hemoglobin level is equal to or greater than 13 g/dL.

CONCLUSION

Almost all dialysis facilities that responded to our request had protocols in place for administering ESAs. Fifty-six percent of protocols explicitly state a target hemoglobin range that is, with few exceptions, consistent with the boxed warning that states ESAs should be administered to achieve and maintain hemoglobin levels in the range of 10 to 12 g/dL. These target hemoglobin ranges are also consistent with the Medicare benefit policy for ESAs.

[23] CMS, "Medicare Claims Processing Manual," §§ 60.4 and 60.7.

However, we could not determine whether the remaining 44 percent of protocols were consistent with the boxed warning and Medicare's benefit policy because they did not specify a target hemoglobin range.

In addition, some protocols contain instructions regarding starting doses, dose adjustments, and withholding ESA doses that differ from selected guidelines on ESAs' labels. For example, the epoetin alfa label states that providers should increase the ESA dose if a patient's hemoglobin level falls *below* 10 g/dL. Of protocols that specify a hemoglobin level at which to increase dosages, 94 percent instruct providers to increase ESA dosages when patients' hemoglobin levels *are already within* the target range of 10 to 12 g/dL.

Finally, all protocols that include a target hemoglobin range or guidelines regarding dose increases conform with the hemoglobin threshold of 13 g/dL specified in CMS's monitoring policy for ESA claims.

Although our review does not address the amount of ESAs providers actually administer to patients at their dialysis facilities, it does demonstrate that just over half of facilities had protocols for administering ESAs that are consistent with the boxed warning and Medicare's benefit policy for ESAs. However, since almost half of the dialysis facilities either did not have protocols or did not specify a target hemoglobin range in their protocols, we cannot determine whether these facilities' policies target the hemoglobin range outlined in the boxed warning that FDA requires on ESA labels to alert physicians and patients with chronic kidney failure about the increased risks associated with higher hemoglobin levels.

This report is being issued directly in final form because it contains no recommendations. If you have comments or questions about this report, please provide them within 60 days. Please refer to report number OEI-03-09-00010 in all correspondence.

APPENDIX A

Confidence Intervals for Selected Estimates

Estimate Description	n	Point Estimate[1]	95-Percent Confidence Interval
Percentage of dialysis facilities that have protocols	366	93.2%	90.3%–96.1%
Percentage of dialysis facilities that do not have protocols	366	6.7%	3.8%–9.6%
Percentage of protocols that include an explicit target hemoglobin range	357	55.9%	49.8%–62.0%
Percentage of protocols that do not include an explicit target hemoglobin range	357	44.0%	37.9%–50.1%
Of protocols that include a target hemoglobin range, percentage that include an upper target limit equal to or less than 12 grams per deciliter (g/dL)	209	94.3%	90.8%–97.7%
Of protocols that include a target hemoglobin range, percentage that include an upper target limit greater than 12 g/dL	209	5.6%	2.2%–9.1%
Of protocols that include a target hemoglobin range, percentage that include a lower target limit equal to 10 g/dL	206	15.7%	10.1%–21.2%
Of protocols that include a target hemoglobin range, percentage that include a lower target limit greater than 10 g/dL	206	84.3%	78.7%–89.8%
Percentage of protocols that include a lower target limit greater than 10 g/dL where the lower target limit equals 11 g/dL	162	97.2%	95.0%–99.4%
Percentage of protocols that include starting dose information	357	56.2%	50.3%–62.1%
Percentage of protocols that do not include starting dose information	357	43.7%	37.8%–49.6%
Of protocols that include starting dose information, percentage that include a starting dose higher than labels' guidelines	202	16.0%	10.9%–21.1%
Percentage of epoetin alfa protocols that specify a hemoglobin level at which to increase dose	299	95.1%	92.6%–97.6%
Percentage of epoetin alfa protocols that do not specify a hemoglobin level at which to increase dose	299	4.8%	2.3%–7.3%

continued on next page

Confidence Intervals for Selected Estimates (continued)

Estimate Description	n	Point Estimate[1]	95-Percent Confidence Interval
Of epoetin alfa protocols that specify a hemoglobin level at which to increase dose, percentage that instruct providers to increase dose when hemoglobin is 10 to 10.9 g/dL	279	26.3%	20.6%–31.9%
Of epoetin alfa protocols that specify a hemoglobin level at which to increase dose, percentage that instruct providers to increase dose when hemoglobin is 11 to 12 g/dL	279	67.8%	61.7%–73.8%
Of epoetin alfa protocols that specify a hemoglobin level at which to increase dose, percentage that include additional conditions for increasing dose	279	61.6%	55.4%–67.8%
Percentage of protocols that specify a hemoglobin level at which to decrease dose	357	90.6%	87.4%–93.8%
Percentage of protocols that do not specify a hemoglobin level at which to decrease dose	357	9.3%	6.1%–12.5%
Of protocols that specify a hemoglobin level at which to decrease dose, percentage that instruct providers to decrease dose when hemoglobin is 12 g/dL or higher	307	42.5%	36.3%–48.8%
Of protocols that specify a hemoglobin level at which to decrease dose, percentage that instruct providers to decrease dose when hemoglobin is less than 12 g/dL	307	57.4%	51.2%–63.6%
Percentage of protocols that specify a hemoglobin level at which to withhold dose	357	94.9%	92.8%–96.9%
Percentage of protocols that do not specify a hemoglobin level at which to withhold dose	357	5.1%	3.0%–7.1%
Of protocols that specify a hemoglobin level at which to withhold dose, percentage where specified hemoglobin equals 13 to 13.4 g/dL	325	81.0%	76.4%–85.5%
Of protocols that specify a hemoglobin level at which to withhold dose, percentage where specified hemoglobin equals 13.5 to 15 g/dL	325	9.4%	5.9%–13.0%
Of protocols that specify a hemoglobin level at which to withhold dose, percentage where specified hemoglobin equals 13 to 13.4 g/dL that include additional conditions for withholding dose	238	66.9%	60.7%–73.1%

Source: Office of Inspector General analysis of dialysis facilities' protocols for administering erythropoiesis-stimulating agents, 2009.

[1]Point estimates are weighted to reflect our stratified sample design.

APPENDIX B

Results of Statistical Significance Tests

Weighted Chi-Square Tests Comparing Percentages of Protocols That Were Consistent With the Boxed Warning Based on Dialysis Facility Characteristics

Dialysis Facility Characteristic		Percentage of Protocols in Which Upper Limit of Target Hemoglobin Range Was Less Than or Equal to 12 g/dL[1]	P-Value for Difference in Percentages
Profit status	For-profit facilities	95.6%	0.3655
	Nonprofit facilities	92.9%	
Type of setting	Hospital-based facilities	89.4%	0.1367
	Freestanding facilities	95.0%	
Chain status	Chain facilities	96.7%	0.0489[2]
	Nonchain facilities	87.3%	

[1]g/dL is grams per deciliter.

[2]The difference between the percentage of protocols from chain facilities that were consistent with the boxed warning and the percentage of protocols from nonchain facilities that were consistent with the warning was statistically significant at the 95-percent confidence level.

Source: Office of Inspector General (OIG) analysis of dialysis facilities' protocols for administering erythropoiesis-stimulating agents, 2009.

Weighted T-Test Comparing Protocols That Were Consistent With the Boxed Warning to Protocols That Were Not Consistent With the Boxed Warning Based on Dialysis Facility Size

	Mean Number of Dialysis Stations as Proxy for Facility Size	Difference in Means	P-Value for Difference in Means
Facilities' protocols in which upper limit of target hemoglobin range was less than or equal to 12 g/dL[1]	18.9	1.7	0.2752
Facilities' protocols in which upper limit of target hemoglobin range was greater than 12 g/dL	17.2		

[1]g/dL is grams per deciliter.

Source: OIG analysis of dialysis facilities' protocols for administering erythropoiesis-stimulating agents, 2009.