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Donald Berwick, MD
Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Hubert H. Humphrey Building
Room 445-G
200 Independence Avenue, SW
Washington, DC 20201

Re: CMS–1577–P; Medicare Program; Changes to the End-Stage Renal Disease Prospective Payment System for CY 2012, End-Stage Renal Disease Quality Incentive Program for PY 2013 and PY 2014

Dear Administrator Berwick:

Amgen Inc. (Amgen) is writing to comment on the proposed rule regarding the Medicare End-Stage Renal Disease Prospective Payment System (ESRD PPS) for calendar year (CY) 2012 and the Quality Incentive Program (QIP) for payment years (PYs) 2013 and 2014 [referenced hereafter as the "Proposed Rule"], which the Centers for Medicare & Medicaid Services (CMS) published in the Federal Register on July 8, 2011.[1] As a science-based, patient-driven company committed to using science and innovation to dramatically improve people's lives, Amgen is vitally interested in improving access to innovative drugs and biologicals (collectively referred to in this letter as "drugs" following the agency's convention) for Medicare beneficiaries. For more than a quarter century, Amgen has been developing, manufacturing and marketing products for treatment of patients with ESRD. Medicare plays an especially important role in the care of this special population. For this reason, we are submitting comments on the following topic areas of the Proposed Rule:

- ESRD QIP for PY 2013,
- ESRD QIP for PY 2014,
- Future ESRD QIP Measures, and
- ESRD PPS for CY 2012.

[1] 76 Fed. Reg. 40498.

EXECUTIVE SUMMARY OF AMGEN'S RECOMMENDATIONS

Amgen supports payment policies that support comprehensive patient management, rely upon evidence-based best practices, and align incentives for efficient care with improved patient outcomes. For this reason, we have consistently supported Congress and CMS in their efforts to implement the ESRD PPS and QIP as required under the *Medicare Improvements for Patients and Providers Act* (MIPPA). In reviewing the proposed changes for the QIP for PY 2013, we appreciate the complex nature of the MIPPA requirements regarding the QIP program and the analysis CMS has performed to propose changes to the current QIP; however, we are deeply concerned about the agency's proposal to retire the measure reporting the percent of patients with hemoglobin levels less than 10 grams per deciliter (g/dL) (referred to hereafter as the "sub-10 measure"), and we strongly urge the agency to retain the measure in the QIP program with eventual payment penalties. Amgen acknowledges that there is an implementation challenge in light of the timing of ESA labeling changes recently announced by the U.S. Food and Drug Administration (FDA) that make the proposed performance standards problematic for determining payment penalties in PY 2013, and we therefore have proposals contained in this letter that will assist in the implementation of our recommendations.

It is important to recognize the distinction between evidence-based quality performance measures (measures) and clinical performance standards (performance standards) as they relate to the QIP. Measures are specific representations of quantifiable outcomes and are generally measured against a standard, which is a quantifiable level of achievement, to track quality improvement outcomes over time. As such, QIP measures are used as a threshold and standards define the proportion of patients above or below the threshold to assess whether quality of care is decreasing or improving over time.

Below, we provide an executive summary of our recommendations on this topic and other important topic areas.

I. ESRD QIP for PY 2013

A. Retain the sub-10 measure; for 2013, use the measure for reporting purposes only – without payment penalties – by applying a weight of zero to the measure.
B. Work expeditiously with the community to determine the appropriate standard to support the sub-10 measure to protect against under-treatment of anemia.
C. Protect patients from underutilization and work with the community to determine the most appropriate anemia management performance standard that optimizes the balance of quality patient care and patient safety.
D. Finalize the proposal to include a measure reporting the percentage of patients with hemoglobin levels greater than 12 g/dL.
E. Finalize the proposal to implement the more rigorous payment reduction scale to ensure that providers are properly incentivized to provide quality care.

II. ESRD QIP for PY 2014

A. Apply the sub-10 measure with payment penalties to the 2012 performance period based on a more contemporary baseline period.
B. Include parathyroid hormone (PTH) testing in the structural measure on mineral metabolism reporting.
C. Weight each measure based on relative risk to priorities for quality improvement.

D. Implement a methodology to ensure that improvement standards do not diminish incentives for achievement.
E. Modify the payment reduction scale to encourage providers to perform well on all measures.

III. Future ESRD QIP Measures

A. Include comprehensive bone mineral disease and secondary hyperparathyroidism (HPT) outcomes measures when oral-only drugs are included in the ESRD PPS.

IV. ESRD PPS for CY 2012

A. Do not apply the productivity adjustment to the oral drug portion of the ESRD PPS.
B. Add a case-mix adjuster for race because it is highly predictive of resource use.
C. Develop mechanisms to promote adoption of innovations with a demonstrated impact on patient outcomes.
D. Test broader payment bundles for ESRD, such as Accountable Care Organizations (ACOs), which may better align incentives for improving patient care.
E. Continue to monitor beneficiaries' access to and experience with renal dialysis services.

DETAILED REVIEW OF AMGEN'S COMMENTS

Below, we review each topic area in detail and provide data to support our recommendations.

I. ESRD QIP FOR PY 2013

A. CMS SHOULD RETAIN THE MEASURE REPORTING THE PERCENT OF PATIENTS WITH HEMOGLOBIN LEVELS LESS THAN 10 G/DL FOR REPORTING PURPOSES ONLY.

As the first pay-for-performance program in the Medicare fee-for-service program, the QIP serves a critical function under the ESRD PPS. Specifically, the QIP quality measures are important for safeguarding against both the over-utilization of services that could put dialysis patients at potential risk of harm, as well as the underutilization of services to help ensure that treatment decisions are not impacted solely by the desire to reduce costs. The ESRD PPS introduced significant financial incentives to underutilize medical services. Since the ESRD PPS was not designed to be a fully integrated care model, dialysis providers are not accountable for adverse outcomes that are associated with underutilization, such as hospitalization or other long-term adverse consequences. Therefore, the concerns about underutilization, reduced access to care, and the resulting detrimental impact on quality of care and patient outcomes are heightened due to the fact that ESRD patients are among the most vulnerable in the Medicare population—with multiple co-morbidities and high rates of mortality.[2] Congress recognized these important facts by mandating the QIP as part of the ESRD PPS.

[2] United States Renal Data System (USRDS) Annual Data Report 2010.

Routine assessment using meaningful quality measures helps ensure that treatment decisions are not impacted solely by the desire to reduce costs at the expense of patient health. In the proposed rule, CMS has chosen to maintain the measure protecting against over-utilization but also has proposed to retire the measure intended to protect against underutilization. We are concerned that the agency's proposal to retire the sub-10 measure leaves neither an effective mechanism to protect patients from under-treatment of anemia, nor adequate protection against increased transfusions and their associated adverse effects. Moreover, removing the sub-10 measure from the QIP sends a negative signal to patients, providers, and Congress that the agency's commitment to maintaining high quality care in a bundled payment system may be focused on preventing over-utilization at the expense of preventing underutilization, rather than achieving the right balance of incentives to achieve appropriate utilization and high quality care.

We do not believe that this is the message that CMS would like to convey, and we respectfully disagree with the agency's rationale for retiring the sub-10 measure in the proposed rule. It is critical to recognize that the sub-10 measure itself is consistent with the recently finalized changes to the labeling approved by the FDA, as the new labeling recognizes the importance of transfusion avoidance and recommends the initiation of ESA therapy when the hemoglobin level falls below 10 g/dL.[3] In asking CMS not to retire the sub-10 measure, Amgen agrees that not all patients should have their hemoglobin levels "maintained" above 10 g/dL. Importantly, nothing in the sub-10 measure requires that all patients be maintained at hemoglobin levels of 10 g/dL. However, a QIP measure requires a performance standard (*e.g.,* currently, a payment penalty occurs if greater than two percent of a dialysis facility's population has a yearly mean hemoglobin less than 10 g/dL if using the 2008 national performance rate standard). Amgen recognizes that, given the recent changes to ESA labeling, the performance standard should be re-defined for this measure.

Under the new bundled payment system, it is critical that CMS maintain transparency and accountability for patient outcomes associated with anemia management in dialysis patients, which includes protecting against patient risk that may be experienced with high hemoglobin concentrations (*i.e.,* above 12 g/dL) and the well known risks associated with under-treatment of anemia (*i.e.,* when hemoglobin is below 10 g/dL*),* leading to increased transfusions and hospitalizations.[4] Below, we review in detail our rationale for requesting that CMS not finalize its proposal to retire the sub-10 measure and provide specific recommendations for how CMS may address the implementation of the measure in the QIP for current and future rulemaking.

MIPPA Requires that the QIP Include Measures on Anemia Management that Reflect FDA Labeling of Management Therapies.

In 2008, Congress enacted MIPPA, establishing a bundled reimbursement system for ESRD effective January 1, 2011. To ensure that patients continue to receive clinically appropriate treatment, Congress included the QIP to be implemented in conjunction with the bundled payment system. Specifically, Section 153(c) of MIPPA requires that CMS incorporate measures based on hemodialysis adequacy and anemia management (that

[3] EPOGEN® (Epoetin alfa) Prescribing Information. Amgen Inc., Thousand Oaks, CA (v25 06/2011).
[4] See Clinical Appendix, Section 1.2.1.1.

reflect FDA labeling of such management) into the QIP.[5] For PY 2012, CMS established two measures for anemia management: percentage of Medicare patients who have an average hemoglobin value less than 10 g/dL and percentage of Medicare patients who have an average hemoglobin value greater than 12 g/dL.

On June 24, 2011, FDA announced approved modified prescribing information for the use of ESAs, including Aranesp® (darbepoetin alfa) and EPOGEN® (Epoetin alfa), in patients with chronic kidney disease (CKD).

CMS proposes to retire the sub-10 measure beginning with the PY 2013 ESRD QIP and cites the label change in their rationale.[6] CMS specifically states, that based on reassessment of the evidence for the use of ESAs in patients with kidney disease through a National Coverage Analysis (CAG-00413N), the agency could not identify a specific hemoglobin lower bound level that has been proven safe for all patients treated with ESA[7] and CMS believes that this change is reflective of the FDA modified dosing recommendation for ESAs.

The goal of ESA therapy, as reflected in the modified ESA labeling, is transfusion avoidance and the sub-10 measure is the appropriate quality measure aligned with this goal.

The explanation provided by CMS in the proposed rule is that the removal of the sub-10 measure was in response to the FDA's updated labeling. However, this fails to recognize that product labeling and quality measures serve fundamentally different purposes. Below, we summarize the fundamental differences between product labeling and quality measures. As part of our comments, we have also included a clinical appendix (see pages 24 - 50), which details the evidence to support the following points:

- While product labeling and the ESRD QIP serve different purposes, both the FDA and CMS share the goal of effective anemia management in ESRD to minimize the risks of red blood cell transfusions and their adverse health consequences. Both agencies also note that ESAs are used to reduce the need for transfusions.

    - The avoidance of RBC transfusions is a clinically important outcome for ESRD patients. Transfusions can cause multiple adverse events, and importantly can cause allosensitization that can jeopardize kidney transplant outcomes.

    - Acknowledging the risk of transfusion increases substantially when the hemoglobin is less than 10 g/dL, the FDA labeling guides clinicians to initiate ESA therapy for dialysis patients when the hemoglobin level falls below 10 g/dL; but importantly, there is no guidance in the label instructing physicians to maintain all or a specific number of dialysis patients at a hemoglobin greater than 10.[8]

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5 Section 153(c) of MIPPA states, "(2) MEASURES.—(A) IN GENERAL.—The measures specified under this paragraph with respect to the year involved shall include—(i) measures on anemia management that reflect the labeling approved by the Food and Drug Administration for such management and measures on dialysis adequacy; (ii) to the extent feasible, such measure (or measures) of patient satisfaction as the Secretary shall specify; and (iii) such other measures as the Secretary specifies, including, to the extent feasible, measures on— (I) iron management; (II) bone mineral metabolism; and (III) vascular access, including for maximizing the placement of arterial venous fistula."

6 76 Fed. Reg. 40519.

7 Id.

8 EPOGEN® (Epoetin alfa) Prescribing Information. Amgen Inc., Thousand Oaks, CA (v25 06/2011).

- FDA labeling guides clinicians about the care of individual patients and the modified ESA labeling provides discretion to physicians to manage each patient based on their individual clinical needs.[9] Quality improvement and measurement is intended to maintain the population quality of care and not address the specific clinical circumstances of individual patients. As such, quality standards are put in place to determine the appropriate percentage of patients that should meet a measurement threshold to address patient heterogeneity and individual clinical circumstances.

- Amgen believes the sub-10 measure is consistent with the modified label. In and of itself, the measure does not obligate any individual physician to treat any individual patient to a higher hemoglobin concentration than is appropriate for that patient and which is consistent with the FDA label. There is nothing about the measure indicating that all patients should have hemoglobin levels maintained at greater than 10 g/dL. The measure is used as a threshold to determine the proportion of patients below the threshold and then to compare that number with a baseline standard to determine whether quality of care (as defined in this measure as the population risk of transfusion) is decreasing or improving over time as part of a pay-for-performance system.

- However, in light of the modified labeling, Amgen acknowledges CMS proposed performance standards for PY 2013 for the remaining measures – measuring 2011 performance against either 2007 individual facility performance or the 2009 national performance rate – are problematic and therefore should be addressed.

- CMS has consistently acknowledged the strong scientific basis for using the sub-10 measure as an assessment of the population risk of transfusion.

  - The clinical consequences of lower hemoglobin concentrations have been established by over 20 years of research findings, and the recent labeling action by the FDA has not erased that research.[10] Consistent data have demonstrated a strong relationship between sub-10 hemoglobin concentrations and clinically relevant clinical outcomes (*e.g.,* transfusion, hospitalization, and decline in patient-reported outcomes).

  - There is a large body of clinical evidence - from randomized controlled trials (RCTs) that were part of the ESA registration program, from re-analyses of RCT data, and from surveillance data on the U.S. hemodialysis population - that have consistently demonstrated that the risk of transfusion increases substantially when hemoglobin concentrations are below 10 g/dL. Moreover, this risk increases substantially the longer hemoglobin concentrations remain under 10 g/dL.[11,12]

  - The recent changes to the FDA label based on ESA safety issues neither changes the scientific basis for CMS to rely on the sub-10 measure, nor the risks of transfusion and their associated adverse health consequences.

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9 Id.

10 See Clinical Appendix, Section 1.2.1.1.

11 Amgen briefing document for March 24, 2010 MEDCAC. (Available at: http://www.cms.gov/determinationprocess/downloads/0716ofmancomment.pdf).

12 Amgen briefing document for January 19, 2011 MEDCAC. (Available at: www.amgen.com/pdfs/misc/amgen_medcac_briefing_Jan2011.pdf).

- In the ESRD PPS final rule, published July 2010, CMS acknowledged that dialysis adequacy and anemia management "are at the core of medical management of ESRD patients."[13] Regarding the risk of low hemoglobin levels, CMS stated in the ESRD QIP Final Rule, published January 5, 2011, that during the development of the performance score methodology, the agency considered weighing all three measures equally for the PY 2012 QIP.
  - However, after further examination and based on public comment, CMS proposed to give greater weight to the hemoglobin less than 10 g/dL quality measure for the following reasons:
    - "Low hemoglobin levels below 10 g/dL can lead to serious adverse health outcomes for ESRD patients such as increased hospitalizations, need for transfusions, and mortality"[14], and
    - "Low hemoglobin levels that are not appropriately managed can lead to increased morbidity and mortality."[15]
  - Further, CMS stated that these measures have significant implications for beneficiaries' quality of life, morbidity, and mortality. The agency has also stated that providers who perform well on these three measures experience better patient outcomes in terms of reduced hospitalizations and other adverse events.

- At the population level, the sub-10 measure remains the most accurate and consistent measure known related to the population risk of transfusion. The agency's use of the sub-10 measure, dating back to the advent of quality reporting in ESRD (1998), has proven to be a valid and accurate surrogate for the population risk of transfusion.
  - With the widespread use of ESAs, the incidence of transfusions tracks the population hemoglobin concentrations under 10 g/dL; as population hemoglobin concentrations rose and the fraction of patients with hemoglobin concentration below 10 g/dL decreased, there was a decline in transfusion rate.[16] Notably, the sub-10 measure used in the PY 2012 QIP demonstrates a linear relationship with the incidence of transfusions.[17] Thus, in using the sub-10 measure, CMS used a surrogate that over the years has accurately and reliably reflected the observed real-world incidence of transfusion in the population of dialysis patients.

- Early evidence under the ESRD PPS, is suggesting that patient care may be compromised, particularly in the higher risk African American population, demonstrating the need to have a strong quality measure with a payment penalty to protect against underutilization.
  - African Americans are disproportionately represented among dialysis patients, and require significantly greater Epoetin alfa doses (7 – 13 percent greater dose on average) to achieve comparable hemoglobin concentrations as non-African

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13 75 Fed. Reg. 49218
14 76 Fed. Reg. 633.
15 76 Fed. Reg. 634.
16 See Clinical Appendix, Figure 1A.
17 See Clinical Appendix, Figure 1B.

American patients.[18] Additionally, studies using U.S. Medicare data and dialysis provider data have shown that African American patients require greater vitamin D doses relative to other racial groups and are also more likely to receive calcimimetics.[19]

- These data provided important evidence suggesting that under a capitated system such as the PPS, underutilization of pharmacologic interventions could potentially affect African Americans differentially relative to other racial groups. CMS recognized this potential, and explicitly stated in its final rule: "As indicated previously, section 185 of MIPPA requires further study to identifying and addressing healthcare disparities in the Medicare program including those related to race or ethnicity. In addition, section 4302 of ACA requires ongoing analysis of race and ethnicity data to detect and monitor for trends in health disparities….In addition, as an integral part of the QIP, a program monitoring plan is in development to identify indicators useful in determining adverse effects on vulnerable (high risk) populations."[20]

- Early evidence in the ESRD PPS suggests that the proportion of patients with hemoglobin concentrations less than 10 g/dL is increasing more in African American versus non-African American dialysis patients. In February 2011, the proportion of patients having a hemoglobin concentration less than 10 g/dL was 28.4 percent higher in African American dialysis patients as compared with non-African American dialysis patients -- a change from prior years. On average, African American patients saw a 17 percent increase in the proportion of patients with hemoglobin concentrations less than 10 g/dL from pre-PPS to post-PPS.[21]

- In a March 2010 Report to Congress, the Government Accountability Office (GAO) found that there are specific dialysis patient populations, including African Americans and those on Medicaid, who have above average treatment costs that make them particularly vulnerable under the new PPS and calls for heightened monitoring of the access to and quality of dialysis care for those beneficiaries.[22] The GAO is scheduled to issue a report assessing access to and quality of care under the ESRD PPS in March 2013.

B. CMS SHOULD WORK EXPEDITIOUSLY WITH THE COMMUNITY TO DETERMINE THE APPROPRIATE PERFORMANCE STANDARD TO SUPPORT THE SUB-10 ANEMIA MEASURE TO PROTECT AGAINST THE UNDER-TREATMENT OF ANEMIA.

The agency's proposal to retire the sub-10 measure will not protect patients from under-treatment of anemia nor protect against increased transfusions and hospitalizations that are likely to occur without a sub-10 measure. As such, CMS should work expeditiously with the nephrology community to ensure that this important quality measure remains in the QIP for PY 2013 and beyond to protect against underutilization in the ESRD PPS.

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18 See Clinical Appendix, 1.2.1.3
19 Id.
20 76 Fed. Reg. 628-46
21 See Clinical Appendix, 1.2.1.3
22 U.S. Government Accountability Office. End Stage Renal Disease: CMS Should Monitor Access to and Quality of Dialysis Care Promptly after Implementation of New Bundled Payment System, GAO-10-295. Washington, DC: Government Accountability Office, March 2010.

Below, we review in detail our reasons for requesting that CMS work with the community to determine the appropriate performance standard to support the sub-10 measure.

The Sub-10 Measure is Critical and Should Be Retained in the QIP with Payment Penalty, But the Performance Standard for Anemia Management Should be Adjusted to Account for the Modified ESA Labeling.

Amgen acknowledges the important new prescribing information for ESAs in the treatment of patients who are on dialysis will likely result in a change in practice patterns for anemia management as physicians begin to provide more individualized anemia treatment. We also understand that the modified ESA labeling may make comparing performance standards to an established baseline prior to the labeling change challenging for CMS under the QIP. As a result of the modified FDA label, the CMS PY 2013 proposal to use all of 2011 as the performance period, which involves data from both pre and post FDA label modification, is not appropriate for implementing a payment penalty based on standards that may no longer be appropriate.

However, as explained in detail in the Clinical Appendix, low hemoglobin levels (*i.e.,* below 10 g/dL) are associated with higher rates of transfusions which can have a detrimental impact on both the accessibility of kidney transplantation and kidney graft viability, as well as worsened anemia symptoms and heightened risk of hospitalization and mortality in ESRD. For these reasons, avoiding low hemoglobin levels remains an important treatment goal for the nephrology community and, therefore, the sub-10 measure should be restored to the QIP program with payment penalties. Amgen makes two specific recommendations below and further urges CMS to work with the nephrology community to determine the appropriate data to support an alternative standard for the sub-10 measure as an appropriate anemia metric to account for an expected change in practice patterns.

Since the inception of the ESRD program, CMS has had a long history of collaboration with the dialysis community in the development of ESRD policies aimed at quality improvement while also providing appropriate financial incentives. From developing payment policies, such as the Hematocrit Measurement Audit Program Memorandum (HMA PM) and the ESA Monitoring Policy (EMP), to developing quality improvement programs like the Clinical Performance Measures (CPM) project, Dialysis Facility Compare (DFC), and the initial QIP framework, there has been robust collaboration between CMS and the nephrology community. This collaboration has developed rational, science-based policies that are in the best interests of patients. Amgen appreciates the agency's willingness to listen to dialysis stakeholders and urges the agency to maintain that commitment to determine the most appropriate data to support an anemia quality metric that has been a long standing protocol for providers when providing care for dialysis patients.

CMS has an important opportunity to work with the community again to determine the appropriate standard to support the use of the sub-10 measure as a meaningful mechanism for protecting against under-treatment in the ESRD PPS and meet the spirit of Congressional intent in MIPPA.

Amgen has two core recommendations in response to the Proposed Rule that affect both 2013 and 2014 payment years:

1. For the 2013 Payment Period, CMS Should Maintain the Sub-10 Measure but Forego Payment Penalties, as Practice Patterns Were Evolving in Response to FDA Label Changes.

As discussed in Section I.A., Amgen urges CMS to reinstate the sub-10 measure for the PY 2013, but recognizes the proposed standards for PY 2013 – measuring 2011 performance against either 2007 individual facility performance or the 2009 national performance rate – are not appropriate for determining individual facility payment penalties given the modified ESA labeling that was announced in June 2011, which is the middle of the performance year.[23] As such, Amgen recommends retaining the measure for reporting purposes only and therefore apply zero weighting toward the total performance score so providers are not financially penalized in PY 2013 for their CY 2011 performance.

By maintaining the measure for reporting purposes, CMS will maintain transparency in tracking the percentage of patients with hemoglobin levels less than 10 g/dL for six months under the previous labeling and for six months under the modified labeling to determine the change in practice patterns and to establish a new baseline for measuring future year's performance. Additionally, Amgen recommends CMS not apply the performance standard (*i.e.,* 2007 individual performance or 2009 national performance rate) and instead report only the percentage of dialysis patients with hemoglobin levels less than 10 g/dL when publishing facility scores. This will ensure that providers are not inappropriately measured against an outdated standard while providing dialysis patients with visible information about their individual facility's anemia management practices until a new standard can be determined and incorporated into future QIP payment years.

2. For the 2014 Payment Period, CMS Should Apply the Sub-10 Measure with Payment Penalties to the 2012 Performance Period based on a more Contemporary Baseline Period.

Amgen believes that CMS has ample time and opportunity to collect the necessary practice data to establish an appropriate baseline and performance standard to employ the sub-10 quality measure with payment penalties in the PY 2014 QIP program. By collecting contemporary practice data on hemoglobin levels and by consulting with the dialysis community, CMS can establish a more appropriate standard that reflects the modified ESA labeling and ensures quality patient care.

Specifically, Amgen recommends that CMS use a baseline period starting July 1, 2011 to July 1, 2012 to collect a full year's worth of practice data that will reflect practice patterns under the modified label. This will enable physicians to individualize ESA treatment under the modified label. It is in the interest of patients, the community, and CMS to collectively establish the appropriate standard for comparison to the new baseline.

[23] The performance standard for PY 2012 applies to facilities' performance in calendar year 2010. This standard continues to be appropriate and is not affected by the change in the FDA labeling for ESAs because it applies to use of ESAs before the labeling change was effective.

C. CMS MUST PROTECT PATIENTS FROM UNDERUTILIZATION AND SHOULD WORK WITH THE COMMUNITY TO DETERMINE THE MOST APPROPRIATE ANEMIA MANAGEMENT PERFORMANCE STANDARD THAT OPTIMIZES THE BALANCE OF QUALITY PATIENT CARE AND PATIENT SAFETY.

Alternatively, should CMS decide not to reinstate the sub-10 measure for payment penalty in any period, at a minimum, it should be maintained as a reporting measure under the QIP to track anemia quality care and determine the utility of measuring hemoglobin for future rulemaking or until CMS can define alternative anemia measures to protect against underutilization of anemia therapies, such as transfusion rates and/or patient satisfaction with anemia care.

Measuring transfusion rates could potentially be considered as a way to measure anemia management since the goal of ESA therapy is to avoid transfusions. Amgen recognizes that transfusions do not occur in the dialysis facilities and mostly in other settings of care which will make tracking and maintaining accountability an operational challenge. However, we believe that CMS has the ability to effectively track transfusion rates related to anemia management in the outpatient setting versus transfusions that may occur as a result of an inpatient stay or not related to their anemia management. Avoiding transfusion is an important aspect of anemia management for dialysis patients, and for this reason, measuring outpatient transfusion rates may be an effective quality measure for protecting against underutilization.

D. CMS SHOULD FINALIZE THE PROPOSAL TO INCLUDE A MEASURE REPORTING THE PERCENT OF PATIENTS WITH HEMOGLOBIN LEVELS GREATER THAN 12 G/DL.

As Congress and CMS have recognized, the ESRD PPS introduced significant financial incentives for dialysis providers to underutilize needed medical services. The QIP is intended to safeguard against treatment decisions that are based on the desire to reduce costs at the expense of what would otherwise be considered appropriate patient care. Amgen believes that the risk of underutilization is significant in the PPS and that quality measures are needed to avoid the unnecessary risks of transfusion, but we also recognize that clinically effective anemia management includes maintaining patients at a hemoglobin level that both reduces the risk for transfusion associated with low hemoglobin levels and avoids the risk of potential negative consequences associated with targeting high hemoglobin levels.

Amgen supports CMS' proposal to retain the hemoglobin greater than 12 g/dL measure in the QIP and agrees that the measure continues to reflect the labeling approved by the FDA for anemia management.[24] The recent FDA label changes refer to clinical trials in which safety signals were observed when ESA's in nephrology were used to target high hemoglobin levels. In response to these risks, the FDA has revised the ESA label by removing the target hemoglobin range (10 – 12 g/dL), and emphasizing physician discretion to individualize care in an effort to balance the proven benefits of transfusion avoidance and the long recognized benefits of EPOGEN® on improved physical function and exercise

[24] 76 Fed. Reg. 40519.

tolerance [25] against increased cardiovascular risk when higher hemoglobin levels are targeted.

Amgen agrees that the hemoglobin greater than 12 g/dL measure focuses on achieved hemoglobin levels, not hemoglobin level targets[26] and appropriately accounts for patient specific factors such as underlying causes of anemia and sensitivity to ESA treatment that can lead to unanticipated excursions of the achieved hemoglobin.[27] It is widely recognized that hemoglobin levels vary within individuals over time[28,29,30] and because of the delayed response between ESA dosing (to a target) and hemoglobin changes that are achieved, physicians cannot simply "dial in" a particular hemoglobin level of any given patients and maintain achieved hemoglobin levels within a narrow range for most patients. In fact, CMS has long recognized the distinction between dosing ESAs to a hemoglobin target versus the actual response in the hemoglobin level that is achieved – which commonly results in "transient excursions" above the target hemoglobin range.[31] Providers have traditionally managed transient excursions with appropriate dose reductions.[32]

The impact of hemoglobin variability and the population hemoglobin distribution that reflects this variability is well recognized by the nephrology community and CMS, and has been incorporated into Medicare's current EMP – that specifies that unless hemoglobin levels are persistently (*i.e.*, greater than 3 months) greater than 12 g/dL, then no regulatory action is warranted.[33] The FDA label has given physicians discretion to interrupt or reduce dosing at these levels, in part, for this reason.[34] Therefore, the hemoglobin greater than 12 g/dL measure is an appropriate and clinically relevant quality measure that is consistent with the FDA label, which is an important measure of the quality of care for the population of dialysis patients.

E. CMS SHOULD FINALIZE THE PROPOSAL TO IMPLEMENT THE MORE RIGOROUS SCALE TO ENSURE THAT PROVIDERS ARE PROPERLY INCENTIVIZED TO PROVIDE QUALITY CARE.

MIPPA requires that CMS ensure that the application of the scoring methodology results in an appropriate distribution of reductions in payments among providers and facilities achieving different levels of total performance scores, with providers and facilities achieving the lowest total performance scores receiving the largest reductions.[35] For PY 2012, CMS implemented a sliding scale, with payment reductions ranging from 0.5 percent to the full two percent, based on the facility's total performance score.[36] Under this approach, a

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25 EPOGEN® (Epoetin alfa) Prescribing Information. Amgen Inc., Thousand Oaks, CA (v25 06/2011). See Clinical Trials.

26 76 Fed. Reg. 40519 .

27 Id.

28 Ebben JP, Gilbertson DT, Foley RN and Collins AJ: Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. *Clin J Am Soc Nephrol*. 2006;1: 1205-1210.

29 Fishbane S and Berns JS: Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int.* 2005;68: 1337-1343.

30 Lacson E Jr., Ofsthun N and Lazarus JM: Effect of variability in anemia management on hemoglobin outcomes in ESRD. *Am J Kidney Dis.* 2003;41: 111-124

31 CMS Pub 100-04, Transmittal 1307, Change Request 5700.

32 Collins AJ, Brenner RM, Ofman JJ, et al.: Epoetin alfa use in patients with ESRD: an analysis of recent US prescribing patterns and hemoglobin outcomes. *Am J Kidney Dis.* 2005;46: 481-488.

33 CMS Pub 100-04, Transmittal 1307, Change Request 5700.

34 EPOGEN® (Epoetin alfa) Prescribing Information. Amgen Inc., Thousand Oaks, CA (v25 06/2011).

35 Social Security Act § 1881(h)(3)(A)(ii).

36 76 Fed. Reg. 40521.

facility needed to achieve very low scores on all measures to receive the full two percent penalty. FY 2013, CMS proposes to implement a more rigorous sliding scale of payment reductions by eliminating the 0.5 percent penalty and raising the minimum total performance score that providers need to achieve from 26 to 30 points to avoid any payment reductions.[37]

Amgen supports the agency's proposal to implement a more rigorous scale to ensure that all providers are properly incentivized to improve the quality of their care for patients. Under the PY 2012 sliding scale, facilities could rely on high scores for some measures to raise their total performance score and avoid or minimize penalties for poor performance on individual measures. We believe that applying a payment reduction of 2 percent to those providers whose performance falls significantly below the performance standards (*i.e.,* 0-20 points), as well as apply the two intermediate payment reduction levels (*i.e.,* 1.5 percent and 1.0 percent) based on marginal performance deficiencies, provides the appropriate incentive to improve quality care for this fragile population.

II. ESRD QIP FOR PY 2014

CMS proposes to use five clinical performance measures and three structural measures for the PY 2014 QIP. Our comments below address these measures, the weights and performance standards applied to them, and the proposed payment reduction scale.

A. QUALITY MEASURES

1. CMS Should Apply the Sub-10 Measure with Payment Penalties to the 2012 Performance Period Based on More Contemporary Data.

As stated in Section I.A., Amgen believes that CMS has an important opportunity to collect contemporary practice data on the percentage of patients with Hb less than 10 g/dL in order to establish an appropriate baseline and performance standard to employ the sub-10 quality measure with payment penalties in the PY 2014 QIP. As physicians begin to individualize ESA treatment under the modified labeling, it is imperative that CMS continue to track the percentage of patients with hemoglobin levels below 10 g/dL and then work with the clinical community to establish an appropriate performance standard and apply that to the more contemporary baseline data.

2. CMS Should Include Parathyroid Hormone (PTH) Testing in the Structural Measure on Mineral Metabolism Reporting.

Amgen strongly supports CMS' efforts to develop quality measures for bone mineral metabolism, as required by the Social Security Act, if feasible.[38] Mechanisms to ensure beneficiary protections and promote quality care are fundamental to a bundled PPS. CMS recognizes the importance of monthly monitoring for early detection of abnormalities and proposes to implement a structural measure to assess whether providers/facilities monitor a patient's phosphorus and calcium levels on a monthly basis throughout the portion of the proposed performance period during which the patient was treated.[39] In the ESRD QIP Final Rule, the agency stated that they will continue to work to improve the program,

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37 76 Fed. Reg. 40521.
38 Social Security Act § 1881(h)(2)(A)(iii)(II)).
39 76 Fed. Reg. 40526.

including adopting robust measures that provide valid assessments of the quality of care delivered to Medicare beneficiaries with ESRD by providers and facilities. We encourage the agency to continue this process by recommending that CMS include parathyroid hormone (PTH) testing in this measure, in addition to calcium and phosphorus, to encourage facilities to both monitor and report all three relevant laboratory values for detection and management of the disorders of bone mineral metabolism.

Disturbances in the regulation of the function of the parathyroid glands are highly prevalent in ESRD patients and often result in very high or very low concentrations of PTH in the blood, one of several abnormalities that represent an integral component of the recently defined syndrome of chronic kidney disease – mineral and bone disorder (CKD MBD). Results from observational studies demonstrate a consistent increase in mortality risk among patients with ESRD when PTH concentrations are markedly elevated or substantially reduced. These observations served as the basis for defining upper and lower threshold values for PTH to define levels of extreme risk in the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for CKD MBD.

Measurements of serum levels of PTH are essential to inform clinical decisions about the diagnosis and management of secondary hyperparathyroidism (HPT) and CKD MBD. Serial measurements over time provide important information about disease progression, the response to treatment, and expected disease-specific outcomes that affect the overall health of ESRD patients. Overt secondary HPT contributes materially to systemic disturbances in calcium and phosphorus metabolism among dialysis patients. Importantly, these biochemical abnormalities contribute to the development of soft tissue and vascular calcification, including cardiovascular calcification in dialysis patients.[40,41]

As such, Amgen recently submitted two PTH outcomes measures to the National Quality Forum (NQF) as part of the Renal Measures Maintenance Project. These measures reflect the recommended upper and lower limits for PTH threshold for treatment in dialysis patients that are specified in the KDIGO clinical practice guidelines.

Nephrologists are already routinely monitoring PTH. Therefore, we strongly encourage the agency to include PTH testing in the mineral metabolism reporting measure.

B. CMS SHOULD WEIGHT EACH MEASURE BASED ON RELATIVE RISK TO PRIORITIES FOR QUALITY IMPROVEMENT.

CMS proposes to assign equal weight of 0.18 to the five proposed clinical performance measures, with the weights adding up to 90 percent of the total performance score, and to assign equal weight of .333 to each of the three structural measures, adding up to 10 percent of the total performance score.[42] In the event that a provider/facility does not report data on at least 11 cases with respect to one of the clinical measures, the weight of each of the reported measures would be adjusted so that the combined weight of the remaining measures would remain 90 percent of the total performance score.[43]

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40 Quinibi W and Kalantar-Zadeh K. Target levels for serum phosphorus and parathyroid hormone. *Seminars in Dialysis.* 2011;24:29-33.

41 Rostand S, Drueke T. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int.* 1999;56:383-92.

42 Id. at 40532.

43 Id.

Rather than weighting each measure equally, Amgen urges CMS to develop a weighting methodology that is based on the relative risk of documented clinical outcomes if the measure is not met. Some measures could arguably be proportionally weighted higher due to their relative risk. As an example, achievement of one proposed clinical measure – *Vascular Access Type Measure, Percentage of patients receiving AV fistula treatment* – represents broadly recognized and documented clinical benefits for dialysis patients and economic benefits for the healthcare system. Not only are per person, per year total costs for patients with an AV fistula 28 percent lower than the costs for patients with a catheter ($64,701 versus $90,110),[44] but infectious complications are greatly reduced (40 percent of patients with an AV fistula have an antibiotic claim during the first 6 months of hemodialysis therapy compared to more than 60 percent of patients with a catheter)[45] and mortality is lower among patients with an AV fistula.[46] Conversely, the clinical measure – hemoglobin greater than 12 g/dL – could be weighted lower given that hemoglobin levels are steadily declining[47] and that the utility of this measure is marginal in a PPS. CMS should also develop a methodology that maintains this relative weighting if a provider does not report sufficient data on a measure for it to be included in the total score.

C. CMS SHOULD IMPLEMENT A METHODOLOGY TO ENSURE THAT IMPROVEMENT STANDARDS DO NOT DIMINISH INCENTIVES FOR ACHIEVEMENT.

CMS proposes to incorporate improvement standards and base improvement scores on how much the performance on a measure improved during the baseline period. Amgen supports the incorporation of improvement standards, as quality improvement was a core element of the new dialysis payment system. However, we are concerned that CMS proposes to determine a facility's performance for each of the clinical measures based on the higher of the achievement score versus its improvement score. Incorporating performance standards for levels of improvement should not erode any incentives for attaining minimal levels of achievement in goals that are identified as important for ESRD patient care. While we recognize that improvement should be rewarded, Amgen encourages CMS to implement a methodology that does not create inappropriate or mis-aligned incentives for provider achievement standards. Amgen believes that minimum thresholds need to be met before improvement can be rewarded. For example, it's possible for a provider to "improve" the rate of fistula placement in a year, but still not achieve an acceptable level of achievement.

D. CMS SHOULD MODIFY THE PAYMENT REDUCTION SCALE TO ENCOURAGE PROVIDERS TO PERFORM WELL ON ALL OF THE MEASURES.

CMS proposes to implement a tiered sliding scale of payment reductions for the PY 2014 QIP, similar to that used in the PY 2012 QIP.[48] This scale would not require each provider to meet or exceed the performance standard with respect to each measure to avoid

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44 USRDS Annual Data Report 2010.

45 Id.

46 Bradbury BD, Fissell RB, Albert JM et al. Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2007; 2: 89–99.

47 Amgen data on file.

48 Id. at 40534.

receiving a payment reduction.[49] CMS does not yet know the performance standard for the clinical measures, but it estimates that the minimum total score to avoid a payment reduction would be 60 points.[50] Providers that fail to meet that threshold would receive at least a 1.0 percent payment reduction.[51] The payment reduction would increase to 1.5 percent for providers that fail to achieve a total performance score that is 10 points below the minimum total performance score, or 2.0 percent for providers whose total performance score is more than 20 points below the minimum.[52]

Amgen supports a rigorous payment reduction scale that ensures that providers are properly incentivized to provide quality care. We are concerned that CMS' proposed approach might permit a provider to avoid a payment reduction even if it achieves very low scores on one or more measures. We urge CMS to develop a payment reduction scale that encourages providers to perform well on all of the measures and not rely on high scores for some measures to make up for lower scores on other measures to avoid payment reductions.

III. FUTURE ESRD QIP MEASURES

A. CMS SHOULD INCLUDE COMPREHENSIVE BONE MINERAL DISEASE AND SECONDARY HPT OUTCOMES MEASURES WHEN ORAL-ONLY DRUGS ARE INCLUDED IN THE ESRD PPS.

Finally, Amgen urges CMS to develop comprehensive bone mineral disease and secondary hyperparathyroidism (HPT) outcomes measures that can be implemented when oral-only drugs are included in the ESRD PPS in 2014. As discussed in section II.A.2, CMS proposes to implement structural monitoring measures for the PY 2014 QIP, but does not believe that it is appropriate to propose clinical measures for bone mineral metabolism at this time due to a lack of consensus about specific target ranges for calcium and phosphorus levels rather than clinical measures for phosphorus and calcium for the PY 2014 QIP.[53] CMS also anticipates that it will adopt one or more mineral metabolism clinical measures for future years of the QIP.[54] In particular, CMS seeks comments on measurement of serum calcium concentration and measurement of serum phosphorus concentration for future years of the QIP.[55] We commend CMS for beginning the process of developing bone mineral metabolism measures now. However, given the slow adaptation of clinical measures based on laboratory values in this space, as well as the documented consequences of poorly treated CKD-MBD, we believe the measures need to assess clinical outcomes in addition to, and/or in the absence of, laboratory values, in order to protect against underutilization of oral-only medications for secondary HPT once they are included in the ESRD PPS.

In our view, patients with secondary HPT are among the most vulnerable to the incentive for under-treatment created by a bundled PPS. In part, this is because these patients are often asymptomatic until the disease reaches advanced stages, and therefore the disease may go undetected and remain untreated. Even among those with diagnosed secondary HPT,

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49 Id.
50 Id.
51 Id.
52 Id.
53 Id. at 40526.
54 Id.
55 Id. at 40535.

under-treatment may not be properly detected because overt manifestations of bone disease such as pain, fracture, and bone loss have yet to appear. Delays in treatment or inadequate treatment can have serious and potentially irreversible consequences that may ultimately require more invasive and less desirable types of medical care, such as surgical parathyroidectomy and hospitalization to manage skeletal fracture,[56, 57, 58, 59, 60, 61] likely leading to greater healthcare resource utilization and implied higher costs in the long-term. Under the ESRD PPS beginning in 2014, the incentive for under treatment for oral-only secondary HPT drugs is heightened because dialysis providers will be at risk for the costs of these drugs but will not be at risk for incurring the costs of the consequences of under-treatment, such as hospitalizations. Evidence suggests that PTH levels are increasing more among African American dialysis patients despite the exclusion of oral-only Part D drugs (such as Sensipar® and phosphate binders) from the PPS in CY 2011. Early surveillance data regarding the PPS suggests that PTH levels have increased substantially during the six months leading up to and the two months following implementation of the PPS and that this change may be more substantial in African American dialysis patients.[62]

Additionally, persistent HPT and ongoing disturbances in mineral imbalances after successful kidney transplantation may have adverse consequences with respect to bone disease and kidney graft survival. In a study of 213 subjects with kidney biopsies obtained post-transplantation, calcification as measured by discrete calcium deposits termed "nephrocalcinosis," increased from 6.1 percent at 6 weeks to 17.8 percent at 6 months. Subjects with calcification had significantly higher PTH and calcium levels than those without calcification.[63] These deposits have been shown to independently predict the occurrence of chronic allograft nephropathy, which is the leading cause of kidney transplant loss.[64,65] In addition, a retrospective study of 422 kidney transplant recipients demonstrated that serum calcium > 10.5 mg/dL (> 2.63 mmol/L) at 12 months post transplantation significantly increased the odds (OR 4.0; 95% CI 1.2 - 14) of death-censored kidney transplant loss.[66]

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56 Danese M, Kim J, Doan Q et al. PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. *Am J Kidney Dis.* 2006;47(1):149-56.

57 Block G, Hulbert-Shearon T, Levin N, Port F. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31:607–17.

58 Ganesh S, Stack A, Levin N et al. Association of elevated serum PO4, Ca x PO4 product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*. 2001;12:2131–8.

59 London G, Guerin A, Marchais S et al. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant.* 2003;18:1731–40.

60 Block G, Klassen P, Lazarus J et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol.* 2004;15:2208–18.

61 Cunningham J, Danese M, Olson K, Klassen P, Chertow G. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney International.* 2005;68:1793-1800.

62 Latest Findings from the DOPPS Practice Monitor (DPM) during Implementation of the Prospective Payment System (PPS) for Hemodialysis: August 2010 – February 2011. (Accessed July, 2011, at www.dopps.org/DPM).

63 Gwinner W, Suppa S, Mengel M, Hoy L, Kreipe, HH, Haller H, Schwarz A. Early calcification of renal allografts detected by protocol biopsies: causes and clinical implications. *Am J Transplant.* 2005;5:1934-1941.

64 Schwarz A, Mengel M, Gwinner W, et al. Risk factors for chronic allograft nephropathy after renal transplantation: A protocol biopsy study. *Kidney Int.* 2005;67:341-348.

65 Nankivell B, Borrows R, Fung C, O'Connell PJ, Allen R, Chapman JR. The natural history of chronic allograft nephropathy. *N Engl J Med.* 2003;349:2326-2333.

66 Egbuna O, Taylor J, Bushinsky D, Zand M. Elevated calcium phosphate product after renal transplantation is a risk factor for graft failure. *Clin Transplant.* 2007;21:556-558.

Without appropriate quality oversight that includes recommendations about optimal target ranges for specific laboratory values such as PTH and the serum levels of calcium and phosphorous, as well as tracking of relevant health outcomes (such as fracture and parathyroidectomy rates), short-term economic incentives under the ESRD PPS could lead physicians to arbitrarily define a course of treatment that either precludes treatment or fails to provide adequate supplies of medications to effectively treat disorders of bone and mineral metabolism. This kind of underutilization is likely to result in potentially serious and irreversible long-term consequences that compromise the overall health status of ESRD patients, but it may not be recognized upon a retrospective review of available data.[67,68]

We believe that outcomes measures which evaluate target values for calcium, phosphorous, and PTH, should be incorporated into the QIP. Outcomes measures give physicians and facilities actionable targets and goals to improve patient health. While Amgen recognizes some controversy about the clinical targets for calcium, phosphorous, and PTH levels, physicians have long relied on clinical targets in these areas to manage secondary HPT, in accordance with US prescribing information for oral-only secondary HPT drugs.

As discussed in Section II.A.2, Amgen recently submitted two PTH outcomes measures to the National Quality Forum (NQF) as part of the Renal Measures Maintenance Project. These measures reflect the recommended upper and lower limits for PTH threshold in dialysis patients that are specified in the KDIGO clinical practice guidelines. While the project is not expected to conclude in time for these measures to gain endorsement before the anticipated publication of the Final Rule, the agency has already demonstrated its willingness to adopt measures into the QIP without NQF endorsement.

In addition to lab-based measures and targets, CMS should develop data and targets related to the clinical consequences of secondary HPT, including skeletal fracture, hospitalizations, and surgical parathyroidectomy. These measures would allow CMS to track the effects of inadequate treatment for secondary HPT.

Amgen appreciates CMS' transparent approach to developing consensus-based quality measures. Amgen believes that CMS needs to initiate efforts to develop meaningful bone mineral metabolism measures in the areas highlighted above through the consensus process for prompt inclusion in the QIP. However, before CMS begins to provide payment for oral-only drugs under the ESRD PPS in 2014, it is essential that consensus-driven, effective patient safeguards are in place. Specifically, CMS should develop appropriate outcomes measures, have baseline data to understand patient outcomes for secondary HPT in current practice, and be able to track performance against these targets under the PPS. Ideally, patient safeguards should be tested to ensure that they sufficiently protect patient access and quality of care.

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[67] Ganesh SK, Stack AG, Levin NW, et al. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients *J Am Soc Neph* 2001;12:2131-8.

[68] Marco MP, Craver L, Betriu A, et al., Higher impact of mineral metabolism on cardiovascular mortality in a European hemodialysis population. *Kidney Int* 2003;(Suppl);111-4.

IV. ESRD PPS FOR CY 2012

A. CMS SHOULD NOT APPLY THE PRODUCTIVITY ADJUSTMENT TO THE ORAL DRUG PORTION OF THE ESRD PPS.

In general, Amgen supports CMS' proposals to make adjustments to the ESRD PPS base rate and composite rate. For CY 2012, CMS proposes to increase the ESRD PPS base rate from $229.63 to $234.04, after applying the ESRD market basket increase, productivity adjustment, and wage index budget-neutrality adjustment factor.[69] CMS proposes to increase the composite rate portion of the blended payment rate from $138.53 to $141.52, after applying the ESRD market basket increase and productivity adjustment.[70]

We are concerned, however, about CMS' proposal to apply the productivity adjustment to the Part D oral drug portion of the transition blended payment rate. The productivity adjustment is calculated using data on output growth, labor output growth and compensation, and capital input growth and capital income.[71] Although this adjustment does not include the costs of drugs and other consumable items, CMS proposes to apply this adjustment to the Part D add-on to the composite rate. While the net effect in CY 2012 may be negligible, we are concerned that CMS will likely employ this same methodology when it incorporates oral-only Part D drugs (such as Sensipar®) to the ESRD PPS in CY 2014 and the lower inflation factor will unfairly decrease the value of oral-only Part D drugs when they are included in the PPS base rate.

In determining the CY 2011 payment for the Part D add-on portion of the blended payment, CMS applied a growth factor that is based on the rates for overall prescription drug prices that were used in the National Health Expenditure Projections.[72] For CY 2012, CMS proposes to add the oral drug add on amount ($.49) to the composite rate and then apply the market basket reduced by the productivity adjustment. We believe it is inappropriate to apply the productivity adjustment to full transition blended payment. Instead, we believe the amount should be split with 50 percent of it paid at the PPI-inflated market basket rates and 50 percent of it adjusted using the update factors because the transition blended payment rate is based on 50 percent of the PPS payment rate and 50 percent on the old composite rate plus drug add-on rate.

While this proposed methodology may not be consistent with the way CMS updates other prospective payment systems, the ESRD PPS is much different from other Medicare payment systems in that drugs represent the majority of overall dialysis facility costs. The drug and consumable components of ESRD payments should be updated by measures related to these components, not productivity in unrelated labor and capital costs. Because Congress did not include any such measure in the productivity adjustment, we recommend that CMS not apply the productivity adjustment to the costs of drugs or other consumable items.

CMS also proposes to maintain the drug add-on to the composite rate at $20.33 per treatment after using its established methodology for assessing changes in per patient expenditures for drugs and biologicals.[73] CMS estimates a 1.4 percent increase in drug

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69 Id. at 40502.
70 Id.
71 Id. at 40504.
72 Id. at 40505.
73 Id. at 40509.

expenditures between CY 2011 and CY 2012, which, when combined with a 4.2 percent increase in enrollment, would produce a 2.7 percent decrease in per patient growth of drug expenditures between CY 2010 and CY 2011.[74] However, CMS explains that it understands the statute's requirement to "annually increase" the drug add-on to mean that updates must be positive or zero, and the agency proposes a zero update for 2012.[75] Amgen agrees with this interpretation of the statute and we recommend that CMS implement this approach in the Final Rule.

B. CMS SHOULD ADD A CASE-MIX ADJUSTER FOR RACE BECAUSE IT IS HIGHLY PREDICTIVE OF RESOURCE USE.

In our comments on the ESRD PPS Proposed Rule for 2011, Amgen recommended that CMS implement a case mix adjuster for race because it is a significant predictor of resource utilization. In the ESRD PPS Final Rule for 2011, CMS did not implement race or ethnicity case-mix adjustments, although it acknowledged that not all of the "incrementally higher dialysis costs among African American patients are accounted for by other characteristics" in CMS' payment model, such as body size and co-morbidities.[76] We strongly recommend that CMS reconsider this decision and implement a case mix adjuster for race to better account for the higher costs of treating African American patients.

The impact of race on the treatment of ESRD and its complications has been well documented. Despite their three-fold higher incidence of ESRD compared to other race groups,[77] once on dialysis, African Americans have between a 25 percent and 40 percent lower risk of mortality,[78, 79] but use a disproportionately higher amount of healthcare resources, particularly medications.[80, 81] Since the early 1990s, African Americans have initiated dialysis with, on average, a 0.4 g/dL lower hemoglobin level as compared to whites.[82]

In the years leading up to the implementation of the PPS, two studies were published: one using US Medicare hemodialysis data[83] and the other using dialysis provider data;[84] both studies showed that African American patients required significantly greater EPOGEN® doses (7 percent to 13 percent on average) to achieve comparable Hb concentrations as non-African American patients.[85] Additionally, studies using US Medicare data[86] and

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74 Id.
75 Id.
76 75 Fed. Reg. 49030, 49111 (Aug. 12, 2010).
77 USRDS Annual Data Report 2009.
78 Goodkin DA, Bragg-Gresham JL, Koenig KG, et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003;14:3270-3277.
79 Bradbury BD, Albert JM, Fissell RB, et al. Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Clin J Am Soc Nephrol* 2007:2:89-99.
80 Lacson E Jr., Rogus J, Teng M, Lazarus JM, Hakim RH. The association of race with Erythropoietin dose in patients on long-term hemodialysis. *Am J Kidney Dis* 2008;52:1104-1114.
81 St. Peter WL, Li S, Liu J, et al., Effect of monthly dose and regular dosing of intravenous active vitamin D use on mortality among patients undergoing hemodialysis. *Pharmacotherapy* 2009;29:154-164.
82 USRDS Annual Data Report 2009.
83 Ishani A, Guo H, Arneson TJ, et al. Possible effects of the new Medicare reimbursement policy on African Americans with ESRD. *J Am Soc Nephrol* 2009;20:1607-13.
84 Lacson E, Jr., Rogus J, Teng M, Lazarus JM, Hakim RM. The association of race with erythropoietin dose in patients on long-term hemodialysis. *Am J Kidney Dis* 2008;52:1104-14.
85 Roach JL, Turenne MN, Hirth RA, Wheeler JR, Sleeman KS, Messana JM. Using race as a case-mix adjustment factor in a renal dialysis payment system: potential and pitfalls. *Am J Kidney Dis;*56:928-36.

dialysis provider data[87,88] have shown that African American patients require greater vitamin D doses relative to other racial groups and are also more likely to receive calcimimetics.[89] These data provided important evidence suggesting that under a capitated system such as the PPS, underutilization of pharmacologic interventions could potentially affect African Americans differentially – and less favorably – relative to other racial groups.

As discussed in Section I.A. and in greater detail in the Clinical Appendix, early surveillance data regarding the PPS suggests that the proportion of patients with hemoglobin concentrations less than 10 g/dL is increasing more in African American versus non-African American dialysis patients.[90] In February 2011, the proportion of patients having a hemoglobin concentration less than 10 g/dL was 28.4 percent higher in African American dialysis patients as compared with non-African American dialysis patients – a change from prior years. On average, African American patients saw a 17 percent increase in the proportion of patients with hemoglobin concentrations less than 10 g/dL from pre-PPS to post-PPS.

Unfortunately, there are currently other areas which demonstrate health disparities across the stages of chronic kidney disease. For example, African Americans have longer waits for transplants, on average 2 years longer than whites.[91] Unless CMS employs methods to help ensure sufficient reimbursement for patients who require higher utilization of ESRD therapies to achieve clinical outcomes, the potential for differences to be exacerbated further exists. We support incorporation of race as a case-mix adjuster as a provision to ensure that adversely impacted minority populations are not further disadvantaged. CMS should take any steps necessary, including adoption of case-mix adjusters, to address racial and ethnic disparities in ESRD treatment and outcomes.

C. CMS Should Develop Mechanisms to Promote Adoption of Innovations with a Demonstrated Impact on Patient Outcomes.

Amgen continues to be concerned that the ESRD PPS does not include any mechanisms that would enable the addition of incremental payments for innovations that improve clinical outcomes, but that do not reduce costs to the dialysis facility immediately. To the contrary, the productivity adjustment reduces payments based on improvements in efficiency in the economy as a whole, but does not support facilities' adoption of technologies that would help them achieve efficiencies in ESRD care. This payment reduction, combined with the lack of an appropriate mechanism to promote adoption of innovations that benefit ESRD patients, could discourage investments in the advancement in ground-breaking drugs, devices, or services for this vulnerable population that is in need of innovative solutions.

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86 Block GA, Zaun D, Smits G, et al. Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients. *Kidney Int* 2010;78:578-89.

87 Kalantar-Zadeh K, Miller JE, Kovesdy CP, et al. Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. *J Bone Miner Res* 2010;25:2724-34.

88 Wolf M, Betancourt J, Chang Y, et al. Impact of activated vitamin D and race on survival among hemodialysis patients. *J Am Soc Nephrol* 2008;19:1379-88.

89 Block GA, Zaun D, Smits G, et al. Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients. *Kidney Int* 2010;78:578-89.

90 Latest Findings from the DOPPS Practice Monitor (DPM) during Implementation of the Prospective Payment System (PPS) for Hemodialysis: August 2010 – February 2011. (Accessed July, 2011, at www.dopps.org/DPM).

91 USRDS Annual Data Report 2009.

CMS has recognized the need for such adjustments in its other PPS systems, including both the inpatient and outpatient prospective payment systems. For example, CMS created new technology ambulatory payment classifications in the hospital outpatient PPS to encourage the use of new technologies whose costs are not recognized in the cost data used to set payment rates (even though that mechanism was not mandated by Congress). CMS developed this mechanism to allow it to "recognize new technologies on an ongoing basis as expeditiously as [its] systems permit."[92]

Prospective payment systems naturally reward new technologies that improve efficiency or lower treatment costs. However, these systems do not reward new technologies or innovations that improve clinical outcomes or quality of care when there is an associated increased cost to the provider. CMS should include formalized procedures for promptly accommodating new technologies that substantially improve the outcomes for ESRD patients or new clinical applications of existing technology. CMS has the authority to make an adjustment for such new technologies in the ESRD PPS under SSA § 1881(b)(14)(D)(iv), which allows the Secretary to make "such other payment adjustments as the Secretary determines appropriate." Another or complementary option may be to create quality measures under the QIP for appropriate use of particular innovations that are demonstrated to substantially improve care.

We believe the ESRD PPS must include mechanisms to promote innovations that improve patient care and urge CMS to address this deficiency in the Final Rule.

D. CMS SHOULD TEST BROADER PAYMENT BUNDLES FOR ESRD, SUCH AS ACOs, WHICH MAY BETTER ALIGN INCENTIVES FOR IMPROVING PATIENT OUTCOMES.

In addition to developing payment adjustments to encourage improvements in treatment of ESRD, CMS should continue to explore broader bundles in ESRD, such as integrated care models, that would foster innovation through the use of its broad demonstration authority. A well-constructed, bundled PPS best aligns the incentives for improving outcomes when providers are responsible for the costs associated with outcomes.[93] We believe that a broader bundle that includes hospitalizations has the potential to better align payment system incentives for optimal patient care as compared to the proposed ESRD PPS, and will help to prevent harmful and needless adverse patient selection and shifts in the sites of care. CMS is well-positioned to test this type of model as the Agency has years of data on Part A and Part B utilization by ESRD patients, and has already conducted demonstrations to test global capitation models for ESRD.

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92 65 Fed. Reg. 18433, 18477.

93 For example, in March 2009, the Chairman of the Medicare Payment Advisory Commission (MedPAC), Glen Hackbarth, J.D. delivered a report before the Energy & Commerce Committee in the House of Representatives on potential system reforms and recommended holding physicians and hospitals jointly accountable for outcomes and resource use noting, "In the longer term, joint responsibility could lead to closer integration and development of a more coordinated health care delivery system." Peter Orzag, Director OMB wrote in Bending the Curve in More Ways Than One, on October 13, 2009, "Bundled payments, which pay a fixed amount for an entire episode of care rather than piecemeal for each individual treatment or procedure, would help improve patient care by encouraging better and more coordinated care than under a fee-for-service system."

E. CMS SHOULD CONTINUE TO MONITOR BENEFICIARIES' ACCESS TO AND EXPERIENCE WITH RENAL DIALYSIS SERVICES.

For many years, CMS has monitored the quality of care provided to dialysis patients, and it continues to do so under the ESRD PPS. In addition to the QIP measures, discussed below, CMS notes that it monitors the provision of dialysis services to ESRD patients in emergency departments.[94] We urge CMS to continue this monitoring effort because increased use of emergency rooms for treatment could indicate that beneficiaries are not receiving appropriate care in dialysis facilities. Finally, the renal community has long recognized that withdrawal from dialysis is the second most common cause of death for ESRD patients. The average dialysis patient lives 8 to 12 days after dialysis is withdrawn.[95] With that said, given the additional burden placed on patients due to the ESRD PPS, we encourage the agency to monitor the PPS for withdrawal rates to ensure that patients aren't withdrawing due to their experience under the bundle and that the necessary protocols are implemented in time to avoid any potential negative impact to patients.

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Amgen appreciates this opportunity to provide these comments and looks forward to working with you to ensure that Medicare ESRD beneficiaries have appropriate access and quality of care under the ESRD PPS. Please contact Sarah Wells Kocsis by phone at (202) 585-9713 or by email at wellss@amgen.com to arrange a meeting or if you have any questions regarding our response. Thank you for your attention to this important matter.

Regards,

Joshua J. Ofman MD, MSHS
Senior Vice President, Global Value and Access

cc: Marilyn Tavenner, Principal Deputy Administrator and Chief Operating Officer, Office of the Administrator, CMS
Jonathan Blum, Deputy Administrator and Director, Center for Medicare, CMS
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94 76 Fed. Reg. 40517.

95 Sekkarie MA, Moss AH: Withholding and withdrawing dialysis: The role of physician. specialty and education and patient functional status. *Am J Kidney Dis* 1998;31:464-472.

Clinical Appendix

Prepared to Supplement

Amgen Inc. Comments on CMS-1577-P

August 30, 2011

CLINICAL APPENDIX

TABLE OF CONTENTS

1.1. CMS should re-instate the sub-10 g/dL anemia measure.

1.1.1. CMS has consistently acknowledged that Hb levels below 10 g/dL increases patient risk for transfusions, hospitalizations, and mortality.

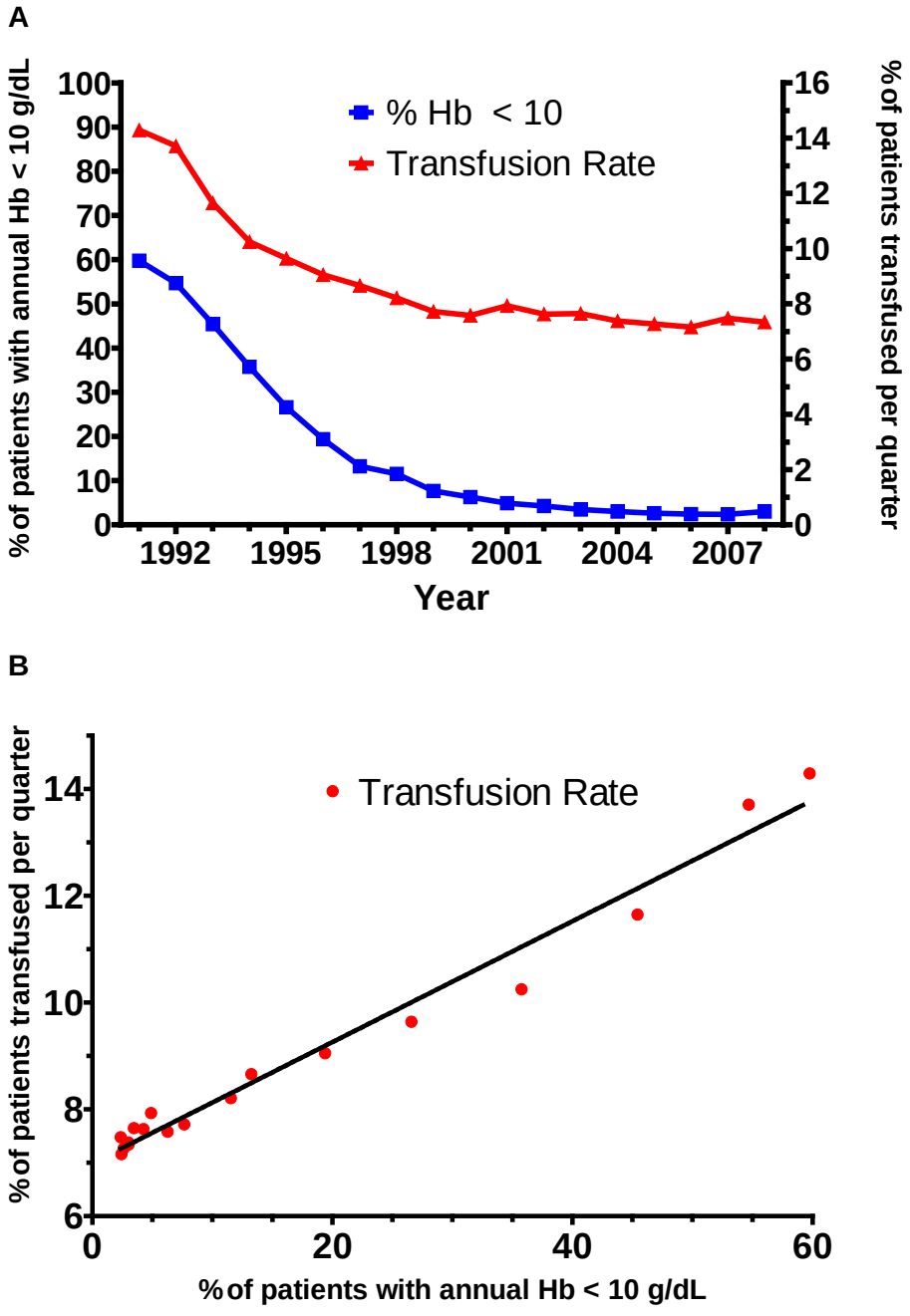
Effective anemia management in dialysis patients first became possible with the introduction of ESAs. During the ESA era, a Hb concentration of 10 g/dL has been recognized as a significant break point in its relationship to important clinical outcomes. **This document provides evidence demonstrating the benefits of treatment with ESAs to Hb concentrations greater than 10 g/dL, and conversely, the risks associated with Hb concentrations below 10 g/dL.** Clinical trials demonstrate that treatment with ESAs to maintain Hb concentrations greater than or equal to 10 g/dL reduces transfusions and improves measures of quality of life; observational data have confirmed a sustained reduction in transfusions over the last few decades. Conversely, multiple analyses described in this document indicate that persistent Hb concentration below 10 g/dL increases the risk of transfusions and is associated with increased hospitalizations. The clinical consequences of lower Hb concentrations have been established by over 20 years of research findings. Consistent data have demonstrated a strong relationship between Hb concentrations below 10 g/dL and clinically relevant clinical outcomes including transfusions and hospitalizations, and a decline in patient-reported outcomes has also been observed. This body of evidence and the risks associated with Hb concentration below 10 g/dL was acknowledged by CMS in their PPS regulation: "*Low hemoglobin levels below 10g/dL can lead to serious adverse health outcomes for ESRD patients such as increased hospitalizations, need for transfusions, and mortality.*"[1] Below is a review of the evidence supporting Hb concentrations below 10 g/dL as a risk factor for complications of anemia in dialysis patients.

The goals of anemia management and the primary indication for ESA use is transfusion reduction; this is recognized in the revised ESA labels (06/2011)[2,3] that acknowledge the risks of transfusions. Allosensitization[4] may result in poor transplant outcomes, as well as other risks such as transmission of blood-borne diseases, transfusion reactions, acute volume and potassium overload, and more chronically, iron overload.[5-10] Chronic transfusions administered as maintenance therapy for severe anemia were common before ESA therapy. In the ESA era, the incidence of transfusions tracks the population Hb concentrations below 10 g/dL; as population Hb concentrations rose and the proportion of patients with Hb concentration below 10 g/dL decreased, there was an accompanying decline in the transfusion rate (Figure 1A).

In selecting the sub-10 metric, CMS chose a surrogate that over the years has accurately and reliably reflected the observed real-world incidence of transfusion in the population of dialysis patients.

The specific QIP measure (sub-10) selected by CMS (*i.e.*, the percent of patients with annual mean Hb concentration < 10 g/dL) demonstrates essentially a linear relationship with the incidence of transfusions (Figure 1B).

Figure 1. (A) Proportion of Patients Receiving Transfusion by Quarter and Proportion of Patients with an Average Hb Concentration below 10 g/dL Over Time (B) Correlation Between Transfusions and Hb Concentrations below 10 g/dL



Source: Amgen data on files[i]

[i] Amgen data on file (average Hb < 10 g/dL).

In addition to transfusions, the anemia of chronic kidney disease (CKD) causes symptoms and loss of function.[8,12] ESA treatment that raises Hb levels above 10 g/dL has been demonstrated in randomized clinical trials (RCTs) to improve patient-reported physical function and exercise tolerance; this is recognized in the EPOGEN® label.[2,13] Moreover, this is supported by a recent meta-analysis (Johansen et al, 2010) showing statistically significantly lower levels of physical function and exercise tolerance in patients with Hb concentrations are below 10 g/dL.[14] In addition to the poor patient-reported outcomes, Hb concentrations below 10 g/dL are also strongly associated with increased rates of hospitalizations.[15-17]

CMS' 2010 QIP policy appeared to be cognizant of the risks associated with Hb concentrations below 10 g/dL and the benefits of Hb concentrations greater than or equal to 10 g/dL when it incorporated and heavily weighted a sub-10 metric to assure quality of care under a PPS that could create incentives for underutilization of therapies including ESAs. In the QIP legislation, CMS clearly acknowledged the potential for underutilization: "*the Hemoglobin Less Than 10 g/dL measure ensures that providers/facilities are incentivized to continue to properly manage and treat anemia. We believe that this is important in light of concerns that have been raised that the new bundled ESRD payment system could improperly incentivize providers/facilities to under-treat patients with anemia by underutilizing ESAs*."[1]

While recent changes in the US prescribing information (USPI) are expected to alter the treatment of individual patients, the scientific rationale that formed the basis for CMS' decision to use a sub-10 metric to address the level of care of the population has not changed.

Data from recent RCTs indicate an increased cardiovascular risk associated with ESA use when raising Hb concentrations to higher levels than previous FDA labeling. Consequently, ESA labels were revised to initiate ESA therapy in dialysis patients when Hb concentration falls below 10 g/dL, and to reduce or interrupt ESA dose as Hb concentration approaches 11 g/dL.[2,3] The revised ESA labels indicate that there is not any one Hb range that has been demonstrated to be appropriate for all CKD patients. For this reason, a specific Hb range has been removed from the revised labels to emphasize individualization of dosing to use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusion. Not every patient will benefit from ESAs dosed to achieve a Hb concentration greater than 10 g/dL regardless of their clinical circumstances. However, on a population level, there are adverse consequences experienced when the proportion of patients with Hb concentrations below 10 g/dL rises, and therefore, a well-constructed sub-10 metric that acts as a counterweight to under-treatment is of considerable value in a PPS and should be part of the QIP. In and of itself, a well-designed sub-10 metric does not obligate any individual physician to treat any individual patient to higher Hb concentrations than is appropriate for that patient, consistent with the revised ESA labels. Therefore, at a population level, a sub-10 metric remains valid and consistent with the label.

In addition, there are identified subgroups within the dialysis population that may be affected disproportionately by changes in clinical practice under PPS. Among these groups are African American patients who are subject to well-known disparities in the occurrence and severity of chronic disease (including CKD) and who receive lower levels of health services[18] despite greater health needs such as diabetes prevention and ESA dose requirements to maintain Hb levels. African Americans are more likely

to develop CKD and have been shown to develop more profound anemia than the general CKD population. Consequently, they often require higher ESA doses to achieve comparable Hb concentrations.[19,20] In general, controlling for age, sex, identified co-morbid conditions, other patient characteristics, and facility characteristics, blacks were shown to have approximately 9 percent higher costs than non-blacks.[21] Identifiable minority groups with specific health disadvantages have been identified both by CMS and by the Government Accounting Office (GAO) as requiring enhanced scrutiny lest they be further disadvantaged by the PPS.

The following Section 1.2.1.1 summarizes the evidence supporting Hb concentrations < 10 g/dL (on average over a year) as the appropriate quality population metric to assure appropriate anemia management to reduce transfusions and their associated risks. In Section 1.2.1.2, we summarize the data supporting the benefits of maintaining Hb levels greater than or equal to 10 g/dL with ESA therapy. Finally, in Section 1.2.1.3, data are presented describing the early effects of the PPS on Hb levels among African American dialysis patients compared with other racial groups. Early trend data presented herein suggests that the proportion of patients with Hb concentrations below 10 g/dL is increasing more rapidly in the African American population than in the remainder of the dialysis population. These data all point to the validity and continued relevance of CMS' rationale for choosing the sub-10 metric and why CMS should retain it in the QIP.

1.2.1.1. The totality of evidence demonstrates that persistent Hb concentration below 10 g/dL increases the risk of transfusions and is associated with increased hospitalizations in dialysis patients.

There is a large body of clinical evidence from RCTs that was part of the ESA registration program, re-analyses of RCT data, and surveillance data on the entire US hemodialysis population that have consistently demonstrated that the risk of transfusion increases substantially when Hb concentrations are below 10 g/dL. Moreover, this risk increases substantially the longer Hb concentrations remain below 10 g/dL.[22, ii, iii] While analyses of surveillance data may be subject to unrecognized confounding, the results of observational analyses are concordant with clinical trials and consistently show an increase in transfusions when Hb persists below 10 g/dL.

The risk of transfusion increases when Hb concentration is below 10 g/dL.

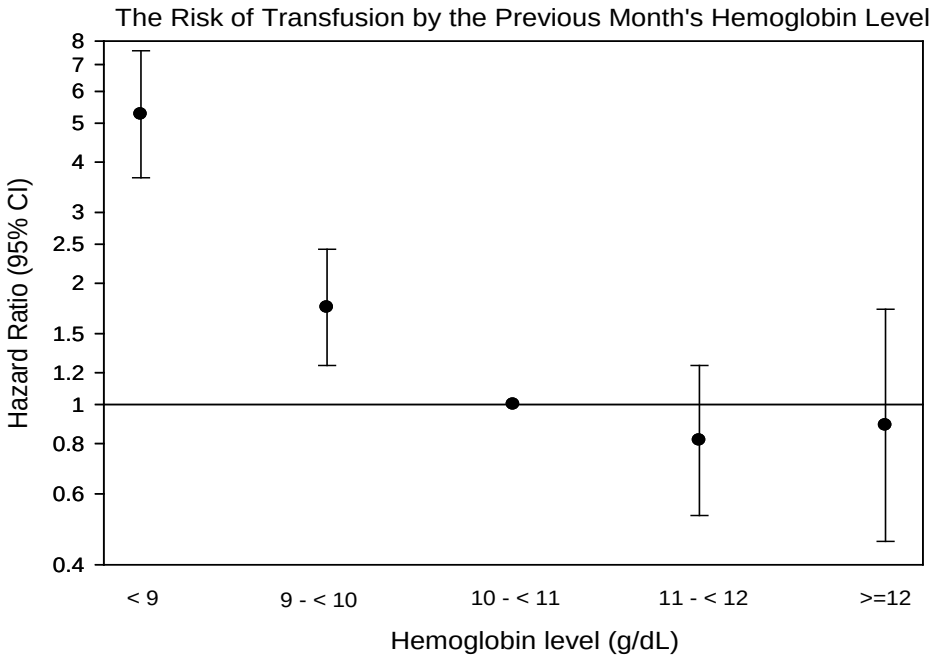
The elevated risk of transfusions in patients with Hb concentrations below 10 g/dL is further supported by a re-analysis of the Normal Hematocrit Cardiac Trial (NHCT), a large (> 1,200 patients), randomized controlled trial in dialysis patients with pre-existing cardiovascular (CV) disease or heart failure and anemia, which lasted approximately 29 months. This study compared the effect of treatment with ESA therapy to alternative Hb levels (14.0 g/dL vs. 10.0 g/dL) on the time to mortality or nonfatal myocardial infarction.[23] Safety data from NHCT demonstrated higher risks associated with randomization to higher Hb levels (hazard ratio [HR] = 1.3, 95% confidence interval [CI]: 0.9-1.8). This study is the largest RCT of anemia

[ii] Amgen briefing document for March 24, 2010 MEDCAC. (Available at: http://www.cms.gov/determinationprocess/downloads/0716ofmancomment.pdf).

[iii] Amgen briefing document for January 19, 2011 MEDCAC. (Available at: www.amgen.com/pdfs/misc/amgen_medcac_briefing_Jan2011.pdf).

management in dialysis patients with the longest duration of patient follow-up, which is important for evaluating transfusion risks at a population level. A re-analysis of the 629 patients enrolled in the lower arm of the NHCT, in which patients were treated to a Hb concentration of 10 ± 1 g/dL, was performed to determine the risk of transfusion as a function of Hb.[iv,v] Patients who were randomly assigned to the lower arm of NHCT experienced fewer adverse events and had a Hb level that did not exceed the upper limit of the revised USPI. The analysis indicates that the risk of transfusion increases significantly in the month following an achieved Hb concentration below 10 g/dL. Compared with a Hb concentration of 10 to less than 11 g/dL, transfusion risk doubles if the Hb concentration is between 9 and below 10 g/dL, and doubles again when the Hb concentration is below 9 g/dL (Figure 2).

Figure 2. Transfusion Risk by the Previous Month's Hb Level in the Lower Hb Arm of the Normal Hematocrit Cardiac Trial (NHCT)[vi]



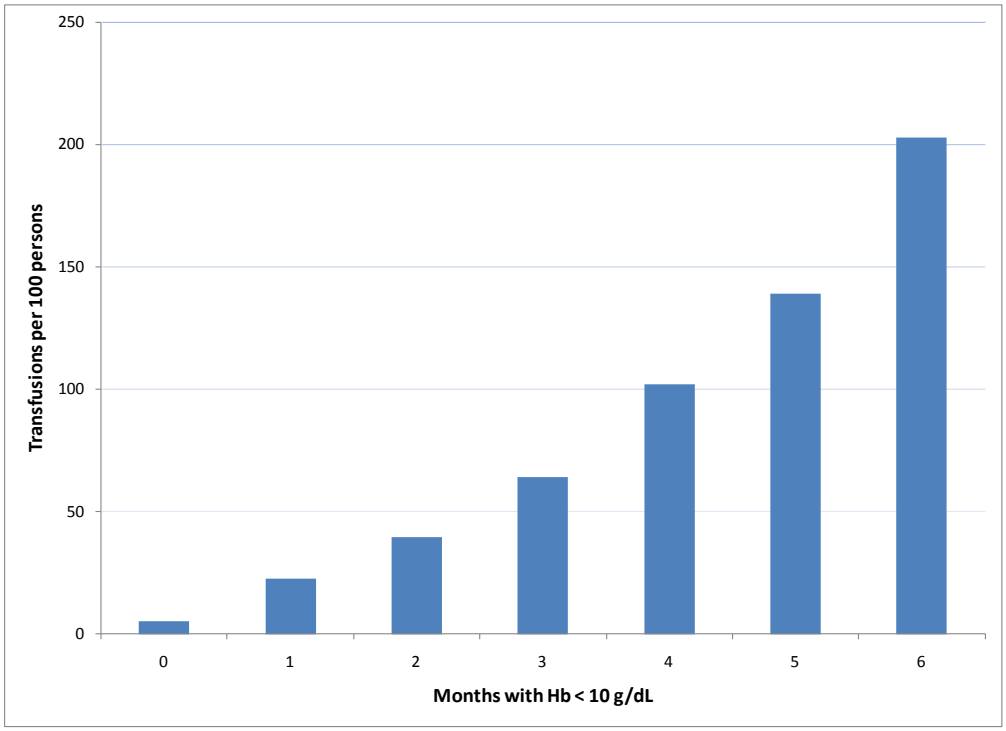
Data Source: NHCT study, data on file

Analyses of US Medicare data show that the likelihood of transfusion increases the longer a patient's Hb concentration remains low.[24] In an analysis of approximately 160,000 Medicare hemodialysis patients, the transfusion rate increased the longer Hb concentrations remained below 10 g/dL, up to 8-fold higher after 6 consecutive months

[iv] Amgen data on file (NHCT re-analysis).
[v] Amgen briefing document for January 19, 2011 MEDCAC. (Available at: http://www.amgen.com/media/amgen_medcac_esa_meeting-Jan2011.html.)
[vi] Amgen data on file (NHCT re-analysis).

with Hb concentrations below 10 g/dL (25 per 100 to 200 per 100 transfusion events) (Figure 3).[vii]

Figure 3. The Risk of Transfusion Increases the Longer Hb Concentration Remains < 10 g/dL (N = 159,720)



Source: Amgen data on file[viii,ix]

As illustrated in Figures 2 – 3, these data provide strong evidence that transfusions increase substantially when Hb concentrations fall below 10 g/dL.

Transfusions pose significant risks to patients on dialysis, including allosensitization that impairs transplant success, and increases risk for volume and potassium overload.

Reducing the need for red blood cell transfusions is recognized as an important treatment goal in dialysis patients, and transfusion reduction is the indication for ESA use. Given the strong association between transfusions and low Hb concentrations, removal of the sub-10 metric would likely lead to increases in rates of transfusion and their associated risks.

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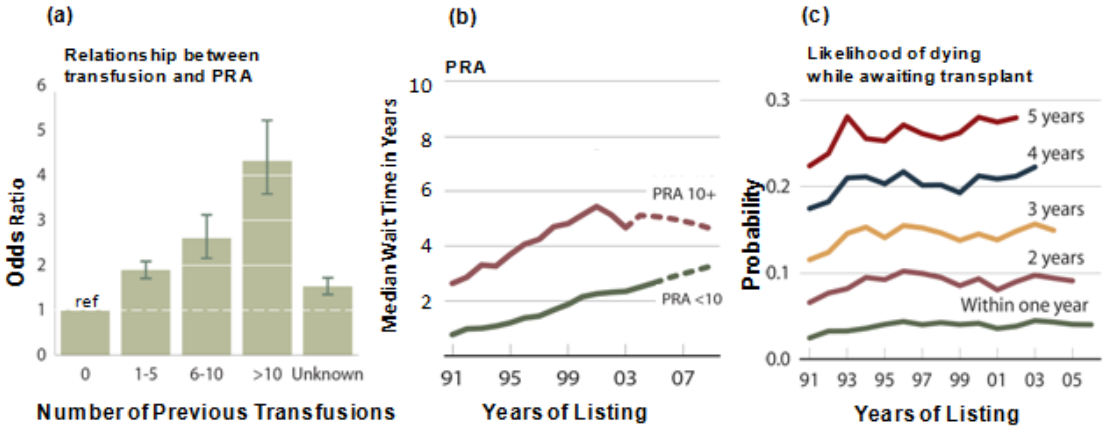
vii Amgen briefing document for January 19, 2011 MEDCAC. (Available at: http://www.amgen.com/media/amgen_medcac_esa_meeting-Jan2011.html).

viii Amgen briefing document for March 24, 2010 MEDCAC. (Available at: http://www.cms.gov/determinationprocess/downloads/0716ofmancomment.pdf).

ix Amgen briefing document for January 19, 2011 MEDCAC. (Available at: http://www.amgen.com/media/amgen_medcac_esa_meeting-Jan2011.html).

A very important transfusion-related risk is allosensitization, which is the development of antibodies to foreign antigens (*i.e.*, panel reactive antibodies [PRA]); the revised USPI recognizes this risk as a reason for ESA use. The risk of allosensitization increases with the number of transfusions (Figure 4A),[11,25,26] which can increase time spent on the transplant waiting-list or even preclude transplant eligibility, and for patients who receive a transplant, can shorten graft survival (Figure 5).[27,28] USRDS data indicate that moderately- to highly-allosensitized patients have the longest median wait times for a kidney transplant (Figure 4B), and the longer wait times are associated with greater likelihood of death (Figure 4C).[26,27]

Figure 4. Relationship Between (A) the Number of Transfusions and Risk of Allosensitization, (B) Allosensitization and Wait Times for Kidney Transplant, and (C) Longer Wait Times and Death

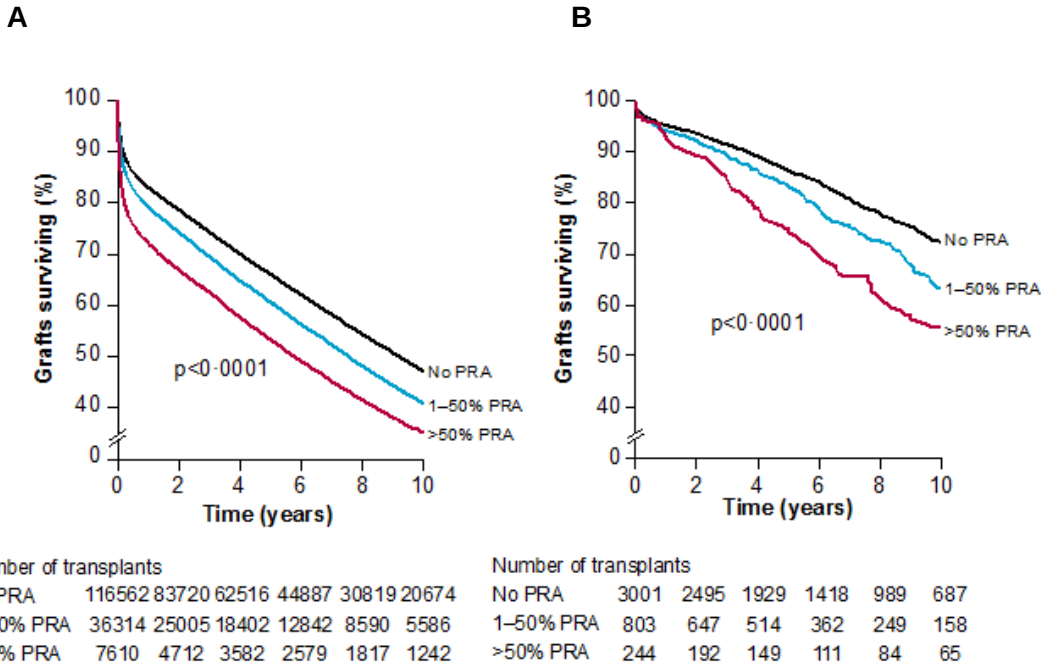


Source: 2009 USRDS Annual Data Report[26]; 2004 USRDS Annual Data Report[27]; Amgen briefing document for January 19, 2011 MEDCAC[x]

If and when a suitable organ is found, transplant allosensitization can still compromise the overall function and longevity of the transplanted kidney (Figure 5).[29] For example, among siblings with identical human leukocyte antigens (HLA) who received a kidney transplant, increasing allosensitization is associated with significantly shorter graft survival. Thus, transfusions can jeopardize chances for successful renal transplantation.[30]

[x] Amgen briefing document for January 19, 2011 MEDCAC. (Available at: http://www.amgen.com/media/amgen_medcac_esa_meeting-Jan2011.html).

Figure 5. (A) Long-Term (10-Year) Graft Survival of Cadaver Kidney Transplants According to Pre-Transplant Allosensitization (Measured as PRA), and (B) 10-Year Follow-Up of Kidney Grafts from HLA-Identical Sibling Donors



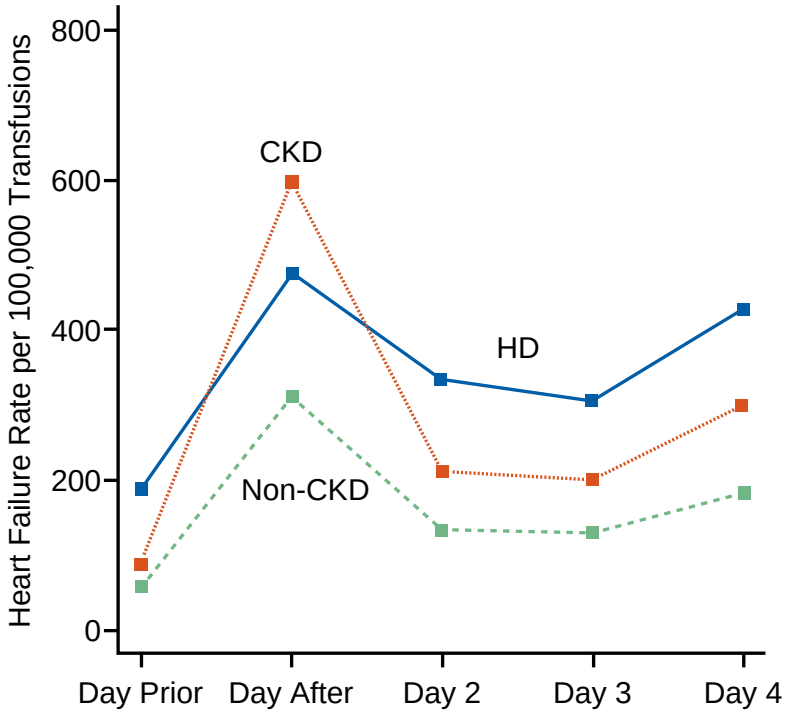
Number of transplants						
No PRA	116562	83720	62516	44887	30819	20674
1–50% PRA	36314	25005	18402	12842	8590	5586
>50% PRA	7610	4712	3582	2579	1817	1242

Number of transplants						
No PRA	3001	2495	1929	1418	989	687
1–50% PRA	803	647	514	362	249	158
>50% PRA	244	192	149	111	84	65

Source: Adapted from Opelz 2005[29]

Additionally, in contrast to the general population, CKD patients have a diminished ability to excrete fluid and electrolytes due to their impaired renal function,[31] and thus, are vulnerable to volume overload (heart failure exacerbation) and hyperkalemia.[5,8,9] These particular transfusion-related risks in CKD patients were identified over four decades ago.[31] The frequency and impact of these transfusion-related risks were examined in a recent analysis of US Medicare data; this analysis showed that in the days immediately following an outpatient transfusion event, hospitalization or emergency room visits with a diagnosis for heart failure occurred at a rate four- to seven-fold higher than in the days immediately preceding the transfusion event (Figure 6).[32] Similar results were observed for hospitalizations for hyperkalemia. Thus, the CKD population demonstrates particular susceptibilities to blood transfusion that may not be present in the general population.

Figure 6. Rate of Hospitalization or Emergency Room Evaluation for Heart Failure Immediately Preceding and Following an Outpatient Transfusion Event in Hemodialysis, CKD-NOD and Non-CKD Medicare Patients Between 2004 and 2008.



CKD = CKD-NOD, HD = Dialysis

Source: Gilbertson et al, 2010[32]

Additional acute but rare consequences of transfusions include transfusion reactions and TRALI,[33] the latter of which can be severe or fatal.

Hb concentrations below 10 g/dL are associated with an increased risk of hospitalization.

In addition to the increased risk of transfusion, there is also recognition that Hb levels below 10 g/dL may also be associated with increased hospitalizations. Evidence from multiple observational studies involving large sample sizes (greater than 10,000 patients) have shown an association between achieved Hb concentrations below 10 g/dL and increased risk of hospitalization (Table 1). These studies include evaluations of large databases from Medicare,[15,17] large dialysis organizations,[34] and the globally recognized Dialysis Outcomes and Practice Patterns Study (DOPPS).[16] All of these studies are representative of the US dialysis population and the majority is of prevalent patients. Although these studies do not establish causality, the risk of hospitalization across all of these studies appears to increase substantially when Hb concentrations fall below 10 g/dL. All study results were adjusted for disease severity including, but

not limited to co-morbidities, age, gender, race, length of time on dialysis, and number of red blood cell transfusions.

Table 1. Evidence Showing the Association of Increased Hospitalizations and Achieved Hb <10g/dL

Study Result	Population and Sample Size	% Increase in Hospitalizations for Achieved Hb < 10g/dL Compared with Hb of 10-11g/dL	Source
Hb < 10g/dL was associated with greater risk of hospitalization and length of stay	US Prevalent HD 71,717	10.2% (based on relative risk)	Xia 1999
Hb < 10g/dL was associated with greater risk of hospitalization	US Incident HD 66,761	17% (based on relative risk)	Collins 2001
Hb < 10g/dL was associated with greater risk of hospitalization and longer length of stay	US Prevalent HD 44,550	15% (based on mean # of hospitalizations)	Ofsthun 2003
Hb < 10g/dL was associated with greater risk of hospitalization	Global Prevalent HD 11,041	12% (based on relative risk)	Pisoni 2004
Hb < 10g/dL was associated with greater risk of hospitalization	US Prevalent PD 13,974	14% (based on hazard ratio)	Li 2004

Methods and footnotes: Risk of hospitalization estimates were calculated by pooling < 10 g/dL groups within each study. To obtain a pooled estimate, risk for each Hb group < 10g/dL are weighted by sample size for each group (< 9, 9 to < 10 g/dL (Xia et al 1999); < 10 g/dL (Collins et al 2001); <9, 9-<10 g/dL (Ofsthun et al 2003); < 8, 8 to < 10 g/dL (Pisoni et al 2004) and < 10 g/dL (Li et al 2004)]. Sample sizes are taken from the starting sample size within Hb category as listed in each publication. Incremental risk was then calculated as the risk relative to a reference group of 10 to < 11 g/dL. Reference groups for Collins et al 2001, Ofsthun et al 2003, Pisoni et al 2004, and Li et al 2004 were originally 11 to < 12 g/dL while Xia et al 1999 was 10 to < 11 g/dL; thus, risks relative to 10 to 11 g/dL were adjusted for Collins et al 2001, Ofsthun et al 2003, Pisoni et al 2004 and Li et al 2004 by dividing the weighted pooled risk of Hb < 10 g/dL by the risk in the 10 to < 11 g/L group within each study.

Summary

In conclusion, the body of evidence presented in this section highlights the poor health outcomes associated with anemic dialysis patients whose Hb concentrations are below 10 g/dL, including increased risks of transfusions and related risks, and increased hospitalizations. For these reasons, there is a strong evidence base supporting a sub-10 Hb measure as an important population metric and indicator of quality of care, and protects against under-treatment, which CMS recognized as a potential consequence of the PPS.[1,35] A well-constructed sub-10 metric is a reflection of the relationship between population Hb and the adverse events of transfusion experienced by a population of patients when Hb concentration is persistently below 10 g/dL. In and of itself, a sub-10 metric does not obligate any individual physician to treat any individual patient to higher Hb concentrations than is appropriate for that patient, consistent with the revised ESA labels.

1.2.1.2. The totality of evidence demonstrates that treatment with ESAs to maintain Hb concentrations greater than or equal to 10 g/dL reduces transfusions and related risks, and improves exercise tolerance and physical function in dialysis patients.

Treatment with ESAs to maintain Hb concentrations greater than or equal to 10 g/dL reduces transfusion.

The original ESA registrational program demonstrated that ESA therapy significantly reduces the need for transfusions when used to raise Hb concentrations greater than or equal to 10 g/dL (Table 2). In fact, across all of these studies, ESA benefits (*e.g.*, anemia correction and transfusion reductions or avoidance) were only observed when Hb concentrations were raised above 10 g/dL.

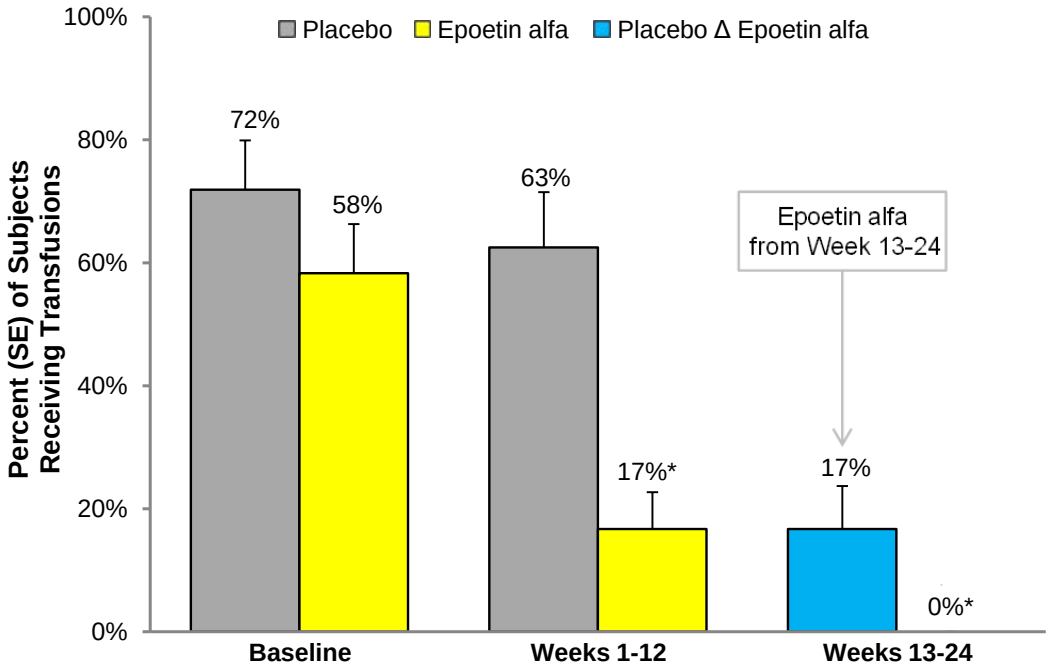
Table 2. Key EPOGEN® Clinical Trials

Study	N	Design	Mean Hb (Placebo or Pre-Treatment vs. Treatment)	Findings
EPO-8601	426	Multi-center, Single Arm	Pre: 7.5 Week 26: 10.7 Week 52: 10.8	Anemia correction, transfusion reduction
EPO-8701	Placebo: 32 Active: 36	Multi-center, Placebo Controlled	Week 12 Placebo: 7.8 Active: 10.6	Anemia correction, transfusion reduction
EP86-004	Placebo: 40 Active (pooled): 78	Multi-center, Placebo Controlled	Week 26 Placebo: 7.4 Active: 11.0	Health-related quality of life
EPO-8904	Placebo: 74 Active: 78	Multi-center, Placebo Controlled	Week 12 Placebo: 8.0 Active: 11.2	Anemia correction, transfusion reduction

For instance, during the six months prior to randomization of the 8701 study, when the average Hb concentration was approximately 7.5 g/dL, the proportion of patients receiving a transfusion ranged from 58 percent to 72 percent. After 12 weeks on-study, the Epoetin alfa-treated patients achieved a mean Hb concentration of 10.6 g/dL compared with placebo-treated patients whose mean Hb concentration remained below 8 g/dL. At 12 weeks, the proportion of Epoetin alfa-treated patients receiving a transfusion was 17 percent compared with 63 percent among placebo-treated patients ($p < 0.05$) (Figure 7).[xi] Between weeks 13 and 24 of the study, those randomized to Epoetin alfa continued to receive Epoetin alfa and received no transfusions; during this same period, those randomized to placebo initiated Epoetin alfa treatment and experienced a decline in transfusions (63 percent to 17 percent) comparable to those initially randomized to the Epoetin alfa group.

[xi] Amgen data on file (ESA registration study 8701).

Figure 7. Percent of Patients Receiving a Transfusion at Baseline and in Weeks 1-12 and Weeks 13-24 for Patients Randomized to Epoetin Alfa and Placebo Treatment

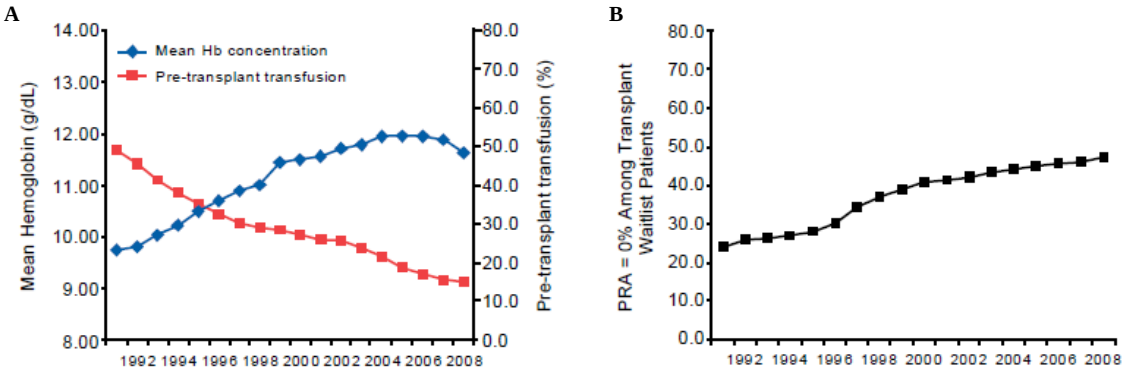


N = 32 (placebo); N = 36 (Epoetin alfa); *p < 0.05 placebo vs. Epoetin alfa
Baseline rates are based on the 6 months before the start of the study.
Placebo Δ Epoetin alfa group: Transfusion requirements for subjects originally randomized to receive placebo in Study 8701 who began to receive Epoetin alfa after week 12.
Source: Amgen data on file[xii]

The availability of ESAs and the ability to raise Hb concentrations above 10 g/dL has significantly reduced the frequency of transfusions, resulting in reduced patient exposure to transfusion-related risks. For example, with regard to allosensitization, USRDS data show that between 1991 and 2008, the population mean Hb concentration increased, transfusions were reduced, the proportion of transplanted patients who had a prior transfusion decreased from 49 percent to 15 percent, and the proportion of patients with no sensitization (PRA levels = 0 percent) doubled from 24 percent to nearly 50 percent (Figure 8).[11]

[xii] Amgen data on file (ESA registration study 8701).

Figure 8. The Proportion of US Patients Between 1991 and 2008 (A) Who Were Transplanted and Received Previous Transfusions, and (B) Who Had a PRA = 0% While on the Transplant Wait List

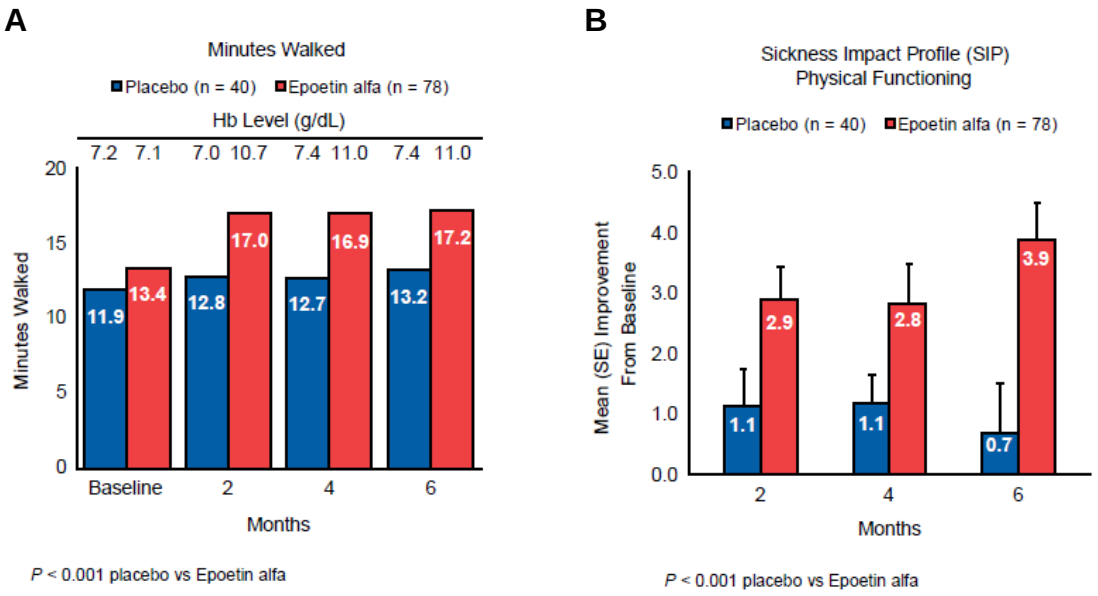


Source: 2010 USRDS Annual Data Report[11]

Treatment with ESAs to maintain Hb concentrations greater than or equal to 10 g/dL improves exercise tolerance, physical function, and reduces patient-reported symptoms of anemia.

Anemia symptoms are more evident when Hb concentration is below 10 g/dL. A number of analyses were conducted on an original ESA registrational trial referred to as the Canadian Erythropoietin Study Group (CESG) trial, which was a double-blind, randomized, placebo-controlled trial in patients with a baseline Hb level of 7g/dL.[36] Reanalysis of the CESG trial in 2007 using updated statistical methods including an intent-to-treat analysis and adjustment for multiple statistical tests serves as the basis for the benefits summarized within the clinical experience section of the EPOGEN® USPI.[2] The analysis found a statistically significant improvement in exercise tolerance and physical function as Hb concentrations rise above 10 g/dL.[13,14,37] Significant improvements in exercise tolerance and physical function were seen at two months and maintained through months four and six (Figure 9).[13] In the same post-hoc analysis, it was reported that correction of Hb was again correlated with improvements in fatigue, energy, shortness of breath, and weakness.[37]

Figure 9. Improvements in (A) Exercise Tolerance and (B) Physical Function with Achieved Hb Concentrations ≥ 10 g/dL Through ESA Treatment



Source: Adapted from Muirhead et al, 2011[13]

A recent systematic review and meta-analysis of more than 20 studies by Johansen et al provides additional evidence supporting the benefits of improvements in exercise tolerance (as defined by exercise stress test, distance walked, and oxygen capacity [VO_2]), and physical function when treating to Hb concentrations greater than 10 g/dL with ESA therapy.[14] The meta-analysis evaluated the role of ESAs in anemia treatment on exercise tolerance and patient-reported and clinician-assessed physical function and performance in adults on maintenance dialysis. The authors concluded that partial correction of anemia through ESA treatment has a consistent and positive impact, and that ESA treatment improves patient-reported and clinician-assessed physical function.

In a recent study, Mayne et al (2011) analyzed real-world data from approximately 30,000 US dialysis patients who completed the Kidney Disease Quality of Life Questionnaire (KDQOL-36) between 2009 and 2010 and evaluated patient-reported outcomes across achieved Hb concentrations, specifically above and below the 10 g/dL threshold. Scores from the KDQOL-36 were converted to a 0 to 100 scale with higher scores representing better health-related quality of life. The unadjusted analysis found statistically significantly ($p < 0.001$) lower scores in patients with Hb concentrations below 10 g/dL compared with those with Hb concentrations greater than or equal to 10 g/dL across items related to symptoms of anemia such as physical health and energy (Table 3).[38] After adjusting for, but not limiting to co-morbidities, age, gender, and dialysis modality, statistical models found a significant relationship between the majority of the KDQOL-36 items (listed below) and Hb concentration, specifically energy and shortness of breath.

Table 3. KDQOL-36* Items Scores with > 5-Point Change

Item Category	Item Description and Direction	< 10 g/dL (N = 1,852)	10-12 g/dL (N = 13,642)	> 12 g/dL (N = 9,273)
Physical health	Higher scores represent accomplish more of what you would have liked	29.5	35.5	37.6
Physical health	Higher scores represent you were not limited in kinds of work or activities	26.2	31.7	33.6
Energy	Higher scores represent more energy	40.1	44.2	46.0
Shortness of breath	Higher score represent less bother by shortness of breath	73.9	78.5	80.4

* Item description provided for clarity; Raw scores ranging from 0 to 100, with higher scores indicating better health-related quality of life; Items not showing > 5 point difference or are not relevant to anemia are not shown.
Source: Adapted from Mayne et al, 2011[38]

Summary

In summary, these data demonstrate that appropriate use of ESA therapy, which can help most patients achieve and maintain Hb concentrations greater than or equal to 10 g/dL, reduces transfusions and transfusion-related risks, as well as improves exercise tolerance and patient-reported outcomes related to anemia, such as physical function, fatigue, and energy. These data further support the need for and highlight the importance of a sub-10 Hb metric to prevent the consequences of persistent Hb concentrations below 10 g/dL.

1.2.1.3. African Americans could be disproportionately impacted if there are no safeguards to protect against underutilization.

There are general health disparities among African Americans.

The inequity in access and quality of care received by African Americans relative to other racial groups is well-recognized. Numerous government reports (CMS,[39] Agency for Healthcare Research and Quality [AHRQ],[40] Centers for Disease Control and Prevention [CDC], National Center for Health Statistics [NCHS][18]) identify important disparities in the incidence of serious adverse outcomes where African Americans are disadvantaged and experience worse care and outcomes. Based on the most recent AHRQ National Health Disparities report for 2010, African Americans continue to have worse outcomes with no change over time in disease areas including, but not limited to, higher breast and colorectal cancer diagnosis and mortality rates as well as higher inpatient admission rates for diabetic related amputations.[40] Another report by the NCHS found in 2004 that African Americans had the highest age-adjusted all-causes death rate of all races/ethnicities.[18] In addition, African Americans had the highest age-adjusted death rate for heart disease, cancer, diabetes, and HIV/AIDS.[18] In 2005, non-Hispanic black persons 18 years of age and over were less likely than non-Hispanic white persons to have received a flu shot during the past 12 months (non-Hispanic black: 26.9 percent; non-Hispanic white: 41.0 percent), and were also less likely to have ever received a pneumococcal vaccination (non-Hispanic black: 40.4 percent; non-Hispanic white: 60.6 percent).[18] A similar report developed by CMS in 2005 provides utilization rates of services across different racial groups.[39] The report found that African Americans also had lower rates of prostate cancer diagnosis and this was likely associated with the higher mortality rates that were reported. In addition, African Americans had higher diabetes prevalence and were most often to be the lowest users of preventive services.[39] Health disparities for African Americans are also present in the dialysis population as described below.

There are identified health disparities among African Americans on dialysis.

African Americans are disproportionately represented among dialysis patients, 35 percent[11] compared with 12.6 percent[41] in the overall population. In the years leading up to the PPS, two studies were published – one using US Medicare hemodialysis data[19] and the other using dialysis provider data[20] – both showing that African American patients required significantly greater Epoetin alfa doses (7 percent to 13 percent on average) to achieve comparable Hb concentrations as non-African American patients.[21] Additionally, studies using US Medicare data[42] and dialysis provider data[43,44] have shown that African American patients require greater vitamin D doses relative to other racial groups and are also more likely to receive calcimimetics.[42] These data provided important evidence suggesting that under a capitated system such as the PPS, underutilization of pharmacologic interventions could potentially affect African Americans differentially relative to other racial groups.

The PPS may be differentially affecting African Americans.

The PPS was implemented by CMS in January 2011 with the primary goal of removing incentives for overutilization of dialysis services. One important consequence of the PPS is the improper incentive to underutilize therapies such as ESAs; the effects of such an incentive may be more prominent among subgroups within the dialysis population in whom anemia is more common and more severe, and who thus require a

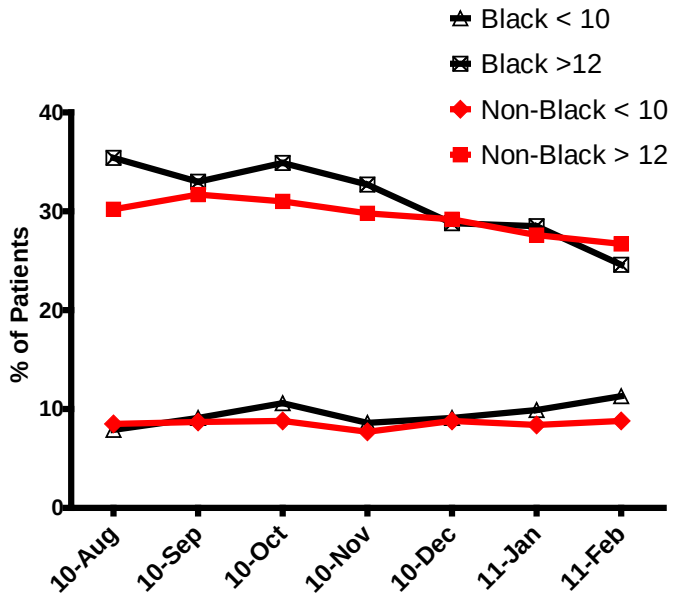
greater intensity of treatment. CMS recognized the potential of under-treatment of identified minority populations and explicitly stated in its final rule: "*As indicated previously, section 185 of MIPPA requires further study to identifying and addressing healthcare disparities in the Medicare program including those related to race or ethnicity. In addition, section 4302 of ACA requires ongoing analysis of race and ethnicity data to detect and monitor for trends in health disparities*….*In addition, as an integral part of the QIP, a program monitoring plan is in development to identify indicators useful in determining adverse effects on vulnerable (high risk) populations*."[1]

In the following sections, Amgen describes early data from two prospective, observational cohort studies (DOPPS and STEPPS) that suggests the PPS may be having a greater effect on black patients than non-black patients. DOPPS provides a representative sample of US hemodialysis centers (~140 centers) and patients (~3,000 patients); STEPPS includes 50 small dialysis organizations (SDO) dialysis centers and approximately 1700 patients.

Evidence suggests that the proportion of patients with Hb concentrations < 10 g/dL is increasing more in black versus non-black dialysis patients.

Data from DOPPS show the Hb distribution between black patients and non-black patients receiving care in large dialysis organization (LDO) facilities during the period August 2010 to February 2011 (Figure 10).[45] During this 7-month period, mean Hb levels fell by 0.30 g/dL in black patients compared with 0.09 g/dL in non-black patients. The proportion of patients with Hb concentrations < 10 g/dL rose from 7.9 percent to 11.3 percent in black patients, with little to no change observed in non-black patients (Figure 10). In February 2011, the proportion of patients having a Hb concentration < 10 g/dL was 28.4 percent higher in black dialysis patients compared with non-black dialysis patients. On average, black patients saw a 17 percent increase in the proportion of patients with Hb concentrations < 10 g/dL from pre-PPS to post-PPS. Substantial reductions in the proportion of patients prescribed EPOGEN® > 50,000 U/week were observed both in African American patients (14.6 percent to 9.3 percent) and non- African American patients (10.9 percent to 7.0 percent). Data describing racial disparities from DOPPS have been accepted for presentation at the American Society of Nephrology (ASN) in November of 2011.[46]

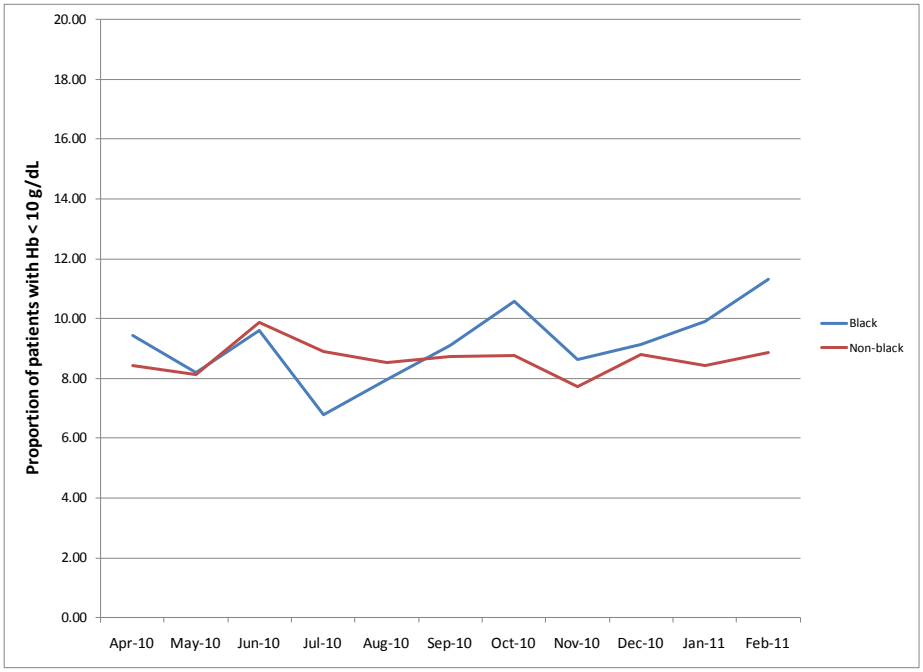
Figure 10. Proportion of Patients with Monthly Hb Concentrations > 12 g/dL and < 10 g/dL Time for Black and Non-Black Hemodialysis Patients (August 2010 – February 2011)



Source: Adapted from DOPPS data;[45] this represents data for Large Dialysis Organizations (LDOs)

The figure below provides data from DOPPS extending back to April of 2010, which is when there was sufficient site and patient enrollment in DOPPS 4 for the sample to be considered nationally representative (Figure 11). Data from previous waves of DOPPS (1996-2001, 2002-2004, and 2005-2007) are not presented because treatment during those periods differed substantively from the period after 2009. During the period from April to August 2010, the proportion of patients with Hb concentrations below 10 g/dL was similar between black and non-black patients (9.4 vs. 8.4 percent in April 2010).

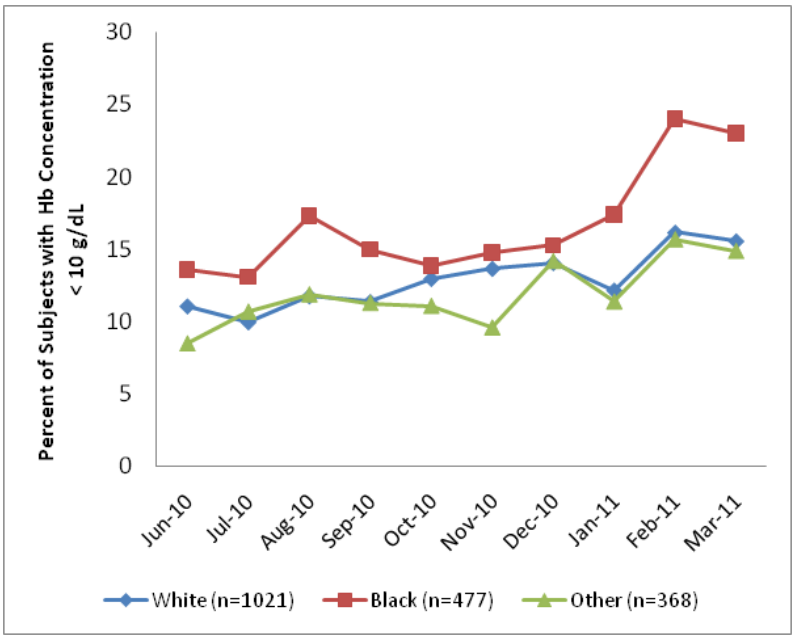
Figure 11. Proportion of Patients with Monthly Hb Concentrations < 10 g/dL for Black and Non-Black Hemodialysis Patients (April 2010 – February 2011)



Source: Amgen data on file (DOPPS data)

Similarly, data from STEPPS also show that the increase in the percentage of patients with Hb levels < 10 g/dL was also more pronounced among blacks than non-blacks or other races (Figure 12).

Figure 12. Proportion of Patients with Monthly Hb Concentrations < 10 g/dL Over Time for Black and Non-Black Patients

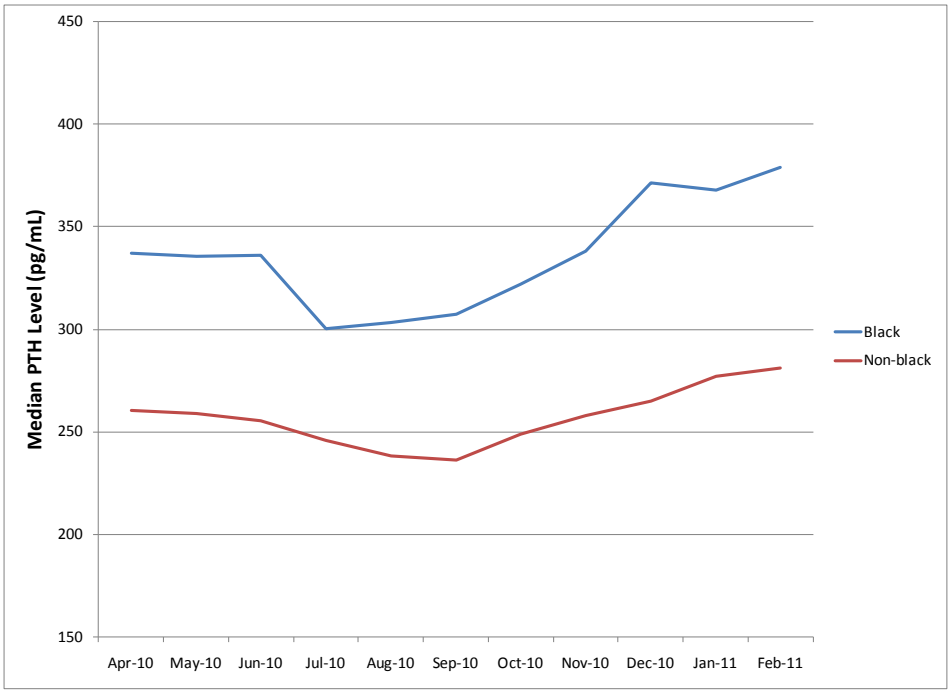


Source: Amgen data on file (STEPPS data)

There is additional evidence of racial disparities in dialysis patients: Evidence suggests that PTH levels are increasing more among black dialysis patients.

Data from DOPPS also suggests that PTH levels have increased substantially during the six months leading up to, and the two months following, implementation of the PPS and that this change may be more substantial among black patients as compared with non-black patients (Figure 13). During the final months of 2010 and into early 2011, the median PTH level among black patients increased from 299 to 374 pg/mL (August 2010 to February 2011). This change was noticeably higher than among non-black patients whose PTH increased from 260 to 281 pg/mL.

Figure 13. Median Monthly PTH Levels Between April 2010 and February 2011 for Black Patients and Non-Black Patients



Source: Amgen data on file (DOPPS data)

Summary

In summary, the African American dialysis population has been identified as vulnerable by virtue of a number of factors; the GAO report recognizes this and calls for heightened scrutiny of the effect of the PPS on this population. A number of early indicators described herein require ongoing attention as early signs reveal potential negative trends. Quality of care metrics, such as the sub-10 anemia measurement, can provide an important safeguard against underutilization of services and pharmacologic interventions that benefit all dialysis patients and protect them from declining quality of care. African Americans have been identified as a vulnerable population at greater risk of declining quality of care than the general population. CMS' proposal to eliminate these metrics may unnecessarily expose the dialysis population and particularly, the vulnerable African American dialysis population, to greater risk of transfusion and associated adverse outcomes.

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