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# Effect of Erythropoiesis-Stimulating Agent Policy Decisions on Off-Label Use in Myelodysplastic Syndromes

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**Background:** Erythropoiesis-stimulating agents (ESAs) are widely used to treat anemia associated with myelodysplastic syndromes (MDS) as an off-label indication. In early 2007, the U.S. Food and Drug Administration (FDA) released safety alerts and mandated label changes, and the Centers for Medicare & Medicaid Services (CMS) implemented a National Coverage Determination (NCD) in August 2007, dramatically restricting ESA coverage based on specific clinical parameters in non-MDS patients. We sought to determine the effect on ESA use in MDS, examining both treatment initiation and concordance with guidelines designed to target patients most likely to benefit from therapy.

**Methods:** We determined receipt of ESA within 6 months of diagnosis. For ESA recipients, we operationalized three National Comprehensive Cancer Network guidelines: serum erythropoietin determination before ESA initiation, transfusion-independent at ESA initiation, and initial ESA treatment episode of >= 8 weeks. Logistic regression models tested the effect of time (half-year increments pre-post the August '07 CMS NCD implementation), controlling for demographics and health status.

**Results:** 17,491 (61.1%) of 28,627 beneficiaries with MDS received ESAs. ESA use increased prior to the reference period (Jan.–July 2007), but declined beginning in August 2007, the date of NCD implementation (marginal probability =–0.05, p-value<0.01). Concordance with treatment guidelines changed during the observation period, with increased rates of serum erythropoietin levels, but declined in the other two guidelines.

**Conclusion:** These results suggest a mixed pattern of change in the face of the FDA safety warnings and CMS NCD in MDS and highlight the importance of monitoring for unintended consequences of policy changes.

**Keywords:** health policy, politics, law, regulation, Medicare, pharmaceuticals, prescribing, use, costs

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## Introduction

The erythropoiesis-stimulating agents (ESAs) epoetin alfa and darbepoetin are indicated for the treatment of anemia caused by end-stage renal disease (ESRD), zidovudine therapy in patients with HIV, chemotherapy in cancer patients, and also to reduce transfusion need in patients scheduled for non-cardiac major surgery. In addition to the approved indications, ESAs are used off-label in patients with myelodysplastic syndromes (MDS). MDS are a group of hematopoietic stem cell neoplasms characterized by ineffective hematopoiesis. Approximately 80% of MDS patients experience symptomatic anemia. ESA use is a central component of the strategy for reducing dependence on red blood cell transfusions. Clinical trial results indicate that approximately 40% of selected patients have a clinically meaningful hemoglobin response to ESAs, with a median response duration of two years (Golshayan *et al.*, 2007; Hellström-Lindberg *et al.*, 1998; Negrin *et al.*, 1996). Based on recent studies, at least two thirds of Medicare beneficiaries with MDS receive ESAs (Davidoff *et al.*, 2013a; Sekeres *et al.*, 2008).

Several studies, published beginning in 2003, raised concerns about the safety of ESAs. Associations were found between ESA use in cancer patients and venous thromboembolic events, tumor progression, and reduced overall survival (Bennett *et al.*, 2008; Danish Head and Neck Cancer Group, 2006; Henke *et al.*, 2003; Leyland-Jones *et al.*, 2005; Ross *et al.*, 2006). Consequently, the U.S. Food and Drug Administration (FDA) issued safety alerts in 2006 and required pharmaceutical companies to add safety warnings to ESA labels (i.e., "black box" warnings) in 2007–2008. (Appendix A provides a timeline of the events involved in the development of safety concerns around ESAs).

In tandem with the FDA's safety warnings, the Centers for Medicare & Medicaid Services (CMS) issued a National Coverage Determination (NCD), effective July 30th, 2007, detailing guidelines for coverage of ESAs. The NCD limited reimbursement in solid tumor, multiple myeloma, lymphoma, and lymphocytic leukemia patients with chemotherapy-induced anemia. The NCD required (1) evidence of anemia through a hematocrit or hemoglobin level, (2) response to ESAs documented by improvement in clinical parameters, and (3) discontinuation of ESAs no more than 8 weeks after the last administration of chemotherapy or if the patient's hemoglobin level exceeded specified levels (Centers for Medicare & Medicaid Services, 2007).

Several studies have investigated changes in ESA utilization patterns in the NCD-targeted population of Medicare patients with chemotherapy-induced anemia (Arneson *et al.*, 2012; Henry *et al.*, 2012; Hess, Nordyke, Hill, & Hulnick, 2010; Yu, Shord, & Cuellar, 2011). Community practice-based studies using medical records data have reported 10.9% to 32.0% pre-post decline in ESA use rates (Henry *et al.*, 2012; Hess *et al.*, 2010). A Medicare claims-based study reported a 19.8 percentage point decline in ESA use rates (35.0% pre-NCD to 15.2% post-NCD) among solid tumor and lymphoma patients with chemotherapy-induced anemia (Arneson *et al.*, 2012). These studies also found increased rates of blood transfusion in this patient population post NCD (Arneson *et al.*, 2012; Henry *et al.*, 2012; Hess *et al.*, 2010; Yu *et al.*, 2011).

The purpose of the current study was to investigate whether the FDA safety warning and CMS NCD had spillover effects on ESA use in Medicare beneficiaries with MDS. We hypothesized that the NCD would constrain ESA utilization in this patient population as a result of uncertainty about reimbursement for ESAs. We also hypothesized that clinicians would respond to the new safety information by trying to improve the risk-benefit balance through increased concordance with therapeutic guidelines designed to ensure that ESAs are used in the population most likely to benefit. In this study we examined trends in ESA utilization and ESA treatment guideline concordance around the period before and after the FDA safety warnings and CMS NCD.

## Methods

### Study design

This observational, population-based study examined trends in the receipt of ESA and in concordance with selected treatment guidelines among patients who received ESAs. As our focus was on the potential effects of the FDA safety warnings and the CMS NCD, we examined utilization during the period from 2005 through 2008, and tested for discontinuities mid-2007. The project was approved by the University of Maryland, Baltimore Institutional Review Board.

## Data

We used a database of Medicare beneficiaries with MDS generated from 100% of Medicare enrollment and claims files from 2004 through 2008. The enrollment files included monthly indicators of participation in Medicare Parts A, B, C (Medicare Advantage), and D, as well as selected demographic characteristics. Medicare claims included detailed information on dates, services provided based on International

Classification of Diseases, version 9–Clinical Modification (ICD-9-CM) procedure codes, Healthcare Common Procedure Diagnosis Coding System (HCPCS) codes and/or National Drug Codes (NDCs), diagnoses, and Medicare reimbursement. U.S. Census data on household income and education from 2000 were linked at the five-digit ZIP Code level (RTI International, 2011).

## Cohort Selection

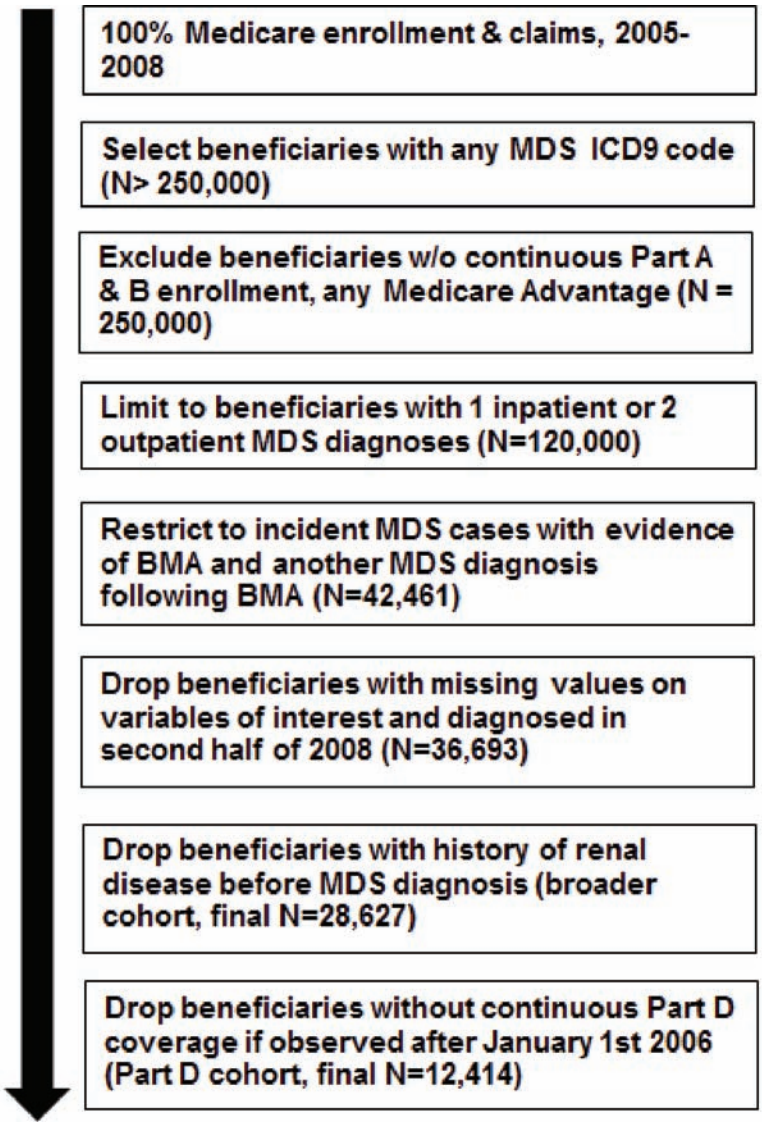
Inclusion in the MDS patient cohort required one inpatient claim with an MDS diagnosis (238.7 prior to October 2006, 239.72-5 beginning October 2006) or two outpatient claims at least 30 days apart, but within 12 months, a claim for a bone marrow aspirate or biopsy within 60 days before or after the initial diagnosis, and at least one claim with an MDS diagnosis after the bone marrow claim. Cases were assigned an index diagnosis week based on the date of the first qualifying MDS claim. A washout period of 12 months without an MDS diagnosis was used to restrict to newly diagnosed cases. We excluded individuals with a diagnosis of renal disease as patterns of ESA use are likely to be different. We also excluded individuals with missing values on variables of interest. In particular, beneficiaries without continuous Medicare Parts A and B or with Medicare Advantage enrollment were excluded as they would have incomplete claims records. Patients diagnosed in the second half of 2008 were dropped to ensure that all beneficiaries had a possible six months of follow-up.

ESA use may have been affected during the study period by the market entry and diffusion of two new types of disease modifying agents, hypomethylating agents (HMA; 5-azacytidine or decitabine, approved by the FDA in 2004 and 2006, respectively) and lenalidomide, approved in late 2005. Although the specific indications for HMAs and lenalidomide are distinct, both may be used as first line therapy in MDS, replacing or delaying ESA use. HMAs are covered under Medicare Part B, so that HMA receipt would be captured for all observations in the cohort. Lenalidomide is an oral medication covered under Part D only, and thus, would only be observed for the subset of beneficiaries with Part D coverage. To account for the diffusion of these new drugs and isolate the impact of the FDA safety warnings and NCD on ESA use, we assigned each observation based on the first therapy received in the first 6 months after the index date (ESA, HMA, neither observed) and dropped those observations receiving an HMA from the multivariate analyses. For the subset of Part D enrolled patients, we assigned each observation based on the first therapy, now including lenalidomide. The multivariate analyses dropped beneficiaries who received HMA or lenalidomide as their first therapy. We were also concerned that the NCD may have increased use of MDS diagnosis codes to justify ESA use in solid tumor patients who were the target of the NCD. In additional sensitivity analyses, we excluded beneficiaries with evidence of a non-hematologic malignancy identified by an ICD-9 diagnostic code. Exhibit 1 provides a summary of the exclusion criteria and the resulting sample sizes.

## Measurements

The outcomes of interest were receipt of any ESA within 6 months of MDS diagnosis and concordance with three treatment guidelines among those receiving ESAs. The National Comprehensive Cancer Network (NCCN) guidelines and relevant measures have been described previously (Davidoff *et al.*, 2013a). For this study, we focused on (1) whether the patient was transfusion-independent at the time of ESA initiation (associated with improved

**Exhibit 1. Study Cohort Selection Criteria**




SOURCE: 100% Medicare enrollment and claims data, 2005–2008.

response rates), (2) whether there was a serum erythropoietin determination prior to the first claim for ESA (used to target patients most likely to benefit), and (3) whether the first episode of ESA was at least 8 weeks in duration, which is deemed to be the minimum therapeutic length needed to assess patient response (National Comprehensive Cancer Network, 2011). We constructed measures needed to assess guideline concordance using person-week summaries of diagnostic tests and treatments, identified based on HCPCS codes on claims. Each weekly observation included indicators for ESA administration, administration of HMAs and lenalidomide, serum erythropoietin determination, and packed red blood cell transfusions. We used the weekly measures to determine whether there was a serum erythropoietin determination on or before the first week when an ESA claim was observed. The weekly indicators were also used to create ESA

episodes and to calculate the duration of the first episode, as detailed in Appendix B. We also constructed weekly measures of transfusion status post MDS diagnosis and captured the transfusion status at the week of ESA initiation. Construction of this measure has been described previously (Davidoff *et al.*, 2013a).

The key independent variable in the analyses was MDS index date; these were grouped, and beneficiaries were assigned to half-year periods beginning with the first half of 2005 and continuing through the first half of 2008.The time periods in 2007 were split into 7 and 5 months to accommodate the CMS NCD that was implemented July 30, 2007.

## Analysis

Bivariate analyses were used to examine changes in ESA utilization over time and concordance with treatment guidelines. Multivariate logistic regression models were estimated to investigate changes in ESA utilization and concordance with ESA treatment guidelines over time, relative to the first half of 2007, controlling for the factors detailed below. The first logistic regression model explored the effect on ESA use within 6 months of MDS diagnosis. As noted previously, we dropped beneficiaries who received HMA prior to ESA therapy among the full cohort, and dropped beneficiaries who received either HMA or lenalidomide prior to ESA among a subcohort of Part D-enrolled beneficiaries. The second set of models examined concordance with treatment guidelines among the subset of individuals initiating ESA within 6 months of diagnosis. All models controlled for beneficiary demographics (age, race, sex), evidence of Medicaid state buy-in for Medicare Part B post diagnosis, other socioeconomic status (income, education, and English language difficulty), region, death within the first 6 months post diagnosis, and urban/rural location. We included two measures of health status. The Charlson Comorbidity Index (CCI) aggregates information from claims on diagnoses of chronic conditions and weights them according to their contribution to non-cancer-related mortality (Charlson, Pompei, Ales, & MacKenzie, 1987). We also included a predicted value for poor disability (performance) status (DS) as described in Davidoff, *et al* (Davidoff *et al.*, 2013b). We present results as marginal probabilities (MP), as they provide information on the magnitude of effects. The alpha level for all statistical tests was .05 and all statistical tests were two-sided. We did not include an MDS risk group in the models due to strong correlation with MDS diagnosis date (resulting from the ICD-9 diagnosis coding changes in October 2006). Analyses used SAS 9.2 (SAS, Cary, NC) or Stata 10 (Statacorp. College Station, TX).

## Results

The study cohort, including 28,627 Medicare beneficiaries with MDS, was relatively old, with 67.4% aged 75 years or older, and was predominantly White (Exhibit 2). ESAs were received by 67.4% of beneficiaries at some point after their MDS diagnosis, with most (84.4%) receiving their first ESA within 6 months of diagnosis.

Exhibit 3A presents the trends in ESA, HMA, and lenalidomide use as initial treatment within the continuous Part D coverage group. ESA as first treatment was 64.4% in the second half of 2006, but dropped to 49.5% in the first half of 2008. The percentage of individuals not receiving any of the three treatments within the first 6 months post diagnosis trended downward until the second half of 2006, but the rate increased from 29.5% to 36.8% in the first half of 2008. The increased proportion of individuals not receiving treatments after the CMS NCD and FDA safety warning activity occurred despite increased rates of HMA

**Exhibit 2. Characteristics of Full MDS Patient Cohort [a]**

| N=28,627 | Frequency | Percent |
|---|---|---|
| **Time period of MDS diagnosis** | | |
| 1st half 2005 | 5,077 | 17.7 |
| 2nd half 2005 | 4,687 | 16.4 |
| 1st half 2006 | 4,428 | 15.5 |
| 2nd half 2006 | 3,799 | 13.3 |
| 1st seven month 2007 | 4,282 | 15.0 |
| Last five months 2007 | 2,965 | 10.4 |
| 1st half 2008 | 3,389 | 11.8 |
| **Sex** | | |
| Male | 15,120 | 52.8 |
| Female | 13,507 | 47.2 |
| **Race** | | |
| White | 26,247 | 91.7 |
| Black | 1,437 | 5.0 |
| Hispanic | 323 | 1.1 |
| Other | 620 | 2.2 |
| **MDS dx subtype** | | |
| Lower grade (ICD-9 238.72) | 5,736 | 20.0 |
| Higher grade(ICD-9 238.73) | 1,788 | 6.2 |
| With 5q deletion (ICD-9 238.74) | 572 | 2.0 |
| NOS, (ICD-9 238.7 or ICD-9 238.75) | 16,894 | 59.0 |
| **Age at diagnosis (years)** | | |
| <65 | 1,092 | 3.8 |
| 65–69 | 2,774 | 9.7 |
| 70–74 | 5,329 | 18.6 |
| 75–79 | 7,074 | 24.7 |
| 80–84 | 7,012 | 24.5 |
| 85–89 | 4,039 | 14.1 |
| 90+ | 1,307 | 4.6 |
| **Charlson Comorbidity Index** | | |
| 0 | 16,273 | 56.8 |
| 1 | 9,502 | 33.2 |
| 2 | 2,228 | 7.8 |
| 3+ | 624 | 2.2 |
| **Predicted DS** | | |
| Good | 26,382 | 92.2 |
| Poor | 2,245 | 7.8 |

**(Continued)**

**Exhibit 2 Continued. Characteristics of Full MDS Patient Cohort [a]**

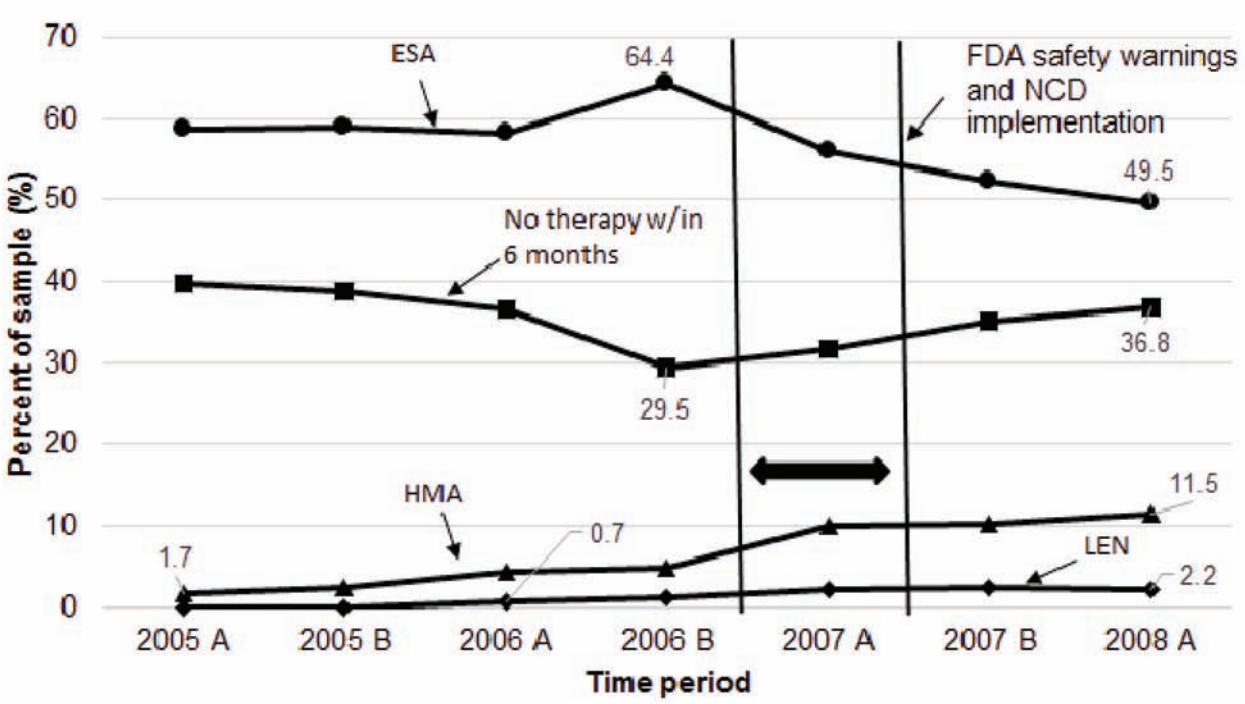
| N=28,627 | Frequency | Percent |
|---|---|---|
| **Died in first 6 months post diagnosis** | | |
| No | 23,929 | 83.6 |
| Yes | 4,698 | 16.4 |
| **At least one month Medicaid state buy-in** | | |
| No | 25,262 | 88.2 |
| Yes | 3,365 | 11.8 |
| **Median household income** | | |
| 1st quartile (LT $33, 585) | 7,459 | 26.1 |
| 2nd quartile (GE $33, 585 and LT $41, 363) | 7,396 | 25.8 |
| 3rd quartile (GE $41, 363 and LT $53, 471) | 7,147 | 25.0 |
| 4th quartile (GE $53, 471) | 6,625 | 23.1 |
| **Census Region** | | |
| Northeast | 4,792 | 16.7 |
| Midwest | 7,721 | 27.0 |
| South | 11,721 | 40.9 |
| West | 4,393 | 15.3 |
| **Urbanization** | | |
| Urban | 22,120 | 77.3 |
| Somewhat urban | 5,799 | 20.3 |
| Rural | 708 | 2.5 |
| **Proportion with less than high school education (mean, standard error)** | 0.157 | (0.001) |
| **Proportion with English language difficulty (mean, standard error)** | 0.183 | (0.001) |

NOTE: [a]Abbreviations: MDS–myelodysplastic syndromes, ICD-9–International Classification of Diseases, version 9, DS–disability status.
SOURCE: 100% Medicare enrollment and claims data, 2005–2008.

and lenalidomide use, suggesting that the drop in ESA utilization resulted from both substitution of newer drugs and declines in any treatment.

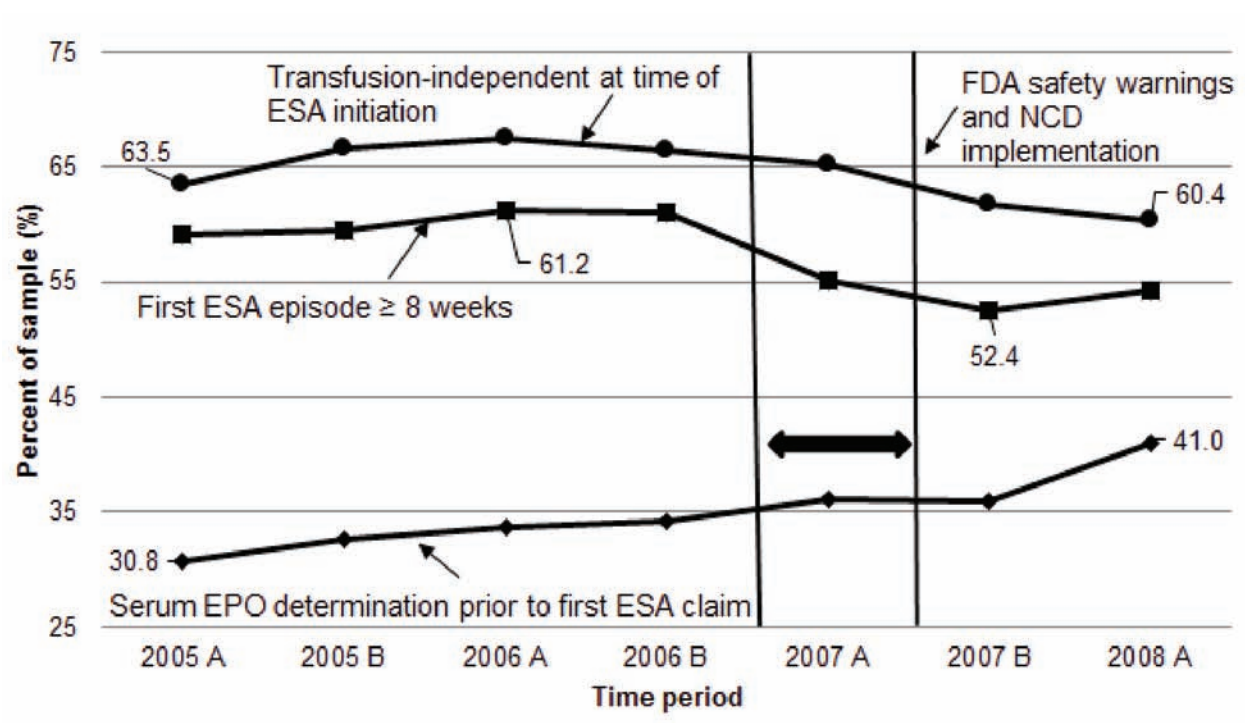
Exhibit 3B shows rates of ESA treatment guideline concordance measures over time among ESA users within 6 months post diagnosis. Patients were less frequently transfusion-independent at ESA initiation following the FDA safety warnings/CMS NCD, with a decrease from 67.4% for patients diagnosed in the first half of 2006 to 60.4% for patients diagnosed in the first half 2008. The serum erythropoietin determination rates prior to ESA initiation increased from a low of 30.8% for patients diagnosed in the first half of 2005 to 41.0% for patients diagnosed in the first half of 2008. The percentage of first ESA episodes of adequate duration dropped from 61.2% for patients diagnosed in the first half of 2006 to 52.4% for patients diagnosed in the last 5 months of 2007. All of the time trends in both Exhibit 3A and Exhibit 3B were statistically significant ($p<0.01$). Sensitivity analyses that dropped individuals with a history or new diagnosis of a solid tumor revealed similar patterns (data not shown).

**Exhibit 3A. Trends in Initial Treatment Within 6 Months Post Diagnosis Over the Time Periods**




SOURCE: 100% Medicare enrollment and claims data, 2005–2008.

**Exhibit 3B. ESA Treatment Guideline Adherence Rates over Study Period**




SOURCE: 100% Medicare enrollment and claims data, 2005–2008.

After excluding beneficiaries who received disease modifying therapies prior to ESAs, the estimation sample size included 26,914 beneficiaries, with 11,535 enrolled in Medicare Part D. The results of the logistic regression models examining the effect of diagnosis period on receipt of ESA and guideline concordance were consistent with the results of the bivariate analyses (Exhibit 4). Relative to the first seven months of 2007, ESA use rates in the prior

**Exhibit 4. Logistic Models Examining ESA Use, Serum EPO Level Before First ESA Episode, First ESA Episode Therapeutic (>= 8 weeks), Transfusion Status at First ESA Episode [a,b]**

| | ESA use within 6 months post diagnosis | ESA use within 6 months post diagnosis | Serum erythropoietin determination before first ESA claim | First ESA episode >= 8 weeks | Transfusion–independent at time of ESA initiation |
|---|---|---|---|---|---|
| | n=26,914[c] | n=11,535[d] | N=17,491[e] | N=17,491[e] | N=17,491[e] |
| | Marginal Probability | Marginal Probability | Marginal Probability | Marginal Probability | Marginal Probability |
| **Time period of MDS diagnosis** | | | | | |
| 1st half 2005 | –0.010 | –0.010 | –0.046* | 0.038** | –0.014 |
| 2nd half 2005 | 0.014 | –0.009 | –0.027* | 0.044** | 0.018 |
| 1st half 2006 | –0.002 | –0.014 | –0.022 | 0.061** | 0.028* |
| 2nd half 2006 | 0.040** | 0.054** | –0.009 | 0.057** | 0.010 |
| 1st seven month 2007 (ref) | — | — | — | — | — |
| Last five months 2007 | –0.051** | –0.034 | –0.002 | –0.028 | –0.029* |
| 1st half 2008 | –0.079** | –0.062** | 0.042** | –0.010 | –0.047** |
| **Sex (ref=male)** | 0.044** | 0.037** | 0.009 | –0.050** | 0.033** |
| **Race (ref=white)** | | | | | |
| Black | –0.016 | –0.023 | –0.056** | –0.046* | 0.044* |
| Hispanic | 0.039 | 0.044 | –0.015 | –0.065 | 0.089* |
| Other | –0.005 | –0.011 | 0.039 | 0.022 | –0.002 |
| **Age at diagnosis (ref=65–69)** | | | | | |
| <65 | –0.061** | –0.093** | –0.040 | –0.046 | –0.000 |
| 70–74 | 0.031* | 0.012 | 0.008 | 0.014 | 0.029* |
| 75–79 | 0.053** | 0.035* | 0.029* | 0.012 | 0.032* |
| 80–84 | 0.089** | 0.051** | 0.029* | 0.016 | 0.039** |
| 85–89 | 0.102** | 0.082** | 0.057** | 0.021 | 0.044** |
| 90+ | 0.108** | 0.071** | 0.042* | –0.006 | 0.001 |
| **Charlson Comorbidity Index (ref=0)** | | | | | |
| 1 | 0.051** | 0.036** | 0.009 | –0.021* | 0.020* |
| 2 | 0.069** | 0.058** | 0.006 | –0.047** | 0.023 |
| 3+ | 0.060** | 0.033 | –0.012 | –0.041 | –0.002 |

**(Continued)**

**Exhibit 4 Continued. Logistic Models Examining ESA Use, Serum EPO Level Before First ESA Episode, First ESA Episode Therapeutic (>= 8 weeks), Transfusion Status at First ESA Episode [a,b]**

| | ESA use within 6 months post diagnosis | ESA use within 6 months post diagnosis | Serum erythropoietin determination before first ESA claim | First ESA episode >= 8 weeks | Transfusion–independent at time of ESA initiation |
|---|---|---|---|---|---|
| | n=26,914[c] | n=11,535[d] | N=17,491[e] | N=17,491[e] | N=17,491[e] |
| | Marginal Probability | Marginal Probability | Marginal Probability | Marginal Probability | Marginal Probability |
| **Predicted disability status [ref=good (DS 0–2)]** | | | | | |
| Poor (DS 3–4) | –0.094** | –0.106** | –0.057** | –0.033* | –0.044** |
| **Died in first 6 months post diagnosis (ref=no)** | | | | | |
| Yes | –0.094** | –0.112** | –0.078** | –0.179** | –0.179** |
| **At least one month Medicaid state buy-in (ref=no)** | | | | | |
| Yes | 0.007 | 0.010 | –0.016 | –0.005 | –0.023 |
| **Median household income (ref=lowest quartile)** | | | | | |
| 2nd quartile | 0.005 | 0.021 | 0.005 | 0.012 | –0.007 |
| 3rd quartile | 0.017 | 0.023 | 0.013 | 0.012 | –0.009 |
| Highest quartile | 0.013 | 0.008 | 0.014 | –0.018 | –0.014 |
| **Census Region (ref=Northeast)** | | | | | |
| Midwest | –0.020* | –0.035* | 0.112** | 0.057** | –0.030* |
| South | 0.072** | 0.066** | 0.009 | 0.041** | 0.007 |
| West | –0.025* | –0.037* | 0.038** | –0.001 | –0.000 |
| **Urbanization (ref=urban)** | | | | | |
| Somewhat urban | –0.017* | –0.016 | –0.001 | 0.006 | –0.034** |
| Rural | –0.049* | –0.039 | 0.042 | –0.066* | –0.016 |
| **10% increase in proportion with less than high school education** | –0.011** | –0.012* | –0.006 | –0.001 | –0.021** |
| **10% increase in proportion with English language difficulty** | 0.006** | 0.009** | 0.004 | –0.005* | 0.004 |

NOTES: [a]Abbreviations: MDS- myelodysplastic syndromes, ESA- erythropoiesis-stimulating agent, DS- disability status.

[b]Statistical significance: *=p-value <.05, **=p-value <.01.

[c]Drops individuals who initially used hypomethylating agents in first 6 months post diagnosis.

[d]Drops individuals who initially used hypomethylating agents or lenalidomide in first 6 months post diagnosis and restricts to individuals with continuous Part D coverage.

[e]Models further restricted to ESA users within 6 months post diagnosis.

SOURCE: 100% Medicare enrollment and claims data, 2005–2008.

period did not reflect a consistent trend, but were either higher or not significantly different from the reference period. However, ESA use rates decreased progressively in the second half of 2007 and first half of 2008. A similar pattern was observed in the subgroup of Part D-enrolled beneficiaries. The temporal patterns with respect to guideline concordance were somewhat more consistent. Rates of serum erythropoietin determination before initiation of first ESA episode did not change until the second half of 2006, when there was a small increase. The trend accelerated in the first half of 2008, with a 4.2 percentage point increase ($p<0.01$). In the first half of 2008, patients were less likely to be red blood cell (RBC) transfusion-independent when compared to patients in the first seven months of 2007 (MP=–0.047, $p<0.01$). Patients diagnosed after 2006 were less likely to have a first ESA episode that was of therapeutic duration when compared to those diagnosed in 2005 and 2006.

In addition to diagnosis period relative to the NCD, other patient characteristics were associated with ESA use and guideline concordance (Exhibit 4). Female sex, increasing age, and higher CCI were associated with increased probability of ESA use, while poor predicted DS and death within the first 6 months post diagnosis were associated with reduced probability of ESA use. Contextual level variables and census region were also significant in the majority of the models, suggesting that geographical and local factors play a role in ESA use and guideline concordance.

## Discussion

This study examined ESA use and concordance with ESA treatment guidelines among Medicare beneficiaries with MDS before and after the FDA safety warnings and the CMS NCD targeted at ESA use in other settings. We observed a drop in ESA use beginning in August of 2007, suggesting that the FDA and CMS policy decisions may have affected the decision to initiate ESAs in MDS patients. There was mixed evidence with respect to the effects on concordance with treatment guidelines. While we found increases in the proportion of patients with a serum erythropoietin level prior to ESA initiation, there were parallel declines in the proportion of patients who were transfusion-independent at initiation, and fewer patients received initial episodes of sufficient duration to determine response. Furthermore, increased assessment of serum erythropoietin levels prior to ESA initiation was a trend observed from the end of 2005, while the shift in transfusion status at ESA initiation began in 2006 and, therefore, it is not clear that either trend was specifically related to the FDA regulatory activities or CMS NCD.

The 13 percentage point drop in ESA use observed after the FDA regulatory changes and NCD falls into the range that has been reported for ESA use for chemotherapy-induced anemia in previous studies (Arneson *et al.*, 2012; Henry *et al.*, 2012; Hess *et al.*, 2010). This result is somewhat unexpected because the national policies were not targeted at off-label use for MDS. However, ESA coverage policies specific to MDS were left to the discretion of local Part A and Part B Medicare Administrative Contractors (A/B MACs), which may have adopted similar policies.

We also observed that individuals were more likely to be transfusion users or transfusion-dependent at first ESA initiation, which suggests that physicians were delaying ESA initiation in response to the national policies. The exact reason for the decrease in frequency of therapeutic-length initial ESA episodes is unclear. Early discontinuation of ESA episodes could represent a more general response to the safety warnings or additional complexity of the reimbursement process. The drop in ESA use, delay in ESA initiation, and early discontinuation of initial ESA episodes could

result in higher transfusion rates, which has been observed in patients with chemotherapy induced anemia (Arneson *et al.*, 2012; Henry *et al.*, 2012; Hess *et al.*, 2010; Yu *et al.*, 2011). The impact of the spillover effects on transfusion rates and other patient outcomes in the Medicare MDS population is an area that requires additional research.

Few CMS NCDs address medication use, as most are not covered under Medicare Part B. However, numerous studies have detailed the effect of the FDA safety communication on healthcare utilization and health behavior in targeted and unintended populations. For example, a number of studies focused on "black box" warnings revolving around the off-label use of selective serotonin reuptake inhibitors (SSRIs) to treat depression in children and adolescents (Dusetzina *et al.*, 2012). In response, the utilization of SSRIs dropped significantly within the targeted population of children, with only a moderate decrease in the secondary adult population (Dusetzina *et al.*, 2012). In contrast, our findings suggest similar effects for both targeted and off-label ESA use.

There are several important limitations to this study. The study is limited in scope to changes in practice patterns, but did not examine clinical outcomes. For example, as we previously stated, the drop in ESA use, delay in ESA initiation, and early discontinuation of initial ESA episodes could result in higher transfusion rates, which has been observed in patients with chemotherapy induced anemia (Arneson *et al.*, 2012; Henry *et al.*, 2012; Hess *et al.*, 2010; Yu *et al.*, 2011). Research assessing the impact of policy changes on clinical outcomes in Medicare beneficiaries with MDS is an area for future research.

The study also faced design limitations. While we controlled for the effect of diffusion of HMAs and lenalidomide during the study time period, the pre-post design did not permit us to control for other trends in practice that may have affected our study population, independent of the effect of the NCD and FDA policy changes. Because the available data did not allow us to identify a comparison group that would not be affected by the policy change, a quasi-experimental comparative design was not feasible. Similarly, we could not isolate the impact of the FDA regulations from those associated with the CMS coverage changes because of the overlapping implementation periods.

Other limitations relate to the use of administrative claims data to select and describe our patient cohort. For example, reliance on ICD-9 diagnostic codes to identify our cohort may have resulted in beneficiaries being included or excluded incorrectly. Physicians could also be assigning MDS diagnosis codes to patients diagnosed with solid tumors to justify payment for ESA treatment. However, the requirement for evidence of a bone marrow aspirate or biopsy and a confirmatory claim with an MDS diagnostic code afterwards increases our confidence in the accuracy of our cohort assignment. Furthermore, in sensitivity analyses, we excluded patients with a history of non-hematologic malignancies prior to MDS diagnosis and found similar results. Claims data also lack information on clinical laboratory values, limiting our ability to fully examine adherence to some of the treatment guidelines. Finally, the data lack information regarding patient preferences and clinician intent, which, if available, might provide explanations for some of the observed patterns.

In recent years, several additional policies have been adopted that could further alter ESA utilization patterns in the MDS population. In 2010, for example, the FDA implemented a Risk Evaluation and Mitigation Strategy in an attempt to improve clinician knowledge concerning risks and benefits associated with ESA use. The effect of this policy on adherence to guidelines for ESA use in indicated and off-label settings requires further study.

In the current study, we investigated the spillover effect of the FDA and CMS national policies on ESA use related to chemotherapy-induced anemia on ESA use in Medicare beneficiaries with MDS. We found statistically significant, but moderate, changes in ESA use and both positive and negative effects on concordance with NCCN ESA treatment guidelines after the national policies were implemented. As CMS and other government organizations implement policy instruments to alter healthcare utilization in the future, it will be important to monitor unintended as well as intended consequences on treatment patterns and patient outcomes. When unintended consequences are identified, including spillover to patient groups not targeted by policy, policy makers will have the opportunity to clarify policy language, and educate providers and patients, in an attempt to minimize harms.

## Disclaimer

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## Appendix A. Timeline of events involved in ESAs safety concerns [a]

**May 2004.** FDA-ODAC discusses safety and recommends more double-blind, placebo-controlled trials with survival as primary endpoint.

**November 2006.** FDA issues safety alert, updated in February and March 2007.

**December 2006.** DAHANCA head and neck cancer trial is stopped early because of negative results in treated patients.

**March 2007.** FDA adds "black box" warning to use lowest possible dose of ESAs for anemia.

**May 2007.** ODAC recommends restrictions on ESA use.

**July 2007.** CMS limits reimbursement of ESAs to treatment initiated at hemoglobin levels less than 10 g/dL.

**November 2007.** FDA labeling change warns of increased tumor progression, blood clots, and death in patients with advanced head and neck, breast, lymphoid, and non–small-cell lung cancers. ASCO/ASH issue updated guidelines for ESA use.

**February 2008.** A meta-analysis in JAMA by Bennett et al. finds that ESAs are associated with greatly increased risks of venous thromboembolism, tumor progression, and death.

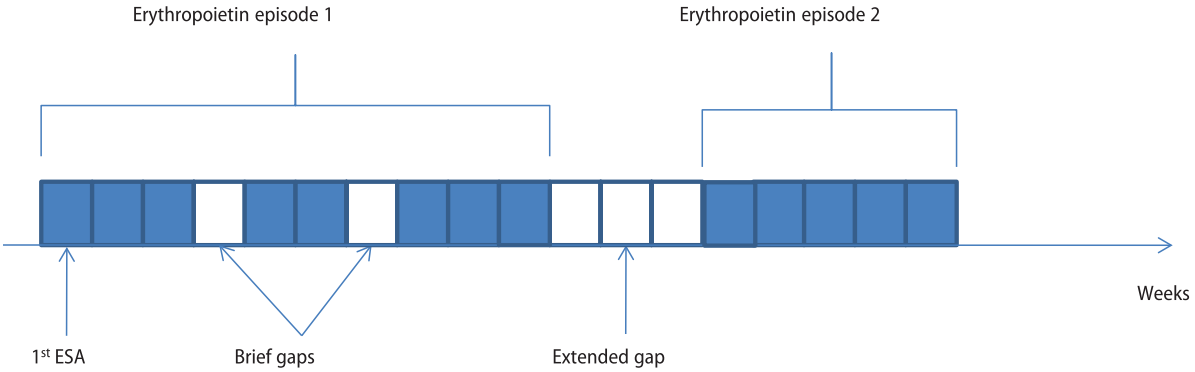
**March 2008.** JCO study by Smith et al. suggests that ESAs do not reduce transfusions and are associated with an increased incidence of cardiovascular events, thrombovascular events, and death in cancer patients who are anemic and taking darbepoetin, but are not receiving chemotherapy.

**July 2008.** FDA orders Amgen to make safety-related labeling changes: ESAs are not indicated for curable cancer patients and should not be used for chemotherapy patients whose hemoglobin levels are greater than or equal to 10 g/dL.

**February 2010.** FDA approves REMS for ESAs.

NOTES: [a]Abbreviations:
FDA—U.S. Food and Drug Administration
ODAC—Oncologic Drugs Advisory Committee
DAHANCA—The Danish Head and Neck Cancer Group
ESA—Erythropoiesis-Stimulating Agents
CMS—Centers for Medicare & Medicaid Services
ASCO—American Society of Clinical Oncology
ASH—American Society of Hematology
JAMA—The Journal of the American Medical Association
JCO—Journal of Clinical Oncology
REMS—Risk Evaluation and Mitigation Strategies
SOURCE: Authors' analysis.

## Appendix B. Measurement of erythropoiesis-stimulating agent (ESA) treatment episodes




NOTES: The first treatment episode began at the first week there was a claim for an ESA and continued weekly until there was a gap in treatment of three weeks for epoetin alfa or six weeks for darbepoetin alfa.
Additional treatment episodes began at the week of the first prescription claim following a gap in treatment.
One week was added to the episode length of each darbepoetin episode to account for the extended half-life of darbepoetin.
SOURCE: Authors' analysis.