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Impacts of Black Box Warning, National Coverage Determination, and Risk Evaluation and Mitigation Strategies on the Inpatient On-Label and Off-label Use of Erythropoiesis-Stimulating Agents

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Impacts of Black Box Warning, National Coverage Determination, and Risk Evaluation and Mitigation Strategies on the Inpatient On-Label and Off-label Use of Erythropoiesis-Stimulating Agents

A dissertation submitted in partial fulfillment of the requirements for the degree of
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This dissertation is dedicated to my father, Prasert Sitasit, my sole inspiration for the pursuit of this graduate degree. Dad, my success would not be possible without your constant support and encouragement.

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Abstract

IMPACTS OF BLACK BOX WARNING, NATIONAL COVERAGE DETERMINATION, AND RISK EVALUATION AND MITIGATION STRATEGIES ON THE INPATIENT ON-LABEL AND OFF-LABEL USE OF ERYTHROPOIESIS-STIMULATING AGENTS

By Arpamas Seetasith, PhD

A dissertation submitted in partial fulfillment of the requirements for the degree of
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Background: FDA black box warning, Risk Evaluation and Mitigation Strategies (REMS), and CMS national coverage determination (NCD) aim to reduce inappropriate use of erythropoiesis-stimulating agents (ESAs) that are widely used in anemic patients. Previous studies have not linked specific safety interventions to changes in ESA utilization patterns in the inpatient settings nor assessed such interventions on off-label use of the drugs. Ineffectiveness of the intervention and lag time between such interventions and the observed change in clinical practice could lead to serious clinical outcomes. In addition, such interventions may unintentionally reduce on-label and some off-label use of ESAs considered "appropriate" in patients who could otherwise benefit.

Objectives: The primary aim of the study is to quantify the impacts of the (1) addition of black box warning, (2) implementation of NCD, and (3) institution of REMS on ESA on-label and off-

label utilization patterns of adult inpatients. Demographic, clinical condition, physician, and hospital characteristics of ESAs users by their use category are also described in detail.

Methods: Electronic health records in Cerner Database from January 1, 2005 to June 30, 2011 were used. The use of the two erythropoietic drugs: epoetin alfa and darbepoetin alfa were categorized into three groups using ICD-9-CM diagnoses and procedures codes and patients' medication information. The three categories were (1) on-label use (approved by the FDA); (2) off-label use supported (use for the indications not approved by the FDA, but there is strong clinical evidence to support its use); and (3) off-label use unsupported (use for the indications not approved by the FDA and lacking clinical evidence). The immediate and trend impacts of the interventions on the proportion of ESAs prescribed for each usage category between 2005 and 2011 were assessed using an interrupted time series technique. The likelihood of receiving ESAs among patients with on-label, off-label supported, off-label unsupported indications was assessed using a generalized estimating equation approach with binary logistic regression technique, clustering for hospitals and controlling for potential confounders such as patient characteristics, patient clinical conditions, physician specialty, and hospital characteristics.

Results: During the study period, there were 111,363 encounters of ESA use. These encounters represented 86,763 patients admitted to Cerner health system between January 1, 2005 and June 30, 2011. Of these patients, 66,121 were prescribed epoetin alfa only (76.2%); 20,088 darbepoetin alfa only (23.2%); and 554 were prescribed both epoetin alfa and darbepoetin alfa (0.6%). Forty-nine percent of the patients used ESAs for the on-label indications, 8.6% for off-label supported indications, and 42.7% for the off-label unsupported indications. The main uses of ESAs in our sample were for CKD (ONS, 41.1%) and chronic anemia (OFU, 31.8%). From 2005 to 2010, the proportion of visits with ESA ONS and OFS use decreased 53.2% and 81.9%,

while ESA OFU increased 112.6%. Results from binary logistic regression using GEE model showed overall decreasing trends in ESA use for the on-label and off-label supported indications, but not off-label unsupported indications. REMS had no impact on the odds of receiving ESAs among patients with on-label and off-label conditions. Black box warning reduced the odds of being prescribed with epoetin alfa in patients with off-label unsupported conditions by 40%. It was also associated with 4% and 15% per month reduction in the odds of using darbepoetin alfa in patients with off-label supported and unsupported conditions. Lastly, there was a significant decline in all categories of ESA use the month after Medicare national coverage determination was implemented. The impact of NCD ranged from a 20% reduction in the odds of off-label supported use to a 37% reduction in on-label use. Age, gender, race, source of payment, admission type, clinical complexity, discharge disposition, and hospital size were significant associated with ESA use on-label and off-label.

Conclusion: This study was the first to determine the impact of safety interventions on ESA on-label and off-label utilization patterns in the inpatient settings using the Cerner database. We demonstrated lag between the interventions and observed change in clinical practice, and the relative impacts of three types of safety interventions on on-label and off-label ESA use in the hospital settings. The indirect impact of the reimbursement change was the potential unintended consequence of reducing the likelihood of receiving ESAs for a patient with indicated conditions who could have otherwise benefited from the drugs.

CHAPTER 1

Introduction

Overview of the document

This dissertation was designed to assess the relative impacts of three events, the revision of product label to include a black box warning, restrictive reimbursement policy from the Center for Medicare and Medicaid Services for the National Coverage Determination (NCD), and implementation of the Risk Evaluation and Mitigation Strategies (REMS) program, on the on-label and off-label use of erythropoiesis-stimulating agents (ESAs) in the inpatient settings in the United States between January 2005 and December 2011.

This introductory chapter provides an overview of the study, background information necessary for the understanding of study significance, conceptual frameworks, objectives, and clinical and political implications of this study. The second chapter provides extensive background of related topics including potential confounding factors and systematically reviews existing literature. Methodology and database used in this study are described in Chapter 3, followed by results in Chapter 4. Discussions and comments are concluded in Chapter 5.

Background

Anemia is a condition characterized by low hemoglobin (Hb) level or red blood cell volume. According to the World Health Organization criteria, anemia is marked by the level of hemoglobin less than 12 g/dL for women and <13 g/dL for men. This decrease in oxygen-carrying capacity of the circulation system results in symptoms such as fatigue, faintness, chest pain or shortness of breath which may affect one's ability to perform activities of daily living and also quality of life (QoL).[1] Anemia is second to tuberculosis as the world's most prevalent health condition; it was estimated that anemia affects 1.62 billion people, one-quarter of the world population.[2] Numerous underlying pathologies that lead to anemia have been identified. Causes of anemia range from blood loss, nutrition deficiency (iron, vitamin B12, and folic acid) morphologic abnormality of hemoglobin or red blood cells (beta-thalassemia and sickle cell anemia), and other chronic diseases such as inflammation, malignancy and chronic kidney disease (CKD).[2]

Anemia is common in patients with chronic kidney disease and a frequent side effect in cancer patients being treated with chemotherapy. Approximately half of patients with cancer[3, 4] or CKD[5] suffer from anemia at some point in their disease course. Severe anemia is linked to increased risks of comorbidities in the elderly such as falls, dementia, depression, and heart failure.[6] Severe anemia often requires blood transfusion, an event which carries its own risks. These risks include transmission of infectious agents, acute lung injury, and development of alloantibodies which reduce a patient's ability to receive organ transplant.[7] Acquisition and storage of blood for transfusion requires special procedures and is costly. Apparently, anemia is economically burdensome to health care payers. It has been estimated that anemic patients have a two-fold greater average annualized medical cost of that for non-anemic patients.[8]

The production of red blood cells, termed erythropoiesis, is regulated by the supply and demand for oxygen in the body. In response to low tissue oxygen level, peritubular fibroblasts of the kidney increase their production of endogenous erythropoietin which in turn acts on the erythroid progenitors in the bone marrow to stimulate late differentiation and maturation of red blood cells. Erythropoiesis-stimulating agents (ESAs) are a class of biological medications approved as an alternative to blood transfusions, the traditional treatment of anemia. Recombinant human erythropoietin possesses the same biological effects as endogenous erythropoietin. Three drugs in this class are marketed for use in the United States: epoetin alfa (Procrit®, Johnson & Johnson's Ortho Biotech Unit and Epogen®, Amgen), darbepoetin alfa (Aranesp®, Amgen), and methoxy polyethylene glycol-epoetin beta (Mircera®, Roche).

Epoetin alfa, the first human recombinant ESA was first approved in 1989 for anemia associated with chronic kidney failure.[9] The drug was later approved to treat chemotherapy-induced anemia, treat zidovudine-related anemia in HIV infected patients, and use as a prophylaxis of allogeneic blood transfusion in non-cardiovascular surgeries. Following in 2001, darbepoetin alfa was introduced into the market for treating anemia associated with chronic kidney failure and later for chemotherapy-induced anemia.[10] With an addition of N-glycosylation at the two sites of epoetin alfa, darbepoetin possesses a three-fold longer half-life for erythropoietin receptors relative to erythropoietin alfa[11], implying greater potency and extended dosing interval that may improve patient compliance and better control anemia. Two other ESAs not available in the US are methoxy polyethylene glycol-epoetin beta, Mircera[12] and epoetin beta, NeoRecormon® (Roche).

The use of erythropoietins as an alternative to red blood cell transfusion therapy represents a major advancement in anemia treatment and has been the mainstay of therapy in

anemia associated with chronic kidney failure since its approval. Global sales of erythropoietin products dramatically increased 95% from 2004 to $12.3 billion in 2005. In that same year, procrit and epogen, each with $3.0 billion US sales, ranked among the top 10 drug products in the United States according to sales.[13] Since the initial entry of ESAs onto the market, the drugs have found their place in the treatment of anemia outside their initial approved uses. This broad array of use includes anemia of chronic heart failure, rheumatoid arthritis, and beta thalassemia. The use of ESAs off-label, the term which refers to the prescribing of medications in a manner different from that approved by the FDA, is common.[14] It was estimated that more than half of ESAs prescribed between 2001 and 2004 were for off-label purposes.[15] Among those off-label prescriptions for ESAs, three-quarters were for indications supported by scientific evidence.[15]

Benefits of ESAs in anemia treatment have been extensively elaborated. Correction of anemia with ESAs translates to a relief of its common symptoms like fatigue, improving one's physical ability and quality of life. The approval of epoetin alfa and darbepoetin, the two ESAs widely used in the United States by the FDA was based mainly by the evidence of reduced needs for blood transfusion in anemic patients. The use of ESAs is thus a promising anemia treatment alternative to blood transfusion. Benefits of ESAs extend beyond a simple reduction in transfusion requirements. ESA therapy in less severe CKD patients has been shown to delay time to dialysis.[16] In addition; a meta-analysis of 60 studies found that anemia is an independent risk factor of death in cancer patients[17] and thus correcting it could improve survival.

Despite their clinical benefits, ESAs have been associated with increased risks of adverse events such as cardiovascular complications, hypertension, and red cell aplasia. In 1998, the Normal Hematocrit Cardiac Trial (NHCT), the first large randomized controlled trial (RCT) aimed at determining the outcomes of treating anemia with epoetin alfa in patients with cardiac

disease who were undergoing hemodialysis was published. Patients who were randomized to receive high dose epoetin alfa to maintain high hematocrit level of 42 percent had 1.3 times higher risk of death or nonfatal myocardial infarction compared to those in the group targeted to lower hematocrit level of 30 percent though this finding was merely a near statistically significant one.[18] A tipping point in ESA therapy started in November 2006 when two RCTs, the correction of hemoglobin and outcomes in renal insufficiency (CHIOR) and cardiovascular risk reduction by early anemia treatment with epoetin beta (CREATE), were published. CHIOR, the largest trial, showed that CKD patients treated with epoetin alfa dosed to a higher target hemoglobin concentration of 13.5 g/dL were at a significantly increased risk for serious cardiovascular events including thrombosis, congestive heart failure, and stroke compared to the treated patients whose hemoglobin was targeted at 11.3 g/dL.[19] Results from another large trial published at the same time showed no benefit or harm of early correction of anemia with epoetin beta in reducing the risk of cardiovascular events in anemic patients with CKD.[20]

Safety concerns of ESA use among patients with cancer were raised with the publication of the two pharmaceutical company-sponsored phase III randomized clinical trials. Patients randomized to receive erythropoietin in the Breast Cancer Erythropoietin Survival Trial (BEST) [21] and the Advanced Head-and-Neck Cancer Treated with Radiotherapy (ENHANCE) [22] showed significant worsening of overall survival and an increase in venous thromboembolic events. A meta-analysis of 57 clinical trials evaluating the use of ESAs in certain types of cancer published in 2006 also pointed toward their negative effects on survival.[23] Similarly, the most recent Danish Head and Neck Cancer Study (DAHANCA 10), terminated early in October 2007, reported in their interim analysis that darbepoetin alfa had shown a low likelihood in improving patient outcomes.[24] Cancer progression acceleration was observed in several studies include the

ENHANCE trial of head and neck cancer, BEST trial of breast cancer, and EPO-CAN 20 of non-small-cell lung cancer.[25] An exception was found in one study of 600 previously untreated patients with extensive-stage small-cell lung cancer where significant difference in progression-free survival was not found.[26] While the mechanisms by which ESAs enhance tumor progression is unclear, it is plausible that the drug stimulates erythropoietin receptors commonly expressed in tumor cells, promoting tumor growth. The results from 154 subjects in the ENHANCE trial support this hypothesis; ESAs were found to be harmful in two thirds of patients with erythropoietin receptor-positive tumors but beneficial in those with receptor-negative tumors.[27]

As evidence pointed toward potential harm associated with the use of high dose ESAs, the FDA issued a series of public health advisories.[28] On November 16, 2006, the FDA issued a public health advisory alerting ESA prescribers to the results from CHIOR trial, emphasizing on maintaining the recommended target hemoglobin range of 10 to12 g/dL in all patients.[29] A combined effort came from Amgen, the manufacturer of epoetin alfa and darbepoetin alfa, sending out a series of dear doctor letters alerting physicians of the FDA updates. In January 26, 2007, Dear Healthcare Professional Letters were sent to highlight the results from recent clinical trials and recommend caution in the off-label use of darbepoetin alfa in cancer patients. The letter specifically warned against the use of ESAs in non-chemotherapy cancer patients and its increased risk of death in this population.[30] These warnings were expected to alert prescribers of risks associated with the use of ESAs at high doses and their use in non-indicated populations. Two similar public health advisories were issued in March and November 2007.

Finally, ESA labeling was revised to include a black box warning on March 9, 2007 to address these concerns. The warning advised prescribers to use the lowest ESA dose possible

that gradually increases hemoglobin to sufficient levels to avoid blood transfusion.[31] An update of the black box warning on March 7, 2008[32, 33] added the findings from two additional clinical studies, Preoperative Epirubicin Paclitaxel Aranesp Study (PREPARE) in patients with breast cancer, and the National Cancer Institute Gynecologic Oncology Group (COG-19) in patients with cervical cancer. These trials showed increased mortality and shortened time to tumor progression in cancers patients treated with Aranesp compared to those who did not receive ESAs.[34, 35]

To supplement the black box warnings, the FDA required on March 24, 2010 that all ESA drugs be prescribed under the Risk Evaluation and Mitigation Strategies (REMS) program.[36, 37] This REMS program requires physicians prescribing ESAs to cancer patients to complete and receive documentation of certification of the online ESA APPRISE Oncology Program Training. To complete such training, physicians must acknowledge that they understand the treatment recommendations and the specific risks associated with the use of ESAs. Also, the program requires prescribers to counsel their patients regarding risks and benefits of ESAs prior to dispensing the medications. More importantly, physicians not enrolled in the ESA APPRISE Oncology program are prohibited from prescribing ESAs for use in cancer patients. The implementation of the ESA REMS program is designed to bring about high awareness of the warnings issued and risks associated with them and increase physician compliance with ESA guidelines. The impact of REMS ESA inpatient prescribing remains unknown.

Recombinant erythropoietin was first approved for Medicare outpatient reimbursement in June 1989[38] when it was reimbursed for up to 80% of the allowed charge.[39] Since that time, ESA reimbursement in Medicare beneficiaries has been through many changes. In January 1991, the Medicare payment policy for ESA treatment of dialysis patients changed from a fixed

payment to a payment based on the doses of ESA administered[40] to increase the use of ESAs in ESRD patients and to improve Hb levels. In September 1997, the Hematocrit Measurement Audit (HMA) policy was implemented to halt reimbursement of ESAs if patient Hb level was greater than 12 g/dL[41] as recommended by the NKF-DOQI clinical practice guidelines.[42] With the rise in ESA utilization, ESAs became Medicare's largest pharmaceutical expense, at approximately $20 billion in 2004.[43] In April 2006, payments for ESA dosing was capped at 500,000 IU/ month for dialysis patients and a 25% dose reduction was mandated for patients whose hemoglobin level exceeded 13 g/dL in the prior month.[44]

National Coverage Determination (NCD) is a nationwide policy initiated by CMS to ensure that services and treatments provided to their beneficiaries are reasonable and necessary.[45] NCD identifies the nationally covered indications for which Medicare will reimburse. On July 30, 2007, NCD restricted payment for ESAs in cancer-related anemia. Nationally covered indications include ESA treatment for anemia secondary to myelosuppressive anti-cancer chemotherapy in solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia. However, CMS no longer pays for the use of ESAs in anemia due to radiotherapy; anemia of cancer not related to concurrent chemotherapy including anemia of bone marrow fibrosis; anemia resulted from the treatment of myelogenous leukemia, chronic myelogenous leukemia, or erythroid cancers; prophylactic use of chemotherapy-associated anemia; or use to reduce tumor hypoxia (which can inhibit radiotherapy and oxygen-dependent chemotherapy effectiveness). Reimbursement is not provided for patients with uncontrolled hypertension even when used to treat of anemia associated with chemotherapy. Additionally, under NCD, Medicare does not reimburse ESA use in anemia due to folate, vitamin B12, and iron deficiencies; anemia of hemolysis; anemia of bleeding; and its use in patients with erythropoietin-type resistance due to

neutralizing antibodies.[46] In addition to indication restrictions, CMS restricted the use of ESAs exclusively to patients whose hemoglobin level is lower than 10 g/dL prior to ESA initiation or maintenance as such drugs "lacks adequate data to establish proof of no harm."[47] Recommendations on dosing, dosage escalation and reduction, discontinuation, and treatment duration were also specified in the NCD.[48] However, NCD restrictions conflicted with FDA-approved labeling and professional society guidelines on ESA initiation, dosage escalation, dosage reduction, and definition of response, creating confusion among health care providers.[49] According to the letters written on behalf of professional societies to CMS, the decision was "inconsistent with available scientific evidence and national guideline on ESA use" and CMS was urged to reconsider "in order to avoid further confusion and harm to Medicare beneficiaries."[50] Despite criticisms from several professional associations that the decision could lead to greater chances for patients subjected to blood transfusion and endanger cancer patients, the NCD was officially implemented on April 7, 2008.

NCD restrictions are not meant to impact ESA use for inpatient care because ESAs are included into the Diagnoses-Related Group (DRG) prospective payment system. Under the DRG system, reimbursement is given for a patient's condition, not the drugs used to treat that condition. Thus, the change in the coverage determination would not affect the payment of ESAs in the hospital setting. However, physicians who work in hospitals often work in outpatient settings where ESA coverage restrictions apply. Thus, the policy change may indirectly change prescribing in both setting. Moreover, the restriction may influence prescribing patterns for non-Medicare payer types because physicians typically treat more than just Medicare patients. As a result, NCD policies may impact off-label use of ESAs outside of their intended purpose. It is of

our interest to determine the impact of Medicare national coverage determination on ESA use in the inpatient settings where the determination does not directly apply.

In summary, a timeline of significant events associated with ESA utilization since its approval is presented in Figure 1.1. These include approval indications for ESA treatment, publications of scientific evidence from larger clinical trials, and interventions from manufacturers and government regulatory agencies.

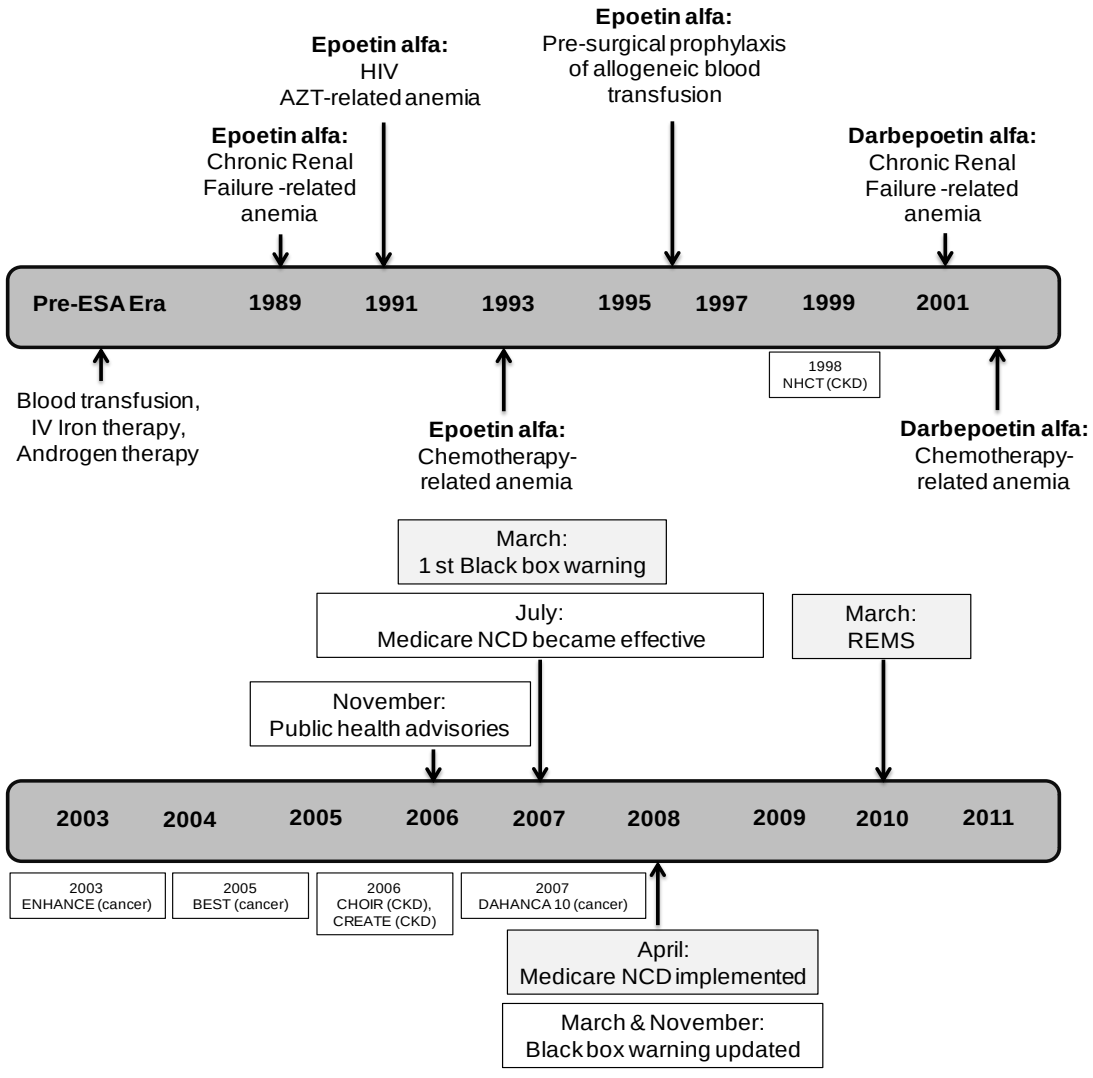

Figure 1.1 Timeline for ESA treatment, scientific evidence from clinical trials, and interventions from government regulatory agencies between 1989 and 2010 (adapted from Arbuckle et. al. 2008)[49]

Conceptual Framework

This study is based on the diffusion of innovation of health care framework and an evidence-based medicine framework. Diffusion of innovation refers to "the process by which an innovation is communicated through certain channels over time among the members of a social system."[51] According to Everett Roger's Diffusion of Innovation model, the spread of innovations follows a sigmoid pattern (the S-shaped curve), describing three stages of adoption: the early slow phase characterized with only the first few individual adopting the innovation, a rapid middle phase, and a slow third phase. The model also illustrates five categories of adopters characterized by their relative rates of adoption of innovations: innovators, early adopters, early majority, late majority, and laggards.[51, 52] Rates of diffusion of innovation vary by various factors. The main factor includes perceptions of the innovations viewed by stakeholders, which predict between 49% and 87% of the variance in the rates of spread of a change. These perceptions include (1) the perceived benefit of the change; (2) compatibility of the innovation with the current values, belief, and needs of the individuals as well as their past history; (3) complexity of the proposed innovation; (4) trialability of the innovation without total commitment or minimal investment; and (5) the extent to which potential adopters observe the adoption by others (observability).[51]

The process by which information is disseminated is similar to the diffusion of innovation. Whether a prescriber will adjust their prescribing pattern to new information depends on several factors such as physician characteristics and the nature of the intervention of which knowledge is disseminated itself. Since high doses of ESAs given to cancer patients or for its use for unsupported purposes could lead to serious adverse events including death, the stakes are significant for reducing the time lag between the interventions aiming at reducing

inappropriate use of ESAs in clinical practice. It is therefore our interest to assess the relative impacts of the FDA black box warning, and FDA REMS, and National Coverage Determination on the rate of change in prescribing patterns.

A systematic classification of indications for the three erythropoietic drugs into three drug use categories will be based on an evidence-based medicine (EBM) framework which provides objective evidence about the effectiveness of interventions through the use of research methods that minimize the risks of bias, such as randomized controlled trials. Evidence synthesized in such manner is considered best to inform treatment decisions.[53]

Objectives

The proposed study aims to quantify the impacts of FDA interventions (adding a black box warning to drug labeling and the addition of a REMS program) and Medicare reimbursement restrictions established by the NCD on the on- and off-label use of ESAs among adult inpatients. The secondary objective is to investigate factors associated with the odds of being prescribed ESAs, controlling for the interventions and other confounding factors.

Study Implications

Correction of anemia is necessary as it has been shown to improve patients' health status and quality of life.[54] Approximately 90% of hemodialysis patients in the US received an ESA[55] to avoid blood transfusion. The adoption of ESAs in clinical practice of anemia has alleviated some of the complications associated with blood transfusion and the issues of constrain blood limited supply. However, concerns regarding serious risks of ESAs have led regulatory authorities to intervene with both regulatory communications and reimbursement changes.

These interventions can lead to have positive outcomes (reasonable and necessary drug use) or negative outcomes (reduced on-label use considered "appropriate" to patients who could otherwise benefit). This study will quantify impacts of the communications from four sources: a public health advisory, an FDA black box warning on ESA labeling, ESA APPRISE Oncology program under REMS, and a reimbursement restriction under CMS National Coverage Determination for ESAs. We hope to demonstrate their relative immediate and trend impacts on ESA prescribing among patients admitted to the U.S. hospitals.

Previous studies that investigated the impacts of FDA risk communications on ESA use did not link specific interventions to the level change in ESA use nor that for the off-label indications for patients treated in the inpatient settings. The knowledge of relative impacts of the interventions would help policymakers make informed decision when designing risk communications and healthcare policies intending to shape prescribing patterns in the future.

To our knowledge, no study has assessed the linkage between FDA risk communication including public health advisory, black box warning issuance, and REMS implementation, or the CMS National Coverage Determination on the prescribing patterns of erythropoiesis-stimulating agents in the inpatient settings. More importantly, the impacts of such interventions on the off-label use of ESAs have never been investigated. Our proposed study quantified the immediate and trend impacts of both on on-label and off-label ESA prescribing and assess factors associated with ESA prescribing patterns in the inpatient settings between 2005 and 2011.

CHAPTER 2

Literature Review

This chapter has been divided into four parts: 1) an overview of ESA treatment of anemia for the on-label and off-label indications as classified by the evidence-based medicine framework; 2) regulatory risk communications and health policies shaping prescribing patterns; 3) potential confounding factors associated with prescribing patterns and methods to control for confounding; and 4) a systematic review of existing studies. This chapter concludes with a summary of literature gaps, research questions, research hypotheses, and specific aims formulated as a result of the literature evaluation.

Erythropoiesis-stimulating agent treatment of anemia overview

This section is further subdivided into two parts. The first part provides an overview of an official compendium, Thomson Micromedex Drugdex®, the system adopted in this study to describe the classification of ESA use by indications. The second part reviews treatment regimens, guidelines, and supporting evidence for the all ESA indications listed in DRUGDEX. Empirical studies of ESA off-label use in the United States are also summarized at this end of this section.

1. Classification System

Official compendia refer to nationally recognized sources of drug information including the US Pharmacopoeia (USP), National Formulary, or any supplements to them. DRUGDEX system (Thomson Micromedex, Greenwood Village, CO) is recognized as a pharmaceutical compendium that provides reliable evidence-based evaluation for the on-label and off-label uses

of prescription drugs listed in the USP Dispensing Information.[56] Information on strength of scientific evidence supplied by DRUGDEX can be used to assess the level of medical evidence supporting the use of ESAs in an off-label manner.

The three dimensions of drug use evaluated by DRUGDEX are efficacy, strength of recommendation, and strength of evidence. Strength of recommendation is categorized into 4 classes: Class I, IIa, IIb, III, and in-determinant. Similar to that, strength of evidence as supported by clinical studies is presented in 4 levels: Category A, B, C, and no evidence. Lastly, drug efficacy is subcategorizes into 4 groups: effective, evidence favors efficacy, evidence is inclusive, and ineffective. The details of recommendation levels, strength of evidence scale and efficacy ratings defined by DRUGDEX are listed in Table 2.1, 2.2, and 2.3, respectively.

Table 2.1 Strength of Recommendations specified by DRUGDEX

Level	**Decision to recommend**	**Definition**
Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa	Recommended, In most cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb	Recommended, In some cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not Recommended	The given test, or treatment is not useful, and should be avoided.
Class In-determinant	Evidence Inconclusive	-

Table 2.2 Strength of Evidence for use of a drug specified by DRUGDEX

Level	Definition
Category A	Evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B	Evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C	Evidence is based on data derived from: Expert opinion or consensus, case reports or case series.
No Evidence	-

Table 2.3 Efficacy ratings of a drug specified by DRUGDEX

Efficacy rating	Definition
Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Evidence favors efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Evidence is inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

2. ESA use in anemia treatment

A review of clinical literature for all ESA indications listed in DRUGDEX is provided in the following section. The review is based on clinical trials that support the FDA approval of such indications or scientific evidence reported in DRUGDEX. Clinical guidelines and recommendations, if available, are also provided. This review of anemia treatment is limited to adults only, as this population aligns with the study inclusion criteria. A summary of DRUGDEX evaluation of scientific evidence ratings of such use of epoetin alfa and darbepoetin alfa is provided in Table 2.4 and 2.5, respectively.

2.1 FDA-approved Indications

Approved indications of ESAs are drug specific. Epoetin alfa, the first erythropoietin in the market was approved for use in anemia of chronic kidney disease, chemotherapy induced anemia, zidovudine-related anemia in HIV infected patients, and prophylaxis of allogeneic blood transfusion in non-cardiovascular surgeries. The second generation ESA, darbepoetin alfa is approved for two indications: anemia of chronic kidney disease and chemotherapy induced anemia.

Anemia of Chronic Kidney Failure: epoetin alfa and darbepoetin alfa

Epoetin alfa has been shown to stimulate erythropoiesis and hence normalize Hb level in chronic kidney failure patients regardless of their dialysis requirement.[57] A meta-analysis of sixteen studies of 982 end-stage renal disease patients receiving epoetin alfa reported 87% effectiveness of the treatment defined as at least a 0.06 increase in hematocrit or a 2 g/dL increase in hemoglobin.[58] In a subsequent study, erythropoietin was proven to have no negative effect on blood pressure and be effective in correcting Hb values in adult with cardiac disease

and hemodialysis-dependent ESRD patients.[59] Similar improvement in Hb level was observed in non-dialysis patients. In a large multi-center, open-label, single-arm, non-randomized trial, epoetin alfa dosed subcutaneously once weekly at 10,000 IU for 16 weeks significantly led to an increase in the mean Hb level of 2.7 g/dL.[60] Likewise, darbepoetin alfa, when given at 0.45 mcg/kg once a week was proven to be as effective as 50 IU/kg epoetin alfa two to three times weekly in correcting anemia in epoetin-naïve dialysis and renal insufficiency patients.[61, 62] The drug was also able to maintain stable Hb concentration in CKD patients when given at an extended dosing interval once monthly.[63, 64] Despite its efficacy, both erythropoietic drugs dosed to high target Hb level was shown to be associated with greater risk of all-cause mortality compared to that of lower Hb group in a meta-analysis of nine randomized controlled trials of 5,143 patients with chronic kidney disease.[65]

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) published guidelines for the management of anemia in CKD patients in 2006. After the 2007 update of the target Hb concentration, no further change in the guidelines was made. In dialysis and nondialysis patients with CKD receiving ESA therapy, a target Hb level between 11.0 g/dL and 12.0 g/dL is recommended. The KDOQI guidelines also emphasize the importance of not exceeding the target HB level beyond 13 g/dL.[66] Of note, this Hb target recommendation does not align with the darbepoetin alfa current labeling, revised in 2011, which suggests physicians to initiate ESA therapy only when Hb level falls below 10 g/dL. As for the dose, an ESA starting dose often depends upon the initial and target Hb level of a patient[67] though a starting dose of epoetin alfa at 50 to 100 units/kg three times weekly is recommended.[9,10] In general, because of a longer half-life of darbepoetin alfa compared to epoetin alfa, darbepoetin alfa is recommended to be administered once weekly in patients who

are receiving epoetin alfa 2 to 3 times weekly and once every 2 weeks in once-weekly epoetin alfa patients.[68] It is important to halt the therapy once Hb level exceeds 10 g/dL for nondialysis and 11 g/dL for dialysis patients.[10] On the other hand, if a patient's Hb level has not increased by more than 1 g/dL after 4 weeks of the initiation of the therapy, ESA dose may be increased by 25%.[10]

Chemotherapy-Induced Anemia (CIA): epoetin alfa and darbepoetin alfa

Several trials demonstrated efficacy of epoetin alfa and darbepoetin alfa in improving Hb levels and reducing the need for blood transfusion.[9,10] Epoetin alfa dosed subcutaneously at 40,000 IU once weekly led to a mean increase of 1.8 g/dL with a mean final Hb level of 11.3 g/dL in patients receiving chemotherapy for nonmyeloid malignancies after the maximum of 16 treatment weeks.[69] Results from a large community-based study also found a similar increase in Hb level of 2 g/dL and a progressive decline in the percentage of patients requiring transfusion during ESA treatment.[70] Similarly, darbepoetin alfa, both dosed weekly or at an extended-dosing regimen every 3 weeks was more effective than placebo in increasing Hb values of anemic cancer patients receiving chemotherapy.[71-74] Based on their clinical efficacy, epoetin alfa and darbepoetin alfa are used widely for the treatment of chemotherapy-induced anemia in nonmyeloid cancer patients.

Three major guidelines are currently being used today in the ESA treatment of chemotherapy-induced anemia: the American Society of Clinical Oncology and the American Society of Hematology (ASCO/ASH), the European Organisation for Research and Treatment of Cancer (EORTC), and the National Comprehensive Cancer Network (NCCN).[75] In 2002 ASCO and ASH published their clinical practice guidelines for epoetin alfa using medical literature

published between 1985 and 1999. The guideline suggests the use of epoetin alfa in CIA patients with Hb level < 10g/dL at 150U/kg, three times a week. Epoetin alfa dose should be escalated to 300 U/kg three times a week if a patient fails to respond after 4 weeks. The target Hb level is recommended at 12 g/dL, with the dose of epoetin alfa adjusted to maintain a patient's Hb at this level. Another reputable source of ESA treatment recommendation is the 2004 EORTC guidelines which include evidence of both epoetin alfa and darbepoetin alfa between 1996 and 2003. The EORTC guidelines recommend clinicians to initiate ESA treatment at Hb level of 9 to 11 g/dL, on the basis of anemia symptoms while targeting a patient's Hb level at 12 to 13 g/dL. Lastly, NCCN, an alliance of 19 major cancer centers in the United States, developed several guidelines in cancer treatment including supportive care.[6] Updated in 2011 the NCCN clinical practice guidelines suggest physicians to consider ESA treatment of anemia in cancer patients with chronic kidney disease, patients undergoing palliative treatment, and patients on myelosuppressive chemotherapy without identifiable cause of anemia.[76] ESAs should not be prescribed for a treatment of anemia in cancer patients under myelosuppressive chemotherapy with curative intent such as early stage breast cancer, Hodgkin lymphoma, non-Hodgkin's lymphoma, testicular cancer, and early stage non-small cell lung cancer. Additionally, co-administration of iron supplement is not required but should be considered with regard to a patient's functional iron deficiency status.

Anemia in zidovudine-treated HIV-infected Patients: epoetin alfa only

Zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI), is one of the most commonly used antiviral drugs for HIV infection. Despite its effectiveness, the prevalence of zidovudine-induced anemia is high (5.42-9.62%).[77-79] Epoetin alfa is the only erythropoietic drug approved for treating anemia in zidovudine-treated HIV-infected patients; results from four

placebo-controlled trials suggest that it could significantly increase hematocrit and reduced blood transfusion requirements in the treatment group compared to the placebo group.[80-83] Nonetheless, correcting anemia related to zidovudine use in HIV-infected patients with epoetin alfa is encouraged only in patients receiving zidovudine ≤ 4200 mg/week with endogenous erythropoietin level less than 500 mUnits/mL. This is because patients with endogenous erythropoietin level greater than that appear to be nonresponsive to epoetin alfa therapy. To treat anemia due to adverse reaction of zidovudine, epoetin alfa is recommended at 100 units per kg body weight, three times weekly.

Prophylaxis of allogeneic blood transfusion in non-cardiovascular surgeries: epoetin alfa only

Epoetin alfa was approved for use as a prophylactic of allogeneic blood transfusion in patients with Hb level greater than but not exceeding 13 g/dL undergoing elective non-cardiovascular surgeries that are at risk of perioperative blood loss, but are not willing to donate autologous blood. In patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥ 2 units of blood, epoetin alfa dosed subcutaneously at 300 units/kg 10 days before surgery, on the day of surgery, and for 4 days after surgery, significantly reduced the need for blood transfusion compared to the placebo group, only when pretreatment Hb level was greater than 10 but not more than 13 g/dL.[84]

2.2 FDA-Unapproved Indication

Several off-label uses of ESAs are documented in DRUGDEX. These indications include the treatment anemia in cancer patients not currently on active chemotherapy, anemia of congestive heart failure, prematurity, puerperium, multiple myeloma, myelodysplastic syndrome, myelofibrosis, rheumatoid arthritis, beta thalassemia, anemia due to radiation, and anemia in

hepatitis C patients being treated with a combination of ribavirin and interferon alfa, and their use for blood unit collection for transfusion. The following section review uses of ESAs for the unapproved indications and studies supporting their uses.

Anemia of congestive heart failure

Anemia, a common complication of congestive heart failure (CHF), often leads to poorer cardiovascular outcomes and higher mortality.[85] The prevalence of anemia in CHF is estimated to be as high as 55 percent.[86] An uncontrolled study of ESAs therapy in anemic patients with CHF found that subcutaneous erythropoietin at an average dose of 5,227 units/week is associated with decreased hospitalization and improvement in several cardiovascular aspects including an increase in left ventricular ejection fraction and decline in the New York Heart Association (NYHA) class.[87] DRUGDEX recommends epoetin alfa to be used in some cases of CHF according to the moderate strength of evidence and efficacy report that favors efficacy for this indication.

Anemia due to radiation

Anemia is widespread in cancer patients undergoing local radiotherapy. An anemia prevalence study using Hb level < 12 g/dL as a cut-off point found that anemic patients increased from 41% at presentation to 54% by the end of radiation.[88] The majority of patients with almost all tumor types have developed anemia and the prevalence of anemia is found to be extremely high in patients with uterine-cervical tumor (75% and increased to 79% after radiation). Epoetin alfa dosed at 200 units/kg/day for 5 consecutive days for up to 7 weeks during radiotherapy was found to significantly increase Hb level in anemic patients with lung, uterine-cervical, prostate, or breast cancer during a randomized, open-label trial of 48 patients.[89] As a result, DRUGDEX

recommends epoetin alfa to be used in certain cases of radiotherapy according to the moderate strength of evidence and efficacy report that favors efficacy for this indication.

Anemia during Puerperium

Iron deficiency during pregnancy and acute blood loss at delivery constitutes a main cause of postpartum anemia.[90] The prevalence postpartum anemia is high in developing countries and was found to be as high as 80%.[91] In a randomized, placebo-controlled trial in which a mother lost an average of 806 mL of blood during delivery, a combination of IV erythropoietin at 300 units/kg/day and IV iron sucrose 200 mg/day given daily for 4 days after the delivery showed to be more effective than placebo or IV iron alone in correcting postpartum anemia.[92] DRUGDEX therefore recommends epoetin alfa to be used in certain cases of puerperium anemia according to the moderate strength of evidence and efficacy report that favors its efficacy.

Anemia of ribavirin and interferon alfa use for treatment of Hepatitis C

Anemia is a common adverse effect observed in 10%-30% of hepatitis C patients receiving ribavirin and interferon alfa combination therapy.[93] This is due to the bone marrow suppression property of interferon and potential red blood cell hemolytic action of ribavirin. Criteria for initiating ESA therapy for hepatitis C treatment-related anemia have been provided based on medical evidence and clinical expert opinion. Physicians may consider using subcutaneous injection of 40,000 IU epoetin alfa weekly (or darbepoetin alfa at 200 mcg weekly, though response is reported to be slower), together with ribavirin dose reduction, to increase Hb level of patients on ribavirin-interferon alfa combination therapy with Hb < 10 g/dL or < 11g/dL but with symptoms of anemia. ESAs and/or ribavirin dosing should be adjusted based on a

patient's Hb level and his response to ESA therapy. Base on the moderate strength of evidence and favorable efficacy reports for this indication, DRUGDEX recommends epoetin alfa to be used in some cases of anemia associated with ribavirin and interferon alfa treatment of HCV-infected patients.

Anemia of multiple myeloma

The cause of anemia observed in more than two thirds of patients with multiple myeloma (MM) is multi-factorial, ranging from the cancer itself, chemotherapy treatment, or deficiency of endogenous erythropoietin.[94] Several studies reported benefits of ESAs in myeloma-associated anemia. A meta-analysis of 39 studies reported 40% effectiveness of erythropoietin in the treatment of anemia of multiple myeloma.[95] Another study shows that 85% of 13 multiple myeloma patients with baseline Hb less than 11.3 g/dL experienced an increase in Hb level of at least 2 g/dL after 5 weeks and a complete resolution of anemia symptoms after receiving 150 units/kg ESAs three times weekly.[96] Recently, consensus guidelines for the management of anemia with ESAs in multiple myeloma were developed by the collaboration of MM specialists known as the International Myeloma Working Group. Once other causes of anemia is ruled out, ESA therapy can be initiated in MM patients with HB level $\leq$ 10 g/dL and in those with higher Hb values but with symptoms of anemia. The guidelines recommend starting epoetin alfa at 40 IU once weekly or 10 IU three times weekly, or darbepoetin alfa 150 mcg once weekly or 500 mcg every 3 weeks. Dose increment is allowable if a patient does not respond but the therapy in non-responding patients should be discontinued within 6-8 weeks.[97] DRUGDEX recommends epoetin alfa to be used in some cases of multiple myeloma according to the moderate strength of evidence and efficacy report that favors efficacy for this indication.

Anemia of myelodysplastic syndrome

Anemia is the most common comorbid condition of myelodysplastic syndrome (MDS), a group of diseases characterized by the malfunction of bone marrow. An MDS patient experiences anemia because of the damaged bone marrow becoming unable to producing sufficient blood cells and approximately 50% of MDS high-risk patients progress to having acute leukemia within 5 years. Risk factors of MDS include certain kinds of cancer treatment such as mechlorethamine and procarbazine, genetic mutation, and smoking. Stem cell transplant is the only curative for MSD but patients are more commonly treated with chemotherapy and/or growth factors including ESAs.[98] Despite significant improvement in Hb level observed in several clinical trials, results show similar rates of overall survival and progression to acute myeloid leukemia[99], and conflicting evidence of transfusion requirement and quality of life associated with ESA treatment.[100] Given as a monotherapy, epoetin alfa subcutaneous treatment of 150 IU/kg three times weekly or 40,000 IU once weekly for 24-26 weeks was found to be associated with 37-68 % erythroid response defined as an increase in Hb or reduction in transfusion requirement in low-risk MDS patients.[101-103] Positive response was also observed with a combination therapy of ESAs and granulocyte colony-stimulating factor (G-CSF).[96, 97] Likewise, the benefit of darbepoetin alfa is also evidenced in a clinical trial of anemic patients with low-risk MDS.[104] As the results of several trials pointed toward favorable erythroid response to erythropoietin in this population, the American Society of clinical Oncology/American Society of Hematology Clinical Practice Guidelines recommend the use of ESAs in low-risk MDS patients whose Hb values approaches 10 g/dL to avoid blood transfusion.[105] In line with ASCO/ASH guidelines, DRUGDEX recommends epoetin alfa to be used in

some cases of myelodysplastic syndrome due to the moderate strength of evidence and efficacy report that favors efficacy for this indication.

Anemia of myelofibrosis

Myelofibrosis refers to the condition by which bone marrow tissues are replaced with fibrous tissue, hindering blood cell productions and resulting in anemia.[106] Profound anemia associated with myelofibrosis is usually treated with transfusion therapy but several small, open-label studies of 7-20 patients suggest the condition occasionally responds to ESAs.[107-111] Epoetin alfa given subcutaneously at 10,000 IU three times weekly was found to be well-tolerated and effective in reducing transfusion requirement and increasing Hb level in myelofibrosis patients with myeloid metaplasia[112] and chronic idiopathic myelofibrosis (CIMF).[113] Due to the small sample size of the trials, DRUGDEX recommends epoetin alfa to be used in some cases of myelofibrosis according to the moderate strength of evidence and efficacy report that favors efficacy for this indication.

Anemia of rheumatoid arthritis

Anemia prevalence in rheumatoid arthritis (RA) is high. A systematic literature review of anemia in RA reveals that between 33% and 60% of RA patients experience mild anemia.[114] More than 60% of anemia cases in RA are classified under anemia of chronic disease in which the increased production of inflammatory cytokines characterized rheumatoid arthritis reduces the response of bone marrow to erythropoietin.[115] A report of two patients with anemia of rheumatoid arthritis showed that erythropoietin dosed at 100 units/kg administered three times weekly for 8 weeks resulted in positive hematologic response but with no change in RA outcomes over a five-month period.[116] According to similar results from other studies,

DRUGDEX recommends epoetin alfa to be used in some cases of RA. The strength of evidence is moderate and favors efficacy for its use in this indication.

Beta Thalassemia

Beta thalassemia is a genetic disorder of beta globin protein that makes up red blood cells. The disease is most common in persons with Mediterranean, Asian, or African origins. Defects in hemoglobin lead to destruction of red blood cells and hence anemia symptoms that can be corrected with blood transfusion.[117] Results from an open-label clinical trial of 10 patients with beta thalassemia suggest potential use of epoetin alfa for this indication. Subcutaneous administration of epoetin alfa at 150 units/kg three times weekly for at least 12 weeks successfully reduced the median blood transfusion units though no significant change in Hb level was found.[118] In addition, a combination of ESAs (200 units/kg/day) and iron (300 mg/day) therapy from week 30 of pregnancy to week 4 of delivery may alleviate the requirement for blood transfusion in pregnant women with beta thalassemia though a larger clinical trial is needed to warrant such findings.[119] DRUGDEX recommends epoetin alfa to be used in some cases of beta thalassemia according to the moderate strength of evidence and efficacy report that favors efficacy for this indication.

Blood unit collection of autotransfusion

As noted earlier, epoetin alfa was approved for use as a prophylactic of allogeneic blood transfusion only in patients who are not willing to donate autologous blood before undergoing elective surgeries. If a patient is willing to donate, erythropoietin may be used off-label to increase capacity donation. DRUGDEX recommends epoetin alfa to be used in some cases of

transfusion prior to elective surgery according to the moderate strength of evidence and efficacy report that favors efficacy for this indication.

Anemia in traumatic, postsurgical patients

The use of erythropoietic drugs as an alternative to blood transfusion is potentially beneficial in a case where a patient of traumatic or surgical blood loss denies blood products due to his religious belief.[120] It was evident from many case reports and case series that epoetin alfa could successfully reverse life-threatening anemia due to trauma, burns, and surgical procedures in Jehovah's Witness patients refusing blood transfusion.[121-123] For example, erythropoietin given IV or SC at 300 IU/kg daily until a patient achieved a suitable response, then reduced to 150 U/kg every other day has resulted in 5% increases in Hb level.[124] DRUGDEX recommends epoetin alfa to be used in some cases despite inconclusive evidence of efficacy and only moderate strength of evidence present to support the use of ESAs in the treatment of anemia in traumatic, postsurgical patients.

Anemia in critical illness

The use of ESAs to treat anemia in critically ill patients shows positive effects in term increasing hematocrit values and reducing the need for blood transfusion. In two randomized, double-blind, placebo-controlled trials of 1,302 and 86 adult ICU patients, weekly subcutaneous administration of 40,000 IU epoetin alfa shows to increase Hb level and reduce the need for blood transfusion[125, 126] and no significant difference in mortality or adverse events was found between the treatment and placebo groups in two trials. Another small study of 36 patients also shows significant between-group differences of Hb values after five doses of subcutaneous erythropoietin at 300 units/kg was given every other day to anemic patients in the intensive care

unit.[127] In contrast, results from a large multi-center randomized double-blind placebo-controlled clinical trial indicate that erythropoietin is ineffective in reducing the need for blood transfusion in this specific group of patients and its use was in fact was associated with greater risk of thrombotic vascular events.[128] The use of erythropoietin in anemia of some critical illness cases is recommended in some cases by DRUGDEX (Class IIb) despite the inconclusive evidence of efficacy and moderate strength of evidence.

Anemia of malignancy - not due to chemotherapy

Causes of cancer-related anemia are multifaceted, ranging from the direct effect of the neoplasm to the products of the cancer. Almost all of cancer patients suffer from anemia over the course of the disease.[3, 4] Improvements in hematologic profile are demonstrated in various cancer trials though the treatment has failed to benefit quality of life or cancer outcome.[129, 130] In fact, the use of ESAs was associated with increased mortality. [131] Epoetin alfa dosed subcutaneously at 40,000 IU once weekly for 12 weeks was found to be associated with lower median survival in the treatment arm that remains significant after adjusting for baseline characteristics (68 versus 131 days).[128] Similar to epoetin alfa, darbepoetin alfa successfully increases Hb level of cancer patients not on active chemotherapy in spite of conflicting evidence on transfusion requirement and quality of life improvement[132-135] but is also associated with an increased incidence of cardiovascular and thromboembolic events though no difference in serious or fatal adverse events was observed. As a result, the ASCO/ASH guidelines caution against the use of ESAs in cancer patients not currently receiving chemotherapy[102] and DRUGDEX does not recommend the use of ESAs in anemia of malignancy not due to chemotherapy in any cases due to its negative effect on survival despite the moderate strength of evidence and evidence that favors efficacy.

Anemia of Porphyria cutanea tarda

Porphyria cutanea tarda (PCT) is the most common type of porphyria, [136] a rare disorder of liver enzyme uroporphyrinogen decarboxylase deficiency which is diagnosed in approximately 1 in 10,000 individuals.[137] Inefficiency of the enzyme causes porphyrin to accumulated in the liver, transported to the skin, and resulted in skin damage. About 20% of PCT diagnosed is hereditary, resulting from a genetic mutation, while majority of causes may be due to use of alcohol, estrogens, smoking, chronic hepatitis C, or HIV infection.[138] A reduction of serum iron through a removal of blood termed phlebotomy is a preferred treatment of PCT. In patients with advance kidney disease, PCT can be extremely severe and a combined ESA therapy and phlebotomy may be beneficial. Two case reports pointed out that ESAs can help manage anemia of porphyria cutanea tarda and hepatoerythrpoietic porphyria. A remission was achieved in a woman with porphyria cutanea tarda after undergoing ESA therapy at 150 units/kg for 4 months.[139] Similarly, subcutaneous administration of erythropoietin at 600 units/kg/week for 1 year partially corrected severe anemia in a 68-year-old male with chronic hepatoerythropoietic porphyria.[140] DRUGDEX recommends epoetin alfa to be used in some cases of anemia of porphyria cutanea tarda though the strength of evidence is low and efficacy evidence is still inconclusive.

Athletic performance enhancement

Abusive use of ESAs in sport is well-recognized. An alternative to blood transfusion, erythropoietin is used to increase the number of red blood cells, oxygen uptake, and hence player's endurance. Risks of erythropoietin use in athletic performance enhancement were widely reported[141] resulting in the prohibition of its use by the International Olympic Committee

and other sport authorities.[142] Similarly, the use of erythropoietin for this indication is not recommended by DRUGDEX because of an inconclusive evidence of efficacy.

Iron-overloaded – Transfusion

Iron overload, an excessive state of tissue iron, may result from repeated blood transfusion or over-absorption of iron from the gastrointestinal tract. Deposition of iron in various organs leads to dysfunctionality of the heart, endocrine system and death.[143] A combination of 150 units/kg erythropoietin therapy and phlebotomy in 5 transfusion-dependent hemodialysis patients was found associated with a reduction mean serum ferritin at the end of the 18-week study period.[144] DRUGDEX therefore recommends the use of epoetin alfa as an alternative to deferoxemine therapy in some cases of transfusional iron overload. Evidence of ESA use for this indication favors efficacy though the strength of evidence is low.

Sexual Dysfunction

Erythropoietin may enhance sexual function in male patients undergoing dialysis by directly affecting the endocrine or by increasing patient Hb level and blood viscosity. Improvement in sexual function was reported in 4 of 7 males undergoing hemodialysis after initiating ESA therapy. Moreover, 5 of 9 dialysis female patients reported a restoration of menstruation during the treatment.[145] Because of inconclusive evidence on efficacy and low strength of evidence, DRUGDEX recommend the use of ESAs for the treatment of sexual dysfunction only in selected cases.

Table 2.4 Use of Epoetin alfa and DRUGDEX ratings

FDA Approval	Therapeutic use	Level of Evidence		
		Strength of Recommendation	Strength of Evidence	Efficacy Rating
Yes	Anemia - Chronic renal failure	IIa	B	Effective
	Anemia - Due to chemotherapy - Neoplastic diseases, Non-myeloid, metastatic	IIa	B	Effective
	Anemia - Zidovudine adverse reaction	IIa	B	Favors efficacy
	Surgical procedure - Transfusion of blood product, Allogeneic; Prophylaxis	IIa	B	Effective
No	Anemia - Congestive heart failure	IIb	B	Favors efficacy
	Anemia - Due to radiation	IIb	B	Favors efficacy
	Anemia - During the puerperium	IIb	B	Favors efficacy
	Anemia - Hepatitis C, In patients being treated with a combination of ribavirin and interferon alfa or ribavirin and peginterferon alfa	IIb	B	Favors efficacy
	Anemia - Multiple myeloma	IIb	B	Favors efficacy
	Anemia - Myelodysplastic syndrome	IIb	B	Favors efficacy
	Anemia – Myelofibrosis	IIb	B	Favors efficacy
	Anemia – Prematurity (pediatric)	IIb	B	Favors efficacy
	Anemia - Rheumatoid arthritis	IIb	B	Favors efficacy
	Beta Thalassemia	IIb	B	Favors efficacy
	Blood unit collection for autotransfusion	IIb	B	Favors efficacy
	Anemia - Traumatic or postsurgical	IIb	B	Inconclusive
	Anemia - Critical illness	IIb	B	Inconclusive
	Anemia - Not due to chemotherapy - Neoplastic disease	III	B	Favors efficacy
	Epidermolysis bullosa (pediatric)	IIb	C	Inconclusive
	Anemia - Porphyria cutanea tarda	IIb	C	Inconclusive
	Athletic performance enhancement	III	B	Inconclusive
	Cancer	III	B	Inconclusive
	Iron overload – Transfusion	IIb	C	Favors efficacy
	Sexual dysfunction	IIb	C	Inconclusive

Table 2. 5 Use of Darbepoetin alfa and DRUGDEX ratings

FDA Approval	Therapeutic use	Level of Evidence		
		Strength of Recommendation	Strength of Evidence	Efficacy Rating
Yes	Anemia - Chronic renal failure	IIa	A	Effective
	Anemia - Due to chemotherapy - Neoplastic diseases, Non-myeloid, metastatic	IIa	B	Effective
No	Anemia - Not due to chemotherapy - Neoplastic disease	III	B	Inconclusive
	Anemia - Myelodysplastic syndrome	IIb	B	Favors efficacy

Table 2. 6 Use of ESAs for conditions not supported by scientific evidence and DRUGDEX ratings

Therapeutic use	Level of Evidence		
	Strength of Recommendation	Strength of Evidence	Efficacy Rating
Anemia due to trauma, postsurgical, and critical illness	IIb	B	Inconclusive
Anemia in neoplastic disease not due to chemotherapy	III	B	Favors efficacy
Anemia in porphyria cutanea tarda	IIb	C	Inconclusive
Sexual dysfunction	IIb	C	Inconclusive
Sickle cell anemia	IIb	C	Inconclusive

Empirical studies of ESA Off-label Use

The use of erythropoiesis-stimulating agents in the hospital settings is extensive and involving multiple hospital units and various indications. A study reports that over a 6-month study period, 120 physicians in a large medical center prescribed approximately 17 million units of erythropoietin, translating into a direct drug cost of $172,390.[146] Hemodialysis and renal indications were found to be the most common indications of ESA use though oncologists accounted for the highest units of ESA use. Off-label prescribing of ESAs is prevalent in inpatient settings. The same study found that 49% of ESAs prescribed for 248 inpatients between February and June 2000 were for off-label indications. Off-label indications of ESAs included bone marrow transplantation and hematologic malignancy (13%), neonatal care (10%), and their use in neurosurgical procedure (8.2%).

Similar patterns of ESA prescribing were observed in a study entailing nearly half a million ESA users in 515 hospitals nationwide.[15] Chronic kidney disease and cancer were the most common reason for ESA use in the hospitals between January 2002 and June 2004. During this period, inpatient off-label prescribing of ESAs was found to be 52%. Interestingly, one-quarters of such off-label use were prescribed for the indications not supported by strong scientific evidence including cardiovascular (3.7%) and pulmonary (3.8%) disorders. This study offers further insight into inpatient off-label prescribing of ESAs patterns. For example, off-label prescribing was more common in teaching hospitals compared to the community ones; surgeons were more likely to prescribed ESA off-label compared to specialists and generalists. Regional variations and patient characteristics such as age, gender, race, insurance status, and hospital length of stay were also found to be associated with off-label prescribing of ESAs.

Efforts of regulatory risk communications and health policies to influence prescribing patterns

The first part of this section describes risk communication approaches undertaken by the FDA to ensure safety use of a medication while the final part summarizes a systematic review of the impact of FDA drug risk communications on health care utilization and health behaviors.

The United States Food and Drug Administration (FDA) takes responsibility in protecting public health, one of which by ensuring that the drug products are safe and effective.[147] At the same time, there is pressure on the FDA's Center for Drug Evaluation and Research (CDER) to put the new drug onto the market as quickly as possible causing the period of premarketing surveillance period of adverse events to be significantly reduced.[148] As a result, the burden of drug safety monitoring relies heavily upon post-marketing surveillance. The primary mechanism for post-marketing surveillance is FDA's MEDWATCH program, which relies on health professionals to spontaneously and voluntarily report drug adverse events. Based upon MEDWATCH adverse event reports, the FDA's CDER and its an advisory committee analyzes drug risk and communicates them to patients and providers. The FDA channels of risk communication of medical products include safety alerts or public health advisories, Dear Healthcare Professional Letters, labeling revisions including black box warnings, and implementation of Risk Evaluation and Mitigation Strategies (REMS).[149]

Safety alert or public health advisory is often the FDA's first step in communicating drug risks to the public. When the evidence of risk accumulates the addition of a black box warning on the drug labeling is often warranted. Sometimes a black box warning occurs soon after a public advisory. An ESA public health advisory was first issued to the general public in

November 2006, highlighting the increased cardiovascular risk associated with epoetin alfa use in CKD patients not on dialysis. This was quickly followed by a black box warning in March 2007. Following that, a second public health advisory was issued which emphasized the black box warning and highlighted additional risks of death in cancer-ESA treatment and blood clot in major surgery. A third advisory was issued in November 2007 which warned that ESAs may shorten time to survival in cancer patients and emphasized maintaining Hb levels at 10-12 g/dL in CKD patients.

Black box warning is a frequently used risk communication tool of the FDA. The name "black box" refers to a prominent section outlined by a black border on the labeling of a drug, of which clinical or animal toxicity data indicate the use of serious adverse reactions.[150] The warning highlights risks associated with and warns prescribers against the use of the drug for certain indications and/or in some population. The use of black box warning, the strongest safety warning issued by the FDA, [151] is limited to "the most serious warnings necessary to ensure the continued safe use of the product." The popularity of black box warnings has been noted in a study that found approximately 8.2% of the 548 new drugs approved between 1975 and 1999 had at least one black box warning.[152] Among all drugs listed in the 1995 Physicians Desk Reference (PDR), 206 carried a black box warning.[153] The most frequent warning found was for the identification of use in high-risk patients, followed by information on dosing and drug interaction, and the need for special training or use in special settings. Nearly 14% of all labeling revisions between 2005 and 2008 were due to black box warnings.[154] In March 2007, a black box warning was added to the label of epoetin alfa and darbepoetin alfa to reflect increased risks associated with ESAs use in cancer and CKD patients reported in many large clinical trials. The boxed warning was later updated in March 2008 to include results from recent trials.

In addition to the public advisories and black box warnings, the FDA also communicates with prescribers using a Dear Health Care Professional letter (DHCP), or Dear Doctor/Dear Health Care Provider letter. DHCP letter is a paper or electronic mailing from the manufacturer, distributor of drugs or biologics, or the FDA to health care providers about the new information concerning a drug. DHCP letters can be of three types: "important drug warning letter", "important prescribing information letter", and "important correction of drug information letter." The "important drug warning letter" alerts health care providers of the safety issue hazardous to patient health such as life-threatening adverse reactions or a subpopulation in which the drug is contraindicated. The "important prescribing information letter" indicates changes in the prescribing information other than those in important drug warning letter type. Such important prescribing information includes a change in the indication, dosage, and route of administration intended to minimize risk or optimize effectiveness of the drug. The "important correction of drug information letter" emphasizes corrections of misleading information in prescription drug advertisements or other forms of promotion. A DHCP letter may either be requested by the FDA or initiated by drug manufacturers according to one of the reasons noted above but is normally done by the manufacturer. Information on DHCP letters can typically be found on the MedWatch website. In the case of ESAs, an important drug warning DHCP letter was sent by Amgen, a manufacturer of erythropoietin, in January 2007 to alert physicians of results from major clinical trials regarding risks associated with ESAs use. The letter specifically warned against the use of ESAs in non-chemotherapy cancer patients and the potential for increased risk of death in this population. In addition, physicians were recommended to use the lowest does of erythropoietin possible to maintain patient Hb at the level sufficient to avoid blood transfusion.

Under the FDA Amendment Act of 2007, the risk evaluation and mitigation strategies (REMS) surveillance system was developed. The FDA is now empowered with the authority to order manufacturer of a drug to provide REMS. The scope of REMS varies by drugs and the risks they carry. For example, REMS of a drug with relatively low risk may require nothing but an addition of package insert. However, because of the apparent risk associated with ESA use in cancer treatment, REMS for ESAs requires physicians prescribing ESA drugs to cancer patients to complete and receive documentation of certification of the online ESA APPRISE Oncology Program Training. Physicians must be enrolled in the ESA APPRISE Oncology program in order to be able to prescribe ESAs for use in patients with cancer.

Before the implementation of Risk Evaluation and Mitigation Strategies programs, no formal system exists to document physician adherence to FDA warnings; adherence to the warning is purely voluntary. One study found that 0.7% of prescriptions violate at least one aspect of the warning, though less than 1% actually resulted in adverse drug events.[155] Moreover, a national survey found the physician knowledge of the FDA-approved indications and evidence base for prescription drugs to be low. [156] The problem of risk communication has not been resolved with the REMS program.

Dusetzina et al. systematically reviewed the impact of FDA drug risk communications on health care utilization and health behaviors from the studies published between January 1990 and November 2010 listed in MEDLINE and Web of Sciences.[157] Among 16 therapeutic classes investigated in the forty-nine studies included in the review, antidepressants were the most common therapeutic class (31%) assessed for the impact of risk interventions, followed by glitazones (13%), cisapride (8%), terfenadine (8%), long-acting β2- agonist (6%), droperidol (6%), and antipsychotics (6%). Black box warnings were the most frequent risk communication

tool (51%), followed by public health advisory or safety alert (47%) and dear healthcare provider letters (29%). None of the studies included in this review investigated the impact of FDA risk communication on prescribing patterns of ESAs.

Nearly all studies of drug risk communications investigate their effect on changes in the level of targeted drug utilization. Drug risk communications fell into four recommendation types: 1) increase patient monitoring; 2) avoid co-prescribing of drugs that may have adverse interaction; 3) avoid use of a drug among subpopulations; and 4) provide general caution of a drug product. Of note, recommendations regarding increased clinical monitoring appeared to have little or no effect on clinical practice. In addition, the effect of the recommendations failed to be sustained in the short term, although physicians appeared to decrease inappropriate prescribing over time. The effect of risk communication also appeared to vary considerably by therapeutic classes. Lastly, spillover effects of the regulatory risk communication messages to non-target user population were assessed in a few studies. A drop in antidepressant use was observed in adult populations even though the communications only warned against its use in youth.[158]

This study seeks to add to the literature in the following ways. This will be the first to assess the impact of safety warnings and funding changes on the use of erythropoietin. It will be one of the few studies that look at the impact of REMS on any type of drug on patient-level changes in utilization. It is also the first to examine the relative impact of safety warnings and funding decisions on on-label and off-label drug use of any type when examined at the patient level.

The following section extensively review potential confounders needed to be considered in the analysis of patient-level data. Lastly, systematic literature review of public interventions on ESA utilization that leads to the formulation of research question concludes the final section of this chapter.

Potential confounding factors associated with prescribing patterns

The diffusion of innovation of health care framework clearly defines factors influencing the decision to adopt an innovation including perceived benefit of the change, compatibility of the innovation with the current values, belief, and needs of the individuals, complexity of the proposed innovation, trialability of the innovation, and the extent to which potential adopters observe the adoption by others. In parallel to the diffusion of innovation theory, influencing factors of prescribing have been extensively studied. Prescribing decisions are a complex and intertwining process where changes in physician's prescribing patterns are a variety of factors. Such influencing factors may be categorized into 3 groups: patient, physician, and external factors. [159]

1. Patient Factors

<u>Patient clinical conditions (admission type, severity of illness, length of hospital stay)</u>

Patient clinical conditions are major influencing factors of treatment patterns. The relationship holds true for ESA use in specific; the likelihood of the off-label use of ESAs showed a positive relationship with patient's length of hospital stay.[15] Similar results were found in oncology where a drug use report indicated that the use of drugs for off-label purposes is more prevalent in patients with advance cancer stages compared to the initial stages.[160] Admission

status, severity of illness calculated using a combined comorbidity score, and length of hospital stay available in electronic medical records can serve as proxies for patient clinical conditions in this study.

Patient characteristics (age, race, gender)

Off-label prescribing is a concern as the drugs tested in adult participants may not work as safely or effectively in the elderly and children because of differences in body composition and pharmacokinetics.[161, 162] In addition, treatment patterns in the older elderly patients may differ from the younger ones. Physician could be more reluctant to prescribe a drug with some risks to older patients who are frailer and the goals of therapy may shift from increasing longevity to improving quality of life. Also, as an individual draw closer to death, health care utilization increases and thus adjusting for patient age in the analyses is essential.[163]

Racial disparities in ambulatory care and pharmacotherapy are well-documented. African-American and other minorities were less likely to be prescribed with medications for certain chronic disease conditions such as diabetes and mental disorders compared to their White counterparts.[164, 165] Even though the association between patient race and off-label prescribing has rarely been assessed, it is crucial to control for potential confounding effect of patient race on ESA prescribing in this study.

Despite evidence suggesting that women are greater users of health care resources than men, gender disparities in the treatment of life-threatening diseases were apparent in the medical literature.[166] Researchers have rigorously examined gender as a predictor of the extent of therapeutic intervention provision in various health conditions. For example, gender differences were found to be correlated with the likelihood of receiving dialysis or a kidney transplant

among patients with kidney diseases.[167-169] It is therefore important to include patient gender into the model to avoid its potential confounding effects on ESAs prescribing.

Primary Payer of Health Insurance

Health insurance has been long identified as enabling factor of healthcare encounter.[170] A study found that physicians also incorporate patient's health insurance in their prescribing decision where participating physicians reported to change their therapeutic treatment due to insurance issues in approximately 16% of the sampled visits.[171] Additionally, this change is most likely to occur when the patients was uninsured. The impact of health insurance on prescribing patterns in the inpatient settings is largely unknown and deserved further investigation.

2. Physician Factors

Physician specialty

Existing literature have identified that specialists and generalists may be different in their treatment intensity. Research has found, for example, that endocrinologists and cardiologists may have been more resource-intensive than generalists in the treatment of diabetes.[172] Another Canadian study also found that early prescribers of celecoxib, a specific cox-2 inhibitor analgesic, were more likely than majority of prescribers to be general practitioners.[173] A possible explanation of such differences may lie in the extent of medical journal use or training. As the literature suggests possible differences in prescribing patterns between physician specialties, it is important to include information on physician specialty in the model. Information on physician specialty is readily available in Cerner data.

3. Hospital Specific Factors

Hospital characteristics (bed size, teaching status, geographic region)

Hospital characteristics including size, teaching status, and geographic region may influence prescribing patterns. Larger hospitals are better equipped with prescribing decision support system that leads to quality prescribing. A study of new drug adoption found that Dutch general practitioners who used a prescribing decision support system were less likely to prescribe angiotensin II receptor blockers (ARBs), an expensive anti-hypertensive medication, compared to those who worked in single-handed practices or in rural areas where decision support system is less likely to exist.[174] In addition, knowledge dissemination may happen at a faster rate in a larger hospital where thought leaders reside. One study found that key opinion leader physicians and those who are socially well connected with their peers will also be one of first to react compared to "patient-oriented" physicians.[175] Though a study of ESA off-label prescribing found no association between hospital bed size and ESA off-label prescribing, it is still important to control for hospital size in this study. Hospital size in this study is measured through the number of beds in a hospital and categorized into 5 groups: <99, 100-199, 200-299, 300-499, 500 or more beds, based on a categorization of the American Hospital Association (AHA).[176]

Small area variation (SAV) is evident in medical practices. For clinical conditions where alternative treatments are available or in the absence of well-defined guidelines, practice styles vary across physicians depending on their preferences. Economists believe that SAV mainly stems from physician's uncertainty and lack of knowledge as a result of inadequate diffusion of medical information.[177, 178] Regional variations were seen in off-label prescribing of ESAs such that hospitals in the northeast and western portions of the country being more likely to prescribe

ESAs for off-label unsupported indications than other regions. Information on geographical region is available in our database and will be categorized into Northeast, South, Midwest, and West.

Teaching status of the hospital may be associated with prescribing patterns. Diffusion of innovation and the uptake of technologies usually occur faster in a larger practice[179, 180] and it is possible that physicians who work in a group practice and those in teaching hospitals would be more likely to follow the warning compared to those in solo practice and nonteaching hospitals. Previous study has identified that off-label use of ESAs occurred more in teaching hospitals than nonteaching hospitals.[15]

To conclude, it is evident from the literature that patient characteristics and their clinical conditions, primary payer of health insurance, physician and hospital characteristics, to a certain extent affect one's decision to prescribe for on-label and off-label purposes. Outside influences including safety issues speculate around the prescribing environment could likewise influence prescribing patterns. Since effects of safety interventions on the ESA prescribing can be masked by these characteristics, it is essential to include them in the analytical model.

Systematic literature review

The systematic review of existing literature is subdivided into four parts: methods, results, discussion, and conclusion. The objectives of this literature search was to summarize existing knowledge on FDA and Medicare actions on ESA use patterns, namely the proportion of patients treated, dose, and duration of ESA treatment. Findings from this review are used to identify gaps in the literature and formulate research questions, research hypotheses, and specific aims that are described at the end of this chapter.

Methods

Three databases were used for this search: MEDLINE, CINAHL, and Web-of-Sciences. First, MEDLINE was searched via PubMed for relevant studies from a combination search of 3 search strings that comprised of MeSH terms and keywords. CINAHL database via EBSCO host and Web-of-Science were searched using a combination search of similar keywords to identify additional articles. Reference lists of selected studies and relevant review articles were also searched. To keep such search at a manageable level, keyword search was applied to title and abstract [tiab] in PubMed. Web-of-Science search was limited to topic field and studies based in the United States only while no search field was specified in CINAHL.

Inclusion criteria are English language articles studies that analyzed empirical data on the impact of interventions of interest on ESA use patterns. This review excluded letters to editors, commentaries, news articles, and meeting abstracts. Review articles were included only for reference mining. The search was limited to English language articles published between 2007 and May 2012. The year 2007 was chosen because the scope of this study focuses interventions that took place only between 2006 and 2010. To be included in this review, a study must have

investigated at least one of the following outcomes during the period of study: proportion of patients treated with ESAs, ESA dose, and treatment duration. Abstracts produced from initial search strategies were reviewed for possible inclusion and exclusion. The corresponding full articles of qualifying abstracts were then retrieved through Virginia Commonwealth University and inclusion and exclusion criteria were then confirmed. Search strings used in for PubMed search are described below. For Web-of-Science and CINAHL, MeSH terms were substituted with exact or similar keywords.

String #1:

"Erythropoiesis-Stimulating Agents" [MeSH] OR "Erythropoietin" [MeSH] OR "Erythropoiesis" [MeSH] OR "ESA" [tiab] OR "Erythropoietic" [tiab]

String #2:

"safety" [tiab] OR "warning" [tiab] OR "black box" [tiab] OR "public health" [tiab] OR "advisory" [tiab] OR "alert" [tiab] OR "dear doctor" [tiab] OR "dear healthcare professional" [tiab] OR "dear healthcare provider" [tiab] OR "letter" [tiab] OR "risk communication" [tiab] OR "risk evaluation and mitigation strategies" [tiab] OR "REMS" [tiab] OR "drug labeling" [MeSH] OR "Food and Drug Administration" [tiab] OR "FDA"[tiab] OR "regulatory" [tiab] OR "United States Food and Drug Administration" [MeSH] OR "National Coverage Determination" [tiab] OR "NCD" [tiab] OR "reimbursement" [tiab] OR "restrict" [tiab] OR "payment" [tiab] OR "policy" [tiab] OR Medicare [MeSH] OR "United States Centers for Medicare and Medicaid Services" [MeSH]

String #3:

"Physician's Practice Patterns" [MeSH] OR "Drug Prescriptions" [MeSH] OR "Drug Utilization" [MeSH] OR "prescribing" [tiab] OR "impact" [tiab] OR "effect" [tiab] OR "change" [tiab] OR "outcome" [tiab] OR "consequence" [tiab] OR "results" [tiab] OR "trend" [tiab]

Results

PubMed search (*string #1* AND *string #2* AND *string #3*) identified 477 articles published between 2007 and 2012, ninety-five of which were review articles. After applying exclusion criteria, abstracts were selected for full text assessment for eligibility. Eight original research article of a qualitative analysis of empirical data was identified. Reference mining of original studies and review articles did not yield additional relevant study. Likewise, no additional eligible studies were found from CINAHL (247 studies) and Web-of-Science (339 studies) search. Thus, a total of eight studies are used for this review.

Studies of impact of regulatory safety warnings and reimbursement restriction through the national coverage determination cover a variety of outcomes. The primary outcomes commonly identified are the proportion of patients treated with ESAs, dose, treatment duration, Hb level, and requirement for blood transfusion. Two studies assessed the change in ESA use in CKD patients while the other six studies investigated such change in cancer patients. Study methods, results, and conclusion are summarized in Table 2.7 and 2.8.

An increasing trend in mean ESA dose was observed among hemodialysis patients internationally between1996 and 2008.[181] MaFarlane and his colleagues analyzed the trend in ESA use and their Hb levels among patients treated in selected dialysis units in 12 countries (US,

Canada, France, Germany, Italy Spain, Belgium, Sweden, the UK, Australia, New Zealand, and Japan) using data from a three-phase large prospective observation study, Dialysis Outcomes and Practice Pattern Study (DOPPS). The study found an increasing trend in mean ESA doses between the DOPPS study phases (1996-2001, 2002-2004, and 2005-2008) in all participating countries but Belgium. An increase in Hb levels was observed in all countries but Sweden.

Contradicting results were reported among CKD patients not on dialysis in the United States between 2005 and 2009.[182] ESA use in this population treated in free-standing US nephrology clinics decline from 60% to 46% during this period with the largest drop in 2007 and 2008 (the study did not test for statistical significance in this difference). A significant decline in the proportion of patients with Hb level > 12 g/dL and an increase in the proportion of patients with Hb within 10-12 g/dL range were observed in 2007. This change was parallel with a decline in ESA dose that began in early 2007 (a 21% drop throughout the 4 years period). Nonetheless, the drop in ESA dose and Hb level was not statistically significant after adjusting for patient case-mix.

A consistent decline in ESA use in cancer treatment was noted in all studies. Vadhan-Raj et al. assessed usage patterns of ESAs and transfusion among patients on active treatment at a cancer center between January 2006 and December 2008 to determine whether changes in the level of ESA use correspond with changes in the safety concerns and reimbursement strategy during the study period.[183] Active treatment was defined as inpatient admission, emergency center visit, blood transfusion, surgery, chemotherapy, radiation therapy, and other therapy for cancer. Compared with 2006, the proportion of patients receiving ESAs decreased by 26% in 2007, and by 61% in 2008. A non-significant increasing trend of 8% in the proportion of patients receiving transfusions was observed during the investigational period. A significant

reduction in Hb values at ESA initiation was also found among ESA-naïve patients such that the proportion of patients first receiving ESAs at Hb level ≤ 10 g/dL increased from 60.6% in 2006 to 88.9% in 2008. Additionally, the proportion of ESA-naïve patients receiving transfusion before any ESA use increased from 26.4% in 2006 to 40.7% in 2008. Moreover, the study used piecewise linear models to detect changes in the numbers of patients treated at the center, ESA units dispensed, blood units transfused, mean Hb values on the day of transfusion and at the initiation of ESAs, proportions of ESA use among transfused patients, and proportions of ESA-receiving patients undergoing transfusion. A significant reduction in ESA units dispensed was observed at 9.8 months (October 2006) and ESA units dispensed reduced by 77% during the three years study period. In the same period, no significant changes in the number of patients treated at the center, RBC units transfused, or mean Hb values on the day of transfusion were found. The greatest reduction in ESA use was in the hematologic services (28%) though this decrease was observed across all services. Finally, after adjusting for patient and clinical characteristics, the authors found that though ESA use decreased, transfusion did not increase significantly. Despite a large number of outcomes studied the study did not investigated differences in such outcomes between patients on and off-chemotherapy.

The impact of the reimbursement change on the level ESA utilization in cancer patients receiving chemotherapy in multiple oncology clinics was first observed in a study by Hess et al.[184] ESAs were used in 41.3% of all episode of chemotherapy care before the implementation of national coverage determination (NCD). In the post-NCD period, only 30.4% of the chemotherapy episodes were associated with ESA use, translating into 26.4% reduction in ESA use. Concurrently, a significant increase in the episodes with blood transfusion was observed (17% relative reduction) while the mean minimum Hb values during the episodes were

significantly lower after NCD (10.7 g/dL vs. 10.9 g/dL). The impact of NCD seemed to be different between the two groups of patients such that more prominent changes in ESA use, blood transfusion, and Hb values were found in patients older than 65 years old (29.1% relative reduction in ESA use and a 31% increase in blood transfusion). In contrast, though ESA use decreased significantly by 24% among those younger than 65 years old, no significant increase in blood transfusion was found.

A study by Henry and his colleagues determined the impact of NCD on utilization of ESAs among Medicare patients with colorectal, lung, and breast cancer patients on concomitant chemotherapy.[185] Information of patients with chemotherapy-induced anemia (Hb values < 11 g/dL while receiving chemotherapy or within 60 days of the last chemotherapy dose) from 49 community oncology clinics with was derived from electronic medical records to assess blood transfusion (proportion of patients receiving transfusion and transfusion units), ESA use, time, and dosing, Hb values, and hospitalization. The proportion of CIA patients receiving ESAs decreased in the post-NCD compared to the pre-NCD period (56% vs. 88%). Duration of ESA use decreased significantly from 48 days to 32 days and doses reduced from 4.6 to 2.9 units. Adjusting for patient demographics, clinical characteristics, tumor types, and chemotherapy treatment, the likelihood of receiving transfusion was found to be 41% greater after NCD. Parallel with this increase, a significant rise in the proportion of patients with Hb < 10 g/dL, mean number of transfusion per patient and mean number of units transfused was found post-NCD period. Nonetheless, no significant differences in the rate of hospitalization between the two periods were observed. In spite of reporting a crude reduction in the proportion of cancer patients receiving ESAs after the implementation of NCD, the study did not assess the likelihood of receiving ESAs, adjusting for covariate.

Hemoglobin trends and anemia treatment among chemotherapy-treated patients with cancer between 2006 and 2009 were assessed by Feinberg and colleagues.[186] Overall, the proportion of chemotherapy episodes in community oncology clinics in which ESA was prescribed decreased significantly from 45.4% to in 2006 to 11.5% in 2009. This change aligned with an increase in chemotherapy episodes with no anemia treatment (44.6% to 77.8%), episodes with transfusion services only (3.4% to 8.73%), and a decrease in episodes with both transfusion and ESA treatment (6.6% to 2.0%). For episodes with ESA treatment, patients showed decreased in mean Hb values. The study implied that over time, initiation of ESAs after chemotherapy was delayed (from 29.4 days in 2006 to 39.0 days in 2009) and patients seemed to be initiated with any anemia treatments at a lower Hb values.

Arneson *et al.* assessed the impact of NCD on ESA and transfusion use in chemotherapy-treated Medicare beneficiaries with cancer using a nationally representative Medicare claims data between 2005 and 2007.[187] The proportion of ESA use among patients aged 66 or older who had lung, breast, or colorectal cancer, or lymphomas, and initiated chemotherapy in the outpatient settings decreased significantly from 35.0% pre-NCD to 15.2% in post-NCD period, adjusting for patient demographic and clinical variables. Though an increasing trend was found in the proportion of patients receiving transfusion or transfusion event rate, a statistical difference could not be detected pre- and post-NCD implementation (9.3% vs 10.4% of patients and 19.0 to 21.8 transfusion events per 100 patient-quarters). The findings were similar across the four types of cancer.

Lastly, appropriateness of ESA use at National Cancer Centre in Singapore was assessed by Chan and Chan.[188] The release of safety advisories appeared to be associated with appropriate ESA prescribing measured through Hb initiation level and target level achieved, but

ESA treatment duration remained unchanged. Furthermore, a smaller proportion of patients required more blood transfusion after ESA therapy was observed after the warnings compared to the pre-warning period. Nonetheless, the study did not statistically compare the proportion of patients using ESA before and after the release of safety advisories considered useful to answer our research questions.

Discussion and Conclusion

ESA use in all patients except those receiving hemodialysis decreased after 2006. Among the six studies of ESA use in cancer patients, a consistent reduction in use was observed over time. The greatest decline in use (number, dose, duration of therapy) occurred between late 2006 and early 2007, corresponding to the release of negative results from clinical trials, black box warning, and restriction in Medicare reimbursement. Though impact of NCD was most prominent among Medicare beneficiaries, studies observed a spillover effect in the younger population. Consistent with safety warnings, patient Hb levels at the initiation of ESA treatment seemed to lower over time. The reduction in ESA prescribing was associated with increases in the use of transfusion services in many, but not all studies. No study examined the impact of safety warnings on off-label prescribing of ESAs.

Table 2.7 Results of systematic literature review: summary of study methods

Author, pub year	Study Design	Study Sample	Data Source	Time period	Intervention	Unit of Analysis
Chronic Kidney Disease						
McFarlane et al., 2010	Descriptive	Hemodialysis patients in 12 countries	DOPPS database	1996-2008	None	Patient
Regidor et al., 2010	Pre-post comparison	CKD non-dialysis patients at free-standing nephrology clinics N = 15,836	Electronic medical records	Mar 05-Jul 09	All possible between the study period	Patient
Cancer						
Vadhan-Raj et al., 2010	Time-series	Cancer patients on active treatment at one cancer center N = 83,399	Electronic medical records	Jan 06-Dec 08	All possible between the study (black box warning and NCD)	Patient
Hess et al., 2010	Pre-post comparison	Cancer patients with chemotherapy-induced anemia at 52 oncology clinics N Pre-NCD = 4,784 N Post-NCD = 5,605	Electronic medical records	Jun 06-Mar 08	NCD	Episode of chemotherapy care

Author, pub year	Study Design	Study Sample	Data Source	Time period	Intervention	Unit of Analysis
			Cancer			
Henry et al., 2011	Pre-post comparison	Adult Medicare patients with colorectal, lung, or breast cancer who were treated at community oncology clinics and developed chemotherapy-induced anemia N = 800 pre-NCD (Jan 00 – Jul 07) N = 994 post-NCD (Aug 07 – Jan 09)	Electronic medical records	January 2000 – January 2009	NCD	Patient
Feinber et al., 2012	Pre-post comparison	Cancer patients at an oncology private practice N =4,021 patients (4,864 episodes of chemotherapy care)	Electronic medical records	Jan 06-Aug 09	All possible between the study period with focus on NCD	Episode of chemotherapy care

Arneson et al., 2012	Pre-post comparison	66 years old Medicare beneficiaries who had lung, breast, colorectal cancer, or lymphomas, and initiated chemotherapy in outpatient settings N = 1,897 pre-NCD N = 1,877 post-NCD	Medicare 5% sample	September 2006-November 2007	NCD	Patient

Author, pub year	Study Design	Study Sample	Data Source	Time period	Intervention	Unit of Analysis
			Cancer			
Chan, 2010	Pre-post comparison	Patients who received at least one dose of ESAs at a cancer center in Singapore N = 91pre-NCD N = 48 post-NCD	Pharmacy electronic dispensing records	January 2005 – December 2009	FDA safety warnings	Patient

Table 2. 8 Results of systematic literature review: summary of study results

Author, pub year	Outcomes Measure	Statistical Approach	Results	Conclusion	Limitations/Gaps in literature
Chronic Kidney Disease					
McFarlane et al., 2010	Trend in mean Hb level and ESA dose	Linear regression analysis adjusting for clustering by facility	Mean Hb level and percentage of patients with Hb level ≥ 12 g/dL, in the US increased significantly. Mean ESA doses increased from 15,959 U/week in DOPPS Phase I to 21,386 U/week in DOPPS Phase III ($p < 0.001$). Percentage of patients with a mean ESA dose greater than 35,000 U/week also increased significantly.	ESA use in the kidney disease in the US increased despite safety warning and reimbursement change	Crude estimates of outcomes change that are loosely tied to an intervention since the study compares Hb level and ESA dose between phases of DOPPS.
Regidor et al., 2010	Proportion of patients treated with ESAs ESA dosing in mcg/month and mean Hb level	Mantel-Haenszel chi-square test and ANOVA for biavariate analysis Multiple linear regression of trends in ESA dosing and Hb level over the study period	ESA use declined from 60% in 2005 to 46% in 2009 with largest decline (20.5%) between 2007 and 2008 Mean dose declined from 176 to 136 mcg/month with the largest decline observed at the beginning of 2007. Mean Hb level declined significantly.	A decline in ESA use between 2005 and 2008 was observed and may be associated with safety warnings, change in clinical practice guidelines, and reimbursement restriction	Did not test for statistical difference in ESA use between years Did not adjust for patient characteristics

Author, pub year	Outcomes Measure	Statistical Approach	Results	Conclusion	Limitations/Gaps in literature
			Cancer		
Vadhan-Raj et al., 2010	Proportion of patients receiving chemotherapy, ESAs, or transfusion Change point during 36-month period and differences in slopes before and after change point for: - ESA use: total ESA unit dispensed and total number of patients treated during the period - Transfusion: Total number of transfusion, proportion of ESA-receiving patient requiring a transfusion, proportion of transfused patients receiving ESAs - Hb profile: mean Hb level on the day of transfusion (implies transfusion threshold), mean Hb at initiation of ESAs in ESA-naïve patients (implies threshold for initiating	Chi-square test for proportion Piecewise linear model to assess change points Wald test to assess change in slope Multiple logistic regression	<u>ESA use</u> Compared to 2006, number of patients who received ESAs decreased by 26% in 2007, 61% in 2008. Total number of standardized ESA units dispensed decreased by 29% in 2007, and by 80% in 2008. Change point occurred at 9.8 months (October 2006), slope before = 31.58 ESA units/month, slope after = -91.38 units/month ($p<0.0001$). <u>Blood transfusion</u> Total number of transfusion increased by 2% in 2007, by 8% by 2008. Number of patients received transfusion increased by 6% in 2007, 8% by 2008 ($p = 0.003$). However, no statistically significant change point was detected. <u>Subgroup analysis of those receiving chemotherapy</u> Proportion of patients receiving ESAs decreased from 26.5% in 2006 to 9.4% in 2008, $p < 0.0001$). No change in the proportion of patient receiving	Safety concerns and reimbursement change were associated with a decrease in ESA use among cancer patients, both receiving and receiving concomitant chemotherapy.	-

	ESAs) Change in ESA use and transfusion use over time, adjusting for patient demographic and clinical characteristics.		transfusion was observed. <u>Hb value at transfusion</u> No change was found in Hb values at transfusion and in proportion of patients with Hb level < 10 g/dL on day of transfusion <u>Hb value at initiation of ESAs</u> Proportion of patients who started ESAs at Hb ≤ 10 g/dL increased from 60.6% in 2006 to 88.9% in 2008 (P < 0.0001).		
Hess et al., 2010	Proportion of patients administered with ESAs Proportion of patients required blood transfusion Frequency of myelosuppressive chemotherapy treatment	Chi-square tests and t-tests	All patients: 26.4% relative decrease ($p < 0.001$) Aged ≥65: 29.1% relative decrease ($p < 0.001$) Blood transfusion increased significantly (17.1% for all patients and 31.3% in elderly)	NCD reimbursement restriction was associated with the reduction in ESA use among cancer patients treated at oncology clinics	The study did not adjust for patient characteristics when testing for the difference in ESA use.

Author, pub year	Outcomes Measure	Statistical Approach	Results	Conclusion	Limitations/Gaps in literature
			Cancer		
Henry et al., 2011	Proportion of patients receiving transfusion during chemotherapy-induced anemia episode Mean number of units of blood transfused Patient hematologic status (mean Hb) Frequency and duration of ESA use Hospitalization	Bivariate analysis comparing pre-post outcomes of interest Logistic regression to evaluate the likelihood of receiving a transfusion and negative binomial regression to estimate the number of units transfused	Proportion of patients receiving ESAs before and during CIA episode decreased significantly pre-post NCD (88% vs 56%, $p < 0.0001$). ESA doses and duration of treatment decrease significantly (48 vs. 32 days and 4.6 vs. 2.9 doses, $p < 0.0001$). NCD is associated with lower Hb level, 41% increase in the odds of receiving a transfusion, and 53% increase in blood utilization. No significant difference in the rate of hospitalization was found.	NCD was associated with decreased frequency and duration of ESA treatment in cancer patients receiving chemotherapy, a modest increase in blood transfusion, and a decreased Hb level, but was not associated with an increase in hospitalization.	The study did not look at the likelihood of receiving ESAs before and after NCD.

Author, pub year	Outcomes Measure	Statistical Approach	Results	Conclusion	Limitations/Gaps in literature
			Cancer		
Feinberg et al., 2012	Number of episodic cohorts (stratified by Hb at anemia treatment initiation < 10 g/dL) with: 1. No anemia treatment 2. ESA use only 3. Transfusion only 4. ESA+transfusion Mean Hb values, stratified by episodic cohorts at: 1. Initiation of anemia treatment 2. Up to 6 weeks before treatment 3. Up to 6 weeks after anemia treatment Average number of days from chemotherapy initiation to Hb < 10 g/dL and average number of days from Hb < 10 g/dL to anemia treatment initiation	Bivariate analysis using chi-square (number of episodic cohorts) and t-test (mean Hb values, time from chemotherapy to Hb < 10 g/dL and to treatment initiation) Comparing yearly number of episodic outcomes, using 2006 as comparator	Chemotherapy episodes with ESA treatment decreased significantly from 45.42% in 2006 to 11.47% in 2009, with significant all year-to-year trends ($p < 0.05$). Mean Hb values at initiation of ESA-anemia treatment decreased from 10.8 g/dL in 2006 to 8.9 g/dL in 2009 ($p < 0.001$). Average number of days between chemotherapy and anemia treatment initiation with ESAs increased each year from 21.2 days in 2006 to 39.0 days in 2009 ($p < 0.001$)	Between 2006 and 2009, there was a decreased use of ESAs, delayed in ESA-anemia treatment, and a decrease in Hb level at time of treatment initiation among cancer patients receiving chemotherapy at a private oncology clinic.	The study did not adjust for patient characteristics when testing for the difference in ESA use.

Author, pub year	Outcomes Measure	Statistical Approach	Results	Conclusion	Limitations/Gaps in literature
			Cancer		
Arneson et al., 2012	Proportion of patient with ESA use Proportion of patients requiring ≥ 1 blood transfusion and transfusion event rates	Logistic regression comparing pre-post proportion and poisson regression comparing pre-post event rates	ESA use in Medicare cancer patients receiving chemotherapy decrease from 35.0% to 15.2%. After adjusting for covariates, NCD was associated with 67% reduction in the odds of ESA use (OR = 0.33, p < 0.0001) No significant change in the adjusted transfusion use and transfusion event rates was found	NCD was associated with a reduction in ESA use among Medicare cancer patients receiving chemotherapy, but was not associated with transfusion use	-
Chan 2010	"Appropriateness" of ESA prescribing measured through Hb initiation and targeted levels, ESA dose adjustment, treatment of duration and presence of concomitant iron supplement "Appropriateness" of ESA efficacy and toxicity monitoring measured through the number of blood transfusion needed before and after ESA therapy and other indicators	Chi-square tests and t-tests	Mean Hb level at treatment initiation was significantly lower (8.52 g/dL vs. 8.95 g/dL, p = 0.032), but the duration of treatment remained unchanged (17 days vs. 20 days, p = 0.844). A significantly smaller proportion of patients requiring more blood transfusion after ESA therapy was observed (44.8% vs. 7.1%, p = 0.016).	Safety guidelines were associated with lower Hb level at the time of treatment initiation and fewer blood transfusions after ESA treatment among patients with cancer in Singapore. No change in duration of ESA treatment was seen.	The study did not test for a significance difference in the proportion of patients receiving ESAs pre- and post-warning period and did not adjust for covariates for other statistical testing.

Gaps in the Literature

Existing literature has provided concrete evidence of changes in ESA prescribing in the outpatient settings from 2005 to 2009. However, the literature is lacking on prescribing patterns of ESAs among hospitalized patients since 2004. Among studies exploring changes in ESA outpatient utilization over time, none of them has attempted to link specific safety interventions to prescribing patterns of ESA. In addition, the effect of REMS, the FDA's most recent risk communication tool implemented in 2010, on ESA use has never been assessed. Finally, the relative impacts of various safety interventions on the on-label and off-label use of ESAs has not been explored.

This study contributes to the literature in the following ways. First, it provides update on the on-label and off-label use of ESAs in the inpatient settings - last studied in 2004. Second, it quantifies relative immediate and trend impacts of various regulatory interventions on inpatient ESA use between November 2006 and November 2010. The study further compares impacts of such interventions across the. Third, this study explores how these interventions might influence three types of ESA prescribing (on-label, off-label supported, and off-label unsupported indications) differently. Finally, the study determines factors associated with the likelihood of receiving ESAs in the inpatient settings between 2005 and 2011.

Research Questions, Specific Aims, and Hypotheses

Descriptive Study: Specific Aim 1

No hypotheses were formulated for the descriptive study.

Research Question 1a

Do differences in demographic characteristics, clinical conditions, insurance status, hospital characteristics, and physician characteristics exist between users of epoetin alfa and that of darbepoetin alfa?

Specific Aim 1a

To compare demographic characteristics, clinical conditions, insurance status, hospital characteristics, and physician characteristics between epoetin alfa users and darbepoetin alfa users.

Research Question 1b

Do differences in demographic characteristics, clinical conditions, insurance status, hospital characteristics, and physician exist among ESA users of on-label, off-label supported, and off-label unsupported indications in the inpatient settings?

Specific Aim 1b

To compare demographic characteristics, clinical conditions, insurance status, hospital characteristics, and physician characteristics among ESA users of on-label, off-label supported, and off-label unsupported indications in the inpatient settings.

Inferential Study: Specific Aim 2 and 3

Specific Aim 2: Impact of Black box warning, NCD, and REMS on the proportions of visits with on-label, off-label supported, and off-label unsupported ESA use

Research Question 2

What are the immediate and trend impacts of 1) black box warning, 2) national coverage determination, and 3) REMS on utilization patterns of ESAs and for the on-label, off-label supported, and off-label unsupported indications?

Specific Aim 2

To quantify the immediate and trend impacts of black box warning, NCD, and REMS on the proportion of visits where a patient was prescribed ESAs for on-label, off-label supported, and off-label unsupported indications

Hypothesis for Question 2

Each of the interventions is associated with a significant change in the immediate and trend of the proportion of ESA use in the three use categories.

$H_{0\text{-}2\text{-}a}$: There exists no significant immediate and trend change in the proportion of visits where a patient was prescribed ESAs for a) on-label, b) off-label supported, or c) off-label unsupported indications in the hospital settings after the issuance of *black box warning*

$H_{0\text{-}2\text{-}b}$: There exists no significant immediate and trend change in the proportion of visits where a patient was prescribed ESAs for a) on-label, b) off-label supported, or c) off-label

unsupported indications in the hospital settings after the implementation of *national coverage determination*.

$H_{0\text{-}2\text{-}c}$: There exists no significant immediate and trend change in the proportion of visits where a patient was prescribed ESAs for a) on-label, b) off-label supported, or c) off-label unsupported indications in the hospital settings after the implementation of *REMS*.

Specific Aim 3: Impact of Black box warning, NCD, and REMS on the odds of a patient being prescribed ESAs for the on-label, off-label supported, and off-label unsupported indications

Research Question 3a

What are the immediate and trend impacts of 1) black box warning, 2) national coverage determination, and 3) REMS on the *odds* of receiving ESA among patients with a) on-label and b) off-label supported indications, adjusting for patient & hospital characteristics? This question is formulated to find out whether the three interventions have an unintended effect on ESA use in the hospital settings. Specifically, we would like to know if there is a decrease in the likelihood of receiving ESAs among patients who could benefit from the on-label and off-label supported indications of ESAs after the interventions.

Hypothesis for Question 3a

Each of the interventions is associated with significant unintended change in the immediate and trend in the odds of receiving ESAs in patients with the on-label and off-label unsupported indications, adjusting for individual patient characteristics, hospital characteristics, and physician specialty.

$H_{0\text{-}3a\text{-}a}$: There exists no significant immediate and trend change in the odds of receiving ESAs in patients with the on-label or off-label supported indications in the hospital settings after the issuance of *black box warning.*

$H_{0\text{-}3a\text{-}b}$: There exists no significant immediate and trend change in the odds of receiving ESAs in patients with the on-label or off-label supported indications in the hospital settings after the implementation of *NCD.*

$H_{0\text{-}3a\text{-}b}$: There exists no significant immediate and trend change in the odds of receiving ESAs in patients with the on-label or off-label supported indications in the hospital settings after the implementation of *REMS.*

Specific Aim 3a

To quantify the immediate and trend unintended impacts of black box warning, NCD, and REMS on the odds of receiving ESAs among the following patients in the hospital settings, adjusting for individual patient characteristics, hospital characteristics, and physician specialty:

1. Those with diagnoses related to the on-label indications of ESA use in the absence of observable contraindications.
2. Those with diagnoses related to the off-label supported indications of ESA use in the absence of observable contraindications.
3. Those with diagnoses related to the documented off-label unsupported indications of ESA use in the absence of observable contraindications.

Specific Aim 3b: Association between patient characteristics, clinical conditions, hospital characteristics, and admitting physician medical specialties on the odds of being prescribed ESAs for the on-label, off-label supported, and off-label unsupported indications

Research Question 3b

What are the associations between patient demographic and clinical characteristics, hospital characteristics, or physician specialty and the *odds* of receiving ESAs between January 2005 and June 2011 among patients with a) on-label and b) off-label supported indications, and c) documented off-label unsupported indications, other things constant?

Hypotheses for Question 3b

We hypothesize that patient demographic, clinical characteristics, hospital characteristics, and ordering physician specialties are associated with the *odds* of receiving ESAs among patients with a) on-label, b) off-label supported indications, and c) documented off-label unsupported indications.

Patient characteristics (age, race, gender, primary payer of health insurance)

$H_{0\text{-}3b\text{-}a}$: There exists no significant association between patient's age and the odds of receiving ESAs in the hospital settings among the three patient populations.

$H_{0\text{-}3b\text{-}b}$: There exists no significant association between patient's race and the odds of receiving ESAs in the hospital settings among the three patient populations.

$H_{0\text{-}3b\text{-}c}$: There exists no significant association between patient's gender and the odds of receiving ESAs in the hospital settings among the three patient populations.

$H_{0\text{-}3b\text{-}d}$: There exists no significant association between patient's primary payer of health insurance and the odds of receiving ESAs in the hospital settings among the three patient populations.

Patient clinical conditions (admission status, severity of illness, discharge disposition)

$H_{0\text{-}3b\text{-}e}$: There exists no significant association between patient's admission status and the odds of receiving ESAs in the hospital settings among the three patient populations.

$H_{0\text{-}3b\text{-}f}$: There exists no significant association between patient's severity of illness and the odds of receiving ESAs in the hospital settings among the three patient populations.

$H_{0\text{-}3b\text{-}g}$: There exists no significant association between patient's place of discharge and the odds of receiving ESAs in the hospital settings among the three patient populations.

Hospital characteristics (teaching status, bed size, geographic region)

$H_{0\text{-}3b\text{-}h}$: There exists no significant association between teaching status and the odds of receiving ESAs in the hospital settings among the three patient populations.

$H_{0\text{-}3b\text{-}i}$: There exists no significant association between hospital size and the odds of receiving ESAs in the hospital settings among the three patient populations.

$H_{0\text{-}3b\text{-}j}$: There exists no significant association between geographic region and the odds of receiving ESAs in the hospital settings among the three patient populations.

Physician specialty

$H_{0\text{-}3b\text{-}m}$: There exists no significant association between physician specialties and the odds of receiving ESAs in the hospital settings among the three patient populations.

Specific Aim 3b

To determine if association exist between patient characteristics, clinical conditions, physician specialty, and hospital characteristics and *odds* of receiving ESAs among patients with a) on-label, b) off-label supported indications, and c) documented off-label unsupported indications.

CHAPTER 3

Methodology

This chapter describes the study methodology used to assess the relative effect of safety regulations on the inpatient on-label and off-label ESA use between January 1, 2005 and June 30, 2011. The chapter is divided into five parts including 1) information regarding the data and subject selection, 2) classification of ESA use, 3) variable measurements, 4) statistical analysis and testing of hypotheses, and 5) data privacy.

Study Design and Data Collection

This was a retrospective time-series study of patients within a multi-hospital database. The data for this retrospective cohort study came from Cerner Millennium and was provided through the Center for Clinical and Translational Research (CCTR) at Virginia Commonwealth University.[a] The Cerner HealthFacts® database provides de-identified, HIPAA-compliant, longitudinal collection of patient information generated from the Cerner® electronic medical record (EMR) from over one hundred community and academic hospitals in the United States. The data

The Cerner HealthFacts® database contained detailed information on inpatient care such as procedure and diagnoses-specific data (in International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) format) from discharge abstract summaries and

[a] The project described was supported by CTSA award No. UL1TR000058 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

inpatient medication orders. Database elements also included patient (age, gender, race, admission date, discharge date and length of stay), hospital (bed size, geographic region), drug (medication started dates), and ordering physician (medical specialty) information.

Study Population

Eligible visits/patients were adult individuals who were admitted to Cerner hospitals with predefined diagnoses codes (on-label, off-label supported, or known off-label unsupported) or received at least one order of erythropoietin during the period of January 1, 2005 and June 30, 2011.

Inclusion and Exclusion Criteria

This study included all visits of adult patients (≥ 18 years of age) who were admitted to Cerner hospitals and received erythropoietin (epoetin alfa or darbepoetin alfa) at least once during their stay. Visits with no recorded information on ICD-9-CM diagnoses codes were excluded. In addition, all visits of adult patients with predefined ICD-9-CM for on-label and off-label indications of ESAs were included in the analysis. Visits without any drug records were excluded from the analyses. Children and adolescence were excluded from all analyses as the indications and level of evidence supporting use of ESAs were different by age within the pediatric population themselves and also between the two populations. A list of pre-specified ICD-9-CM codes used to define on-label, off-label supported, and documented off-label unsupported uses are described in Table 3.1 – 3.4 and detail use categorization is described in the later part.

Classification of ESA use

Use of ESAs was classified into three categories using ICD-9-CM diagnoses codes, procedures codes, and/or their medication use, into (1) on-label use, ONS (approved by the FDA); (2) off-label use supported, OFS (use for the indications not approved by the FDA, but there is strong clinical evidence to support its use); and (3) off-label use unsupported, OFU (use for the indications not approved by the FDA and lacking clinical evidence). The DRUGDEX system is described in detail in Section 1 of Chapter 2.

First, the list of all FDA-approved indications provided in the drug's package inserts was compared with the FDA-approved indication listed by DRUGDEX. Conditions that matched with the indications stated in the drug's package insert and confirmed by DRUGDEX were identified as on-label (ONS). Discrepancies existing between the two sources were resolved by consulting with the clinical expert, Dr. Donald F. Brophy, Pharm.D., M.Sc., FCCP, FASN, BCPS. ICD-9-CM diagnoses codes, ICD-9-CM procedures codes, and certain use of medications related to the conditions were used to identify patients with ONS conditions. The ONS conditions for epoetin alfa and darbepoetin alfa included anemia of chronic kidney disease, chemotherapy-induced anemia, zidovudine-induced anemia, and an indication of a patient undergoing a major, non-cardiovascular surgery that may result in loss of significant amount of blood.

The categorization of a specific off-label indication using the strength of evidence, level of recommendation, and treatment effectiveness provided by DRUGDEX were proposed by Walton et al. [189] In their study, off-label use was categorized into three groups: evidence-based off-label use, uncertain evidence for off-label use, and inadequate evidence for off-label use.

However, to avoid classifying off-label as uncertain, we categorized off-label use into two groups: supported and unsupported, as suggested by other off-label studies.[15, 190] A use of a drug for a condition was off-label supported (OFS) if its use in such condition was recommended by the compendium (Class I-IIb) and/or supported by published clinical evidence (Category A, B). On the other hand, the use was classified as off-label unsupported (OFU) if it was for a condition not recommended by DRUGDEX (Class III or In-determinant) and minimal evidence regarding such use was present (Category C or No evidence).[56] An indication receiving an efficacy rating of "effective" and "evidence favors efficacy" was classified as off-label supported use while that with "inconclusive evidence" and "ineffective" was labeled off-label unsupported.[56] Should conflicts between these three drug evaluation dimensions arise; a conservative approach was taken; an indication was categorized into the group that the least favorable level of evidence indicates. For example, if a use falls under Class IIb, Category C, with an evidence that favors efficacy, it was classified as off-label unsupported, not off-label supported, based on its strength of evidence (Category C).

In a similar fashion to ONS, ICD-9-CM diagnoses codes, ICD-9-CM procedures codes, and certain use of medications related to the conditions were use to identify visits of a patient with OFS conditions. Examples of OFS conditions for ESAs were non-chronic kidney diseases, anemia due to adverse effect of ribavirin and interferon alfa in hepatitis C patients, congestive heart failure, and rheumatoid arthritis.

Listed OFU use included treatment of anemia in cancer patients not undergoing concurrent chemotherapy, anemia in traumatic patients, porphyria cutanea tarda, and sickle cell anemia. Additional unsupported off-label uses of ESAs were identified from the published off-label literature.[15] Examples of such use included the treatment of anemia of chronic diseases,

hemorrhage, and cardiac surgery. The algorithmic categorization used in this study is described in Figure 3.1 and complete list of ICD-9-CM diagnoses/procedure codes and drug orders used to identify the ONS, OFS, and OFU cohorts can be found in Table A.1, A.2, and A.3, respectively.

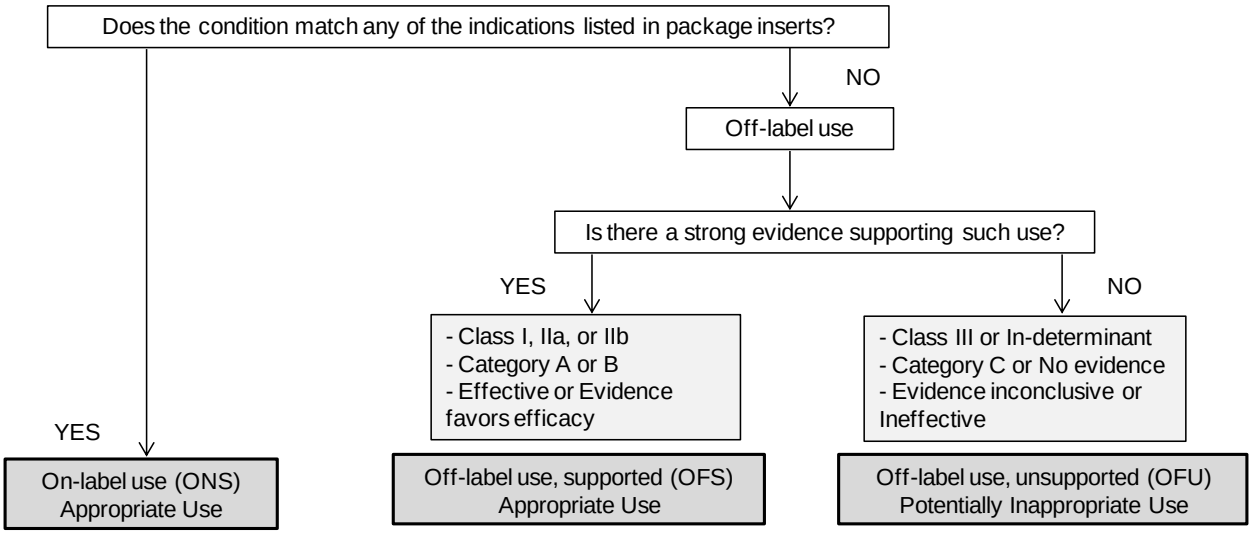

Figure 3.1 Schematic algorithm of categorizing ESA use

Despite the fact that darbepoetin alfa was only approved for the treatment of chronic kidney disease and chemotherapy-induced anemia, hospitals may choose to include solely darbepoetin alfa in their formulary and the drug can be used solely in place of epoetin alfa be used on-label and off-label. As a result, this study did not distinguish the two erythropoietins for on-label or off-label indications.

Table 3.1 ICD-9-CM procedures and diagnoses codes used to identify on-label use of ESAs

Therapeutic use of epoetin alfa	Selection criteria (ICD-9-CM diagnoses & procedure codes and drug use)	ICD-9-CM descriptions
On-label indications (ONS)		
1. Anemia of chronic renal failure	285.21	Anemia in chronic kidney disease
	585	Chronic kidney disease (CKD)
	403	Hypertensive kidney disease
	404	Hypertensive heart and kidney disease
	753.0	Congenital anomalies of urinary system - Renal agenesis and dysgenesis
	753.3	Other specified anomalies of kidney
	996.73	Other complications of internal (biological) (synthetic) prosthetic device, implant, and graft - Due to renal dialysis device, implant, and graft
	996.81	Complications of kidney transplant
	V42	Kidney transplant
	V45.1	Renal dialysis status
	V45.73	Acquired absence of kidney
	V56.0	Aftercare involving extracorporeal dialysis
	V56.1	Fitting and adjustment of extracorporeal dialysis catheter
	V56.2	Fitting and adjustment of peritoneal dialysis catheter
	V56.3	Encounter for adequacy testing for hemodialysis or peritoneal dialysis
	V 56.8	Aftercare involving other dialysis
	38.95	Venous catheterization for renal dialysis
	39.27	Ateriovenostomy for renal dialysis
	39.95	Hemodialysis
	54.98	Peritoneal dialysis
2. Anemia due to chemotherapy in patients with metastatic, non-myeloid malignancies	285.22 combined with any of the following codes or chemotherapeutic agents (see chemotherapeutic agents list)	Anemia in neoplastic disease
	V58.1	Encounter for antineoplastic chemotherapy and immunotherapy
	E933.1	Antineoplastic and immunosuppressive drugs causing adverse effects in therapeutic use
	V66.2	Convalescence following chemotherapy
	V67.2	Follow-up examination following chemotherapy
	00.10	Implantation Of Chemotherapeutic Agent
	99.25	Injection Or Infusion Of Cancer Chemotherapeutic Substance
3. Anemia due to	042	Human immunodeficiency virus (HIV) disease

zidovudine adverse reaction	Any order of zidovudine	Zidovudine, abacavir/lamivudine/zidovudine, or lamivudine-zidovudine
	E931.7	Antiviral drugs causing adverse effects in therapeutic use
4. Prophylaxis of blood transfusion before and during surgical procedure	Any of the following V codes or major surgical procedure codes (see Table X in Appendix) with codes for injury, cardiac dx/surgeries, or procedural bleeding (see lists of injury diagnoses and procedural bleeding codes in Table 3.3)	
	V54.0	Aftercare involving internal fixation device
	V54.9	Unspecified orthopedic aftercare
	V58.4	Other aftercare following surgery
	V58.7	Aftercare following surgery to specified body systems not elsewhere classified
	V66.0	Convalescence following surgery

Generic names of chemotherapy agents used as inclusion criteria of on-label use of ESAs were specified below:

Arsenic trioxide, azacitidine, bleomycin, busulfan, capecitabine, carboplatin, carmustine, cisplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gemcitabine, idarubicin, ifosfamide, irinotecan, lomustine, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitomycin, mitoxantrone, oxaliplatin, paclitaxel, pemetrexed, procarbazine, streptozocin, teniposide, thioguanine, thitepa, topotecan, vinblastine, vincristine, and vinorelbine[191]

Table 3.2 ICD-9-CM procedures and diagnoses codes used to identify off-label supported use of ESAs

Therapeutic use of epoetin alfa	Selection criteria (ICD-9-CM diagnoses & procedure codes and drug use)	ICD-9-CM descriptions
Off-label Supported indications (OFS)		
1. Non-chronic kidney disease	581	Nephrotic syndrome
	582	Chronic glomerulonephritis
	583	Nephritis and nephropathy not specified as acute or chronic
	584	Acute kidney failure
	586	Renal failure unspecified
	587	Renal sclerosis unspecified
	588.89	Other specified disorders resulting from impaired renal function
	593.0	Nephroptosis
	593.1	Hypertrophy of kidney
	593.2	Cyst of kidney acquired
	593.6	Postural proteinuria
	593.8	Other specified disorders of kidney and ureter
	593.9	Unspecified disorder of kidney and ureter
	753.1	Cystic kidney disease
	794.4	Nonspecific abnormal results of function study of kidney
2. Anemia in patients with hepatitis C being treated with a combination of ribavirin and interferon alfa or ribavirin and peginterferon alfa	070.41	Acute hepatitis c with hepatic coma
	070.44	Chronic hepatitis c with hepatic coma
	070.51	Acute hepatitis c without hepatic coma
	070.54	Chronic hepatitis c without hepatic coma
	070.70	Unspecified viral hepatitis c without hepatic coma
	070.71	Unspecified viral hepatitis c with hepatic coma
	Any order of ribavirin and interferon alfa	interferon alfa-2a, interferon alfa-2b, interferon alfacon-1, interferon alfa-n1, interferon alfa-n3, interferon alfa-2b-ribavirin, or ribavirin
3. Anemia due to congestive heart failure	398.91	Rheumatic heart failure (congestive)
	402.91	Unspecified hypertensive heart disease with heart failure
	428	Heart failure
4. Anemia due to radiation	V58.0	Encounter for radiotherapy
	V66.1	Convalescence following radiotherapy
	V67.1	Follow-up examination following radiotherapy
	990	Effects of radiation unspecified
	E879.2	Radiological procedure and radiotherapy as the cause of abnormal reaction of patient or of later complication without misadventure at time of procedure
	E926.3	Exposure to x-rays and other electromagnetic ionizing radiation

	E926.5	Exposure to radioactive isotopes
	92.2	Therapeutic Radiology And Nuclear Medicine
5. Anemia during the puerperium	641	Antepartum hemorrhage abruptio placentae and placenta previa
	646	Other complications of pregnancy not elsewhere classified
	648	Other current conditions in the mother classifiable elsewhere but complicating pregnancy childbirth or the puerperium
	664	Trauma to perineum and vulva during delivery
	666	Postpartum hemorrhage
	674	Other and unspecified complications of the puerperium not elsewhere classified
	677	Late effect of complication of pregnancy childbirth the puerperium
	72	Forceps, Vacuum, And Breech Delivery
	73	Other Procedures Inducing Or Assisting Delivery
	74	Cesarean Section And Removal Of Fetus
	75	Other Obstetric Operations
6. Anemia due to multiple myeloma	203.0	Multiple myeloma and immunoproliferative neoplasms
7. Anemia due to myelodysplastic syndrome	238.72	Low grade myelodysplastic syndrome lesions
	238.73	High grade myelodysplastic syndrome lesions
	238.74	Myelodysplastic syndrome with 5q deletion
	238.75	Myelodysplastic syndrome, unspecified
8. Anemia due to myelofibrosis	238.76	Myelofibrosis with myeloid metaplasia
	289.83	Myelofibrosis
9. Anemia due to rheumatoid arthritis	714	Rheumatoid arthritis and other inflammatory polyarthropathies
10. Beta Thalassemia	282.49	Other thalassemia
11. Blood unit collection for autotransfusion	99.02	Transfusion of previously collected autologous Blood

Table 3.3 ICD-9-CM procedures and diagnoses codes used to identify documented off-label unsupported use of ESAs

Therapeutic use of epoetin alfa	Selection criteria (ICD-9-CM diagnoses & procedure codes and drug use)	ICD-9-CM descriptions
Known Off-label Unsupported Indications (OFU Known)		
1. Cancer with no indication of chemotherapy	285.22	Anemia in neoplastic disease
	141-239	Various types of neoplasm
	V10	Personal history of malignant neoplasm
2. Anemia of chronic disease	280	Iron deficiency anemias
	281	Other deficiency anemias
	282	Hereditary hemolytic anemias
	283	Acquired hemolytic anemias
	284	Aplastic anemia
	285	Other and unspecified anemias
	286	Coagulation defects
	287	Purpura and other hemorrhagic conditions
	289	Other diseases of blood and blood-forming organs
3. Hemorrhage	430	Other diseases of blood and blood-forming organs
	431	Intracerebral hemorrhage
	432	Other and unspecified intracranial hemorrhage
	456.20	Esophageal varices in diseases classified elsewhere with bleeding (bleeding)
	455.2	Internal hemorrhoids with other complication
	455.5	External hemorrhoids with other complication (bleeding)
	455.8	Unspecified hemorrhoids with other complication (bleeding)
	459	Other disorders of circulatory system
	511.8	Other specified forms of pleural effusion except tuberculous
	530.21	Ulcer of esophagus with bleeding
	530.82	Esophageal hemorrhage
	530.0	Acute gastric ulcer with hemorrhage
	531.1	Acute gastric ulcer with perforation
	531.2	Acute gastric ulcer with hemorrhage and perforation
	531.4	Chronic or unspecified gastric ulcer with hemorrhage
	531.5	Chronic or unspecified gastric ulcer with perforation
	531.6	Chronic or unspecified gastric ulcer with hemorrhage and perforation
	532.1	Acute duodenal ulcer with perforation

532.4	Chronic or unspecified duodenal ulcer with hemorrhage
532.5	Chronic or unspecified duodenal ulcer with perforation
532.6	Chronic or unspecified duodenal ulcer with hemorrhage and perforation
533.4	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage without obstruction
534.4	Chronic or unspecified gastrojejunal ulcer with hemorrhage
534.9	Gastrojejunal ulcer unspecified as acute or chronic without hemorrhage or perforation
535.01	Acute gastritis with hemorrhage
535.11	Atrophic gastritis with hemorrhage
535.41	Other specified gastritis with hemorrhage
535.51	Unspecified gastritis and gastroduodenitis with hemorrhage
535.61	Duodenitis with hemorrhage
535.71	Eosinophilic gastritis with hemorrhage
537.83	Angiodysplasia of stomach and duodenum with hemorrhage
537.84	Dieulafoy lesion (hemorrhagic) of stomach and duodenum
562.12	Diverticulosis of colon with hemorrhage
562.13	Diverticulitis of colon with hemorrhage
568.81	Hemoperitoneum (nontraumatic)
569.3	Hemorrhage of rectum and anus
569.85	Angiodysplasia of intestine with hemorrhage
569.86	Dieulafoy lesion (hemorrhagic) of intestine
578	Gastrointestinal hemorrhage
635.11	Legally induced abortion incomplete complicated by delayed or excessive hemorrhage
640.03	Threatened abortion antepartum
729.92	Nontraumatic hematoma of soft tissue
784.7	Epistaxis
786.3	Hemoptysis
790.92	Abnormal coagulation profile
998.11	Hemorrhage complicating a procedure
998.12	Hematoma complicating a procedure
E870.0	Accidental cut puncture perforation or hemorrhage during surgical operation
28.7	Control Of Hemorrhage After Tonsillectomy And Adenoidectomy
44.4	Control Of Hemorrhage And Suture Of Ulcer Of Stomach Or Duodenum

	49.95	Control Of (Postoperative) Hemorrhage Of Anus
	57.93	Control Of (Postoperative) Hemorrhage Of Bladder
	60.94	Control Of (Postoperative) Hemorrhage Of Prostate
4. Cardiac surgery	V72.81	Pre-operative cardiovascular examination
	00.4	Adjunct Vascular System Procedures
	00.5	Other Cardiovascular Procedures
	00.6	Procedures On Blood Vessels
	17.5	Additional Cardiovascular Procedures
	35	Operations On Valves And Septa Of Heart
	36	Operations On Vessels Of Heart
	37	Other Operations On Heart And Pericardium
	38	Incision, Excision, And Occlusion Of Vessels
	39	Other Operations On Vessels
5. Acute use in critical care/injury/trauma/fracture	733.1	Pathologic fracture
	733.8	Malunion and nonunion of fracture
	733.93-733.98	Stress fracture of bones (various sites)
	800-829	Fracture (various sites)
	850-854	Intracranial Injury, Excluding Those With Skull Fracture
	860-869	Internal Injury Of Chest, Abdomen, And Pelvis
	870-879	Open Wound Of Head, Neck, And Trunk
	880-887	Open Wound Of Upper Limb
	890-897	Open Wound Of Lower Limb
	900-904	Injury To Blood Vessels
	905-909	Late Effects Of Injuries, Poisonings, Toxic Effects, And Other External Causes
	910-919	Superficial Injury
	920-924	Contusion With Intact Skin Surface
	925-929	Crushing Injury
	958	Certain early complications of trauma
	959	Injury other and unspecified
	E887	Fracture cause unspecified
	V54.1	Aftercare for healing traumatic fracture
	V54.2	Aftercare for healing pathologic fracture
	16.89	
6. Other known off-label use	277.1	Anemia in porphyria cutanea tarda
	282.6	Sickle-cell disease
	410	Acute myocardial infarction
	411	Other acute and subacute forms of ischemic heart disease
	412	Old myocardial infarction
	555	Regional enteritis
	556	Ulcerative enterocolitis
	607.84	Sexual dysfunction
	99.0	Blood transfusion

Table 3.4 ICD-9-CM procedures codes of major surgeries used to identify on-label use of ESAs

Therapeutic use of epoetin alfa	ICD-9-CM procedure	ICD-9-CM descriptions
Prophylaxis of blood transfusion before and during surgical procedure*	00.7	Other Hip Procedures
	00.8	Other Knee Procedures
	01-05	Operations On The Nervous System
	06-07	Operations On The Endocrine System
	30-34	Operations On The Respiratory System
	40-41	Operations On The Hemic And Lymphatic System
	42-54	Operations On The Digestive System
	55-59	Operations On The Urinary System
	60-64	Operations On The Male Genital Organs
	65-71	Operations On The Female Genital Organs
	72-75	Obstetrical Procedures
	76-84	Operations On The Musculoskeletal System
	85-86	Operations On The Integumentary System

*Codes related to diagnostic procedures were not included

Variable Measurements for Inferential Statistics

Independent variables

Independent variables of the multivariable regression models assessing the impact of safety interventions on ESA prescribing patterns were the three events of the safety interventions. During the six years period, five types of interventions had occurred, namely the issuance of a public health advisory (November 2006), Dear Health Care Professional Letter (January 2007), FDA black box warning (March 2007), reimbursement restriction (July 2007 and April 2008), and REMS (March 2010). Interventions that occurred very close to one another were consolidated because time-series study design suggested at least 10-12 time points between each segment to accurately assess seasonality and trend impact. [192] As a result of event consolidation, three specific events were chosen to represent interventions at three time points. These events were the addition of black box warning in March 2007; the official implementation of NCD in April 2008; and the implementation of REMS in March 2010. In the first period between January 2005 and April 2008, three events had occurred: the issuance of the first public health advisory (November 2006), Dear Health Care Professional Letter (January 2007), labeling revision to include a black box warning (March 2007), and the announcement of NCD effective (July 2007). The addition of a black box warning was chosen as a main intervention during this nine months period. Black box warning was chosen over a public health advisory because we believe that black box warning was more publicized and would have a more prominent effect on ESA utilization than an advisory. We did not choose July 2007, the month which NCD first was announced effective as the first intervention because the change in reimbursement policy was not directly applicable to the inpatient setting and should have little effect in our sample. Moreover,

little effect of the NCD during this period was anticipated because the announcement was only made public in the CMS website and without any press release.

The second period of this analysis was between April 2008 and March 2010. During this period, two events occurred: the official implementation of NCD on April 7, 2008 and the revision of the black box warning on March 14, 2008. The official implementation of NCD was chosen as a main event in this period because we believed that the official implementation of the reimbursement restriction would have created a greater impact of the level of drug use, compared to a revision of a black box warning already in place.

The third and final period of the analysis lasted between March 2010 and June 2011. The implementation of REMS in March 2010 was the only event considered significant enough to influence ESA prescribing.

Table 3.5 Independent variables for Specific Aim 2 and 3

Event	**Time period**
First Intervention	
Public health advisory	November 2006
Dear Healthcare Provider letter	January 2007
Black box warning	**March, 2007**
National Coverage Determination announced effective	July 2007
Black box warning update	November 2007
Second Intervention	
Black box warning update	March 2008
National Coverage Determination Implemented	**April 2008**
Third Intervention	
REMS initial approval	February 2010
REMS Implementation	**March 2010**

*Bolded event and time period indicate the event and time of the intervention used in this study

Dependent variables

Specific Aim 2

Monthly aggregated proportions of visits with ESA use for on-label, off-label supported, and off-label unsupported indications were dependent variables for the time-series analysis. Definitions for ONS, OFS, and OFU proportions used as dependent variables were provided below.

1. On-label proportion

The proportion of encounters which ESAs were prescribed for on-label indications was defined as the number of encounters with diagnoses codes that matched with on-label indications for ESA use and had one order of ESAs (A), divided by the total number of encounters with those diagnoses codes (1), in a given time period.

2. Off-label supported proportion

The proportion of encounters being prescribed ESAs for the off-label supported indication was defined as the number of encounters with diagnoses codes that matched with on-label indications for ESA use and had one order of ESAs (B), divided by the total number of encounters with those diagnoses codes (2), in a given time period.

3. Off-label unsupported proportion

Since the total number of eligible encounters for ESA off-label unsupported indications could not feasibly be obtained from the database, the proportion of visits with ESAs prescribed for the off-label unsupported indication was calculated by dividing the number of encounters with ESAs, but did not have diagnoses codes that matched with on-label or off-label supported

indications of ESA use (C) + (D) by the total number of encounters with known OFU (3), in a given time period.

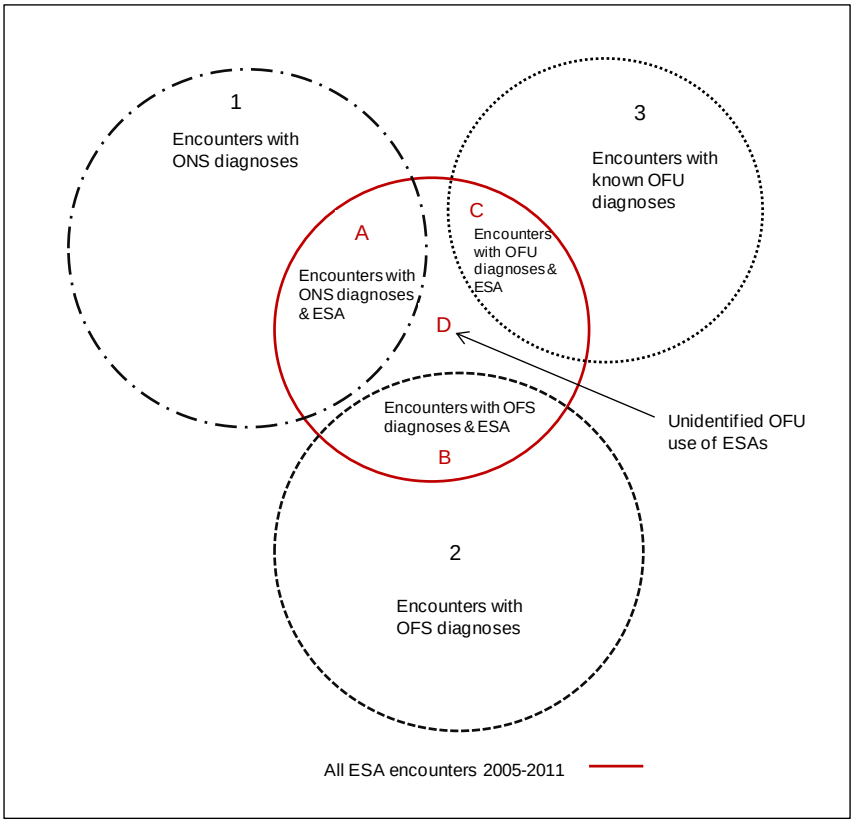

Figure 3.2 Proportion of ESA use as dependent variables for Specific Aim 2
ONS: On-label supported indications, OFS: Off-label supported indications, OFU: Off-label unsupported indications.

First, all inpatient visits of patients aged 18 and above who had at least one record of ESAs (epoetin alfa or darbepoetin alfa) were identified in the database. Two separate cohorts of epoetin alfa and darbepoetin alfa were formed. Each user's diagnoses, procedures, and medications records were searched to categorize use of ESAs into ONS, OFS, or OFU using the algorithm shown in Figure 3.2. The number of visits which ESAs were for prescribed for ONS, OFS, and OFU indications in a month was calculated as respective numerator cohorts.

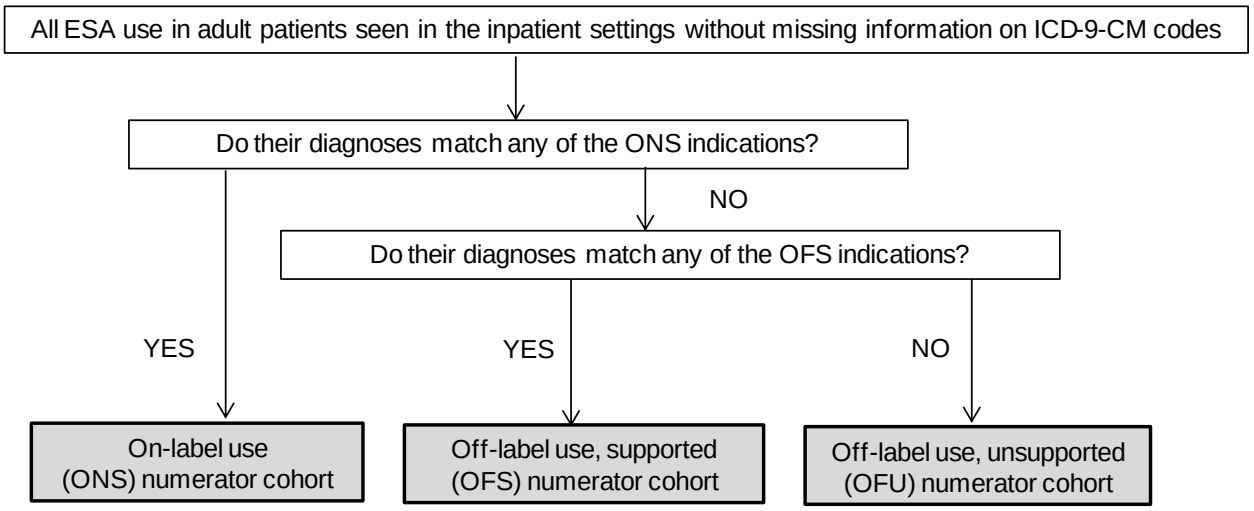

Figure 3.3 Schematic algorithm defining numerator cohorts for Specific Aim 2

Next, the monthly number of admissions eligible for receiving ESAs was calculated as denominator cohorts. All visits of adult patients admitted to the inpatient settings during the study period with diagnoses, procedure codes, and drug use of interest were included in the sample and categorized into the ONS, OFS, or OFU cohorts using a hierarchy categorization approach. First, diagnoses, procedures, and medication records of all admissions were searched for ONS indications, if none of their diagnoses matched the ONS indications, the same sets of records were searched for OFS indications and OFU accordingly. If diagnoses did not match ONS, OFS, or documented OFU indications, such encounters were excluded from this part of the analysis. It is important to note that the OFU denominator cohort only included visits with conditions known to be treated with ESAs off-label identified earlier in Table 3.3. This approach of using documented OFU conditions was taken because it was almost impossible to identify encounters with all possible off-label unsupported use of ESAs. Examples of documented OFU indications used in this study included its use in anemia of neoplastic disease not due to

chemotherapy, anemia due to trauma, bleeding, and other chronic anemia. Categorization of denominator cohorts followed the algorithm is shown in Figure 3.4.

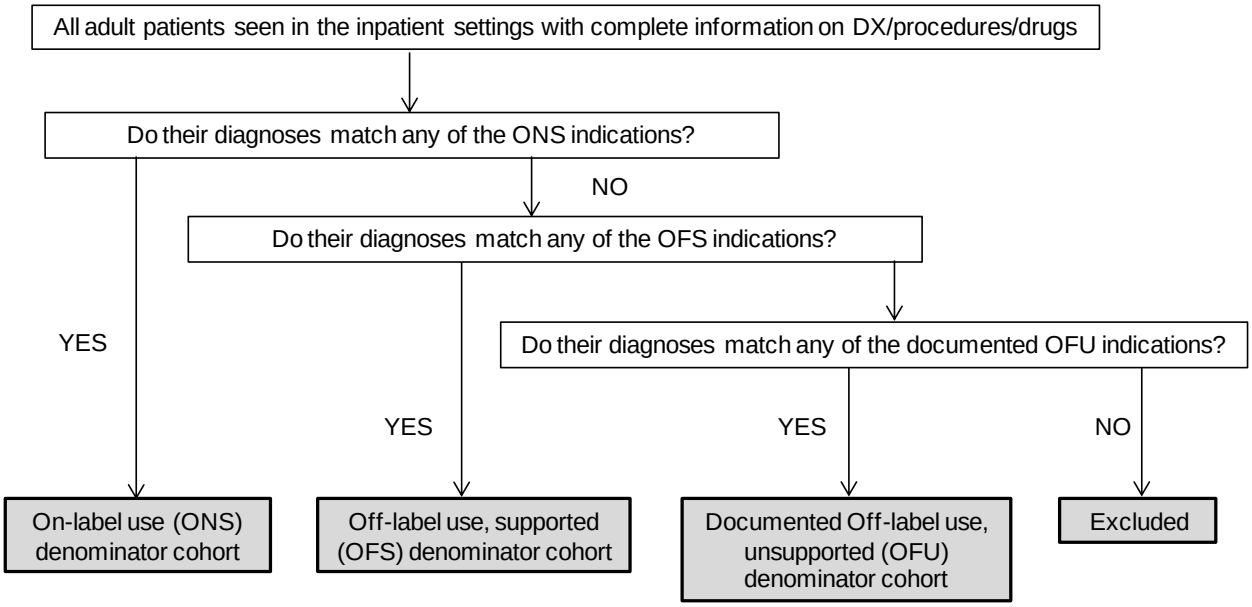

Figure 3.4 Schematic algorithm defining denominator cohorts for Specific Aim 2

Specific Aim 3

Dependent variable was ESA use, defined as whether or not an eligible patient received ESAs in a given month.

To assess the impact of the intervention on ESA prescribing patterns for the on-label, off-label supported, and off-label unsupported indications, three population proportions which were used as dependent variables were identified as following.

1. On-label: Proportion of patients with on-label conditions that were prescribed ESAs.
2. Off-label supported use: Proportion of patients with off-label supported conditions that were prescribed ESAs.
3. Off-label unsupported use: Proportion of patients with off-label unsupported conditions that were prescribed ESAs.

Similar steps were taken to identify the three cohorts: ONS, OFS, and documented OFU. Once the three cohorts were identified, drug records of these eligible patients were searched to determine if ESAs (epoetin alfa or darbepoetin alfa) were prescribed during a hospital stay. If a record of ESAs was found, that patient was classified as a user (ESA use = 1). Without a record of ESAs, that patient was a non-user (ESA use = 0). Schematic algorithm used to identify patient cohorts for the analysis is shown in Figure 3.5.

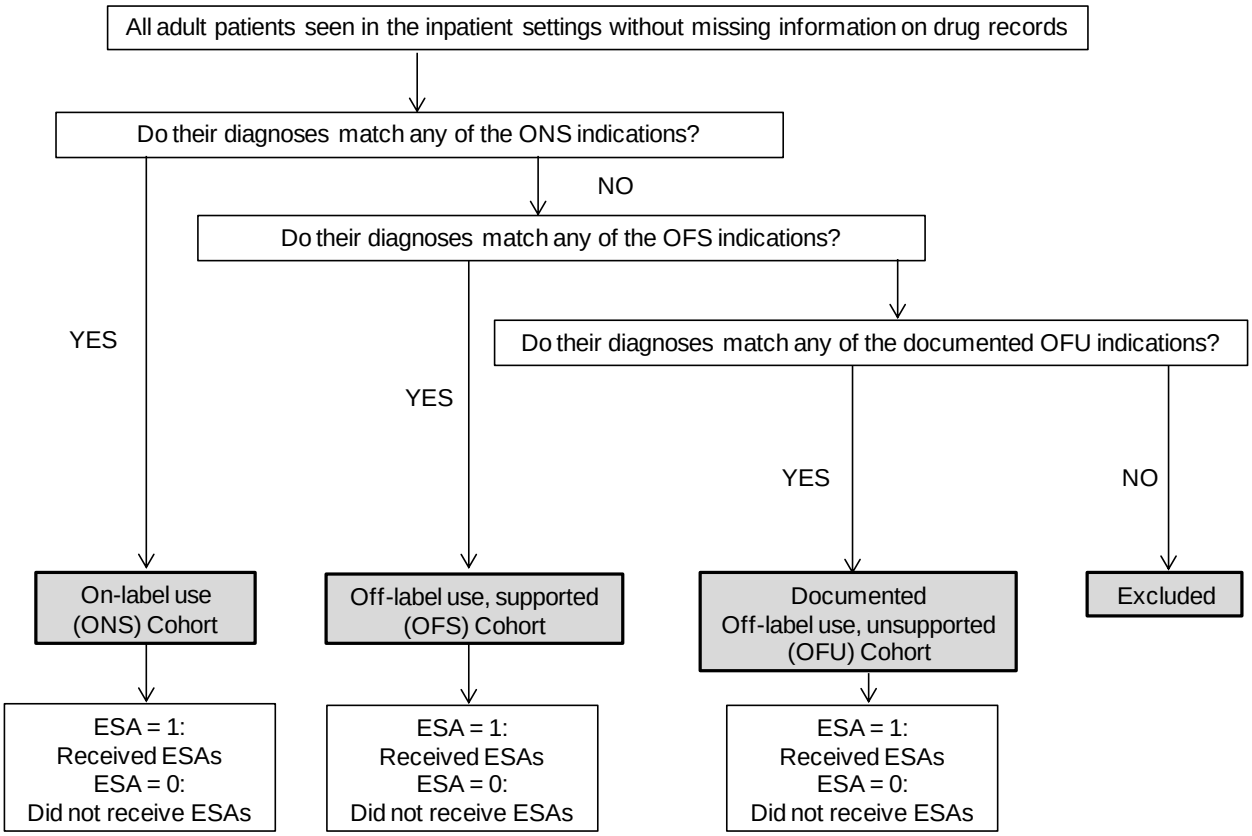

Figure 3.5 Schematic algorithm selecting study sample for Specific Aim 3

Covariates

Covariates included in the multivariable model used in Specific Aim 3 were patient demographics of age, gender, and race; primary payer of the hospital services; patient clinical conditions described by the proxies of admission type, discharge disposition, length of stay, Combined Comorbidity Index; hospital characteristics including teaching status, bed size, and geographic region, and physician specialty classified as specialist and non-specialist. We did not differentiate between the rural and urban status because very few hospitals in our sample were identified as rural hospitals. Due to small number of patients in the 'other' group of the admission type and discharge disposition, the other 'group' was combined with 'missing' group to obtain reliable estimates. Relevant studies identifying the aforementioned covariates as predictors of drug use were described in detail under Section 3 of Chapter 2. Table 3.6 describes the categorization of covariates used in the analytical models.

Table 3.6 Categorization of Covariates used in Specific Aim 3

Variable	Variable Name	Description
Patient Characteristics		
Demographics		
Age	age_in_years regrouped to age_cat	18-30 = 1 **31-50 = 6** 51-64 = 2 65-74 = 3 75-84 = 4 85 and above = 5
Race	race regrouped to race_cat	Missing = 0 African American = 1 Other = 2 **Caucasian = 3**
Gender	Gender recoded to gender_cat	Female = 0 Male = 1
Clinical Conditions		
Admission type	admission_type_code regrouped to admission_ cat	Missing/Other = 0 Urgent = 1 Elective = 2 **Emergency =** 3

Charlson Comorbidity Index	cci	Calculated from ICD-9-CM codes
Length of Stay	hos_los	Continuous, number of days from admission date to discharge date
Discharge status	discharge_disposition_key regrouped to discharge_cat	Missing/Other = 0 Expired = 1 Discharged to Hospice = 2 Discharged/transferred to institutionalized care = 3 Discharged/transferred to noninstitutionalized care = 4 **Discharged to home/self care = 5**
Payer Type		
Source of Payment	payer_id regrouped to payer_ cat	Missing = 0 Medicaid = 1 Commercial/Private/HMO Managed Care = 2 Self-pay = 3 Other = 4 **Medicare = 5**
Hospital Characteristics		
Geographic region	census_region regrouped to region_cat	Midwest = 1 South = 2 West = 3 **Northeast = 4**
Bed size	bed_size_range recoded to bed_cat	≤ 99 = 1 100-199 = 2 **200-299 = 5** 300-499 = 3 ≥500 = 4
Teaching status	teaching_facility_ind recoded to teaching	Teaching = 0 **Non-teaching = 1**
Physician and Care Characteristics		
Physician Specialty	medical_specialty regrouped to medical_specialty_cat	Missing = 0 Specialist = 1 **Non-specialist = 2**

*Bolding indicates reference group. Reference group was coded into the last order for convenience

Data Integration

Encounter information was captured in four main SAS datasets including patient, diagnoses, procedure, and medication files containing patient demographic information, ICD-9-CM codes, procedure codes, and medications used, respectively. Specific information including dosing unit, diagnoses type, care setting, admission type, physician specialty, payer, and hospital information are also provided in separate SAS files. Two master datasets were built by integrating the files using the selection criteria specified above. The first dataset was used for descriptive analysis of ESA users (patient level) and as numerator cohorts for aggregated time-series analysis (visit level). The second dataset was used for the patient level analysis of the impacts of safety interventions (Aim 3).

Descriptive analysis of ESA users and numerator cohorts for aggregated time-series analysis

Encounters with any order of epoetin alfa or darbepoetin alfa were first identified in the medication dataset. This medication dataset contained medication information like generic name, medication entered date, started date, and stopped date, care setting where medications were ordered and dispensed, dose quantity, frequency, and route of administration. Visits which ESAs were prescribed were linked to the two datasets containing diagnoses and procedure information, and encounters file which comprised of patient's age, admitted and discharged dates, patient type, admission source, discharge disposition, primary payer information, patient ID, and hospital ID. Only encounters of adult patients (18 years and above) admitted and received medication on January 1, 2005 onward were retained in the sample. Lastly, the file was merged with hospital and patient dataset for hospital and patient demographic information. For

the patient level analysis (descriptive analyses), in such case that the same patients had more than one encounter with the health system, only the first records were used in the study.

Outpatient encounters (hospital outpatient department, day surgical services, clinic, dialysis centers, laboratory, and emergency department and observational units) constituted 22.0% of our overall sample. Visits to outpatient settings, institution, nursing home, and home health services were excluded. The final inpatient cohort of 86,763 patients consisted of patients who were admitted to a hospital (inpatient), pre-admitted patient, patients in an obstetrics department, hospice, and skilled nursing facility (SNF). Hospice and SNF patients were included in the inpatient group because of similarity in insurance reimbursement toward the services (covered by Medicare Part A). The details of ESA use in each patient type reported in Cerner database are shown in Table 3.6 and 3.7.

The integrated data contained information of 111,363 encounters (86,763 unique patients) with at least one order of ESAs during their visit to the health system. Of these 111,363 encounters, 83,876 received epoetin alfa only (75.3%); 26,772 received darbepoetin alfa only (24.0%); and 715 (0.64%) received both epoetin alfa and darbepoetin alfa during that single visit. These encounters translated into 66,121 patients with epoetin alfa only (76.2%); 20,088 patients with darbepoetin alfa only (23.2%); and 554 patients with both use of epoetin alfa and darbepoetin alfa (0.6%)). Data integration steps used to identify ESA users (for descriptive analysis numerator in Specific Aim 2a) are described in Figure 3.6.

Table 3.7 ESA inpatient users (encounter level) identified in Cerner database

Care settings	N Encounters (column %)			
	Any ESAs	Epo	Darbe	Epo & Darbe
Inpatient				
Hospice	7 (0.01)	5 (0.01)	2 (0.01)	0 (0.00)
Inpatient	110,880 (99.57)	83,441 (99.48)	26,731 (99.85)	708 (99.02)
Obstetrics	2 (0.00)	2 (0.00)	0 (0.00)	0 (0.00)
Preadmit	121 (0.11)	101 (0.12)	19 (0.07)	1 (0.00)
Skilled Nursing Facility	353 (0.32)	327 (0.39)	20 (0.07)	6 (0.84)
Total (row %)	111,363 (100.00)	83,876 (75.32)	26,772 (24.04)	715 (0.64)

Table 3.8 ESA inpatient users (patient level) identified in Cerner database

Care settings	N Patient (column %)			
	Any ESAs	Epo	Darbe	Epo & Darbe
Inpatient				
Hospice	5 (0.01)	3 (0.01)	2 (0.01)	0 (0.00)
Inpatient	86,429 (99.62)	65,825 (99.55)	20,056 (99.84)	548 (98.92)
Obstetrics	3 (0.00)	3 (0.00)	0 (0.00)	0 (0.00)
Preadmit	82 (0.09)	65 (0.10)	16 (0.08)	1 (0.00)
Skilled Nursing Facility	244 (0.28)	225 (0.34)	14 (0.07)	5 (0.90)
Total (row %)	86,763 (100.00)	66,121 (76.21)	20,088 (23.15)	554 (0.64)

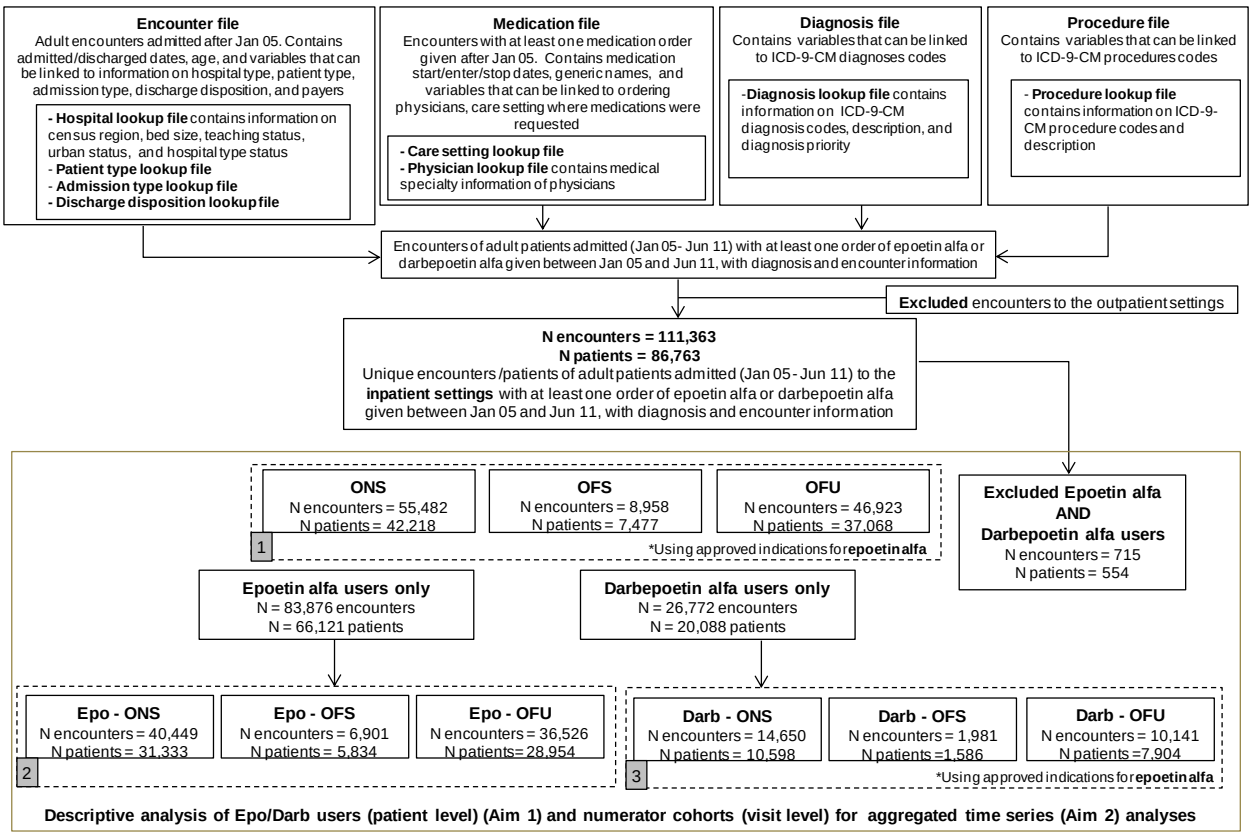

Figure 3.6 Data integration step of ESA users

Denominator cohorts for aggregated time-series analysis (Aim 2) and Specific Aim 3

The denominator cohort for Specific Aim 2 and analytic cohort for Specific Aim3 consisted of any visits (or patients – Aim 3) with diagnoses of interest (See Table 3.1-3.4). For consistency, we identified only visits from same hospitals as the ESA users that contributed medication records into Cerner database. The dataset included inpatient visits (inpatient, pre-admitted, obstetrics, hospice, and skilled nursing facility (SNF) encounters) in 128 unique hospitals. The initial cohort included a total of 2,170,654 unique visits (1,815,028 patients) with at least one condition specified as ONS, OFS, or documented OFU.

Of 2,170,654 encounters (1,815,028 patients), 912,141 encounters (750,321 patients) had diagnoses that made them eligible for ESA approved treatments. These visits (or patients) were classified as ONS cohort. 595,193 encounters (505,694 patients) had OFS diagnoses (OFS cohort), and 663,320 encounters (559,031 patients) had documented OFU diagnoses (OFU cohort). Data integration steps adopted in identifying all eligible cohorts for Specific Aim 2 and 3 are shown in Figure 3.7.

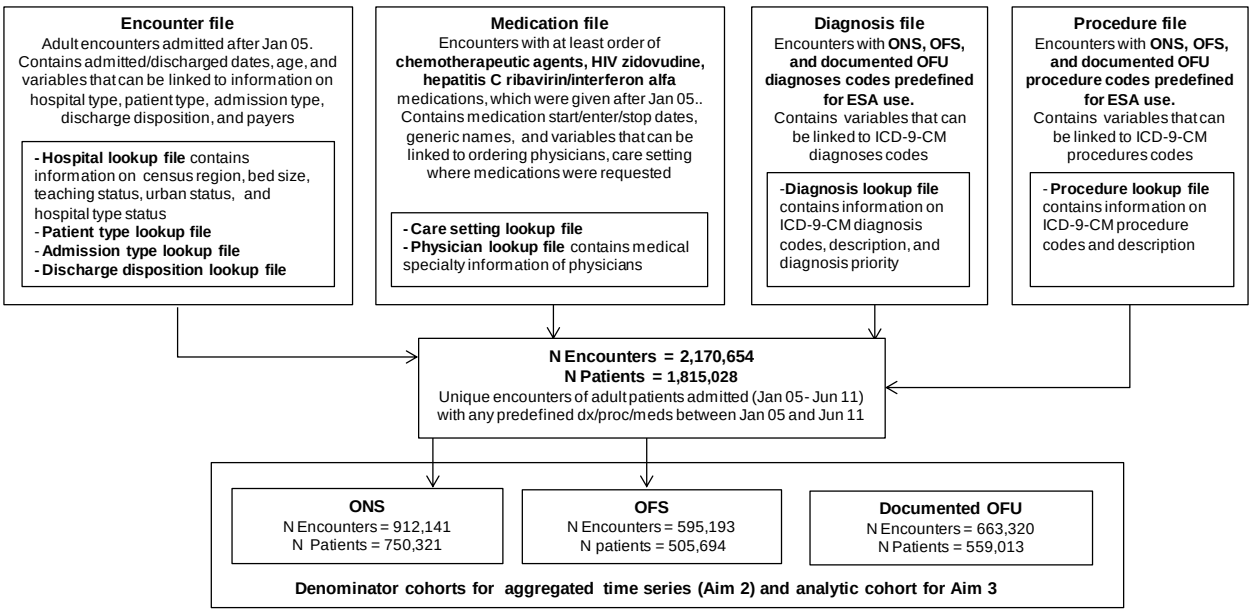

Figure 3.7 Data integration steps of all eligible admissions

Patient Risk Adjustment

This study made use of a combined comorbidity score developed to appraise a patient's mortality risk based on his ICD-9-CM diagnoses codes[193] to model patient's clinical complexity. The combined score of the Charlson Index with the Romano modification and van Walraven's adaptation of the Elixhauser system was developed by the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School to improve upon existing scores in predicting 1-year mortality in older adults. SAS codes we adapted to calculate validated combined comorbidity scores for this study were provided by the developers.[194] The use of the combined comorbidity score was justifiable in our study as our population of users consisted largely of older adults. Since no specific comorbidities were suggested by the literature as predictors of ESA prescribing, we did not include specific cormobid conditions in the multivariable models but instead the combined

comorbidity score to avoid multicollinearity between a set of comorbidities and comorbidity score.

Statistical Analysis

To understand the prevalence of ESA therapy in patients admitted to Cerner hospitals, descriptive analysis was performed. Patient demographics, clinical conditions, hospital characteristics, and ordering physician specialties of patients receiving epoetin alfa or darbepoetin alfa were aggregated over the study period of six and a half year and described with means, standard deviations, and column percentages. The differences in these variables among the two user groups were tested with chi-squares and t- statistics. Similarly, aggregated characteristics of ONS, OFS, and OFU users were also tested with chi-squares and t- statistics.

The inferential analyses were based on two techniques: segmented regression modeling for interrupted time-series (Aim 2), and generalized estimating equation (GEE) approach with binary logistic regression technique (Aim 3a and 3b).

Segmented Times Series (Aim 2)

Segmented time series study design provided the strongest quasi-experimental approach for investigating the longitudinal effect of the intervention. The lack of random assignment and a control group accustomed in observational studies hindered the true estimation of an exposure (intervention) on the outcomes. Internal validity of such study was therefore questionable because systematic differences in observed and unobserved characteristics of the treatment and non-treatment group were not accounted for. The time-series approach allowed for both visual statistical assessment of how much the intervention affects the outcomes immediately and over

time, transiently or permanently. The use of a control group was not necessarily with this study design because each segment served as a control for the preceding segments. In this study, monthly aggregate proportions of visits at which a patient received ESAs for a specific group of indications (ONS, OFS, or OFU) were a unit of analysis. ONS proportion was defined as the proportion of visits at which a patient was prescribed with ESAs for the indications approved by the FDA (ONS), over the total number of visits at which a patients had clinical conditions eligible for receiving ESAs on-label, the a given month. OFS and OFU proportions were classified in a similar manner. Ordinary least square was chosen as the distribution of the data was approximately continuous i.e. the data did not consists of a mass at the limits (zero and/or one). First-differencing and suitable number of lags was included in the model to correct for autocorrelation of each observation in the series and to obtain accurate standard errors of the estimates.

Generalized Estimating Equations (Aim 3)

Previous studies identified hospital level differences in practices where patient's responses, though homogeneous within hospitals, may not be so across hospitals. In the presence of clustered data and in the situation where consecutive observation was not independent, the use of generalized estimating equations (GEE) approach was most appropriate. Clustered GEE model improved inferences as accounting of correlation structure between repeated observations provides unbiased and more efficient estimates of standard errors compared to the falsely small standard errors in the un-clustering model.[195, 196] In GEE, correlation structure that adequately described the known or suspected correlations between repeated observations was specified. The types of correlation structures commonly adopted included exchangeable, autoregressive, dependent, independent and unstructured. The choice of

correlation structure relied on the nature of the data. This study specified an exchangeable correlation structure as such type of correlation structure was the only one appropriate for clustered data with no natural ordering of the subjects with the cluster.[197]

We chose binary logistic regression method as it allows for non-normal distribution of the data. The binomial distribution and logit link function were specified to model with a dichotomous outcome variable. An outcome variable in the binary logistic regression model is defined as whether a patient with on-label, off-label supported, or off-label unsupported conditions received ESAs in that given month. To obtain robust standard errors of the estimates, we adjust for hospital level differences using hospital ID as a cluster variable.

A two-sided alpha of 0.05 is considered statistically significant for all analyses. SAS (version 9.3 for Windows; SAS Institute, Cary, NC) and Stata (Stata 11; Stata Corp, College Station, TX) was used for all analyses in this study.

Statistical Models

Specific Aim 2

To quantify the immediate and trend impact of the black box warning, NCD policy, and REMS on the change in the proportion of visits which a patient was treated with ESAs, three separate ordinary least square regressions for on-label, off-label supported, and off-label unsupported ESA use were fit. Impacts of black box warning, NCD, and REMS on the level of ESA use for the on-label and off-label indications were specified in the models shown below. A set of month indicators was included in the model to adjust for monthly seasonality.

Model 1: On-label (ONS)

$$Y_{ONSt} = \beta_0 + \beta_1 t + \beta_2 \text{intervention1} + \beta_3 \text{intervention1} \times t_1 + \beta_4 \text{intervention2} + \beta_5 \text{intervention2} \times t_2 + \beta_6 \text{intervention3} + \beta_7 \text{intervention3} \times t_3 + M + e_t$$

Model 2: Off-label Supported (OFS)

$$Y_{OFSt} = \beta_0 + \beta_1 t + \beta_2 \text{intervention1} + \beta_3 \text{intervention1} \times t_1 + \beta_4 \text{intervention2} + \beta_5 \text{intervention2} \times t_2 + \beta_6 \text{intervention3} + \beta_7 \text{intervention3} \times t_3 + M + e_t$$

Model 3: Off-label Unsupported (OFU)

$$Y_{OFUt} = \beta_0 + \beta_1 t + \beta_2 \text{intervention1} + \beta_3 \text{intervention1} \times t_1 + \beta_4 \text{intervention2} + \beta_5 \text{intervention2} \times t_2 + \beta_6 \text{intervention3} + \beta_7 \text{intervention3} \times t_3 + M + e_t$$

Figure 3.8 Segmented regressions modeling interrupted time-series used in assessing the impact of the interventions on ESA prescribing

Y_{ONSt}: Proportion of ESA use among eligible visits

Coefficients: β_0 Baseline proportion of ESA on-label use at t = 0; β_1 Change in proportion of ESA on-label use (Y_t) that occurs with each month before the first intervention; β_2 Level change in proportion of ESA on-label use immediately after the first intervention; β_3 Change in the trend in proportion of ESA on-label use after the first intervention

Independent variables: intervention1 = Black Box Warning; intervention2 = National Coverage Determination; intervention3 = REMS

Time variable: t = number of month of the study period (1-78); t1 = number of month since the occurrence of the *first* intervention (Mar 07) till the end of the study period (t1 =1-52); t2 = number of month since the occurrence of the *second* intervention (April 08) (t1 = 1-39); t3 = number of month since the occurrence of the *third* intervention (Mar10) (t1 = 1- 16)

M: a set of month indicator variable to control for monthly seasonal effect;

A similar interpretation was applied for all three models. For the purpose of presentation simplicity, only interpretation of Model 1 was given below.

In Specific Aim 2, Y_{ONSt} was the monthly proportion of visits at which a patient was prescribed with ESAs for on-label purposes over the total number of eligible visits in that month. Variable *t* was a continuous variable indicating the number of month since the beginning of the

study takes on values from 1 to 78. Intervention 1 was a dichotomous variable indicating the issuance of black box warning; t_1 equaled 0 for the months prior to that issuance and took the values 1 to 51 indicating the numbers of months since issuance (March 2007; $t_1 = 1$ in March 2007) to the end of the study period. Intervention 2 was a dichotomous variable indicating the official implementation of NCD; t_2 equaled 0 for the months prior to that when NCD was release and took the values 1 to 39 indicating the numbers of months since the implementation (April 2008; $t_2 = 1$ in April 2008) to end of the study period. Intervention 3 was a final dichotomous variable marking the point in time when REMS was implemented; t_3 takes a value of 0 for the months prior to the third intervention and 1 through 15 indicating the numbers of months since the implementation of REMS (March 2010; $t_3 = 1$ in March 2010) until the end of the study period.

The coefficients in the model can be interpreted as followed: β_0 represents baseline proportion of ESA use at t = 0; β_1 was the change in proportion of ESA use (Y_t) that occurred with each month before the release of black box warning (Intervention 1); β_2 level change in proportion of ESA use immediately after the black box labeling change; β_3 change in the trend in the proportion of ESA use after black box warning. Similarly, β_4, and β_6 represented level change in the dependent variables immediately after the release of NCD (Intervention 2) and the implementation of REMS (Intervention 3), respectively. Finally, β_5, and β_7 represented changes in the trend in the Y variables after the occurrence of each intervention, respectively.

Specific Aim 3a and 3b

Three models using the same set of independent variables and covariates were fit separately to determine the impacts of the interventions on the odds of an ESA being prescribed to a patient with 1) on-label, 2) off-label supported, and 3) documented OFU conditions. Figure 3.3 specifies the models that were fit to examine the trend and immediate effects of the three interventions on the odds of an ESA being prescribed to a patient.

Model 1: On-label (ONS)

$$\text{Logit(ESA=1)} = \beta_0 + \beta_1 t + \beta_2 \text{intervention1} + \beta_3 \text{intervention1} \times t_1 + \beta_4 \text{intervention2} + \beta_5 \text{intervention2} \times t_2 + \beta_6 \text{intervention3} + \beta_7 \text{intervention3} \times t_3 + \text{DEM} + \text{HEALTH} + \text{HOS} + \text{PHYS} + e_t$$

Model 2: Off-label Supported (OFS)

$$\text{Logit(ESA=1)} = \beta_0 + \beta_1 t + \beta_2 \text{intervention1} + \beta_3 \text{intervention1} \times t_1 + \beta_4 \text{intervention2} + \beta_5 \text{intervention2} \times t_2 + \beta_6 \text{intervention3} + \beta_7 \text{intervention3} \times t_3 + \text{DEM} + \text{HEALTH} + \text{HOS} + \text{PHYS} + e_t$$

Model 3: Documented Off-label Unsupported (Known OFU)

$$\text{Logit(ESA=1)} = \beta_0 + \beta_1 t + \beta_2 \text{intervention1} + \beta_3 \text{intervention1} \times t_1 + \beta_4 \text{intervention2} + \beta_5 \text{intervention2} \times t_2 + \beta_6 \text{intervention3} + \beta_7 \text{intervention3} \times t_3 + \text{DEM} + \text{HEALTH} + \text{HOS} + \text{PHYS} + e_t$$

DEM = a vector of patient demographic variables; HEALTH = a vector of clinical conditions; HOS = hospital characteristics; PHYS = physician specialty.

Figure 3.9 Models used to assess the impact of interventions on odds of being prescribed with ESAs for a patient with on-label and off-label supported indications.

Again, since similar interpretation was applied for all three models. For the purpose of presentation simplicity, only interpretation of Model 1 was given below.

In Model 1, logit (ESA=1) represented the odds of receiving ESAs in a patient with an on-label conditions. All other independent variables were the same as specified under Specific

Aim 1. DEM denotes a vector of patient demographic variables which included age (18-30, 31-50, 51-60, 61-64, 65-74, 75-84, and 85 and above years old), gender (Male and Female), and race (Caucasian, African-American, Hispanic, Other); Payer was specified as the primary payer of the hospital services (Medicare, Medicaid, Private, Self-pay, and Other); HEALTH was a vector of patient clinical conditions including admission status (Elective, Emergency, Urgent, Other), length of stay, Comorbidity Index, and discharge status (Expired, Discharged to home, Hospice, Institutionalized care, Non-institutionalized care, Other); HOS include hospital characteristics variables such as geographic region (Northeast, Midwest, South, West), teaching status (Teaching, Non-teaching), and bed size (<99, 100-199, 200-299, 300-499, 500 or more). Lastly PHYS denotes physician specialty as non-specialist and specialist. Due to a large number of observations with missing information, we created a category 'Missing' for the race, payer, admission type, discharge status, and physician specialty variables.

The coefficients in the model can be interpreted as followed: β_0 is the intercept presenting baseline odds of receiving ESAs among patients with on-label indications when the effects of all independent variables in the model were turned off; β_1 represented the time trend prior to the first intervention, the black box warning. β_2 estimated the immediate effects of the first intervention (black box warning). In a similar manner, β_4 and β_6 estimated the immediate effects of NCD and REMS, respectively. β_3 estimated the change in time trend after the issuance of black box warning. β_5 and β_7 represented the change in time trends after the implementation of NCD and REMS, respectively. Finally, e_t was the error term represents the variability not explained by the model.

Human subjects' protection and data privacy

Cerner data are encrypted in such a way that no patient will be identified in order to ensure minimal confidentiality risks to the patients. Access to the dataset was restricted to individuals listed in the protocol. The data were maintained in a password-protected environment. The study proposal was submitted to the Institution Review Board (IRB) at Virginia Commonwealth University for an exemption 45 CFR 46.101(b)(4).[198] The approval number was HM 14257.

CHAPTER 4

Results

Research results are presented in this chapter. The results are summarized into five following sections:

1. Data Description
    - Study cohort for each specific aims
    - Overall prevalence and trend in ESA use from 2005 to 2011 by use category
2. Specific Aim 1
    - Descriptive summary of patient, hospital, and physician characteristics of ESA users
    - Descriptive summary of patient, hospital, and physician characteristics of epoetin alfa and darbepoetin alfa by use category
    - Specific indications of ESAs in ONS, OFS, and OFU use category
3. Specific Aim 2
    - Trend in ESA On-label, off-label supported, and off-label unsupported therapy
    - Outlier Identification and Data manipulation
    - Time-series model selection
    - Impacts of black box warning, NCD, and REMS on proportion of visits with ESA use
4. Specific Aim 3
    - Outlier Identification and Data manipulation
    - Bivariate analysis of ESA users
    - GEE model selection
    - Impacts of black box warning, NCD, and REMS on odds of being prescribed with ESAs

- Associations of demographic, clinical, and hospital characteristics and the odds of being prescribed with ESAs.

Data Description

Study cohorts for each specific aim

A total of 166,741 unique visits of 108,489 unique patients were reported to Cerner health system, and received at least one order of any ESAs between January 1, 2005 and June 30, 2011. Among them, 111,363 encounters (66.8%) were admitted to the inpatient health system while the rest were seen in the outpatient settings and excluded accordingly. Approximately 75.3% of the total inpatient encounters (n = 83,876 encounters: 66,121 patients) were prescribed epoetin alfa only, and 24.0% (n = 26,772 encounters: 20,088 patients) were prescribed darbepoetin alfa only. Less than one percent of them were prescribed both epoetin alfa and darbepoetin alfa during the same visit (0.8%, n = 715 encounters: 554 patients). A total of 128 unique hospitals reported using any ESAs during the study period. Epoetin alfa was used in 124 hospitals in our sample while darbepoetin alfa was used in 91 hospitals. Sixty-four hospitals reported the use of both epoetin alfa and darbepoetin alfa during the study period. The number of reporting hospitals increased from 37 hospitals in the first year to 71 hospitals in the last year of the study period. On average, the report of any use of ESAs came from approximately 50 hospitals per month. Lastly, during the 6.5-year study period, a total of 112 unique hospitals reported ESA ONS use while 89 and 127 unique hospitals reported OFS and OFU use of ESAs, respectively.

The proportion of visits with ESA use for the ONS, OFS, and OFU indications was set up from 111,363 unique visits with at least one ESA orders and 2,170,654 eligible admissions to assess the impact of the interventions on ESA prescribing patterns (Specific Aim 2).

Finally, in order to assess the impacts of the interventions on the odds of receiving ESAs in patients with specific on-label and off-label supported conditions and the associations of demographic, clinical, and hospital characteristics on such likelihood (Specific Aim 3), a patient is used as a unit of analysis. This analysis consisted of a total of 1,815,028 patients (750,321 ONS, 505,694 OFS, and 559,013 documented OFU).

Overall prevalence and trend in ESA use

ESA utilization patterns over time measured through the number of visits with any use of erythropoietic drugs (epoetin alfa or darbepoetin alfa) per reporting hospital during the study period is shown in Table 4.1 (annually) and Figure 4.1 (monthly).

Number of cases which an ESA was prescribed increased 44% from 240 per hospital in 2005 to 346 cases in 2006. ESA use decreased 13% to 302 cases in 2007; then utilization level went up 9% to 328 cases in 2008. The largest reduction in use was in 2009 when there was a 50% reduction from 2008. ESA utilization level remained low from then through 2010. Overall, ESA use in our sample decreased 33% from 2005 to 2010.

Epoetin alfa use increased 47% from approximately 211 cases per reporting hospital in 2005 to 310 cases in 2006. This increase was followed by a 27% drop in 2007 and a 15% increase in epoetin alfa use in the following year. The number of visits which epoetin alfa was

prescribed per hospital declined 54% in 2009, but increase again to 131 cases per hospital in 2010 (10% increase from 2009). Overall, epoetin alfa use decreased 38% from 2005 to 2010.

Overall use of darbepoetin alfa, however, increased 20% from 63 cases in 2005 to 76 cases in 2010. A year by year analysis showed that its use also increased in 2006 (44%). However, in contrary to epoetin alfa, the number of visits which darbepoetin alfa was prescribed per hospital continued to increase in 2007 (66% increase from 2006). After 2007, the level of darbepoetin alfa use decreased every year until the end of the study period.

Table 4.1 Overall annual trend in the number of visits with ESA use per reporting hospital*

Drug	**Number of visits with ESA use per reporting hospital**						
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**%Δ (2005-2010)**
Total (any ESAs)	239.7	345.8	302.0	327.9	163.1	161.6	
Δ from preceding year	**-**	**+44.0%**	**-12.6%**	**+8.6%**	**-50.3%**	**-0.9%**	**-32.6%**
Epoetin alfa	211.0	310.4	225.9	259.0	118.6	131.0	
Δ from preceding year	**-**	**+47.1%**	**-27.2%**	**+14.6%**	**-54.2%**	**+10.5%**	**-37.9%**
Darbepoetin alfa	63.3	91.1	151.0	131.1	103.6	75.7	
Δ from preceding year	**-**	**+44.0%**	**+65.7%**	**-13.2%**	**-21.0%**	**-26.9%**	**+19.7%**

*Only years with full-year reports were included

To compare the trends in epoetin alfa and darbepoetin alfa over time, a graphical representation of monthly drug use is shown in Figure 4.1. Any use of ESAs (epoetin alfa or darbepotin alfa) is marked with -○- symbol while the use of epoetin alfa or darbepoetin alfa alone is portrayed with -×- and -◊-, respectively. In general, changes in the level of darbepoetin alfa use were delayed and fluctuated at a lesser extent compared to that of epoetin alfa.

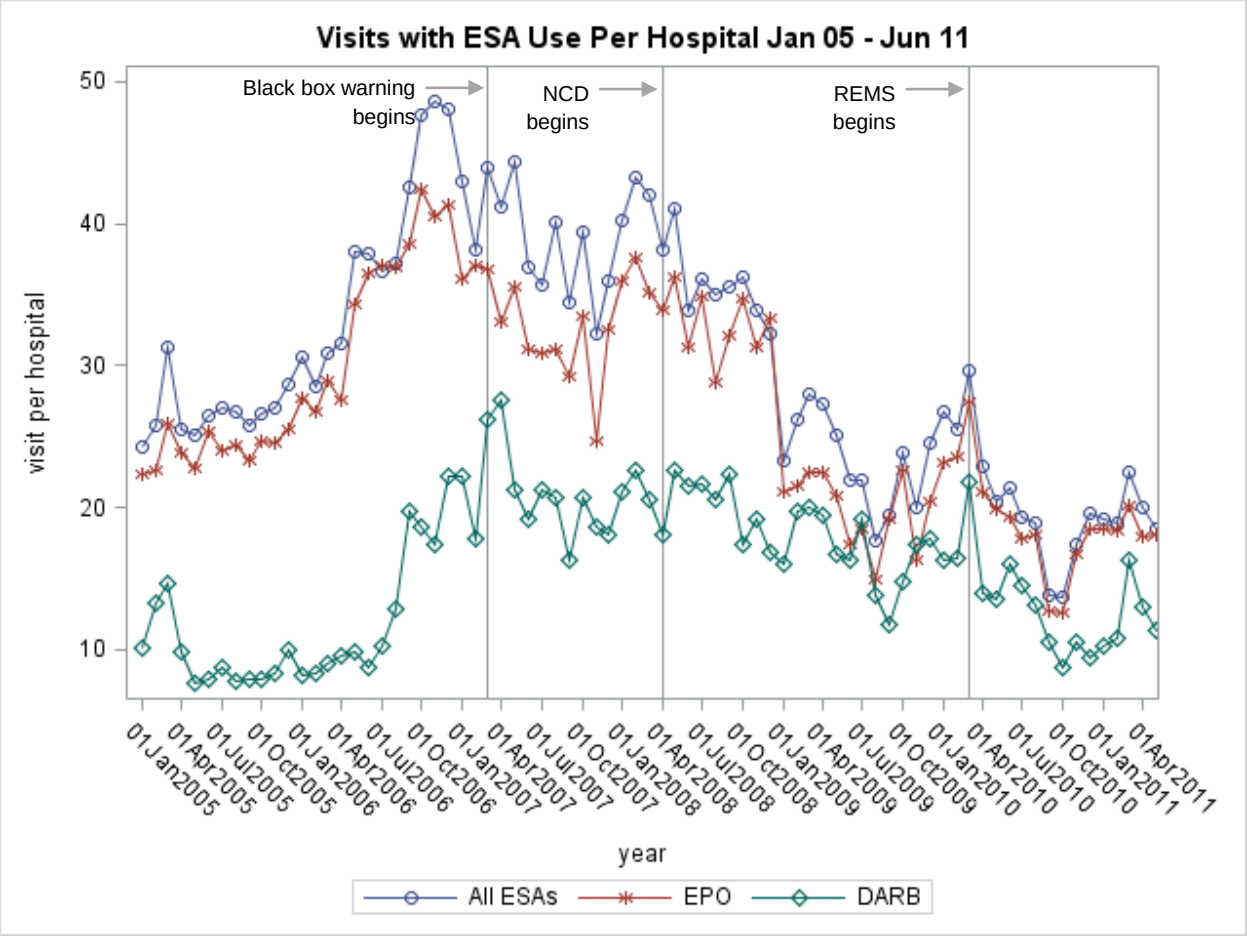

Figure 4.1 Monthly trend in use of ESAs, epoetin alfa, and darbepoetin alfa from January 2005 to June 2011 expressed in term of number of visits with ESA use per hospital

The number of visits which at least one ESA order was prescribed in a month in a hospital increased steadily from 24 visits at the beginning of the study period to 32 visits per

hospital per month in April 2006. After that, a sharp rise in the average number of visits with ESAs was observed. There were close to 50 visits at which ESAs were ordered per hospital per month during that period. However, beginning in October 2006, use of ESAs in our sample started to show a declining trend that continued until the end of the study period. In the last month of the study, there were as few as 16 visits per hospital which patients were prescribed ESAs. The trend in overall ESA use in our sample was likely to be caused by epoetin alfa because darbepoetin alfa utilization level, on the other hand, did not drop after October 2006 but instead remained relatively stable at approximately 20 visits per hospital per month until April 2010. After April 2010, darbepoetin alfa use decreased to about 10 cases per hospital monthly until the end of the study period.

ONS, OFS, and OFU use per hospital

The use of ESAs per hospital for the on-label, off-label supported, and off-label unsupported indications is shown in Table 4.2 (annually) and Figure 4.2 (monthly).

Between 2005 and 2010, the number of visits with ESA on-label (ONS) use decreased 63% from 196 cases to 72 cases. The decline in ESA ONS use was observed starting in 2007 (21% reduction from 2006) with the largest decline seen in 2009 (57% reduction from 2008). A similar trend was observed with ESA OFS use. ESA OFS use decreased 78.2% from 53 cases per hospital in 2005 to only 11.6 cases in 2010, with the largest decline in 2009 (57%). ESA OFU use, on the other hand, increased 80% from 57 cases to 102 cases. The largest increase in ESA OFU use was in 2006. During that year, the number of visits with ESA OFU use per hospital increased 78%.

Table 4.2 Annual trend in the number of visits with ESA use per reporting hospital by use category*

Use Category	Number of visits with ESA use per reporting hospital						
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**%Δ (2005-2010)**
Total (any ESAs)							
ONS	195.9	245.8	194.6	202.5	86.6	72.2	
Δ from preceding year	**-**	**+25.5%**	**-20.8%**	**+4.1%**	**-57.3%**	**-16.7%**	**-63.2%**
OFS	53.3	44.3	46.1	36.8	15.8	11.6	
Δ from preceding year	**-**	**-16.8%**	**3.9%**	**-20.2%**	**-57.1%**	**26.3%**	**-78.2%**
OFU	56.7	100.9	114.7	128.6	95.9	102.0	
Δ from preceding year	**-**	**+78.0%**	**+13.7%**	**+12.1%**	**-25.4%**	**+6.4%**	**+80.0%**

*Only years with full-year reports are shown

Monthly trends in ESA use on-label and off-label (supported and unsupported) is shown in Figure 4.2. On-label use of ESA is outlined with a long-dashed line while off-label supported and off-label unsupported use are marked with solid and dotted lines, respectively.

On-label use of ESAs in our sample increased steadily from 20 visits per hospital per month in January 2005 to 32 cases in November 2006. After than month, ESA on-label use declined sharply. During the last months of the study, a hospital on average approximately prescribed ESA in less than 10 visits per month. On the other hand, no fluctuation of level of ESA use for off-label supported indications was observed in our sample; there was a slight downward trending in the off-label supported use of ESAs throughout the study period. ESA OFS use decreased from 7 visits per hospital per month to only one to two visits in the later months. In contrast to ESA ONS and OFS use, ESA use for the unsupported indications (OFU) increased from 6 visits in 2005 to 19 visits December 2006. This OFU use remained high, with a slight increasing trend throughout the study period.

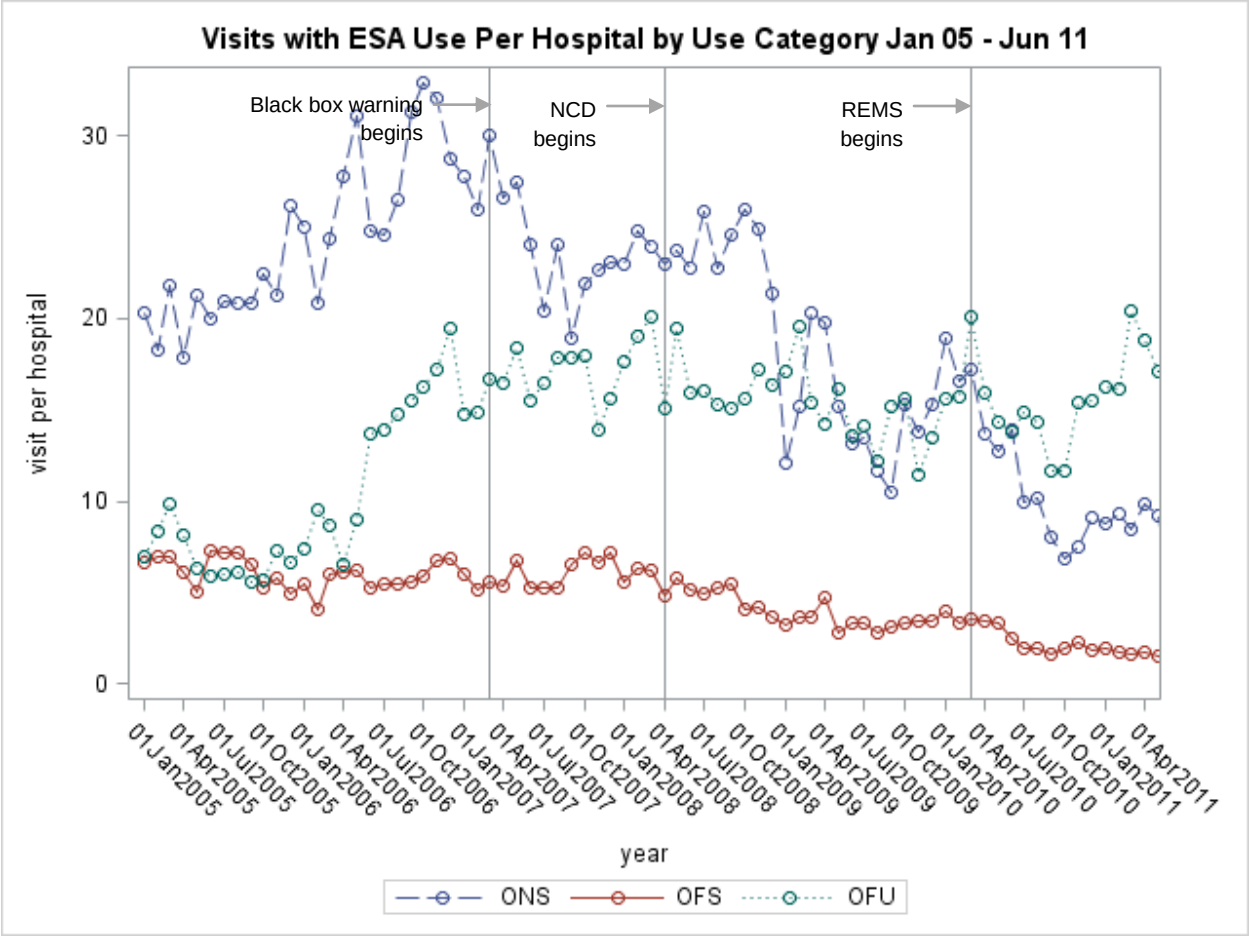

Figure 4.2 Monthly trend in ESA use for the on-label, off-label supported, and off-label unsupported indications from January 2005 to June 2011 expressed in term of number of visits with ESA use per hospital

The annual trends in ESA use were broken down by drug. Changes in epoetin alfa and darbepoetin alfa use per hospital per year for the on-label, off-label supported, and off-label unsupported indications are shown Table 4.3.

The observed trends in ESA use described in the previous section were likely to be contributed by the use of epoetin alfa which made up more than 75% of all ESA use in our sample. Epoetin alfa ONS use increased 23% in the first year of the study period, but decreased thereafter. Overall, similar to ESAs, epoetin alfa ONS use decreased 67% between 2005 and

2010, with the largest decline in 2009 (-65%). Epoetin alfa OFS use also declined throughout the whole study period (75%, 2005-2010), with the largest drop of 61% in 2009. Lastly, epoetin alfa OFU use increase 93% over six years. The largest increase in epoetin alfa OFU use was observed in 2006 where its use was almost doubled (99%).

In contrast to epoetin alfa, darbepoetin alfa ONS use did not decrease after 2005. Instead, its use continued to increase until 2007, and decreased thereafter. There was also an increase of 73% and 71% in darbepoetin alfa OFS and OFU use in our sample in that year (2007), respectively. At the end of the study period, darbepoetin alfa OFS use decreased 45% while OFU use increased more than 111%.

Table 4.3 Annual trend in the number of visits with epoetin alfa and darbepoetin alfa use per reporting hospital by use category*

Use Category	**Number of visits with ESA use per reporting hospital**						
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**%Δ (2005-2010)**
Epoetin alfa							
ONS	179.6	220.8	141.1	156.4	54.8	60.0	
Δ from preceding year	**-**	**+22.9%**	**-36.1%**	**+10.8%**	**-64.9%**	**+9.4%**	**-66.6%**
OFS	48.5	44.6	35.7	33.1	12.8	11.9	
Δ from preceding year	**-**	**-8.0%**	**-20.1%**	**-7.3%**	**-61.2%**	**-7.0%**	**-75.4%**
OFU	45.9	91.1	95.3	116.2	82.4	88.4	
Δ from preceding year	**-**	**+98.5%**	**+4.6%**	**+21.9%**	**-29.1%**	**+7.3%**	**+92.6%**
Darbepoetin alfa							
ONS	52.8	68.9	112.4	98.5	82.8	48.6	
Δ from preceding year	**-**	**+30.5%**	**+63.1%**	**-12.3%**	**-16.0%**	**-41.3%**	**-8.0%**
OFS	14.1	13.7	23.8	20.7	14.7	7.8	
Δ from preceding year	**-**	**-2.6%**	**+73.3%**	**-12.8%**	**-28.9%**	**-47.2%**	**-44.7%**
OFU	23.6	29.1	49.7	45.9	51.4	50.0	
Δ from preceding year	**-**	**+23.4%**	**+70.5%**	**-7.6%**	**+12.0%**	**-2.7%**	**+111.8%**

*Only years with full-year reports are shown

Figure 4.3 and 4.4 show monthly trend in epoetin alfa and darbepoetin alfa use per hospital, respectively. In general, ONS and OFS use in our sample decreased while OFU use increased drastically after April 2006.

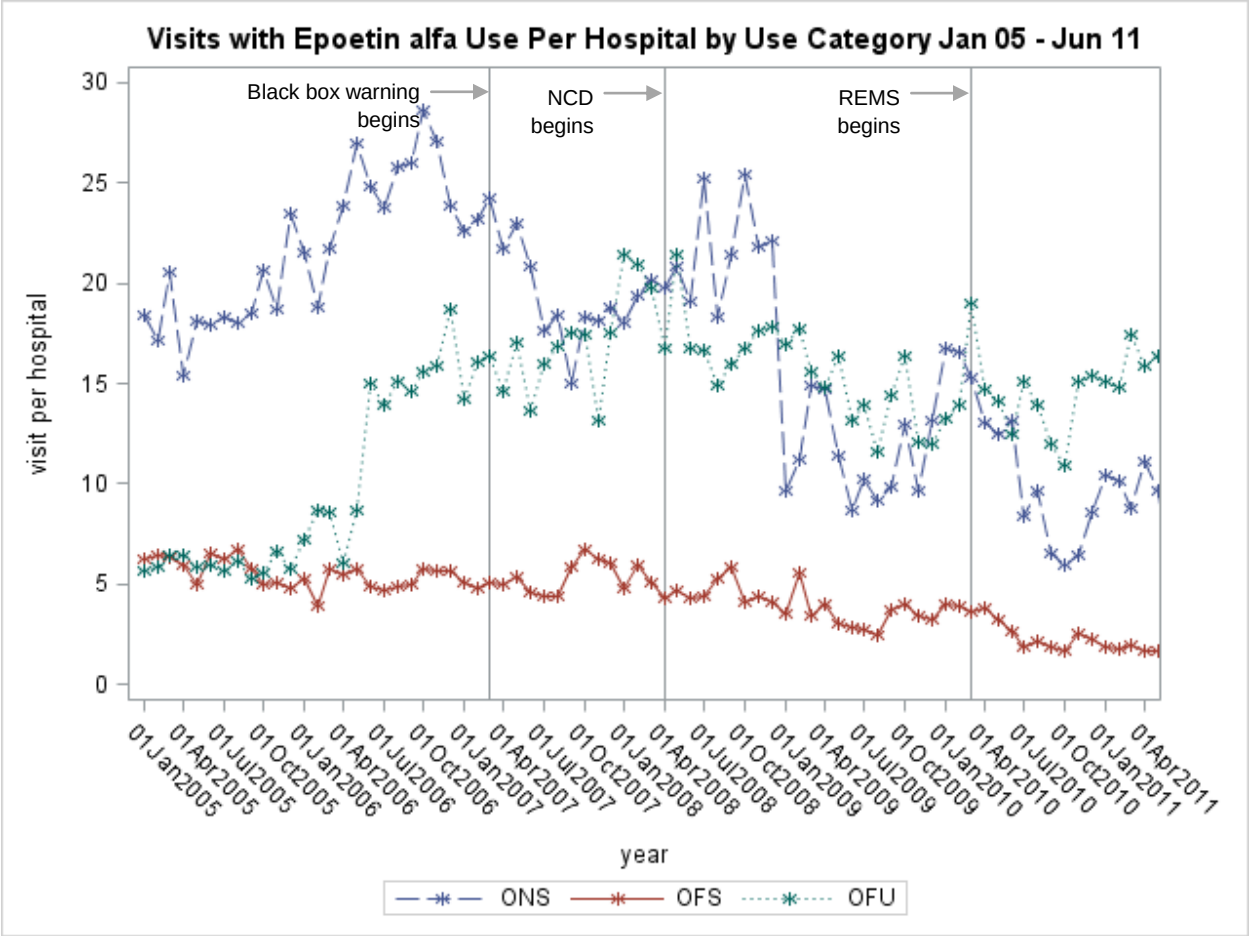

Figure 4.3 Monthly trend in epoetin alfa use for the on-label, off-label supported, and off-label unsupported indications from January 2005 to June 2011 expressed in term of number of visits with ESA use per hospital

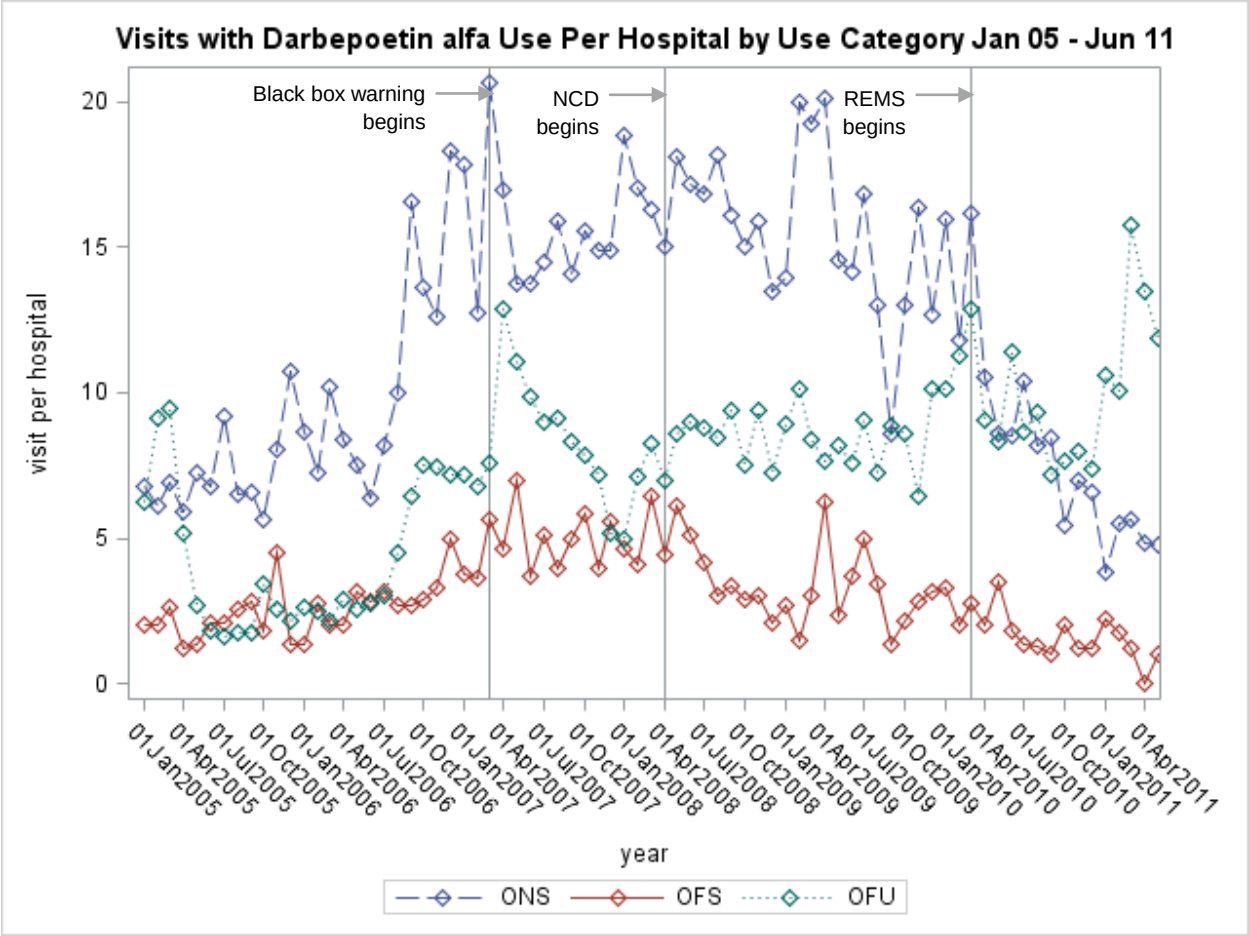

Figure 4.4 Monthly trend in darbepoetin alfa use for the on-label, off-label supported, and off-label unsupported indications from January 2005 to June 2011 expressed in term of number of visits with ESA use per hospital

The graphic representation shown in Figure 4.4 confirmed that the decline in the use of darbepoetin alfa for the on-label indications was delayed compared to that in epoetin alfa ONS use. Instead of a declining trend at the end of 2006, darbepoetin alfa ONS use continued to rise until mid-2006, after which it remained relatively stable until early 2010. Darbepoetin alfa ONS use then dropped drastically toward the end of the study period. In contrast to epoetin alfa OFS use which trended downward throughout the study period, OFS use of darbepoetin alfa in fact increased at first, and then leveled off after 2008. Finally, similarly to epoetin alfa, the use of

darbepoetin alfa for the off-label unsupported indications rose after 2006, and remained relatively stable until the end of the study period.

Specific Aim 1

Descriptive Statistics

Descriptive statistics were divided into three parts. The first part describes and compares demographic data (age, race, sex, admission type, comorbidity, length of stay, and discharge status), source of payment and hospital and physician characteristics between epoetin alfa (EPO) and darbepoetin alfa (DARB) users. The EPO+DARB user group was not included in the analysis due to its small sample size (554 patients). In the second part, differences in patient demographic and clinical characteristics, and hospital and physician characteristics between ESA users of each category (ONS, OFS, and OFU) were tested separately for each drug. Actual use of ESA for specific ONS, OFS, and OFU indications was described under the final section.

Descriptive statistical analysis of demographic information of patients prescribed with epoetin alfa or darbepoetin alfa only

Demographic data for patients who received only epoetin alfa or only darbepoetin alfa were tested for statistically significant differences. Bivariates results are shown in Table 4.4. The age of patients ranged from 18 to 85 years old, with the average age being 66 years old. The late middle aged (51-64 years), young old (65-74 years), and older old (75-84 years) comprised the largest group of ESA users. Slightly more female than male patients received ESAs. Majority of ESA users in our sample were white (62.4%), had Medicare as their primary payer, were admitted as emergency cases, and discharged home. The average length of stay was 12

days (0 to 1,362 days) and on average, an ESA user had a comorbidity score of 1.6. Majority of ESA users in this study were admitted to the hospitals located in the Northeast and the South with more than 300 beds. Most of the hospitals were teaching hospitals (74.8%). Lastly, among users without missing information on physician specialty, 61.1% of them were prescribed by a specialist. It is important to note that though age, gender, race, discharge disposition, and hospital characteristics were well captured in Cerner data, more than half of the payer information of ESA users, and as high as 30-40% of the admission type and ordering physician specialty were missing from the records.

There were significant differences between the EPO and DARB users with respect to patient demographic characteristics, clinical characteristics, physician characteristics and hospital characteristics. Overall, compared with those prescribed with epoetin alfa, those prescribed with darbepoetin alfa were significantly younger (40.5% vs 46.9% non-elderly), and consisted of slightly more male and Caucasians. Greater proportion of DARB users, compared to EPO users, had Medicare as their primary payer. Fewer DARB users were admitted as emergency cases compared to EPO users. Discharge status of both users was similar. However, drug utilization was drastically different across the census regions. Patients admitted to the hospitals located in the Midwest and the northeast received darbepoetin alfa to a greater extent compared to patients in any other regions. On the other hand, epoetin alfa was used mostly in the hospitals located in the Northeast and the South. Drug utilization was quite similar across hospital bed size, teaching status, and ordering physician specialty categories.

Table 4.4 Descriptive statistics for patients admitted to inpatient settings and had at least one order of ESAs between January 01, 2005 and June 30, 2011

Variable	N Patients 2005- 2011 (column %)			Chi-sq, p-value
	Any ESAs	Epo	Darb	
Patient Characteristics				
Demographics				
Age				
18-30	2,273 (2.64)	1,580 (2.39)	693 (3.45)	389.15
31-50	12,362 (14.34)	8,912 (13.48)	3,450 (17.17)	p < 0.0001
51-64	21,686 (25.16)	16,350 (24.73)	5,336 (26.56)	
65-74	19,430 (22.54)	15,035 (22.74)	4,395 (21.88)	
75-84	20,811 (24.14)	16,470 (24.91)	4,341 (21.61)	
85+	9,647 (11.19)	7,774 (11.76)	1,873 (9.32)	
Total (row %)	86,209 (100.00)	66,121 (76.70)	20,088 (23.30)	
Average age (SD)	66.1 (15.81)	66.7 (15.62)	64.1 (16.28)	p < 0.0001
Gender*				
Male	41,564 (48.22)	31,583 (47.77)	9,981 (49.70)	22.91
Female	44,636 (51.78)	34,533 (52.23)	10,103 (50.30)	p < 0.0001
Total (row %)	86,200 (100)	66,116 (76.70)	20,084 (23.30)	
Race				
Caucasian	53,799 (62.41)	40,517 (62.28)	13,282 (66.12)	783.95
African-American	24,473 (28.39)	19,332 (29.24)	5,141 (25.59)	p < 0.0001
Other	6,149 (7.13)	5,254 (7.95)	895 (4.46)	
Not recorded	1,788 (2.07)	1,018 (1.54)	770 (3.83)	
Total (row %)	86,209 (100.00)	66,121 (76.70)	20,088 (23.30)	
Primary Payer				
Source of Payment				
Medicare	24,548 (60.35)	17,666 (58.50)	6,882 (65.67)	888.47
Medicaid	3,471 (8.53)	2,541 (8.41)	930 (8.87)	p < 0.0001
Commercial/Private/HMO	5,839 (14.35)	4,338 (14.36)	1,501 (14.32)	
Managed Care				
Self-pay	1,700 (4.18)	1,162 (3.85)	538 (5.13)	
Other	5,120 (12.59)	4,492 (14.87)	628 (5.99)	
Not recorded	45,531 (52.81)	35,922 (54.33)	9,609 (47.83)	
Total (row %)	86,209 (100.00)	66,121 (76.70)	20,088 (23.30)	
Clinical Conditions				
Admission type				
Emergency	38,243 (64.09)	29,639 (64.90)	8,604 (61.44)	648.90
Urgent	10,598 (17.76)	8,675 (19.00)	1,923 (13.73)	p < 0.0001
Elective	10,694 (17.92)	7,249 (15.87)	3,445 (24.60)	
Other	137 (0.23)	106 (0.23)	31 (0.22)	
Not recorded	26,537 (30.78)	20,452 (30.93)	6,085 (30.29)	
Total (row %)	86,209 (100.00)	66,121 (76.70)	20,088 (23.30)	
Average CCI (SD)	1.62 (1.991), -1 to 13	1.56 (1.967), -1 to 13	1.80 (2.058) -1 to 13	p < 0.0001
Average LOS (SD), range	12.4 (18.72), 0 – 1,362	12.1 (18.85), 0 - 1,362	13.4 (18.24), 0 - 540	p < 0.0001

Discharge status				
Expired	5,974 (7.24)	4,615 (7.29)	1,359 (7.07)	41.55
Discharged to home/ self care	37,211 (45.08)	28,465 (44.95)	8,746 (45.49)	p < 0.0001
Discharged to Hospice	1,769 (2.17)	1,367 (2.16)	425 (2.22)	
Discharged/transferred to institutionalized care	24,014 (29.09)	18,216 (28.77)	5,798 (30.15)	
Discharged/transferred to noninstitutionalized care	12,942 (15.68)	10,163 (16.05)	2,779 (14.45)	
Other	617 (0.75)	498 (0.79)	119 (0.62)	
Not recorded	3,657 (4.24)	2,797 (4.23)	860 (4.28)	
Total (row %)	86,209 (100.00)	66,121 (76.70)	20,088 (23.30)	
Hospital Characteristics				
Geographic region				
Northeast	35,167 (40.79)	27,914 (42.22)	7,253 (36.11)	13384.40
Midwest	18,197 (21.11)	8,406 (12.71)	9,791 (48.74)	p < 0.0001
South	26,628 (30.89)	23,793 (35.98)	2,835 (14.11)	
West	6,217 (7.21)	6,008 (9.09)	209 (1.04)	
Total (row %)	86,209 (100.00)	66,121 (76.70)	20,088 (23.30)	
Bed size				
≤ 99	2,358 (2.74)	1,889 (2.86)	469 (2.33)	1174.51
100-199	7,823 (9.07)	5,324 (8.22)	2,390 (11.90)	p < 0.0001
200-299	15,864 (18.40)	10,919 (16.51)	4,945 (24.62)	
300-499	26,270 (30.47)	21,419 (32.39)	4,851 (24.15)	
≥500	33,894 (39.32)	26,461 (40.02)	7,433 (37.00)	
Total (row %)	86,209 (100.00)	66,121 (76.70)	20,088 (23.30)	
Teaching status				
Teaching	64,455 (74.77)	49,660 (75.10)	14,795 (73.65)	17.26
Non-teaching	21,754 (25.23)	16,461 (24.90)	5,293 (26. 53)	p < 0.0001
Total (row %)	86,209 (100.00)	66,121 (76.70)	20,088 (23.30)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	13,577 (15.75)	11,317 (17.12)	2,260 (11.25)	1550.28
Surgeon	5197 (6.03)	3,253 (4.92)	1,944 (9.68)	p < 0.0001
Specialist	29,535 (34.26)	21,208 (32.07)	8,327 (41.45)	
Not recorded	37,900 (43.96)	30,343 (45.89)	3,557 (37.62)	
Total (row %)	86,209 (100.00)	66,121 (76.70)	20,088 (23.30)	

*Nine patients with missing gender information were not tested.

Descriptive statistical analysis of demographic information of patients prescribed with epoetin alfa and darbepoetin alfa by use category

This part of the descriptive analysis examined characteristics of the ESA users by their use category. Majority of ESA use in our sample was for on-label indications (48.7%), followed by off-label unsupported (42.7%), and off-label supported indications (8.6%).

There were significant differences in the utilization of epoetin alfa and darbepoetin alfa with respect to use categories. Darbepoetin alfa was used to a larger extent for on-label indications compared to epoetin alfa; of 20,008 darbepoetin alfa users, 52.8% were for on-label indications compared to 47.4% ONS of epoetin alfa users. Unsupported use of both drugs constituted about 83.2% of all off-label use of the drugs. Table 4.5 summarizes percentages of patients with epoetin alfa and darbepoetin alfa use by indication category.

Table 4.5 Number of ESA users in the inpatient settings by use categories

Use category	N Patients (column %)			Chi-sq, p-value
	All ESA users	Epo only	Darbe only	
ONS	42,218 (48.66)	31,333 (47.39)	10,598 (52.76)	177.90
OFS	7477 (8.62)	5,834 (8.82)	1,586 (7.90)	p < 0.0001
OFU	37,068 (42.72)	28,954 (43.79)	7,904 (39.35)	
Total (row %)	86,763	66,121 (76.70)	20,088 (23.30)	

Part 2.1: Any ESAs

There were statistically significant differences between users of ESAs for ONS, OFS, and OFU indications with respect to all variables: age, gender, race, insurance status, admission type, comorbidity index, length of stay, discharge disposition, geographic region, hospital size, teaching status, and physician specialty. ESAs, regardless of their indications, were also for a greater extent prescribed off-label to female. ESA utilization patterns were similar across geographic regions, hospital bed size, teaching status, and ordering physician specialty categories.

Compared with ONS and OFU users, there was greater proportion of older patients in the OFS group. The average age of ESA-OFS group was 70 years old while that of ESA-ONS and ESA-OFU groups were 65 and 66 years old, respectively. Greater proportion of ESA-OFS users died in the hospital or was discharged to institutionalized care. There were fewer White and Medicare patients in the OFU group compared to the other two groups. Also, admission type of the OFU patients was, to the highest extent, not recorded in the database (60.3% compared 8.8% and 11.1% of the ONS and OFS groups, respectively). However, among those with recorded information, admission type did not vary across the three user groups. We found that the majority of ESA patients in our sample were admitted to the hospitals as emergency cases. Hospital length-of-stay was longest in the OFS group (14.7 days), followed by OFU (12.9 days), while ONS patients stayed in the hospital for 11.8 days on average. Lastly, OFU patients had much lower comorbidity index compared to the ONS and OFS patients (0.3 vs. 2.7 and 2.0). Average age, L-O-S, and comorbidity indices of ESA drug recipients are illustrated in Figure 4.5 and 4.6, respectively. Descriptive statistics of ESA users by use category was shown in Table 4.6.

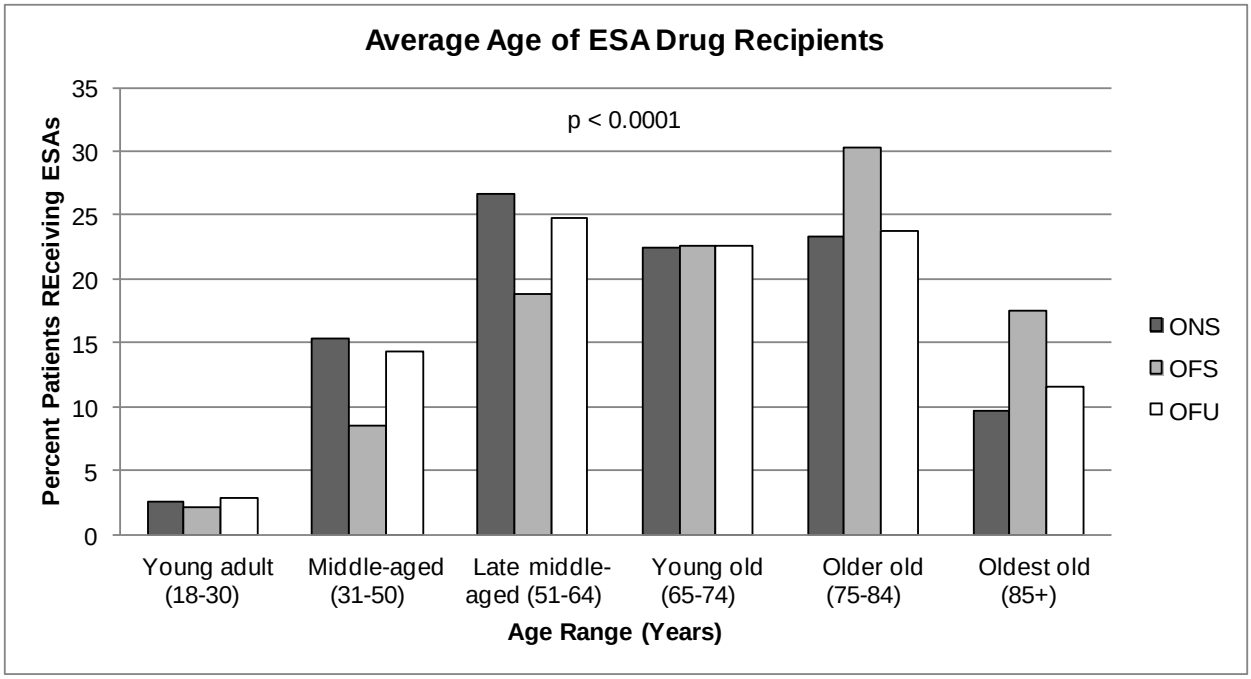

Figure 4.5 Average age of ESA drug recipients

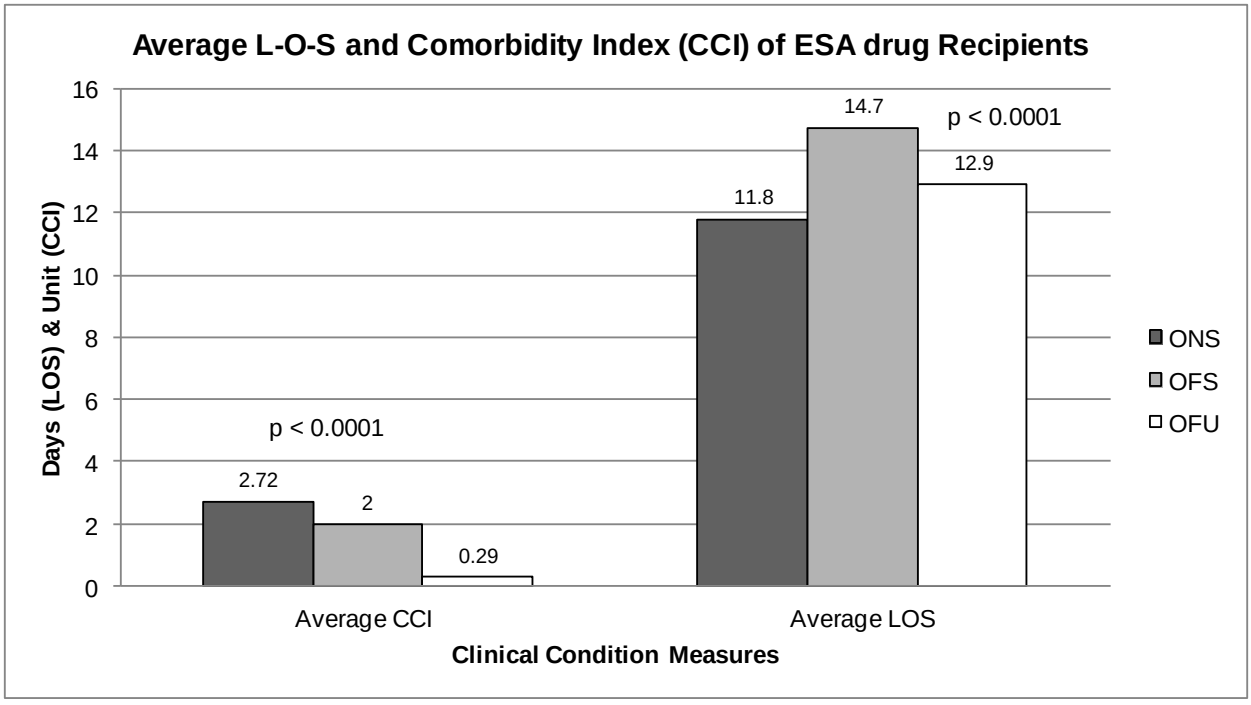

Figure 4.6 Average L-O-S and Average CCI of ESA drug recipients

Table 4.6 Descriptive statistics for ESA users in the inpatient settings by use categories

Variable	N Patients by Use Category 2005-2011 (column %)				Chi-sq, p-value
	Any indications	ONS	OFS	OFU	
Patient Characteristics					
Demographics					
Age					
18-30	2,286 (2.63)	1,078 (2.55)	164 (2.19)	1,044 (2.82)	870.35
31-50	12,432 (14.33)	6,473 (15.33)	640 (8.56)	5,319 (14.35)	p < 0.0001
51-64	21,836 (25.17)	11,253 (26.65)	1,404 (18.78)	9,179 (24.76)	
65-74	19,553 (22.54)	9,461 (22.41)	1,688 (22.58)	8,404 (22.67)	
75-84	20,952 (24.15)	9,863 (23.36)	2,266 (30.31)	8,823 (23.80)	
85+	9,704 (11.18)	4,090 (9.69)	1,315 (17.59)	4,299 (11.60)	
Total (row %)	86,763 (100.00)	42,218 (48.66)	7,477 (8.62)	37,068 (42.72)	
Average age (SD)	66.1 (15.81)	65.3 (15.64)	70.5 (15.07)	66.0 (16.00)	p < 0.0001
Gender*					
Male	41,837 (48.22)	21,229 (50.29)	3,501 (46.82)	17,107 (46.16)	140.94
Female	44,917 (51.78)	20,988 (49.71)	3,976 (53.18)	19,953 (53.84)	p < 0.0001
Total (row %)	86,754 (100.00)	42,217 (48.66)	7,477 (8.62)	37,060 (42.72)	
Race					
Caucasian	54,172 (64.44)	26,636 (63.09)	5,799 (77.56)	21,737 (58.64)	1046.09
African-American	24,608 (28.36)	12,105 (28.67)	1,220 (16.32)	11,283 (30.44)	p < 0.0001
Other	6,179 (7.12)	2,720 (6.44)	334 (4.47)	3,125 (8.43)	
Not recorded	1,804 (2.08)	757 (1.79)	124 (1.66)	923 (2.94)	
Total (row %)	86,763 (100.00)	42,218 (48.66)	7,477 (8.62)	37,068 (42.72)	
Primary Payer					
Source of Payment					
Medicare	24,689 (28.46)	1,4550 (34.46)	2,910 (38.92)	7,229 (19.50)	4907.39
Medicaid	3,486 (4.02)	1,902 (4.51)	345 (4.61)	1,239 (3.34)	p < 0.0001
Commercial/ Private/ HMO Managed Care	5,886 (6.78)	3,008 (7.12)	623 (8.33)	2,255 (6.08)	
Self-pay	1,702 (1.96)	855 (2.03)	192 (2.57)	655 (1.77)	
Other	5,152 (5.94)	3,424 (8.11)	482 (6.45)	1,245 (3.36)	
Not recorded	45,848 (52.84)	18,478 (43.77)	2,925 (39.12)	24,445 (65.95)	
Total (row %)	86,763 (100.00)	42,218 (48.66)	7,477 (8.62)	37,068 (42.72)	
Clinical Conditions					
Admission type					
Emergency	38,475 (44.34)	24,791 (58.72)	4,231 (56.59)	9,453 (25.50)	26164.05
Urgent	10,665 (12.29)	6,445 (15.27)	1,376 (18.40)	2,844 (7.67)	p < 0.0001
Elective	10,755 (12.40)	7,288 (17.26)	1,038 (13.88)	2,429 (6.55)	
Other/Not recorded	26,868 (30.97)	3,694 (8.75)	832 (11.13)	22,342 (60.27)	
Total (row %)	86,763 (100.00)	42,218 (48.66)	7,477 (8.62)	37,068 (42.72)	
Average CCI (SD)	1.62 (1.991), -1 to 13	2.72 (1.909), -1 to 13	2.00 (1.844), 0 to 11	0.29 (1.116), 0 to 9	p < 0.0001
Average LOS (SD), range	12.5 (18.97), 0 to 1362	11.8 (16.42), 0 to 1029	14.7 (17.99), 0 to 340	12.9 (21.64), 0 to 1362	p < 0.0001

Discharge status					
Expired	6,031 (6.95)	2,794 (6.62)	872 (11.66)	2,365 (6.07)	5502.15
Discharged to home/self care	37,362 (43.06)	17,708 (41.94)	2,011 (26.90)	17,643 (47.60)	p < 0.0001
Discharged to Hospice	1,809 (2.08)	940 (2.23)	258 (3.45)	611 (1.65)	
Discharged/ transferred to institutionalized care	24,243 (27.94)	12,394 (29.36)	2,873 (38.42)	8,976 (24.21)	
Discharged/ transferred to noninstitutionalized care	13,006 (14.99)	7,772 (18.41)	1,397 (18.68)	3,837 (10.35)	
Other/Not recorded	4,312 (4.97)	610 (1.44)	66 (0.88)	3,636 (9.81)	
Total (row %)	86,763 (100.00)	42,218 (48.66)	7,477 (8.62)	37,068 (42.72)	
Hospital Characteristics					
Geographic region					
Northeast	35,513 (40.93)	16,422 (38.90)	3,415 (45.67)	15,676 (42.29)	1207.08
Midwest	18,300 (21.09)	10,700 (25.34)	1,488 (19.90)	6,112 (16.49)	p < 0.0001
South	26,712 (30.79)	12,607 (29.86)	2,192 (29.32)	11,913 (32.14)	
West	6,238 (7.19)	2,489 (5.90)	382 (5.11)	3,367 (9.08)	
Total (row %)	86,763 (100.00)	42,218 (48.66)	7,477 (8.62)	37,068 (42.72)	
Bed size					
≤ 99	2,374 (2.74)	962 (2.28)	240 (3.21)	1,172 (3.16)	1,360.49
100-199	7,886 (9.09)	4,400 (10.42)	659 (8.81)	2,827 (7.63)	p < 0.0001
200-299	16,053 (18.50)	7,711 (18.26)	1,668 (22.31)	6,678 (18.00)	
300-499	26,371 (30.39)	13,878 (32.87)	2,789 (37.30)	9,704 (26.18)	
≥500	34,079 (39.28)	15,267 (36.16)	2,121 (28.37)	16,691 (45.03)	
Total (row %)	86,763 (100.00)	42,218 (48.66)	7,477 (8.62)	37,068 (42.72)	
Teaching status					
Teaching	64,819 (74.71)	32,051 (75.92)	5,406 (72.30)	27,362 (73.82)	71.23
Non-teaching	21,944 (25.29)	10,167 (24.08)	2,071 (27.70)	9,706 (26.18)	p < 0.0001
Total (row %)	86,763 (100.00)	42,218 (48.66)	7,477 (8.62)	37,068 (42.72)	
Physician Characteristics					
Ordering Physician Specialty					
Non-specialist	13,632 (15.71)	5,855 (13.87)	1,324 (17.71)	6,453 (17.41)	692.13
Surgeon	5,229 (6.03)	2,835 (6.72)	464 (6.21)	1,930 (5.21)	p < 0.0001
Specialist	29,669 (34.20)	15,698 (37.18)	2,748 (36.75)	11,223 (30.28)	
Not recorded	38,233 (44.07)	17,830 (42.23)	2,941 (39.33)	17,462 (47.11)	
Total (row %)	86,763 (100.00)	42,218 (48.66)	7,477 (8.62)	37,068 (42.72)	

*Nine patients with missing gender information were not tested.

Part 2.2: Use of Epoetin alfa Darbepoetin alfa

Descriptive analysis of patient characteristics, clinical conditions, hospital characteristics, and physician specialty were done separately for epoetin alfa and darbepoetin alfa. Bivariate results for epoetin alfa and darbepoetin alfa are described in Table 4.7 and 4.8, respectively. Significant differences between the ONS, OFS, and OFU users of epoetin alfa and darbepoetin with respect to patient demographic characteristics, clinical characteristics, physician characteristics and hospital characteristics were comparable to those described above in the ESA section. For example, those who used the drug for off-label supported indications were the oldest, mostly White female, had higher hospital mortality, and were transferred to other institutionalized care settings to a greater extent compared to patients in the other two groups.

Table 4.7 Epoetin alfa by use category in the inpatient settings

Variable	N Patients by Use Category 2005-2011 (column %)				Chi-sq, p-value
	Any indications	ONS	OFS	OFU	
Patient Characteristics					
Demographics					
Age					
18-30	1,580 (2.39)	715 (2.28)	108 (1.85)	757 (2.61)	719.96
31-50	8,691 (13.48)	4,494 (14.34)	457 (7.83)	3,961 (13.68)	p < 0.0001
51-64	16,350 (24.73)	8,198 (26.16)	1,024 (17.55)	7,128 (24.62)	
65-74	15,035 (22.74)	7,102 (22.67)	1,326 (22.73)	6,607 (22.82)	
75-84	16,470 (24.91)	7,609 (24.28)	1,837 (31.49)	7,024 (24.26)	
85+	7,774 (11.76)	3,215 (10.26)	1,082 (18.55)	3,477 (12.01)	
Total (row %)	66,121 (100.00)	31,333 (47.39)	5,834 (8.82)	28,954 (43.79)	
Average age (SD)	66.6 (15.62)	65.9 (15.43)	71.3 (14.70)	66.5 (15.84)	
Gender*					
Male	31,583 (47.77)	15,633 (49.89)	2,698 (46.25)	13,252 (45.78)	108.12
Female	34,533 (52.23)	15,700 (50.11)	3,136 (53.75)	15,697 (54.22)	p < 0.0001
Total (row %)	66,116 (100.00)	31,333 (47.39)	5,834 (8.82)	28,949 (43.79)	
Race					
Caucasian	40,517 (61.28)	19,471 (62.14)	4,486 (76.89)	16,560 (57.19)	911.14
African-American	19,332 (29.24)	9,266 (29.57)	995 (17.04)	9,072 (31.33)	p < 0.0001
Other	5,254 (7.95)	2,225 (7.10)	275 (4.71)	2,754 (9.51)	
Not recorded	1,018 (1.54)	371 (1.18)	79 (1.35)	568 (1.96)	
Total (row %)	66,121 (100.00)	31,333 (47.39)	5,834 (8.82)	28,954 (43.79)	
Primary Payer					
Source of Payment					
Medicare	17,666 (26.72)	10,058 (32.10)	2,305 (39.51)	5,303 (18.32)	4551.74
Medicaid	2,541 (3.84)	1,354 (4.32)	258 (4.42)	929 (3.21)	p < 0.0001
Commercial/ Private/ HMO Managed Care	4,338 (6.56)	2,079 (6.64)	443 (7.59)	1,816 (6.27)	
Self-pay	1,162 (1.76)	472 (1.51)	143 (2.45)	547 (1.89)	
Other	4,492 (6.79)	3,247 (10.36)	448 (7.68)	797 (2.75)	
Not recorded	35,922 (54.33)	14,123 (45.07)	2,237 (38.34)	19,562 (67.56)	
Total (row %)	66,121 (100.00)	31,333 (47.39)	5,834 (8.82)	28,954 (43.79)	
Clinical Conditions					
Admission type					
Emergency	29,639 (44.83)	18,950 (60.48)	3,449 (59.12)	7,240 (61.06)	21689.07
Urgent	8,675 (13.12)	5,259 (16.78)	1,206 (20.67)	2,210 (25.01)	p < 0.0001
Elective	7,249 (10.96)	4,719 (15.06)	704 (12.07)	1,826 (7.63)	
Other/Not recorded	20,558 (31.09)	2,405 (7.68)	475 (8.14)	17,678 (61.06)	
Total (row %)	66,121 (100.00)	31,333 (47.39)	5,834 (8.82)	28,954 (43.79)	
Average CCI (SD)	1.56 (1.967), -1 to 13	2.66 (1.911), -1 to 13	2.00 (1.823), 0 to 11	0.29 (1.128), 0 to 9	
Average LOS (SD), range	12.1 (18.85), 0 to 1362	11.3 (15.91), 0 to 1029	13.8 (16.49), 0 to 329	12.7 (21.94), 0 to 1362	

Discharge status					
Expired	4,615 (6.98)	2,037 (6.50)	665 (11.40)	1,913 (6.61)	4041.55
Discharged to home/self care	28,465 (43.05)	12,952 (41.34)	1,573 (26.96)	13,940 (48.15)	p < 0.0001
Discharged to Hospice	1,367 (2.07)	715 (2.28)	207 (3.55)	445 (1.54)	
Discharged/ transferred to institutionalized care	18,216 (27.55)	9,084 (28.99)	2,185 (37.45)	6,947 (23.99)	
Discharged/ transferred to noninstitutionalized care	10,163 (15.37)	6,025 (19.23)	1,143 (19.59)	2,995 (10.34)	
Other/Not recorded	3,295 (4.98)	520 (1.66)	61 (1.05)	2,714 (9.37)	
Total (row %)	66,121 (100.00)	31,333 (47.39)	5,834 (8.82)	28,954 (43.79)	
Hospital Characteristics					
Geographic region					
Northeast	27,914 (42.22)	12,618 (40.27)	2,688 (46.07)	12,608 (43.54)	713.65
Midwest	8,406 (12.71)	4,763 (15.20)	759 (13.01)	2,884 (9.96)	p < 0.0001
South	23,793 (35.98)	11,597 (37.01)	2,030 (34.80)	10,166 (35.11)	
West	6,008 (9.09)	2,355 (7.52)	357 (6.12)	3,296 (11.38)	
Total (row %)	66,121 (100.00)	31,333 (47.39)	5,834 (8.82)	28,954 (43.79)	
Bed size					
≤ 99	1,889 (2.86)	675 (2.15)	184 (3.15)	1,030 (3.56)	1947.62
100-199	5,433 (8.22)	3,251 (10.38)	490 (8.40)	1,692 (5.84)	p < 0.0001
200-299	10,919 (16.51)	5,429 (17.33)	1,107 (18.97)	4,383 (15.14)	
300-499	21,419 (32.39)	11,036 (35.22)	2,466 (42.27)	7,917 (27.34)	
≥500	26,461 (40.02)	10,942 (34.92)	1,587 (27.20)	13,932 (48.12)	
Total (row %)	66,121 (100.00)	31,333 (47.39)	5,834 (8.82)	28,954 (43.79)	
Teaching status					
Teaching	49,660 (75.10)	23,625 (75.40)	4,379 (75.06)	21,656 (74.79)	2.96
Non-teaching	16,461 (24.90)	7,708 (24.60)	1,455 (24.94)	7,298 (25.21)	p = 0.2282
Total (row %)	66,121 (100.00)	31,333 (47.39)	5,834 (8.82)	28,954 (43.79)	
Physician Characteristics					
Ordering Physician Specialty					
Non-specialist	11,317 (17.12)	4,699 (15.00)	1,127 (19.32)	5,491 (18.96)	729.28
Surgeon	3,253 (4.92)	1,740 5.55)	277 (4.75)	1,236 (4.27)	p < 0.0001
Specialist	21,208 (32.07)	11,123 (35.50)	2,158 (36.99)	7,927 (27.38)	
Not recorded	30,343 (45.89)	13,771 (43.95)	2,272 (38.94)	14,300 (49.39)	
Total (row %)	66,121 (100.00)	31,333 (47.39)	5,834 (8.82)	28,954 (43.79)	

*Five patients with missing gender information were not tested.

Table 4.8 Darbepoetin alfa by use category in the inpatient settings

Variable	N Patients by Use Category 2005-2011 (column %)				Chi-sq, p-value
	Any indications	ONS	OFS	OFU	
Patient Characteristics					
Demographics					
Age					
18-30	693 (3.45)	356 (3.36)	54 (3.40)	283 (3.58)	146.21
31-50	3,450 (17.17)	1,734 (18.25)	180 (11.35)	1,336 (16.90)	p < 0.0001
51-64	5,336 (26.56)	2,982 (28.14)	367 (23.14)	1,987 (25.14)	
65-74	4,395 (21.88)	2,295 (21.66)	350 (22.07)	1,750 (22.14)	
75-84	4,341 (21.61)	2,182 (20.59)	412 (25.98)	1,747 (22.10)	
85+	1,873 (9.32)	849 (8.01)	223 (14.06)	801 (10.13)	
Total (row %)	20,088 (100.00)	10,598 (52.76)	1,586 (7.90)	7,904 (39.35)	
Average age (SD)	64.10 (16.28)	63.3 (16.08)	67.6 (16.01)	64.4 (16.51)	
Gender*					
Male	9,981 (49.70)	5,452 (51.45)	776 (48.93)	3,753 (47.50)	28.63
Female	10,103 (50.30)	5,145 (48.55)	810 (51.07)	4,148 (52.50)	p < 0.0001
Total (row %)	20,084 (100.00)	10,597 (52.76)	1,586 (7.90)	7,901 (39.34)	
Race					
Caucasian	13,282 (66.12)	6,959 (64.56)	1,274 (79.46)	5,049 (63.88)	172.85
African-American	5,141 (25.59)	2,778 (27.14)	212 (14.29)	2,151 (27.21)	p < 0.0001
Other	895 (4.46)	480 (4.60)	57 (3.65)	358 (4.53)	
Not recorded	770 (3.83)	381 (3.60)	43 (2.71)	346 (4.38)	
Total (row %)	20,088 (100.00)	10,598 (52.76)	1,586 (7.90)	7,904 (39.35)	
Primary Payer					
Source of Payment					
Medicare	6,682 (34.26)	4,403 (41.55)	592 (37.33)	1,887 (23.87)	1245.31
Medicaid	930 (4.63)	540 (5.10)	84 (5.30)	306 (3.87)	p < 0.0001
Commercial/ Private/ HMO Managed Care	1,501 (7.47)	907 (8.56)	173 (10.91)	421 (5.33)	
Self-pay	538 (2.68)	383 (3.61)	48 (3.03)	107 (1.35)	
Other	628 (3.13)	168 (1.59)	32 (2.02)	428 (5.41)	
Not recorded	9,609 (47.83)	4,197 (39.60)	657 (41.42)	4,755 (60.16)	
Total (row %)	20,088 (100.00)	10,598 (52.76)	1,586 (7.90)	7,904 (39.35)	
Clinical Conditions					
Admission type					
Emergency	8,604 (42.83)	5,701 (55.38)	753 (43.47)	2,150 (27.20)	4707.65
Urgent	1,923 (9.57)	1,141 (10.78)	166 (10.51)	616 (7.79)	p < 0.0001
Elective	3,445 (17.15)	2,529 (23.32)	326 (23.86)	590 (7.46)	
Other/Not recorded	6,116 (30.45)	1,227 (11.58)	341 (21.50)	4,548 (57.54)	
Total (row %)	20,088 (100.00)	10,598 (52.76)	1,586 (7.90)	7,904 (39.35)	
Average CCI (SD)	1.80 (2.058)	2.92 (1.888)	2.01 (1.938)	0.26 (1.078)	
	-1 to 13	-1 to 13	0 to 11	0 to 9	
Average LOS (SD), range	13.4 (18.34) 0 to 540	12.9 (17.06) 0 to 398	17.45 (20.84) 0 to 340	13.3 (19.07) 0 to 540	

Discharge status					
Expired	1,359 (6.77)	724 (6.83)	200 (12.61)	435 (5.50)	1550.59
Discharged to home/self care	8,746 (43.54)	4,677 (44.13)	426 (26.86)	3,643 (46.09)	p < 0.0001
Discharged to Hospice	427 (2.13)	216 (2.04)	51 (3.22)	160 (2.02)	
Discharged/ transferred to institutionalized care	5,798 (28.86)	3,185 (30.15)	659 (41.55)	1,954 (24.72)	
Discharged/ transferred to noninstitutionalized care	2,779 (13.83)	1,709 (16.13)	245 (15.45)	825 (11.44)	
Other/Not recorded	979 (4.87)	87 (0.82)	5 (0.32)	887 (11.22)	
Total (row %)	20,088 (100.00)	10,598 (52.76)	1,586 (7.90)	7,904 (39.35)	
Hospital Characteristics					
Geographic region					
Northeast	7,253 (36.11)	3,610 (34.06)	691 (43.57)	2,952 (37.35)	800.45
Midwest	9,791 (48.74)	5,892 (55.60)	719 (45.33)	3,180 (40.23)	p < 0.0001
South	2,835 (14.11)	969 (9.14)	154 (9.71)	1,712 (21.66)	
West	209 (1.04)	127 (1.20)	22 (1.39)	60 (0.76)	
Total (row %)	20,088 (100.00)	10,598 (52.76)	1,586 (7.90)	7,904 (39.35)	
Bed size					
≤ 99	469 (2.33)	281 (2.65)	56 (3.53)	132 (1.67)	347.01
100-199	2,390 (11.90)	1,118 (10.55)	163 (10.28)	1,109 (14.03)	p < 0.0001
200-299	4,945 (24.62)	2,176 (20.53)	535 (33.73)	2,234 (28.26)	
300-499	4,851 (24.15)	2,790 (26.33)	315 (19.86)	1,746 (22.09)	
≥500	7,433 (37.00)	4,233 (39.94)	517 (32.60)	2,683 (33.94)	
Total (row %)	20,088 (100.00)	10,598 (52.76)	1,586 (7.90)	7,904 (39.35)	
Teaching status					
Teaching	14,795 (73.65)	8,229 (77.65)	994 (62.67)	5,572 (70.50)	226.22
Non-teaching	5,293 (26.35)	2,369 (22.35)	592 (37.33)	2,332 (29.50)	p < 0.0001
Total (row %)	20,088 (100.00)	10,598 (52.76)	1,586 (7.90)	7,904 (39.35)	
Physician Characteristics					
Ordering Physician Specialty					
Non-specialist	2,260 (11.25)	1,130 (10.66)	195 (12.30)	935 (11.83)	46.21
Surgeon	1,944 (9.68)	1,086 (10.25)	183 (11.54)	675 (8.54)	p < 0.0001
Specialist	8,327 (41.45)	4,506 (42.52)	580 (36.57)	3,241 (41.00)	
Not recorded	7,557 (37.62)	3,876 (36.57)	628 (39.60)	3,053 (38.63)	
Total (row %)	12,531 (100.00)	6,722 (53.64)	958 (7.65)	4,851 (38.71)	

*Four patients with missing gender information were not tested.

Specific indications of ESAs in ONS and OFU use category

Uses of epoetin alfa and darbepoetin alfa were further analyzed into individual indications. Specific on-label uses of all ESAs, epoetin alfa, and darbepoetin alfa are described in Table 4.9, 4.10, and 4.11 respectively). Chronic kidney disease (CKD) presented the highest use of on-label ESA use (84.4%). On-label utilization pattern of epoetin alfa was similar to that of the overall ESAs. As expected, the use of darbepoetin alfa on-label was prominent in CKD while few HIV, anemic patients received darbepoetin alfa as this indication was not officially approved for darbepoetin alfa by the FDA.

Part 3.1 On-label use of ESAs

Over the period of 6.5 years, the use of ESAs in CKD, among other on-label indications increased from 78.6% in 2005 to 91.5% in 2011. ESA use in chemotherapy-induced anemia remained relatively stable, while its use in HIV and surgical procedure fluctuated greatly throughout the study period. Approximately 14% of ONS drug use was for patients undergoing major elective surgery. Less than 10% of ESA ONS use was to treat anemia due to chemotherapy. ESA drug use for zidovudine-induced anemia constituted less than 2% of on-label drug use.

Table 4.9 ONS use of ESA (either Epoetin alfa or Darbepoetin alfa, or both) indications within a category are not mutually exclusive

ONS conditions	Year							
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
CKD	4,731	6,947	6,881	7,734	4,204	4,104	1,041	35,642
	(78.61)	(81.26)	(86.01)	(84.41)	(87.78)	(89.96)	(91.48)	(84.42)
CIA	420	660	538	524	309	281	78	2,810
	(6.98)	(7.72)	(6.73)	(5.72)	(6.45)	(6.16)	(6.85)	(6.66)
HIV	90	159	143	185	84	60	13	734
	(1.50)	(1.86)	(1.79)	(2.02)	(1.75)	(1.32)	(1.14)	(1.74)
Surgery	350	1,732	1,090	1,620	652	478	105	6,027
	(5.82)	(20.26)	(13.63)	(17.68)	(13.61)	(10.48)	(9.23)	(14.28)
Any ONS	6,018	8,549	8,000	9,162	4,789	4,562	1,138	45,213

Table 4.10 ONS use of Epoetin alfa only, indications within a category are not mutually exclusive

ONS conditions	Year							
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
CKD	4,049	5,672	4,708	5,481	2,628	2,941	786	26,265
	(77.49)	(81.19)	(86.64)	(84.09)	(86.70)	(89.72)	(91.29)	(83.83)
CIA	375	518	361	318	189	196	60	2,017
	(7.18)	(7.41)	(6.64)	(4.88)	(6.24)	(5.98)	(6.97)	(6.44)
HIV	87	142	92	149	57	45	11	583
	(1.67)	(2.03)	(1.69)	(2.29)	(1.88)	(1.37)	(1.28)	(1.86)
Surgery	1,203	1,385	704	1,186	411	326	88	5,303
	(23.02)	(19.83)	(12.96)	(18.20)	(13.56)	(9.95)	(10.22)	(16.92)
Any ONS	5,225	6,986	5,434	6,518	3,031	3,278	861	31,333

Table 4. 11 ONS use of Darbepoetin alfa only, indications within a category are not mutually exclusive

ONS conditions	Year							
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
CKD	604	1,214	2,128	2,221	1,562	1,147	252	9,128
	(94.08)	(91.48)	(93.83)	(93.36)	(95.89)	(95.03)	(94.03)	(93.91)
CIA	40	135	173	202	117	84	17	768
	(6.23)	(10.17)	(7.63)	(8.49)	(7.18)	(6.96)	(6.34)	(7.90)
HIV	3	16	51	36	27	13	2	148
	(0.47)	(1.21)	(2.25)	(1.51)	(1.66)	(1.08)	(0.75)	(1.52)
Surgery	135	331	380	427	241	151	17	1,682
	(21.03)	(24.94)	(16.75)	(17.95)	(14.79)	(12.51)	(6.34)	(17.30)
Any ONS	642	1,327	2,268	2,379	1,629	1,207	268	9,720

*Epo indications for HIV and surgery

Separate analyses of use for epoetin alfa and darbepoetin alfa showed that chronic kidney disease was the main use of both drugs in our sample. Approximately 83% and 93% of epoetin alfa and darbepoetin alfa, respectively, in the ONS cohort, used the drugs to treat anemia of CKD. Approximately 17% of the on-label use was for patients undergoing major surgeries. Chemotherapy-induced anemia and zidovudine-induced anemia was responsible for approximately 7% and 1.5% of ONS use in the sample. Comparison of ONS use of epoetin alfa and darbepoetin alfa between 2005 and 2011 in the inpatient settings is illustrated in Figure 4.7.

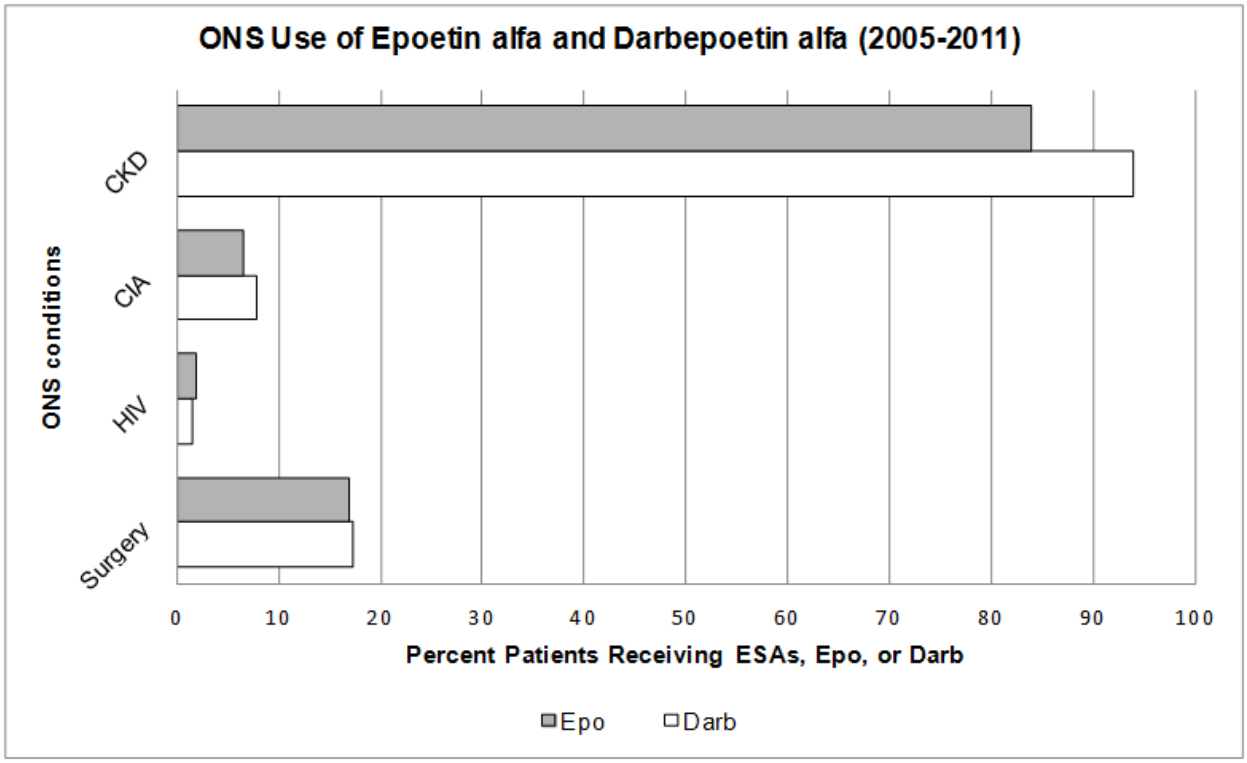

Figure 4.7 ONS use of ESAs, epoetin alfa, and darbepoetin alfa from 2005-2011

Part 3.2 Off-label supported use of ESAs

Among the eleven off-label indications with strong supporting scientific evidence (OFS), acute kidney disease contributed the highest use of ESAs (4,514 patients, 60.4%), epoetin alfa only (3,436 patients, 58.9%), and darbepoetin alfa only (1,369 patients, 55.6%) – data not shown. Due to the relatively small sample size and large number of indications in this category, off-label supported use of ESAs was not further subcategorized into individual conditions.

Part 3.3 Off-label unsupported use of ESAs

We were able to identified specific use of approximately 18% of the total off-label unsupported use of ESAs in the dataset. The majority of identifiable OFU patients (60%) used ESAs for chronic anemia conditions such as iron deficient-related anemia. The second largest use of ESAs for identifiable off-label unsupported indications included anemia of neoplastic disease in those not receiving concomitant chemotherapy, cardiac surgery, fractures and other injuries, and various GI bleeding. Identifiable indications of ESAs neither approved nor supported by scientific evidence are summarized in Table 4.12-4.14, and compared in Figure 4.8. We additionally found that approximately four percent (1,072 patients) of epoetin alfa users with OFU conditions had blood transfusion while 328 (4.1%) darbepoetin alfa users with OFU conditions had blood transfusion.

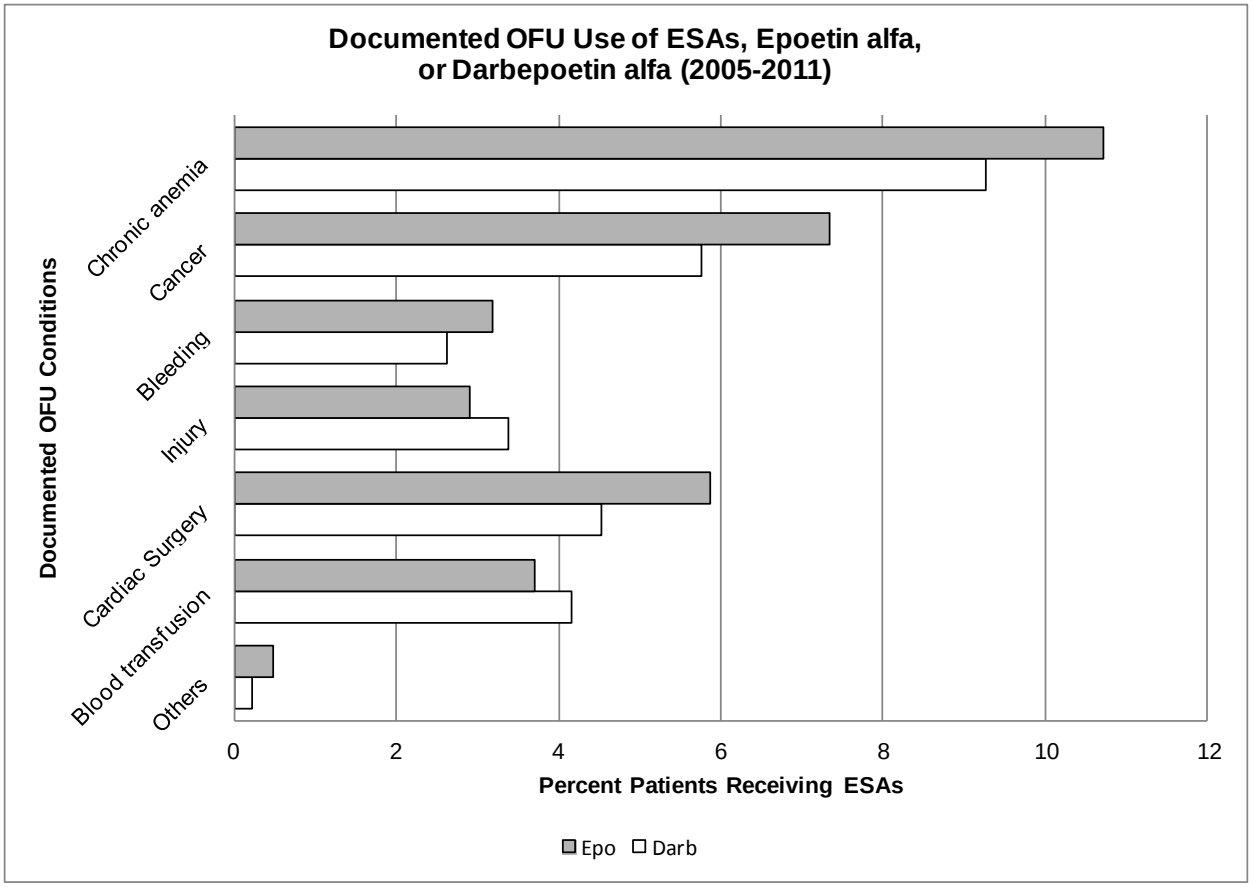

Figure 4.8 Documented OFU use of ESAs, epoetin alfa, and darbepoetin alfa from 2005-2011

Table 4.12 Defined OFU use of any ESAs, indications within a category are not mutually exclusive

ONS conditions	Year							
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
Chronic	675	1,000	865	648	395	241	31	3,855
Anemia	(30.36)	(24.33)	(15.12)	(10.34)	(7.16)	(3.19)	(0.55)	(10.40)
Cancer	510	727	611	386	212	132	15	2,593
	(22.94)	(17.69)	(10.68)	(6.16)	(3.84)	(1.75)	(0.26)	(7.00)
Bleeding	194	268	260	206	112	85	8	1,133
	(8.73)	(6.52)	(4.54)	(3.29)	(2.03)	(1.12)	(0.14)	(3.06)
Injury	177	279	334	166	102	57	4	1,119
	(7.96)	(6.79)	(5.84)	(2.65)	(1.85)	(0.75)	(0.07)	(3.02)
Cardiac	350	504	333	494	225	156	12	2,074
surgery	(15.74)	(12.26)	(5.82)	(7.88)	(4.08)	(2.06)	(0.21)	(5.60)
Blood	284	355	224	288	125	122	13	1,411
transfusion	(12.78)	(8.64)	(3.91)	(4.60)	(2.26)	(1.61)	(0.23)	(3.81)
Other known	19	25	32	50	20	13	2	161
OFU	(0.85)	(0.61)	(0.56)	(0.80)	(0.36)	(0.17)	(0.04)	(0.43)
Defined OFU	1,127	1,584	1,464	1,116	581	440	45	6,357
	(50.70)	(38.54)	(25.59)	(17.81)	(10.53)	(5.82)	(0.79)	(17.15)
Any OFU	2,223	4,110	5,722	6,267	5,520	7,563	5,663	37,068

Table 4.13 Defined OFU use of epoetin alfa only, indications within a category are not mutually exclusive

ONS conditions	Year							
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
Chronic	629	850	604	489	316	188	27	3,103
Anemia	(35.48)	(24.42)	(13.46)	(9.85)	(7.25)	(3.22)	(0.67)	(10.72)
Cancer	471	611	465	304	164	100	13	2,128
	(26.57)	(17.55)	(10.36)	(6.13)	(3.76)	(1.71)	(0.32)	(7.35)
Bleeding	180	227	194	151	92	69	8	921
	(10.15)	(6.52)	(4.32)	(3.04)	(2.11)	(1.18)	(0.20)	(3.18)
Injury	165	242	177	114	88	52	4	842
	(9.31)	(6.95)	(3.94)	(2.30)	(2.02)	(0.89)	(0.10)	(2.91)
Cardiac	328	427	209	402	188	135	10	1,699
surgery	(18.50)	(12.27)	(4.66)	(8.10)	(4.31)	(2.31)	(0.25)	(5.87)
Blood	256	280	125	206	91	101	13	1072
transfusion	(14.44)	(8.04)	(2.79)	(4.15)	(2.09)	(1.73)	(0.32)	(3.70)
Other known	18	22	28	44	17	13	1	143
OFU	(1.02)	(0.63)	(0.62)	(0.89)	(0.39)	(0.22)	(0.02)	(0.49)
Defined OFU	1,051	1,347	991	869	477	368	40	5,143
	(59.28)	(38.70)	(22.09)	(17.51)	(10.94)	(6.30)	(0.99)	(17.76)
Any OFU	1,773	3,481	4,487	4,962	4,360	5,839	4,052	28,954

Table 4.14 Defined OFU use of darbepoetin alfa only, indications within a category are not mutually exclusive

ONS conditions	Year							
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
Chronic	44	144	252	158	78	52	4 (0.26)	732
Anemia	(10.30)	(24.00)	(20.79)	(12.35)	(6.83)	(3.09)	(0.13)	(9.26)
Cancer	38	112	143	82	47	32	2	456
	(8.90)	(18.67)	(11.80)	(6.41)	(4.12)	(1.90)	(0.00)	(5.77)
Bleeding	13	39	65	54	20	16	0	207
	(3.04)	(6.50)	(5.36)	(4.22)	(1.75)	(0.95)	(0.00)	(2.62)
Injury	9	35	155	49	14	5	0	267
	(2.11)	(5.83)	(12.79)	(3.83)	(1.23)	(0.30)	(0.00)	(3.38)
Cardiac	18	74	117	91	36	20	2	358
surgery	(4.22)	(12.33)	(9.65)	(7.11)	(3.15)	(1.19)	(0.13)	(4.53)
Blood	25	73	94	82	33	21	0	328
transfusion	(5.85)	(12.17)	(7.76)	(6.41)	(2.89)	(1.25)	(0.00)	(4.15)
Other known	1	3	4	6	3	0	1	18
OFU	(0.23)	(0.50)	(0.33)	(0.47)	(0.26)	(0.00)	(0.06)	(0.23)
Defined OFU	69	226	459	244	103	70	5	1176
	(16.16)	(37.67)	(37.87)	(19.08)	(9.02)	(4.16)	(0.32)	(14.88)
Any OFU	427	600	1212	1279	1142	1684	1560	7904

Specific Aim 2: Estimating the impacts of black box warning, NCD, and REMS on the on proportion of visits with ESA use

Trends in ESA On-label, off-label supported, and off-label unsupported therapy

Annual trends in ESA ONS, OFS, and OFU use from 2005 to 2010 are shown in Table 4.15. These trends were measured in term of the proportion of visits which the drug was prescribed over the total number of eligible admissions. Only full-year data was used to describe the annual trends. In general, the proportions of epoetin alfa and darbepoetin alfa use for on-label (ONS) and off-label supported (OFS) indications decreased from 2005 to 2011, while that for off-label unsupported use (OFU) increase drastically.

Epoetin alfa ONS use increased 57% from 6.0% (2005) to 7.3% (2006) to 7.4% (2007). At the same time, Darbepoetin alfa ONS use increased 250% from 1.0% (2005) to 1.7% (2006) to 3.5% (2007). In 2008, ONS use of both drug started to decline. Epoetin alfa ONS use decreased 76% from 7.4% (2007) to 5.0% (2008) to 1.8% (2009), after which its use increased again slightly in 2010 (+1.3%). Darbepoetin alfa ONS use decreased 71% from 3.5% (2007) to 2.1% (2008) to 1.4% (2009), and to 1.0% (2010). Overall, in 6 years, epoetin alfa ONS use declined 53% while the level of darbepoetin alfa ONS use remained the same.

We observed a continual reduction in the proportion of visits which epoetin alfa was used in patients with OFS conditions. In contrast, darbepoetin alfa OFS use increased at the beginning of the study period from 0.3% (2005) to 08% (2007) before it started to decreased. Overall, epoetin alfa and darbepoetin alfa OFS use declined 85% and 54%, respectively.

Similar to ONS use, we found that the OFU proportions increased at the beginning of the study period (from 2005 to 2007), but reduced in 2008 and 2009. OFU use then surged in 2010. These annual trends resulted in the overall increase in OFU use of 103% and 147% for epoetin alfa and darbepoetin alfa between 2005 and 2011, respectively.

Table 4.15 Annual trend in the proportion of ESA use by use category*

Use Category	**Percent of visits with ESA use (%)**						
	2005	2006	2007	2008	2009	2010	**%Δ (2005-2010)**
Total (any ESAs)							
ONS	6.9	8.9	10.8	7.1	3.2	3.2	
Δ from preceding year	**-**	**+29.4%**	**+21.2%**	**-34.6%**	**-55.0%**	**+1.3%**	**-53.2%**
OFS	2.8	2.4	2.4	1.7	0.6	0.5	
Δ from preceding year	**-**	**-11.3%**	**-2.5%**	**-28.9%**	**-65.1%**	**-15.4%**	**-81.9%**
OFU	3.7	6.3	7.0	7.0	5.2	7.8	
Δ from preceding year	**-**	**+71.9%**	**+11.3%**	**-1.0%**	**-24.6%**	**+48.8%**	**+112.6%**
Epoetin alfa							
ONS	6.0	7.3	7.4	5.0	1.8	2.2	
Δ from preceding year	**-**	**+22.0%**	**+1.4%**	**-32.3%**	**-63.5%**	**+21.9%**	**-62.7%**
OFS	2.5	2.0	1.6	1.3	0.4	0.4	
Δ from preceding year	**-**	**-19.1%**	**-19.2%**	**-23.1%**	**-67.8%**	**-7.4%**	**-85.0%**
OFU	3.0	5.4	5.6	5.5	4.1	6.0	
Δ from preceding year	**-**	**+80.6%**	**+3.8%**	**-0.6%**	**-26.8%**	**+48.8%**	**+103.0%**
Darbepoetin alfa							
ONS	1.0	1.7	3.5	2.1	1.4	1.0	
Δ from preceding year	**-**	**+68.5%**	**+105.1%**	**-40.1%**	**-34.3%**	**-26.3%**	**+.03%**
OFS	0.3	0.5	0.8	0.4	0.2	0.1	
Δ from preceding year	**-**	**+67.6%**	**+68.5%**	**-42.4%**	**-57.2%**	**-33.3%**	**-53.5%**
OFU	0.7	1.0	1.5	1.4	1.2	1.8	
Δ from preceding year	**-**	**+34.0%**	**+50.3%**	**-2.0%**	**-16.7%**	**+50.2%**	**+147.0%**

*Only years with full-year reports are shown

The proportions of visits with ESA use for the on-label, off-label supported, and off-label unsupported were plotted against time to illustrate monthly trends in ESA use. In Figure 4.5, monthly proportions of visits with ESA use for on-label indications are marked with -○- symbol while that for off-label supported and off-label unsupported are marked with -×- and -□-, respectively.

ESA use for on-label indication showed an increasing trend from 5.5% at month 1 (January 2005) to 10.3% at month 22 (October 2006), after which its use leveled off slightly to 7.7% in June 2007. A sudden increase in the percent of visits with ESA use was observed at month 31 (July 2007). ESA on-label use level remained high for six months at approximately 18%. After that, a rapid drop to 7.9% at month 37 (January 2008) was observed. Off-label supported use of ESAs (OFS) remained relative stable from 2005 to early 2008, and declined slightly afterward. OFU use, however, began to increase from an average of 3.6% in 2005 to 6.4% (2006-September 2008). After October 2008, OFU use started to rise sharply (> 500%). Similar trends were observed when use was broken down by drug. Monthly trends for each use category of epoetin alfa and darbepoetin alfa are illustrated in Figure 4.9 and 4.11, respectively.

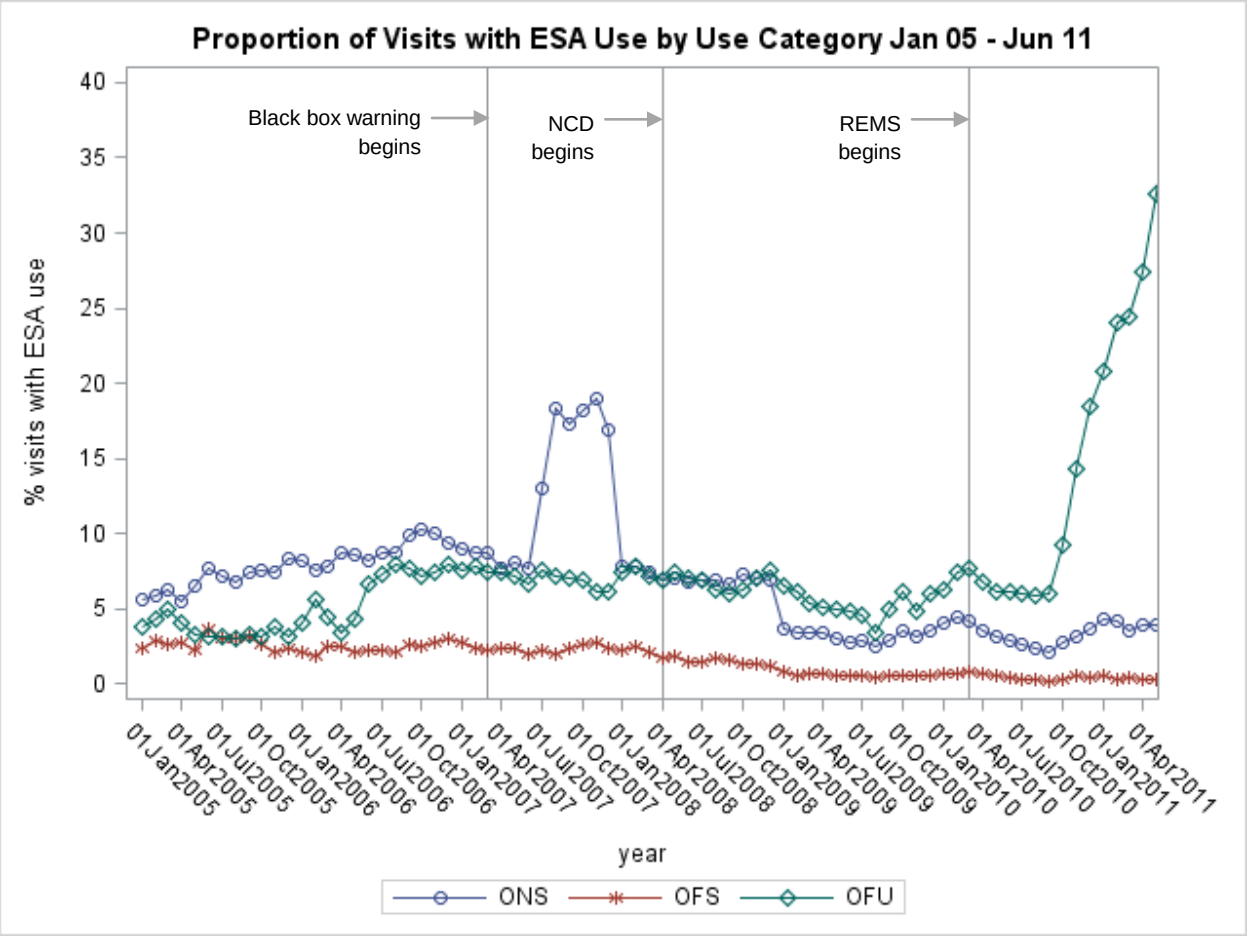

Figure 4.9 Monthly trend in ESA use for the on-label, off-label supported, and off-label unsupported indications from January 2005 to June 2011 expressed in term of proportion of visits with ESA use over total number of eligible visits

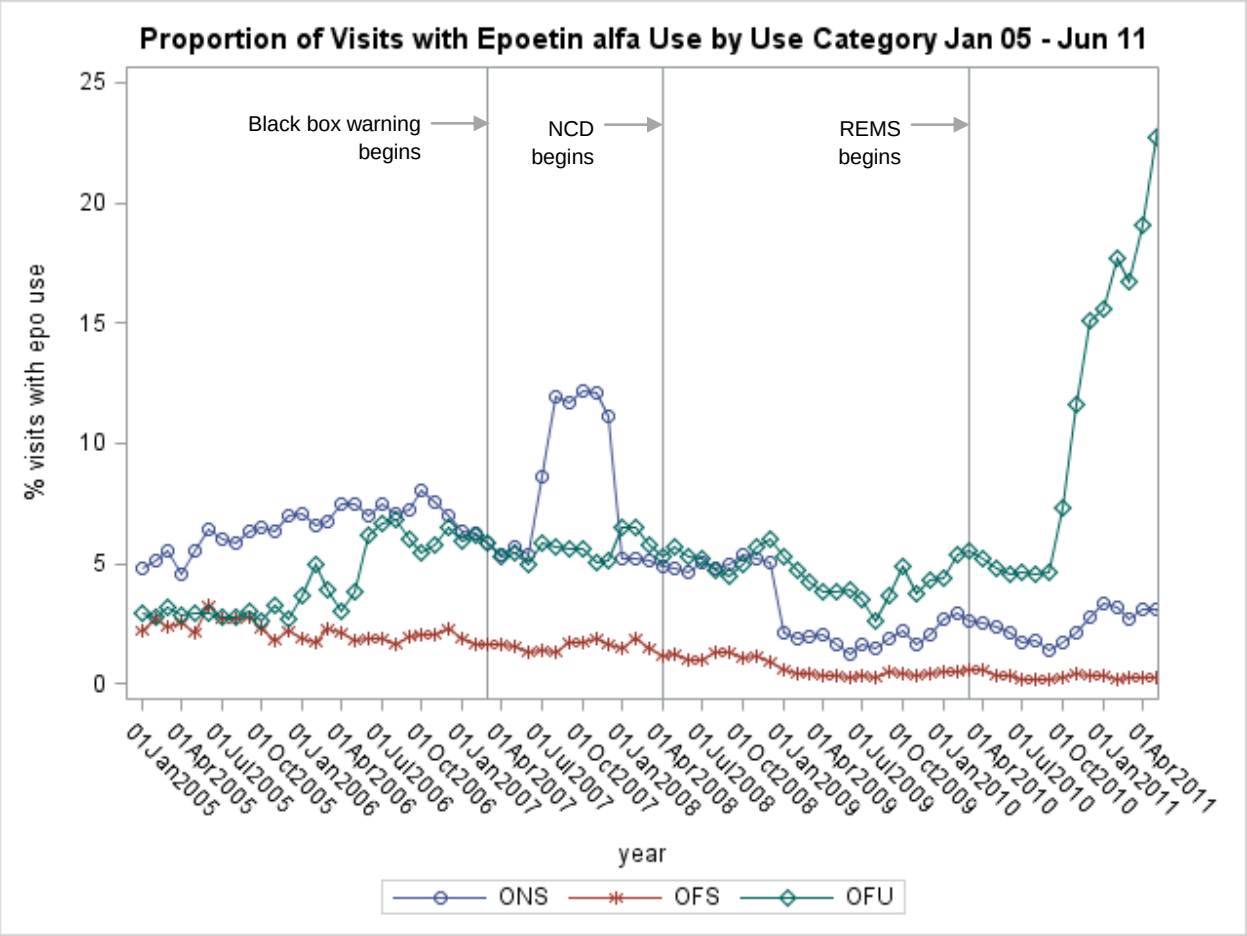

Figure 4.10 Monthly trend in epoetin alfa use for the on-label, off-label supported, and off-label unsupported indications from January 2005 to June 2011 expressed in term of proportion of visits with ESA use over total number of eligible visits

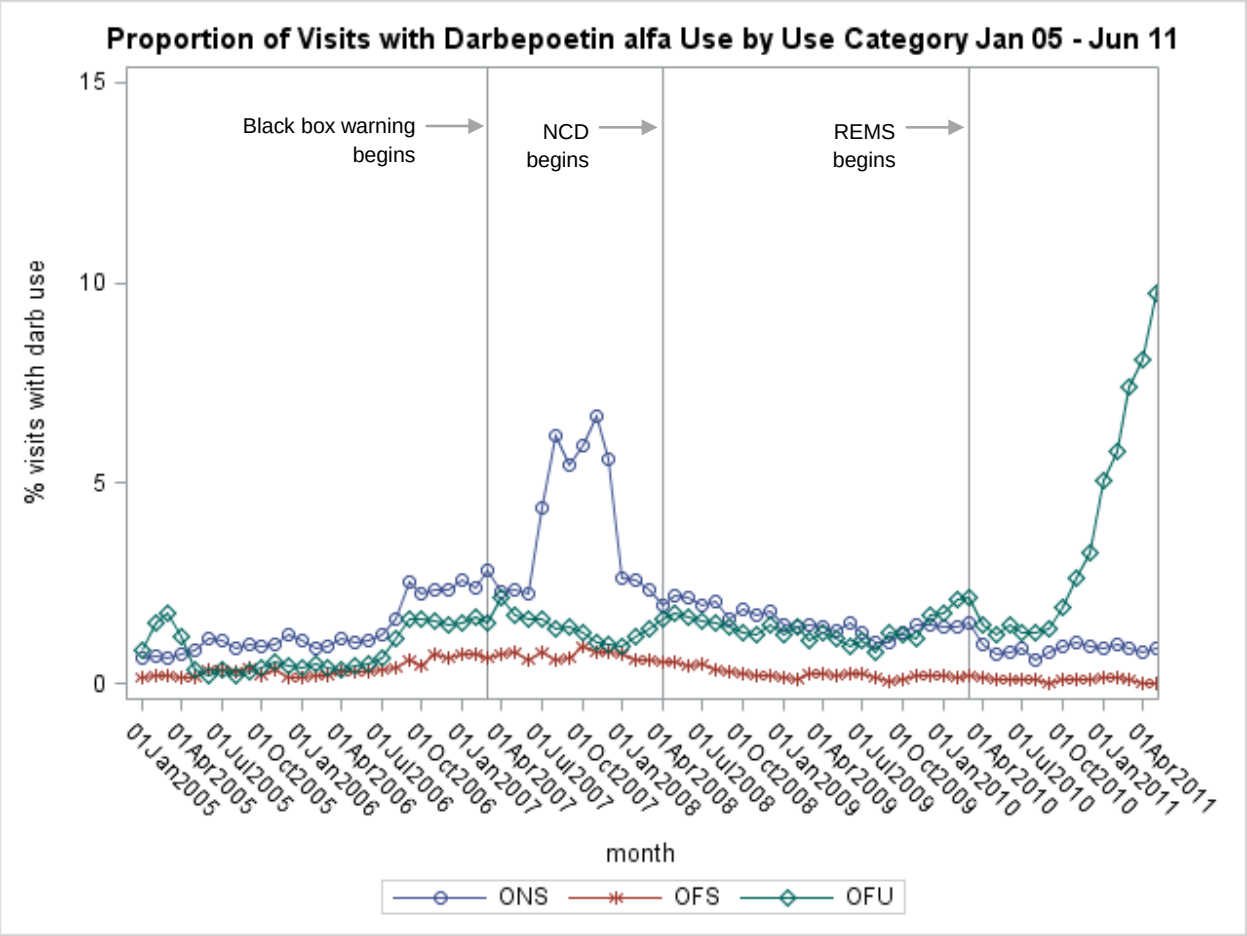

Figure 4.11 Monthly trend in darbepoetin use for the on-label, off-label supported, and off-label unsupported indications from January 2005 to June 2011 expressed in term of proportion of visits with ESA use over total number of eligible visits

Outlier Identification and Data Manipulation

Outliers or wild data points referred to spurious observations that were highly inconsistent with the rest of the series. An outlier was usually dealt with by checking the original data for errors, replacing the observation with imputed values, or deleting such observations.[189] Outliers oftentimes make the inference unreliable or even invalid and thus it was important to detect and remove such outliers.

Two possible set of outliers were detected in our data. In the ONS series, we observed a drastic increase in the percent of visits after month 30. ONS utilization level remained high for six month then dropped off suddenly at month 37. Secondly, possible outliers were detected in the all OFU series after month 70 when the proportion increased sharply. We did not believe that such extreme changes in the series were caused by any external interventions, but such sudden changes were likely to cause by errors in data collection and reporting of the eligible admissions that could not be corrected. At month 31-36, we found that even though the number of visits which a drug was prescribed remained relatively stable, the number of ONS eligible admission changed suspiciously. During those six months, the number of admissions with ONS conditions was halved from that at month 30 and resumed to normal level at month 37. Likewise, at month 70, there was a rise in the number of visits with ESA OFU use and a drop in the number admissions with known OFU conditions, leading to an extreme shift on the OFU proportion after month 70. Similar outliers were also detected for both EPO and DARB series.

To account for these spurious data points before modeling interrupted time-series (Specific Aim 2), values during the outlier months were imputed using time-series forecasting method. A series that minimized root mean square errors was fit to generate predicted y values

that were to be used in the subsequent analysis. Forecasting assumes that the trend in proportion continued from month 30 into month 31 to 36 as if the ONS series was left to continue without any interventions. The same approach was used from month 71 onward for the OFU series. The adjusted series with imputed values replacing the outliers are shown in Figure 4.12-4.14. These series were used in the subsequent interrupted time-series analysis.

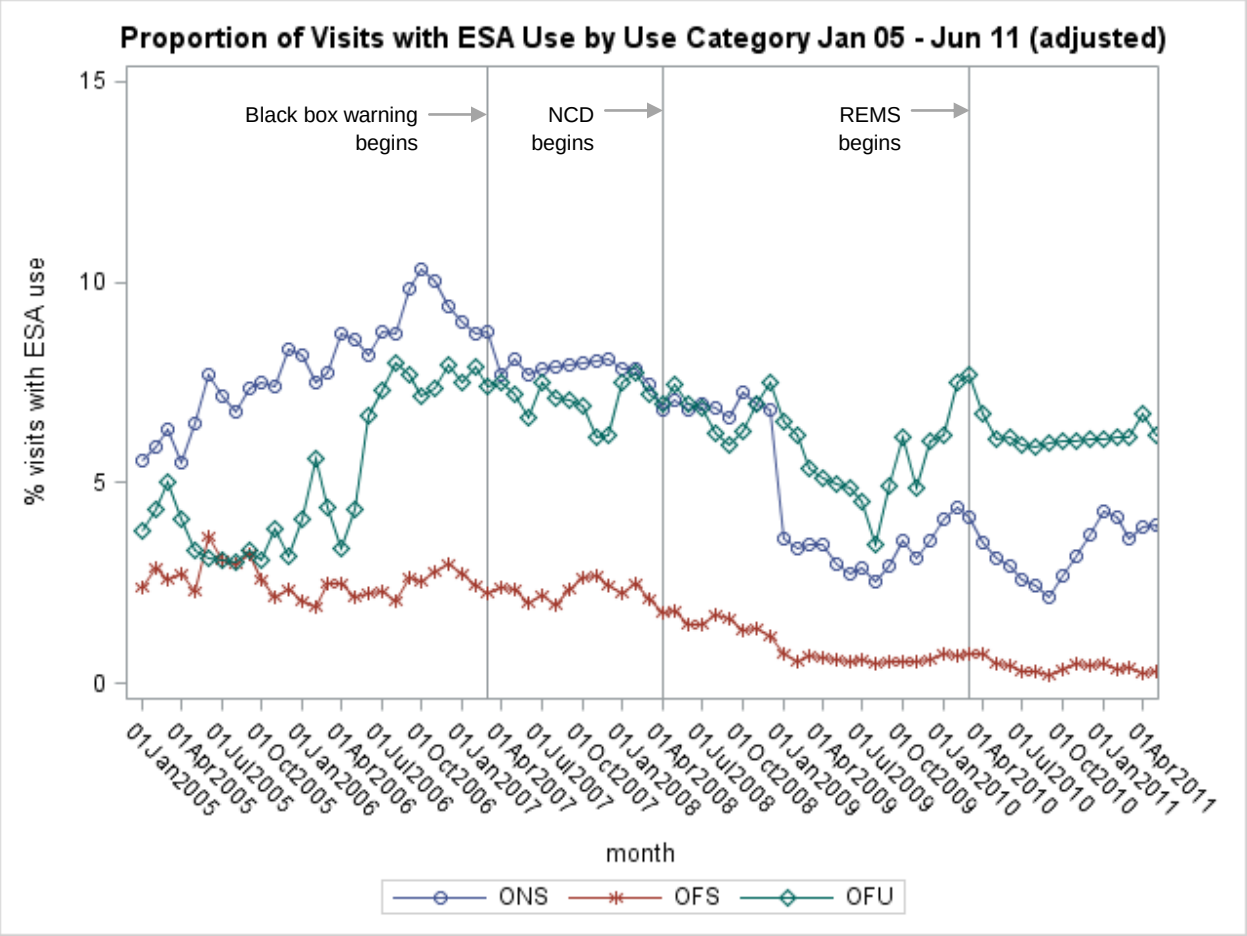

Figure 4.12 Monthly trend in ESA use for the on-label, off-label supported, and off-label unsupported indications from January 2005 to June 2011 expressed in term of proportion of visits with ESA use over total number of eligible visits after data manipulation

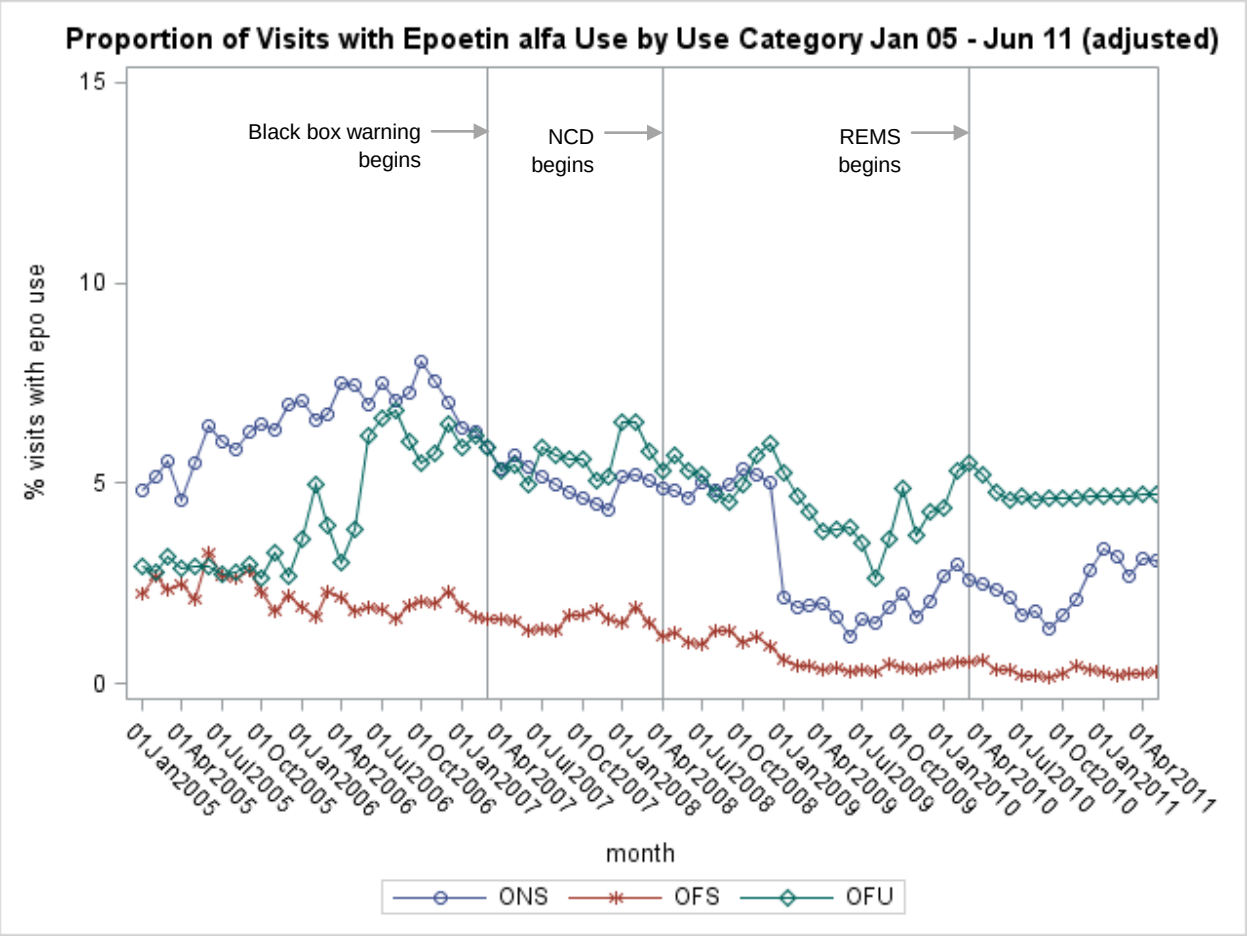

Figure 4.13 Monthly trend in epoetin alfa use for the on-label, off-label supported, and off-label unsupported indications from January 2005 to June 2011 expressed in term of proportion of visits with ESA use over total number of eligible visits after data manipulation

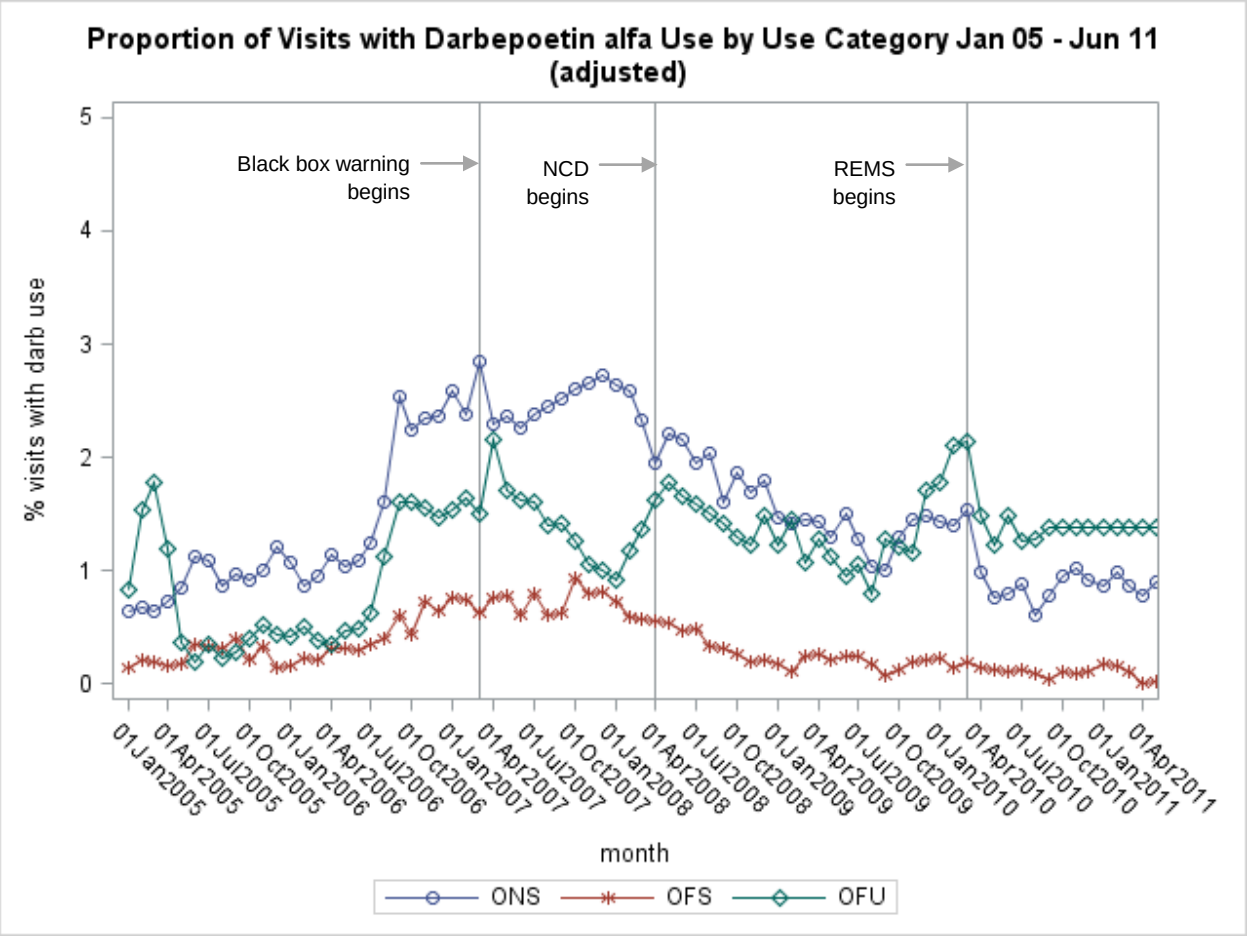

Figure 4.14 Monthly trend in darbepoetin alfa use for the on-label, off-label supported, and off-label unsupported indications from January 2005 to June 2011 expressed in term of proportion of visits with ESA use over total number of eligible visits after data manipulation

Time-Series Model selection

The application of time series to model ESA prescribing patterns and the effects of the intervention on the utilization patterns relied on several statistical assumptions. In order to obtain unbiased OLS estimation, it was important to assume that the error terms and all explanatory variables were uncorrelated for all time periods. More importantly, serial correlation (autocorrelation) must not be present in the data. Serial correlation referred to the existence of the correlations between the observations' errors terms in different periods. The existence of serial correlation implied heteroskedasticity of the variance over time resulting in falsely estimation of the standard errors. Only once the assumption of having no serial correlation was fulfilled that the OLS estimator became the best linear unbiased estimator (BLUE).

In an attempt to fit the best time-series model for our data, several approaches were taken to attenuate serial correlations and produce stationary series. First, autocorrelation patterns at different lags were assessed. Serial correlation was virtually detected with the sample autocorrelation function plot (ACF) generated by -*proc arima*- with identify statement. The slow decay in the ACF plot shown in Panel B of Figure 4.15, 4.16, and 4.17 indicated that correlation exists between the dependent variable (proportion of visits with ESA use) and the value in the previous period for all three models (ONS, OFS, and OFU). This slow decay in the ACF plots also implied that the series was nonstationary. Second, white noise test, which intended to test a hypothesis that none of the autocorrelations were significantly different from zero, confirmed the existence of autocorrelation as the null hypothesis was rejected strongly for all possible lag values ($p < 0.0001$). Autocorrelations were tested in epoetin alfa and darbepoetin alfa model and similar results of strong autocorrelation were observed (data not shown).

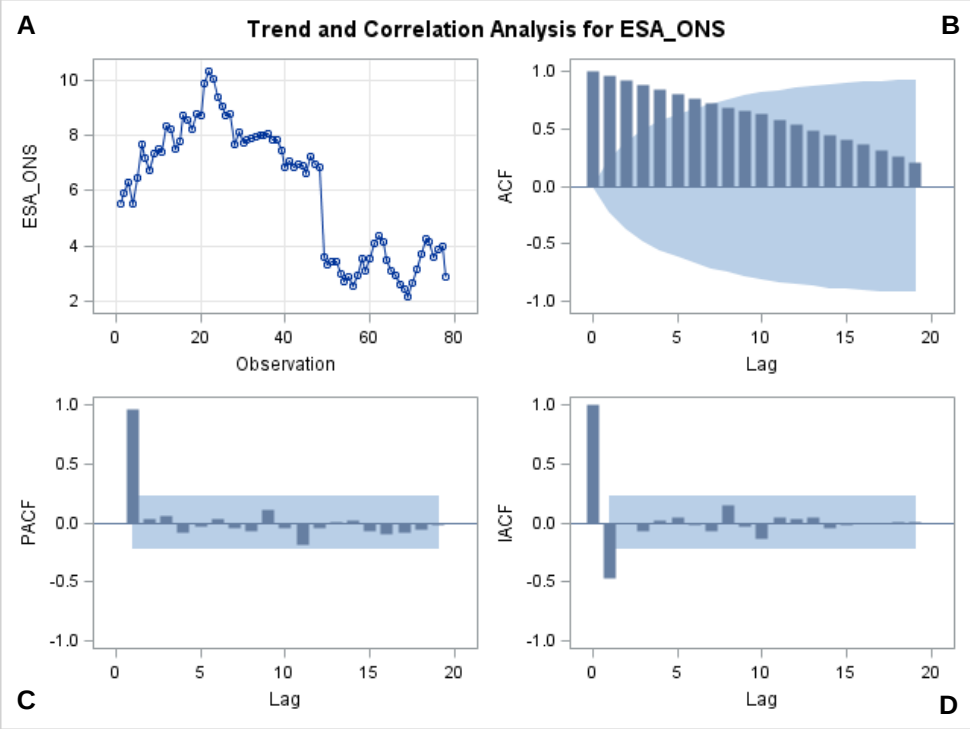

Figure 4.15 Diagnostic of autocorrelation in the ESA-ONS series

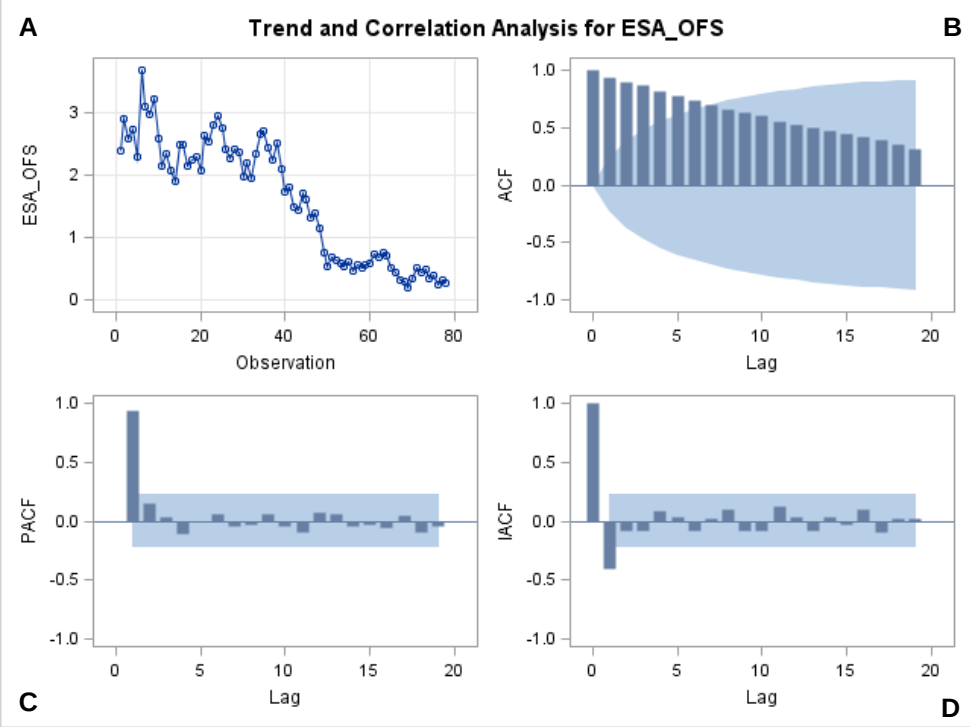

Figure 4.16 Diagnostic of autocorrelation in the ESA-OFS series

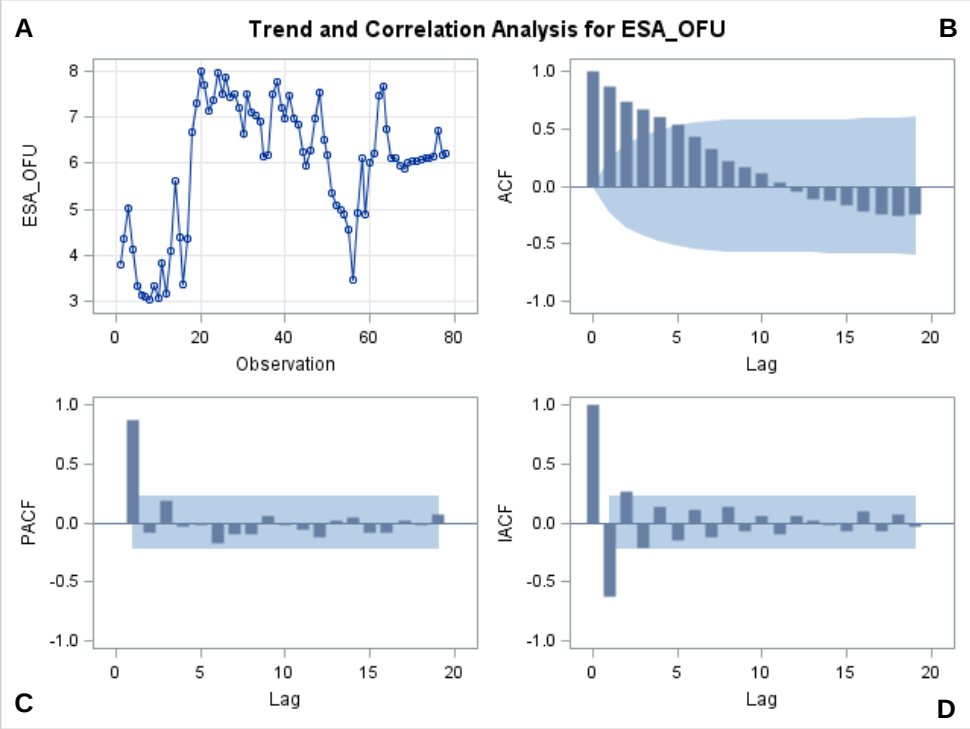

Figure 4.17 Diagnostic of autocorrelation in the ESA-OFU series

To eliminate serial correlation, the use of first-differencing method of the series was suggested.[199, 200] First-differencing referred to a transformation on a time series constructed by taking the difference of adjacent time period, where the earlier time period was subtracted from the later time period.[201] First differencing of the data resolved the issue of serial correlation in the ONS and OFU models (all white noise test p-values > 0.05, data not shown). However, the white noise test revealed the remaining of serial correlations in the OFS model (all p-value < 0.05, data not shown). First-differencing series and autocorrelation plots after first-differencing of the ESA- ONS, ESA-OFS, and ESA-OFU series are shown in Figure 4.18, 4.19, and 4.20.

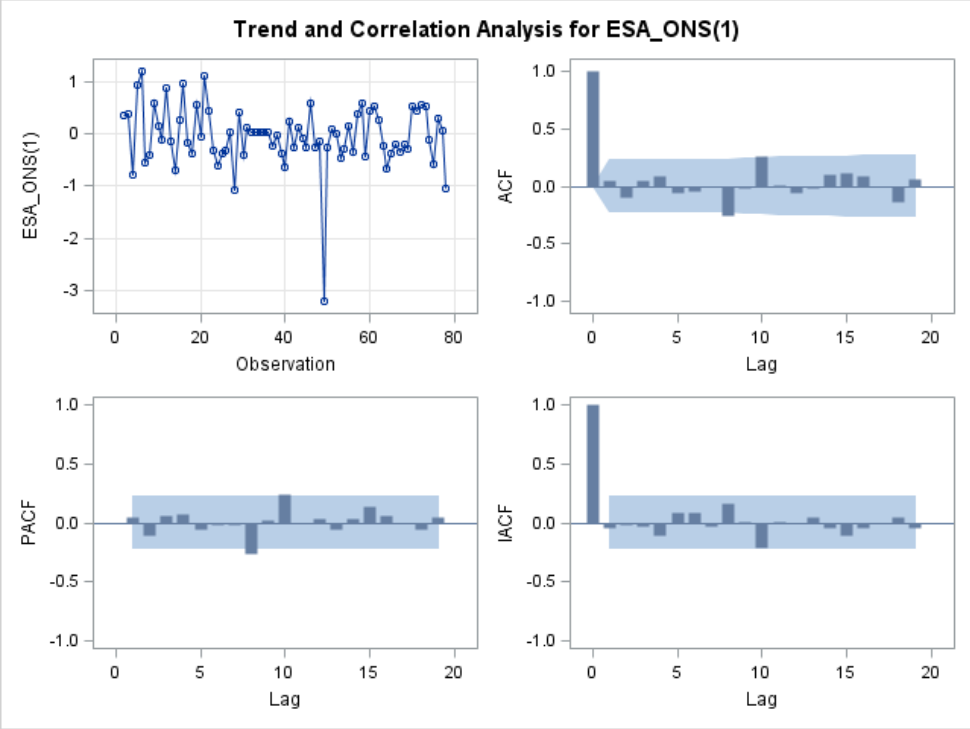

Figure 4.18 Diagnostic of autocorrelation in the ESA-ONS series after first-differencing

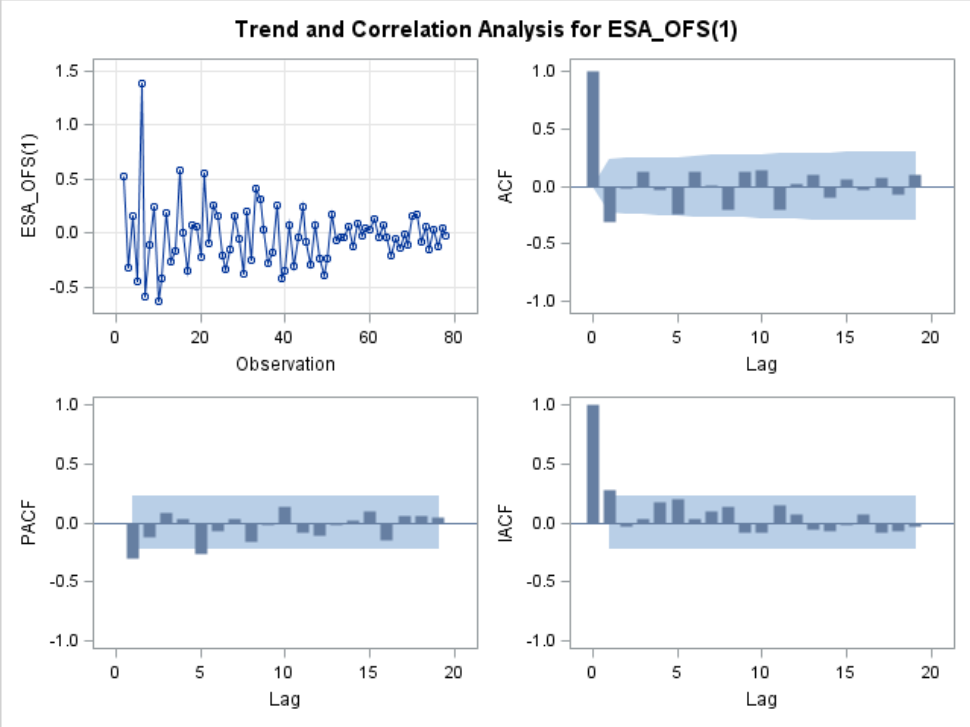

Figure 4.19 Diagnostic of autocorrelation in the ESA-OFS series after first-differencing

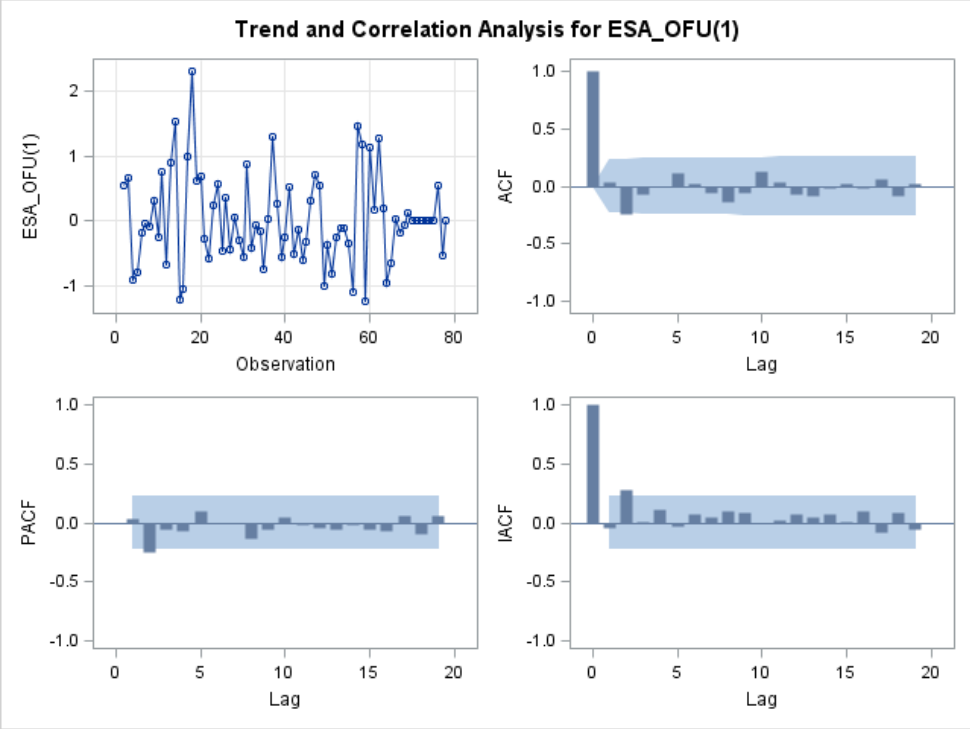

Figure 4.20 Diagnostic of autocorrelation in the ESA-OFU series after first-differencing

As mentioned earlier, the presence of autocorrelation in the model resulted in inaccuracy of standard errors even when the coefficients were estimated in an unbiased manner. To correct for autocorrelation remained in the OFS series and to obtain accurate standard errors of the estimates, Newey-West's serial correlation-robust estimation was applied to all models. Newey and West suggested the integer part of $4(\frac{n}{100})^{(2/9)}$ as the number of lags in the model if no specific theory can otherwise be specified.[201] This approach corrected for autocorrelation remained in the first-differencing OFS series and was also a more conservative approach of correcting for any autocorrelation that may still remain undetected in the ONS and OFU series. Figure 4.21 – 4.23 show the residual plots of the first-differencing ONS, OFS, and OFU when the series were re-estimated with a lag of four (as calculated with Newey-West's method). The residuals for all three series appeared to follow a normal distribution.

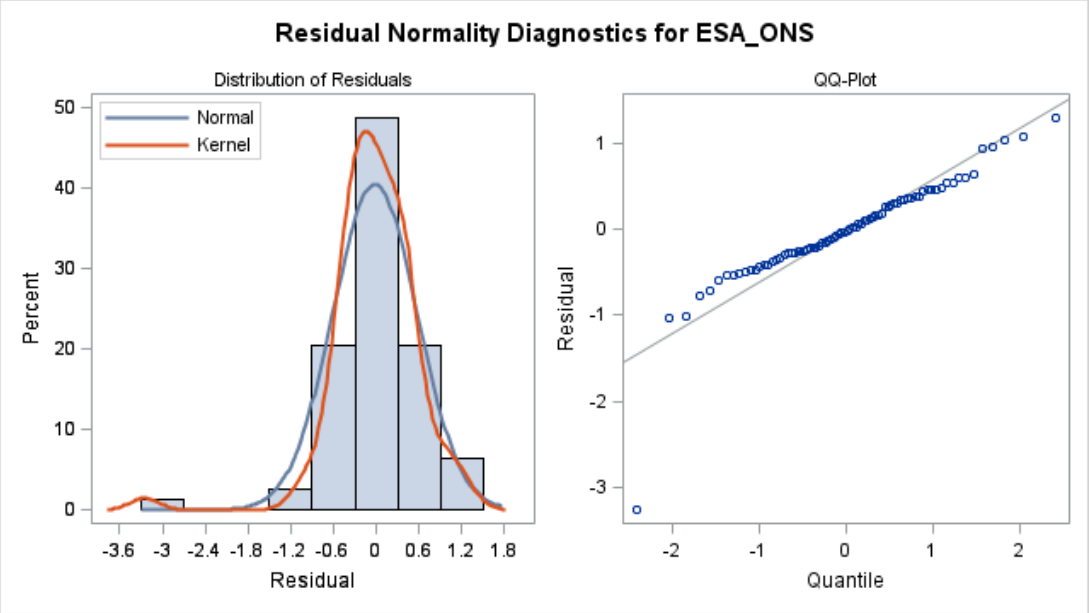

Figure 4.21 Residual normality diagnostic of first-differenced ESA-ONS series with a lag of four

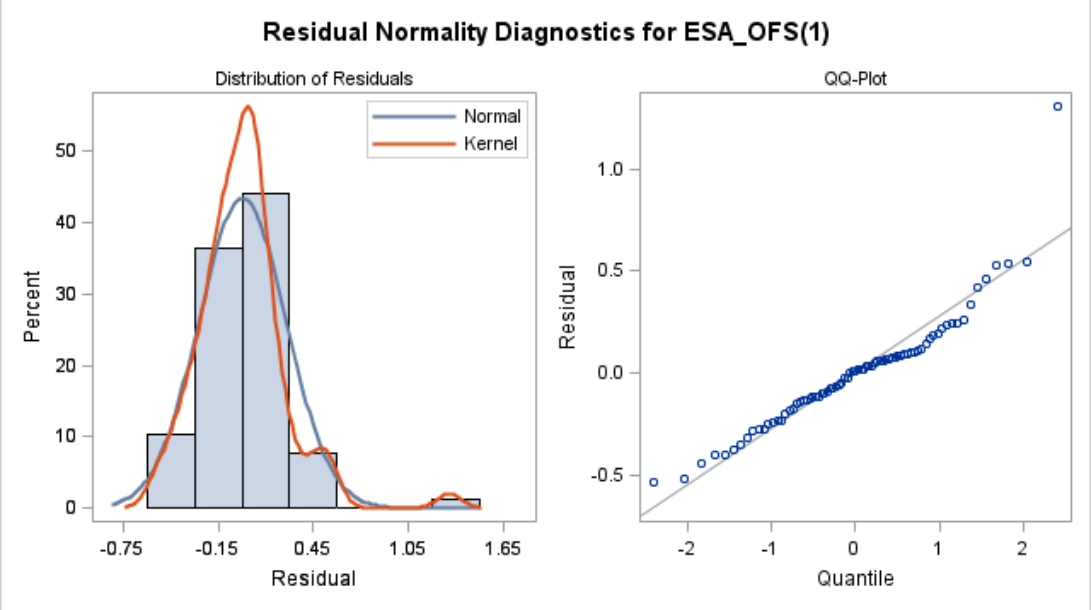

Figure 4.22 Residual normality diagnostic of first-differenced ESA-OFS series with a lag of four

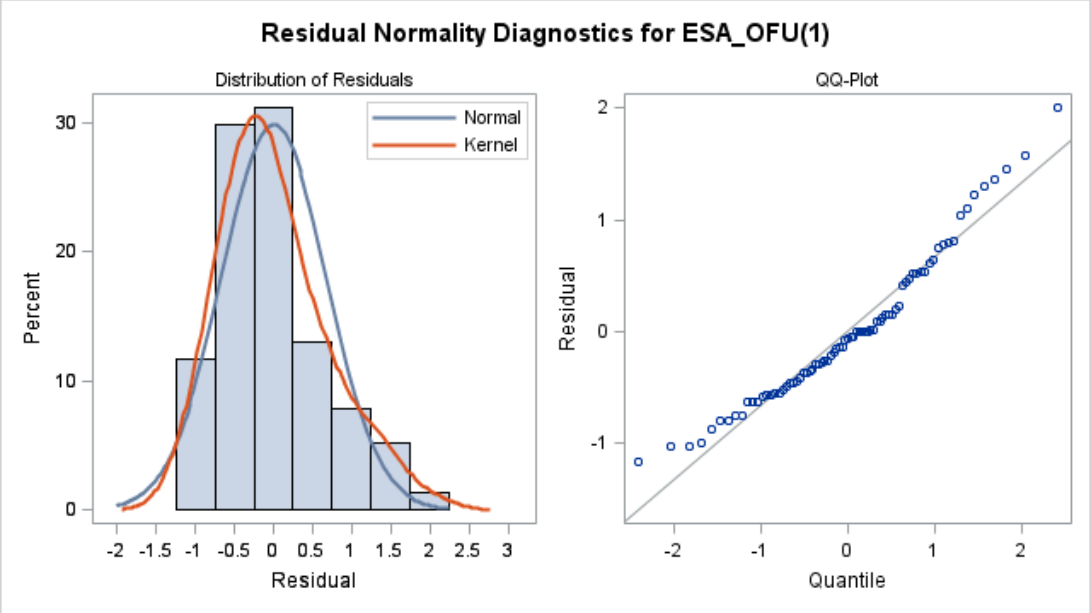

Figure 4.23 Residual normality diagnostic of first-differenced ESA-OFU series with a lag of four

The interventions were tested with segmented ordinary least-square regressions once that the endogeneous pattern in the series was reduced to random through transformation and modeling. Using the estimating equations specified in Chapter 3: $Y_t = \beta_0 + \beta_1 t + \beta_2 \text{intervention1} + \beta_3 \text{intervention1} \times t_1 + \beta_4 \text{intervention2} + \beta_5 \text{intervention2} \times t_2 + \beta_6 \text{intervention3} + \beta_7 \text{intervention3} \times t_3 + \text{M2-M12} + e_t$, the final model included first-differencing of all variables and Newey-West's serial correlation-robust estimation with the lag of four time periods. Since the aggregated time series was monthly, a set of 11 months variables (M2-M12) were included in the model to account of seasonal cycles.

Impacts of Safety interventions on the proportion of visits with ESA use

The aim of this analysis was to determine if the three safety interventions: black box warning (BBW), national coverage determination (NCD), and risk evaluation and mitigation strategies program (REMS) were associated with change in ESA on-label, off-label supported, and off-label unsupported use. The parameters estimated from the time-series analysis are given in Table 4.16, 4.17, and 4.18 for overall ESAs, epoetin alfa, and darbepoetin alfa, respectively.

<u>On-label use of ESAs (ONS)</u>

From the beginning of our study period in January 2005 to the issuance of a black box warning there was a non-significant, increasing trend in ESA on-label use (0.1% increase in the use proportion per month, $p = 0.1360$). The addition of a black box warning onto ESA label in March 2007 was associated with a significant 1.2 percentage point drop in the proportion of visits with ESA on-label use to all ONS eligible visits (95% CI -1.979, -0.358, $p = 0.0050$). The use of ESAs for the on-label indications continued in a decreasing trend after the first intervention ($\beta = -0.142$, $p = 0.1970$). No other statistical significant reduction in the proportion was found though NCD and REMS resulted in non-significant decreased in the level of ONS prescribing ($\beta_{NCD} = -0.608$, $p = 0.1340$; $\beta_{REMS} = -0.738$, $p = 0.0730$).

<u>Off-label supported use of ESAs (OFS)</u>

Black box warning issuance did not significantly lead to a significant reduction in ESA on-label supported use (OFS) like the change in reimbursement policy National Coverage Determination did in April 2008. NCD was the only significant intervention for OFS use. There was a significant 0.3 percentage point drop in the proportion of visits with ESA-OFS use after the coverage change in April 2008 (95% CI -0.447, -0.182, $p < 0.0001$). Finally, REMS did not

have any significant impact on the level of ESA use for OFS indications (β_{REMS} = -0.017, p = 0.7720).

Off-label unsupported use of ESAs (OFU)

None of the intervention appeared to have an effect on the utilization patterns of ESAs for the off-label unsupported indications (OFU).

Epoetin alfa

The analysis was re-performed by specific drug: epoetin alfa (Table 4.17) and darbepoetin alfa (Table 4.18). Black box warning appeared to have no significant effect on the level of epoetin alfa use, for any indications (all p-values > 0.5). NCD resulted in a 0.3% immediate drop in the proportion of OFS-EPO use in at the first month after the intervention was implemented (95% CI -0.437, -0.170, p < 0.0001) and non-significant decreasing trends afterward. REMS, on the other hand, did not have any significant impact of epoetin alfa utilization patterns.

Darbepoetin alfa

Black box warning reduced level of darbepoetin alfa on-label use significantly - darbepoetin alfa use drop 0.6% after the intervention took place (95% CI -0.670, 0.433, p < 0.0001). In our sample, the reversed effect of black box warning was observed in the off-label use. Black box warning resulted in a significant rise in off-label supported and unsupported use of darbepoetin alfa in April 2007 (02% and 0.9% increase for OFS and OFU darb use, respectively). National coverage determination led to a significant increase in on-label use only (0.4% point reduction, 95% CI -0.466, -0.256, p < 0.0001). Finally, the use of darbepoetin alfa

was most affected by REMS. There was a significant 0.5% percentage point drop in the proportion of visits which darbepoetin alfa was used on-label (95% CI -0.637, -0.443, $p < 0.0001$) and also for off-label unsupported indications (95% CI -0.805, -0.223, $p < 0.0010$) in April 2010, one month after the implementation of REMS.

None of the intervention effect appeared to be permanent. No significant changes in the trend of use continued after the implementation of the interventions though non-significantly decreasing trends were observed.

Table 4.16 Relative Impacts of Interventions on proportion of ESA use by use category

Variable	Parameters				
	β	Newey-West SE	95 % Confidence Interval	t-statistics	p-value
Model 1: ONS					
Time	0.131	0.0867	[-0.042, 0.305]	1.51	0.1360
BBW					
Immediate	-1.169*	0.4052	[-1.979, - 0.358]	-2.88	0.0050
Level Change	-0.142	0.1090	[-0.360, 0.076]	-1.30	0.1970
NCD					
Immediate	-0.608	0.4001	[-1.409, 0.192]	-1.52	0.1340
Level Change	-0.101	0.1791	[-0.459, 0.257]	-0.56	0.5750
REMS					
Immediate	-0.738	0.4035	[-1.545, 0.070]	-1.83	0.0730
Level Change	0.076	0.2369	[-0.398, 0.550]	0.32	0.7490
Model 2: OFS					
Time	-0.005	0.0634	[-0.132, 0.121]	-0.08	0.9330
BBW					
Immediate	0.167	0.0876	[-0.008, 0.343]	1.91	0.0610
Level Change	-0.023	0.0889	[-0.201, 0.155]	-0.26	0.7940
NCD					
Immediate	-0.315*	0.0661	[-0.447, -0.182]	-4.76	< 0.0001
Level Change	-0.014	0.0732	[-0.160, 0.133]	-0.19	0.8520
REMS					
Immediate	-0.017	0.0597	[-0.137, 0.102]	-0.29	0.7720
Level Change	0.011	0.0537	[-0.097, 0.118]	0.20	0.8420
Model 3: OFU					
Time	0.134	0.1578	[-0.182, 0.450]	0.85	0.3980
BBW					
Immediate	0.597	0.4455	[-0.295, 1.488]	1.34	0.1860
Level Change	-0.202	0.1900	[-0.582, 0.178]	-1.06	0.2920
NCD					
Immediate	0.205	0.4205	[-0.637. 1.046]	0.49	0.6280
Level Change	0.078	0.1651	[-0.252, 0.409]	0.47	0.6370
REMS					
Immediate	-0.434	0.4667	[-1.368, 0.500]	-0.93	0.3560
Level Change	-0.047	0.1647	[-0.377, 0.282]	-0.29	0.7760

Table 4.17 Relative Impacts of Interventions on proportion of epoetin alfa use by use category

Variable	Parameter				
	β	Newey-West SE	95 % Confidence Interval	t-statistics	p-value
Model 1: ONS					
Time	0.046	0.0927	[-0.140, 0.232]	0.50	0.6220
BBW					
Immediate	-0.596	0.4294	[-1.456, 0.263]	-1.39	0.1700
Level Change	-0.063	0.1594	[-0.382, 0.255]	-0.40	0.6920
NCD					
Immediate	-0.177	0.4048	[-0.987, 0.633]	-0.44	0.6630
Level Change	-0.078	0.1976	[-0.474, 0.317]	-0.40	0.6930
REMS					
Immediate	-0.138	0.4058	[0.0950, 0.674]	-0.34	0.7340
Level Change	0.070	0.2090	[-0.348, 0.488]	0.33	0.7390
Model 2: OFS					
Time	-0.026	0.0520	[-0.130, 0.079]	-0.49	0.6250
BBW					
Immediate	0.021	0.0770	[-0.133, 0.175]	0.27	0.7880
Level Change	0.014	0.0691	[-0.124, 0.152]	0.20	0.8390
NCD					
Immediate	-0.303*	0.0669	[-0.437, -0.170]	-4.54	< 0.0001
Level Change	-0.015	0.0563	[-0.128, 0.097]	-0.27	0.7870
REMS					
Immediate	0.043	0.0585	[-0.074, 0.160]	0.73	0.4660
Level Change	0.001	0.0467	[-0.092, 0.095]	0.03	0.9750
Model 3: OFU					
Time	0.117	0.1150	[-0.113, 0.347]	1.02	0.3120
BBW					
Immediate	-0.117	0.2737	[-0664, 0.431]	-0.43	0.6710
Level Change	-0.114	0.1465	[-0.407, 0.179]	-0.78	0.4410
NCD					
Immediate	-0.014	0.2653	[-0.545, 0.517]	-0.05	0.9580
Level Change	-0.016	0.1288	[-0.273, 0.242]	-0.12	0.9040
REMS					
Immediate	0.221	0.2941	[-0.367, 0.810]	0.75	0.4550
Level Change	-0.044	0.1393	[-0.323, 0.235]	-0.32	0.7540

Table 4.18 Relative Impacts of Interventions on proportion of darbepoetin alfa use by use category

Variable	Parameter				
	β	Newey-West SE	95 % Confidence Interval	t-statistics	p-value
Model 1: ONS					
Time	0.088	0.0437	[0.000, 0.175]	2.00	0.0500
BBW					
Immediate	-0.552*	0.0591	[-0.670, -0.433]	-9.34	< 0.0001
Level Change	-0.084	0.0564	[-0.197, 0.028]	-1.50	0.1400
NCD					
Immediate	-0.361*	0.0524	[-0.466, -0.256]	-6.90	< 0.0001
Level Change	-0.021	0.0498	[-0.121, 0.078]	-0.43	0.6700
REMS					
Immediate	-0.540*	0.0485	[-0.637, -0.443]	-11.13	< 0.0001
Level Change	0.007	0.0429	[-0.079, 0.093]	0.17	0.8650
Model 2: OFS					
Time	0.020	0.0163	[-0.013, 0.053]	1.22	0.2260
BBW					
Immediate	0.158*	0.0533	[0.052, 0.265]	2.97	0.0040
Level Change	-0.038	0.0533	[-0.098, 0.022]	-1.26	0.2140
NCD					
Immediate	0.011	0.0485	[-0.086, 0.108]	0.23	0.8160
Level Change	0.002	0.0286	[-0.056, 0.059]	0.06	0.9540
REMS					
Immediate	-0.049	0.0471	[-0.143, 0.046]	-1.03	0.3080
Level Change	0.010	0.0170	[-0.024, 0.044]	0.59	0.5540
Model 3: OFU					
Time	0.018	0.0652	[-0.113, 0.148]	0.27	0.7880
BBW					
Immediate	0.870*	0.1775	[0.515, 1.255]	4.90	< 0.0001
Level Change	-0.102	0.0786	[-0.259, 0.056]	-1.29	0.2010
NCD					
Immediate	0.361*	0.1625	[0.036, 0.686]	2.22	0.0300
Level Change	0.101	0.0604	[-0.020, 0.222]	1.68	0.0990
REMS					
Immediate	-0.537*	0.1568	[-0.850, -0.223]	-3.42	0.0010
Level Change	-0.007	0.0515	[-0.110, 0.096]	-0.14	0.8900

Specific Aim 3: Estimating the impact of of black box warning, NCD, and REMS on odds of a patient being prescribed with ESAs

Outlier identification and Data manipulation

Similar to the visit level analysis in the previous section, we observed a sudden drop in the number of patients admitted to Cerner hospitals with ONS conditions at month 31-36. This reduction was similar to that in the denominator cohort of eligible visits used for a time-series analysis and was likely to cause by errors in data recording. Since it was not possible to impute the number of eligible patients, we decided to drop observations at month 31-36 completely from the analysis. No other possible outliers were found in other use cohorts and all patients with OFS and OFU indications were retained in the subsequent analysis.

As demonstrated in the descriptive analysis of ESA users, missing information on race, admission type, discharge disposition, primary payer, and medical specialty was common in our data. To retain as many subjects as possible in our final analytical cohort, we opted to conctruct a 'Missing' category to be in the analytical models. This approach was adopted for all variables with vast number of missing values. However, due to a small number of observations with missing gender information (N = 174 patients), these observations were excluded completely from the analysis.

The ONS cohort consisted of 730,412 patients with ONS conditions. Among them, 33,004 patients (15.6%) received ESAs (N epoetin alfa = 25,494 (77.2%) and N darbepoetin = 7,724 alfa (23.4%)). The OFS cohort consisted of 505,658 patients with OFS conditions, 5,140 (1.0%) of which were prescribed with ESAs (N epoetin alfa = 4,093 (%), N darbepoetin alfa = 1,089 (%)). The OFU cohort consisted of 559,917 patients with documented OFU conditions,

4,491 (0.80%) of which received ESAs (N epoetin alfa = 3,736 (83.1%), N darbepoetin alfa = 780 (17.4%)). Number of epoetin alfa and darbepoetin alfa users did not sum to the total number of ESA users as some patients received both drugs during the same visit.

Bivariate analysis

Patients with ONS conditions

Bivariate chi-square tests showed statistically significant differences for all demographic, hospital characteristic, and physician characteristic variables between ONS+ESA users and ONS patients who did not use ESAs. Compared to patients with ONS conditions who did not receive the drug, ESA users appeared to older (mean age 65.4 (SD 15.61) vs. 58.4 (SD 18.52)), consisted of greater proportion of male, African-American, and had Medicare as their primary payer. ESA users were more complex than the non-users as they had greater comorbidity score (CCI 2.64 (SD 1.917) vs. CCI 1.19 (1.804)) and tended to stay in the hospital for a longer period of time (LOS 11.6 (SD 15.63) vs. 4.3 (6.42)). Greater proportion of ESA users was admitted as emergency cases, but fewer were discharged home. To a larger extent, ESA ONS users were discharged to hospice, institutionalized and non-institutionalized care, or died in the hospital compared to the non-users with the same indications. Patients admitted to larger hospitals with greater than 300 beds, and teaching hospitals received ESAs to a greater extent than patients in seen in non-teaching, and small hospitals. Finally, greater proportion of ESA users were admitted by non-specialists compared to the ONS patients who did not receive the drug. Similar results were observed in the separate analyses of epoetin alfa and darbepoetin alfa. Descriptive results are shown in Table 4.19, 4.20, and 4.21 for ESA, epoetin alfa, and darbepoetin alfa users, respectively).

Table 4.19 Descriptive analysis of users and non-users of ESAs with ONS conditions

Variable	N Patients with ONS conditions (column %)			Chi-sq, p-value
	Total	ESA Users	Non-users	
Patient Characteristics				
Demographics				
Age				
18-30	62,556 (8.56)	831 (2.52)	61,725 (8.85)	4652.73
31-50	180,601 (24.73)	4,969 (15.06)	175,632 (25.19)	p < 0.0001
51-64	184,676 (25.28)	8,777 (26.59)	175,899 (25.22)	
65-74	129,368 (17.71)	7,432 (22.52)	121,936 (17.48)	
75-84	117,046 (16.02)	7,722 (23.40)	109,324 (15.68)	
85+	56,165 (7.69)	3,273 (9.92)	52,892 (7.58)	
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	
Average age (SD)	58.8 (18.45)	65.4 (15.61)	58.4 (18.52)	p < 0.0001
Gender				
Male	302,245 (41.38)	16,525 (50.07)	285,720 (40.97)	1076.00
Female	428,167 (58.62)	16,479 (49.93)	411,688 (59.03)	p < 0.0001
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	
Race				
Caucasian	561,384 (76.86)	20,571 (62.33)	540,813 (77.55)	5195.68
African-American	115,395 (15.80)	9,622 (29.15)	105,773 (15.17)	p < 0.0001
Other	34,898 (4.78)	2,212 (6.70)	32,686 (4.69)	
Not recorded	18,735 (2.56)	599 (1.81)	18,136 (2.60)	
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	
Primary Payer				
Source of Payment				
Medicare	163,596 (22.40)	10,970 (33.24)	152,626 (21.88)	6044.95
Medicaid	40,052 (5.48)	1,462 (4.43)	38,590 (5.53)	p < 0.0001
Commercial/Private/HMO	134,077 (18.36)	2,246 (6.81)	131,831 (18.90)	
Managed Care				
Self-pay	23,582 (3.23)	676 (2.05)	22,906 (3.28)	
Other	105,115 (14.39)	2,865 (8.68)	102,250 (14.66)	
Not recorded	263,990 (36.14)	14,785 (44.80)	249,205 (35.73)	
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	
Clinical Conditions				
Admission type				
Emergency	256734 (35.15)	19962 (60.48)	236772 (33.68)	12650.48
Urgent	81658 (11.18)	5145 (15.59)	76513 (10.97)	p < 0.0001
Elective	290265 (39.74)	5487 (16.63)	284778 (40.83)	
Other/ Not recorded	101,755 (13.93)	2,410 (7.30)	99,345 (14.24)	
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	
Average CCI (SD)	1.26 (1.834), -1 to 14	2.64 (1.917), -1 to 13	1.19 (1.804), -1 to 14	p < 0.0001
Average LOS (SD), range	4.6 (7.25), 0 to 814	11.6 (15.63), 0 to 588	4.3 (6.42), 0 to 814	p < 0.0001
Discharge status				
Expired	16,526 (2.26)	2,285 (6.92)	14,241 (2.04)	14167.57

Discharged to home/ self care	428,180 (58.62)	13,729 (41.60)	414,451 (59.43)	p < 0.0001
Discharged to Hospice	8,356 (1.14)	753 (2.28)	7,603 (1.09)	
Discharged/transferred to institutionalized care	106,950 (14.64)	9,820 (29.75)	97,130 (13.93)	
Discharged/transferred to noninstitutionalized care	95,472 (13.07)	5,978 (18.11)	89,494 (12.83)	
Other/Not recorded	74,928 (10.26)	439 (1.33)	74,489 (10.68)	
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	
Hospital Characteristics				
Geographic region				
Northeast	331,785 (45.42)	12,578 (38.11)	319,207 (45.77)	768.88
Midwest	153,858 (21.06)	8,157 (24.72)	145,701 (20.89)	p < 0.0001
South	202,856 (27.77)	10,084 (30.55)	192,772 (27.64)	
West	41,913 (5.74)	2,185 (6.62)	39,728 (5.70)	
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	
Bed size				
≤ 99	43,083 (5.90)	756 (2.29)	42,327 (6.07)	2424.64
100-199	107,679 (14.74)	3,582 (10.85)	104,097 (14.93)	p < 0.0001
200-299	146,974 (20.12)	5,953 (18.04)	141,021 (20.22)	
300-499	178,578 (24.45)	11,150 (33.78)	167,428 (24.01)	
≥500	254,098 (34.79)	11,563 (35.04)	242,535 (34.78)	
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	
Teaching status				
Teaching	523,350 (71.65)	24,799 (75.14)	498,551 (71.49)	207.04
Non-teaching	207,062 (28.35)	8,205 (24.86)	198,857 (28.51)	p < 0.0001
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	73,589 (10.07)	4,765 (14.44)	68,824 (9.87)	988.76
Specialist	288,084 (39.44)	11,032 (33.43)	277,052 (39.73)	p < 0.0001
Not recorded	368,739 (50.48)	17,207 (52.14)	351,532 (50.41)	
Total (row %)	730,412 (100.00)	33,004 (4.52)	697,408 (95.48)	

Table 4.20 Descriptive analysis of users and non-users of epoetin alfa with ONS conditions

Variable	N Patients with ONS conditions (column %)			Chi-sq, p-value
	Total	Epo Users	Non-users	
Patient Characteristics				
Demographics				
Age				
18-30	62,556 (8.56)	584 (2.29)	61,972 (8.79)	4079.00
31-50	180,601 (24.73)	3,656 (14.34)	176,945 (25.10)	p < 0.0001
51-64	184,676 (25.28)	6,668 (26.16)	178,008 (25.25)	
65-74	129,368 (17.71)	5,785 (22.69)	123,583 (17.53)	
75-84	117,046 (16.02)	6,155 (24.14)	110,891 (15.73)	
85+	56,165 (7.69)	2,646 (10.38)	53,519 (7.59)	
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	
Average age (SD)	58.5 (18.50)	66.0 (15.45)	58.8 (18.45)	p < 0.0001
Gender				
Male	302,245 (41.38)	12,643 (49.59)	289,602 (41.08)	734.39
Female	428,167 (58.62)	12,851 (50.41)	415,316 (58.92)	p < 0.0001
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	
Race				
Caucasian	561,384 (76.86)	15,593 (61.16)	545,791 (77.43)	4904.77
African-American	115,395 (15.80)	7,721 (30.29)	107,674 (15.27)	p < 0.0001
Other	34,898 (4.78)	1,870 (7.34)	33,028 (4.69)	
Not recorded	18,735 (2.56)	310 (1.22)	18,425 (2.61)	
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	
Primary Payer				
Source of Payment				
Medicare	163,596 (22.40)	7,899 (30.98)	155,697 (22.09)	4064.66
Medicaid	40,052 (5.48)	1,128 (4.42)	38,924 (5.52)	p < 0.0001
Commercial/Private/HMO	134,077 (18.36)	1,672 (6.56)	132,405 (18.78)	
Managed Care				
Self-pay	23,582 (3.23)	390 (1.53)	23,192 (3.29)	
Other	105,115 (14.39)	2,756 (10.81)	102,359 (14.52)	
Not recorded	263,990 (36.14)	11,649 (45.69)	252,341 (35.80)	
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	
Clinical Conditions				
Admission type				
Emergency	256,734 (35.15)	15,736 (61.72)	240,998 (34.19)	11220.11
Urgent	81,658 (11.18)	4,295 (16.85)	77,363 (10.97)	p < 0.0001
Elective	290,265 (39.74)	3,739 (14.67)	286,526 (40.65)	
Other/ Not recorded	101,755 (13.93)	1,724 (6.76)	100,031 (14.19)	
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	
Average CCI (SD)	1.26 (1.834), -1 to 14	2.58 (1.913), -1 to 13	1.21 (1.813), -1 to 14	p < 0.0001
Average LOS (SD), range	4.6 (7.25), 0 to 814	11.1 (15.4), 0 to 588	4.4 (6.69), 0 to 814	p < 0.0001
Discharge status				
Expired	16,526 (2.26)	1,728 (6.78)	14,798 (2.10)	10584.91

Discharged to home/ self care	428,180 (58.62)	10,505 (41.21)	417,675 (59.25)	p < 0.0001
Discharged to Hospice	8,356 (1.14)	598 (2.35)	7,758 (1.10)	
Discharged/transferred to institutionalized care	106,950 (14.64)	7,450 (29.22)	99,500 (14.12)	
Discharged/transferred to noninstitutionalized care	95,472 (13.07)	4,829 (18.94)	90,643 (12.86)	
Other/Not recorded	74,928 (10.26)	384 (1.51)	74,544 (10.57)	
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	
Hospital Characteristics				
Geographic region				
Northeast	331,784 (45.42)	9,860 (38.68)	321,925 (45.67)	1794.34
Midwest	153,858 (21.06)	4,000 (15.69)	149,858 (21.26)	p < 0.0001
South	202,856 (27.77)	9,541 (37.42)	193,315 (27.42)	
West	41,913 (5.74)	2,093 (8.21)	39,820 (5.65)	
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	
Bed size				
≤ 99	43,083 (5.90)	540 (2.12)	42,543 (6.04)	2634.36
100-199	107,679 (14.74)	2,714 (10.65)	104,965 (14.89)	p < 0.0001
200-299	146,974 (20.12)	4,386 (17.20)	142,588 (20.23)	
300-499	178,578 (24.45)	9,306 (36.50)	169,272 (24.01)	
≥500	254,098 (34.79)	8,548 (33.53)	245,550 (34.83)	
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	
Teaching status				
Teaching	523,350 (71.65)	18,930 (74.25)	504,420 (71.56)	88.01
Non-teaching	207,062 (28.35)	6,564 (25.75)	200,498 (28.44)	p < 0.0001
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	73,589 (10.07)	3,993 (15.66)	69,596 (9.87)	992.29
Specialist	288,084 (39.44)	8,762 (34.37)	279,322 (39.62)	p < 0.0001
Not recorded	368,739 (50.48)	12,739 (49.97)	356,000 (50.50)	
Total (row %)	730,412 (100.00)	25,494 (3.49)	704,918 (96.51)	

Table 4.21 Descriptive analysis of users and non-users of darbepoetin alfa with ONS conditions

Variable	N Patients with ONS conditions (column %)			Chi-sq, p-value
	Total	Darb Users	Non-users	
Patient Characteristics				
Demographics				
Age				
18-30	62,556 (8.56)	251 (3.25)	62,305 (8.62)	653.79
31-50	180,601 (24.73)	1,348 (17.45)	179,253 (24.80)	p < 0.0001
51-64	184,676 (25.28)	2,154 (27.89)	182,522 (25.26)	
65-74	129,368 (17.71)	1,701 (22.02)	127,667 (17.67)	
75-84	117,046 (16.02)	1,624 (21.03)	115,422 (15.97)	
85+	56,165 (7.69)	646 (8.36)	55,519 (7.68)	
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	
Average age (SD)	58.8 (18.46)	63.7 (16.01)	58.7 (18.47)	p < 0.0001
Gender				
Male	302,245 (41.38)	3,983 (51.57)	298,262 (41.27)	333.94
Female	428,167 (58.62)	3,741 (48.43)	424,426 (58.73)	p < 0.0001
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	
Race				
Caucasian	561,384 (76.86)	5,133 (66.46)	556,251 (76.97)	598.96
African-American	115,395 (15.80)	1,949 (25.23)	113,446 (15.70)	p < 0.0001
Other	34,898 (4.78)	347 (4.49)	34,551 (4.78)	
Not recorded	18,735 (2.56)	295 (3.82)	18,440 (2.55)	
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	
Primary Payer				
Source of Payment				
Medicare	163,596 (22.40)	3,133 (40.56)	160,463 (22.20)	2651.50
Medicaid	40,052 (5.48)	340 (4.40)	39,712 (5.50)	p < 0.0001
Commercial/Private/HMO	134,077 (18.36)	583 (7.55)	133,494 (18.47)	
Managed Care				
Self-pay	23,582 (3.23)	287 (3.72)	23,295 (3.22)	
Other	105,115 (14.39)	116 (1.50)	104,999 (14.53)	
Not recorded	263,990 (36.14)	3,265 (42.27)	260,725 (36.08)	
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	
Clinical Conditions				
Admission type				
Emergency	256,734 (35.15)	4,336 (56.14)	252,398 (34.92)	1643.67
Urgent	81,658 (11.18)	884 (11.44)	80,774 (11.18)	p < 0.0001
Elective	290,265 (39.74)	1,775 (22.98)	288,490 (39.92)	
Other/ Not recorded	101,755 (13.93)	729 (9.44)	101,026 (19.98)	
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	
Average CCI (SD)	1.26 (1.834), -1 to 14	2.83 (1.916), -1 to 13	1.24 (1.826), -1 to 14	p < 0.0001
Average LOS (SD), range	4.6 (7.25), 0 to 814	13.4 (17.71), 0 to 398	4.6 (7.00), 0 to 814	p < 0.0001
Discharge status				
Expired	16,526 (2.26)	582 (7.53)	15,944 (2.21)	3682.14

Discharged to home/ self care	428,180 (58.62)	3,277 (42.43)	424,903 (58.79)	p < 0.0001
Discharged to Hospice	8,356 (1.14)	162 (2.10)	8,194 (1.13)	
Discharged/transferred to institutionalized care	106,950 (14.64)	2,465 (31.91)	104,485 (14.46)	
Discharged/transferred to noninstitutionalized care	95,472 (13.07)	1,182 (15.30)	94,290 (13.05)	
Other/Not recorded	74,928 (10.26)	56 (0.73)	74,872 (10.36)	
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	
Hospital Characteristics				
Geographic region				
Northeast	331,785 (45.42)	2,879 (37.27)	328,906 (45.51)	5622.26
Midwest	153,858 (21.06)	4,183 (54.16)	149,675 (20.71)	p < 0.0001
South	202,856 (27.77)	566 (7.33)	202,290 (27.99)	
West	41,913 (5.74)	96 (1.24)	41,817 (5.79)	
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	
Bed size				
≤ 99	43,083 (5.90)	220 (2.85)	42,863 (5.93)	246.02
100-199	107,679 (14.74)	886 (11.47)	106,793 (14.78)	p < 0.0001
200-299	146,974 (20.12)	1,648 (21.34)	145,326 (20.11)	
300-499	178,578 (24.45)	1,882 (34.37)	176,696 (24.45)	
≥500	254,098 (34.79)	3,088 (39.98)	251,010 (34.73)	
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	
Teaching status				
Teaching	523,350 (71.65)	6,016 (77.89)	517,334 (71.58)	149.44
Non-teaching	207,062 (28.35)	1,708 (22.11)	205,354 (28.42)	p < 0.0001
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	73,589 (10.07)	816 (10.56)	72,773 (10.07)	308.29
Specialist	288,084 (39.44)	2,310 (29.91)	285,774 (39.54)	p < 0.0001
Not recorded	368,739 (50.48)	4,598 (59.53)	364,141 (50.39)	
Total (row %)	730,412 (100.00)	7,724 (1.06)	722,688 (98.94)	

Patients with OFS conditions

Bivariate chi-square tests showed statistically significant differences between OFS+ESA users and OFS patients for all demographic, hospital characteristic, and physician characteristic variables with an exception of teaching status and darbepoein alfa ESA-OFS use.

Overall OFS patients consisted of relatively young population (average age 49.5 (SD 24.14)) who were largely women (75.4%). Interestingly, OFS+ESA group consisted of much older patients than the non-users population (average age 70.1 (SD 15.40)). Due to the nature of conditions defined as eligible OFS conditions such as postpartum anemia, only 25% of the OFS cohort was men. However, almost 50% of ESA-OFS users were male. More than half of ESA users had Medicare as their primary payer compared to the non-users (38% vs 17% Medicare patients). ESA users with OFS conditions were also sicker than the non-users (CCI 1.94 (SD 1.823) vs. CCI 1.02 (1.443)), stayed in the hospital much longer, (L-O-S 15.7 (SD 19.48) vs. 4.2 (6.67)), more frequently were admitted as emergency cases (57.2%), discharged to hospice, institutionalized and non-institutionalized care, or died in the hospital. Results from bivariate analysis of the OFS cohort showed a similar pattern in patient and hospital characteristics of ESA users compared to the ONS cohort. For instance, erythropoietins were used to a much higher extent in large and teaching hospitals. Descriptive results are shown in Table 4.22, 4.23, and 4.24 for ESA, epoetin alfa, and darbepoetin alfa users, respectively).

Table 4.22 Descriptive analysis of users and non-users of ESAs with OFS conditions

Variable	N Patients with OFS conditions (column %)			Chi-sq, p-value
	Total	ESA Users	Non-users	
Patient Characteristics				
Demographics				
Age				
18-30	171,290 (33.87)	132 (2.57)	171,158 (34.20)	4081.87
31-50	104,642 (20.69)	464 (9.03)	104,178 (20.81)	p < 0.0001
51-64	57,998 (11.47)	976 (18.99)	57,022 (11.39)	
65-74	52,212 (10.33)	1,177 (22.90)	51,035 (10.200	
75-84	69,200 (13.69)	1,488 (28.95)	67,712 (13.53)	
85+	50,316 (9.95)	903 (17.57)	49,413 (9.87)	
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	
Average age (SD)	49.5 (24.14)	70.1 (15.40)	49.2 (24.13)	p < 0.0001
Gender				
Male	124,431 (24.61)	2,408 (49.85)	122,023 (24.38)	1384.49
Female	381,227 (75.39)	2,732 (53.15)	378,495 (75.62)	p < 0.0001
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	
Race				
Caucasian	359,136 (71.02)	3,901 (75.89)	355,235 (70.97)	142.80
African-American	83,978 (16.61)	877 (17.06)	83,101 (16.60)	p < 0.0001
Other	48,549 (9.60)	256 (4.98)	48,293 (9.65)	
Not recorded	13,995 (2.77)	106 (2.06)	13,889 (2.77)	
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	
Primary Payer				
Source of Payment				
Medicare	89,213 (17.64)	1,954 (38.02)	87,259 (17.43)	1925.67
Medicaid	68,541 (13.55)	250 (4.86)	68,291 (13.64)	p < 0.0001
Commercial/Private/HMO	85,682 (16.94)	441 (8.58)	85,241 (17.03)	
Managed Care				
Self-pay	17,817 (3.52)	124 (2.41)	17,693 (3.53)	
Other	63,645 (12.59)	328 (6.38)	6,3317 (12.65)	
Not recorded	180,760 (35.75)	2,043 (39.75)	178,717 (35.71)	
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	
Clinical Conditions				
Admission type				
Emergency	190,791 (37.73)	2,938 (57.16)	187,853 (37.53)	1107.60
Urgent	115,098 (22.76)	953 (18.54)	114,145 (22.81)	p < 0.0001
Elective	160,897 (31.82)	729 (14.18)	160,168 (32.00)	
Other/ Not recorded	38,872 (7.69)	520 (10.12)	38,352 (7.66)	
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	
Average CCI (SD)	1.03 (1.450), 0 to 13	1.94 (1.823), 0 to 11	1.02 (1.443), 0 to 13	p < 0.0001
Average LOS (SD), range	4.3 (7.02), 0 to 1354	15.7 (19.48), 0 to 340	4.2 (6.67), 0 to 1354	p < 0.0001
Discharge status				
Expired	16,428 (3.25)	682 (13.27)	15,746 (3.15)	6930.42

Discharged to home/ self care	358,259 (70.85)	1,284 (24.98)	356,975 (71.32)	p < 0.0001
Discharged to Hospice	6,327 (1.25)	185 (3.60)	6,142 (1.23)	
Discharged/transferred to institutionalized care	62,864 (12.43)	2014 (39.18)	60850 (12.16)	
Discharged/transferred to noninstitutionalized care	45,160 (8.93)	926 (18.02)	44,234 (8.84)	
Other/Not recorded	16,620 (3.29)	49 (0.95)	16,571 (3.31)	
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	
Hospital Characteristics				
Geographic region				
Northeast	206,082 (40.76)	2,148 (41.79)	203,934 (40.74)	50.48
Midwest	116,911 (23.12)	1,105 (21.50)	115,806 (23.14)	p < 0.0001
South	143,890 (28.46)	1,601 (31.15)	142,289 (28.43)	
West	38,775 (7.67)	286 (5.56)	38,489 (7.69)	
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	
Bed size				
≤ 99	51,918 (10.27)	152 (2.96)	51,766 (10.34)	977.44
100-199	73,374 (14.51)	385 (7.49)	72,989 (14.58)	p < 0.0001
200-299	130,516 (25.81)	1,015 (19.75)	129,501 (25.87)	
300-499	135,871 (26.87)	2,062 (40.12)	133,809 (26.73)	
≥500	113,979 (22.54)	1,526 (29.69)	112,453 (22.47)	
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	
Teaching status				
Teaching	345,003 (68.23)	3,828 (74.47)	341,175 (68.16)	93.46
Non-teaching	160,655 (31.77)	1312 (25.53)	159,343 (31.84)	p < 0.0001
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	56,927 (11.26)	850 (16.54)	56,077 (11.20)	151.16
Specialist	206,183 (40.78)	1,887 (36.71)	204,296 (40.82)	p < 0.0001
Not recorded	242,548 (47.97)	2,403 (46.75)	240,145 (47.98)	
Total (row %)	505,658 (100.00)	5,140 (1.02)	500,518 (98.98)	

Table 4.23 Descriptive analysis of users and non-users of epoetin alfa with OFS conditions

Variable	N Patients with OFS conditions (column %)			Chi-sq, p-value
	Total	Epo Users	Non-users	
Patient Characteristics				
Demographics				
Age				
18-30	171,290 (33.87)	93 (2.27)	171,197 (33.87)	3455.82
31-50	104,642 (20.69)	331 (8.09)	104,311 (20.69)	p < 0.0001
51-64	57,998 (11.47)	726 (17.74)	57,272 (11.47)	
65-74	52,212 (10.33)	939 (22.94)	51,273 (10.33)	
75-84	69,200 (13.69)	1,237 (30.22)	67,963 (13.69)	
85+	50,316 (9.95)	767 (18.74)	49,549 (9.95)	
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	
Average age (SD)	49.5 (24.14)	70.9 (15.07)	49.3 (24.13)	p < 0.0001
Gender				
Male	124,431 (24.61)	1,882 (45.98)	122,549 (24.43)	1016.04
Female	381,227 (75.39)	2,211 (54.02)	379,016 (75.57)	p < 0.0001
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	
Race				
Caucasian	359,136 (71.02)	3,072 (75.05)	356,064 (70.99)	106.89
African-American	83,978 (16.61)	731 (17.86)	83,247 (16.60)	p < 0.0001
Other	48,549 (9.60)	219 (5.53)	48,330 (9.64)	
Not recorded	13,995 (2.77)	71 (1.73)	13924 (2.78)	
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	
Primary Payer				
Source of Payment				
Medicare	89,213 (17.64)	1,539 (37.60)	87,674 (17.48)	1499.30
Medicaid	68,541 (13.55)	187 (4.57)	68,354 (13.63)	p < 0.0001
Commercial/Private/HMO	85,682 (16.94)	327 (7.99)	85,355 (17.02)	
Managed Care				
Self-pay	17,817 (3.52)	90 (2.20)	17,727 (3.53)	
Other	63,645 (12.59)	308 (7.53)	63,337 (12.63)	
Not recorded	180,760 (35.75)	1,642 (40.12)	179,118 (35.71)	
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	
Clinical Conditions				
Admission type				
Emergency	190,791 (37.73)	2,437 (59.54)	188,354 (37.55)	1038.18
Urgent	115,098 (22.76)	826 (20.18)	114,272 (22.78)	p < 0.0001
Elective	160,897 (31.82)	495 (12.09)	160,402 (31.98)	
Other/ Not recorded	38,872 (7.69)	335 (8.18)	38,537 (7.68)	
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	
Average CCI (SD)	1.03 (1.450), 0 to 13	1.94 (1.801), 0 to 11	1.02 (1.445), 0 to 13	p < 0.0001
Average LOS (SD), range	4.3 (7.02) 0 to 1354	14.8 (18.24), 0 to 329	4.3 (6.78), 0 to 1354	p < 0.0001
Discharge status				
Expired	16,428 (3.25)	533 (13.02)	15,895 (3.17)	5382.59

Discharged to home/ self care	358,259 (70.85)	1,019 (24.90)	357,240 (71.23)	p < 0.0001
Discharged to Hospice	6,327 (1.25)	154 (3.76)	6,173 (1.23)	
Discharged/transferred to institutionalized care	62,864 (12.43)	1,564 (38.21)	61300 (12.22)	
Discharged/transferred to noninstitutionalized care	45,160 (8.93)	777 (18.98)	44,383 (8.85)	
Other/Not recorded	16,620 (3.29)	46 (1.12)	16,574 (3.30)	
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	
Hospital Characteristics				
Geographic region				
Northeast	206,082 (40.76)	1,740 (42.51)	204,342 (40.74)	243.69
Midwest	116,911 (23.12)	585 (14.29)	116,326 (23.19)	p < 0.0001
South	143,890 (28.46)	1,497 (36.57)	142,393 (28.39)	
West	38,775 (7.67)	271 (6.62)	38,504 (7.68)	
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	
Bed size				
≤ 99	51,918 (10.27)	121 (2.96)	51,797 (10.33)	1023.39
100-199	73,374 (14.51)	285 (6.96)	73,089 (14.57)	p < 0.0001
200-299	130,516 (25.81)	722 (17.64)	129,794 (25.88)	
300-499	135,871 (26.87)	1,832 (44.76)	134,039 (26.72)	
≥500	113,979 (22.54)	1,133 (27.68)	112,846 (22.50)	
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	
Teaching status				
Teaching	345,003 (68.23)	3,113 (76.06)	341,890 (68.16)	116.65
Non-teaching	160,655 (31.77)	980 (23.94)	159,675 (31.84)	p < 0.0001
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	56,927 (11.26)	764 (18.67)	56,163 (11.20)	227.39
Specialist	206,183 (40.78)	1,555 (37.99)	204,628 (48.00)	p < 0.0001
Not recorded	242,548 (47.97)	1,774 (0.81)	240,774 (40.80)	
Total (row %)	505,658 (100.00)	4,093 (0.81)	501,565 (99.19)	

Patients with OFU conditions

In contrary to the ONS and OFS cohort, small differences in the average age of ESA users and non-users were observed in patients with OFU indications (average age OFU+ESAs 64.8 vs 61.6 for OFU group). Slightly greater proportion of female and African American OFU patients received ESAs (17% vs 12%). Medicare remained as the major payer of ESA in the OFU population but the differences between the users and non-users were less obvious compared to that in the ONS and OFS cohorts. ESA users with OFU conditions were sicker, stayed in the hospital longer, more frequently discharged to institutionalized and non-institutionalized care. Finally, the use of ESAs for OFU indications was higher in medium to large hospitals (300-499 beds). Descriptive results are shown in Table 4.24, 4.25, and 4.26 for ESA, epoetin alfa, and darbepoetin alfa users, respectively).

Table 4.24 Descriptive analysis of users and non-users of darbepoetin alfa with OFS conditions

Variable	N Patients with OFS conditions (column %)			Chi-sq, p-value
	Total	Darb Users	Non-users	
Patient Characteristics				
Demographics				
Age				
18-30	171,290 (33.87)	40 (3.67)	171,250 (33.94)	736.48
31-50	104,642 (20.69)	136 (12.49)	104,506 (20.71)	p < 0.0001
51-64	57,998 (11.47)	260 (23.88)	57,738 (11.44)	
65-74	52,212 (10.33)	248 (22.77)	51,964 (10.30)	
75-84	69,200 (13.69)	262 (24.06)	68,938 (13.66)	
85+	50,316 (9.95)	143 (13.13)	50,173 (9.94)	
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	
Average age (SD)	49.5 (24.14)	66.8 (16.12)	49.4 (24.15)	p < 0.0001
Gender				
Male	124,431 (24.61)	546 (50.14)	123,885 (24.55)	383.41
Female	381,227 (75.39)	543 (49.86)	380,684 (75.45)	p < 0.0001
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	
Race				
Caucasian	359,136 (71.02)	859 (78.88)	358,277 (71.01)	56.51
African-American	83,978 (16.61)	156 (14.33)	83,822 (16.61)	p < 0.0001
Other	48,549 (9.60)	38 (3.49)	48,511 (9.61)	
Not recorded	13,995 (2.77)	36 (3.31)	13,959 (2.77)	
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	
Primary Payer				
Source of Payment				
Medicare	89,213 (17.64)	425 (39.03)	88,788 (17.60)	452.61
Medicaid	68,541 (13.55)	66 (6.06)	68,475 (13.57)	p < 0.0001
Commercial/Private/HMO	85,682 (16.94)	120 (11.02)	85,562 (16.96)	
Managed Care				
Self-pay	17,817 (3.52)	34 (3.12)	17,783 (3.52)	
Other	63,645 (12.59)	21 (1.93)	63,624 (12.61)	
Not recorded	180,760 (35.75)	423 (38.84)	180,337 (35.74)	
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	
Clinical Conditions				
Admission type				
Emergency	190,791 (37.73)	525 (48.21)	190,266 (37.71)	263.10
Urgent	115,098 (22.76)	130 (11.94)	114,968 (22.79)	p < 0.0001
Elective	160,897 (31.82)	241 (22.13)	160,656 (31.84)	
Other/ Not recorded	38,872 (7.69)	193 (17.72)	38,679 (7.67)	
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	
Average CCI (SD)	1.03 (1.450), 0 to 13	1.90 (1.885), 0 to 10	1.03 (1.449), 0 to 13	p < 0.0001
Average LOS (SD), range	4.3 (7.02), 0 to 1354	20.4 (25.06), 0 to 340	4.3 (6.89), 0 to 1354	p < 0.0001
Discharge status				
Expired	16,428 (3.25)	154 (14.14)	16,274 (3.23)	1650.54

Discharged to home/ self care	358,259 (70.85)	272 (24.98)	357,987 (70.95)	p < 0.0001
Discharged to Hospice	6,327 (1.25)	31 (2.85)	6,296 (1.25)	
Discharged/transferred to institutionalized care	62,864 (12.43)	472 (43.34)	62,392 (12.37)	
Discharged/transferred to noninstitutionalized care	45,160 (8.93)	157 (14.42)	45,003 (8.92)	
Other/Not recorded	16,620 (3.29)	3 (0.28)	16,617 (3.29)	
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	
Hospital Characteristics				
Geographic region				
Northeast	206,082 940.76)	433 (39.76)	205,649 (40.76)	481.16
Midwest	116,911 (23.12)	527 (48.39)	116,384 (23.07)	p < 0.0001
South	143,890 (28.46)	111 (10.19)	143,779 (28.50)	
West	38,775 (7.67)	18 (1.65)	38,757 (7.68)	
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	
Bed size				
≤ 99	51,918 (10.27)	31 (2.85)	51,887 (10.28)	197.97
100-199	73,374 (14.51)	105 (9.64)	73,269 (14.52)	p < 0.0001
200-299	130,516 (25.81)	309 (28.37)	130,207 (25.81)	
300-499	135,871 (26.87)	236 (21.67)	135,635 (26.88)	
≥500	113,979 (22.54)	408 (37.47)	113,571 (22.51)	
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	
Teaching status				
Teaching	345,003 (68.23)	744 (68.32)	344,259 (68.23)	0.0042
Non-teaching	160,655 (31.77)	345 (31.68)	160,310 (31.77)	p = 0.9485
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	56,927 (11.26)	93 (8.54)	56,834 (11.26)	67.88
Specialist	206,183 (40.78)	341 (31.31)	205,842 (40.80)	p < 0.0001
Not recorded	242,548 (47.97)	655 (60.15)	241,893(47.94)	
Total (row %)	505,658 (100.00)	1,089 (0.22)	504,569 (99.78)	

Table 4.25 Descriptive analysis of users and non-users of ESAs with documented OFU conditions

Variable	N Patients with OFU conditions (column %)			Chi-sq, p-value
	Total	ESA Users	Non-users	
Patient Characteristics				
Demographics				
Age				
18-30	37,399 (6.69)	215 (4.79)	37,184 (6.71)	165.33
31-50	110,811 (19.83)	688 (15.32)	110,123 (19.86)	p < 0.0001
51-64	145,430 (26.02)	1,057 (23.54)	144,373 (26.04)	
65-74	107,065 (19.16)	969 (21.58)	106,096 (19.14)	
75-84	104,715 (18.74)	1,062 (23.65)	103,653 (18.70)	
85+	53,497 (9.57)	500 (11.13)	52,997 (9.56)	
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	
Average age (SD)	61.7 (17.94)	64.8 (17.19)	61.6 (17.95)	p < 0.0001
Gender				
Male	275,478 949.29)	1,922 (42.80)	273,556 (49.34)	76.32
Female	283,439 (50.71)	2,569 (57.20)	280,870 (50.66)	p < 0.0001
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	
Race				
Caucasian	452,164 (80.900	3,358 (74.77)	448,806 (80.95)	182.33
African-American	69,234 (12.390	773 (17.21)	68,461 (12.35)	p < 0.0001
Other	22,491 (4.02)	284 (6.32)	22207 (4.01)	
Not recorded	15,028 (2.69)	76 (1.69)	14,952 (2.70)	
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	
Primary Payer				
Source of Payment				
Medicare	137,606 (24.62)	1,254 (27.92)	136,352 (24.59)	321.63
Medicaid	25,966 (4.65)	234 (5.21)	25,732 (4.64)	p < 0.0001
Commercial/Private/HMO	88,676 (15.87)	586 (13.05)	88,090 (15.89)	
Managed Care				
Self-pay	26,006 (4.65)	126 (2.81)	25,880 (4.67)	
Other	83,757 (14.99)	347 (7.73)	83,410 (15.04)	
Not recorded	196,906 (35.23)	1,944 (43.29)	194,962 (35.16)	
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	
Clinical Conditions				
Admission type				
Emergency	302,620 (54.14)	2,201 (49.01)	300,419 (54.19)	292.36
Urgent	75,339 (13.48)	860 (19.15)	74,479 (13.43)	p < 0.0001
Elective	121,033 (21.65)	729 (16.23)	120,304 (21.70)	
Other/ Not recorded	59,925 (10.72)	701 (15.61)	59,224 (10.68)	
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	
Average CCI (SD)	0.65 (1.373), 0 to 11	1.48 (2.164), 0 to 9	0.64 (1.363), 0 to 11	p < 0.0001
Average LOS (SD), range	4.6 (7.96), 0 to 1430	14.4 (19.02), 0 to 369	4.5 (7.75), 0 to 1430	p < 0.0001
Discharge status				
Expired	13,947 (2.50)	280 (6.23)	13,667 (2.47)	2570.57

Discharged to home/ self care	340,227 (60.87)	1,524 (33.93)	338,703 (61.09)	p < 0.0001
Discharged to Hospice	7,457 (1.33)	144 (3.21)	7,313 (1.32)	
Discharged/transferred to institutionalized care	92,573 (16.56)	1,658 (36.92)	90,915 (16.40)	
Discharged/transferred to noninstitutionalized care	60,531 (10.83)	838 (18.66)	59,693 (10.77)	
Other/Not recorded	44,182 (7.90)	47 (1.05)	44,135 (7.96)	
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	
Hospital Characteristics				
Geographic region				
Northeast	242,258 (43.34)	1,778 (39.59)	240,480 (43.37)	122.56
Midwest	114,295 (20.45)	769 (17.12)	113,526 (20.48)	p < 0.0001
South	173,037 (30.96)	1,598 (35.58)	171,439 (30.92)	
West	29,327 (5.25)	346 (7.70)	28,981 (5.23)	
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	
Bed size				
≤ 99	27,733 (4.96)	79 (1.76)	27,654 (4.99)	786.64
100-199	76,368 (13.660	291 (6.48)	76,077 (13.72)	p < 0.0001
200-299	109,642 (19.620	841 (18.73)	108,801 (19.62)	
300-499	148,829 (26.630	1,951 (43.44)	146,878 (26.49)	
≥500	196,345 (35.13)	1,329 (29.59)	195,016 (35.17)	
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	
Teaching status				
Teaching	405,948 (72.63)	3,349 (74.57)	402,599 (72.62)	8.57
Non-teaching	152,969 (27.37)	1,142 (25.43)	151,827 (27.38)	p = 0.0034
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	77,760 (13.91)	799 (17.79)	76,961 (13.88)	62.84
Specialist	193,374 (34.600	1,558 (34.69)	191,816 (34.60)	p < 0.0001
Not recorded	287,783 (51.49)	2,134 (47.52)	285,649 (51.52)	
Total (row %)	558,917 (100.00)	4,491 (0.80)	554,426 (99.20)	

Table 4.26 Descriptive analysis of users and non-users of epoetin alfa with documented OFU conditions

Variable	N Patients with OFU conditions (column %)			Chi-sq, p-value
	Total	Epo Users	Non-users	
Patient Characteristics				
Demographics				
Age				
18-30	37,399 (6.69)	145 (3.88)	37,254 (6.71)	174.31
31-50	110,811 (19.83)	563 (15.07)	110,248 (19.86)	p < 0.0001
51-64	145,430 (26.02)	897 (24.01)	144,533 (26.03)	
65-74	107,065 (19.16)	813 (21.76)	106,252 (19.14)	
75-84	104,715 (18.74)	900 (24.09)	103,815 (18.70)	
85+	53,497 (9.57)	418 (11.19)	53,079 (9.56)	
Total (row %)	555,181 (100.00)	3,736 (0.67)	558,917 (99.33)	
Average age (SD)	61.7 (17.94)	65.3 (16.70)	61.6 (17.95)	p < 0.0001
Gender				
Male	275,478 (49.29)	1,599 (42.80)	273,879 (49.33)	63.34
Female	283,439 (50.71)	2,137 (57.20)	281,302 (50.67)	p < 0.0001
Total (row %)	555,181 (100.00)	3,736 (0.67)	558,917 (99.33)	
Race				
Caucasian	452,164 (80.90)	2,782 (74.46)	449,382 (80.94)	181.29
African-American	69,234 (12.39)	646 (17.29)	68,588 (12.35)	p < 0.0001
Other	22,491 (4.02)	252 (6.75)	22,239 (4.01)	
Not recorded	15,028 (2.69)	56 (1.50)	14,972 (2.70)	
Total (row %)	555,181 (100.00)	3,736 (0.67)	558,917 (99.33)	
Primary Payer				
Source of Payment				
Medicare	137,606 (24.62)	1,027 (27.49)	136,579 (24.60)	277.47
Medicaid	25,966 (4.65)	196 (5.25)	25,770 (4.64)	p < 0.0001
Commercial/Private/HMO	88,676 (15.87)	473 (12.66)	88,203 (15.89)	
Managed Care				
Self-pay	26,006 (4.65)	87 (2.33)	25,919 (4.67)	
Other	83,757 (14.99)	310 (8.30)	83,447 (15.03)	
Not recorded	196,906 (43.98)	1,643 (43.98)	195,263 (35.17)	
Total (row %)	555,181 (100.00)	3,736 (0.67)	558,917 (99.33)	
Clinical Conditions				
Admission type				
Emergency	302,620 (54.14)	1,898 (50.80)	300,722 (54.17)	219.66
Urgent	75,339 (13.48)	787 (21.07)	74,552 (13.43)	p < 0.0001
Elective	121,033 (21.65)	613 (16.41)	120,420 (21.69)	
Other/ Not recorded	59,925 (10.72)	438 (11.72)	59,487 (10.71)	
Total (row %)	555,181 (100.00)	3,736 (0.67)	558,917 (99.33)	
Average CCI (SD)	0.65 (1.373), 0 to 11	1.50 (2.17), 0 to 9	0.64 (1.365), 0 to 11	p < 0.0001
Average LOS (SD), range	4.6 (7.96), 0 to 1430	14.1 (19.06), 0 to 369	4.5 (7.79), 0 to 1430	p < 0.0001
Discharge status				
Expired	13,947 (2.50)	230 (6.16)	13,717 (2.47)	2077.96

Discharged to home/ self care	340,227 (60.87)	1,284 (34.37)	338,943 (61.05)	p < 0.0001
Discharged to Hospice	7,457 (1.33)	132 93.53)	7,325 (1.32)	
Discharged/transferred to institutionalized care	92,573 (16.56)	1,353 (36.22)	91,220 (16.43)	
Discharged/transferred to noninstitutionalized care	60,531 (10.83)	695 (18.60)	59,836 (10.78)	
Other/Not recorded	44,182 (7.90)	42 (1.12)	44,140 (7.95)	
Total (row %)	555,181 (100.00)	3,736 (0.67)	558,917 (99.33)	
Hospital Characteristics				
Geographic region				
Northeast	242,258 (43.34)	1,405 (37.61)	240,853 (43.38)	284.76
Midwest	114,295 (20.45)	531 (14.21)	113,764 (20.49)	p < 0.0001
South	173,037 (30.96)	1,462 (39.13)	171,575 (30.90)	
West	29,327 (5.25)	338 (9.05)	28,989 (5.22)	
Total (row %)	555,181 (100.00)	3,736 (0.67)	558,917 (99.33)	
Bed size				
≤ 99	27,733 (4.96)	69 (1.85)	27,664 (4.98)	1022.68
100-199	76,368 (13.66)	216 (5.78)	76,152 (13.72)	p < 0.0001
200-299	109,642 (19.62)	570 (15.26)	109,072 (19.65)	
300-499	148,829 (26.63)	1,822 (48.77)	147,007 (26.48)	
≥500	196,345 (35.13)	1,059 (28.35)	195,286 (35.18)	
Total (row %)	555,181 (100.00)	3,736 (0.67)	558,917 (99.33)	
Teaching status				
Teaching	405,948 (72.63)	2,881 (77.11)	403,067 (72.60)	38.03
Non-teaching	152,969 (27.37)	855 (22.89)	152,114 (27.40)	p < 0.0001
Total (row %)	555,181 (100.00)	3736 (0.67)	558,917 (99.33)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	77,760 (13.91)	666 (17.83)	77,094 (13.89)	72.97
Specialist	193,374 (34.60)	1,372 (36.72)	192,002 (34.58)	p < 0.0001
Not recorded	287,783 (51.49)	1,698 (45.45)	286,085 (51.53)	
Total (row %)	555,181 (100.00)	3,736 (0.67)	558,917 (99.33)	

Table 4.27 Descriptive analysis of users and non-users of darbepoetin alfa with documented OFU conditions

Variable	N Patients with OFU conditions (column %)			Chi-sq, p-value
	Total	Darb Users	Non-users	
Patient Characteristics				
Demographics				
Age				
18-30	37,399 (6.69)	71 (9.10)	37,328 (6.690	24.22
31-50	110,811 (19.83)	129 (16.54)	110,682 (19.83)	p = 0.0002
51-64	145,430 (26.02)	165 (21.15)	145,265 (26.03)	
65-74	107,065 (19.16)	161 (20.64)	106,904 (19.15)	
75-84	104,715 (18.74)	171 (21.92)	104,544 (18.73)	
85+	53,497 (9.57)	83 (10.64)	53,414 (9.57)	
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	
Average age (SD)	61.66 (17.94)	62.3 (19.17)	61.7 (17.94)	p < 0.0001
Gender				
Male	275,478 (49.29)	335 (42.95)	275,143 (49.30)	12.56
Female	283,439 (50.71)	445 (57.05)	282,994 (50.70)	p = 0.0004
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	
Race				
Caucasian	452,164 (80.90)	595 (76.28)	451,569 (80.91)	14.57
African-American	69,234 (12.39)	131 (16.79)	69,103 (12.38)	p = 0.0022
Other	22,491 (4.02)	34 (4.36)	22,457 (4.02)	
Not recorded	15,028 (2.69)	20 (2.56)	15,008 (2.69)	
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	
Primary Payer				
Source of Payment				
Medicare	137,606 (24.62)	234 (30.00)	137,372 (24.61)	70.82
Medicaid	25,966 (4.65)	38 (4.87)	25,928 (4.65)	p < 0.0001
Commercial/Private/HMO	88,676 (15.87)	116 (14.87)	88,560 (15.87)	
Managed Care				
Self-pay	26,006 (4.650	39 (5.00)	25,967 (4.65)	
Other	83,757 (14.99)	37 (4.74)	83,720 (15.00)	
Not recorded	196,906 (35.23)	316 (40.51)	196,590 (35.22)	
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	
Clinical Conditions				
Admission type				
Emergency	302,620 (54.14)	312 (40.00)	302,308 (54.16)	481.11
Urgent	75,339 (13.48)	75 (9.62)	75,264 (13.48)	p < 0.0001
Elective	121,033 (21.65)	120 (15.38)	120,913 (21.66)	
Other/ Not recorded	59,925 (10.72)	273 (35.00)	59,652 (10.69)	
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	
Average CCI (SD)	0.65 (1.373), 0 to 11	1.39 (2.113), 0 to 9	0.65 (1.372), 0 to 11	p < 0.0001
Average LOS (SD), range	4.6 (7.96), 0 to 1,430	16.4 (19.22), 1 to 141	4.6 (7.92), 0 to 1,430	p < 0.0001
Discharge status				
Expired	13,947 (2.50)	51 (6.54)	13,896 (2.49)	537.65

Discharged to home/ self care	340,227 (60.87)	246 (31.54)	339,981 (60.91)	p < 0.0001
Discharged to Hospice	7,457 (1.33)	14 (1.79)	7,443 (1.33)	
Discharged/transferred to institutionalized care	92,573 (16.56)	319 (40.90)	92,254 (16.53)	
Discharged/transferred to noninstitutionalized care	60,531 (10.83)	145 (18.59)	60,386 (10.82)	
Other/Not recorded	44,182 (7.90)	5 (0.64)	44,177 (7.92)	
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	
Hospital Characteristics				
Geographic region				
Northeast	242,258 (43.34)	388 (49.74)	241,870 (43.34)	120.70
Midwest	114,295 (20.45)	244 (31.28)	114,051 (20.43)	p < 0.0001
South	173,037 (30.96)	139 (17.82)	172,898 (30.98)	
West	29,327 (5.25)	9 (1.15)	29,318 (5.25)	
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	
Bed size				
≤ 99	27,733 (4.96)	10 (1.28)	27,723 (4.97)	171.94
100-199	76,368 (13.66)	77 (9.87)	76,291 (13.67)	p < 0.0001
200-299	109,642 (19.62)	285 (36.54)	109,357 (19.59)	
300-499	148,829 (26.63)	131 (16.790	148,698 (26.64)	
≥500	196,345 (35.13)	277 (35.51)	196,068 (35.13)	
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	
Teaching status				
Teaching	405,948 (72.63)	481 (61.67)	405,467 (72.65)	47.24
Non-teaching	152,969 (27.37)	299 (38.33)	152,670 (27.35)	p < 0.0001
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	
Physician Characteristics				
Ordering Physician Specialty				
Non-specialist	77,760 (13.91)	134 (17.18)	77,626 (13.91)	37.90
Specialist	193,374 (34.60)	189 (24.23)	193,185 (34.61)	p < 0.0001
Not recorded	287,783 (51.49)	457 (58.59	287,326 (51.48)	
Total (row %)	558,917 (100.00)	780 (0.14)	558,137 (99.86)	

GEE Model Selection

The objective of this specific aim was to determine the impacts of safety interventions on ESA utilization patterns and associations of patient demographics, clinical characteristics, hospital characteristics, and physician characteristics with ESA on-label and off-label prescribing. These variables were selected a priori based on the literature review described in Chapter 2.

In order to obtain reliable estimates of the parameter, it was important to identify whether multicollinearity existed. Multicollinearity referred to linear correlations among explanatory variables in the estimating which can result in bias estimation of coefficients. A diagnostics of multicollinearity was done using OLS estimation because such test was not possible in logistic regression. Multicollinearity was not detected (VIF[b] values < 4 for all time-constant explanatory variables, data not shown). The final model included all variables used in the bivariate analysis except for hospital length of stay because its inclusion caused failure in the convergence of the correlation matrix and iteration process of standard errors of the GEE models.

The GEE models were specified using a binomial distribution and a logit link. The link and distribution was appropriate in modeling categorical dependent variable, ESA use, in this case. Exchangeable correlation structure was selected because of the non-ordering nature of patients within the hospital clusters.[197] An alternative to exchangeable correlation structure is unstructured matrix. However, this choice was not selected because of the large number of time

[b] Variance Inflation Factor (VIF) value represents the inflation of the variance of an estimated coefficient beyond what would have resulted if there was no collinearity. VIF less than 4 implies acceptable level of correlation among explanatory variables in the models.

points in our data. All correlations at all time points must be estimated if unstructured correlation matrix were specified. If unstructured matrix were to be used instead of the exchangeable matrix, we were likely to have encountered a computation constraint, reduction of power of statistical tests, and non-convergence issues of the estimates.

The variables included in the model came from five main domains: intervention and time variables, patient demographic characteristics, patient clinical characteristics, hospital characteristics, and physician characteristics. The selected binary logistic regression model can be specified as followed: $\text{Logit}(\text{ESA}=1) = \beta_0 + \beta_1 t + \beta_2 \text{intervention1} + \beta_3 \text{intervention1} \times t_1 + \beta_4 \text{intervention2} + \beta_5 \text{intervention2} \times t_2 + \beta_6 \text{intervention3} + \beta_7 \text{intervention3} \times t_3 + \text{DEM} + \text{HEALTH} + \text{HOS} + \text{PHYS} + e_t$

Intervention variables: Three indicator variables: black box warning (BBW), NCD, and REMS, were included in the model. The intervention indicator variable indicated the immediate month after which the intervention was implemented. The interaction terms of intervention indicator variable and time indicated the monthly time trend after the intervention.

Patient demographic variables (DEM): Patient demographics included were age, race, gender, and primary payer. The variable age was categorized into six different age groups: young adult (18-30 years), middle-aged (31-50 years), late middle-age (51-64 years), young old (65-74 years), older old (75-84 years), and oldest old (85 years and above). The reference group used for age group was adult aged between 31 and 50 years old. The gender reference group was male. The race variables included Caucasian, African-American, Other, and Missing. Caucasian group was used as a reference. The primary payer variable included Medicare, Medicaid, Private, Self-pay, Other, and Missing. Medicare was the reference category.

Patient clinical characteristics (HEALTH): Clinical variables included admission type, comorbidity index, and discharge disposition. Variable indicating hospital length-of-stay was dropped from the final model because addition of this variable created convergence issue of the estimate: Admission type was categorized into Emergency, Urgent, Elective, and Other/Missing, and admission through an emergency department was used as the reference category. Comorbidity index was added into the model as a continuous variable. Finally, discharge type was categorized into Discharged to home, Expired, Discharged to hospice, Discharged to institutionalized care, Discharged to non-institutionalized care, and Other/Missing. Discharged to home category was use as a reference group.

Hospital characteristics (HOS): These variables included census region where the hospital was located: Northeast, Midwest, South, and West, where the Northeast region was use as a reference, teaching status, where non-teaching hospital group was used as a reference category, and hospital size (number of beds), Bed size variable was categorized in less than 99 beds, 100-199 beds, 200-299 beds (reference), 300-499 beds, and more than 500 beds.

Physician characteristics (PHY): The only physician characteristic used in the analytical model was physician specialty. Medical specialty of admitting physicians were categorized into Non-specialist, Specialist, and Missing, with Non-specialist as the reference category.

Aim 3a: Impacts of black box warning, NCD, and REMS on odds of being prescribed ESAs

Impacts of the interventions on ESA utilization patterns

Impact of black box warning, NCD, and REMS on the odds of being prescribed ESAs for the on-label, off-label supported, and off-label unsupported indications are summarized in Table 4.28, 4.29, and 4.30, respectively.

Addition of a black box warning onto ESA labels did not significantly affect the odds of a patient receiving the drug for any indications. However, there was a marginally insignificant decrease in the odds of receiving ESAs among patients with ONS indications (OR 0.870, 95% CI 0.750, 1.008, $p = 0.0645$). National coverage determination (NCD), on the other hand, was associated with significant reduction in the odds of using the drugs once implemented. The impact of NCD was observed across three use categories. Patients with ONS, OFS, and OFU conditions were 0.13 times (95% CI 0.760, 0.986, $p = 0.0299$), 0.20 times (95% CI 0.716, 0.891, $p < 0.0001$), and 0.38 times (95% 0.474, 0.817, $p < 0.0006$), respectively, less likely to receive ESAs after the change in reimbursement policy. Moreover, patients with on-label and off-label supported conditions were 0.046 times (95% CI 0.931, 0.977, $p = 0.000$) and 0.06 times (95% 0.902, 0.974, $p = 0.0009$) less likely to use the drugs, with every month after NCD. No significant impact of REMS was found on the on-label and off-label use of ESAs.

Impacts of the interventions on epoetin alfa utilization patterns

The impact of safety interventions on individual erythropoietic drugs were assessed using the binary logistic regression models with the same set of independent variables. In the epoetin alfa mode, the impact of black box warning was observed in off-label unsupported prescribing

only. A patient with off-label unsupported indications admitted in April 2007 was 0.394 times less likely to received epoetin alfa, compared to than those admitted in before that month. NCD, on the other hand, significantly reduced the odds of a patient receiving epoetin alfa off-label immediately after its implementation. A patient admitted to the hospital with off-label supported indication and off-label unsupported indications in April 2008 was 0.20 times (95% CI 0.691, 0.921, p = 0.0021) and 0.47 times (95% 0.383, 0.729, p = 0.0001) less likely to be prescribed with epoetin alfa, compared than similar patients admitted before that month. Moreover, after the NCD, the odds of a patient with off-label supported indication in receiving the drug was reduced by 0.07 times per month (95% CI 0.879, 0.975, p = 0.0032). Finally, the implementation of REMS was not associated with any change in the odds of receiving epoetin alfa.

Impacts of the interventions on darbepoetin alfa utilization patterns

There appeared to be small but statistically significant increases in the off-label unsupported use of darbepoetin alfa during the study period (OR 1.079, 95% CI 1.038, 1.122, p <0.0001). While we observed neither the impact of black box warning nor REMS on the on-label use of darbepoetin alfa, NCD was associated with significant reduction in the odds of receiving darbepoetin alfa on-label. A patient with ONS conditions was 9.6% less likely to use darbepoetin alfa after the change in reimbursement policy was put in place. There were small but statistically significant decreases in the use of darbepoetin alfa for OFS and OFU conditions after the issuance of a black box warning (OR 0.957, 95% CI 0.918, 0.998, p = 0.0410, and OR 0.848, 95% CI 0.75, 0.958, p = 0.0079). Similarly, we found small but statistically significant decreases in the use of darbepoetin alfa associated with NCD implementation in patients with the

conditions for OFS indications. Risk Evaluation and Mitigation Strategy program (REMS) did not have any significant impacts on the use of darbepoetin for any indications.

Table 4.28 Relative Impacts of Interventions on the odds of receiving any ESA therapy by Use Category

Variable	Parameter					
	β	Exp (β)	SE of Exp (β)	95% Confidence Interval	Chi-Square	p-value
Model 1: ONS						
Time	-0.04	0.967	0.0024	[0.992, 1.001]	2.06	0.1516
BBW						
Immediate	-0.140	0.870	0.0657	[0.750, 1.008]	3.42	0.0645
Level Change	0.005	1.005	0.0067	[0.992, 1.019]	0.61	0.4354
NCD						
Immediate	-0.143*	0.867*	0.0572	[0.762, 0.986]	4.71	0.0299
Level Change	-0.047*	0.954*	0.0120	[0.931, 0.977]	14.28	0.0002
REMS						
Immediate	0.097	1.102	0.1163	[0.896, 1.355]	0.84	0.3594
Level Change	0.027	1.028	0.0257	[0.979, 1.079]	1.19	0.2748
Model 2: OFS						
Time	0.0004	1.000	0.0071	[0.987, 1.014]	< 0.01	0.9554
BBW						
Immediate	-0.101	0.904	0.0922	[0.740, 1.104]	0.99	0.3208
Level Change	0.007	1.007	0.0115	[0.985, 1.030]	0.42	0.5170
NCD						
Immediate	-0.225*	0.799*	0.0445	[0.716, 0.891]	16.26	<0.0001
Level Change	-0.065*	0.937*	0.0184	[0.902, 0.974]	10.97	0.0009
REMS						
Immediate	0.197	1.218	0.1557	[0.948, 1.565]	2.38	0.1231
Level Change	0.008	1.008	0.0310	[0.949, 1.071]	0.07	0.7890
Model 3: Documented OFU						
Time	0.012*	1.011*	0.0049	[1.002, 1.021]	5.66	0.0173
BBW						
Immediate	-0.245	0.783	0.1407	[0.550, 1.114]	1.85	0.1734
Level Change	-0.029	0.971	0.0196	[0.934, 1.011]	2.08	0.1495
NCD						
Immediate	-0.474*	0.622*	0.0865	[0.474, 0.817]	11.63	0.0006
Level Change	-0.008	0.992	0.0279	[0.939, 1.049]	0.08	0.7835
REMS						
Immediate	-0.079	0.924	0.1839	[0.626, 1.365]	0.16	0.6926
Level Change	-0.010	0.991	0.0274	[0.938, 1.046]	0.12	0.7309

*Statistically significance at α = 0.05

Table 4.29 Relative Impacts of Interventions on odds of receiving epoetin alfa therapy by Use Category

Variable	Parameter					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Model 1: ONS						
Time	-0.006	0.995	0.0043	[0.986, 1.003]	1.65	0.1991
BBW						
Immediate	-0.184	0.832	0.0931	[0.668, 1.036]	2.70	0.1004
Level Change	0.004	1.004	0.0107	[0.983, 1.025]	0.13	0.7133
NCD						
Immediate	-0.159	0.853	0.0861	[0.700, 1.040]	2.47	0.1159
Level Change	0.051*	0.950*	0.0177	[0.916, 0.986]	7.47	0.0063
REMS						
Immediate	0.236	1.266	0.1642	[0.982, 1.633]	3.31	0.0687
Level Change	0.044	1.045	0.0323	[0.983, 1.110]	2.01	0.1561
Model 2: OFS						
Time	-0.006	0.994	0.0085	[0.978, 1.011]	0.47	0.4926
BBW						
Immediate	-0.202	0.817	0.1195	[0.613, 1.088]	1.91	0.1667
Level Change	0.022	1.022	0.0157	[0.992, 1.053]	2.02	0.1548
NCD						
Immediate	-0.226*	0.798*	0.0585	[0.691, 0.921]	9.49	0.0021
Level Change	-0.077*	0.926*	0.0243	[0.879, 0.975]	8.68	0.0032
REMS						
Immediate	0.223	1.250	0.2215	[0.883, 1.769]	1.59	0.2077
Level Change	0.026	1.026	0.0392	0.952, 1.106	0.46	0.4990
Model 3: Documented OFU						
Time	0.004	1.004	0.0054	[0.993, 1.014]	0.48	0.4879
BBW						
Immediate	-0.502*	0.606*	0.1130	[0.420, 0.873]	7.23	0.0072
Level Change	0.009	1.009	0.0184	[0.974, 1.046]	0.25	0.6187
NCD						
Immediate	-0.638*	0.528*	0.0868	[0.383, 0.729]	15.08	0.0001
Level Change	-0.031	0.970	0.0285	[0.915, 1.027]	1.10	0.2949
REMS						
Immediate	-0.116	0.891	0.2054	[0.567, 1.400]	0.25	0.6153
Level Change	-0.010	0.991	0.0310	[0.932, 1.053]	0.09	0.7607

*Statistically significance at α = 0.05

Table 4.30 Relative Impacts of Interventions on odds of receiving darbepoetin alfa therapy by Use Category

Variable	Parameter					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Model 1: ONS						
Time	0.005	1.001	0.0067	[0.992, 1.018]	0.55	0.4575
BBW						
Immediate	-0.046	0.955	0.1043	[0.771, 1.183]	0.18	0.6713
Level Change	0.008	1.008	0.0138	[0.981, 1.035]	0.34	0.5602
NCD						
Immediate	-0.101*	0.904*	0.0272	[0.852, 0.959]	11.29	0.0008
Level Change	-0.047*	0.955*	0.0128	[0.930, 0.980]	11.98	0.0005
REMS						
Immediate	-0.261	0.770	0.1367	[0.544, 1.091]	2.17	0.1410
Level Change	0.003	1.003	0.0426	[0.923, 1.090]	< 0.01	0.9504
Model 2: OFS						
Time	0.039	1.039	0.0122	[1.016, 1.064]	10.80	0.0010
BBW						
Immediate	-0.007	0.993	0.1197	[0.784, 1.258]	0.00	0.9559
Level Change	-0.044*	0.957*	0.0205	[0.918, 0.998]	4.17	0.0410
NCD						
Immediate	-0.205	0.814	0.0923	[0.652, 1.017]	3.28	0.0700
Level Change	-0.046*	0.955*	0.0170	[0.923, 0.989]	6.59	0.0103
REMS						
Immediate	0.164	1.178	0.1738	[0.883, 1.573]	1.24	0.2658
Level Change	-0.051	0.950	0.0460	[0.864, 1.045]	1.11	0.2918
Model 3: Documented OFU						
Time	0.076*	1.079*	0.0213	[1.038, 1.122]	14.93	0.0001
BBW						
Immediate	0.199	1.220	0.5823	[0.479, 3.109]	0.17	0.6774
Level Change	-0.165*	0.848*	0.0526	[0.751, 0.958]	7.05	0.0079
NCD						
Immediate	0.113	1.120	0.3500	[0.607, 2.066]	0.13	0.7180
Level Change	0.024	1.025	0.0645	[0.906, 1.159]	0.15	0.7004
REMS						
Immediate	0.277	1.319	0.6838	[0.477, 3.643]	0.28	0.5938
Level Change	-0.051	0.950	0.0617	[0.837, 1.079]	0.62	0.4302

*Statistically significance at α = 0.05

Aim 3b Associations of covariates and ESA On-label use

The same binary logistic regressions using GEE used in Specific Aim 3a were fit to assess the associations of patient demographics, clinical characteristics, hospital characteristics, and physician characteristics with ESA on-label and off-label prescribing. The three models include: ESA-ONS, ESA-OFS, and ESA-Documented OFU. We did not distinguish between the two erythropoietic drugs in these models. The reference categories for each of the categorical independent variables in the model made up of White males aged 31-50 who had Medicare as their primary payer, admitted as emergent patients, discharged to home, by a non-specialist, to non-teaching hospitals located in the Northeast region which had between 200 and 299 beds. Results from each model were divided for ease of understanding into three parts: patient demographic, clinical condition, and hospital and physician characteristics. Associations of these variables and on-label, off-label supported, and off-label unsupported of ESAs in the inpatient settings are shown in Table 4.31-4.39.

Part 1: On-label use of ESAs

The regression results of patient demographics as possible predictors of ESA on-label prescribing are summarized in Table 4.31. Young adult (18-30 years) were 0.29 times less likely to be prescribed with ESA for on-label indications compared to the middle aged adult in the age range of 31 to 50 years (95% CI 0.658, 0.763, $p < 0.0001$). The late middle-age (51-64 years), on the other hand, were 1.20 times more likely to be prescribed with ESAs (95% CI 1.119, 1.296, $p < 0.0001$). Being of aged 65 to 84 years, a patient was not found to be statistically more or less likely than the young adult to be prescribed with ESAs. Lastly, being the oldest old (above 85 years) was associated with decreased odds of receiving ESAs on-label (0.31 times less

likely, 95% CI 0.597, 0.790, $p < 0.0001$). The odds of receiving ESAs also depended on patient's gender. Female patients were 0.12 time less likely to receive ESAs on-label (95% 0.857, 0.915, $p < 0.0001$). Patient's race was strongly associated with the odds of being prescribed with ESAs. Compared to Caucasian, African-American were 1.715 times more likely to receive ESAs (95% CI 1.557, 1.889, $p < 0.0001$). Similarly, patients of 'Other' race were 1.46 times more likely than Caucasian to receive ESAs (95% CI 1.307, 1.621, $p < 0.0001$). Finally, compared to Medicare patients, patients with other health insurance types were less likely to receive ESA on-label. For example, private insurance patients were 0.40 times less likely than Medicare patients to be prescribed with ESAs. Those who had to pay for the healthcare services out-of-pocket (the "Self-pay" group) were 0.48 times less likely to use ESAs, compared to Medicare patients.

The regression results of patient clinical conditions as possible predictors of ESA on-label prescribing are shown in Table 4.32. Compared to "Emergent" patients, patient who were admitted to the hospitals as elective cases were 0.60 times less likely to be prescribed ESAs on-label (95% CI 0.322, 0.490, $p < 0.0001$). The odds of receiving ESAs increased substantially with more complex patients measured through combined comorbidity score. The odds of receiving ESAs increased 1.20 times with one unit increase in the comorbidity index (95% 1.174, 1.232, $p < 0.0001$). Lastly, discharge disposition was a strong predictor of ESA on-label prescribing. Compared to the patients who were discharged to home, those who expired in the hospitals were 1.98 times more like to use ESAs (95% 1.784, 2.196, $p < 0.0001$). Patients who needed to be transferred to hospice, institutionalized, or non-institutionalized care were all more likely to use ESAs compared to those who were discharged to home.

No significant differences in the odds of ESA on-label prescribing were found among hospitals across geographic regions. Being admitted to small hospitals of fewer than 99 beds reduced the odds of receiving ESAs 0.48 times compared to medium-sized hospitals (95% CI 0.0036, 0.819, $p < 0.0001$). On the other hand, the odds of receiving ESAs increased 1.59 times if a patient was being admitted to relatively larger hospitals (300-499 beds). Finally, admitting physicians, whether be a non-specialist or specialist, was not associated with the odds of using ESA on-label. Associations of hospital characteristics and physician specialty and ESA on-label prescribing can be found in Table 4.33.

Table 4.31 Associations of patient demographic and ESA ONS use

Variable	Parameters					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Demographics						
Age						
18-30	-0.345*	0.709*	0.0269	[0.658, 0.763]	82.66	<.0001
31-50 (reference)	-	-	-	-	-	-
51-64	0.186*	1.204*	0.0450	[1.119, 1.296]	24.73	<.0001
65-74	0.053	1.054	0.0593	[0.944, 1.177]	0.89	0.3458
75-84	-0.055	0.946	0.0613	[0.834, 1.074]	0.73	0.3938
85+	-0.376*	0.687*	0.0492	[0.597, 0.790]	27.52	<.0001
Gender						
Male (reference)	-	-	-	-	-	-
Female	-0.122*	0.885*	0.0148	[0.857, 0.915]	53.06	<.0001
Race						
Caucasian (reference)	-	-	-	-	-	-
African-American	0.539*	1.715*	0.0845	[1.557, 1.889]	119.99	<.0001
Other	0.375*	1.455*	0.0799	[1.307, 1.621]	46.62	<.0001
Missing	0.071	1.074	0.0624	[0.958, 1.203]	1.49	0.2218
Source of Payment						
Medicare (reference)	-	-	-	-	-	-
Medicaid	-0.260*	0.771*	0.0599	[0.662, 0.898]	11.20	0.0008
Commercial/ Private/ HMO Managed Care	-0.504*	0.604*	0.0386	[0.533, 0.684]	62.38	<.0001
Self-pay	-0.654*	0.520*	0.0334	[0.459, 0.590]	103.93	<.0001
Other	-0.274*	0.760*	0.0716	[0.632, 0.915]	8.46	0.0036
Missing	-0.217*	0.805*	0.0589	[0.697, 0.929]	8.80	0.003

Table 4.32 Associations of clinical conditions and ESA ONS use

Variable	Parameters					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Clinical Conditions						
Admission type						
Emergency (reference)	-	-	-	-	-	-
Urgent	-0.037	0.964	0.0532	[0.865, 1.074]	0.45	0.5015
Elective	-0.924*	0.397*	0.0426	[0.322, 0.490]	74.21	<.0001
Other/Missing	-0.478*	0.620*	0.0604	[0.512, 0.751]	24.05	<.0001
Average CCI (SD)	0.184*	1.203*	0.0147	[1.174, 1.232]	228.08	<.0001
Discharge status						
Discharged to home/self care (reference)	-	-	-	-	-	-
Expired	0.683*	1.979*	0.1050	[1.784, 2.196]	165.56	<.0001
Discharged to Hospice	0.174*	1.191*	0.0767	[1.049, 1.351]	7.34	0.0068
Discharged/ transferred to institutionalized care	0.658*	1.932*	0.0778	[1.785, 2.090]	267.43	<.0001
Discharged /transferred to noninstitutionalized care	0.434*	1.543*	0.0528	[1.443, 1.650]	160.71	<.0001
Other/Missing	-0.167	0.847	0.1032	[0.667, 1.075]	1.87	0.1715

Table 4.33 Associations of hospital and physician characteristics and ESA ONS use

Variable	Parameters					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Hospital Characteristics						
Geographic region						
Northeast (reference)	-	-	-	-	-	-
Midwest	0.147	1.158	0.2375	[0.775, 1.731]	0.51	0.4739
South	0.112	1.119	0.2636	[0.705, 1.775]	0.23	0.6343
West	0.142	1.153	0.3265	[0.662, 2.008]	0.25	0.6158
Bed size						
<99	-0.646*	0.524*	0.1192	[0.336, 0.819]	8.07	0.0045
100-199	-0.032	0.968	0.2022	[0.643, 1.458]	0.02	0.8774
200-299 (reference)	-	-	-	-	-	-
300-499	0.465*	1.592*	0.3635	[1.018, 2.490]	4.15	0.0418
≥500	0.214	1.238	0.3184	[0.748, 2.049]	0.69	0.4063
Teaching status						
Non-teaching (reference)	-	-	-	-	-	-
Teaching	-0.049	0.952	0.1904	[0.643, 1.409]	0.06	0.8061
Physician Characteristics						
Physician Specialty						
Non-specialist (reference)	-	-	-	-	-	-
Specialist	-0.057	0.945	0.0976	[0.772, 1.157]	0.30	0.5835
Missing	0.020	1.020	0.1321	[0.792, 1.315]	0.02	0.8776

Part 2: Off-label supported of ESAs

Results of binary logistic regression assessing association of patient demographics and the prescribing of ESAs for the off-label supported indications are shown in Table 4.34. Older age appeared as a strong possible predictor of the off-label supported use of ESAs. Being older was associated with the increased odds of receiving ESAs for the off-label supported indications. For example, the young old at age of 65 to 74 years old were 1.91 times more likely than the middle-aged patients to be prescribed with ESAs off-label (95% 1.494, 2.434, $p < 0.0001$) while the young adult (aged 18-30 years) were 0.65 times less likely than the reference group to receive ESAs for these indications. Female patients were 0.20 times less likely to use ESAs for the off-label supported indications. Being and African-American remained a significant predictor of ESA off-label (OR 1.214, 95% CI 1.082, 1.362, $p = 0.0010$). In general, patients with other type of health insurance were less likely than Medicare patients to received ESAs for off-label indications. Having to pay for the services out-of-pocket reduced the odds of using the drug by 0.46 times compared to using Medicare coverage (95% CI 0.402, 0.739, $p <0.0001$).

Associations between clinical conditions and the odds of receiving ESAs for the off-label supported indications are shown in Table 4.35. Neither patient's admission type nor comorbidity index was associated with the odds of receiving ESAs in patients with ESAs off-label supported conditions. Nonetheless, patients admitted as elective cases were marginally significant of being of greater odds of receiving the drugs compared to the emergent cases. Lastly, discharge disposition remained as one of the strongest predictors of this type of ESA prescribing. For instance, compared to those who were discharged to home, patients who expired had a 4.92 times greater odds of receiving the drug (95% CI 4.075, 5.932, $p < 0.0001$). Likewise, those

discharged to hospice, institutionalized, or non-institutionalized care were approximately four times more likely to use ESAs off-label (all p-values < 0.0001).

Similar logistic regression results were observed between ESA on-label and off-label supported prescribing, with regards to hospital and physician characteristics. Teaching status, hospital geographic region, or physician specialty was not associated with the increased odds of receiving the drug. On the other hand, being admitted to smaller hospitals of less than 199 beds decreased the odds of using ESAs for these indications about half ($OR_{<99\ beds}$ 0.504, 95% CI 0.278, 0.912, $p < 0.0236$; $OR_{100\text{-}199\ beds}$ 0.593, 95% CI 0.405, 0.868, $p < 0.0072$), while admission to larger hospitals with 300-499 beds was associated with 2.433 times increase in the odds of drug use (95% CI 1.630, 3.630, $p < 0.0001$). Associations of hospital and physician characteristics and ESA off-label supported use are summarized in Table 4.36.

Table 4.34 Associations of patient demographic and ESA OFS use

Variable	Parameters					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Demographics						
Age						
18-30	-1.032*	0.356*	0.0351	[0.294, 0.432]	109.90	<.0001
31-50 (reference)	-	-	-	-	-	-
51-64	0.588*	1.800*	0.1681	[1.499, 2.162]	39.65	<.0001
65-74	0.645*	1.907*	0.2373	[1.494, 2.434]	26.88	<.0001
75-84	0.397*	1.488*	0.2231	[1.109, 1.996]	7.02	0.0080
85+	0.062	1.064	0.1626	[0.789, 1.436]	0.16	0.6849
Gender						
Male (reference)						
Female	-0.228*	0.796*	0.0324	[0.735, 0.862]	31.47	<.0001
Race						
Caucasian (reference)	-	-	-	-	-	-
African-American	0.194*	1.214*	0.0713	[1.082, 1.362]	10.88	0.0010
Other	0.055	1.056	0.0908	[0.892, 1.250]	0.40	0.5265
Missing	0.035	1.036	0.0982	[0.860, 1.248]	0.14	0.7096
Source of Payment						
Medicare (reference)	-	-	-	-	-	-
Medicaid	-0.274*	0.760*	0.0645	[0.644, 0.898]	10.43	0.0012
Commercial/ Private/ HMO Managed Care	-0.153	0.858	0.0680	[0.734, 1.002]	3.75	0.0528
Self-pay	-0.607*	0.545*	0.0847	[0.402, 0.739]	15.27	<.0001
Other	-0.298*	0.742*	0.0830	[0.596, 0.924]	7.10	0.0077
Missing	-0.234*	0.791*	0.0910	[0.632, 0.992]	4.14	0.0419

Table 4.35 Associations of clinical conditions and ESA OFS use

Variable	Parameters					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Clinical Conditions						
Admission type						
Emergency (reference)	-	-	-	-	-	-
Urgent	0.150	1.162	0.0902	[0.998, 1.613]	0.07	0.7936
Elective	-0.179	0.836	0.0626	[0.722, 1.352]	3.72	0.0539
Other/Missing	0.056*	1.058*	0.2276	[0.694, 0.968]	5.72	0.0168
Average CCI (SD)	0.010	1.010	0.0173	[0.977, 1.045]	0.35	0.5525
Discharge status						
Discharged to home/self care (reference)	-	-	-	-	-	-
Expired	1.593*	4.917*	0.4709	[4.075, 5.932]	276.43	<.0001
Discharged to Hospice	1.434*	4.194*	0.5560	[3.234, 5.438]	116.94	<.0001
Discharged/ transferred to institutionalized care	1.457*	4.291*	0.3494	[3.658, 5.034]	320.01	<.0001
Discharged/ transferred to noninstitutionalized care	1.121*	3.067*	0.2029	[2.694, 3.492]	287.01	<.0001
Other/Missing	-0.043	0.958	0.3291	[0.489, 1.878]	0.02	0.9009

Table 4.36 Associations of hospital and physician characteristics and ESA OFS use

Variable	Parameters					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Hospital Characteristics						
Geographic region						
Northeast (reference)	-	-	-	-	-	-
Midwest	-0.295	0.744	0.1893	[0.452, 1.226]	1.35	0.2458
South	0.140	1.150	0.2392	[0.765, 1.729]	0.45	0.5020
West	-0.070	0.932	0.3249	[0.471, 1.846]	0.04	0.8402
Bed size						
<99	-0.686*	0.504*	0.1526	[0.278, 0.912]	5.12	0.0236
100-199	-0.522*	0.593*	0.1154	[0.405, 0.868]	7.21	0.0072
200-299 (reference)	-	-	-	-	-	-
300-499	0.889*	2.433*	0.4968	[1.630, 3.630]	18.94	<.0001
≥500	0.522	1.686	0.4588	[0.989, 2.874]	3.68	0.0551
Teaching status						
Non-teaching (reference)						
Teaching	-0.198	0.820	0.1849	[0.527, 1.276]	0.77	0.3789
Physician Characteristics						
Physician Specialty						
Non-specialist (reference)	-	-	-	-	-	-
Specialist	-0.024	0.976	0.1227	[0.763, 1.249]	0.04	0.8479
Missing	-0.118	0.889	0.1480	[0.642, 1.232]	0.50	0.4805

Part 3: Off-label unsupported use of ESAs

Results from logistic regression of demographic domain and off-label unsupported indications are shown in Table 4.37. Age was not predictor of ESA use in this case. Being a female with off-label unsupported indications, opposite to other indications, increased the odds of receiving ESAs by 1.15 times. Race remained statistically associated with the increased odds of ESAs prescribing where African-American were 1.40 times more likely to use ESAs (95% CI 1.222, 1.610, $p < 0.0001$), and patient with "Other" race were 1.24 times more likely (95% CI 1.088, 1.417, $p = 0.0013$), compared to Caucasian. The effect of primary payer on ESA prescribing was also less prominent for the off-label unsupported indications. Compared to Medicare patients, no other insurance type but "Self-pay" was associated with the decreased odds of receiving ESAs for such indications. Patients with off-label unsupported indications who paid for the care by themselves were 0.24 times less likely than Medicare patients to use the drugs.

Patients with off-label unsupported indications admitted to the hospital as urgent cases were 1.41 times more likely to be prescribed ESAs as compared to patients admitted to the hospital as emergency cases. With one unit increase in patient's comorbidity index measuring clinical complexity, the odds of being prescribed ESAs for off-label unsupported indications increased 1.23 times (95% CI 1.168, 1.289, $p < 0.0001$). Similar results as other type of ESA prescribing were observed for discharge disposition, with the odds of receiving the drugs being increased as a patient was discharged to anywhere else but home. For instance, the odds of using the drugs for an admitted patient with off-label unsupported indications who were discharged to institutionalized care increased by 3.58 times compared to patients who were discharged home

(95% CI 2.981, 4.309, $p < 0.0001$). Associations of patient clinical conditions and ESA off-label unsupported use are summarized in Table 4.38.

Finally, hospital size was the only significant predictor of ESA off-label unsupported prescribing. Patients admitted to smaller hospitals with fewer than 99 beds were 0.57 times less likely to be prescribed ESAs (95% CI 0.209, 0.875, $p = 0.0200$) compared to those admitted to "200-299 beds" category. On the other hand, patients in 300-499 and ≥ 500 beds hospitals were 2.19 times (95% CI 1.334, 3.609, $p = 0.0020$) and 1.91 times (95% CI 1.143, 3.193, $p = 0.0136$) more likely to use ESAs for off-label unsupported indications. Associations of hospital and physician characteristics and ESA off-label unsupported use are summarized in Table 4.39.

Table 4.37 Associations of patient demographic and ESA OFU use

Variable	Parameters					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Demographics						
Age						
18-30	0.007	1.007	0.1197	[0.798, 1.271]	0.00	0.9529
31-50 (reference)	-	-	-	-	-	-
51-64	0.062	1.064	0.0501	[0.971, 1.167]	1.75	0.1859
65-74	0.131	1.140	0.0817	[0.991, 1.312]	3.36	0.0667
75-84	0.045	1.046	0.0911	[0.882, 1.241]	0.27	0.6049
85+	-0.176	0.838	0.0887	[0.681, 1.032]	2.77	0.0958
Gender						
Male (reference)	-	-	-	-	-	-
Female	0.137*	1.147*	0.0344	[1.081, 1.216]	20.80	<.0001
Race						
Caucasian (reference)	-	-	-	-	-	-
African-American	0.339*	1.403*	0.0987	[1.222, 1.610]	23.17	<.0001
Other	0.217*	1.242*	0.0837	[1.088, 1.417]	10.35	0.0013
Missing	-0.156	0.855	0.0934	[0.690, 1.059]	2.05	0.1521
Source of Payment						
Medicare (reference)	-	-	-	-	-	-
Medicaid	0.096	1.101	0.1056	[0.912, 1.329]	1.00	0.3166
Commercial/ Private/ HMO Managed Care	-0.058	0.944	0.0772	[0.804, 1.108]	0.50	0.4795
Self-pay	-0.278*	0.758*	0.0557	[0.656, 0.875]	14.26	0.0002
Other	-0.092	0.912	0.0978	[0.739, 1.125]	0.74	0.3899
Missing	0.013	1.013	0.1422	[0.769, 1.333]	0.01	0.9287

Table 4.38 Associations of clinical conditions and ESA OFU use

Variable	Parameters					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Clinical Conditions						
Admission type						
Emergency (reference)	-	-	-	-	-	-
Urgent	0.341*	1.406*	0.0978	[1.224, 1.611]	23.94	<.0001
Elective	-0.019	0.981	0.0794	[0.837, 1.150]	0.06	0.8139
Other/Missing	0.549*	1.732*	0.2885	[1.249, 2.401]	10.86	0.0010
Average CCI (SD)	0.205*	1.227*	0.0309	[1.168, 1.289]	66.15	<.0001
Discharge status						
Discharged to home/self care (reference)	-	-	-	-	-	-
Expired	1.011*	2.747*	0.4199	[2.036, 3.706]	43.70	<.0001
Discharged to Hospice	0.713*	2.040*	0.3243	[1.494, 2.786]	20.10	<.0001
Discharged/ transferred to institutionalized care	1.277*	3.584*	0.3367	[2.981, 4.309]	184.63	<.0001
Discharged/ transferred to noninstitutionalized care	0.981*	2.666*	0.2833	[2.165, 3.283]	85.12	<.0001
Other/Missing	-0.651	0.521	0.1528	[0.293, 0.926]	4.94	0.0263

Table 4.39 Associations of hospital characteristics and ESA OFU use

Variable	Parameters					
	β	Exp (β)	SE	95% Confidence Interval	Chi-Sq	p-value
Hospital Characteristics						
Geographic region						
Northeast (reference)	-	-	-	-	-	-
Midwest	-0.244	0.784	0.2048	[0.470, 1.308]	0.87	0.3511
South	0.137	1.147	0.3079	[0.678, 1.941]	0.26	0.6098
West	-0.265	0.768	0.2907	[0.365, 1.613]	0.49	0.4849
Bed size						
<99	-0.851*	0.427*	0.1562	[0.209, 0.875]	5.41	0.0200
100-199	-0.452	0.637	0.1624	[0.386, 1.049]	3.14	0.0766
200-299 (reference)	-	-	-	-	-	-
300-499	0.786*	2.194*	0.5571	[1.334, 3.609]	9.57	0.0020
≥500	0.647*	1.910*	0.5007	[1.143, 3.193]	6.10	0.0136
Teaching status						
Non-teaching (reference)	-	-	-	-	-	-
Teaching	-0.2674	0.7654	0.2211	[0.4344, 1.3484	0.86	0.3547
Physician Characteristics						
Physician Specialty						
Non-specialist (reference)	-	-	-	-	-	-
Specialist	0.206	1.229	0.1541	[0.961, 1.572]	2.71	0.0998
Missing	0.296	1.344	0.1403	[1.095, 1.649]	8.02	0.0046

CHAPTER 5

Discussion and Conclusions

This chapter summarizes the findings and provides discussion of the results by specific aims. Limitations of the database and study design are described, and their effects on the internal and external validity of the study results are acknowledged. Practical implications of the study finding and suggestions of possible future direction of the research are also discussed in this final chapter.

Summary of Findings

In this research, we examined demographics, clinical conditions, hospital characteristics, and physician specialty of epoetin alfa and darbepoetin alfa users who were admitted to Cerner hospitals. Differences in such characteristics between the three patient groups were also described and statistically tested. Descriptive results indicated that users of epoetin alfa and darbepoetin alfa were statistically different with respect to demographics, clinical conditions, hospital characteristics, and physician specialty. Additionally, significant differences were also found among ONS, OFS, and OFU users of epoetin alfa and darbepoetin alfa.

The first primary objective of this study was to determine if the three major safety interventions implemented during the study period had significant impacts on these three types of ESA prescribing. Prior to the first black box warning in 2007, ESA prescribing in all three labeling categories showed increasing use trends (Figure 4.14). Black box warning significantly reduced the level of ESA ONS use. This reduction in ONS use was driven by darbepoetin alfa use (0.6% decrease in use), not epoetin alfa. OFS use, on the other hand, was affected only by

the change in reimbursement policy (NCD) in April 2008. In contrast to the effect of black box warning on ONS use, this reduction in the level of OFS use was driven by epoetin alfa (0.3% reduction) and not darbepoetin. Lastly, we did not find that any safety interventions significantly affected the level of ESA use for OFU indications. However, we found that when OFU use of ESAs was reanalyzed by specific drugs, there were insignificant reductions in the level of epoetin alfa OFU use following all three interventions. Nonetheless, the level of OFU darbepoetin alfa use instead significantly increased after black box warning and NCD, causing the overall non-significant effects of the interventions when the two drugs were analyzed collectively. REMS, on the other hand, significantly reduced the level of OFU darbepoetin use.

In order to determine if the interventions were associated with the reduction in the likelihood of the receiving ESAs, three patients groups eligible to receive ESAs were defined a priori based on an evidence-based medicine framework. The ONS eligible cohort included any patients admitted to Cerner hospitals with ICD-9-CM diagnoses and procedure codes, and drug codes indicated the presence of CKD, chemotherapy-induced anemia, HIV, and major surgical procedures. The OFS cohorts included patients with non-chronic kidney disease, hepatitis C, congestive heart failure, radiotherapy, anemia due to puerperium, multiple myeloma, myelodysplastic syndrome, myelofibrosis, rheumatoid arthritis, beta thalassemia, and autotransfusion. The known OFU cohort included only patients with conditions known to be treated with ESAs, but did not have sufficient scientific evidence supporting its use. These conditions were anemia of neoplasm diseases without the use of concurrent chemotherapy, chronic anemia, bleeding, injury, cardiac surgeries, blood transfusion, and other OFU use such as irritable bowel syndromes (IBS) and Crohns' disease. We found that NCD significantly reduced the odds of using ESAs for patients with on-label, off-label supported, and off-label unsupported

conditions. Black box warning and REMS, on the other hand, did not significantly affect ESA prescribing patterns.

In the final specific aim, we used the same logistic regression models to assess associations of patient demographics, clinical conditions, and hospital and physician characteristics with ESA on-label and off-label prescribing. A few predominant characteristics of patients receiving ESA therapy suggested by the binary logistic regression results included age, gender, race, source of payment admission type, discharge status, bed size, and teaching status of the hospitals.

The odds of receiving ESAs in patients with ONS and OFS conditions increased with age, up until the older old age of 75 years old was reached. After this age, a patient became less likely to receive the drug. Female patients with ONS and OFS conditions were less likely to use ESAs compared to male. The opposite gender effect was found in OFU use. In this use category, female patients with OFU conditions were more likely to use ESAs compared to male patients. African-American and patients with Medicare were more likely to receive the drugs compared to their counterparts, for all three conditions.

Clinical conditions, especially places of discharge, were strongly associated with the odds of receiving ESAs for all indications. Compared to those discharged to home, patients who needed to be transferred, or discharged to other units/care settings were much more likely to be prescribed with ESAs. Patients admitted as elective cases were less likely to use ESAs compared to those admitted as emergent cases, though the results were marginally significant in OFU prescribing. More complex patients with ONS and OFU conditions were more likely to use

ESAs. Nonetheless, associations of patient's clinical complexity and the increased odds of using ESAs were not observed in patients with OFS conditions.

Finally, our finding suggested that hospital size was strongly associated with the ESA use. Being admitted to larger hospitals increased the odds of receiving ESAs for on-label, off-label supported, and off-label unsupported indications. No significant associations between hospital geographic regions or teaching status, and ESA use were found for any use category.

Discussion of Results by Aim

Specific Aim 1

Previous studies focused on the impact of safety interventions on the use of erythropoiesis-stimulating agents in the outpatient settings,[184, 185] thus very little was known regarding its use in patient admitted to the hospitals. Additionally, most studies collectively analyzed darbepoetin alfa and epoetin alfa as ESAs and rarely distinguish between the two drugs.[181-184, 187] Our descriptive findings shows that the two erythropoietic drugs were used differently in the inpatient settings. Darbepoetin alfa was used to a greater extent for on-label indications (52.8%) compared to epoetin alfa (47.4%). Greater proportion of darbepoetin alfa users was prescribed the drug for chronic kidney disease (93.9% darbepoetin alfa vs 83.8% epoetin alfa), while the use of the two drugs for chemotherapy-induced anemia, zidovudine-induced anemia, and surgical procedures was similar. These findings were consistent with the growth in popularity of darbepoetin alfa use in CKD due to its superiority over epoetin alfa in hemoglobin control, [202, 203]dosing efficacy, [204-206] and cost efficacy[207] claimed in many reports since the approval of darbepoetin alfa in 2001.[208]

Differences in the characteristics of users of epoetin alfa and darbepoetin alfa were also observed in our sample. Greater proportion of patients older than 65 years of age used epoetin alfa compared to darbepoetin alfa (59.4% vs. 52.8%). It is possible that physicians were more comfortable prescribing epoetin alfa which has been in the market longer to the older and frailer patients. Greater proportion of Medicare patients used darbepoetin alfa compared to epoetin alfa (65.7% vs. 58.5%). This was likely due to the fact that darbepoetin alfa was used extensively in the population with CKD usually covered by Medicare in our sample. Greater proportion of patient admitted as emergency or urgent cases used epoetin alfa rather than darbepoetin alfa (emergency+urgent: 83.9% epoetin alfa vs. 75.2% darbepoetin alfa). Lastly, more patients who used darbepoetin alfa were prescribed by specialists while the use of epoetin alfa was to a greater extent, initiated by non-specialists. We believe that this finding was also due to familiarity of the two ESA drugs. The study by Patkar et al, 2007, reported that almost all of the ESAs used in the hospitals from 2002 to 2004 were epoetin alfa.[15] Specialists, especially nephrologists, are likely to be more familiar with the newer darbepoetin alfa compared to the non-specialists who might be more familiar with epoetin alfa since it has been in the market since 1989. It is important to note that the findings on certain variables such as primary payer, admission type, and physician specialty may be tempered because as many as 50% of the hospitals did not report such information.

Descriptive statistics, bar chart, and graphs were used to understand the prevalence of ESA therapy for on-label, off-label supported, and off-label unsupported indications among patients seen in the inpatient settings. The results of this study revealed that off-label prescribing of ESAs constituted more than half of the utilization of the drugs in the hospitals. The use of epoetin alfa and darbepoetin alfa for off-label treatment (both supported and unsupported) was

52.6% and 47.2%, respectively, between 2005 and 2011. Our findings were consistent with previous study investigating off-label use of ESAs in the hospital settings between 2002 and 2004.[15]

However, in contrary to the similar study which found the majority of the off-label use to be supported with evidence, our results indicated that as high as 83% of the off-label use in our sample was for indications unsupported by strong scientific evidence. These OFU use included chronic anemia and neoplastic diseases without concurrent chemotherapy. This high level of off-label unsupported use was however consistent with the study assessing off-label drug use in the physician's office which found that most off-label drug mentions in 2001 (73%) had little or no scientific support.[190] It is possible that contradicting results between Patkar's finding and ours were due to the differences in the inclusion of patient population and the identification of the on-label and off-label use with ICD-9-CM codes. First, we only included adult patients in this study while they included the pediatric population. The study then found that off-label use was highly prevalent in pediatric population. Second, in addition to ICD-9-CM diagnoses codes, we identified additional patients underwent major surgery with ICD-9-CM procedures codes. We also strictly classified ESA use as for chemotherapy-induced anemia (on-label) only if a patient presented with cancer had procedures codes or drug records indicated the use of chemotherapeutic agents during that visits. Patients who had cancer diagnoses but did not receive concurrent chemotherapy were categorized into the off-label unsupported group. We believe that our on-label and off-label classification was a conservation approach that accurately captured all patients.

Differences in characteristics of ESA users for the on-label, off-label supported, and off-label unsupported indications were observed in our sample. Patients who used ESAs for OFS

indications were oldest compared to than patients in the ONS or OFU groups. There were a greater proportion of patients in the OFS group who expired in the hospitals. This was likely due to the high prevalence of acute renal failure (ARF) which contributed the highest off-label supported use of ESAs in very old hospitalized patients.[209, 210] In addition to the high prevalence, death rates among hospitalized patients with ARF was reported to be as high as 25 to >70%.[211] Chronic kidney disease, on the other hand, began relatively earlier in life, progressed slowly, and rarely the main cause of inpatient death.[2] Lastly, OFU patients appeared to be the "least sick" patients among the three users groups with comorbidity index of 0.29 compared to that of the ONS (2.72) and OFS (2.00). With such low level of clinical complexity, it is possible that OFU use seen in our study truly reflected inappropriate use of ESAs in patients who may not need the drug. However, it was also possible these patients were identified as OFU only because of the inadequate records of their diagnoses.

Specific Aim 2

Segmented ordinary regression with interrupted time-series technique was used to quantify the impacts of safety interventions. Our initial hypothesis was that we could detect the impacts of black box warning, national coverage determination, and REMS as a decline in the proportion of visits that a patient was prescribed ESAs for on-label, off-label supported, and off-label unsupported indications. However, this hypothesis was proven to be partially correct. When the use of epoetin alfa and darbepoetin alfa was analyzed collectively as ESAs, we found only two significant immediate drop related to the safety interventions. These significant impacts of the interventions included a significant immediate 1.2% drop in ONS use in the month after the implementation of black box warning, and a 0.3% drop in ESA OFS use after

NCD. The decrease in the proportion of visits with ESA use on-label was consistent with the study by Vadhan-Raj et al, 2010 that found a 26% reduction in the use of ESAs in cancer patients concurrently on chemotherapy in 2007 from that in 2006.[183]

Despite the downward trends in ONS, OFS, and OFU use, the decline after the interventions did not reach a statistically significant level. After the analysis of ESAs was broken down by specific drugs, we found that only epoetin alfa OFS use was only affected by NCD (0.3% decrease). The use of darbepoetin alfa on-label, on the other hand, was sensitive to several safety interventions. We found that black box warning led to a 0.6% rise in darbepoetin alfa ONS use. NCD and REMS were associated with 0.4% and 0.5% drop in darbepoetin alfa ONS use, respectively. Finally, REMS reduced darbepoetin alfa OFU use by 0.5%. Contradictorily to our hypotheses, we found that darbepoetin alfa OFS and OFU use increased immediately after the release of black box warning and NCD, though slight decreasing trends were observed after such interventions took place. It is possible that some of these spurious results were due to the delay in the effect of the interventions that would be discussed in the section below.

Our aggregate time-series technique used a small number of data points to detect changes in the proportion of ESA use at the time point which an intervention started; these time points were specified a priori. As a results, our findings were sensitive to noises, impact of other possible intervention unspecified in our time-series models, and time lags in the change in the utilization patterns. These confounding factors may have created spurious statistical results. Therefore, the following discussion was based on the actual graphical representation of the proportion of visits with ESA use rather the results from the specified time-series models. The

graphical representations of ESA, epoetin alfa, and darbepoetin alfa utilization patterns are shown in Figure 4.12, 4.13, and 4.14, respectively.

The use of epoetin alfa in our sample hospitals increased from 2005 to October 2006, after which drug utilization started to decline. The only exception was found in the OFS use of epoetin alfa that showed a decreasing trend throughout study period. The increase in epoetin alfa use on-label (ONS) and off-label unsupported (OFU) before 2007 was consistent with many studies.[182, 183] Since the time of approval, ESAs had been promoted rigorously by their manufacturers as an alternative to blood transfusion. No safety warning attempts were present before the release of negative clinical trial results that led to a release of public health advisory in November 2006.[28] The results of the clinical trials published in late 2006 later revealed the increased risk of mortality in cancer patients who use ESAs.[19-23]

As a result of these published trials, declining trends in epoetin alfa use were observed even before the release of a black box warning. The decline in the proportion of visits with epoetin alfa use after the release of negative results from the clinical trials and public health advisory in November 2006 was confirmed in a separate time-series analysis (data not shown). In that analysis, we specified the first intervention as the negative results from the clinical trials and public health advisory in November 2006 as the first intervention, instead of a black box warning in March 2007. We found a significant immediate drop of 0.8% in the proportion of visits with on-label epoetin alfa use. This drop was followed by a non-significant decreasing trend in epoetin alfa ONS use after the intervention.

Since declining trends in epoetin alfa use existed even before the institution of a black warning, no significant reduction in utilization was detected at the release of the FDA black box

warning or NCD though non-significant declining slopes were observed. However, a noticeable drop in the proportion of visits which epoetin alfa was used for on-label and off-label was seen in December 2008 (month 48). This sharp decline coincided with the FDA revision of epoetin alfa label in August 2008 (month 44) to strengthen the safety information for healthcare professionals. Changes in the labeling included a statement that ESAs were not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.[212] The FDA later approved the use a Medication Guide and Patient Instruction for Use in place of the old patient package insert in November 2008. The Medication Guide which was created to disclose possible side effects of ESAs were to be distributed to all patients who were dispensed ESAs. This medication guide, alone with physician's judgment, can affect patients' decision to use the drug. At the same time, Amgen and J&J Ortho Biotech, the manufacturers of epoetin alfa and darbepoetin alfa released a Dear Health Care Professional Letter to emphasize the content of the labeling change.[213] In addition to the labeling revision in August 2008, several published clinical trials started reporting negative results of epoetin alfa could have led to a reduction in epoetin alfa use at the end of 2008. One of the largest impacts could have resulted from the German Stroke Study. In September 2008, results from a large German trial investigating effectiveness of ESAs as an aid to improve the ability of patients to care for themselves after their strokes. Results of the trial revealed the increased risk of death in post-stroke patients receiving high dose epoetin alfa. Among 522 post-stroke patients involved in the trial, 16 percent of the patients who received epoetin alfa 40,000 units daily for 3 days died, compared to only 9 percent of patients in the placebo group.[214]

Interestingly, we found a slow rebound in the level of epoetin alfa use one year after the decline. This gradual increase in ESA use was likely to be due to prescribers being comfortable

with ESAs again after a long period of the absence of alerts since there were no published alerts in the FDA website that year. This increase in the epoetin alfa use continued from August 2009 to February 2010, after which we observed a non-statistically significant decline in epoetin alfa on-label and off-label use. This decline coincided with the implementation of REMS in March 2010. Despite it being officially implemented on March 24, 2010, the creation of REMS was announced by the FDA on February 16, 2010 to mitigate the risk of decreased survival in patients with cancer. REMS restricted prescribing of ESAs in cancer patients only to physicians who underwent a manufacturer-created risk management and training program which emphasized the FDA-approved indications and the increased risks of using the drugs off-label. We believe that this decline was a true reduction in inappropriate use of epoetin alfa related to REMS restriction. However, because our ONS, OFS, and OFU cohorts did not consist entirely of cancer patients, but instead a mixture of cancer patients and other conditions which were not directly affected by REMS, the reduction was not sufficient to reach a statistically significant level.

Similar to epoetin alfa, the use of darbepoetin alfa on-label and off-label grew rapidly from 2005 to the beginning of the last quarter of 2006. However, unlike epoetin alfa where an immediate drop was observed after the release of negative results trials and the first public health advisory in November 2006 November 2006, the use of darbepoetin continued to grow, but at a decreasing rate. This slow increase in the use of darbepoetin alfa despite the warning may due to Amgen's illegal promotion of Aranesp® off-label. From 2001 to 2007, Amgen was found guilty of promoting off-label use of darbepoetin alfa by marketing dosing information not approved by the FDA as being an advantage to that of epoetin alfa.[215]

According to the actual use of darbepoetin alfa shown Figure 4.14, the addition of a black box warning onto the label significantly reduced the proportion of visits which darbepoetin alfa was use on-label and off-label. ESA labeling was revised in March 2007 to include a black box warning which highlighted the negative results several completed cancer trials. Though the warning applies to all products in this drug class: darbepoetin alfa, Aranesp®, Amgen, Inc) and epoetin alfa (Epogen® and Procrit®, Amgen), the fact the most of trials were based on the use of darbepoetin alfa and the possibility that physicians were less comfortable with using the newer darbepoetin alfa in cancer patients, a stronger impact of the black box warning on darbepoetin alfa compared to epoetin alfa was observed.

The strongest reduction in darbepoetin alfa use was observed after the change in Medicare reimbursement policy. NCD was announced effective in July 2007 and officially implemented in April 2008 to restrict payment of Medicare to only on-label use of ESAs. With NCD, use of ESAs for unapproved indications to Medicare beneficiaries seen in the outpatient settings were no longer reimbursed under Medicare Part B. Previous studies showed strong impact of NCD on ESA prescribing patterns in both Medicare and non-Medicare patients in the outpatient settings.[187] Strictly speaking, NCD did not financially affect payment of Medicare to ESA use in the hospitals because charges for inpatient drug use were bundled as total hospital charges and were covered under Medicare Part A. Our study was the first to show its significant impact in the inpatient settings which NCD was not directly applied. Such strong impact that was observed in both on-label and off-label ESA utilization merits further investigation. We believe that the coverage change sent out a strong message about inappropriate use of ESAs to prescribers tending all patients in all settings. A decline in use may also due to the fact that

physicians who worked in the hospitals also worked concurrently in the outpatient settings and were familiar with the coverage change.

Lastly we observed a significant reduction in the proportion of visits with darbepoetin alfa on-label and off-label use after the implementation of REMS in March 2010. This was a similar reduction was observed with epoetin alfa use that did not reach a statistically significant level. It was likely to be due to the true effect of REMS.

Specific Aim 3

Binary logistic regression using generalized estimating equations (GEE), clustered by hospitals was used to identify the impacts of safety interventions on the odds of receiving ESA therapy. Studies highlighting changes in prescribing patterns were important to measure the relative impact of various safety communications put in place to promote safe drug use. The use of patient-level information in the logistic regression allowed for the inclusion of demographic, clinical condition, physician and hospital characteristics, all of which had been proposed to influence prescribing patterns. This inclusion adjusted for the confounding effects these covariates may have imposed onto the effect of safety interventions on ESA utilization patterns. The use of GEE model therefore offered superiority to the aggregated time-series technique.

Our results indicated that black box warning had low impact on all three ESA use categories. These findings were consistent with previous literature investigating the impact of black box warning on ESA therapy for CKD and cancer patients in the outpatient settings.[182, 183] Interestingly, we again found strong impact of national coverage determination (NCD) on ESA use, both on-label and off-label, despite the fact that this coverage change did not directly apply to our population. As mentioned earlier, NCD implemented in April 2008 restricted

reimbursement only to on-label use of ESAs for patients covered under Medicare Part B seen the outpatient settings. Our results highlight such strong safety messages sent from payers that could be seen in the care settings not financially affected. Finally, we did not observe any significant impact of REMS in our sample. It is possible that oncologists have adjusted to ESA guidelines after the black box warning and NCD that no change was observed after the implementation of REMS.

Using the same logistic regression models with GEE to assess associations between patient, clinical, hospital, and physician characteristics, we observed apparent differences in patient, clinical, hospital, and physician characteristics between the users and non-users of ESAs for all the three use categories. Characteristics of ESA on-label and off-label supported recipient were found to be similar, but very different from those of the off-label unsupported group.

Among patients with ONS, and OFS conditions, the odds of receiving the drugs increased with age. The relationship was flipped when a patient was in oldest age group; the oldest old patients were less likely to receive ESAs. This age relationship may also be due to the fact that older patients were sicker and naturally needed ESAs more than the younger and healthier patients. However, physicians may become more conscious to prescribe the drug the very patients (85+). Interestingly, such age relationship was not found in the off-label unsupported (OFU) ESA prescribing. We believe that because there was no consensus guidelines on the off-label unsupported prescribing of ESAs, physicians would tend to prescribe the drugs to those patients with very low Hb, regardless of their age. Additionally, we found that gender and racial differences exists in ESA use. Female patients with ONS and OFS conditions were less likely to use the drugs. On the other hand, female patients with OFU conditions were more likely to receive ESAs. The associations of higher odds of female gender and ESA OFU prescribing

shown in our study were uniform with the finding by Patkar et al.[15] It is possible these female patients with OFU conditions in our sample, despite having similar comorbidity scores, were more anemic than their male counterparts. The very low Hb level of these patients could have led physicians to be more inclined to prescribe ESAs. African-American were more likely to receive ESAs for any indications. This finding contradicts many published studies of racial disparities in prescription drug use.[164, 165] Results of our study led us to believe that there were differences in prescribing behaviors between the inpatient and outpatient/office-based settings. In the case of critical care like in the treatment of anemia, patient's socioeconomic status, to a lesser extent, influenced physician's decision to prescribe. This might partially resulted from the fact that, opposite to the outpatient care where patients were fully responsible for paying for their medications, drug use in the hospitals was included as one charge. This mechanism could help mask the price of the drugs from the ordering physicians. Also, the situation where charges were paid off by the hospital as a charity care if patients were not able to pay for the services was not at all uncommon. Lastly, our results indicated that financial resources were a key determinant of ESA prescribing. Compared to Medicare patients, ONS and OFS patients with other type of payment were less likely to use ESAs. The findings were unsurprising as Medicare pledged to pay for the health care of the patients with end-stage renal disease (ESRD) - the conditions which ESAs were approved for use. Moreover, Medicare was the largest payer of ESAs with approximately three billion ESA spending in 2011.[216] However, this relationship was not observed in the OFU group. We believe that this finding reflects in part from Medicare's strict off-label reimbursement policy after 2008. Nonetheless, other results indicated that for all three use categories, self-pay patients were the least likely to use the drugs. This is truly intuitive since listed price of one dose of 10,000 IU of epoetin alfa could cost a patient over $100.[217]

Other predictors of ESA ONS and OFS use were patient clinical conditions and hospital size. The greater severity of illness as measured through combined comorbidity scores, admission type, and discharge status, may have influenced physicians to prescribe ESAs. Finally, consistent with our hypothesis, we found that patients admitted to larger hospitals were more likely that any other patients to receive ESAs. This might due to the fact that larger hospitals, to a greater extent, admitted more severely anemic patients. Physicians working the larger hospitals should have seen more anemic patients and were more familiar with using ESAs compared to those in the smaller hospitals.

Practical Implications

Our results confirm previous research of a strong impact of national coverage determination and moderate impact of black box warning and REMS on ESA prescribing. Despite extensive effort of risk communications, the FDA should be concerned as more than half of ESAs was used for off-label purposes. Our findings indicate that as high as 43% of all ESA use in the hospitals between January 2005 and June 2011 were for off-label unsupported indications. The use of the drug off-label without strong supporting scientific evidence could pose threats to patient's health. Though no causal relationship could be established, it is noteworthy to mention the distinguishably longer length of stay and high inpatient mortality in patients who used the drug for off-label label unsupported indications compared to patients in other groups.

Results of our study highlight the importance of different means of communicating drug risks to the health care community. Off-label drug use can have serious safety implications. The FDA needs to regulate prescribing of high-risk drugs more strictly. Patient characteristics

associated with ESA off-label drug use identified in this study show that physicians were more likely to administer the drugs to the sicker patients. Another area of intervention could be in large hospitals with more than 200 beds where ESAs were prescribed significantly to a greater extent. Efforts from the safety regulatory authority should be emphasized on the sickest population of admitted patients, and in large hospitals to promote appropriate use of ESAs.

This research adds incremental knowledge to ESA off-label prescribing and Cerner hospital database of electronic health records. The Cerner database is a rich source of information on patient characteristics, diagnoses and procedures codes, drug administration, and clinical outcomes new to most researchers. The use of electronic health records in observational study can offer insight into clinical conditions, detailed drug administration, and timing of the treatments unavailable in surveyed, publicly-available, or government-provided database such as National Ambulatory Medical Care Survey (NAMCS) and Medicare Provider and Analysis Review (MedPAR) Files. Additionally, Cerner data has a good mix of teaching and non-teaching hospitals as well as small and large sized hospitals across different geographic regions in the United States.

We developed a novel systematic algorithm to identify two types of off-label drug use from the domain of strength of evidence, level of recommendation, and efficacy provided in a reputable compendium, DRUGDEX. Furthermore, we extensively provide all possible ICD-9-CM diagnoses and procedures codes that could be used to identify on-label, off-label supported, and off-label unsupported use of ESAs from any electronic health records. This knowledge can be useful to any researcher interested in assessing ESA off-label use.

Limitations

Our study offers insights into the impacts safety interventions had on the on-label and off-label use of ESAs, but limitations of the study must be noted. The first limitation was the possibility of other interventions not being captured in our study. Our study design did not allow for the determination of the impacts of any other interventions that may have occurred during the same period as the interventions of interest such as news articles, and publication of large clinical trials. In this study, those external factors were considered as a part of the respective intervention of interest. In addition, we were not able to separate the effect of the updated black box warning in March 2008 from the implementation of NCD in April 2008. Nonetheless, the implementation of NCD is chosen as an intervention instead of the black box warning update because we believed that the reimbursement change would have a greater impact on prescribing pattern than updating the already-exist black box warning.

One of the possible limitations of the study included threats to internal validity relating to any longitudinal study designs that did not include the use of a control group. Instrumental threat refer to the fact that aspects of the record keeping procedures in the database may have changed at the same time as the intervention and thus any changes observed could not be concluded whether they were related to the intervention. [218] Moreover, this study relied heavily on the ICD-9-CM classification system; coding misclassification may lead to false estimations of the effects. However, ICD-9-CM classification has been use in the use in studies identifying off-label prescribing including ESAs.[15] The use of ICD-9-CM classification for various health conditions in hospital data has also been validated. [219-222]

Even though we were able to identify the off-label use of ESAs for indications other than the ones approved by the FDA using ICD-9-CM codes, their doses and use in targeting a hemoglobin level exceeding the suggested level could not be readily determined from the database. This was because the dosing information could only was provided by Cerner with a low level of confidence. Utilizing the dosing information in our case would therefore add errors into the analyses and should be avoided. As a result of this data issue, identification of the ESA off-label usage in terms of dose and target hemoglobin level was not undertaken in this study. This may lead to an underestimation of the off-label usage in our study findings.

Another limitation was that physicians may be more inclined to prescribe ESAs to patients who have had encounters with the medications even though it was for the indication lacking supporting evidence. Since patient medication history in the non-participating outpatient and inpatient hospitals were not captured in our data, it could have posed a potential confounding effect on the off-label ESA use in the analysis. It was also important to note that the physician specialties information included in the GEE models was based specifically to attending physicians and not ordering physicians. For example, a patient with CKD could be admitted by a generalist, developed anemia during his stay, referred to a nephrologist within the same hospital who prescribed him with an ESA. In this specific case, a generalist was recorded under physician specialty and not nephrologist.

Only inpatients of participating Cerner hospitals were included for analyses. Thus, any changes in prescribing trends found in this study may not be generalized to patients in the outpatient setting or patients hospitalized at other hospitals. However, we believe that there is good external validity of our findings. This was a multi-hospital study that included 128 hospitals of various sizes from different geographical regions across the nation. As mentioned

earlier, Cerner database was a rich source of information on patient characteristics, diagnoses and procedures codes, drug records, and clinical outcomes. More importantly, their electric health records accurately captured dates and times of admission, discharge, and drug administration most crucial in this study. Hence, in spite of some limitations of existing database and retrospective analysis, Cerner database served as a very insightful resource in studying impacts of safety interventions on ESA utilization patterns in the inpatients settings.

Last but not least we recognized that there could have been errors created from the way we dealt with outliers in our data. We were certain that spurious data points observed in the third and fourth quarter of 2007, and the last two quarters of our study period in 2011 were due to data recording system that could not be corrected on our end. We used a conservative method of forecasting missing values from the continual trends in utilization if the intervention has not occurred. We were confident that our data manipulation method produced accurate predictions of values that could be used in place of the outliers.

Future Research

Our study methods, database, and results provide basis to future research in off-label drug use. We developed a categorization scheme of ESA off-label use with drug records, and diagnoses, and procedures codes of patients admitted to the Cerner Health System inpatient settings rarely known exists to researchers. We found that while REMS had little to no impact on the on-label and off-label utilization patterns of ESAs in our sample hospitals, black box warning could potentially have affected off-label unsupported use of epoetin alfa, and both off-label supported and unsupported use of darbepoetin alfa. Interestingly, we found that a significant decline in the on-label, off-label supported, and off-label unsupported use of ESAs

after the month Medicare national coverage determination was implemented. This impact of NCD was similar for both epoetin alfa and darbepoetin alfa prescribing patterns.

Despite the exciting findings, this study focused mainly on the impacts of the safety interventions on the likelihood of receiving ESAs, without looking into other aspect of treatment such as ESA doses and days of therapy. Moreover, patient clinical outcomes such as length-of-stay, inpatient mortality, and blood transfusion were beyond the scope of this investigation. Further analysis of such outcomes can provide insight into the impacts of different risk communication tools attempted to reduce inappropriate drug use.

We quantified relatively few ESA users in our Cerner database. There were on average 130 patients who used ESAs per hospital in 2010 who used ESAs. Future study should consider using larger database such as Marketscan® commercially provided by Thompson Reuters. With a larger sample size, future study could focus on individual indications of ESA use instead of a collective on-label, off-label supported, or off-label unsupported use to determine which conditions was the main driver of the change in ESA utilization. Additionally, with sufficient sample size, future study can focus on assessing the impact of REMS on ESA prescribing and utilization among the target cancer population. Finally, pharmaceutical marketing efforts in counteracting the decline in the prescribing of ESAs resulted from these warning messages merit further exploration.

Conclusions

This study was the first to determine the impacts of safety interventions on ESA on-label and off-label utilization patterns in the inpatient settings using Cerner database. In this study we attempted to quantify the impacts of the three types of safety interventions: black box warning, national coverage determination, and risk evaluation and mitigation strategy (REMS) program on ESA prescribing and utilization patterns. Analysis of data collected from 128 hospitals from 2005 to 2011 highlights the decreasing trend in ESA on-label use after the last quarter of 2006, increasing trend in ESA use for unsupported indications, and overall very low and decreasing prevalence of off-label supported use of ESAs (8.6%). From 2005 to 2010, the proportion of visits with ESA ONS and OFS use decreased 53.2% and 81.9%, while ESA OFU increased 112.6%. The trends were similar for both epoetin alfa and darbepoetin alfa. ESAs were used to the greatest extent to treat anemia in patients with chronic kidney disease (41.1%). Almost all of ESA use classified as off-label supported (60.4% OFS) in our sample were for non-chronic kidney disease patients. Lastly, a total of 42.7% of ESA use in our sample was for the unsupported indications. The greatest unsupported use of ESAs was for the treatment of chronic anemia (31.8%).

Differences in the impacts of risk communication techniques were observed in the ESA inpatient prescribing patterns. Black box warning and REMS appeared to have little effect on physician's prescribing patterns compared to Medicare national coverage determination. Despite the intention of reducing inappropriate (off-label unsupported use of ESAs), we found that these three risk communication techniques were as likely to affect appropriate on-label and off-label supported use of the drug rather the potentially inappropriate off-label unsupported use.

Results from binary logistic regression using GEE model showed that REMS had no impact on the odds of receiving ESAs among patients with on-label and off-label conditions. Black box warning reduced the odds of being prescribed with epoetin alfa in patients with off-label unsupported conditions by 40%. It was also associated with 4% and 15% per month reduction in the odds of using darbepoetin alfa in patients with off-label supported and unsupported conditions. Finally, we found a significant decline in the on-label, off-label supported, and off-label unsupported use of ESAs after the month Medicare national coverage determination was implemented. The impact of NCD ranged from 20% reduction in odds of off-label supported use, to 37% in the on-label use. Patient demographic, clinical condition, and hospital and physician characteristics associated with ESA on-label and off-label drug use included age, gender, race, source of payment, admission type, clinical complexity, discharge disposition, and hospital size.

We demonstrated lag time between these interventions and the observed change in clinical practice and also the relative impacts the three types of safety interventions had on the on-label and off-label ESA use in the hospital settings. The indirect impacts of NCD may have unintended consequences of reducing ESA use in patients with indicated conditions that could have otherwise benefited from the drugs. Policymakers should keep in mind of the lag time between the intervention and changes in clinical practice, their relative effectiveness, and potential unintended consequences of these safety interventions.

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Vita

Arpamas Seetasith was born on February 9th, 1983 in Bangkok, Thailand. She graduated from Anglo-Chinese Junior College, Singapore in 2002 and received her Bachelor of Sciences in Pharmacy from Chulalongkorn University, Bangkok, Thailand in 2008.

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Education

August 2008 - February 2013:

Doctor of Philosophy
Virginia Commonwealth University, School of Pharmacy, Richmond, VA
(in the tradition of the Medical College of Virginia)

- Dissertation: "Impacts of Safety Warnings, National Coverage Determination, and Risk Evaluation and Mitigation Strategies on the Inpatient On-label and Off-label use of Erythropoiesis-Stimulation Agents"
    - Quantified impacts of safety interventions on inpatient drug use using time-series technique and logistic regression with generalized estimating equation

May 2003 – March 2008:

Bachelor of Science in Pharmacy (First Class Honors)
Chulalongkorn University, Bangkok, Thailand

January 2001 – December 2002:

Singapore-Cambridge General Certificate of Education Advanced Level
Anglo-Chinese Junior College, Singapore

Work/Research Experience

May 2012 – August 2012:

Healthcare Consulting Intern
IHS Global Insight, Washington DC

- Assisted various international pricing, reimbursement, and market access consulting projects.
    - Gathered pricing information; reviewed clinical guidelines, market landscapes, and Health Technology Assessment (HTA) documents; and produced deliverables for clients
- Demonstrated "Values of Pharmaceutical Interventions in Mexico" through the development of a cost-effectiveness analysis.

    - Led the team on conceptual planning, model inputs gathering, and data manipulating
- Initiated "Disease Prevention Micro-simulation Model" to forecast disease burden
    - Preliminarily explored and analyzed NHANES data using regression techniques

August 2009 – May 2012:

Teaching Assistant
School of Pharmacy, Virginia Commonwealth University

- Delivered lectures on health insurance, managed care, and pharmacy benefit management to Class of 2014-2015 pharmacy students
- Supervised pharmacy lab counseling and case presentations

May 2008 - August 2008:

Research Assistant
Pharmaceutical System Research & Intelligence Center (PSyRIC), Thailand

- Assisted the development of educational drug information website for patients and healthcare providers: yaandyou.net

January 2007 - December 2007:

Pharmaceutics Research Principle Investigator
Chulalongkorn University, Thailand

- Senior Project: "Formulation of Andrographolide Oral Fast-Dissolving Strips"

November 2003 - March 2008:

English Tutor
Wayama Tuition Center, Bangkok, Thailand

- Tutored English to students in grades 5-11 and to 12th grade students for preparation to take the national entrance examination (classes of 10-15 students)

Publications & Presentation

Inocencio TJ. **Seetasith A**, Newland A, Bose P, Holdford DA. International Society for Pharmacoeconomics and Outcome Research 17th Annual International Research Meeting, Washington DC, June 4-6, 2012

- Poster Presentation: Cost-effective Analysis of Nilotinib compared to Imatinib for Newly Diagnosed Chronic Myeloid Leukemia (CLM) in Chronic Phase

Zhang JX, **Seetasith A**, Szymanski KA. AcademyHealth Annual Research Meeting, Seattle, WA, June 12-13, 2011

- Poster Presentation: Insurance Mix and Quality of Care in Elderly Medicare Beneficiaries with Diabetes: What are the Opportunities and Challenges for Improvement?

Seetasith A, Zhang JX. International Society for Pharmacoeconomics and Outcome Research 4th Asia-Pacific Conference, Phuket, Thailand, September 6-7, 2010

- Poster Presentation: A Difference-in-Differences Analysis of the Offsetting Effect of Statins on Non-Pharmacy Medical Resource Utilization among Patients with Diabetes in the US.

Zhang JX, **Seetasith A**. International Health Economics Association 6th World Congress, Beijing, China, July 12-15, 2009

- Podium Presentation: Insurance Status, Out-of-Pocket Payment, and Drug Utilization in patients with Diabetes in the US.

Seetasith A, Zhang JX. AcademyHealth Annual Research Meeting, Chicago, IL, June 28-30, 2009

- Poster Presentation: Racial Disparities and Out-of-Pocket Payment in Drug Utilization in Patients with Diabetes in the United States.
- Developed a manuscript for publication in a peer-review journals (work-in-progress)

Seetasith A, Zhang JX. International Society for Pharmacoeconomics and Outcomes Research 14th Annual International Meeting, Orlando, FL, May 16-20, 2009

- Podium Presentation: Racial Disparities and Barriers to Drug Utilization in Patients with Diabetes in the United States.

Professional Honors

August 2012 – December 2012:

Dissertation Assistantship Award Recipient
Graduate School, Virginia Commonwealth University

May 2011:

Annual Student Research Competition Champion
International Society for Pharmacoeconomics and Outcomes Research, 16th Annual International Meeting, Baltimore, Maryland

September 2010:

Best Student Research Poster Award Finalist
International Society for Pharmacoeconomics and Outcome Research, 4th Asia-Pacific Conference, Phuket, Thailand

August 2008 - May 2009:

Pharmaceutical Economics and Policy (PEP) Program Graduate Fellowship Recipient
School of Pharmacy, Virginia Commonwealth University

June 2009:

AcademyHealth Disparities Interest Group Emerging Scholar Award Recipient
The Robert Wood Johnson Foundation, AcademyHealth Annual Research Meeting, Chicago, Illinois

May 2009:

Best Student Research Podium Presentation Award Recipient
International Society for Pharmacoeconomics and Outcomes Research, 14th Annual International Meeting, Orlando, Florida

Pharmacy Profession Training

January 2008 – February 2008:

Cosmetic R&D and Regulatory Affairs trainee
Beiersdorf (Thailand) Co., Ltd., Samutprakarn, Thailand

- Prepared product claim documents for FDA approval submission

April 2007 – May 2007:

Production, R&D, and Quality Assurance trainee
Greater Pharma Manufacturing Co., Ltd., Nakhon Pathom, Thailand

- Collaborated with industrial pharmacists and scientists in formulation development, production, and quality control of drug products

March 2007 – April 2007:

Clinical Pharmacist trainee
Phetchaboon Hospital, Phetchaboon, Thailand

- Assisted clinical pharmacists on their rounds, counseling, dispensing, and in-house drug product compounding

2004 – 2006:

Community Pharmacist trainee
Huay Kwang Community Health Center, Osot Sala at Chulalongkorn University, Keew Makok Drug Store, and Drug Mart, Bangkok, Thailand

- Help community pharmacists in diagnosing and drug dispensing
- Learned about independent pharmacies' business models and strategies

Leadership

October 2005 – September 2006:

Vice President
Pharmacy Volunteer Club, Chulalongkorn University, Bangkok, Thailand

January 2002 – December 2002:

Funding Director
Interact Club, Anglo-Chinese Junior College, Singapore

Professional Organization

Member since 2008:

The Pharmacy Council of Thailand
International Society for Pharmacoeconomics and Outcome Research (ISPOR)

Research Knowledge & Skill

International pharmaceutical P&R and policy analysis

- Experienced in international regulatory and pricing and reimbursement process including HTA reviews in US, UK, EU5, and BRIC-MT
- Well-versed in clinical guidelines and landscape assessment of various disease areas including mental health, neurology, oncology, and cardiovascular disease
- Familiarized with advocacy strategic planning and primer development

Pharmacoepidemiology

- Expert in the analysis of prevalence using ICD-9-CM codes, cost estimations, drug utilization, and quality of care
- Skilled in Medicare Physician Fee Schedules and Facility Fees calculation

Pharmacoeconomics

- Proficient in MS Excel-based Markov and semi-Markov modeling of cost-effectiveness analysis

Databases

- Competent user of claims data, electronic medical records datasets, and large and nationally representative databases including Medical Expenditure Panel Survey (MEPS), Medicare Current Beneficiaries Survey (MCBS), Medicare claims data, National Ambulatory Medical Care Survey (NAMCS, NHAMCS), National Health and Nutrition Examination Survey (NHANES), Cerner Health Solution's ERM

Statistical Software

- Experienced user of SAS, Stata, JMP, SPSS, and Microsoft Office Excel

Statistical Methods

- Knowledgeable in various statistical modeling such as linear regression, logistic regression, generalized linear model, difference-in-differences analysis

Systematic Literature Review

- Trained in targeted literature search and network meta-analysis

Others

- Familiarized with healthcare micro-simulation modeling
- Strong commanding in deliverable development and professional conference presentation skills

Languages

Fluent in English and Thai