Utilization patterns and economic impact of IV iron and Erythropoiesis Stimulating Agents in Chronic Kidney Disease patients: A multi-hospital study

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Utilization patterns and economic impact of IV iron and Erythropoiesis Stimulating Agents in Chronic Kidney Disease patients: A multi-hospital study

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

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Dedication

This dissertation is dedicated to my family. Mom and Dad, your constant support and encouragement is the sole reason for my success.

Surbhi, there is no situation in my life in which a conversation with you will not provide comfort.

Parth, I still remember the incredible feeling of holding you as a baby. Now I know why you are my most favorite person in the whole wide world.
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Abstract

**Background:** Chronic kidney disease (CKD) affects approximately 20 million Americans and is the cause of significant morbidity and mortality. Anemia, common in CKD, develops early in the disease process. It contributes to increased risk of cardiovascular disease, hospitalization, mortality, and diminishes health-related quality of life. Intravenous iron and Erythropoiesis Stimulating Agents (ESAs) are recommended for anemia management in CKD. The utilization patterns of IV iron and ESA, and their impact on hospital costs and length of stay merits investigation.

**Objectives:** There were five general objectives of this investigation. The rate and extent of utilization of IV iron in anemic CKD patients was quantified across teaching hospitals in the US. Patient characteristics of those receiving IV iron and ESA and ESA alone were evaluated in detail. Predictors of IV iron and ESA use were determined. The impact of IV iron and ESA use was examined separately for total hospital costs and length of stay (LOS) while adjusting for confounding.

**Methods:** This is a retrospective cohort analysis within the University Health System Consortium data warehouse. Eligible patients are those who were admitted to a hospital and received either IV iron and ESA or both at least once during the period of January 1, 2006, and December 31, 2008. Inclusion criteria include age > 18 years old with a primary or secondary diagnosis of CKD. The exposure of interest was IV iron and ESA therapy, and the outcome was the difference in total hospital costs and length of stay between patients only on ESA, and those on ESA and IV iron. A clustered binomial logistic regression using the GEE methodology was
used to identify predictors of IV iron utilization. Propensity scores were used to control for confounding. A generalized estimating equations (GEE) model using a gamma distribution and log link was used to determine the adjusted hospital cost and length of stay for the IV iron and ESA and ESA alone therapy groups.

**Results:** During the study period, 82,947 patients met all the inclusion and exclusion criteria. Of the 82,947 CKD patients on ESA therapy, only 8% (n = 6678) patients were on IV iron supplementation. Age, race, primary payer, admission status, severity of illness, dialysis status and physician specialty were identified as strong predictors of IV iron use in CKD patients. According to the multivariate model, the overall mean hospital cost for all 82,947 patients was $31,674. For patients using both IV iron and ESA (n=6678), mean costs were $34,756 compared to $31,404 for ESA users alone (n=76,269) – a difference of $3,352. The overall mean LOS for all patients was 9.75 days. For those using IV iron, the LOS was 10.71 days, and for those only using ESA, the LOS was 9.66 days– a difference of approximately 1 day.

**Conclusions:** This inquiry is the first large multi-center investigation to quantify the impact of IV iron and ESA use on total hospital costs and LOS. Our investigation showed significant reduction in ESA doses with the use of IV iron supplementation, however, the overall prevalence of IV iron usage was low. Intravenous iron users were associated with a higher total hospital cost and longer length of stay than ESA users.
CHAPTER 1

Introduction

Overview of the document
This dissertation describes a study designed to quantify the rate and extent of IV iron and ESA utilization in anemic CKD patients and quantify the differences in LOS and total hospital costs resulting from the utilization of IV iron and ESA and ESA therapy-alone. This chapter provides background information necessary to understand the significance of the project. The second chapter systematically reviews the available literature and provides more extensive background on previous investigations, economic issues and confounding factors. Chapter 3 describes the methodology used for the dissertation project. The results are provided in Chapter 4, followed by a discussion and concluding remarks in Chapter 5.
Background

Chronic kidney disease (CKD) is a worldwide public health issue. In the United States, CKD affects approximately 20 million Americans and is the cause of significant morbidity and mortality in 1 in 9 adults. According to a recent US Renal Data System Annual Data Report, the percent growth in Medicare patients was greatest in CKD (128%) and end stage renal disease (ESRD) (83%) when compared with diabetes mellitus (54%) and chronic heart failure (21%).

The national initiative, Healthy People 2010, identified CKD as one of the areas to focus on in an effort to reduce the number of patients reaching ESRD, and decrease health care costs within Medicare. The prevalence of earlier stages of CKD is approximately 100 times greater than the prevalence of kidney failure, affecting almost 11% of adults in the United States.

Patients with CKD often have 5 to 6 other conditions which require extensive therapeutic treatment. Common comorbidities include anemia, diabetes mellitus, hypertension and coronary artery disease. Anemia, common in CKD, develops early in the disease process and contributes to a poor quality of life in this population. The PAERI (Prevalence of Anemia in Early Renal Insufficiency) study reported an overall anemia prevalence of 47%, increasing from 26.7% in patients with Stage 1 CKD to 75.5% in those with Stage 5 CKD who are not on dialysis.

Anemia of CKD results from underproduction of endogenous erythropoietin by the kidneys. In patients with CKD not requiring dialysis, untreated anemia increases cardiovascular risk, hospitalization, and all-cause mortality, impaired cognitive function, and diminishes health-related quality of life and exercise capacity. Heightened risk for progression of kidney failure has also been linked to untreated anemia of CKD. Thus, management of anemia throughout the CKD continuum is essential.
The recombinant human erythropoietin, epoetin alfa (EPO), introduced in 1989, was the first erythropoiesis-stimulating agent (ESA) available for the treatment of anemia in the United States. The availability of ESAs substantially reduced the need for transfusions and became the first line of therapy for anemia of CKD.\textsuperscript{19} Epoetin alfa, which must be injected 2 to 3 times per week to achieve efficacy, remained the only exogenous ESA for more than a decade. Although ESAs can be beneficial in treating patients with anemia of CKD, they have inherent risks. Randomized trials in patients undergoing dialysis have found higher rates of cardiovascular complications with higher (13-15 g/dl) versus lower (10-11.5 g/dl) Hb targets.\textsuperscript{20-22} Increased risk of adverse events, such as cardiovascular complications,\textsuperscript{23,24} hypertension\textsuperscript{25} and pure red cell aplasia,\textsuperscript{26} have been reported with the use of ESAs. The U.S. Food and Drug Administration (FDA) recently amended the labeling of all epoetin and darbepoetin products by adding a boxed warning instructing prescribers to use the lowest dose of ESAs that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion.\textsuperscript{27} Also, the FDA recently stated that all ESAs prescribed must be a part of the Risk Evaluation and Mitigation Strategies (REMS) program to ensure the safe use of these drugs.\textsuperscript{28} Hence, minimizing the dose of ESAs may be beneficial for patients. Besides the clinical issues, there are several economic challenges associated with the use of ESAs. The approximate annual cost of EPO is estimated to be about $5,000.\textsuperscript{29} ESAs are considered specialty pharmaceuticals and usually have the highest co-pay allocation (Tier 4). They may require prior authorization and may have quantity limits in place. Medicare Part B covers ESAs for eligible patients but only when doses are administered in the physician’s office or clinic. Patients who self-administer ESA are not covered by Medicare Part B.
Iron deficiency occurs in most patients during therapy with ESAs because of the increase in erythropoiesis and subsequent increase in iron demand. Iron is the core raw material for the production of red blood cells (RBCs). Without iron, hemoglobin can be neither synthesized nor can RBCs be reproduced or maintained in the circulation at an adequate level. Optimal red cell production requires both erythropoietin as the controlling factor and iron as the raw material. Deficiency can occur in all patients, even those with initially adequate stores of iron because the rate of iron supply cannot meet the demands of accelerated erythropoiesis. Iron supplementation should therefore be considered for all patients, and iron status should be closely monitored. According to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines, it is suggested that supplemental iron be administered intravenously in hemodialysis dependent CKD patients. Non-dialysis-dependent CKD patients and peritoneal dialysis dependent CKD patients may receive iron orally or intravenously. Ongoing administration of parenteral iron preserves levels of hemoglobin and reduces the requirement for administration of erythropoietin. Given the relative costs of iron and erythropoietin, an appropriate use of iron can have substantial cost savings. Moreover, considering the adverse event profile of erythropoietin, reduction in its dose and ongoing administration of parenteral iron can help improve survival rate and quality of life for CKD patients.

The current literature suggests the need to further evaluate the medication utilization patterns of IV iron in anemic CKD patients, and understand its impact on hospital resource use and total hospital costs. There is currently no evidence in the literature comparing the long term utilization of IV iron and ESA, and their economic impact on hospital costs and LOS. A careful analysis of utilization patterns and economic impact of the recommended treatment options for anemic CKD patients is necessary in determining the optimal care that could be provided to the
patient. The cost and resource use of providing such care should be considered in order to either validate or cause the health care provider to reconsider a selected pharmacological treatment. This investigation looks to quantify the rate and extent of IV iron and ESA utilization in anemic CKD patients and quantify the differences in LOS and total hospital costs resulting from the utilization of IV iron and ESA and ESA therapy-alone.

An economic analysis of drug and resource use requires further explanation in order to ensure correct interpretation. For example, the terms costs and charges must be clearly defined and their difference be explicitly stated. These terms may have been used interchangeably, but this is incorrect. Costs and charges reflect different economic values. Specifically, charges always over-inflate cost. For the purposes of this report, great care has been given to use the terms costs and charges appropriately. Previous investigations have used costs or charges as outcomes depending on study design and data availability. The economic background section provides a more thorough discussion of costs versus charges.

A pharmacoepidemiologic investigation attempting to describe the relationship between an exposure and outcomes must consider potential confounders. Confounding factors are variables that are associated with the outcome as well as the exposure, and are not variables in the causal pathway. If confounding exists, an association may appear to be present when one does not exist or there may seem to be no association when a true association does exist. Therefore, it is crucial to identify confounders and control for them. In most situations confounders are identified a priori based on previous investigations or expert opinion. Several variables have been acknowledged as potential confounders in the relationship between drug use and total costs in anemia in chronic kidney disease. Specifically, patient demographics (age, race, sex), underlying severity of illness, dialysis status, drug insurance coverage type, physician
specialty, mortality and comorbid conditions, have been identified.\textsuperscript{7,11,38-43} Hospital level factors (e.g. bed size, geographic location) can also confound the relationship between drug utilization and total cost.

Propensity scores are another way to control for confounding. Observational studies employ this method to eliminate bias from an unequal distribution of confounders thereby mimicking the purpose of randomization in a randomized, controlled clinical trial. Propensity scores are the probability of exposure given measured baseline variables.\textsuperscript{44} This probability can then be used as a matching or stratification factor, as a covariate in a multivariable model or to perform inverse probability of exposure weighting.\textsuperscript{45}

Long term IV iron usage and resultant hospital costs and outcomes remain untested. There has been a single previous investigation attempting to report the trends in IV iron use among US Medicare dialysis patients.\textsuperscript{46} The study reported an increase in the use of IV iron in ESRD patients from 1997 to 2002. Ferric gluconate and iron sucrose were reported as the predominant form of therapy in this population. Racial and geographical variability were observed in overall IV iron usage in the United States.\textsuperscript{46} From an economic perspective, Pizzi et al demonstrated that the administration of IV iron in conjunction with ESA is more cost-effective as compared to ESA therapy alone in anemic dialysis patients.\textsuperscript{47} Clinical inputs for this study were obtained from the DRIVE I \textsuperscript{48} and DRIVE II \textsuperscript{49} studies, and cost inputs were estimated based on published sources of Medicare reimbursement rates for dialysis services. Use of IV iron represented a net-savings of $1390 per g/100 ml increase in Hb over a 12 week period.\textsuperscript{47} Two single center investigations evaluated the potential economic benefit of IV iron in hemodialysis patients. Sepandj et al. projected an annual cost reduction of $3016 Canadian dollars in chronic dialysis patients (n = 50).\textsuperscript{50} Bhandari et al. evaluated the economic benefit of IV iron in 22
hemodialysis patients. Use of IV iron led to reduced requirements of ESA, and hence resulted in cost-savings of £21/week.\textsuperscript{51}

**Objectives**

The current investigation has four primary objectives which are listed below.

1. Quantify the utilization of IV iron in chronic kidney disease patients across teaching hospitals in the US
2. Determine the prevalence of concomitant IV iron administration when Erythropoiesis Stimulating Agents (ESA) therapy is initiated
3. Determine predictors of IV iron use among the domains of patient characteristics, clinical conditions, physician characteristics, hospital characteristics and treatment characteristics.
4. Determine the impact of IV iron and ESA use versus ESA use alone on length of stay (LOS) while adjusting for confounders
5. Determine the impact of IV iron and ESA use versus ESA use alone on total hospital costs while adjusting for confounders

**Significance and practical implications**

A large national database of academic medical centers will be used to ascertain the medication utilization patterns in anemic CKD patients. Knowledge of their anemia medication use patterns may highlight practices that are at odds with current recommendations and identify opportunities to improve care. Identification of anemia treatment patterns in national academic centers may also assist evidence-based policy making by understanding the variations in physician prescriptions for CKD and reason for such variation.
The scientific community and healthcare professionals have acknowledged the importance of understanding the utilization of IV iron supplementation and its impact on healthcare costs and outcomes in hospitalized patients. Understanding the financial implications associated with IV iron use will equip hospitals and healthcare professionals to make informed decisions to better manage anemia in CKD patients.

The proposed investigation will be the first to study anemia management in CKD patients and its impact on total hospital costs and LOS, using data from multiple academic hospitals. A couple of single center reports have been published studying utilization of IV iron and its impact on costs. These investigations agree that use of IV iron along with ESA have near optimal outcomes in anemic patients with chronic kidney disease and lead to lower costs. Several randomized clinical trials have established the safety and efficacy of IV iron in anemic CKD patients. However, long term usage of IV iron remains untested by randomized trials. A single previous investigation report the trends of IV iron use among US Medicare dialysis patients. This study did not evaluate the economic impact of IV iron utilization. From an economic perspective, Pizzi et al demonstrated through a literature based decision-analytic model that the administration of IV iron in conjunction with ESA is more cost-effective as compared to ESA-alone therapy in anemic dialysis patients. Clinical inputs for this study were obtained from the DRIVE studies, hence results of this study may not be generalizable to clinical practice.

A large multi-center investigation may help to quantify the economic impact of IV iron utilization in anemic chronic kidney disease patients. Interesting utilization patterns of IV iron and ESA therapies in multiple hospitals across the nation will provide a relatively clear picture of the medication profile and resulting economic impact in anemic CKD patients. The proposed
investigation should have greater external validity than previous studies. Data from forty teaching hospitals will be considered making it a large multi-center investigation. A multi-center investigation will provide a larger sample size than previous single center reports.
CHAPTER 2

Literature review

This chapter has been divided into five parts: 1) an overview of anemia in CKD, 2) pharmacological treatment associated with anemia of CKD, 3) economic background from a hospital costs perspective, 4) confounding factors and methods to control for confounding, and 5) a systematic review of existing studies. This chapter will be concluded with a summary and the research hypotheses formulated as a result of the literature evaluation.

CKD anemia overview

*Chronic Kidney Disease*

Chronic kidney damage is defined as structural abnormalities of the kidney that can lead to decreased kidney function. The level of glomerular filtration rate (GFR) is accepted as the best measure of overall kidney function in health and disease.

The NKF-KDOQI work group has defined CKD as:

1. Kidney damage for 3 or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR) manifest by either
   a. Pathological abnormalities; or
   b. Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR \(< 60 \text{ ml/min/1.73m}^2\) for \(\geq 3\) months, with or without kidney damage.
Until 2002, a common staging system for CKD did not exist and numerous terms were used to describe it. In 2002, the NKF-KDOQI developed a staging system (Table 1). CKD is now defined according to the presence or absence of kidney damage and level of kidney function—regardless of the patient’s underlying diagnosis. KDOQI designates 5 stages, with stage 5 being End Stage Renal Disease (ESRD), when loss of kidney function precipitates a need for dialysis or kidney transplant. Patients in stages 1 and 2 may have robust, normal, or slightly lowered GFR with evidence of underlying kidney damage, including proteinuria; large or small kidneys on an ultrasound; or other evidence of compromised function. All people with GFR < 60 ml/min/1.73m$^2$ for more than 3 months are classified as having CKD. This classification represents a loss of 50% or more of the adult level of normal kidney function.\textsuperscript{6} Additionally, all people with kidney damage are classified as having CKD regardless of their GFR.\textsuperscript{6}

Table 2.1: Classification of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild decrease in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure (dialysis or replacement needed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>End Stage Renal Disease (ESRD)</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>
CKD is usually silent until its later stages, and without aggressive screening, detection may not occur until immediately before symptomatic kidney failure develops. At this point in the disease process, few opportunities exist to prevent adverse outcomes, such as further decline in kidney function necessitating dialysis, cardiovascular complications, shortened life span, and poor quality of life.

Patients at higher risk for CKD include patients with diabetes, hypertension, or a family history of hypertension, diabetes or CKD itself. CKD appears more often in minority ethnic groups; African American, Native American, Hispanic, Asian and Pacific Islander populations are at higher risk of developing CKD than are white Americans. In these populations, diabetes and hypertension, which are predominant causes of ESRD, are more common and tend to be familial. Patients who have a family history of those disorders or CKD are also at risk for developing CKD.

Anemia in CKD

Anemia is the clinical manifestation of a decrease in circulating red blood cell mass and usually is detected by low blood hemoglobin (Hb) concentration. The normal physiological response to a reduction in RBCs is to increase the secretion of endogenous erythropoietin from the kidneys. Secreted erythropoietin binds to surface receptors on red blood cell precursors in bone marrow to enhance differentiation and proliferation and the body responses by increasing the amount of hemoglobin (Hb). Therefore, due to a decline in the number of RBCs within the blood, patients that are diagnosed with anemia due to CKD have an impaired ability to maintain optimal levels of hemoglobin due to the disease’s effect on the kidneys.
The numerous causes of anemia include blood loss, shortened red cell life span, vitamin deficiencies, erythropoietin deficiency, iron deficiency and inflammation. In most CKD patients, anemia develops due to less erythropoietin production by the impaired kidneys. Moreover, the dialysis patients are in a state of continuous iron loss from gastrointestinal bleeding, blood drawing, and the dialysis treatment itself. Hemodialysis patients lose an average of 2 g of iron per year. Thus iron deficiency will develop in virtually all dialysis patients receiving erythropoietin unless supplemental iron therapy is given orally or intravenously.

Practice guidelines
The National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI) documented clinical practice guidelines for anemia of CKD. The 2006 NKF-KDOQI clinical practice guidelines suggest that a CKD patient’s hemoglobin (Hb) be checked annually regardless of the cause or state of their CKD. If a patient’s Hb is < 13.5 g/dl in males and < 12 g/dl in females, a diagnosis of anemia should be made and further evaluation is needed. Once diagnosed with anemia of CKD, the target range for Hb is between 11 g/dl and 12 g/dl, and should not go beyond 13 g/dl. Once a patient is prescribed an ESA, their Hb should be monitored monthly. The guidelines recommend providing iron supplementation in order to maintain adequate iron indices i.e. transferring saturation (TSAT) and serum ferritin levels. It is recommended that the patient’s iron levels be evaluated by determining their TSAT and serum ferritin levels. It is also suggested that the patient’s levels of TSAT and serum ferritin are monitored when ESA therapy is initiated, while increasing the dose, and when the patient is receiving iron supplementation. To achieve and maintain the target Hb level of 11g/dl, IV iron
is strongly recommended to be administered on a regular basis to most hemodialysis patients.© Iron supplementation can be oral or IV in non-dialysis and peritoneal dialysis patients.

**Pharmacological treatment of anemia associated with CKD**

*ESAs*

Erythropoietin (EPO) is produced within the kidneys in response to a decrease in tissue oxygenation and regulates the production of red blood cells.© The lack of EPO is a major cause of anemia for CKD patients.© Two ESAs, recombinant epoetin alfa and darbepoetin alfa, are available within the United States to treat anemic CKD patients. Improved quality of life and symptomatic relief of anemia (fatigue, reduced exercise capacity, decreased cognition) with the use of ESA has been documented in clinical studies.© In addition to improving quality of life, ESAs are shown to significantly reduce the need for transfusions in patients with CKD who were receiving hemodialysis.© In a two year historical cohort study of patients undergoing maintenance dialysis and had targeted Hb levels of 11 to 12 g/dl, those who received ESA therapy lived longer than those who did not. Among those receiving an ESA, a higher dose was associated with lower survival.©

ESAs can be beneficial in treating patients with anemia of CKD, but they have inherent risks. Two randomized controlled trials in patients with stage 3 and stage 4 CKD, Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) © and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), © suggest that targeting higher than recommended Hb levels with ESAs poses a safety risk leading to cardiovascular complications.

The CREATE study was designed to investigate the effect of early anemia correction on cardiovascular risk in 600 predialysis patients.© The primary objective of the study was to
determine the effect of complete versus partial correction of anemia on cardiovascular risk reduction; the effect of this treatment strategy on the left ventricular mass index and the progression of kidney disease were secondary end points. Patients with moderate anemia (Hb 11.0-12.5 g/dL) were randomized to receive either early or late treatment with epoetin beta. For the management of early treatment patients, a target Hb of 13.0 to 15.0 g/dL was used; for late-treatment patients, 10.5 to 11.5 g/dL. By the end of the 48-month study, 127 patients assigned to the early-treatment group (Hb, 13.0-15.0 g/dL) had progressed to dialysis versus 111 patients assigned to the late-treatment group (Hb, 10.5-11.5 g/dL) (p=0.03). The study also found a higher risk of cardiovascular events in the early-treatment group (58 events with early treatment versus 47 with late treatment), but the difference was not statistically significant. Quality of life was the only end point that was significantly better in the high-target treatment arm.

The CHOIR study, an open-label, prospective, randomized trial, evaluated the effect of correcting Hb to a target of 13.5 g/dL (n=715) or a target of 11.3 g/dL (n=717) in patients with CKD who were not yet receiving dialysis. The primary end point of the study was a composite of death, myocardial infarction, congestive heart failure, hospitalization, and stroke. A total of 125 end-point events occurred in the high-Hb group (target Hb, 13.5 g/dL) versus 97 events in the low-Hb group (p=0.03) before the early termination of the trial. Quality of life was also measured during the study; however, no significant differences were observed between the groups with any of the measures used.

Increased risk of other adverse events has been reported with the use of ESAs. Evidence suggests that the presence of clinically evident cardiac disease (congestive heart failure or ischemic heart disease) in ESA-treated patients increased their risk of mortality and of nonfatal myocardial infarctions, vascular access thromboses, and other thrombotic events when epoetin
alfa was dosed to a target hematocrit of 42%.\textsuperscript{21, 65, 66} Consequently, extreme caution should be used when exceeding the recommended Hb levels in patients with established heart disease.

In March 2007, the Food and Drug Administration (FDA) issued a “black box” warning for ESAs based on its evaluation of the CHOIR and CREATE studies, as well as on the results of trials in patients with cancer whose outcomes were worse when treated with ESAs to higher Hb levels.\textsuperscript{27} The FDA warning advised physicians as follows: (1) use the lowest dose of ESA possible to gradually raise the Hb concentration and avoid the need for transfusion; (2) monitor Hb levels twice a week for 2 to 6 weeks after any dosage adjustment to ensure that Hb levels do not exceed 12 g/dL; and (3) withhold the dose of ESA if the Hb level exceeds 12 g/dL or increases by 1 g/dL in any 2-week period.

Hypertension associated with the use of ESAs is considered a major adverse effect of therapy. In clinical trials, the onset of treatment-related hypertension occurred in the first 90 days of therapy, was more common in patients receiving hemodialysis, and was associated with a more rapid increase in hematocrit.\textsuperscript{65, 66} In rare cases, hypertensive encephalopathy and seizures have occurred. Pure red cell aplasia, a serious but very rare complication of ESA use, has been reported,\textsuperscript{26} primarily with subcutaneous administration.

Of further concern are the recent announcements by the FDA about stating that all ESAs prescribed must be part of REMS to ensure the safe use of these drugs.\textsuperscript{28} More specifically, the FDA stated the program should provide patients with material and guidance to understand the risks associated with the use of ESAs. REMS inform healthcare professionals and patients about the risks associated with a medication. For medications with significant safety concerns, such as ESAs, REMS involve increased surveillance and/or performance/safety assessment programs. Healthcare professionals prescribing ESAs for anemia in patients without cancer are required to
provide a copy of a medication guide to each patient or their representative when an ESA is dispensed.28

Besides the clinical issues, there are several economic challenges associated with the use of ESAs. Reimbursement policies for the coverage of ESAs vary by patient type and insurance coverage. Most patients with CKD who require dialysis receive Medicare, which covers ESA therapy. Medicare Part B covers ESAs for eligible patients but only when doses are administered in the physician’s office or clinic, making it difficult for patients who choose to self-administer to receive coverage. Patients who are not undergoing dialysis and those who are not eligible for Medicare may use private insurance for ESA coverage. Erythropoiesis-stimulating agents are considered specialty items and usually have the highest copay allocation (Tier 4), may require prior authorization, and may have quantity limits in place.

Iron supplementation

Iron supplementation in CKD-related anemia can be administered either orally or intravenously (IV). Based on the 2005 U.S. Renal Data System Annual Report, approximately 70% of hemodialysis patients in the United States receive parenteral iron.67 Although oral iron is less expensive and easier to administer, IV iron enables the administration of larger doses of iron and may be better tolerated by patients.68 The main adverse reactions to oral iron are gastrointestinal, such as nausea, abdominal pain and bloating, darkening of the stools, constipation, diarrhea and vomiting. Such gastrointestinal side effects may limit adherence and dose.69 To overcome these problems, intravenous iron preparations, such as iron dextran, sodium ferric gluconate and iron sucrose, have been used for iron replacement. Meta-analysis of studies evaluating the use of IV iron compared to oral or no iron show that in general IV iron therapy seems to be no more
efticacious than oral or no iron in increasing Hb or Hct within 2 months from the start of the
treatment. However, when nondextran iron (i.e. iron sucrose and sodium ferric gluconate) is
considered, IV iron was found to be more efficacious than oral or no iron in increasing short term
Hb or Hct levels. Results also showed that IV iron caused more drug intolerance, but it is still not
clear if it causes more serious adverse events compared to oral iron. Another meta-analysis of
randomized clinical trials assessing IV iron versus oral iron supplementation shows that in
hemodialysis patients IV iron was more efficacious in improving Hb levels as compared with
oral iron regardless of ESA use and type of IV iron preparation used. In non-dialysis anemic
CKD patients, the overall benefit of IV iron compared to oral iron was of a small magnitude and
its clinical significance was not clear. Furthermore, ESA dose was significantly decreased by the
use of IV iron compared with oral iron.

Iron dextran has been associated with several adverse events, anaphylactoid reactions
being most common. Hypersensitivity reactions that are considered serious and life-
threatening along with the occurrence of delayed reactions such as arthralgia, myalgia, fever and
malaise have been associated with the use of IV iron dextran. Relative to low molecular
weight dextran, total and life-threatening adverse drug reactions were significantly more frequent
among recipients of high molecular weight iron dextran and significantly less frequent among
recipients of sodium ferric gluconate and iron sucrose. Sodium ferric gluconate and iron
sucrose have a much lower rate of serious adverse events. Iron sucrose and sodium ferric
gluconate have been proven to be safe for use in ‘iron-dextran sensitive’ population. Iron
may also have other important toxic effects. Excessive use of iron could theoretically increase
the risk of sepsis and infection-related mortality, worsen atherogenesis, and increase the
risk of cardiovascular disease events.
Several randomized clinical trials have established the safety and efficacy of IV iron preparations in anemic CKD patients. The Dialysis Patients Response to IV Iron with Elevated Ferritin (DRIVE) study demonstrated the efficacy of intravenous ferric gluconate to improve hemoglobin levels in anemic hemodialysis patients who were receiving adequate epoetin doses and who had high serum ferritin and low transferrin saturation. IV iron resulted in a greater increase Hb levels in the IV iron group (1.6 ± 1.3 g/dl vs 1.1 ± 1.4 g/dl, p = 0.028) than in the control group. Hemoglobin response occurred faster (p = 0.035) and more patients responded after IV iron than in the control group (p = 0.041). As a follow up, DRIVE-II study reported a 6 week observational extension designed to investigate how ferric gluconate impacted epoetin dosage after DRIVE. The study concluded that patients in the IV iron group required significantly less epoetin dose than their DRIVE dose (mean change of -7527 ± 18,021 IU/wk, p = 0.003). Over the entire study period (DRIVE and DRIVE-II), the control group experienced significantly more serious adverse events than the IV iron group (incidence ratio = 1.73, p = 0.041). Nissenson et al. showed in their multi-center, randomized clinical study that hemodialysis patients with serum ferritin below 100 ng/ml or transferring saturations below 18% need supplementation with IV iron in excess of 1 gm to achieve optimal response in hemoglobin and hematocrit levels, and confirm the National Kidney Foundation Dialysis Outcomes Quality Initiative (NFK-DOQI) guidelines regarding IV iron supplementation. A randomized, controlled, parallel-group trial comparing iron sucrose and sodium ferric gluconate found both drugs to be equally effective in maintaining hemoglobin levels, and equally well tolerated in a stable ESA treated hemodialysis population.
Economic background

Admission to a hospital is a frequent event among chronic kidney disease patients, occurring in almost 50% of ESRD patients each year, compared with 22% in the general Medicare population. Hospitalization accounts for a large fraction of the cost of care in the CKD population, followed by dialysis and non-dialysis physician and supplier costs. Understanding the terminology of costs, charges and reimbursements from a hospital’s perspective are important. From a hospital’s perspective, costs refer to the price a hospital pays for the resources it consumes. This is different than a charge, which is simply a list price. Charges will always be higher than the actual hospital costs, hence patients who can pay will cover the losses from those who cannot afford to pay.

Charges are known to inflate the economic burden of hospitalization, hence cost-to-charge ratios are used to better approximate actual cost from charges. For each patient discharge at a teaching hospital, a charge for the various service categories is reported to the University HealthSystem Consortium (UHC) database. Two corrections are applied to each of these service category charges. The first correction is to multiply the service category charge by the ratio of cost to charge (RCC). This factor is derived for each cost center for each hospital, on the basis of annual reports to Health Care Financing Administration, by dividing the total costs by the total charges for each cost center. The RCCs vary from hospital to hospital and are also analyzed to estimate percentiles for trimming the data to eliminate outliers. The second correction is that UHC applies a labor adjustment to take into account differences in geographic wage indices. After these two corrections are made, the resultant cost values for each patient discharge are entered into the database. The use of the RCC has shown a correlation with internal accounting costs at a level above 0.90. While this method does not report absolute costs, the
calculation provides data that have internal consistency within each institution, and that makes it possible to compare the costs of one disease with those of another, as well as to compare the costs for the same disease (DRG) at different institutions. The accuracy of the derived costs is to a large extent governed by the accuracy of the data submitted by each institution.

In the United States, the government is the major payer of hospital services through Medicare and Medicaid. In 1982, Medicare adopted a prospective payment system (PPS) for hospital reimbursement to control costs by capping the allowable reimbursement. The PPS works by dividing admissions into diagnosis-related group (DRG) categories. A DRG is computed by taking into consideration the affected organ system, up to nine ICD-9-CM diagnosis codes, up to 6 ICD-9-CM procedure codes and morbidity and gender. Hospitals are then reimbursed a fixed rate depending on the DRG. Each DRG has an associated DRG weight that reflects the average level of resources a Medicare patient in a particular DRG will utilize. The DRG weight can range from greater than 0 to less than 20. An average hospital stay would have a DRG weight of 1. Conditions with greater costs are assigned a higher DRG weight. Hospitals are then reimbursed a fixed rate depending on the relative weight of the DRG. Besides this, reimbursements are also adjusted for geographic differences in wage, hospital teaching status, proportion of low income individuals a hospital treats and cost outliers.

**Confounding factors**

Assessing economic impact of drug utilization can be complicated by variations in population demographics, the heterogeneity of physician prescribing habits, variations in institutional drug use formulary controls across different hospital settings, and the clinical condition of the patient. There is empirical evidence in the literature suggesting stage of kidney disease, white race, female gender, older age (>74 years), referral to a nephrologist, presence of cardiovascular
disease, diabetes, dyspnea, psychiatric disorders, gastrointestinal bleeding in previous year and patient laboratory measures (Hb, serum ferritin, TSAT levels) to be important predictors of ESA and IV iron use in anemic CKD patients. 7, 38, 39 This study will examine five main domains for predicting IV iron utilization, consisting of patient characteristics, clinical conditions, physician characteristics, hospital characteristics and treatment characteristics.

Any epidemiologic investigation attempting to describe the relationship between exposure and outcome must consider potential confounders. 88 Confounding factors are variables that are associated with the outcome as well as the exposure, and they pose a serious threat to the accurate interpretation of study results. 89 To explain the phenomenon of confounding, it is necessary to consider the relationship between an exposure and the occurrence of a disease state (refer Figure 1). In order for a variable to be a potential confounder, it needs to have the following three properties: 1) the variable must have an association with the disease, that is, it should be a risk factor for the disease; 2) it must be associated with the exposure, that is, it must be unequally distributed between the exposed and unexposed groups; and 3) it must not be an effect of the exposure, nor be a factor in the causal pathway of the disease. 89 In the presence of confounders, an association may appear to be present when one does not exist or there may seem to be no association when a true association does exist. 89 Confounders should be identified from the base population, not the study sample, preferably a priori based on previous investigations or expert opinion. 36, 37 Since almost all investigations examine a small subset of a larger population, it is possible that a confounding effect within the population may not be present within the sample. Known confounders should be included regardless of their “statistical significance” in the sample.
Once confounders are identified they must be controlled. They can be controlled through restriction, matching, randomization in the design phase, and stratification and multivariate analysis in the analytic phase. Random allocation of exposure should equalize the distribution of all potential confounders, even unknown ones, across different levels of drug exposure. Randomization is aimed at making the two groups perfectly similar apart from the independent intervention variable under assessment as exposure. However, this method is appropriate only in prospective, experimental study designs and the retrospective nature of database analyses does not allow the use for this technique. Retrospective database investigations more commonly use matching and restriction. Matching is a way to control for confounding where two compared groups are made “similar” with regard to the distribution of selected known extraneous factors. In practice, matching maybe difficult, especially when there are several factors to match for. In case-control studies matching may also lead to “overmatching”. Restriction limits scope of design to only one level of confounding factor (e.g. age category 18-24 years), which is the simplest way of dealing with confounding, but may limit the generalizability of the investigation.
Stratification or multivariate analysis/modeling can be used to control for confounding at the analysis phase. Stratification quantifies the relationship between exposure and outcome as a pooled estimate with respect to the confounder. It is performed in two stages: the first stage requires computation of a stratum-specific rate ratio for each level of the stratifying (confounding) variable. The second stage involves pooling the results into a single estimate that represents the overall effect of the exposure, adjusted for the effect of the confounding factor.

Multivariate modeling helps determine the relationship between risk factors and outcomes, allowing assessment of many factors simultaneously.

Several variables have been acknowledged as potential confounders in the relationship between drug use and total costs in anemia in chronic kidney disease. Specifically, patient demographics (age, race, sex), underlying severity of illness, dialysis status, drug insurance coverage type, physician specialty, mortality and comorbid conditions, have been identified. Differences in mortality are especially important in drug utilization and cost studies since patients who die during their hospitalization have truncated costs and curbed utilization. The risk of death due to comorbid conditions has been estimated using the Stoke Cormobidity Grade (SCG), the Khan index, the Davies index, and the Charlson comorbidity index. DRG categories have been used as a surrogate for underlying severity of illness.

There is currently no well-validated severity of illness score for CKD. Other investigations have used a variety of techniques including the Stoke Cormobidity Grade (SCG), the Khan index, the Davies index and the Charlson comorbidity index. Unlike other indices, the Davies index does not include age, because it was specifically designed to be used in conjunction with age as an independent covariate. Other comorbidity indices that are in use in studies on ESRD patients assign different weights to different comorbidities, such as the Khan or
the Charlson index, with the weights based on the impact of comorbid diseases on survival.\textsuperscript{96} However, the impact of comorbid diseases on survival may be rather different from their impact on health status and resource use.\textsuperscript{96} The All Patient Refined Diagnosis Related Groups (APR-DRG) classification system is used to adjust for severity of underlying illness.\textsuperscript{97} The APR-DRG system is an enhancement of the DRG structure and is considered a good predictor of hospital costs and resource use.\textsuperscript{98, 99}

Hospital level factors can also confound the relationship between drug utilization and total cost. As previously mentioned, DRG payments are calculated by adjusting for hospital specific factors. Hospital bed size, geographical region of the hospital are also confounders to be considered. These factors are confounders since they directly impact hospital costs and drug utilization can vary depending on anemia management policy of different hospitals.

\textbf{Previous investigations}

\textit{Economic burden of CKD}

Several economic studies have been conducted to examine the resource use and costs associated with CKD. Robbins et al. conducted a retrospective claims analysis of a nationwide managed care medical and pharmacy database from 1998 to 2001.\textsuperscript{100} The main outcome measures were total healthcare charges, primary diagnoses and diagnosis-related groups (DRGs). The per-patient-per-month charges were $4,265 in the pre-dialysis period, $35,292 in the dialysis period, and $15,399 in the post-dialysis period.\textsuperscript{100} The most common primary diagnosis categories during all time periods were chronic renal failure and congestive heart failure. Hence CKD patients generated significant charges to the health plan both before and after dialysis. Submitted charges were used in this analysis, and not allowed charges, which may result into overstating
the actual financial burden for the managed care plan. Claims for medications were measured; however, this study did not assess the impact of medications on patient outcomes such as mortality, hospitalizations or hospital length of stay.

Another retrospective study evaluated medical and pharmacy claims for 1,936 incident dialysis patients from 22 states in the 12-month period preceding initiation of dialysis. Of these, 48.7% did not have any interventions associated with optimal care for CKD. Only a minority of patients received prescription iron preparations (6.8%), ESA therapy (10.5%), yet more than 40% were diagnosed with anemia. Of the ESA users, 72.4% were also receiving other interventions (such as vascular access placement) to appropriately manage anemia of CKD. Estimated mean charges per patient over the study period of $26,204, $9,623, and $1,505 for facility services, professional services and outpatient pharmacy respectively were reported. Estimated charges reported in this analysis were calculated from a Medicare-based fee schedule.

St. Peter et al. conducted a retrospective cohort study of 1995 through 1998 incident dialysis patients to study the distribution of costs during the 24 months prior to initiation of dialysis. Patient data were obtained from Centers for Medicare and Medicaid Services (CMS). Costs sharply increased in the last six months prior to initiation of dialysis. Hospitalization was the major component of cost throughout the study period. Patients who initiated hemodialysis incurred a higher cost compared to patients who initiated other modes of kidney replacement therapy. Increased comorbidity burden, such as presence of diabetes and cardiovascular disease was associated with higher cost. The inclusion criteria limited entry to patients aged ≥ 67 years, hence limiting generalizability of the results mainly to the Medicare population with CKD.
The studies discussed so far mainly focused on the increasing economic burden of CKD and suggested that a focus on timely management of CKD may prevent future morbidity and resultant resource use and costs. The following section discusses studies examining the economic burden of anemia in CKD.

Economic burden of Anemia

The presence of anemia may be a significant contributor to health-related costs among patients with CKD. Wish et al. conducted a retrospective claims database analysis to examine the association of anemia and anemia management with healthcare expenditure and utilization in CKD patients before onset of dialysis.\textsuperscript{102} Of the 37,105 CKD patients, 9,807 (26\%) had anemia; 59\% of these received some form of anemia treatment, with 48\% receiving ESA therapy. The total adjusted per patient per month healthcare expenditure for all CKD patients was estimated to be $2,749.\textsuperscript{102} Patients with anemia had significantly higher overall expenditure, which was 52\% higher than those without anemia ($4,076 vs. $2,664; P < 0.0001). Total expenditure was 17\% higher for untreated versus treated anemic patients, largely due to higher inpatient expenditure in the untreated cohort ($4,470 vs. $3,806; P < 0.0001).\textsuperscript{102}

Two other studies examined the economic burden of anemia in selected disease states.\textsuperscript{29,40} Ershler et al. conducted a cross-sectional comparison of direct and indirect costs between anemic and non-anemic populations in six chronic disease conditions (rheumatoid arthritis, inflammatory bowel disease, cancer, chronic kidney disease, chronic obstructive pulmonary disease, and chronic heart failure) in the time period of 1991 to 2001. The CKD population had the highest prevalence of anemia, and the CKD anemic patients incurred the greatest average annual direct costs ($78,209).\textsuperscript{40} After adjusting for baseline characteristics including severity, the
difference in direct costs between anemic and non-anemic patients for the CKD group was $20,529.\textsuperscript{40} Nissenson et al estimated an average annualized healthcare payment per patient difference as $28,757 between anemic and non-anemic patients in the CKD population ($41,292 versus $12,535; \( P <0.0001 \)).\textsuperscript{29} Overall, medical costs for anemic patients were twice as much for non-anemic patients with the same comorbid conditions.\textsuperscript{29, 40}

*Utilization of IV iron and ESA*

The goal of anemia management in patients on hemodialysis is to use a low ESA dose in conjunction with IV iron therapy to achieve and maintain appropriate Hb levels. Taylor et al. showed that the regular IV iron supplementation in hemodialysis patients improved the response to ESA therapy in terms of serum ferritin and Hb levels.\textsuperscript{103} This was a single center study studying 46 hemodialysis patients receiving ESA therapy. At the end of the 6-month study period, the patients receiving IV iron supplementation showed significant increments in Hb and serum ferritin levels, and significant reductions in epoetin dose.\textsuperscript{103} The DRIVE-II study reported a 6-week observational extension designed to investigate how ferric gluconate impacted epoetin dosage after DRIVE.\textsuperscript{49} By the end of the observation, patients in the ferric gluconate group required significantly less epoetin than their DRIVE dose (mean change of -7527 ± 18,021 IU/week, \( P = 0.003 \)), whereas the epoetin dose essentially did not change for patients in the control group (mean change 649 ± 19,987 IU/week, \( P = 0.809 \)). A prospective multi-centre clinical trial in iron-replete hemodialysis patients found a regular 50 mg weekly dosing schedule of IV iron sucrose to maintain stable iron stores and Hb levels, and allowed considerable dose reductions of ESA therapy.\textsuperscript{104}
The proposed investigation will be the first to study anemia management in CKD patients and its impact on total hospital costs and LOS, using data from multiple academic hospitals. A couple of single center reports have been published studying utilization of IV iron and its impact on costs.\textsuperscript{50, 51} These investigations agree that use of IV iron along with ESA have near optimal outcomes in anemic patients with chronic kidney disease and lead to lower costs. Sepandj et al. conducted a prospective study with economic analysis comparing use of IV iron and oral iron in a group of 50 hemodialysis patients on epoetin therapy. More than half of the patients were unable to maintain adequate iron stores and experienced severe gastrointestinal intolerance in the oral supplementation group. Use of IV iron led to an annual cost reduction of $3,016 Canadian dollars in chronic dialysis patients (n = 50).\textsuperscript{50} The study concluded IV iron regimen is a safe, effective and economically favorable means of iron supplementation in a subset of hemodialysis patients in whom oral iron supplementation has failed. Bhandari et al. evaluated the economic benefit of IV iron in a prospective non-blinded study of 22 hemodialysis patients. Patients were established on subcutaneous epoetin and given IV iron over seven consecutive dialysis sessions and supplemental monthly doses with regular monitoring for four months. Use of IV iron led to reduced requirements of ESA (4000 units/week vs 2000 units/week; $P = 0.03$), and hence resulted in cost-savings of £21/week.\textsuperscript{51}

There is a dearth of research done studying the utilization of IV iron in anemic CKD patients. A single previous investigation reported the trends in IV iron use among US Medicare dialysis patients.\textsuperscript{46} The study reported a consistent increase in the use of IV iron in ESRD patients from 1997 to 2002 across all age, sex, race, and primary ESRD diagnosis categories. Ferric gluconate and iron sucrose were reported as the predominant form of therapy in this population. Intravenous iron therapy was used in a much smaller percentage of peritoneal
dialysis patients compared to hemodialysis patients, and racial and geographical variability were observed in overall IV iron usage in the United States. However, the study did not evaluate the economic impact of IV iron utilization.

There have been several studies investigating the utilization of ESAs in CKD patients and its impact on healthcare utilization and costs. Powe et al conducted a longitudinal, matched cohort study using Medicare claims data to examine the effects of ESA therapy on hospital admission, readmissions, length of stay (LOS) and hospital costs. Dialysis patients who received ESA were matched with controls on age, sex, race, cause of ESRD and dialysis modality. The results suggested that anemic dialysis patients treated with ESA during the study period had a slightly increased (8%) probability of being admitted to the hospital. However, among those patients admitted, treatment with ESA appeared to decrease the number of readmissions, resulting in a net decrease in overall hospital admissions (176 vs 138 admissions per 1000 patients, P = 0.029). The study also suggested that treatment with ESA decreased both the number of days that dialysis patients spent in the hospital (2911 vs 1602 days per 1000 patients, P = 0.0001) and the cost to hospitals ($2695 vs $2324 per 1000 patients, P = 0.03) for the care of these patients. Maddux et al conducted a retrospective claims analysis using a large U.S. health plan database to compare clinical outcomes, healthcare utilization, and costs of care in anemic patients with CKD not on dialysis receiving or not receiving ESAs. ESA recipients had lower total monthly healthcare costs than did untreated anemic patients ($3876 vs $4758; p = 0.0061). Lower monthly inpatient and emergency department costs in treated versus untreated anemic patients ($2507 vs 3849 and $46.56 vs $81, respectively; both p < 0.0001) outweighed higher outpatient and laboratory costs from ESA use ($602 vs $397 and $23.50 vs $14.34, respectively; both p < 0.0001) multivariate analyses revealed that ESA users had lower adjusted
monthly total costs ($2962 vs $3373) compared with non-ESA patients. ESA use was associated with mean total cost savings of $411 per patient per month, reflecting reduced inpatient and emergency department visits and costs. Moyneur et al. quantified the economic impact of pre-dialysis epoetin on healthcare and work loss costs in CKD, with a focus on employer’s perspective.\textsuperscript{106} Using employer claims data from January 1998 to January 2005, direct and indirect costs were compared between CKD-anemic patients treated with ESA before dialysis and those not treated with an ESA. Anemic CKD patients treated with ESA before dialysis had significantly lower direct and indirect costs compared to non-ESA treated patients. Incremental direct and indirect cost savings for ESA treated patients were $1443 and $328 per member per month (PMPM) (p < 0.0001), respectively compared to non-ESA treated patients with anemia. After multivariate adjustment, direct and indirect costs remained significantly lower by $852 and $308 PMPM (p < 0.001), respectively for the ESA-treated group.\textsuperscript{106}

From an economic perspective, Pizzi et al demonstrated that the administration of IV iron in conjunction with ESA is more cost-effective as compared to ESA therapy alone in anemic dialysis patients.\textsuperscript{47} A cost-effectiveness model was developed, consistent with the DRIVE studies, using decision analysis with a 12-week time horizon. The primary effectiveness measure was the mean hemoglobin increase in the intent to treat patient groups comparing ESA with or without sodium ferric gluconate. Costs were computed using projected 2007 US Medicare reimbursements for the treatments and for serious adverse events, with effectiveness factored by the increase in hemoglobin. Use of IV iron represented a net-savings of $1,390 per g/100 ml increase in Hb over a 12 week period.\textsuperscript{47}
In summary, there has been no investigation looking at long term utilization of IV iron and ESA in anemic CKD patients, and evaluating the resultant economic impact on hospital LOS and costs. CKD of anemia has a high economic burden in terms of resource use and costs. Several single center investigations have suggested economic benefit with the use of IV iron supplementation in hemodialysis patients on ESA therapy. Use of IV iron along with ESA has been shown to be a cost-effective option as compared to using ESA alone. Also, it is established that use of ESA therapy is associated with better outcomes, shorter LOS and lower hospital costs. The recent NKF-KDOQI guidelines recommend the use of iron supplementation in all anemic CKD patients on ESA therapy. To achieve and maintain the target hemoglobin (Hb) level of 11g/dl, IV iron is strongly recommended to be administered on a regular basis to most hemodialysis patients. Iron supplementation can be oral or IV in non-dialysis and peritoneal dialysis patients.

Clinical trials have established the safety and efficacy of IV iron supplementation in anemic CKD patients already on ESA therapy. However, long term utilization of IV iron remains untested by clinical trials. A large multi-center investigation may help to quantify the economic impact of IV iron utilization in anemic chronic kidney disease patients. Interesting utilization patterns of IV iron and ESA therapies in multiple hospitals across the nation will provide a relatively clear picture of the medication profile and resulting economic impact in anemic CKD patients. The proposed investigation should have greater external validity than previous studies. Data from forty teaching hospitals will be considered making it a large multi-center investigation. A multi-center investigation will provide a larger sample size than previous single center reports.
Statement of research hypotheses

As a result of the review of the CKD literature and information regarding utilization of IV iron and ESA, the following hypotheses were postulated and tested in this inquiry.

Research question 1:

Utilization and days of therapy for IV iron and ESA therapy

H0-1a: There is no significant change in the utilization of IV iron and ESA over time.

H0-1b: There are no significant difference in the utilization of IV iron and ESA, compared to ESA-therapy alone over time.

Research question 2:

Predictors of IV iron and ESA use

Patient characteristics

H0-2a: There exists no significant association between patient age and IV iron and ESA use relative to ESA use alone.

H0-2b: There exists no significant association between patient race and IV iron and ESA use relative to ESA use alone.

H0-2c: There exists no significant association between patient gender and IV iron and ESA use relative to ESA use alone.

H0-2d: There exists no significant association between patients’ length of hospital stay and IV iron and ESA use relative to ESA use alone.

H0-2e: There exists no significant association between patients’ source of payment and IV iron and ESA use relative to ESA use alone.

Patient clinical condition

H0-3a: There exists no significant association between patients’ admission status and IV iron and ESA use relative to ESA use alone.
H$_{0.3b}$: There exists no significant association between patient severity of illness and IV iron and ESA use relative to ESA use alone.

H$_{0.3c}$: There exists no significant association between patient dialysis status and IV iron and ESA use relative to ESA use alone.

H$_{0.3d}$: There exists no significant association between patient discharge status and IV iron and ESA use relative to ESA use alone.

**Physician characteristics**

H$_{0.4}$: There exists no significant association between physician specialty and IV iron and ESA use relative to ESA use alone.

**Hospital characteristics**

H$_{0.5a}$: There exists no significant association between total hospital costs and IV iron and ESA use relative to ESA use alone.

**Research question 3:**

**Impact of IV iron use on hospital LOS**

H$_{0.6}$: Given other things constant, patients with anemia of CKD on ESA therapy alone incur greater LOS compared to patients on IV iron +ESA therapy.

**Research question 4:**

**Impact of IV iron use on total hospital costs**

H$_{0.7}$: Given other things constant, patients with anemia of CKD on ESA therapy alone incur greater total hospital costs compared to patients on IV iron +ESA therapy.
CHAPTER 3

Methodology

Data

The data for this research comes from University HealthSystem Consortium (UHC) hospital database. The UHC is a member-driven alliance of approximately 90% of the nonprofit academic medical centers in the United States. Table 3.1 describes organizational characteristics such as bed size and geographical region of the teaching hospitals within the UHC database. The hospitals in the UHC database were compared with the latest American Hospital Association (AHA) statistics to assess their national representation. The AHA is the national organization that represents and serves all types of hospitals, health care networks, patients and communities. It contains information on more than 5,000 hospitals, health care systems and other providers of care and over 37,000 individual members. According to the National Center for Health Statistics, the AHA is considered a national standard for comparing U.S. hospitals and their characteristics. In comparison with the national statistics, small bed-sized hospitals were under-represented in the database. The database contained more hospitals from the north-east and south-east region than the national average. Overall, the sample from the UHC database appeared to be an adequate national representation of hospitals listed in the AHA database.
Table 3.1: Representation of hospitals in the UHC database

<table>
<thead>
<tr>
<th>Variables</th>
<th>UHC data (%)</th>
<th>National AHA Statistic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bed size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-199</td>
<td>0.05</td>
<td>74</td>
</tr>
<tr>
<td>200-299</td>
<td>3.47</td>
<td>11.21</td>
</tr>
<tr>
<td>300-399</td>
<td>14.02</td>
<td>6.40</td>
</tr>
<tr>
<td>400-499</td>
<td>10.39</td>
<td>3.26</td>
</tr>
<tr>
<td>500 or more</td>
<td>72.07</td>
<td>5.06</td>
</tr>
<tr>
<td><strong>Geographical region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>22.57</td>
<td>13.98</td>
</tr>
<tr>
<td>Southeast</td>
<td>22.08</td>
<td>15.33</td>
</tr>
<tr>
<td>Southwest</td>
<td>13.52</td>
<td>29.58</td>
</tr>
<tr>
<td>Midwest</td>
<td>23.75</td>
<td>22.91</td>
</tr>
<tr>
<td>West</td>
<td>18.08</td>
<td>18.20</td>
</tr>
</tbody>
</table>

For this study, UHC’s Clinical Resource Manager (CRM) Data Base was used. This electronic repository combines administrative, clinical, and financial data from participating UHC member institutions. Data are gathered from hospital discharge summaries and Uniform Billing-92 data. Patient records contain detailed information on inpatient care, and this includes: primary and secondary diagnoses (in *International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] format), inpatient procedure codes (in ICD-9-CM format), patient demographic information (age, race, gender, primary and secondary insurer), and hospital demographic information (bed size and geographical location). The database also contains admission and discharge dates as well as information on comorbidities, severity of illness, physician specialty, length of stay (LOS), costs, and clinical outcomes such as inpatient mortality and complications rates. Cost estimates of inpatient care are available for every discharge, and this information can be aggregated on multiple levels, including diagnosis-related groups (DRGs). For each hospital, the total costs have been broken down by component sources. The UHC database provides information on both the median and mean costs for any component service.
**Study population**

The data warehouse was electronically queried for patients with *Chronic Kidney Disease* using ICD-9-CM codes. Eligible patients were those who were admitted to a UHC hospital with primary or secondary diagnoses of CKD and received either IV iron or ESA or both at least once during the period of January 1, 2006, and December 31, 2008.

**Inclusion and exclusion criteria**

Patients eligible for inclusion had to be at least 18 years of age with primary or secondary diagnosis of CKD. The patients in the treatment cohort were required to have received ESA or IV iron treatment during the study’s time period. Patients with evidence of cancer diagnosis, chemotherapy or radiotherapy, blood transfusion, severe gastrointestinal bleeding, HIV/AIDS, during the observation period were excluded to avoid including patients receiving ESA or IV iron for reasons other than anemia of CKD. Diagnoses and procedure codes used for inclusion and exclusion are described in Tables 3.2 and 3.3.
Table 3.2: Diagnoses codes (ICD-9-CM) and Procedure codes used to identify Chronic Kidney Disease patients

<table>
<thead>
<tr>
<th>Diagnoses Codes</th>
<th>Description</th>
<th>ICD-9-CM Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal failure</td>
<td>585.1-585.6, 585.9</td>
<td></td>
</tr>
<tr>
<td>Renal failure, unspecified</td>
<td>586</td>
<td></td>
</tr>
<tr>
<td>Renal sclerosis, unspecified</td>
<td>587</td>
<td></td>
</tr>
<tr>
<td>Hypertensive renal disease</td>
<td>403.00-403.9</td>
<td></td>
</tr>
<tr>
<td>Hypertensive heart and renal disease</td>
<td>404.00-404.9</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>581.0-581.9</td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>582.0-582.9</td>
<td></td>
</tr>
<tr>
<td>Nephritis (NOS as acute or chronic)</td>
<td>583.0-583.9</td>
<td></td>
</tr>
<tr>
<td>Chronic pyelonephritis (without lesion of renal medullary necrosis)</td>
<td>590.00</td>
<td></td>
</tr>
<tr>
<td>Chronic pyelonephritis (with lesion of renal medullary necrosis)</td>
<td>590.01</td>
<td></td>
</tr>
<tr>
<td>Renal Dialysis status</td>
<td>V45.1</td>
<td></td>
</tr>
<tr>
<td>Fitting or adjustment to dialysis catheter</td>
<td>V56.1-V56.2</td>
<td></td>
</tr>
<tr>
<td>Adequacy testing for hemodialysis or peritoneal dialysis</td>
<td>V56.3, V56.31, V56.32</td>
<td></td>
</tr>
<tr>
<td>Encounter for dialysis and dialysis catheter care</td>
<td>V56.0, V56.8</td>
<td></td>
</tr>
<tr>
<td>Anemia of Chronic Kidney disease</td>
<td>285.21</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure codes</th>
<th>Description</th>
<th>ICD-9-CM Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis</td>
<td>39.95</td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>54.98</td>
<td></td>
</tr>
</tbody>
</table>


Table 3.3: Diagnoses codes (ICD-9-CM) and Procedure codes used in exclusion criteria

<table>
<thead>
<tr>
<th>Diagnoses Codes</th>
<th>Description</th>
<th>ICD-9-CM Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms</td>
<td></td>
<td>140.00-239.00</td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td></td>
<td>V58.2</td>
</tr>
<tr>
<td>Kidney/other organ transplant</td>
<td></td>
<td>996.8, E878.0, V42</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td></td>
<td>569.3, 578.9, 626, 627</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td></td>
<td>042, V08, 795.71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure codes</th>
<th>Description</th>
<th>ICD-9-CM Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
<td>00.10, 99.85, 99.25, 92.28, 99.28</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
<td>14.26, 92.41, 92.25, 92.21, 92.22, 0.18, 14.27, 92.26</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td></td>
<td>99.03, 38.92, 38.94, 99.02</td>
</tr>
<tr>
<td>Kidney/organ transplant</td>
<td></td>
<td>00.91-00.93</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td></td>
<td>44.43, 44.44</td>
</tr>
</tbody>
</table>

Study Design

This was a retrospective cohort analysis of patients within the University Health System Consortium database. The exposure of interest was IV iron and ESA therapy, and the outcome was the difference in total hospital costs and length of stay between patients only on ESA, and those on ESA and IV iron. Only incident users of IV iron and ESA were included in the study.
**Data Collection**

The UHC data warehouse was electronically queried for CKD patients who have received at least one dose of IV iron and ESA (epoetin or darbepoetin) or both, using the UHC Generic Drug codes. Data elements important from a hospital perspective were collected. This includes: age, insurer, gender, race, admission source, primary and secondary diagnosis, additional ICD-9 codes (e.g. underlying medical condition), physician specialty, discharge severity of illness codes, total LOS, dates of admission and discharge, DRG weight, procedure codes, hospital bed size, geographical region, dose, frequency and type of IV iron and ESA prescribed.

The subject information was received in four main SAS datasets from UHC. The master dataset was built by integrating the information using the selection criteria shown in Figure 3.1 below. The first dataset contained information on 210,296 patient records from UHC hospitals who received either ESA or IV iron at least once during the 30 month study period from January 2006 to December 2008. This dataset also contained primary diagnoses codes, primary procedure codes, primary and secondary payer codes, admission and discharge dates, admission and discharge status, severity of illness and risk of mortality codes, ICU days, LOS and total hospital costs for each patient record. There was complete information on hospital location by state and hospital bed size for hospitals. The second dataset contained complete secondary diagnoses information for 210,296 patients. The third dataset contained information on comorbidities for 206,680 patients. The fourth dataset contained complete information on the number of units and charges for each drug administered for 94,668 patients. The information from these four datasets was merged to create the master dataset. The patient files that contained the primary and secondary diagnoses codes were matched from both the first and second datasets and only those patient files containing both primary and secondary diagnoses codes of CKD were included in
the master dataset. On merging patient information from the two datasets, duplicate patient identifiers were identified. Only those patient records with unique patient identifiers (N=84,447) were retained in the master dataset.

After creating the master dataset, a few variables had missing values (refer Table 3.4). Considering the small proportion of missing values, for the categorical independent variables, a separate category of ‘Unknown/Other’ was created for all the missing values. Patients with missing values for hospital costs were dropped from further analyses.

Figure 3.1: Data integration steps to determine subject selection

**Dataset 1**
In-patients using IV or ESA with primary diagnoses, procedures, admission and discharge codes, SOI, LOS, total hospital costs, hospital information listed (N = 210,296)

**Dataset 2**
In-patients using IV or ESA with secondary diagnoses listed (N = 210,296)

**Dataset 3**
In-patients using IV or ESA with information on comorbidities (N = 206,680)

**Dataset 4**
Information on drug use, charges, units and date of charge (N = 94,668)

**Master Dataset**
In-patients using IV iron or ESA with complete information on outcome and independent variables (N = 84,447)
Table 3.4: Variables with missing values

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Variable name</th>
<th>Missing values (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admission Status</td>
<td>811 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>Physician specialty</td>
<td>3984 (4.5%)</td>
</tr>
<tr>
<td></td>
<td>Bed size</td>
<td>112 (0.12%)</td>
</tr>
<tr>
<td></td>
<td>Geographical region (hospital)</td>
<td>903 (1.03%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome variables</th>
<th>Variable name</th>
<th>Missing values (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total hospital costs</td>
<td>1118 (1.28%)</td>
</tr>
</tbody>
</table>

**Outcomes**

There were two outcomes of interest in this analysis. First, the total hospital length of stay and ICU length of stay were evaluated in number of days. Second, total costs in US dollars were assessed. Costs were adjusted for inflation using the 2008 Consumer Price Index for hospitals.\textsuperscript{110} When comparing economic values over multiple years, it is crucial to adjust for the time value of money. The consumer price index (CPI) measures the average change in inflation over time of goods and services. The reference index for the CPI is set at 100 which represents the average price level for the 36 month period between 1982 and 1984.\textsuperscript{111} The reported annual CPI reports changes relative to the reference index. For example, an index of 135 means a 35\% increase in price since the reference period. Similarly, an index less than 100 reflects a decrease in price. Movements of the index from one date to another can be expressed as the difference between index levels, usually expressed as percent changes. The CPI allows for comparisons of consumer costs over time. Table 3.5 shows the CPI of medical care services that pertain to hospital and related services.
Table 3.5: Consumer Price Indices (CPI) for Hospital and Related Services

<table>
<thead>
<tr>
<th>Year</th>
<th>CPI for Hospital and Related Services</th>
<th>Percent change from previous year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>468.1</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>498.9</td>
<td>6.58</td>
</tr>
<tr>
<td>2008</td>
<td>534.0</td>
<td>7.04</td>
</tr>
</tbody>
</table>

**Independent variables**

The independent variables in the study were patient characteristics (age, race, gender, source of payment), 2) patient clinical conditions (admission status, severity of illness, discharge status, dialysis status), 3) physician characteristics (physician specialty), 4) hospital characteristics (bed size, geographical region). These variables have been selected based on a review of literature and their availability in the final dataset for this study. A description of independent variables for this study can be found in Table 3.6.
Table 3.6: Independent variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Variable name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT CHARACTERISTICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>18-30 years = 3, 31-50 years = 2, 51-64 years = 1, &gt;=65 years = 0</td>
<td>Age_group</td>
</tr>
<tr>
<td>Race</td>
<td>White = 3, Hispanic = 2, Black = 1, Other = 0</td>
<td>Race</td>
</tr>
<tr>
<td>Gender</td>
<td>Male = 0, Female = 1</td>
<td>Sex</td>
</tr>
<tr>
<td>Source of payment</td>
<td>Medicare = 3, Medicaid = 2, Commercial/Private payer = 1, Self-pay = 3, Other = 0</td>
<td>Primary_payer</td>
</tr>
<tr>
<td><strong>Clinical conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission status</td>
<td>Elective = 2, Emergency = 1, Urgent = 3, Other = 0</td>
<td>Admission</td>
</tr>
<tr>
<td>Severity of illness</td>
<td>Extreme = 0, Major = 1, Moderate = 2</td>
<td>SOI</td>
</tr>
<tr>
<td>Discharge status</td>
<td>Expired = 2, Discharged/Transferred alive = 1, Other = 0</td>
<td>Discharge_status</td>
</tr>
<tr>
<td>Dialysis status</td>
<td>On dialysis = 1, Not on dialysis = 0</td>
<td>Dialysis</td>
</tr>
<tr>
<td><strong>HOSPITAL CHARACTERISTICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bed size</td>
<td>1-199 = 0, 200-399 = 1, 400-599 = 2, 600-799 = 3, 800-999 = 4, 1000 or more = 5</td>
<td>BedSize</td>
</tr>
<tr>
<td>Geographical region</td>
<td>Midwest = 0, Northeast = 1, Southeast = 2, Southwest = 3, West = 4, Unknown = 5</td>
<td>Region</td>
</tr>
<tr>
<td><strong>PHYSICIAN CHARACTERISTICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician specialty</td>
<td>Internal medicine = 7, Surgery = 6, Hospitalist = 5, Pulmonary/Critical care = 4, Transplant = 3, Cardiology = 2, Nephrology = 1, Other = 0</td>
<td>Phys_specialty</td>
</tr>
</tbody>
</table>
Statistical analysis by objective

Statistical analyses were performed using Statistical Analysis Software (SAS v. 9.2) and Predictive Analytical Software (PASW v. 17.0, previously SPSS) statistical software. Estimates for continuous variables were reported using Mean, Standard deviation and Ranges, and for categorical variables using Frequencies and Proportions. Proportions between the groups were compared using Pearson’s chi-square. Continuous variables were compared using a t-test or a Wilcoxon Rank sum test depending on the variable’s distribution. A two-sided alpha of 0.05 was considered significant. Following is a discussion of the statistical methods that was used to address each objective.

Modeling economic data is complicated. Ordinary least squares (OLS) regression is not the optimal choice due to the nature of economic data.\textsuperscript{112-114} Firstly, observed cost data, is rarely normally distributed (positively skewed) and this violates the normality assumption necessary with OLS regression.\textsuperscript{114, 115} Secondly, with economic data the variance often increases as the mean increases due to the presence of heteroskedasticity (non-constant variance), violating the homogeneous variance assumption, hence making OLS inappropriate.\textsuperscript{114, 115} Various statistical solutions have been proposed to model charges more appropriately.

A log transformation can be performed to make the observed cost data more normally distributed. However, interpretation of resulting estimates may not be accurate, as it would be in ‘log costs’, and not actual costs. Smearing factors used to transform economic data from logarithmic back to natural units can introduce substantial bias in the presence of heteroskedasticity.\textsuperscript{88, 115}

A generalized linear modeling (GLM) approach provides appropriate and flexible methods for analysis of mean costs that explicitly allow for the non-normal distribution of the data.\textsuperscript{116}
GLMs have a variety of forms characterized by two features: a distribution function (F) for the outcome data and a link function (g) which describes the scale on which covariates in the model are related to the outcome. The most appropriate distributions for cost data would be the gamma or inverse Gaussian distribution. Both of these distributions are appropriate for non-zero continuous outcomes. However, most economic data analysis utilizes the gamma distribution. The gamma distribution is appropriate since it assumes that variance is proportional to the square of the mean. Economic data are non-zero, continuous and usually have a variance which increases with the mean. The negative binomial distribution would not be appropriate since it assumes a categorical outcome. The link function is not a transformation on the data, but a transformation of the population mean. The most commonly used link function for economic analysis is the log link. GLM using gamma distribution and log link is theoretically the preferred approach. Situations in which multiple observations are obtained from the same subjects or in the presence of clustered data, generalized estimating equations (GEE) within the framework of GLM are preferred. In a GEE, the researcher chooses a functional form (distribution) and link function as with any GLM, but then also chooses a covariance structure that adequately describes the known or suspected correlations between repeated observations. Commonly used types of covariance structures include exchangeable, autoregressive, dependent, independent and unstructured.

Observational studies are aimed at investigating the effect of an exposure (treatment) by comparing outcomes for subjects not randomly assigned to the exposure of interest. In randomized clinical trials, random assignment to different treatments guarantees that on average there should be no systematic differences in observed or unobserved covariates so that the study groups are comparable with respect to the distribution of their covariates. However, in non-
randomized observational studies, investigators have no control over treatment assignment, and therefore direct comparisons of outcomes from the treatment groups maybe misleading. The absence of random assignment can introduce systematic error into an observational study.

Propensity scores are the conditional probability of exposure given measured baseline variables. Observational studies use this method to adjust for observable bias with the goal to eliminate bias from unequal distribution of confounders. The actual propensity score is estimated using a logit or probit model, where a group of potential confounders is converted into one scalar score. The score is the probability (0 ≤ propensity score ≤ 1) of receiving the exposure (i.e., treatment) based on the set of identified covariates. The resulting score can be used as a matching or stratification factor, as a covariate in multivariable model or to perform inverse probability of exposure weighting. Each of these techniques is a way to make an adjustment for covariates prior to (matching and stratification) or while (stratification and regression adjustment) calculating the treatment effect.

In order for propensity scoring to work efficiently, all covariates that affect both the treatment assignment and outcome must be included in the propensity score model, and all subjects must have some non-zero probability of receiving each treatment. This is referred to as the strongly ignorable assumption. The most crucial decision in propensity scores is which covariates to include in the propensity score model. Every effort must be made to ensure that all variables related to both the treatment and response, are included in the propensity score model. It is also very important not to include the response in the propensity score model. In theory, covariates that are known to be related to the treatment but not to the outcome should not be included because they may potentially reduce the effectiveness of the method used in balancing the distributions of confounding covariates. In practice, however, there may be covariates for
which this issue is not clear. Unimportant covariates can add noise to the model and inflate variance estimates, while omitting an important covariate can result in serious bias. Rubin et al., indicate that it is better to include an unimportant covariate and lose some efficiency than increase the bias by omitting an important covariate. \footnote{121} Figure 3.2 is a suggested conceptual model adapted from Shever et al.\footnote{1} as a guide for variable selection in propensity score analysis. Once the propensity score is calculated, it can be used as a matching or stratification factor, as a covariate in multivariable model or to perform inverse probability of exposure weighting.\footnote{45}

Propensity scores can be used to match patients between exposure groups on multiple confounders. Matching is specifically performed when the control group is larger than the cases and obtaining the response (outcome) is costly or otherwise very difficult; and when there are significant covariate differences between the two treatment groups.\footnote{118} In whichever case, the possibility of over-matching and significant loss of cases/controls must be considered. This occurs when matching is done incorrectly or unnecessarily. The more variables used to calculate the propensity score, the greater the likelihood of overmatching. To avoid overmatching, the propensity score should preferably include only established confounders.\footnote{44,119,121}

Sub-classifying or stratifying on propensity scores requires that subjects be grouped together or matched based on having similar covariate values. Once the strata are defined, treated (cases) and control subjects who are in the same stratum are compared directly. It is established that five strata based on the propensity score will remove over 95 per cent of the bias in each of these covariates. Stratification becomes difficult when many confounders are present since there are not enough observations in each stratum. Stratification on propensity score limits the number of stratum thus making stratification a more robust method to control for confounding.\footnote{44}
If the score is used in a multivariable model, the second part of the two-stage regression process is the traditional model where the dependent variable is the outcome of interest and the propensity score is used as a covariate. The advantage of including propensity scores over traditional regression is in not over-parameterizing the model. Normally each confounder would require one degree of freedom (df) while the propensity score, which could be comprised of many confounders, only requires 1 df. However, use of a continuous, linear score makes a strong assumption about the relationship between propensity and disease risk, and estimated treatment effects can be biased if this assumption does not hold.

Propensity scores have their own set of limitations. They do not balance unmeasured characteristics and confounders. Large sample sizes are required for this methodology to work optimally. It only controls for unobserved covariates to the extent that they are correlated with the observed covariates. When creating the propensity score, strong and weak confounders are handled the same way in calculating the score. It is possible that a weak confounder has the same or larger coefficient in calculating the propensity score (e.g., a covariate having moderate association with treatment and weak association with outcome) than a stronger confounder (e.g., a covariate having moderate association with treatment and outcome). Additionally, covariates that are directly affected by the exposure of interest and not related to the outcome cannot be used in the propensity score model. Also, the models used to generate the propensity score rely on the same assumptions as logistic regression. If the model uses the propensity score as a continuous variable, the assumption of a (log-) linear association with the dependent variable must be tested using categories.
Figure 3.2: Conceptual model for variable selection in propensity score analysis

Potential confounders
- Patient characteristics
- Clinical conditions
- Physician characteristics
- Hospital characteristics
- Treatment characteristics

Treatment variable of interest (dichotomous)
IV iron + ESA / ESA alone

Is the variable related to both the treatment and outcome variables?

No

Independent variables available for second step of propensity score analysis
- Is the variable related to the outcome variable?

No

Do not include variable in the analysis

Yes

Methods
- Matching
- Covariance-adjusted regression
- Stratification

Outcomes
- Total hospital costs
- Length of stay

Choose one of the three methods

Yes

Propensity scores (generated from those independent variables thought to be confounders)

Adapted from Shever et al. 1
Statement and testing of research hypotheses by objective

This section is presented in the form of objectives and statements of the research hypotheses in their null form (Ho), followed by a discussion of the statistical testing of the hypotheses.

*Objective 1a: Quantify the extent of utilization of IV iron in anemic chronic kidney disease patients*

\[ H_{0.1a}: \text{There is no significant change in the utilization of IV iron and ESA over time.} \]

*Objective 1b: Determine the prevalence of concomitant IV iron administration when Erythropoiesis Stimulating Agents (ESA) therapy is initiated*

\[ H_{0.1b}: \text{There is no significant difference in the utilization of IV iron and ESA, compared to ESA-therapy alone over time.} \]

The first research objective of this inquiry was to quantify the extent of utilization of IV iron and ESA use, relative to the use of ESA alone, for the time period between 2006 and 2008. The drug utilization over time provides informative data useful for prescribers, hospital administrators, and marketers. Studies highlighting changes in drug use are important to measure the impact of events occurring in a certain time period that influence such changes.

A trend evaluation of the prevalence rate of usage of ESA and IV iron over time was performed for both the drugs. Differences between the study groups were calculated using t-tests, statistical significance set at \( p < 0.05 \). The days of therapy (DOTs) for ESA and IV iron therapy administered to individual patients was determined. The mean duration of therapy for each drug was calculated. The aggregate of drug use in each hospital for each year was expressed as DOTs per 100 patient-days (PDs). For example, if a patient received a single dose of a drug (ESA or IV iron) on a given day, whether or not multiple doses are usually administered, it was registered as
1 DOT. If a patient received more than 1 ESA drug (epoetin or darbepoetin) on the same day, it was counted as 1 DOT for ESA therapy. Days of hospitalization for each patient at each hospital were summed to provide total patient-days (PDs).

**Objective 2:** Determine predictors of IV iron use among the domains of patient characteristics, clinical conditions, physician characteristics, and hospital characteristics

*H₀₂:* There exists no significant association between patient characteristics, clinical conditions, physician characteristics, or hospital characteristics and IV iron and ESA use relative to ESA use alone.

A clustered binomial logistic regression model (Eqn. 1) using the GEE methodology was used to identify the predictors of IV iron use. The dependent variable was drug use, and the independent variables to be included in the model were 1) patient characteristics (age, race, gender, length of stay, primary payer), 2) patient clinical conditions (admission status, severity of illness, discharge status, dialysis status), 3) physician characteristics (physician specialty), 4) hospital characteristics (total hospital costs). A Wald’s statistic was used to test the significance of regression coefficients. The relationship between variables described above was evaluated for statistical significance. Comparisons were considered statistically significant at p < 0.05.

\[
IV \text{ iron + ESA/ESA-alone} = \beta_0 + \beta_1 \text{Patient Demographics} + \beta_2 \text{Patient Clinical Characteristics} + \beta_3 \text{Hospital Characteristics} + \beta_4 \text{Physician Specialty} + e\ldots\ldots\text{Eqn. 1}
\]

A goodness of fit test (QIC and QICC) was performed and was used to evaluate how well the model fits the observations. This was then useful in determining which of the correlation structures was more appropriate and the best subset of predictors. A Huber-White sandwich estimator (robust estimator) was used as a way to ensure that the variances were robust.
Specifically, robust variances are important as they provide accurate assessments of the sample-to-sample variability of the parameter estimates even if the model is misspecified.\textsuperscript{126}

For the test of model effects, Type III, was selected for all analysis as it does not depend on the entry order of the variables like Type I does. Test Type III is typically preferred unless order of the variables is important, which in this case it is not.

\textit{Objective 3: Determine the impact of IV iron and ESA use vs. ESA use alone on length of stay (LOS) while adjusting for confounders}

\textit{H_{0,3}: Given other things constant, patients with anemia of CKD on ESA therapy alone incur greater LOS compared to patients on IV iron +ESA therapy.}

The impact of drug use on LOS will be calculated using a GEE with a gamma distribution and a log link while adjusting for various factors. Known confounders and potential covariates will be eligible for inclusion. In the first step, a clustered binomial logistic regression model using the GEE methodology was used to calculate the propensity scores. Considering the characteristics of individual hospitals, hospital ID was used as a cluster variable in the GEE to account for correlations of drug utilization patterns, costs, LOS etc. of patients from the same hospital. This model includes age, gender, race, primary payer, physician specialty, severity of illness, discharge status, dialysis status as the independent variables and the treatment variable (ESA +IV iron and ESA alone) as the dependent variable. A propensity score was estimated for each subject based on the values of the observed covariates using the clustered logistic regression. The observations were then stratified by quintiles of the distribution of the estimated propensity scores. Chi-square tests of independence between treatment assignment and each categorical predictor, and t-tests of equality of means with the treatment assignment as the classification variable and continuous covariates as response variables were done within each strata to test the
success of the propensity-score model in balancing the covariates. In the second step, multivariable regression analysis using GEE methodology was performed to assess the length of stay (LOS) associated with the use of IV iron while controlling for the propensity quintile. Inclusion of quintile in the model inherently controls for all factors included in the propensity model. The conceptual model (Figure 3.2) was used as a guide to variable selection for the propensity score analysis. Using the predicted values from the multivariable regression model, the mean LOS of IV iron + ESA use was subtracted from the mean LOS of ESA use alone.

Objective 4: Determine the impact of IV iron and ESA use vs. ESA use alone on total hospital costs while adjusting for confounders

$H_{0.4}$: Given other things constant, patients with anemia of CKD on ESA therapy alone incur greater total hospital costs compared to patients on IV iron +ESA therapy.

The impact of drug use on hospital costs was calculated using a GEE with a gamma distribution and a log link while adjusting for various factors. Known confounders and potential covariates were included. In the first step, a clustered binomial logistic regression model using the GEE methodology was used to calculate the propensity scores. Considering the characteristics of individual hospitals, hospital ID was used as a cluster variable in the GEE to account for correlations of drug utilization patterns, costs, LOS etc. of patients from the same hospital. This model included age, gender, race, hospital level factors (total hospital costs), primary payer, physician specialty, severity of illness, discharge status, dialysis status as the independent variables and the treatment variable (ESA +IV iron and ESA alone) as the dependent variable. A propensity score was estimated for each subject based on the values of the observed covariates using the clustered logistic regression. The observations were then stratified by quintiles of the
distribution of the estimated propensity scores. Chi-square tests of independence between
treatment assignment and each categorical predictor, and t-tests of equality of means with the
treatment assignment as the classification variable and continuous covariates as response
variables were done within each strata to test the success of the propensity-score model in
balancing the covariates. In the second step, multivariable regression analysis was performed to
assess the total hospital costs associated with the use of IV iron while controlling for the
propensity quintile. Inclusion of quintile in the model inherently controls for all factors included
in the propensity model. The conceptual model (Figure 3.2) was used as a guide to variable
selection for the propensity score analysis. Using the predicted values from the multivariable
regression model, the mean hospital costs of IV iron + ESA use was subtracted from the mean
hospital costs of ESA use alone.

**Human subjects’ protection and data privacy**

VCU IRB exemption is obtained for this study. A dataset was constructed from the University
Health System Consortium (UHC) data warehouse. To ensure minimal risk to the patients, the
data has been coded and encrypted. Access to the dataset was restricted to those individuals
listed on this protocol, and the dataset was centrally maintained in a password-protected
environment. Disclosure of any kind of information did not take place without the expressed
written permission of UHC or as required by law. Results will be published in such a way that no
subject will be individually identifiable. Data within UHC’s Clinical Resource Manager is
compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). This
study qualified for exemption according to 45 CFR 46.101(b) Category 4 at Virginia
Commonwealth University internal review board (IRB). (VCU IRB#: HM12609). A copy of the IRB Approval form can be found in the Appendix A.
CHAPTER 4

Results

The results of this inquiry are presented in this chapter. The results have been summarized into the following sections:

Data manipulation

- Outlier analysis
- Hospital cost adjustment by Consumer Price Index

Descriptive Statistics

- brief descriptive summary of IV iron and ESAs
- summary statistics of patient and hospital characteristics characterizing drug use

Utilization and days of therapy for ESA and IV iron over the study time period

- overall prevalence of IV iron and ESA use across hospitals
- t-tests and ANOVA to understand utilization of IV Iron and ESA relative to ESA alone

Predictors of Off-label Uses

- clustered binomial logistic regression using the GEE methodology
Impact of IV iron and ESA use versus ESA use alone on length of stay while adjusting for confounders

- generalized estimating equation to estimate length of stay while adjusting for confounders using propensity scores

Impact of IV iron and ESA use versus ESA use alone on total hospital costs while adjusting for confounders

- generalized estimating equation to estimate total hospital costs while adjusting for confounders using propensity scores

Data Manipulation

Before further analysis (n = 84,447), the dataset was examined for erroneous data points. Some observations existed with a negative LOS. These observations were removed. Some observations reported incredibly low costs (less than $100) in spite of having a long LOS. The data were explored but there was no apparent pattern to the low costs. The investigator chose a reasonably conservative criterion that would exclude patients with low and high extremes in hospital costs or length of stay. The 1st and 99th percentile patients were deleted since they were mainly outliers with extremely low or extremely high cost (< $100 or > $300,000) and LOS (> 70 or 0 days) values. Also, patients with missing values for hospital costs and LOS were dropped from further analyses (N = 82,497).

Hospital costs were inflated to their 2008 value. CPI adjusted rates (compounded annually) were calculated for each year. Table 4.1 assumed a $1.00 reference value. Total hospital costs were adjusted to the 2008 value by multiplying the reported cost by the CPI adjusted rate. For
example, 2006 values were increased by 6%, and 2007 values by 13% to estimate their 2008 value. Figure 4.1 shows step by step how the CPI adjusted rates were calculated. The inflation rates can be found in Table 4.1.

Table 4.1: CPI adjusted rates

<table>
<thead>
<tr>
<th></th>
<th>2006 to 2008</th>
<th>2007 to 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>1.06</td>
<td>1</td>
</tr>
<tr>
<td>2008</td>
<td>1.13</td>
<td>1.07</td>
</tr>
</tbody>
</table>

Figure 4.1: Calculation of CPI adjusted rate

Calculation of CPI adjusted rate

2006 to 2007 had an inflation rate of 6.58%
2007 to 2008 had an inflation rate of 7.04%
Assuming the value in 2006 was $1, the value in 2007 would be: $1.00 \times (1 + 0.0658) = $1.06
The value in 2008 would be: $1.06 \times (1 + 0.0704) = $1.13.
This means that the adjusted inflation rate for 2006 to 2007 was 6% and for 2006 to 2008 was 13%.
Summary Description of Sample Characteristics by Drug Usage

Demographic data for the categorical variables (age, race, sex, admission source, payer type, admission status, severity of illness, discharge status, physician specialty, bed size and geographical region of hospital, ESA and IV iron type) are described in Tables 4.2. Of the 82,947 patients, 76,270 were ESA users (92%) and 6678 (8%) were IV iron + ESA users. Overall, white males in the higher age group (> 50 years) made up the largest demographic subgroup. The majority of patients in both drug use groups had Medicare as their primary payer.

There was a significant difference between the ESA users and IV iron + ESA users with respect to all the patient demographic characteristics, clinical characteristics, physician characteristics and hospital characteristics.

The age of patients ranged from 18 to more than 65 years. Middle aged (31-50 years) and higher age groups ranging from 51-65 years or more comprised the largest group of patients, although there were patients in all age categories as shown in Table 4.2. More IV iron users were in the elderly age group (≥ 65 years) than ESA users ($\chi^2 = 76.04$, df = 3, p-value < 0.0001). The majority of the patients were admitted as “Emergency” patients to the hospital, and more IV iron users were admitted as “Emergency” than the ESA users alone ($\chi^2 = 76.73$, df = 3, p-value < 0.0001). More than half of the patients were in the “Major” severity of illness category; 58% of IV iron users were “majorly” sick as compared to 54% of ESA users ($\chi^2 = 24.88$, df = 2, p-value < 0.0001). Discharge status was examined strictly as alive, dead or not available. More IV iron users were discharged and more ESA users expired in the hospital. The majority of the patients were discharged or transferred alive from a UHC hospital. Higher percentage of ESA users (4.5%) expired in the hospital compared to 3.5% of IV iron ($\chi^2 = 14.56$, df = 2, p-value = 0.0007).
The prescribing patterns for IV iron and ESA drugs were studied based on physician specialty as shown in Table 4.2. Internal medicine physicians and nephrologists prescribed the study drugs to a greater extent than any other specialists or surgeons. Univariate chi-square tests showed statistically significant difference across the two drug groups and the physician specialty categories.

In the study sample, patients admitted to hospitals located in the Midwest and the Northeast received the drugs to a greater extent than patients in any other region. IV iron utilization was the lowest in the Southwestern region of the U.S and highest in the Midwestern region. Overall the drug utilization was quite similar across hospital bed size categories. Univariate chi-square tests showed statistically significant differences between IV iron + ESA users and ESA user groups for the hospital characteristics such as the bed size and the hospital geographical region.

In terms of drug use, the majority of the patients received epoetin as their ESA therapy. More patients in the ESA alone group received epoetin compared to patients in the IV iron group ($\chi^2 = 105.93$, df = 1, p-value < 0.0001). Within the IV iron group (n = 6678), 85% patients received iron sucrose and only 15% patients received iron dextran as their IV iron supplementation.

Descriptive data for the continuous variables can be found in Table 4.3. Data is reported as medians and interquartile ranges since the variables were not normally distributed. The Wilcoxon Rank Sum test indicated both the continuous variables were significantly different between the IV iron and ESA and ESA alone groups. Information on mean costs and LOS is shown to provide an estimate of the unadjusted difference in mean costs and LOS between the two drug groups.
Table 4.2: Descriptive statistics for categorical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESA + IV Iron (column %)</th>
<th>ESA alone N (column %)</th>
<th>Total</th>
<th>Pearson Chi-Square</th>
<th>p &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>369 (5.53)</td>
<td>4728 (6.20)</td>
<td>5097 (6.14)</td>
<td>76.04, p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>31-50</td>
<td>1476 (22.10)</td>
<td>19349 (25.37)</td>
<td>20825 (25.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-64</td>
<td>2074 (31.06)</td>
<td>24,546 (32.18)</td>
<td>26620 (32.09)</td>
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<td></td>
</tr>
<tr>
<td>≥65</td>
<td>2759 (41.31)</td>
<td>27647 (36.25)</td>
<td>30406 (36.66)</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>6678</td>
<td>76269</td>
<td>82497</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>276.49, p&lt;0.0001</td>
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</tr>
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<td>White</td>
<td>3348 (50.13)</td>
<td>30504 (40)</td>
<td>33852 (40.81)</td>
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<td>Black</td>
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<td>32010 (41.97)</td>
<td>34310 (41.36)</td>
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<td></td>
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<td>Hispanic</td>
<td>514 (7.70)</td>
<td>7742 (10.15)</td>
<td>8256 (9.95)</td>
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<td>Other</td>
<td>517 (7.74)</td>
<td>6013 (7.88)</td>
<td>6530 (7.87)</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>6678</td>
<td>76269</td>
<td>82947</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>7.68, p=0.0056</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3615 (54.13)</td>
<td>39940 (52.37)</td>
<td>43555 (52.51)</td>
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<td></td>
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<td>Female</td>
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<td>39393 (47.49)</td>
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<td>Total</td>
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<td>76269</td>
<td>82947</td>
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<td></td>
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<td>Primary payer</td>
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<td></td>
<td>45.85, p&lt;0.0001</td>
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<td>Commercial/ Private payer</td>
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<td>11092 (14.54)</td>
<td>12249 (14.77)</td>
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<tr>
<td>Medicare</td>
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<td>53834 (70.58)</td>
<td>58422 (70.43)</td>
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<td>Medicaid</td>
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<td>9026 (11.83)</td>
<td>9736 (11.74)</td>
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<td>Self-pay</td>
<td>97 (1.45)</td>
<td>924 (1.21)</td>
<td>1021 (1.23)</td>
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<tr>
<td>Other</td>
<td>126 (1.89)</td>
<td>1394 (1.83)</td>
<td>1520 (1.83)</td>
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<tr>
<td>Total</td>
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<td>76269</td>
<td>82947</td>
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*Patient clinical conditions*
<table>
<thead>
<tr>
<th>Admission status</th>
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<th>Urgent</th>
<th>Elective</th>
<th>Other</th>
<th>Total</th>
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<tr>
<td></td>
<td>4130 (61.84)</td>
<td>1436 (21.50)</td>
<td>1017 (15.23)</td>
<td>95 (1.42)</td>
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<td>10636 (13.95)</td>
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<td>48490 (58.46)</td>
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<table>
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<th>Major</th>
<th>Extreme</th>
<th>Total</th>
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<td>817 (12.32)</td>
<td>3859 (57.79)</td>
<td>2002 (29.98)</td>
<td>6678</td>
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<tr>
<td></td>
<td>10205 (13.38)</td>
<td>41673 (54.64)</td>
<td>24392 (31.98)</td>
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<tr>
<td></td>
<td>11022 (13.29)</td>
<td>45532 (54.89)</td>
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<tr>
<td>Severity of illness</td>
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<table>
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<tr>
<th>Discharge status</th>
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<th>Expired</th>
<th>Other</th>
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<td>6440 (96.44)</td>
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<td>2 (0.03)</td>
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<tr>
<td></td>
<td>72782 (95.43)</td>
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<td>26 (0.03)</td>
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<td>79222 (95.51)</td>
<td>3697 (4.46)</td>
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<table>
<thead>
<tr>
<th>Dialysis status</th>
<th>On dialysis</th>
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<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1776 (26.59)</td>
<td>4902 (73.41)</td>
<td>6678</td>
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<tr>
<td></td>
<td>23546 (30.87)</td>
<td>52724 (69.13)</td>
<td>76269</td>
</tr>
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<td></td>
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<td>57626 (69.47)</td>
<td>82497</td>
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<td>Dialysis status</td>
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<table>
<thead>
<tr>
<th>Physician specialty</th>
<th>Internal Medicine</th>
<th>Nephrology</th>
<th>Cardiology</th>
<th>Transplant</th>
<th>Pulmonary/Critical</th>
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<tbody>
<tr>
<td></td>
<td>2182 (32.67)</td>
<td>1319 (19.75)</td>
<td>750 (11.23)</td>
<td>273 (4.09)</td>
<td>196 (2.94)</td>
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<tr>
<td></td>
<td>25652 (33.63)</td>
<td>12793 (16.77)</td>
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<td>2635 (3.45)</td>
</tr>
<tr>
<td></td>
<td>27834 (33.56)</td>
<td>14112 (17.01)</td>
<td>8891 (10.72)</td>
<td>3969 (4.78)</td>
<td>2831 (3.41)</td>
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</tbody>
</table>

<p>| Physician specialty | 64.28, p&lt;0.0001 |</p>
<table>
<thead>
<tr>
<th>Care</th>
<th>320 (4.79)</th>
<th>3391 (4.45)</th>
<th>3711 (4.47)</th>
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<td>Hospitalist</td>
<td>823 (12.32)</td>
<td>9260 (12.14)</td>
<td>10083 (12.16)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
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**Hospital characteristics**

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<th>Bed size</th>
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<th>12309 (16.14)</th>
<th>14037 (16.92)</th>
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<tr>
<td>1-399</td>
<td>201 (30.02)</td>
<td>25584 (33.54)</td>
<td>27589 (33.26)</td>
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<tr>
<td>400-599</td>
<td>1281 (19.18)</td>
<td>22099 (28.98)</td>
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<tr>
<td>600-799</td>
<td>2005 (30.02)</td>
<td>25584 (33.54)</td>
<td>27589 (33.26)</td>
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<tr>
<td>800 or more</td>
<td>1664 (24.92)</td>
<td>16278 (21.34)</td>
<td>17942 (21.63)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6678</td>
<td>76269</td>
<td>82947</td>
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**Geographical region**

<table>
<thead>
<tr>
<th>Midwest</th>
<th>2416 (36.18)</th>
<th>17498 (22.94)</th>
<th>19914 (24.01)</th>
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<tbody>
<tr>
<td>Northeast</td>
<td>1826 (27.34)</td>
<td>17045 (22.35)</td>
<td>18871 (22.75)</td>
</tr>
<tr>
<td>Southeast</td>
<td>848 (12.70)</td>
<td>17264 (22.64)</td>
<td>18112 (21.84)</td>
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<tr>
<td>Southwest</td>
<td>456 (6.83)</td>
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<td>11335 (13.67)</td>
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<tr>
<td>West</td>
<td>1132 (16.95)</td>
<td>13583 (17.81)</td>
<td>14715 (17.74)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
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<td>76269</td>
<td>82947</td>
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</table>

**Treatment characteristics**

<table>
<thead>
<tr>
<th>ESA type</th>
<th>3428 (51.3)</th>
<th>44106 (57.8)</th>
<th>47534 (57.3)</th>
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<tbody>
<tr>
<td>Epoetin</td>
<td>3428 (51.3)</td>
<td>44106 (57.8)</td>
<td>47534 (57.3)</td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>2082 (31.2)</td>
<td>33393 (43.8)</td>
<td>35475 (42.8)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6678</td>
<td>76269</td>
<td>82947</td>
</tr>
</tbody>
</table>

**IV iron type**

<table>
<thead>
<tr>
<th>Iron sucrose</th>
<th>5678 (85)</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran</td>
<td>1000 (15)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6678</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.3: Descriptive statistics for continuous variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV Iron +ESA therapy</th>
<th>ESA therapy alone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
<td>IQR</td>
</tr>
<tr>
<td>Total hospital costs</td>
<td>34933</td>
<td>20014</td>
<td>10412-43330</td>
</tr>
<tr>
<td>LOS</td>
<td>10.7</td>
<td>7</td>
<td>4-14</td>
</tr>
</tbody>
</table>


Objective 1: Trends for IV iron and ESA use and days of therapy

Detailed description of IV iron use by patient demographics, patient clinical conditions, physician specialty, hospital characteristics and treatment characteristics is given in Table 4.2. This section describes the overall prevalence and trends in use for IV iron and ESA therapy from 2006-2008. Of the 82,947 CKD patients using ESA, only 6678 patients were prescribed IV iron. Figure 4.2 displays the overall time trend in IV iron and ESA therapy use in CKD patients.

The figure 4.2 shows a steady increasing trend in the use of ESA therapy from 2006 to 2007. The use of ESA therapy (ESA alone) gradually decreased from the last quarter of 2007 to 2008. There was a steady increase in the use of IV iron therapy in CKD patients already on ESA. Comparing the two therapeutic groups, fewer patients used IV iron along with ESA from 2006 to the second quarter of 2007. There was a notable increase in the number of patients using IV iron along with ESA as compared to ESA alone from the third quarter of 2007 to 2008.
Figure 4.2: Trend showing IV iron and ESA use from 2006-2008
Within the sample of patients on IV iron, 85% (n = 5678) of the patients received iron sucrose, and the remaining 15% (n = 1000) received iron dextran. Annual percentages of CKD patients prescribed IV iron, in addition to ESA therapy from 2006 to 2008 are listed in Table 4.4. IV iron use in dialysis patients, and also in CKD patients not on dialysis, increased sharply from 2006 to 2008. Of all the patients that got IV iron (n = 6678), only 26% of the patients were on dialysis. In 2006, amongst the patients on hemodialysis, 91% patients were prescribed iron sucrose and only 9% were prescribed iron dextran. A similar trend was followed in 2007 and 2008, where iron sucrose was more often used as compared to iron dextran.

<table>
<thead>
<tr>
<th>Table 4.4: Annual percentages of patients treated with IV iron</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodialysis</strong></td>
</tr>
<tr>
<td><strong>Total number of patients</strong></td>
</tr>
<tr>
<td>Iron sucrose (%)</td>
</tr>
<tr>
<td>Iron dextran (%)</td>
</tr>
<tr>
<td><strong>Peritoneal dialysis</strong></td>
</tr>
<tr>
<td><strong>Total number of patients</strong></td>
</tr>
<tr>
<td>Iron sucrose (%)</td>
</tr>
<tr>
<td>Iron dextran (%)</td>
</tr>
<tr>
<td><strong>Not on dialysis</strong></td>
</tr>
<tr>
<td><strong>Total number of patients</strong></td>
</tr>
<tr>
<td>Iron sucrose (%)</td>
</tr>
<tr>
<td>Iron dextran (%)</td>
</tr>
</tbody>
</table>
IV iron and ESA days of therapy

The days of therapy (DOTs) for ESA and IV iron therapy administered to individual patients was determined. The mean duration of therapy for each drug was calculated. The aggregate of drug use for each year was expressed as DOTs per 100 patient-days (PDs). Table 4.5 lists the mean DOTs/100 PDs for IV iron and ESA therapy. The mean (±SD) ESA DOTs/100 PDs was 12.36 ±21.92 in the ESA group and 8.66 ±20.28 in the IV iron group. T-test results showed a statistically significant mean difference of 3.7 [(95% CI = 3.15, 4.24), SE = 0.278, p < 0.0001].

Table 4.5: Mean days of therapy/100 patient days by drug group

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV Iron +ESA therapy</th>
<th>ESA therapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>ESA DOT/100 PDs</td>
<td>8.66</td>
<td>20.28</td>
</tr>
<tr>
<td>IV Iron DOTs/100 PDs</td>
<td>30.41</td>
<td>28.20</td>
</tr>
</tbody>
</table>

Figure 4.4 shows change in the mean ESA DOTs/100 PDs with each quarter of drug use from 2006-2008. There is a significant increase in the mean ESA use in the first quarter of 2006 (p = 0.032). Notice the significant (p = 0.005) decrease in the use of ESA from the second quarter of 2006 to the third quarter of 2007. A substantial drop in the mean use of ESA occurred from the third quarter of 2006 to the first quarter of 2008 (p<0.0001).

Figure 4.5 shows the change in the mean IV Iron DOTs/100PDs with each quarter of drug use from 2006-2008. Note the significant increase of IV iron use from the first quarter of 2007 to the second quarter of 2008 (p < 0.0001).
Figure 4.3: Mean ESA DOTs/100 PDs use (with 95% CI) from 2006-2008 (by each quarter)
Figure 4.4: Mean IV Iron DOTs/100 PDs use (with 95% CI) from 2006-2008 (by each quarter)
Objective 2:

Predictors of IV iron use

The objective of the second research question was to determine predictors of IV iron and ESA use relative to ESA use alone. Based on the literature review and clinical relevance several component hypotheses were postulated a priori, which address the possible antecedents of drug use in CKD patients as described in Table 4.2 which can be found in the second chapter. The variables included in the model came from four main domains:

Patient demographic characteristics: Patient demographics included were age, race, gender and primary payer. The variable age was categorized into different age groups; ‘adult’ (18 to 30 years), ‘middle-aged’ (31 to 50 years), ‘young old’ (51 to 64 years) and ‘old old’ (65 years and above). The reference category used for age group was adults aged between 18 and 30 years. The gender base category was male. The primary payer variable included Medicare, Medicaid, some commercial/private payer, and self-pay categories. Medicare was the reference category. The variable race included White, Black and Hispanics, with White as the reference category.

Patient clinical characteristics: These included admission status, severity of illness, dialysis status, length of stay and discharge status. Admission status was categorized into ‘emergency’, ‘urgent’ and ‘elective’, with ‘urgent’ being the reference category. Severity of illness was categorized into ‘moderate’, ‘major’ and ‘extreme’, and ‘moderate’ was used as the reference category. The dialysis base category was ‘not on dialysis’. Discharge status was categorized into ‘discharged/transferred alive’ or ‘expired’, and ‘expired’ was used as a reference category.
**Physician characteristics:** The only physician characteristic used in the regression model was the physician specialty. Physicians were categorized into Internal medicine, Nephrology, Cardiology, Transplant, Pulmonary/Critical care, Hospitalists, and Surgeons, with Internal Medicine as the reference category.

**Hospital characteristics:** These included the total hospital costs. Other variables available were the bed size and the region where the hospital was located. However, addition of these variables to the model seriously affected the overall fit of the model. Hence, predictors of drug use were estimated without these variables. Fit was assessed using the Quasi-likelihood under Independence Criterion (QIC) and Corrected Quasi-likelihood under Independence Criterion (QICC). QIC was used for choosing the best working correlation structure assumption, and QICC was used for choosing the best subset of predictors in the GEE model. Lower QIC and QICC values imply a better fit model.

A clustered binomial logistic regression model (Eqn. 1) using the GEE methodology was used to identify the predictors of IV iron use. We put a restriction that patients within a hospital are nested and related when compared with patients between different hospitals, especially with respect to treatment patterns. The dependent variable was drug use, and the independent variables to be included in the model were 1) patient characteristics (age, race, gender, length of stay, source of payment), 2) patient clinical conditions (admission status, severity of illness, dialysis status, discharge status), 3) physician characteristics (physician specialty), 4) hospital characteristics (total hospital costs). A Wald’s statistic was used to test the significance of regression coefficients. The relationship between variables described above was evaluated for
statistical significance. Comparisons were considered statistically significant at $p < 0.05$. No pairwise multicollinearity was found.

$$\text{IV iron + ESA/ESA-alone} = \beta_0 + \beta_1 \text{Patient Demographics} + \beta_2 \text{Patient Clinical Characteristics} + \beta_3 \text{Hospital Characteristics} + \beta_4 \text{Physician Specialty} + \beta_5 \text{Drug Characteristics} + e \ldots \text{Eqn. 1}$$

The reference categories for each of the categorical independent variables in the model made up of White males prescribed ESA, and having Medicare as their drug coverage. All the patients in the reference category were admitted as “Urgent” patients with moderate severity of illness, who were not on dialysis, were seen by Internal Medicine physicians and expired on discharge.

The results in Tables 4.6 to 4.8 belong to the same binomial logistic regression model and have been divided into 3 tables for ease of understanding.

**Patient Demographics**

The regression results of patient demographics as possible predictors of IV drug use have been summarized in Table 4.6. Older adults ($\geq 65$ years) were 1.246 times more likely to be prescribed IV iron for anemia of CKD compared to young adults in the age range of 18-30 years [95% CI (1.108, 1.402), $p < 0.0001$]. Race was found to be a strong predictor of drug use in the anemic CKD population: The Blacks and the Hispanics were 0.685 [95% CI (0.647, 0.726) $p < 0.0001$] times and 0.627 [95% CI (0.567, 0.695) $p < 0.0001$] times as likely to receive IV iron compared to the White population on ESA therapy. Patients covered under the Medicaid, any commercial/private insurance or who paid out of pocket for insurance were 1.141 [95% CI (1.044, 1.247) $p = 0.003$], 1.265 [95% CI (1.178, 1.360) $p < 0.0001$] and 1.451 [95% CI (1.171,
times more likely to receive IV iron therapy as compared to patients covered under Medicare.

Table 4.6: Binomial logistic regression with Drug use (IV Iron + ESA vs. ESA) as dependent variable and Patient demographics as Independent variables

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β</th>
<th>exp(β)</th>
<th>Standard Error</th>
<th>Wald Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group (Base 18-30 years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-50 years</td>
<td>-0.0260</td>
<td>0.974</td>
<td>0.0608</td>
<td>0.183</td>
<td>0.669</td>
</tr>
<tr>
<td>51-64 years</td>
<td>0.042</td>
<td>1.043</td>
<td>0.0595</td>
<td>0.498</td>
<td>0.480</td>
</tr>
<tr>
<td>&gt;= 65 years</td>
<td>0.220</td>
<td>1.246</td>
<td>0.06</td>
<td>13.451</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Gender (Base-Female)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-0.031</td>
<td>0.969</td>
<td>0.026</td>
<td>1.423</td>
<td>0.233</td>
</tr>
<tr>
<td><strong>Race (Base-White)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>-0.378</td>
<td>0.685</td>
<td>0.0295</td>
<td>164.889</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>-0.466</td>
<td>0.627</td>
<td>0.0517</td>
<td>81.154</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>-0.238</td>
<td>0.788</td>
<td>0.0497</td>
<td>22.959</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Primary Payer (Base-Medicare)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>0.132</td>
<td>1.141</td>
<td>0.0452</td>
<td>8.535</td>
<td>0.003</td>
</tr>
<tr>
<td>Commercial/Private</td>
<td>0.235</td>
<td>1.265</td>
<td>0.0366</td>
<td>41.297</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Self-pay</td>
<td>0.372</td>
<td>1.45</td>
<td>0.1096</td>
<td>11.543</td>
<td>0.001</td>
</tr>
<tr>
<td>Other</td>
<td>0.210</td>
<td>1.234</td>
<td>0.0960</td>
<td>4.795</td>
<td>0.029</td>
</tr>
</tbody>
</table>

**Patient clinical characteristics**

Patient admission status, severity of illness, dialysis status and patient length of stay were strong predictors of drug use in the anemic CKD population (Table 4.7). Patients admitted to the hospital as emergency and elective cases were 1.34 [95%CI (1.256, 1.430) p < 0.0001] times and 1.307 [95%CI (1.202, 1.421) p < 0.0001] times more likely to be prescribed IV iron as compared to patients admitted to the hospital as urgent cases. ‘Extremely’ sick CKD patients were less likely to receive IV iron as compared ‘moderately’ sick patients. CKD patients not on dialysis were 0.851 [95%CI (0.8, 0.907) p < 0.0001] times as likely to receive IV iron as
compared to CKD patients on dialysis. As the length of stay increased, CKD patients were more likely to receive IV iron. [1.007, p < 0.0001])

Table 4.7: Binomial logistic regression with Drug use (IV Iron + ESA vs. ESA) as dependent variable and Patient clinical characteristics as Independent variables

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β</th>
<th>exp(β)</th>
<th>Standard Error</th>
<th>Wald Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admission status</strong> (Base-Urgent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>0.293</td>
<td>1.34</td>
<td>0.0331</td>
<td>78.316</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Elective</td>
<td>0.268</td>
<td>1.307</td>
<td>0.047</td>
<td>39.305</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>0.088</td>
<td>1.092</td>
<td>0.1110</td>
<td>0.636</td>
<td>0.425</td>
</tr>
<tr>
<td><strong>Severity of Illness</strong> (Base-Moderate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>0.073</td>
<td>1.075</td>
<td>0.0409</td>
<td>3.142</td>
<td>0.076</td>
</tr>
<tr>
<td>Extreme</td>
<td>-0.182</td>
<td>0.833</td>
<td>0.0485</td>
<td>14.142</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Dialysis status</strong> (Base-Not on dialysis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On dialysis</td>
<td>-0.161</td>
<td>0.851</td>
<td>0.0319</td>
<td>25.386</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Discharge status</strong> (Base-Expired)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged/Transferred alive</td>
<td>0.012</td>
<td>1.012</td>
<td>0.7383</td>
<td>0.000</td>
<td>0.987</td>
</tr>
<tr>
<td>Other</td>
<td>-0.323</td>
<td>0.724</td>
<td>0.7426</td>
<td>0.189</td>
<td>0.664</td>
</tr>
<tr>
<td><strong>LOS</strong></td>
<td>0.007</td>
<td>1.007</td>
<td>0.0020</td>
<td>11.923</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Physician and hospital characteristics

Physician specialty and total hospital costs were significant predictors of drug use in this population (Table 4.8). Nephrologists were 1.216 [95% CI (1.131, 1.308) p < 0.0001]) times more likely to prescribe IV iron to CKD patients already on ESA therapy, compared to Internal Medicine physicians. Transplant specialists and surgeons were 0.772 [95% CI (0.664, 0.898) p = 0.001]) and 0.912 [95% CI (0.836, 0.995) p = 0.038]) times as likely to prescribe IV iron to CKD patients compared to internal medicine physicians. As the total hospital costs increased, CKD patients were more likely to receive IV iron [1.007, p < 0.0001]).
Table 4.8: Binomial logistic regression with Drug use (IV Iron + ESA vs. ESA) as dependent variable and Physician and hospital characteristics as Independent variables

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β</th>
<th>exp(β)</th>
<th>Standard Error</th>
<th>Wald Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physician specialty</strong> (Base- Internal Medicine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrology</td>
<td>0.196</td>
<td>1.216</td>
<td>0.0371</td>
<td>27.748</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiology</td>
<td>-0.050</td>
<td>0.951</td>
<td>0.0463</td>
<td>1.182</td>
<td>0.277</td>
</tr>
<tr>
<td>Transplant</td>
<td>-0.259</td>
<td>0.772</td>
<td>0.0772</td>
<td>11.218</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulmonary/Critical Care</td>
<td>-0.137</td>
<td>0.872</td>
<td>0.0798</td>
<td>2.932</td>
<td>0.087</td>
</tr>
<tr>
<td>Surgery</td>
<td>-0.092</td>
<td>0.912</td>
<td>0.0442</td>
<td>4.32</td>
<td>0.038</td>
</tr>
<tr>
<td>Hospitalist</td>
<td>0.049</td>
<td>1.05</td>
<td>0.0631</td>
<td>0.612</td>
<td>0.434</td>
</tr>
<tr>
<td>Other</td>
<td>-0.094</td>
<td>0.91</td>
<td>0.0431</td>
<td>4.729</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Total hospital costs</strong></td>
<td>2.226E-6</td>
<td>1.00</td>
<td>5.4354E-7</td>
<td>16.770</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


Objective 3:

Adjusted difference in hospital costs by drug group

A GEE utilizing a gamma distribution and logarithmic link was used to estimate total hospital costs while adjusting for potential confounders, while clustering for hospitals. Before a multivariate model could be analyzed, a propensity score was calculated for bias adjustment.

A propensity score was calculated for the patient baseline covariates such as age, race, gender, primary payer, admission status, severity of illness, dialysis status, discharge status, and physician specialty using a clustered binomial logistic regression. The analysis was clustered by hospital ID to account for any correlations between patients in the same hospital. The independent variable was drug group (IV iron and ESA or ESA alone) and the dependent variables were the covariates mentioned above. Hospital level variables were not included in the propensity score analysis, and were used in the final multivariate model. Propensity scores were only calculated for 81,565 patients since 932 patients had missing data on admission status and discharge status variables. The model with the lowest Quasi-likelihood under Independence Criterion (QIC) and Corrected Quasi-likelihood under Independence Criterion (QICC) was selected for analysis. QIC was used for choosing the best working correlation structure assumption, and QICC is used for choosing the best subset of predictors in the GEE model. A lower QIC and QICC values imply a better fit model.

The distribution of propensity scores is shown in Figure 4.5. Table 4.9 shows a list of covariates used in the propensity score analysis along with results of chi-square tests indicating significant differences between the two drug user groups on baseline covariates.
The observations were stratified by quartiles based on their propensity scores. The selection of 4 sub-groups was based on an iterative process of testing the overall balance of covariates by stratifying into 3 to 10 sub-groups. Stratifying the propensity scores into 4 sub-groups provided maximum success in balance between the two drug groups on the baseline covariates within each stratum.

Table 4.9 depicts the balance of covariates between the two drug groups, within each quartile. The baseline covariates were well balanced within the propensity score quartiles. Within individual quartiles, few characteristics had statistically significant different distributions.
Imbalance between drug groups was rectified by collapsing categories for categorical variables such as physician specialty, race, and primary payer to improve the distribution between quartiles. Compared to the 9 unbalanced variables before stratification, the magnitude of imbalance was significantly reduced after stratification on propensity scores.

Table 4.9: Balance on baseline covariates within each quartile

<table>
<thead>
<tr>
<th>Baseline covariates</th>
<th>Before propensity score adjustment</th>
<th>Quartiles</th>
<th>After propensity score adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 0.0001</td>
<td>1</td>
<td>0.3987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.0155</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.0027</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.8103</td>
</tr>
<tr>
<td>Race</td>
<td>&lt; 0.0001</td>
<td>1</td>
<td>0.0061</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.0007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>0.0068</td>
<td>1</td>
<td>0.0067</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.2708</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.3523</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.8122</td>
</tr>
<tr>
<td>Primary payer</td>
<td>&lt; 0.0001</td>
<td>1</td>
<td>0.0149</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.9525</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.0166</td>
</tr>
<tr>
<td>Admission status</td>
<td>&lt; 0.0001</td>
<td>1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.0002</td>
</tr>
<tr>
<td>Severity of illness</td>
<td>&lt; 0.0001</td>
<td>1</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.0655</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.0002</td>
</tr>
<tr>
<td>Dialysis status</td>
<td>&lt; 0.0001</td>
<td>1</td>
<td>0.2177</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.1910</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.2747</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Discharge status</td>
<td>0.0003</td>
<td>1</td>
<td>0.0819</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.0019</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.5393</td>
</tr>
</tbody>
</table>
Kolmogorov-Smirnov tests for cost values were statistically significant (p-value < 0.001) which indicated non-normality with the cost data. This was accounted for by conducting GEE using gamma distribution for the cost data. Additionally, no multicollinearity among independent variables was found, since the VIF values for none of the variables were greater than 2. Results of the GEE estimating total hospital costs, while controlling for propensity quintile are reported in Table 4.10. The parameter estimates were exponentiated for interpretation. Figure 4.6 shows the scatter plot of Pearson residuals versus predicted value.
Table 4.10: GEE estimating total hospital costs, while controlling for propensity quintile (dependent variable: total hospital costs)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β</th>
<th>Exp(β)</th>
<th>Standard error</th>
<th>Wald Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>10.314</td>
<td>30162.286</td>
<td>0.0195</td>
<td>279469.926</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Drug group (ESA alone vs IV Iron + ESA)</td>
<td>-0.117</td>
<td>0.89</td>
<td>0.0143</td>
<td>66.275</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bed size (800 ≥ vs 1-399)</td>
<td>0.254</td>
<td>1.289</td>
<td>0.015</td>
<td>287.316</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bed size (600-799 vs 1-399)</td>
<td>0.226</td>
<td>1.254</td>
<td>0.0152</td>
<td>219.939</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bed size (400-599 vs 1-399)</td>
<td>0.306</td>
<td>1.358</td>
<td>0.0141</td>
<td>470.924</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Geographical region (Midwest vs West)</td>
<td>0.007</td>
<td>1.007</td>
<td>0.0137</td>
<td>0.293</td>
<td>0.588</td>
</tr>
<tr>
<td>Geographical region (Northeast vs West)</td>
<td>-0.175</td>
<td>0.840</td>
<td>0.014</td>
<td>157.035</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Geographical region (Southeast vs West)</td>
<td>-0.228</td>
<td>0.796</td>
<td>0.0156</td>
<td>215.183</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Geographical region (Southwest vs West)</td>
<td>-0.029</td>
<td>0.971</td>
<td>0.0159</td>
<td>3.332</td>
<td>0.068</td>
</tr>
<tr>
<td>Quartile (1 vs 4)</td>
<td>0.037</td>
<td>1.037</td>
<td>0.0118</td>
<td>9.594</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Quartile (2 vs 4)</td>
<td>0.014</td>
<td>1.014</td>
<td>0.0114</td>
<td>1.519</td>
<td>0.147</td>
</tr>
<tr>
<td>Quartile (3 vs 4)</td>
<td>0.028</td>
<td>1.029</td>
<td>0.0114</td>
<td>6.209</td>
<td>0.006</td>
</tr>
</tbody>
</table>

GEE with gamma distribution and log link and exchangeable correlation structure
QIC = 83684.698
QICC = 83675.072
According to the GEE model, patients using ESA therapy alone will have 11% lower hospital costs than patients using IV iron in addition to ESA, given other things constant. Among quartiles, patients in quartile 1 and quartile 3 will have 3.7% and 2.9% higher hospital costs compared to the patients in quartile 4. This means that patients with a higher probability of receiving IV iron will end up having higher hospital costs than patients with lower probability of receiving IV iron. With respect to the hospital level variables, patients admitted to hospitals with
large bed capacities were associated with significantly higher (p < 0.0001) hospital costs than patients in hospitals with a small bed capacity (1-399). Patients admitted in the hospitals located in the Northeast and Southeast regions of the nation will have significantly (p < 0.0001) lower costs than the patients admitted to the hospitals located in the Western region of the nation.

The GEE model predicted an overall mean hospital cost of $31,674. The total hospital costs for IV iron users and ESA users are presented in Table 4.11. According to the model, a patient with anemia of CKD taking IV iron therapy in addition to ESA has an affiliated cost of $3,352 more than a patient taking ESA therapy alone.

Table 4.11: Predicted total hospital costs in US dollars

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>IV Iron +ESA therapy</th>
<th>ESA therapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>31674</td>
<td>34756</td>
<td>31404</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>4114</td>
<td>4598</td>
<td>3956</td>
</tr>
</tbody>
</table>
Objective 4:

Adjusted difference in hospital length of stay by drug group

A GEE utilizing a gamma distribution and logarithmic link, clustering for hospitals, was used to estimate hospital length of stay while adjusting for potential confounders.

Kolmogorov-Smirnov tests for cost values were statistically significant (p-value < 0.001) which indicated non-normality with the LOS data. This was accounted for by conducting GEE using gamma distribution and log link for the LOS data. Additionally, no multicollinearity among independent variables was found, since the VIF values for none of the variables were greater than 2. Results of the GEE estimating hospital length of stay, while controlling for propensity quintile are reported in Table 4.12. The parameter estimates were exponentiated for interpretation. Figure 4.7 shows the scatter plot of Pearson residuals versus predicted value.

According to the GEE model, patients using ESA therapy alone will have 14% (p<0.0001) lower hospital LOS than patients using IV iron in addition to ESA, given other things constant. Among quartiles, patients in quartile 1, 2 and 3 will have 9.9%, 5.1% and 6.5% higher hospital length of stay compared to the patients in quartile 4. This means that patients with a higher probability of receiving IV iron will end up having longer hospital LOS than patients with lower probability of receiving IV iron. With respect to the hospital level variables, patients admitted to hospitals with large bed capacities were associated with significantly longer (p < 0.0001) hospital stay than patients in hospitals with a small bed capacity (1-399). Patients admitted in the hospitals located in the Northeast and Southwest regions of the nation will have significantly (p < 0.0001) longer hospital stay than the patients admitted to the hospitals located in the Western region of the nation.
Table 4.12: GEE estimating hospital LOS, while controlling for propensity quintile (dependent variable: LOS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\beta$</th>
<th>Exp($\beta$)</th>
<th>Standard error</th>
<th>Wald Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.136</td>
<td>8.467</td>
<td>0.0173</td>
<td>15272.424</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Drug group (ESA alone vs IV Iron + ESA)</td>
<td>-0.149</td>
<td>0.862</td>
<td>0.0128</td>
<td>135.809</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Bed size (800 ≥ vs 1-399)</td>
<td>0.193</td>
<td>1.212</td>
<td>0.0126</td>
<td>234.145</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Bed size (600-799 vs 1-399)</td>
<td>0.144</td>
<td>1.155</td>
<td>0.0123</td>
<td>138.54</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Bed size (400-599 vs 1-399)</td>
<td>0.269</td>
<td>1.309</td>
<td>0.0116</td>
<td>541.858</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Geographical region (Midwest vs West)</td>
<td>-0.002</td>
<td>0.998</td>
<td>0.0115</td>
<td>0.031</td>
<td>0.86</td>
</tr>
<tr>
<td>Geographical region (Northeast vs West)</td>
<td>0.092</td>
<td>1.096</td>
<td>0.0118</td>
<td>60.476</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Geographical region (Southeast vs West)</td>
<td>-0.007</td>
<td>0.993</td>
<td>0.0129</td>
<td>0.291</td>
<td>0.589</td>
</tr>
<tr>
<td>Geographical region (Southwest vs West)</td>
<td>0.232</td>
<td>1.261</td>
<td>0.0133</td>
<td>305.015</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Quartile (1 vs 4)</td>
<td>0.094</td>
<td>1.099</td>
<td>0.0102</td>
<td>85.253</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Quartile (2 vs 4)</td>
<td>0.051</td>
<td>1.052</td>
<td>0.01</td>
<td>25.683</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Quartile (3 vs 4)</td>
<td>0.066</td>
<td>1.069</td>
<td>0.0097</td>
<td>46.677</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

GEE with gamma distribution and log link and exchangeable correlation structure
QIC = 83684.698
QICC = 83675.072
Figure 4.7: Scatter plot for testing homoskedasticity for Dependent variable = LOS after GEE with gamma distribution and log link
The GEE model predicted an overall mean hospital LOS of 9.75 days (Table 4.13). The hospital length of stay for IV iron users and ESA users are presented in table. According to the model, a patient with anemia of CKD taking IV iron therapy in addition to ESA has a LOS of 1 day more than a patient taking ESA therapy alone.

Table 4.13: Predicted hospital LOS in days

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>IV Iron +ESA therapy</th>
<th>ESA therapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>9.75</td>
<td>10.71</td>
<td>9.66</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>1.25</td>
<td>1.309</td>
<td>1.207</td>
</tr>
</tbody>
</table>

**Confirmatory matched cohort analysis**

A matched analysis was done to compare the final estimates for total hospital costs and LOS for the two drug user groups with the estimates obtained after using stratification. Optimal (exact) matching on propensity score led to a loss of 4158 cases (IV iron users). A matched analysis was done on 2324 IV iron users and 2324 ESA users. The total hospital costs incurred by IV iron users were $3,802 more than the costs incurred by ESA users and a hospital length of stay of 1.5 days more than the ESA users. A Wilcoxon signed rank test confirmed these costs to be significantly different (p < 0.0001). These results confirm the significant difference in the mean hospital costs obtained by the multivariate analysis using stratification on propensity scores.

Table 4.14: Mean hospital costs and LOS after matching

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV Iron +ESA therapy</th>
<th>ESA therapy alone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
<td>IQR</td>
</tr>
<tr>
<td>Total hospital costs</td>
<td>36254 (41058)</td>
<td>20545</td>
<td>10639-44941</td>
</tr>
<tr>
<td>LOS</td>
<td>11.24 (11.03)</td>
<td>7</td>
<td>4-14</td>
</tr>
</tbody>
</table>
CHAPTER 5

Discussion and conclusions

Summary of Findings

This chapter summarizes the study, providing discussions on the study results, conclusions reached and any limitations. Some suggestions for future research are also presented.

In this inquiry we attempted to describe the utilization of IV iron and ESA in anemic CKD patients, with a focus on understanding predictors of drug use and the overall economic impact of drug use on hospital length of stay and total hospital costs.

Objective 1 explored the utilization of IV iron and ESA therapy in the CKD population. Of the 82,497 CKD patients on ESA therapy, only 8% (n = 6678) were on IV iron supplementation. Of the 6678 patients on IV iron, 91% were prescribed iron sucrose, and the remaining 9% were prescribed iron dextran. The mean ESA days of therapy/100 patient-days was 12.36 ± 21.92 DOT/100 PDs in the ESA alone group, and 8.66 ± 20.28 in the IV iron therapy group with a significant mean difference (p < 0.0001). Within the IV iron group, the mean IV iron days of therapy/100 patient-days were 30.41 ± 28.2.

Objective 2 identified important predictors of IV iron and ESA use within the domains of patient demographics, patient clinical characteristics, physician and hospital characteristics. The binomial clustered logistic regression results suggest a few predominant themes on the demographic traits of patients receiving the IV iron and ESA therapy. Age, race and primary payer and physician specialty were identified as strong predictors of IV iron use. Patients admitted as emergency cases, with ‘moderate’ severity of illness, and not on dialysis are more likely to receive IV iron. There exists a strong positive association between total hospital costs, LOS, and IV iron use in this population.
Objective 3 estimated the total hospital cost in CKD patients using IV iron and ESA therapy. According to the multivariate model, the overall mean hospital cost was $31,674, which can be divided into $34,756 for IV iron users and $31,404 for ESA users alone. The difference in the hospital costs for IV iron users over ESA users was $3,352.

Objective 4 was very similar to objective 3, except the dependent variable was hospital length of stay instead of hospital costs. The overall mean LOS was 9.75 days which can be broken into 10.71 days and 9.66 days for IV iron and ESA users respectively. The difference was approximately 1 day.

**Discussion of results by objective**

*Objective 1*

Descriptive statistics and bar charts were used to understand the prevalence of ESA therapy and IV iron supplementation in CKD patients admitted to UHC hospitals. The drug utilization over time provides informative data useful for prescribers, hospital administrators, and marketers. Studies highlighting changes in drug use are important to measure the impact of events occurring in a certain time period that influence such changes.

Of the 82,497 CKD patients on ESA therapy, only 8% (n = 6678) were on IV iron supplementation. Almost 30% of the population was on hemodialysis (n = 25,322); however only 8% of the population received IV iron. Previous investigations have found varying prevalences of IV iron usage. Bailie et al. found IV iron being prescribed to 20% of the patients with anemia of CKD.\(^7\) This study included patients from four academic nephrology centers where prescribing physicians might have been more familiar with CKD treatment guidelines. Rasu et al. examined anemia management patterns in outpatient settings of the US.\(^52\) Only 3% of
the CKD patients with anemia were prescribed IV iron. Reasons for low prevalence of IV iron use in this investigation are unclear, particularly because the NKF-KDOQI clinical practice guidelines for anemia, which are repeatedly published since 1997, make firm recommendations for optimal use of IV iron supplementation in hemodialysis patients. Concerns regarding long term safety of IV iron may have had a role in such low prevalence of use. These concerns arise from the known effect of iron as a growth factor of bacteria, its suspected inhibition of neutrophil function, and increased oxidative stress leading to atheromatous change as well as anaphylactic and other adverse events associated with the use of IV iron. No large prospective clinical trials have investigated the relationship between iron dosing and infectious morbidity or mortality. Two observation studies by Feldman et al. examined the effect of IV iron on mortality and hospitalization. The second study evaluated 32,566 hemodialysis patients dialyzing at Fresenius Medical Care units during 1996 and 1997. These patients were followed up for all-cause mortality through mid-1998. When the time-varying effect of iron dosing, lab values and epoetin dosing during 20 months were entered in the multivariable model, no significant association between cumulative iron dose and all-cause mortality was observed. Results of this report provide cautious support for the safety of the judicious administration of cumulative iron doses greater than 1000 mg during 6 months if needed to maintain target Hb levels in hemodialysis patients. However, some clinicians may still be reluctant to optimally use iron because of lingering concerns about iron toxicity issues.

A decreasing trend in the use of ESA was observed from the last quarter of 2007 to 2008. Looking at the trends in the use of IV iron, a steady increase in prevalence of IV iron use was observed from 2006 to 2008. Several events could explain these trends. The National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI) revised the clinical practice
guidelines for anemia of CKD in 2006. The 2006 NKF-KDOQI clinical practice guidelines suggest that a CKD patient’s hemoglobin (Hb) be checked annually regardless of the cause or state of their CKD. The guidelines firmly recommend providing iron supplementation in order to maintain adequate iron indices i.e. transferrin saturation (TSAT) and serum ferritin levels and Hb levels. The decreasing trend in ESA use can be a result of all the safety concerns with ESA use that have led to the amendment of the labeling of all ESA products by adding a boxed warning instructing prescribers to use the lowest dose of ESAs that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion. Also, the FDA recently stated that all ESAs prescribed must be a part of the Risk Evaluation and Mitigation Strategies (REMS) program to ensure the safe use of these drugs.

Of all the patients that got IV iron (n = 6678), more than 90% of the patients were prescribed iron sucrose and hardly 9% were prescribed iron dextran. The known risk of anaphylactoid and other life-threatening adverse reactions with the use of iron dextran and the introduction of safer alternatives may explain the finding of sparse use of iron dextran. However, usage of sodium ferric gluconate was not captured in this data. The FDA approved generic iron dextran in 1999 and generic iron sucrose in 2004, while sodium ferric gluconate still maintains its brand name status. This may explain the lack of sodium ferric gluconate usage within the study time frame.

The days of therapy for ESA and IV iron therapy administered to individual patients was determined to get a precise understanding of the drug utilization. The mean (±SD) ESA DOTs/100 PDs was 12.36 ±21.92 in the ESA group and 8.66 ±20.28 in the IV iron group. T-test results showed a statistically significant mean difference of 3.7 [(95% CI = 3.15, 4.24), SE = 0.278, p < 0.0001]. This finding is consistent with the literature where IV iron use has
demonstrated a ‘dose-sparing’ effect on ESA use in CKD patients.\textsuperscript{49, 136} Considering the adverse event profile of ESA and the economic challenges associated with its use, reduction in its dose and ongoing administration of IV iron can help improve survival rate, quality of life as well as provide substantial cost-savings with respect to medication use in CKD patients.

Although the defined daily dose (DDD) method is recommended by the World Health Organization to estimate drug use, important deficiencies of the defined daily dose method compared with direct measure of the DOTs have recently been reported.\textsuperscript{137-139} Specifically, the defined daily dose method is intended to estimate the DOTs from the quantity of drug purchased by the hospital.\textsuperscript{140} In most countries, purchase data are more readily available than measures of the DOTs. Electronic capture of pharmacy dispensing and administration data now makes it feasible to measure DOTs directly. Moreover, in the UHC data, different hospitals have different measurement of units (vial, mg, mcg, ml, units etc), making it difficult to quantify the dose of ESA or IV iron therapy using the DDD methodology. DDD methods will underestimate drug exposure when the administered daily dose is reduced for a patient with impaired bodily function or sudden adverse events. Also, if the administered daily dosage differs significantly from the WHO-approved DDD, then DDD methodology will not provide an accurate assessment of the number of days of therapy. Days of therapy (DOTs) are the most common alternative measure of drug consumption in hospitals.

**Objective 2**

A clustered binomial logistic regression using generalized estimating equations (GEE) was used to identify potential predictors of IV iron use in anemic CKD patients. Older adults (\( \geq 65 \) years) were significantly more likely to be prescribed IV iron for anemia of CKD compared to young
adults in the age range of 18-30 years. This finding is consistent with the literature demonstrating a high prevalence of IV iron use among older adults. Race was found to be a strong predictor of drug use in the anemic CKD population. The Blacks and the Hispanics were significantly less likely to receive IV iron compared to the White population on ESA therapy. This finding is consistent with the current literature and can be associated to the socioeconomic status of these races. Patients covered under the Medicaid, any commercial/private insurance or who paid out of pocket for insurance were significantly more likely to receive IV iron therapy as compared to patients covered under Medicare. This finding is debatable considering the ambiguity in Medicare coverage decisions for ESRD and pre-dialysis CKD patients. Dialysis patients, regardless of age, have been entitled to Medicare coverage since 1972. As a result of widespread coverage, Medicare serves as primary insurance for the majority of ESRD patients after the initiation of dialysis. Most dialysis patients below the age of 65, however, are not eligible for Medicare benefits until the fourth month after initiating dialysis. Medicare does not cover any costs of treatment during these first three months of dialysis unless the patient already has primary Medicare coverage because of age or disability. The private health plan is the only payer for the first three months of dialysis. When a patient becomes eligible for Medicare due to ESRD in the fourth month of dialysis, there is a 30 month ‘coordination period’ when the health plan serves as the primary payer for health care services and Medicare becomes the secondary payer. At the end of this 30 month period, Medicare pays for all Medicare covered services as a primary payer, and the health plan becomes the secondary payer. Only 31% of the sample CKD population (N = 82,497) was on dialysis, while majority (> 60%) of the patients were pre-dialysis CKD patients and in the age range of less than 65 years who may not be covered by Medicare as their primary payer.
Patients admitted to the hospital as emergency and elective cases were significantly more likely to be prescribed IV iron as compared to patients admitted to the hospital as urgent cases. ‘Extremely’ sick CKD patients were less likely to receive IV iron as compared ‘moderately’ sick patients. This finding can be explained by the concerns physicians may have regarding the use of IV iron in terminally ill patients and toxicity issues with IV iron. These concerns arise from the known effect of iron as a growth factor of bacteria,$^{127-129}$ its suspected inhibition of neutrophil function,$^{130}$ and increased oxidative stress leading to atheromatous$^{131-133}$ change as well as anaphylactic and other adverse events associated with the use of IV iron. CKD patients on dialysis were less likely to receive IV iron as compared to CKD patients not on dialysis. However, this finding is unusual considering that IV iron is highly recommended to CKD patients on dialysis. As the length of stay increased, CKD patients were more likely to receive IV iron. This is reasonable, as the patients’ length of stay increases, there is a higher likelihood of dialysis treatment, and hence requiring IV iron supplementation in addition to ESA therapy.

With regards to physician specialty, nephrologists were more likely to prescribe IV iron to CKD patients already on ESA therapy compared to internal medicine physicians; whereas transplant specialists and surgeons were significantly less likely to prescribe IV iron to these patients. This finding is consistent with our hypothesis. Recent emphasis has called for early referral of CKD patients to nephrologists, since this approach has been demonstrated to improve patient outcomes and result in earlier preparation for an initiation of dialysis and prescribe the appropriate therapy as needed.$^{141}$
Objective 3 and 4

A multivariable model clustered by hospitals was used to determine the economic impact of drug use (IV iron versus ESA) on total hospital costs and LOS. A propensity score was calculated on important baseline covariates. A meta-analyses identified key components necessary for any investigation using propensity scores. Essential components included sufficient events per variable (EPV), continuous variable conformity with linear gradient, interactions, multicollinearity, assessment of model fit, discrimination of the model, adequate balance achieved between the confounders, and adjustment methodology. In a logistic regression model, as a rule of thumb, there need to be at least 10 outcomes per variable. This rule has also been extrapolated to propensity scores to ensure EPV. This investigation used nine variables for more than 80,000 observations. Continuous variable conformity relates to continuous variables used to create the propensity score. All the variables used to create the propensity score were categorical. No pairwise multicollinearity was found in the model. Fit was assessed using the Quasi-likelihood under Independence Criterion (QIC) and Corrected Quasi-likelihood under Independence Criterion (QICC) was selected for analysis. QIC was used for choosing the best working correlation structure assumption, and QICC was used for choosing the best subset of predictors in the GEE model. Lower QIC and QICC values imply a better fit model. Assessment of fit relates closely to balance between the IV iron and ESA treatment groups. The IV iron and ESA groups appeared to be balanced after stratification on propensity scores (Table 4.9). Propensity scores from a poorly fit model and without sufficient balance between treatment groups can lead to biased estimates of treatment effect.

Propensity scores can be either used as a continuous variable or stratified into quintiles or as a matching factor between the treatment groups. Since there was a sufficient overlap between
the IV iron and ESA groups with respect to propensity scores (Figure 4.5), the scores could have been used as a continuous variable in the second stage regression model or as a matching factor. However, use of propensity score as a continuous variable does not allow any post hoc diagnostics to confirm the level of balance achieved, and matching lead to a loss of a significant number of cases. In a post hoc fashion, exact one to one matching on propensity scores was conducted. Less than 1% change occurred in the parameter estimates for hospital costs and LOS. This indicates using the propensity score for stratifying observations was not inappropriate.

Adjusting for confounders, the overall mean hospital cost was $31,674, which can be divided into $31,404 for ESA users and $34,756 for IV iron users. The difference in ESA over IV iron users was $3,352. These estimates adjusted for the propensity score quintile and the hospital level variables.

A multivariable model clustered by hospitals was used to determine the economic impact of drug use (IV iron versus ESA) on total hospital length of stay. The multivariable model adjusted for the propensity quartile and the hospital level variables such as geographical region and the bed size. The overall mean LOS was 9.75 days, which can be broken down into 10.71 days for IV iron and ESA users and 9.66 days for ESA users alone.

After the multivariable models were calculated for the estimation of hospital costs and LOS respectively, an analysis of residuals was conducted. The Pearson residual plots (Figure 4.6 and 4.7) show a striped pattern instead of a more favorable random scatter. The striped pattern was considered a function of the categorical variables used in the regression. On the graphs, the Pearson residuals were all small, and there does not seem to be an obvious pattern, except a slight downward pattern as the predicted values increase.
Practical implications

This investigation contradicts previous single center analyses that show that IV iron use in addition to ESA therapy may lead to cost-savings compared to ESA use alone. The multivariable model controlled for known confounders. While controlling for confounders, the predicted hospital cost and LOS were still higher for IV iron users versus ESA users alone.

Why would IV iron users be associated with higher total hospital costs and longer LOS as compared to ESA users? The most obvious difference between IV iron and ESA users might be the severity of illness. Although this investigation attempted to control for severity of illness using the All Patient Refined Diagnosis Related Groups (APR-DRG), there may still have been uncontrolled disparity in patients’ underlying disease status. For example a patient with heart failure is not necessarily comparable to a patient with simple iron deficiency anemia. The patient with heart failure will most likely be sicker and hence use more resources. However, the APR-DRG severity of illness index should help control for this dissimilarity. The APR-DRG system is an enhancement of the DRG structure and is a good predictor of hospital costs and resource use.

In this investigation almost 58% of the IV iron users were ‘majorly’ sick compared to 54% of the ESA users ($\chi^2 = 24.88$, df = 2, p-value < 0.0001). In terms of admission status, almost 62% of IV iron users were admitted as ‘emergency’ patients, compared to 58% of the ESA users ($\chi^2 = 76.73$, df = 2, p-value < 0.0001).

Incidence of severe adverse events following drug administration, such anaphylaxis, cardiac arrest, bronchospasm, coma, shock, allergic reactions can also explain the longer length of stay and hence higher total hospital costs. Almost 22% of the IV iron users had one or more diagnoses codes for these adverse events related to IV iron use which could lead to a longer stay in the hospital and hence higher costs, compared to ESA users. However, the UHC data does not
provide dates for diagnoses; hence there is no way to determine if these adverse events followed drug administration.

Further analysis of individual comorbidities revealed a greater proportion of IV iron users having comorbidities like congestive heart failure, peripheral vascular disease, hypertension, diabetes, chronic pulmonary disease, hypothyroidism, and deficiency anemias, as compared to ESA users. As mentioned earlier, individual comorbidities were not included in the regression model to avoid multicollinearity with the APR-DRG severity of illness index. A post-hoc analysis was performed using the individual comorbidities in the propensity score analysis, instead of the APR-DRG severity of illness index. In the second step, multivariate regression analysis using the GEE methodology was done to estimate hospital costs and length of stay while controlling for the propensity quartile, drug group, hospital level variables and the APR-DRG severity of illness index. No significant difference (< 1%) was observed in the final estimates for the total hospital costs and LOS.

The effects of mortality on total hospital costs and LOS merits further discussion. In this investigation almost 5% of the ESA users expired in the hospital as compared to 3% of IV iron users ($\chi^2 = 14.56$, df = 2, p-value = 0.0007). Increased mortality could either increase or decrease total hospital costs. If the patient died sooner the hospital stay cost would be truncated. However, the patient could have complications prior to death which would lengthen the hospital stay. A drawn out hospital stay ending in death could increase the resulting total hospital costs, especially if major treatments and procedures were conducted surrounding the end-of-life period. Since this investigation had a large sample size, the overall effects of extended and truncated LOS were assumed to be minimal.
A number of randomized and observational studies have found a low incidence of acute reactions to IV iron products.\textsuperscript{77,78,144-147} Longer prospective observations have not clearly identified safety issues.\textsuperscript{145,148,149} A cohort study of US dialysis patients showed those billed for > 10 vials of IV iron dextran (> 1000 mg) over 6 months had an elevated rate of death [adjusted relative risk: 1.11; 95\% CI (1.00, 1.24)].\textsuperscript{134} A subsequent cohort study used multivariate models and accounted for time-varying measures of iron administration as well as other fixed and time-varying measures of morbidity and found no statistically significant association between any level of iron administration and mortality.\textsuperscript{135} Thus, associations between iron administration and higher mortality may be confounded. Intravenous iron is hypothesized to increase infection risk, although trials have not found an increased infection rate and observational data are contradictory.\textsuperscript{74} Some hypothesize that IV iron may contribute to cardiovascular events by increasing oxidative stress.\textsuperscript{150-152} Although markers of oxidative stress may be increased by iron, observational studies have been contradictory in linking IV iron use to adverse clinical outcomes. At usual clinical doses, the dangers of IV iron remain unproven. Thinking about the additional day and hospital costs, if one is not looking at individual drug costs, then it is arguably possible that using IV iron does not reduce overall hospital length of stay. Also, a hospital stay of one day may be statistically significant, but might not have clinical relevance, and the same argument might apply to the total hospital costs since the bulk of that maybe attributable to the extra day.

The results of this study should have good external validity. This was a multi-hospital investigation that included 62 hospitals of various sizes and from different geographical regions of the country. However the study population was refined to make the ESA and IV iron groups as similar as possible with respect to known confounders. The purpose of this data manipulation was to isolate the effect of drug use on total hospital costs and length of stay. By excluding
outliers the generalizability does decrease. These omissions were necessary to maximize internal validity.

**Limitations**

Inevitably, there were limitations to this investigation. The first limitation is the difference in hospitals with respect to anemia and CKD management policies and formularies/protocols that cause variations in hospital cost patterns. However, hospital level factors were used in an attempt to control for inter-hospital variability while modeling costs. Also, a clustered analysis using the GEE methodology was used to account for nesting of patients within hospitals to control for erroneous inferences of associations between independent variables and drug use, total costs and length of stay. In the clustered models we put a restriction that patients within a hospital are nested and correlated when compared with patients between different hospitals.

Another potential limitation is the use of cost-to-charge ratios to approximate actual costs from hospital charges. Charges are known to inflate the economic burden of hospitalization, hence cost-to-charge ratios have been used to better approximate actual cost from charges. However, this approach may raise some concern as assignment of costs to departments is not uniform from hospital to hospital, given the variability of hospital accounting systems, and because cost information is often not timely available. In contrast, costs based on relative value units are considered more accurate, but they are costly to determine. Schwartz et al evaluated the accuracy of costs derived from cost-to-charge ratios by using costs based on relative value units as the “gold standard” and concluded that for almost 70 percent of the DRGs, average cost-to-charge ratios were within 10 percent of the average relative value unit calculated costs. Cost-to-charge ratios were found to be even more reliable for comparing relative costs for patients in a
DRG in one hospital to the average cost for patients in that DRG in a group of hospitals. The use of cost-to-charge ratios has shown a correlation with internal accounting costs at a level above 0.90.\textsuperscript{84} Hence, cost-to-charge ratios can be considered convenient and a straightforward estimate of total hospital costs.\textsuperscript{84,85}

Adjusting for underlying severity of illness was a major concern in this investigation. There is currently no well-validated severity of illness score for CKD. Other investigations have used a variety of techniques including the Stoke Cormobidity Grade (SCG),\textsuperscript{91} the Khan index,\textsuperscript{92} the Davies index\textsuperscript{93} and the Charlson comorbidity index.\textsuperscript{94} Unlike other indices, the Davies index does not include age, because it was specifically designed to be used in conjunction with age as an independent covariate. Other comorbidity indices that are in use in studies on ESRD patients assign different weights to different comorbidities, such as the Khan or the Charlson index, with the weights based on the impact of comorbid diseases on survival.\textsuperscript{96} However, the impact of comorbid diseases on survival may be rather different from their impact on health status and resource use.\textsuperscript{96} This investigation used the All Patient Refined Diagnosis Related Groups (APR-DRG) classification system to adjust for severity of underlying illness.\textsuperscript{97} The APR-DRG system is an enhancement of the DRG structure and is a good predictor of hospital costs and resource use.\textsuperscript{98,99}

This investigation does not assess the appropriateness of the patients’ iron supplementation therapy. This could raise a concern as costs maybe higher for patients with delayed initiation of appropriate therapy. Additionally, differences in IV iron supplementation play a role in patients outcomes for CKD anemia.\textsuperscript{49} A cross-sectional study of the US National Ambulatory Medical Care Survey (NAMCS) revealed that only 10\% of CKD-related visits addressing anemia management are receiving anemia medications in US outpatient settings.\textsuperscript{52}
This investigation does not evaluate the efficacy of IV iron as an appropriate drug for treating anemia in CKD patients.

This investigation did not examine any patient clinical sub-populations in the multivariable analysis. Diabetes, heart failure and hypertension are serious and frequent complications of anemia of CKD and hemodialysis. Several studies have been published specifically evaluating the economic impact of anemia in CKD patients with chronic heart failure.\textsuperscript{40,153,154} This investigation deliberately did not focus on any particular diagnosis sub-populations in an attempt to increase external validity.

The database used for this study is derived from a group of university teaching hospitals providing tertiary care. University hospitals typically have higher costs, longer LOS and perform more complex procedures than community hospitals.\textsuperscript{155} The results from this study may not be directly extrapolated to the general hospital community of the U.S.

Finally, this study used archived inpatient hospital data from the University HealthSystem Consortium (UHC). Retrospective data can be convenient since the researcher does not have to wait for the data to be prospectively collected. However, invariably problems with inadequate or inaccurate codes in databases may introduce bias in the results. Also, retrospective analyses depend on data availability. While we have incorporated potential predictors from the patient and hospital characteristics, there may be other factors that influence the prediction of IV iron use and the resultant hospital costs and length of stay. Factors such as physician’s intent and knowledge level as well as pharmaceutical industry influence, important lab values for hemoglobin, transferring saturation, serum ferritin and other iron indices have been reported in the literature as possible predictors of IV iron use in anemic CKD patients.
However, these factors cannot be assessed, as the database does not provide that information. Hence these factors which can contribute to drug use are excluded from the study.

The UHC consists of all-payer hospital discharge data from most of the nation’s academic medical centers. This database is a rich source of information on key cost components, LOS, baseline patient characteristics, and clinical outcomes such as inpatient mortality, comorbidities and complication rates.\textsuperscript{85} The Clinical Resource Manager (CRM) database within the UHC, provides useful pharmacy data enabling in-depth study of drug utilization patterns in several thousands of hospitalized patients. Cost estimates of inpatient care are available for every discharge and this information can be aggregated on multiple levels. Hence, in spite of some inherent limitations, this database provided as a very useful resource in studying utilization patterns of IV iron and ESA and the resultant impact of drug utilization on hospital costs.

**Future research**

The study provides the basis for some interesting future research. Although methodological differences (e.g. patient selection, criteria for anemia, dosage calculation) complicate comparison of IV iron use in CKD, the prevalence that we found maybe comparable with other recently reported prevalences.\textsuperscript{7,52} Only about 8\% of the anemic patients on ESA therapy received IV iron supplementation. This low treatment rate represents a major gap in treatment practices and signals an opportunity for healthcare improvement. Geographic, demographic, patient clinical conditions, physician and hospital level characteristics were explored in this investigation to understand IV iron and ESA use and the resultant impact on hospital costs and LOS. Pathologic factors, physician practice patterns, pharmaceutical industry influence affecting rates of IV iron use in anemia of CKD along with clinical and economic outcomes of such treatment merit further research.
Our results confirm previous research on ESA dose sparing effect of IV iron use of patients on ESA therapy. However, this dose-sparing does not seem to translate into any substantial cost-savings in hospitalized CKD patients. Future research should focus on understanding the complex relationship between drug use (IV Iron/ESA), hospital length of stay and final total hospital costs. Post-dialysis length of stay may be considered an intermediate between drug use and hospital costs. The complex relationships involving LOS can be explored using advanced analyses like path analysis to tease out why IV iron users seem to cost more than ESA users.

Pharmaceutical industry-effects and their influence on likelihood of IV iron and ESA prescribing could be explored. The recently implemented REMS may have a significant impact on ESA prescribing and utilization. Influence of such policy related changes on IV iron and ESA therapy prescribing would be an interesting area of future research.

The safety aspect of IV iron was not in the scope of this study. Longitudinal data on long term IV iron utilization with data on important iron indices would be more appropriate to understand the incidence of adverse events with the use of IV iron and ESAs and study its association with hospital length of stay and total costs. Several publicly available databases such as the Freedom of Information surveillance database administered by the US Food and Drug Administration (FDA), together with market research data can provide review for the adverse event profiles of IV iron preparations available in the US.

This investigation was conducted from a hospital’s perspective, and estimated the final total hospital costs and length of stay. Further analysis of various component costs such as hospitalizations costs, pharmacy costs, physician visits, and laboratory costs, inpatient and ambulatory costs can help break down the economic impact of drug use in anemia of CKD.
Costs were not able to be sub-categorized in the current study. Only an overall aggregate cost was available for each subject since the data came from a large multi-hospital database.

Finally, the results and suggested conclusions can only be generalized to the IV iron and ESA utilization in teaching hospitals. Future studies should look at IV iron and ESA drug use in non-teaching and general community hospitals and other settings such as nursing homes, community, home health care and compare the results to establish external validity.

Conclusions

In this inquiry we attempted to describe the utilization of IV iron and ESA in anemic CKD patients, with a focus on understanding predictors of drug use and the overall economic impact of drug use on hospital length of stay and total hospital costs.

Analysis of the data collected from 62 teaching hospitals between 2006 and 2008 highlights the increasing trend in the use of IV iron in anemic CKD patients already on ESA therapy. Use of IV iron supplementation lead to a significant decrease in the dose of ESA [3.7, 95%CI = (3.15, 4.24)]. However, overall prevalence of IV iron (8%) use was very low. Several predominant themes were identified on the demographic traits, clinical conditions, physician and hospital level characteristics of patients receiving IV iron and ESA therapy. Age, race, primary payer, admission status, severity of illness, dialysis status and physician specialty were identified as strong predictors of IV iron use in CKD patients.

The optimal use of IV iron has shown to reduce ESA dose requirements and reduced total drug expenditures for anemia management in CKD patients. Our investigation showed significant reduction in ESA doses with the use of IV iron supplementation, however, this dose reduction did not translate into reduced hospital length of stay and total hospital costs.
Multivariate models adjusted for potential confounders estimated $3,352 higher costs and an additional day of hospital stay for IV iron users, compared to ESA users. Matched analysis confirmed the results obtained by the multivariate models.
Reference List


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(48) Coyne DW, Kapoian T. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: Results of the DRIVE Study. *Journal of American Society of Nephrology* 2007;18(3):975-84.


(97) Shen Y. Applying the 3M All Patient Refined Diagnosis Related Groups Grouper to measure inpatient severity in the VA. Med Care 2003 June;41(6 Suppl):II103-II110.


APPENDIX A
VCU IRB APPROVAL

Virginia Commonwealth University

Office of Research Subjects Protection
BioTechnology Research Park
BioTech One, 600 E. Leigh Street, #114
P.O. Box 980568
Richmond, Virginia 23228-0568
(804) 828-0808, fax (804) 827-1448

DATE: December 22, 2009

TO: David A. Holdford, PhD
Pharmacy
Box 980533

FROM: Lloyd H. Byrd, MS
Chairperson, VCU IRB Panel E
Box 980568

RE: VCU IRB #: HM12609
Title: Utilization Patterns and Economic Impact of IV Iron and Erythropoiesis Stimulating Agents (ESA) in Chronic Kidney Disease Patients: A Multi-Hospital study

On December 21, 2009 the following research study qualified for exemption according to 45 CFR 46.101(b) Category 4. This approval includes the following items reviewed by this Panel:

RESEARCH APPLICATION/PROPOSAL: NONE

PROTOCOL: Utilization Patterns and Economic Impact of IV Iron and Erythropoiesis Stimulating Agents (ESA) in Chronic Kidney Disease Patients: A Multi-Hospital study, version 11/17/09, received 11/19/09

ADDITIONAL DOCUMENTS:
* None

The Primary Reviewer assigned to your research study is Janet P. Niemeier, PhD. If you have any questions, please contact Dr. Niemeier at jniemeier@vcu.edu and 628-1633; or you may contact Donna Gross, IRB Coordinator, VCU Office of Research Subjects Protection, at dgross@vcu.edu or 827-2261.

Attachment – Conditions of Approval
Conditions of Approval:

In order to comply with federal regulations, industry standards, and the terms of this approval, the investigator must (as applicable):

1. Conduct the research as described in and required by the Protocol.

2. Obtain informed consent from all subjects without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate (unless Waiver of Consent is specifically approved or research is exempt).

3. Document informed consent using only the most recently dated consent form bearing the VCU IRB “APPROVED” stamp (unless Waiver of Consent is specifically approved).

4. Provide non-English speaking patients with a translation of the approved Consent Form in the research participant's first language. The Panel must approve the translated version.

5. Obtain prior approval from VCU IRB before implementing any changes whatsoever in the approved protocol or consent form, unless such changes are necessary to protect the safety of human research participants (e.g., permanent/temporary change of PI, addition of performance/collaborative sites, request to include newly incarcerated participants or participants that are wards of the state, addition/deletion of participant groups, etc.). Any departure from these approved documents must be reported to the VCU IRB immediately as an Unanticipated Problem (see #7).

6. Monitor all problems (anticipated and unanticipated) associated with risk to research participants or others.

7. Report Unanticipated Problems (UPs), including protocol deviations, following the VCU IRB requirements and timelines detailed in VCU IRB WPP VIII-7).

8. Obtain prior approval from the VCU IRB before use of any advertisement or other material for recruitment of research participants.

9. Promptly report and/or respond to all inquiries by the VCU IRB concerning the conduct of the approved research when so requested.

10. All protocols that administer acute medical treatment to human research participants must have an emergency preparedness plan. Please refer to VCU guidance on [http://www.research.vcu.edu/irb/guidance.htm](http://www.research.vcu.edu/irb/guidance.htm).

11. The VCU IRBs operate under the regulatory authorities as described within:
   a) U.S. Department of Health and Human Services Title 45 CFR 46, Subparts A, B, C, and D (for all research, regardless of source of funding) and related guidance documents.
   b) U.S. Food and Drug Administration Chapter I of Title 21 CFR 50 and 56 (for FDA regulated research only) and related guidance documents.
   c) Commonwealth of Virginia Code of Virginia 32.1 Chapter 5.1 Human Research (for all research).
APPENDIX B
SAS CODE

Propensity score analysis

/* Assign appropriate numerical categories to treated/untreated groups*/
DATA PhD_DATA.Quint_x;
set PhD_DATA.Quint;
IF DRUG_GROUP = 'IV' then DRUG_GROUP = 1;
if DRUG_GROUP = 'ESA' then DRUG_GROUP = 0;
run;

/*Check for initial differences between IV iron and ESA users */
PROC FREQ
DATA = PhD_DATA.Quint_x;
TABLES DRUG_GROUP*AGE_GROUP DRUG_GROUP*Sex DRUG_GROUP*Race
DRUG_GROUP*Admission DRUG_GROUP*Primary_payer DRUG_GROUP*Phys_specialty
DRUG_GROUP*Dialysis DRUG_GROUP*SOI DRUG_GROUP*DischargeStatus
DRUG_GROUP*Region DRUG_GROUP*BedSize/ MISSING chisq NOCOL NOROW;
RUN;

/*Calculate propensity scores*/
proc genmod data = PhD_DATA.Quint_x descending;
CLASS HCO_ID AGE_GROUP Sex Race Primary_payer Phys_specialty Dialysis
Admission DischargeStatus SOI;
model DRUG_GROUP = AGE_GROUP Sex Race Primary_payer Phys_specialty Dialysis
Admission DischargeStatus SOI / dist=binomial link=log;
repeated subject = HCO_ID/type = exch;
OUTPUT OUT= PhD_DATA.final_OBJ7 prob=prob;
run;
quit;

/*Understand the distribution of the propensity scores between the treatment groups*/
symbol1 v=triangle c = r;
proc boxplot data=PhD_DATA.final_OBJ7;
plot prob*DRUG_GROUP / boxstyle=skeletal
vaxis=axis2
cboxes = bl;
label prob = 'Propensity Score';
label DRUG_GROUP = 'DRUG_GROUP';
RUN;
/*Stratification on propensity scores*/

```
proc rank data = PhD_DATA.final_OBJ7 groups = 5 out = PhD_DATA.rank;
  ranks rnks;
  var prob;
run;

data PhD_DATA.quint_x_1;
  set PhD_DATA.rank;
  quintile = rnks + 1;
run;

/*Check for balance between treatment groups within each strata*/

PROC FREQ
DATA = PhD_DATA.Quint_x_1;
TABLES quintile*DRUG_GROUP*Race quintile*DRUG_GROUP*Sex
  quintile*DRUG_GROUP*AGE_GROUP quintile*DRUG_GROUP*Primary_payer
  quintile*DRUG_GROUP*Admission quintile*DRUG_GROUP*DischargeStatus
  quintile*DRUG_GROUP*Phys_specialty quintile*DRUG_GROUP*Dialysis
  quintile*DRUG_GROUP*SOI /MISSING chisq NOCOL NOROW;
run;
```

**Exact/optimal one to one matching on propensity scores**

```
DATA PhD_DATA.Cases PhD_DATA.Control;
  set PhD_DATA.Matching;
  rand_num = uniform(0);
  if cases=1 then output PhD_DATA.Cases;
  else output PhD_DATA.control;
run;

PROC SQL;
CREATE table PhD_DATA.abcdef
  as select
    one.RecordId as cases_Id,
    two.RecordId as control_Id,
    one.prob as cases_prob,
    two.prob as control_prob,
    one.rand_num as rand_num
  from PhD_DATA.Cases one, PhD_DATA.Control two
  where (one.prob=two.prob);

PROC SORT
DATA = PhD_DATA.abcdef nodupkey;
BY control_Id;
RUN;
```
PROC SORT
DATA = PhD_DATA.abcdef nodupkey;
BY cases_Id rand_num;
RUN;

data PhD_DATA.Matching_done PhD_DATA.not_enough;
set PhD_DATA.abcdef;
by cases_Id ;
retain num;
if first.cases_Id then num=1;
if num le 2 then do;
output PhD_DATA.Matching_done;
num=num+1;
end;
if last.cases_Id then do;
if num le 2 then output PhD_DATA.not_enough;
end;
run;

PROC SORT
DATA = PhD_DATA.Quint_x;
by RecordId;
RUN;

DATA PhD_DATA.Case_control (RENAME = (cases_id = RecordId));
SET PhD_DATA.casecontrol;
RUN;

PROC SORT
DATA = PhD_DATA.Case_control;
by RecordId;
RUN;

DATA PhD_DATA.MATCH;
MERGE PhD_DATA.Quint_x (IN=count1)
   PhD_DATA.Case_control (IN=count2);
BY RecordId;
IF count1=1 AND count2=1;
Run;

PROC SORT
DATA = PhD_DATA.MATCH;
BY CASES;
RUN;

proc univariate data = PhD_DATA.MATCH;
by CASES;
var Hospital_costs LOS;
run;
Generalized estimating equations controlling for propensity quartile and hospital level variables

/*GEE with gamma distribution and log link to estimate hospital costs*/

proc genmod data = PhD_DATA.Quint_x_1;
CLASS DRUG_GROUP quintile Region BedSize HCO_id;
model Hospital_costs = DRUG_GROUP quintile Region BedSize / dist=gamma
link=log;
repeated subject = HCO_ID/type = exch;
output out=PhD_DATA.gencook_1 resraw=resraw reschi=reschi
stdreschi=stdreschi pred=pred resdev=resdev;
run;

/*Predicted mean costs*/

proc univariate data = PhD_DATA.gencook_1;
var pred;
run;
proc sort data = PhD_DATA.gencook_1;
by DRUG_GROUP;
run;
proc univariate data = PhD_DATA.gencook_1;
by DRUG_GROUP;
var pred;
run;

/*Plot residuals*/

proc gplot data=PhD_DATA.gencook_1;
plot Hospital_costs*pred;
plot stdreschi * pred;
plot resraw * pred;
plot reschi * pred;
plot resdev * pred;
run;

/*GEE with gamma distribution and log link to estimate hospital LOS*/

proc genmod data = PhD_DATA.Quint_x_1;
CLASS DRUG_GROUP quintile Region BedSize HCO_id;
model LOS = DRUG_GROUP quintile Region BedSize / dist=gamma link=log;
repeated subject = HCO_ID/type = exch;
output out=PhD_DATA.gencook_2 resraw=resraw reschi=reschi
stdreschi=stdreschi pred=pred resdev=resdev;
run;

/*Predicted mean LOS*/

proc univariate data = PhD_DATA.gencook_2;
var pred;
run;
proc sort data = PhD_DATA.gencook_2;
by DRUG_GROUP;
run;
proc univariate data = PhD_DATA.gencook_2;
by DRUG_GROUP;
var pred;
run;

/*Plot residuals*/
proc gplot data=PhD_DATA.gencook_2;
plot LOS*pred;
plot stdreschi * pred;
plot resraw * pred;
plot reschi * pred;
plot resdev * pred;
run;
VITA

PERSONAL INFORMATION
Name: Avani Devdatt Joshi
Date and place of birth: May 28, 1984; Gujarat, India
Citizenship: Indian citizen

EDUCATION
2006 - Present PhD student in Pharmacy Administration
Major: Pharmacoeconomics and Outcomes Research
Primary advisor: Dr. David Holdford
Virginia Commonwealth University, Department of Pharmacy
Cumulative GPA = 3.8

2002 - 2006 Bachelors in Pharmacy (BPharm)
Maharaja Sayajirao University (MSU), Department of Pharmacy, Baroda, India
Major: Pharmacy
Cumulative GPA = 3.9

RESEARCH SKILLS:
Software skills: SAS, STATA, SPSS, JMP, TreeAge DATA, MS Excel, MS Office, MS Access, Survey Monkey

Techniques: Decision Analysis, Markov Analysis, Survey Research, Content Analysis, Regression Analysis, Multivariate Analysis

Techniques in Survey Research: Survey interviewing, Pre-testing questionnaires, Cognitive interviewing, Analysis and interpretation of survey data

PUBLICATIONS
Joshi AD, Botteman MF., “Assessment of cost effectiveness of zoledronic acid in the management of skeletal metastases in lung cancer patients in five European countries (France, Germany, Portugal, Netherlands and the United Kingdom).” *Journal of Medical Economics* (Submitted September 2010)

Patel D., Joshi AD., Holdford D., “Content Analysis of off-label drug use: Reporting print media coverage.” *Drug Information Journal* (Submitted July 2010)

Joshi AD, Botteman MF., “Bisphosphonates: A pharmacoeconomic review of their use in the management of bone metastases of solid tumors.” (Submission planned for November 2010)


**POSTER PRESENTATIONS:**

Mayer S. and Joshi AD., “Use of Reflection for course feedback in an Introduction to Pharmacy Course integrating Active Learning”. Virginia Commonwealth University and Center for Teaching Excellence. [Poster presented at the American Association of Colleges of Pharmacy (AACP) 2008 meeting])

Patel D., Joshi AD., Holdford D., “Content Analysis of Off-label drug use: Reporting print media coverage.” [Poster presented at the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) meeting 2009 and at VCU School of Pharmacy Research and Career Day 2009]

**WORK EXPERIENCE:**

**Summer 2009** Health Economics/Outcomes research intern - Pharmerit International NA, Bethesda, MD

2006 - 2009 Graduate Teaching Assistant School of Pharmacy, VCU

*Important teaching experience*

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**JOURNAL REVIEWER:**

Served as an Editorial Consultant for Clinical Therapeutics, an international peer-reviewed journal of drug therapy, Volume 30, Number 9, Sept. 2008.
AWARDS:

Dissertation Award Scholarship 2010, Virginia Commonwealth University (VCU)

Phi Kappa Phi Membership Induction award (2007)

Gold medal for academic excellence from the Maharaja Sayajirao University (MSU) Pharmacy Alumni Association, Department of Pharmacy, Baroda, India

LEADERSHIP:

Indian Pharmaceutical Association (IPA)  President - MSU Student Chapter (2002-2006)

ISPOR (Student Network)  President - Educational teleconference Committee (2008 – 2009)

President - VCU Chapter (2008 – 2009)