Individualized Medicine and Biophysical System Dynamics: An Example from Clinical Practice in End Stage Renal Disease

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Abstract:

Erythropoietic Stimulating Agents (ESAs), have been used in hemodialysis patients since 1988, largely eliminating the need for transfusions to correct the anemia of chronic renal failure. However, current ESA protocols lead to suboptimal anemia control. Questions about the safety of ESAs and clinically desirable hemoglobin levels remain open, despite a series of clinical trials. Moreover, ESAs are expensive: Medicare reimbursements for ESA's in 2008 approached two billion dollars. A process improvement project conducted at Mayo Clinic initiated in 2007 revealed that current ESA protocols lead to (undesirable) oscillations in hemoglobin levels. Recognizing the behavior as a system signature, we developed a bio-pharmacokinetic model of erythropoiesis. Using prior data for a specific patient, the model provides parameters for individualized ESA response profiles. Parameter values are then used to design dosing regimens that achieve the desired results. 650 patients are enrolled in this prototype information system. The percentage of patients who achieved target and stable hemoglobin levels has improved by 40%, ESA costs have been reduced by 35%, and anemia management resource requirements have been reduced by more than 50%. Indications that hospitalizations may have been reduced by 25% are currently under study. Commercial development is underway.

Key Words: Erythropoiesis, Erythropoietic Stimulating Agents (ESA), Chronic Renal Failure, Hemodialysis, Pharmacokinetics, Pharmacodynamics, Hemoglobin (Hgb), Individualized Medicine.

Background

Despite its obvious function of producing urine, the kidney is also an endocrine organ(Jacobs et al., 1985). In response to hypoxemia, it produces the hormonal growth factor erythropoietin (EPO). EPO, in turn, is the main regulator of red blood cell (RBC) production in the bone marrow. Red blood cells undergo continual turnover with approximately 1% of the total number dying every day. To maintain homeostasis the same number of red blood cells must be produced every day by the bone marrow. Erythropoiesis is a multistep process in which erythroid precursors replicate and differentiate into mature red blood cells. At the root of erythropoiesis are the hematopoietic stem cells (McCulloch and Till, 1964). Hematopoietic stem cells divide and give rise to the erythroid progenitor cells, including erythroid burst forming units (BFU-E), in a series of replications and differentiation that are independent of erythropoietin. BFU-E cells generate erythroid colony forming units (CFU-E), whose survival and further differentiation is strictly dependent upon the presence of EPO (Broudy et al., 1991; Sawada et al., 1987). Therefore, this stage of RBC development is a critical step in erythropoiesis and is the main site of regulation of red blood cell production. Indeed cell maturation downstream of the CFU-E units is also EPO independent. There are however, other components required for the latter stages of RBC production. Especially important are adequate iron stores and the local availability of iron for the synthesis of hemoglobin (Hgb). Common causes of iron deficiency include blood loss due to occult bleeding or repeated phlebotomy and inadequate iron intake due to poor diet or malabsorption. Clinical scenarios characterized by inflammation, infection or undiagnosed cancer result in the sequestration of iron, making it unavailable for erythropoiesis also leading to anemia.

Anemia is a common complication in patients with chronic renal failure and end stage renal disease (ESRD). As renal function deteriorates, the kidneys lose their ability to produce EPO and therefore, patients develop worsening anemia. Anemia is associated with fatigue, shortness of breath, and poor quality of life. In most patients with ESRD, EPO deficiency is the major cause of anemia.

Though EPO deficiency is the major cause of anemia in ESRD patients, a common clinical measurement used to detect anemia is a patient's Hgb. Hgb is a hemoprotein composed of globin and heme that gives rise to the function of RBCs: to transport oxygen from the lungs to the cells of the body and to return carbon dioxide from the body to the lungs. In healthy adults, the normal range for Hgb is 13.6 - 17.2 grams per deciliter (g/dl) for males and 12.0 -15.0 g/dl for females. In ESRD patients, for a variety of reasons, the desired Hgb range is currently believed to be 10-12 g/dl, although this desired range is still a topic of inquiry (Besarab et al., 1998; Regidor et al., 2006). Values that are too low lead to anemia, fatigue, and poor quality of life, whereas values that are too high are associated with increased risk of cardiovascular disease and stroke (Pfeffer et al., 2009; Singh et al., 2006).

The availability of an exogenous source of recombinant human EPO enables the clinician to administer EPO to ameliorate anemia and essentially all dialysis patients receive some form of EPO replacement therapy (Elliott et al., 2008). However, EPO is associated with risks: (i) it may raise blood pressure (Felker et al., 2004; Zhu and Perazella, 2006), (ii) there is a yet to be quantified risk of accelerating tumor growth (Hadland and Longmore, 2009), (iii) it may be thrombogenic at high doses (Smith et al., 2003), and (iv) therapy is very expensive. Indeed, Medicare costs for EPO replacement therapy *alone* currently exceed $2B per year. The optimal hemoglobin in patients with ESRD is being increasingly well defined, yet with current protocols for dose adjustment, it is often very difficult to avoid major swings in hemoglobin, meaning that patients either are anemic at some times or have an undesirably high hemoglobin level at other times. Clearly, the 'average' Hgb value is not acceptable in these circumstances. Better ways to optimize therapy are required. The problem is compounded by several additional factors: (i) some patients have variable levels of endogenous EPO production despite failing kidneys, (ii) individual responses to identical EPO doses may not be the same, (iii) there are various preparations of EPO available with different pharmacokinetic properties, and (iv) concomitant co-morbidities in patients may attenuate the response to therapy with these agents.

Recognizing that many physiologic systems are regulated via feedback mechanisms, we elected to develop a simulation model of erythropoiesis. The model includes the known pharmacology of the various ESAs (Elliott et al., 2008), along with their cellular mechanism of action (Gross and Lodish, 2006). Simulations are compared with historical ESA doses and Hgb levels to provide a unique set of parameter estimates for each individual patient. The model requires a learning phase where the individual patient's physiological characteristics are defined, followed by the exploration of various therapeutic scenarios with defined goals. Once the optimal regimen is identified, the patient is issued a prescription for therapy. Weekly Hgb measurements are obtained to confirm whether the actual response of the patient matches the Hgb values predicted by the model.

In the following we provide a description of this methodology and show how a system dynamics approach led to (i) improvement in anemia management for a large cohort of patients with ESRD, (ii) improvement in quality of life, and (iii) substantial cost savings, which is highly relevant in the current age of economic austerity. Such an approach can be applied to other pathophysiologic systems.

Methods

General Comment

We provide a narrative description in stepwise fashion of how this model was constructed using the method listed in table 3-1 of Business Dynamics, (Sterman, 2002)as a guide. Our intent is to encourage modelers to follow the process outlined therein letting successive versions of their models in other areas of application inform them.

Clinical Data Set

In clinical practice, care providers reflect upon contemporaneous laboratory values and prescriptions in order to prescribe EPO therapy. However, laboratory measurements for all the patients with ESRD who undergo renal replacement therapy at Mayo Clinic are maintained in a database that is continuously updated. Thus the frequency and dose of EPO therapy and the resulting Hgb measurements were available serially for all patients. Co-morbidities that develop over time as well as hospitalizations are also prospectively monitored and documented.

As a first step in the process, we developed behavior over time (BOT) charts including Hgb, EPO doses, iron measurements, iron therapy, and a number of additional variables.

Our first observation was of the pattern of Hgb variation over time for each patient in the database. Figure 1 illustrates the variation in Hgb values over time for three typical patients that we observed.

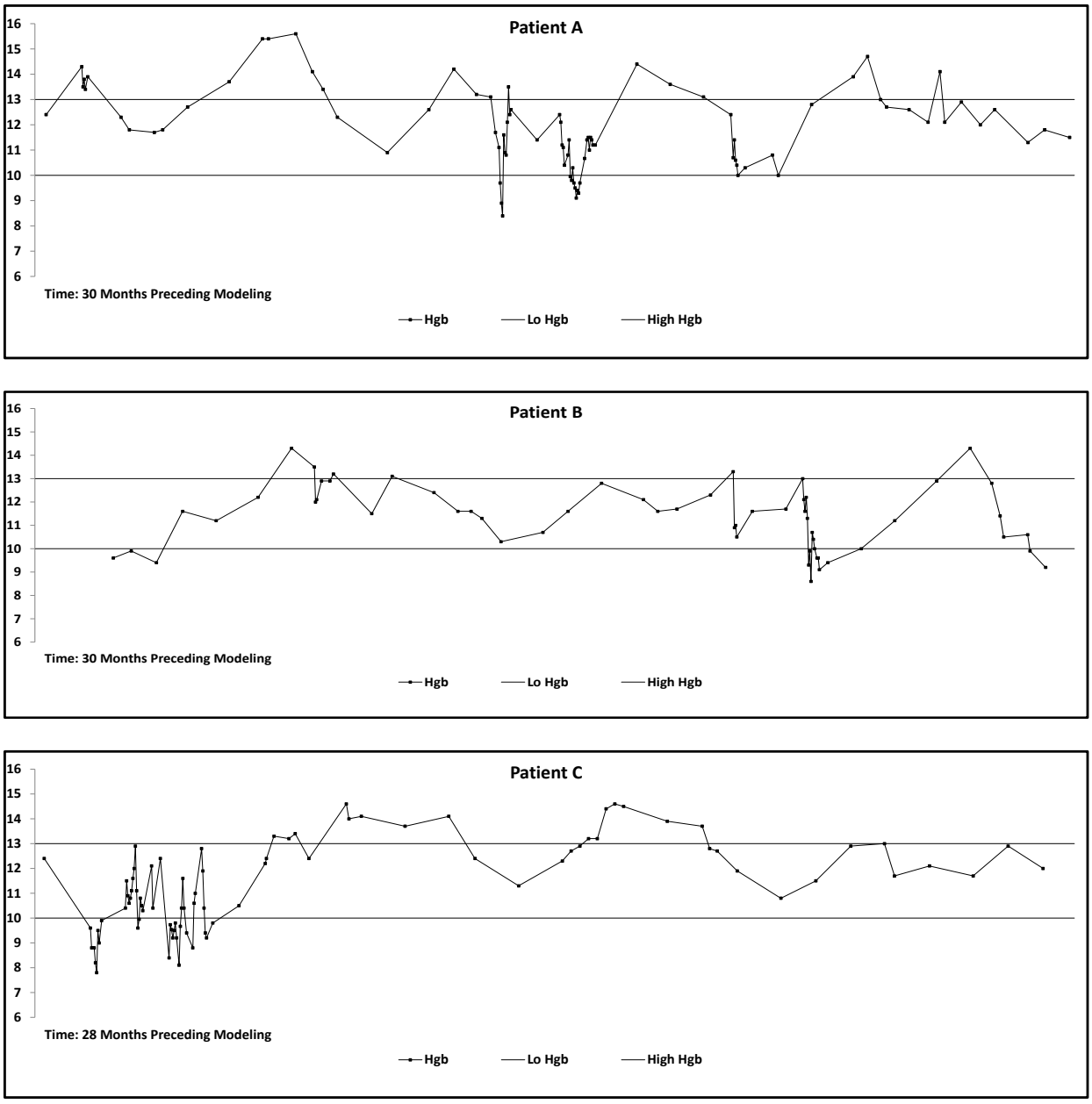

Figure 1: Hgb values for three patients for various time periods before the implementation of the optimization protocol. The values illustrate high variability and excursions above and below the target range of 10-13 g/dl. (Abrupt drops typically indicate hospitalizations and repeated phlebotomy.)

This pattern of variation is well known in the field and well documented (Fishbane and Berns, 2005). Because structure causes behavior, the observed patterns of variation were the primary motivation in seeking an understanding of the causal structure of this variation using system dynamics.

Model Development

The core team in the model development project consisted of a physician assistant, a model developer skilled in pharmacokinetics and pharmacodynamics (PK/PD), a process engineer, a hematologist, a medical director, and an application developer.

We then elicited expert responses to the question: "What causes Hgb levels to rise or fall?" We posed the question with the stock and flow diagram shown in figure 2.

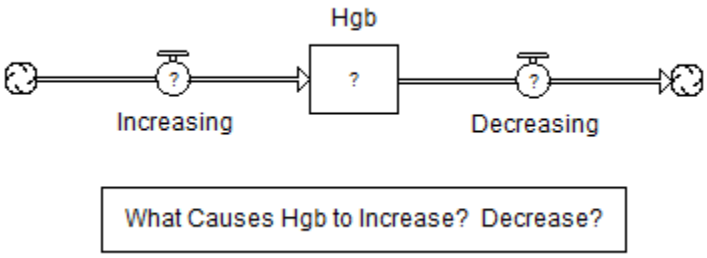

Figure 2: How hematology neophytes who do systems thinking inquire about Hgb values.

The answer was "Hgb levels are determined by the reticulocytes (nascent RBC's) and RBC's in circulation". For the purpose of our model actual Hgb was assumed to be a scalar multiple of reticulocytes and RBCs in circulation. This extended the model "upstream" in the erythropoietic process, shown in figure 3.

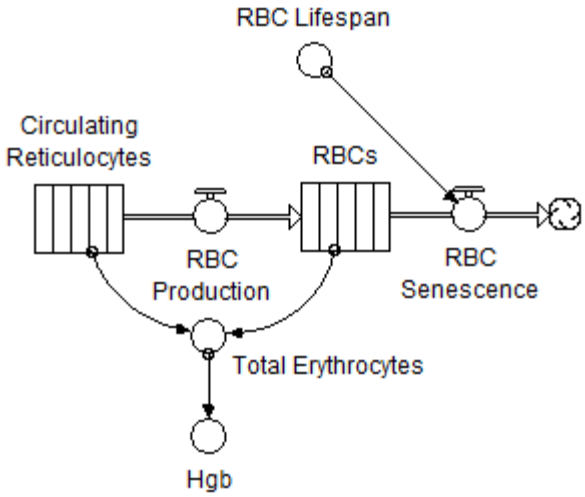

Figure 3: Conceptual relationship between erythrocytes and Hgb values.

The lifespan of an RBC in a healthy adult is about 120 days. In ESRD patients, RBC lifespans range from 60 to 100 days (Eadie and Brown, 1955). In either case, the lifespan of reticulocytes (or transit time in SD parlance) was assumed to be 2-3 days.

At this point, since the hematologist had not yet joined the project team, and in order to understand the causal factors of RBC production, we conducted a basic study of RBC development, a process which we learned was named "erythropoiesis" (originated from the Greek: "red making"). After a review of basic hematology, we learned that a useful stock and flow structure that can be used to simulate erythropoiesis might appear as in Figure 4.

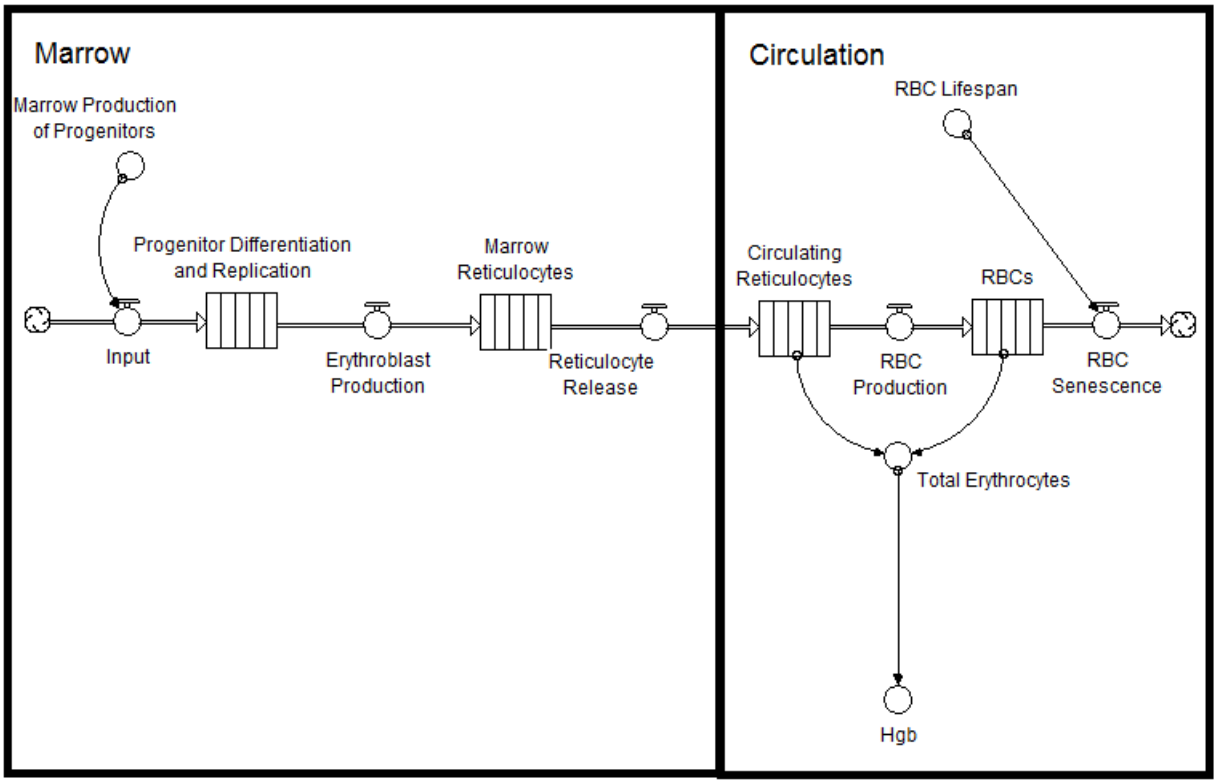

Figure 4: Conceptual map of erythropoiesis.

Based upon our literature review, the transit time from "Marrow Production of Progenitors" to "Reticulocyte Release" was assumed to be 18 days.

This structure began to inform us about how to answer the next question: "What determines the number of RBCs in circulation"?

The answer depends on two components: the rate of production of these cells ("Marrow Production of Progenitors") and their destruction ("RBC Senescence"). Normally, ~1% of the red cells are dying per day as a result of changes in RBC membrane proteins that mark them for destruction in the spleen and liver (Rous and Robertson, 1917). This rate of destruction is relatively constant, although it is higher in patients with ESRD. Here we are assuming that there are no pathologic losses of RBC's as occurs in bleeding (e.g. into the gut, urine, or as a result of surgery). If we consider that in most patients the rate of RBC turnover is constant, then the next step is to estimate two exogenous parameter values: "Marrow Production of Progenitors" (a rate)

and "RBC Lifespan" (a constant). We obtained reasonable initial parameter values from the literature (Dingli et al., 2007).

At this point our model was capable of simulating steady state erythropoiesis. Using the parameter values we had obtained, our model could generate appropriate counts of circulating reticulocytes and RBC's, and the resulting simulated Hgb value.

The next event in the modeling project underscores what is already well known among systems thinkers: causal stock and flow structures are powerfully efficient communication tools!

Recapping:

- We had a structure that could simulate Hgb values.
- We knew that ESRD patients frequently suffer from anemia (i.e., low Hgb).
- EPO replacement therapy can correct anemia.
- However, EPO replacement therapy often leads to Hgb oscillations ("Hgb cycling").

What is the cause of the oscillation?

EPO replacement therapy is delivered by the administration of Erythropoietic Stimulating Agents (ESAs). Approved for use in 1988, a variety of ESAs have been developed with differing characteristics the most notable of which is the bioavailable half-life(Elliott et al., 2008). The original formulation had a half-life of 5-8 hours. The particular ESA used at Mayo Clinic has a half-life of approximately 24 hours. Other available formulations have even longer half-lives. (The purpose behind the production of ESA's with longer half-lives by the pharmaceutical industry was to reduce the frequency of drug administration and operational costs, as well as to simplify the patient-provider relationship.)

Our dynamic hypothesis at the time was "Whatever causes Hgb cycling to occur, it must have something to do with the half-life of the ESA".

Modeling intravenous (IV) administration of the ESA used at Mayo Clinic was straightforward, conceptually diagrammed in Figure 5.

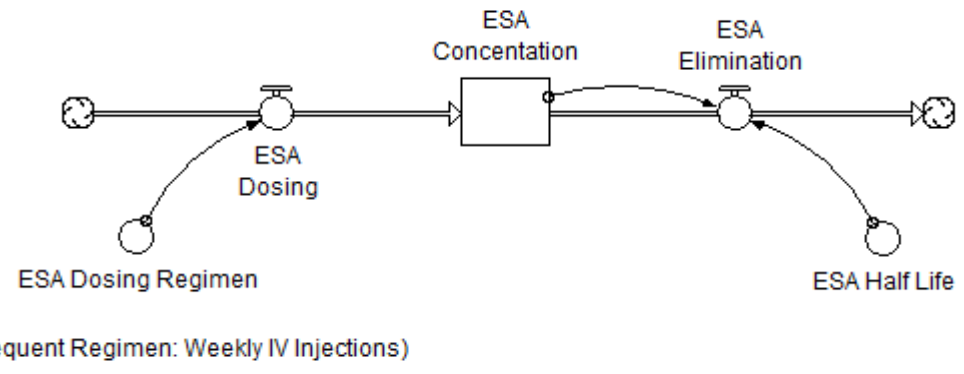

Figure 5: Conceptual map of ESA Concentration.

Before our first meeting with a hematologist, we took the name of Erythropoietic *Stimulating* Agents at face value, leading to the structure in Figure 6.

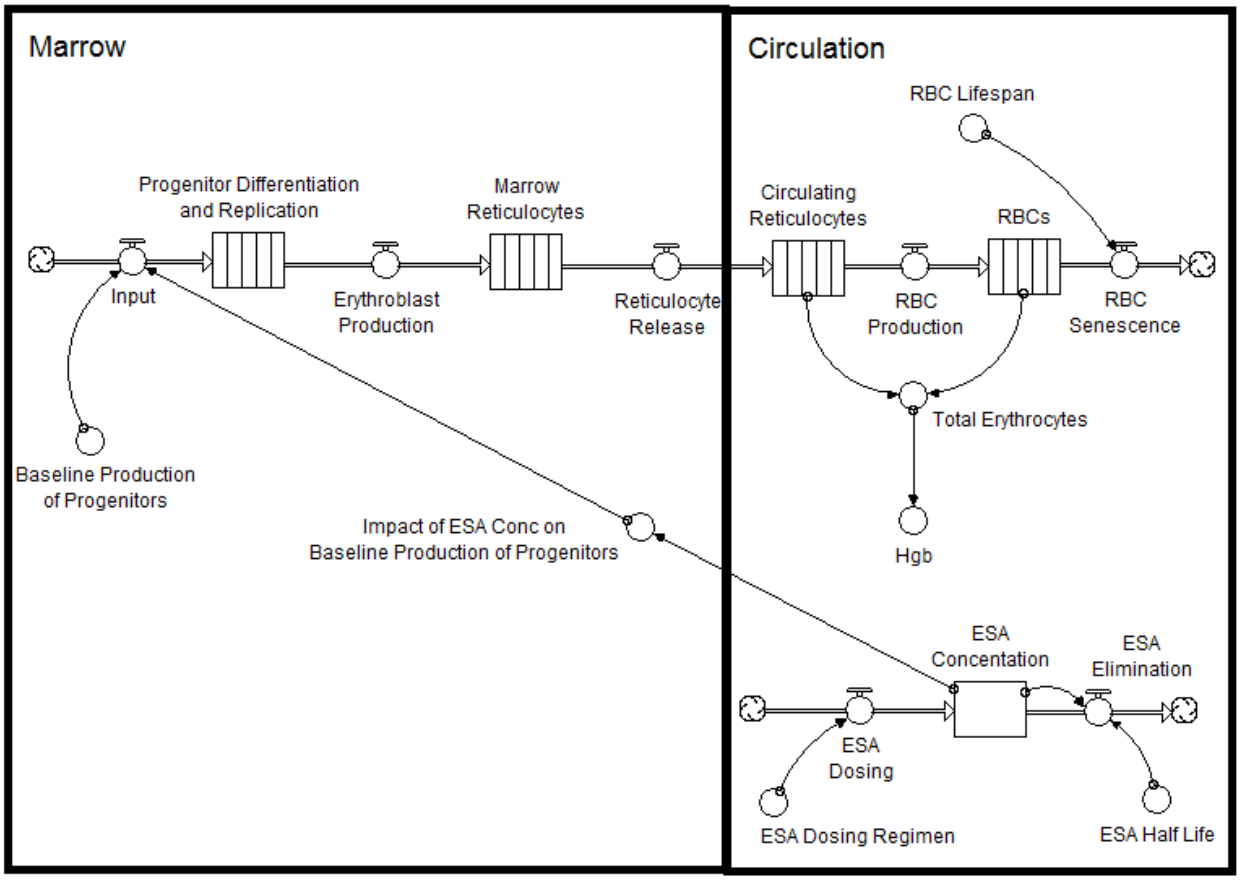

Figure 6: How hematology neophytes who do systems thinking prepare for an interview with a leading hematologist about the PK/PD of ESAs.

A review of the hypothesized model shown in figure 6, in our first meeting with a hematologist who was not familiar with system dynamics, required approximately 15 minutes. After a single walk through the model structure, his response was immediate:

"What you have portrayed here depicts a common misconception in the field. Indeed the agents are named Erythropoietic *Stimulating* Agents, and their overall effect is to increase RBC production. But they are not called stimulating agents because they increase the production of progenitors.

"The actual mechanism by which RBC production is increased is by decreasing progenitor cell apoptosis (Broudy et al., 1991; Sawada et al., 1987). (Apoptosis: derived from the Greek, "falling leaves.") Apoptosis, or programmed cell death, is a process by which "excess" progenitor cells exit the RBC developmental pathway. ESAs, or EPO, reduce the apoptosis rate, which allows more progenitors to survive, which ultimately (i.e. after a delay) results in more RBC's and thus higher Hgb values. Of course, complementary components for RBC production (such as iron) must be available downstream in the erythropoietic process for RBC's to fully

mature and enter the circulation. When this process succeeds, the oxygen carrying capacity is increased and anemia is minimized."

We assert that if we had relied upon delay differential equations, for example, to pose our question, no such clarity could have been obtained. Causal stock and flow structures are highly effective communication tools.

We therefore adopted a multicompartment mathematical model of hematopoiesis (the overall process of the generation of blood cells of all types) which captures the process from hematopoietic stem cell (HSC) replication to the generation of reticulocytes (Dingli et al., 2007). The latter are released from the bone marrow where they mature to form red blood cells. The steps between the HSC and BFU-E (generalized in the figures above and below as progenitor cells) are considered to be independent of EPO and one can consider that production of cells up to the BFU-E occurs at a constant rate (in the absence of concomitant disease or therapy that interferes with this process, e.g. chemotherapeutic agents). However, EPO is critical for the survival of CFU-E (also generalized as progenitors in the figures above and below) that replicate and differentiate to produce proerythroblasts (Broudy et al., 1991).

This transition from CFU-E colonies to proerythroblast is the critical step since it marks the commitment of cells towards the erythroid (RBC) lineage. Cells downstream of the proerythroblast are independent of EPO and therefore, EPO serves to regulate the bottleneck in erythropoiesis – low EPO levels leads to considerable apoptosis of CFU-E cells and a reduction in RBC production while high levels of EPO increase the survival of CFU-E cells and increased production and release of RBCs. *Therefore, unless EPO dosing is correctly scheduled, swings in red blood cell counts will be inevitable, albeit with a delay since cells require time to mature* (Fishbane and Berns, 2005). This delay between EPO administration and its effect on red blood cell output by the bone marrow is a signature of the architecture and dynamics of hematopoiesis and unless understood will inevitably lead to swings in hemoglobin levels. Given the exponential growth of populations in hematopoiesis (due to cell replication) (Dingli et al., 2007), even small changes in EPO concentration and the size of the CFU-E population will have dramatic changes in bone marrow output – hence the undesirable swings in hemoglobin levels.

Hematopoiesis/erythropoiesis is the same process across all patients but the *details* in each individual patient differ – (i) endogenous production of EPO varies from patient to patient due to some production from any residual kidney function as well as production by the liver (Yigit et al., 1978), (ii) presence of iron deficiency, (iii) co-morbid conditions such as infection that limit bioavailable iron for erythropoiesis (Eleftheriadis et al., 2009).

We estimated these parameter values for individual patients by using the individual's serial data where EPO therapy was followed up with successive hemoglobin measurements. The multi-compartment model of erythropoiesis (bone marrow and circulation) was then individually fitted to each patient's data in order to determine individualized parameter values. It was assumed that the pharmacokinetics of the ESA were standard across all patients. The best fit was determined by Monte Carlo simulation using a least squares fit approach. Subsequently, using the literature to guide us on the known pharmacology of the ESA, the model generated various prescriptions that would generate sufficient RBC production to maintain Hgb values within the desired range.

Insights from the hematologist led to the final (conceptual) structure of the model shown in figure 7.

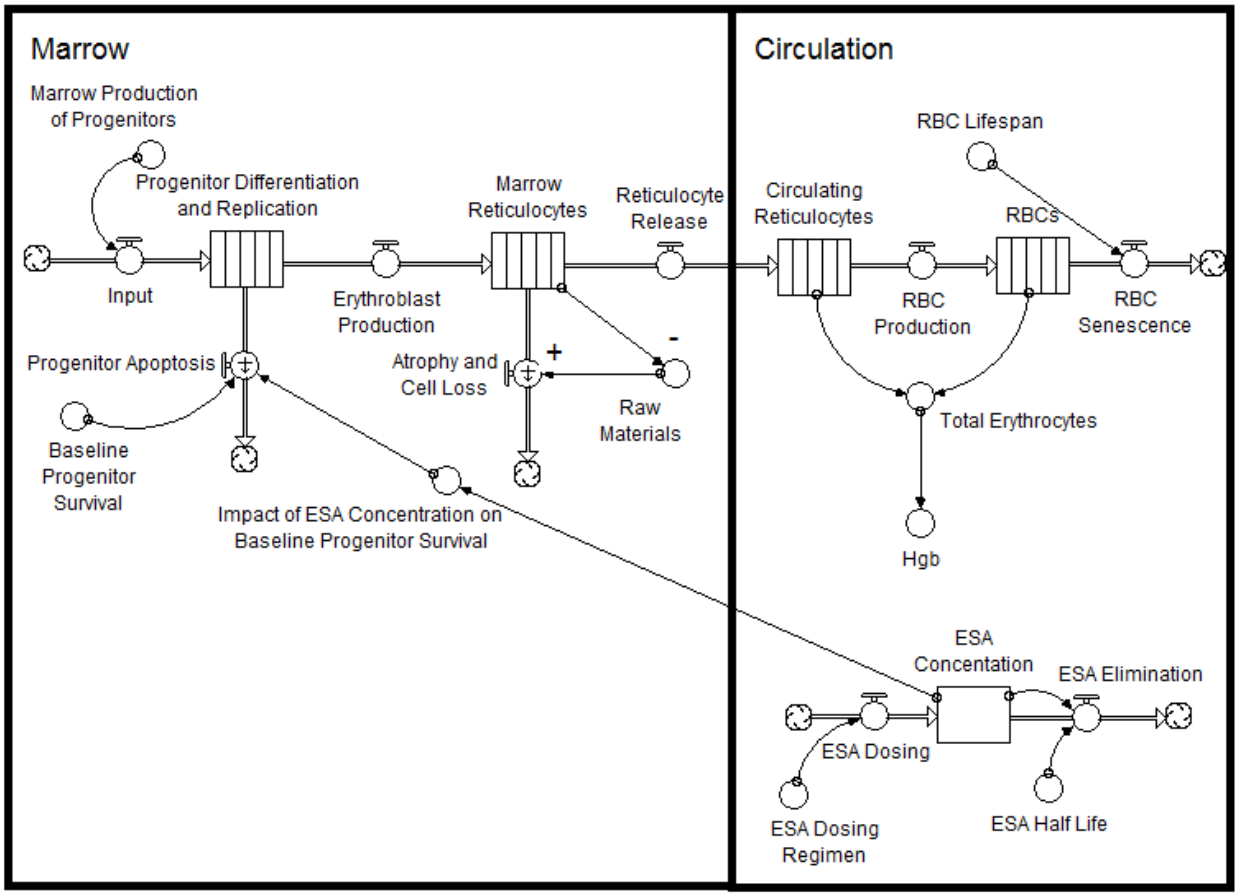

Figure 7: The result of cross functional experts allowing successive iterations of a model to inform them: a deep operational understanding of the PK/PD of ESAs in dynamic interaction with erythropoiesis.

Testing the Model

The prescription generated for each patient was then issued, and the response to this prescribed therapy was monitored under an IRB approved protocol. Patients enrolled in the study were administered ESA strictly according to the prescribed plan. The patient's hemoglobin was then monitored on a weekly basis for a minimum of 12 weeks. The efficacy of the approach was determined in two ways: (i) actual Hgb values obtained were compared to the Hgb values predicted from the forward simulation of the model. Variances between actual and predicted Hgb values were skeptically and meticulously examined. For example, among 18 patients with actual Hgb values that differed from the projected values, we found that 13 of the 18, despite our best efforts to ensure compliance to novel dosing regimens indicated by the model, had dose misadministration (either in the amount of ESA given or the timing of the dose), 4 of the 18 had emergent medical conditions that served as confounding factors since the model could not

capture this level of complexity, and for 1 of the 18 patients, no clear explanation for the discrepancy could be identified. (ii) A global analysis of all patients to determine the frequency distribution of patients with Hgb values in the desired range before and after implementation of the system dynamics approach.

To add statistical rigor, we are currently conducting an analysis in which essentially each patient is his own control, comparing the variation in hemoglobin values before and after implementation of the methodology.

Implementation in Clinical Practice

In order to interact with the information produced by the model in clinical practice, we developed a web based application to display the serial behavior of individual patient hemoglobin values, both actual and projected. The application presents, as behavior over time charts, the prescribed and actual ESA dosages, actual iron dosages, hospitalizations, iron labs, MCV, interdialytic weight gain, blood pressure and other measurements. The user may filter groups of patients displayed to include only those with hgb excursions outside the target range. Notes produced by the physician and a simulation analyst are maintained and presented together with medications and prescription status.

The application enables the administering physician to rapidly scan and analyze the status of a large number of individual patients. Deviations of hgb values from predicted values can be examined to determine the cause and, in several cases, have been the first indicator of emergent clinical issues. Timely intervention in these cases has avoided potential hospitalizations. Indeed, an analysis of hospitalization records we performed indicates that the number of hospitalizations per year as well as the number of days hospitalized per year may have been reduced by more than 25% for patients treated according to the recommendations of the new dosing algorithm.

Results

Fluctuations in Hemoglobin Levels

In figure 1 we provide representative results of the variation in hemoglobin levels for 3 patients receiving EPO therapy. As can be seen, considerable variability in hemoglobin levels occurs when the "standard dosing algorithm" is followed. Note that patients invariably had episodes when the hemoglobin was either above or below the limits of the target range.

Model-Based Therapy

In figure 8, we extend the story of the three patients shown in figure 1 to include an additional 18 months of follow up after adopting model-based therapy. Prior to the implementation of the new algorithm, Hgb measurements reveal wide oscillations. After individual data fitting and definition of the optimal dosing regimen for these patients, the amplitude of the oscillations decreased and Hgb values were in the desirable range essentially all the time.

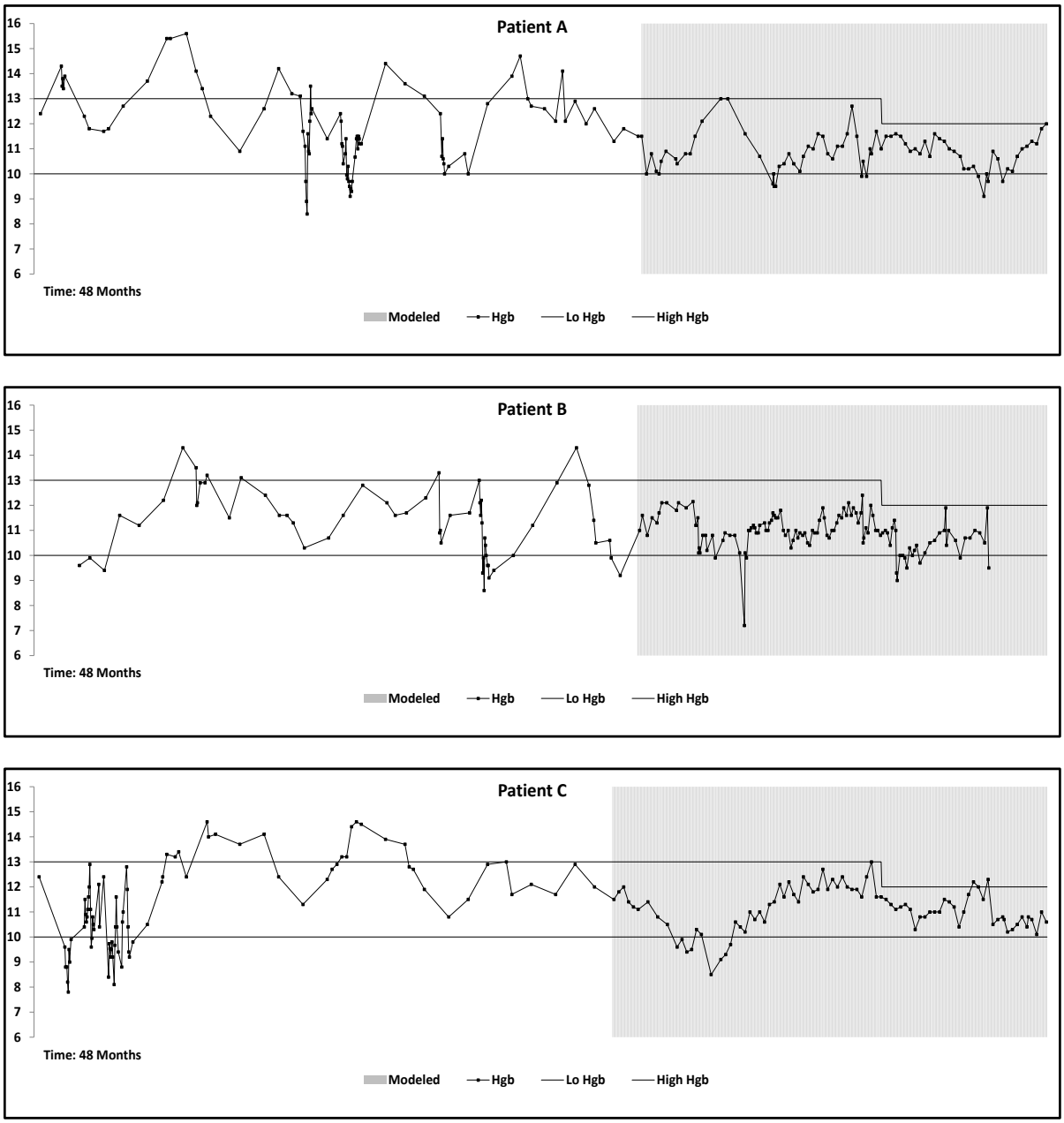

Figure 8: Before and after Hgb comparison for patients A, B, and C.

Note that the target range was narrowed from 10-13 g/dl to 10-12 g/dl in mid-2010. This was done for two reasons: (i) anticipation of the target range that would be mandated beginning in January 2011, and (ii) *growing confidence among the clinical team members that the simulation model and the information system in which it was embedded, constituted a reliable operational model of erythropoiesis*. The new algorithm was able to generate prescriptions that kept Hgb values within this more stringent range.

The modeling project had surfaced and examined prevailing mental models of erythropoiesis and brought about significant changes in understanding:

- Dynamic hypothesis before the project: "Hgb cycling has something to do with the extended half-life of the ESA we are using."
- Dynamic hypothesis after the project: "Hgb cycling is *caused by* ignoring the structure of erythropoiesis and the impact of ESA at a critical stage of RBC precursor formation and by failing to ensure adequate complementary RBC building blocks are available exactly when needed. Given effective attention to these factors, adequate and stable Hgb values can be achieved."

This new understanding has compounded healthcare value delivery in a number of significant ways: (i) Patients feel better, are more compliant and more motivated to continue with the rigors of life on hemodialysis, (ii) since patients have adequate and stable Hgb values, patient care is simplified and (iii) when Hgb values change or even make excursions above or below the target range, this triggers a search for the development of concomitant problems (e.g. bleeding) leading to an improvement in medical care.

Compliance with Current Metrics

Medicare requires that the outcomes of patients with ESRD and EPO therapy be reported. They are interested in the proportion of patients with hemoglobin levels below, within and above their recommended range, which, as described above, was narrowed to 10-12 g/dl as of January 1, 2011.

Reimbursement depends on patients achieving the defined goals. Despite the best efforts of the providers, almost 40% of patients were outside the target range in 2007. With the introduction of the model based therapy, the percentage of patients with Hgb above 13g/dl (the target in 2007) fell from 30% to less than 11%. This is quite important since it implies that a considerable fraction of patients were being *over-treated* with EPO – a fact that has both medical as well as economic implications. The fraction of patients with Hgb values less than 10 did not change significantly – in most of these patients, concomitant disease is present that precludes an optimal response to EPO therapy. Therefore, "failure" of the model to accurately prescribe and predict a response should serve as a stimulus for the medical provider to look for additional co-morbidities that could be contributing to the anemia, further improving patients' quality of life.

The results for consecutive years since implementation of the program are presented in Figure 8.

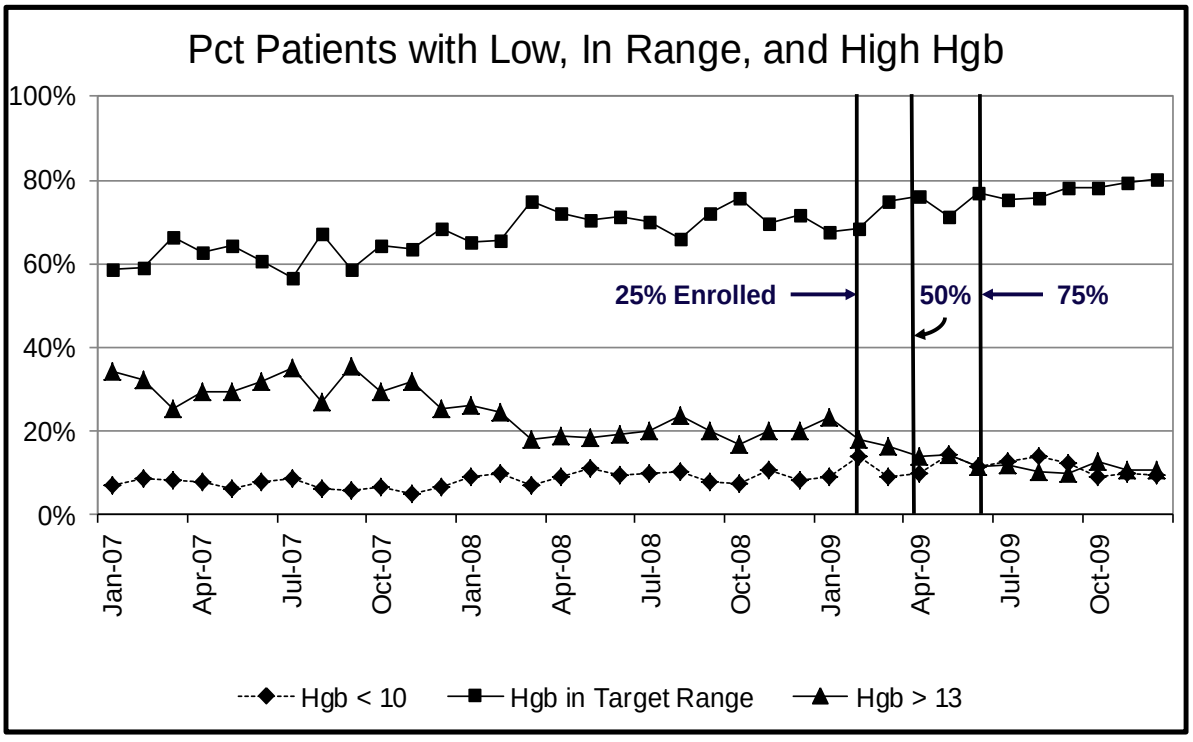

Figure 8: Key metrics dialysis providers report to Medicare include the percentage of patients with Hgb < 10 and Hgb > 13. In fact, beginning in 2011, the range has been narrowed to 10-12 g/dl. Moreover, reimbursement will be based upon these metrics, with penalties applied for excessive percentages below 10 or above 12. The model based protocol has consistently and steadily improved these metrics. Notably, the percentage of patients with Hgb > 13 has been reduced from 30% in 2007 to 11% at the end of 2009. In the industry, this is exceptional performance.

EPO Consumption

Endogenous EPO production is a variable that can be understood with our modeling approach. In addition, as mentioned above, our data suggests that without the system dynamics approach, a considerable number of patients are *over-treated* with EPO. Therefore, we measured the total EPO consumption not just in our cohort of patients before and after introduction of the dynamic modeling approach, but among *all* hemodialysis patients under Mayo Clinic's care, whether participating or not in this protocol. As can be seen from Figure 9, as more patients were enrolled in the program, EPO utilization was reduced by 37%, resulting in total cost savings of more than $1 million per year. By limiting this analysis to the actual cohort of participants, reductions would of course exceed 37%.

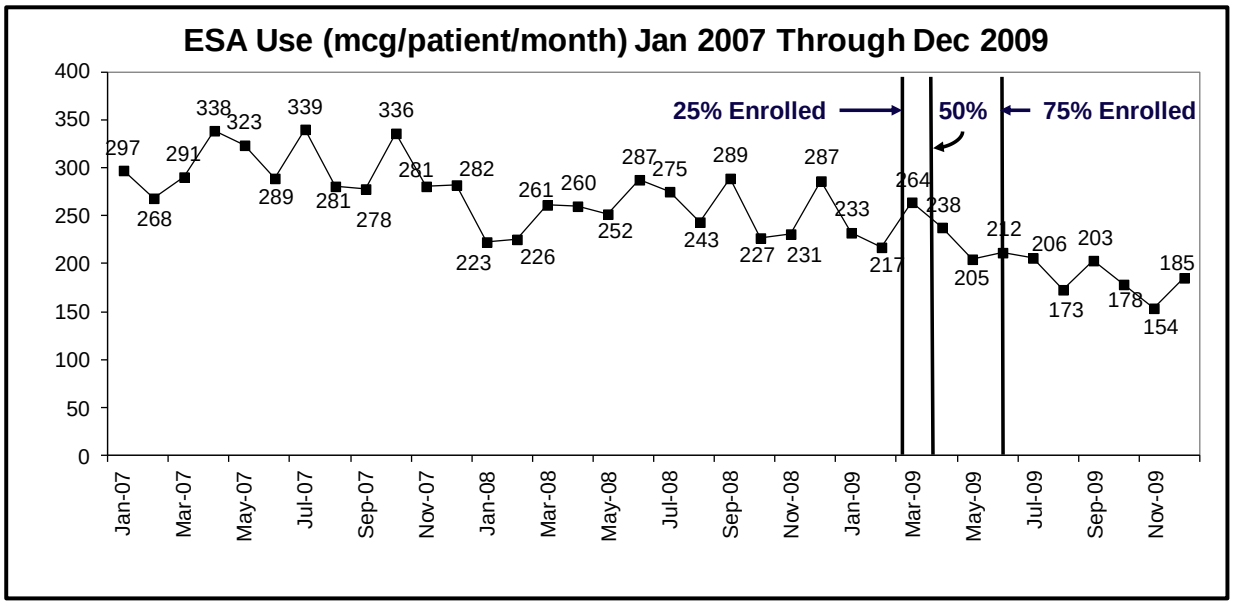

Figure 9: During January 2007 through January 2009, we tested the model based protocol extensively. As our confidence in the model increased, we enrolled patients at a faster rate. ESA use was reduced by 37%, reducing expenses by $1.1M per year over the 36 month period. (297 - 185) * $2.66 per mcg * 311 patients * 12 months per year = $ 1.1 M per Year.)

Future Work

The "model failures" mentioned above are a consequence of the model boundary chosen for the first version of the model. Future extensions to the current model under consideration include:

- Changing exogenous (and constant valued) model parameters to endogenous model variables.
- Introducing the effects of infection and iron sequestration on red blood cell output.
- Considering the variable fluid dynamics that occur in patients with ESRD that result in hemodilution and resultant variations in Hgb measurements.
- Including iron metabolism and dynamics.

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