An Individualized ESA Dosing Regimen for Hemodialysis Patients To Stabilize Hemoglobin Levels in a Target Range

James Rogers, MS, MBA
Advance Management Group, LLC
4447 Manchester Lane, NW, Rochester, MN 55901
T: 507-289-4680
rogers.james@amgresults.com

Edward J. Gallaher, Ph.D.
Applied System Dynamics, LLC
533 NE 37th Avenue, Hillsboro, Oregon 97214-6307
T: 503-577-7547; F: 503-648-5637
ed@appliedsd.net

Craig Hocum, P.A. -C
Mayo Clinic
200 First Street, SW, Rochester, MN 55905
T: 507-312-4353; F: 507-266-1963
hocum.craig@mayo.edu

David Dingli, M.D., Ph. D.
Mayo Clinic
200 First Street, SW, Rochester, MN 55905
T: 507-284-3417; F: 507-266-4972
dingli.david@mayo.edu

Introduction

We previously reported on a modeling project designed to determine erythropoietic stimulating agent (ESA) dosing regimens for hemodialysis patients, (Rogers, Gallaher, and Hocum). There, we describe the stages of model development, its implementation, and the results obtained.

Here, we revisit the project to describe the model structure, focusing on the empirical foundations of the formulations and parameters as found in biomedical and clinical literature. We describe the model behavior, its replication of the clinical issue at hand, and show how the model was used to develop superior policies. We then discuss how the new policies were implemented in the host organization, and present the results which accrued over time. After a discussion of the limitations and possible extensions to the model, we suggest how so-called "inside the skin" dynamic modeling could shape the future of individualized medicine.

Contextual Background

End stage renal disease (ESRD) is the last stage of chronic kidney disease (CKD). At this stage the kidneys are functioning below 10 percent of their normal function, and cannot support a person's day-to-day life by removing waste and excess water. ESRD is usually the result of chronic kidney disease (CKD) which causes declining kidney function to the point of complete failure.

ESRD imposes a significant burden on the US healthcare system. Modalities of renal replacement therapy are transplantation, peritoneal dialysis, and hemodialysis (HD). In 2014 the US had 410,000 HD patients, 63% of all prevalent ESRD cases, at the end of 2014. USRDS ADR (2016).

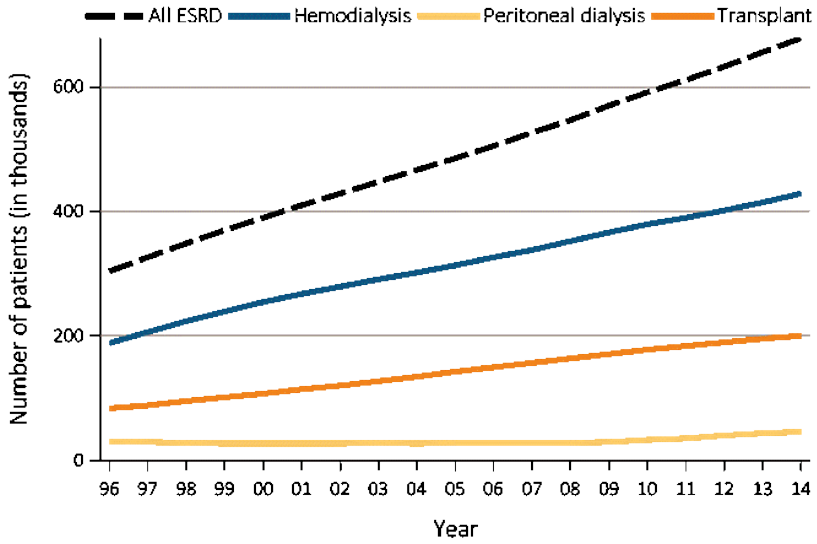

Figure 1. Trends in the number of ESRD prevalent cases (in thousands) by modality, in the U.S. population, 1996-2014

When Medicare eligibility was extended to persons with ESRD in 1972, only about 10,000 were receiving dialysis. This patient group grew to nearly 400,000 patients by 2014. Even though the ESRD population has remained at less than 1% of the total Medicare population, it has accounted for about 7% of Medicare fee-for-service spending in recent years. The cost to Medicare at year end 2014 was approximately $26B, as shown in figure 2. USRDS ADR (2016).

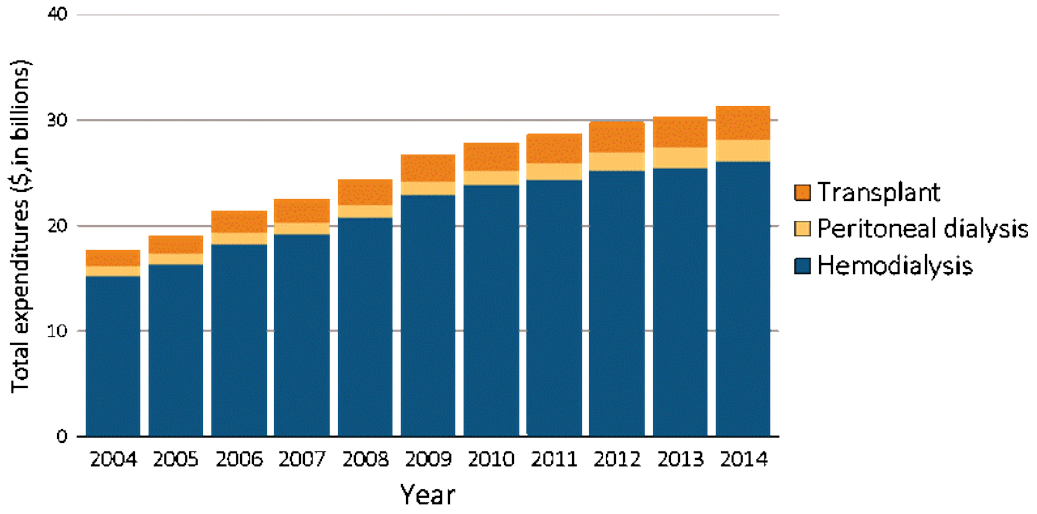

Figure 2. Total Medicare ESRD expenditures, by modality, 2004-2014. Cite USRDS.

It is beyond our scope to provide a detailed analysis of the Medicare reimbursement policies for ESA use for HD patients. Summarizing, the cost of ESA "injectables" for HD patients had grown to just under $2B by year end 2010. A bundled payment system was implemented in year 2011 after which Medicare reimbursements for these drugs were no longer tracked. For our purposes we note that ESA expenditures were indeed significant and any improvement in their use would be of great value.

HD therapy in 2014 was primarily performed by 6,750 in-center Dialysis Care Facilities (DCF) organized into 18 regional networks. In 2014 the two largest dialysis organizations, Fresenius and DaVita, collectively treated 69% of patients in 65% of all dialysis units.

HD patients typically receive therapy 3 times per week in a 3- to 4-hour session at their assigned DCF.

The quality of Hemodialysis therapy is under constant review, with a focus upon these key indicators:

Dialysis Adequacy: the extent to which removal of wastes and excess fluids is achieved per dialysis session.

Access Method: how the patients' bloodstream is accessed and routed to external filtration, with a preference for a surgically implanted fistula versus an inserted catheter, which is more susceptible to infection.

Bone Health: Various lab measurements involving calcium, phosphorous, and parathyroid hormone

Infection Rate: With a goal of zero.

Anemia Management: as measured primarily by a patient's Hemoglobin (Hgb) conformance to a target range. At the initiation of this project, the nationally recommended target range for Hgb was 10-13 grams per deciliter of blood volume.

The Clinical Setting

This project addressed anemia management issues for HD patients receiving care through Mayo Clinic Dialysis Services (MCDS), the service arm of the Mayo Clinic's Department of Nephology and Hypertension.

By way of introduction, MCDS is classified as a Small Dialysis Organization (SDO) by the Centers for Medicare & Medicaid Services (CMS), having fewer than 100 DCF's in service. MCDS is part of:

- An academic, non-profit institution, caring for
- 650-700 prevalent HD patients, across
- 17 DCFs, staffed by
- 15 nephrologists, 7 allied staff - 2 PAs, 2 NPs, 3 RNs, following
- Common policies & procedures, supported by a
- Shared dialysis database

At the initiation of the project in 2008, MCDS anemia management performance goals were:

Best Practice: 85% or more of dialysis patients with mean Hgb [average of first-of-the-month values for previous three months] between 10 and 13 g/dl, and

Recommended Practice: 80% or more of dialysis patients with mean Hgb between 10 and 13 g/dl

At that time, 34% of MCDS hemodialysis patients had mean Hgb levels above 13, 59% had levels within the target of 10 to 13, and 7% had levels below 10. (McCarthy.)

Plans were underway within CMS at that time to initiate bundled pay for performance reimbursement policies in 2011. Reimbursements to providers would be reduced if performance objectives were not met. It was important to MCDS to understand why anemia management performance levels were below target and develop strategies to improve them.

A Problem within the Problem

Hgb values are reported in g/dl, while hematocrit denotes the volume percent of packed RBCs; both measurements refer to whole blood samples. Normal values for healthy adults lie within the ranges shown below (Billet).

	Hgb	Hematocrit
Male	14-18 g/dl	40-54%
Female	12-16 g/dl	36-48%

Table 1. Normal Hgb and Hematocrit Ranges

Healthy adults have a total of about 2-3e+13 red blood cells (RBCs), consistent with the Hgb and hematocrit values shown above. RBCs have a lifespan of about 120 days; senescent cells are removed by the spleen and iron is recycled for use in new cells. RBCs must therefore be replaced at a rate of 2e+6/second, or 1.7e+11/day (Elliott).

RBC production takes place in the bone marrow and is critically dependent on the hormone erythropoietin (EPO). EPO is synthesized and released into the circulation by specialized cells in the kidney as a response to tissue hypoxia, thus creating an endogenous balancing loop to maintain adequate tissue oxygenation. Although the pathogenesis of anemia of CKD is multifactorial, the decreased production of EPO with declining renal mass is considered the primary etiologic factor.

For reasons that are unclear, optimal Hgb values are somewhat lower for dialysis patients, between 10 and 12 g/dl. Values below 10 g/dl are evidence of anemia, leading to poor tissue oxygenation, fatigue, cognitive deficits, dyspnea, an increased likelihood of falls, along with a worsening quality of life. Hazards of levels above 12 g/dl are less obvious; however, increased blood viscosity contributes to an increased probability of congestive heart failure, heart attacks, and strokes.

Recombinant human EPO (rHuEPO; Epogen) has been cloned, and was approved for use in 1989 with the following indication: “treatment of anemia associated with chronic renal failure, including patients on dialysis (end stage renal disease) and patients not on dialysis.” (Luksenburg). Along with iron, exogenous replacement of EPO quickly became a standard of care for ESRD patients. (Kalantar-Zadeh). A derivative of EPO, darbepoetin-alfa (Aranesp) became available in 2001, with similar indications.

In this paper we refer to these drugs as erythropoietic stimulating agents (ESAs). Millions of people worldwide have benefited from these drugs over the past 28 years. Before their availability, the standard of care for the treatment of anemia among dialysis patients was blood transfusion, a therapy which included risks of immunologic sensitization, infection, and iron overload.

Results of pre-approval Phase I and II clinical trials conducted in 1987 demonstrated that recombinant human erythropoietin [ESA] is effective, can eliminate the need for transfusions ... and can restore the hematocrit [and Hgb] to normal in many patients with the anemia of end-stage renal disease. (Eschbach et al). Figure 3 shows how effective ESA therapy was – it was revolutionary.

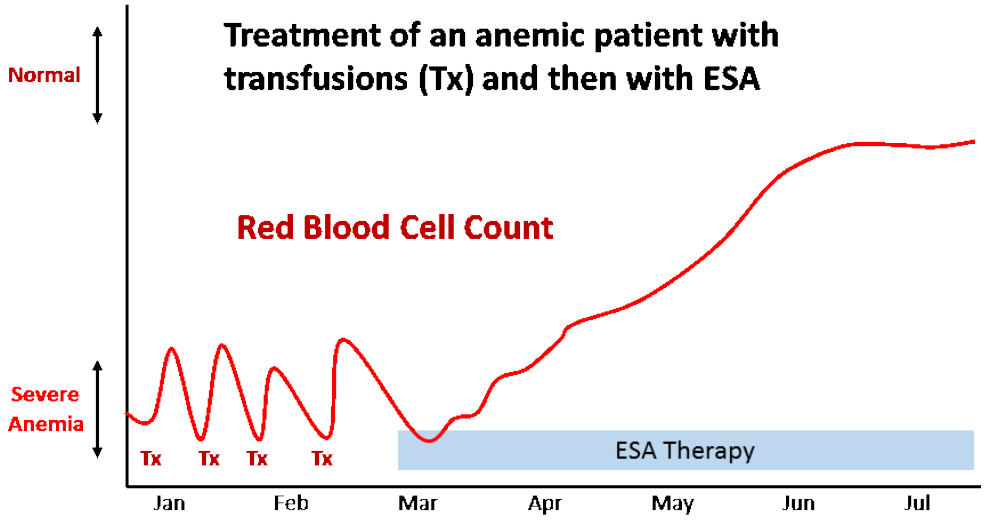

Figure 3. ESA replaces transfusions as the preferred standard of care. Adapted from Eschbach.

Treatment with recombinant human erythropoietin (rHuEPO) [ESA] has been a major advance for the management of anemia in patients on hemodialysis. Therapy, however, is typically observed to be associated with recurrent cyclic fluctuations in hemoglobin levels. It is most closely associated with frequent rHuEPO dose changes, hospitalization, and iron treatment practices. (Fishbane).

The Clinical Challenge

In addition to the problems with low and high Hgb levels described above, Hgb cycling itself is detrimental. Blood viscosity is highly sensitive to hematocrit, creating additional burdens on the cardiovascular system.

Late in 2007, we began an effort to understand why so many MCDS patients had Hgb values outside the target range through a comprehensive review of the available data. We too observed Hgb cycling, with many patients having a longitudinal history Hgb lab value measurements similar to those of figure 4.

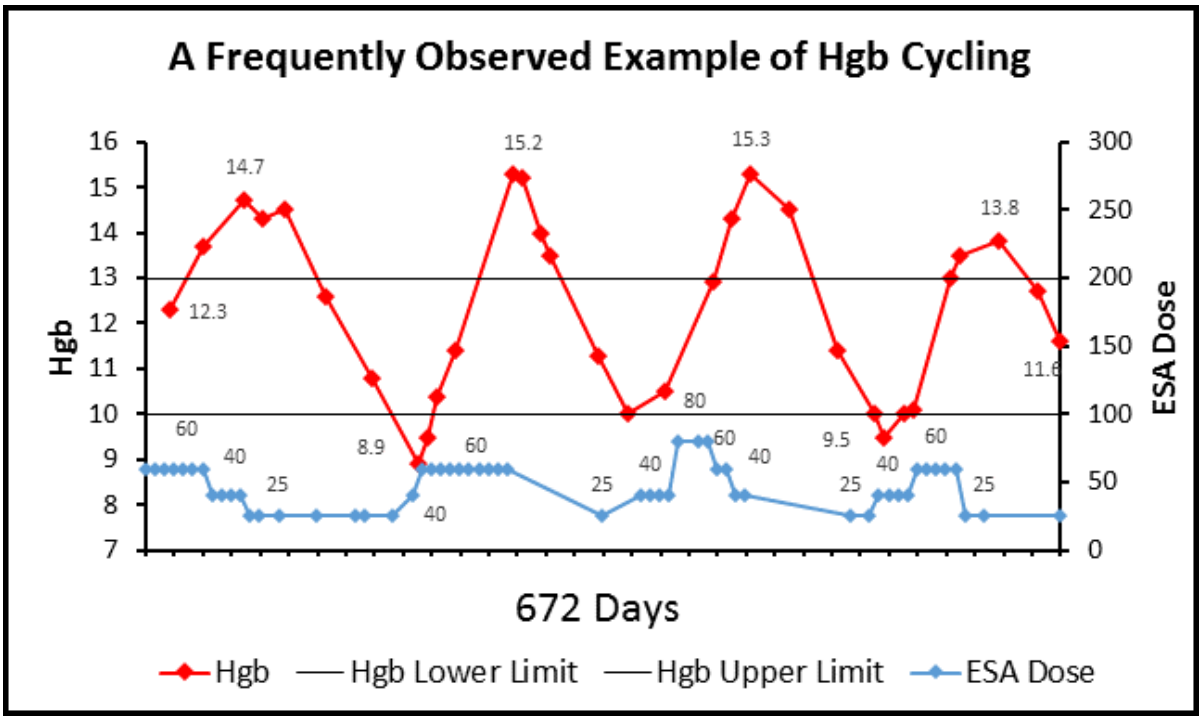

Figure 4. Typical pattern of Hgb cycling among MCDS HD patients following standard protocol. (McCarthy).

We had two issues to resolve. We needed to understand why so many patients' Hgb lab values were out of range, and we needed to understand why individual patient hemoglobin values displayed cycling.

Our initial hypothesis was that the system shortcoming to be improved was tightly connected to the standard ESA dosing protocol, shown in Table 2.

Titration of ESA Dosage: Given IV once weekly (Maximum dose 300 mcg/week)	
Hgb < 10 g/dL	Increase by 3 vials
Hgb 10.1-10.5 g/dL	Increase by 2 vials
Hgb 10.6-11.4 g/dL	Increase by 1 vial
Hgb 11.5-12.5 g/dL	No change in dose
Hgb 12.6-13.9 g/dL	Decrease by 1 vial
Hgb $\geq$ 14 g/dL	HOLD 2 weeks; then decrease by 2 vials
Available Vial Sizes (mcg) 25, 40, 60, 100, 150, 200, 300	

Table2. MCDS Standard ESA Protocol. (McCarthy).

The next section describes a compact model that shows how undesired oscillations in individual patient Hgb levels are caused as a results of the dosing protocol in place.

A Model that Explains Why Hgb Oscillation Occurs and How to Prevent It

Having observed many examples of hemoglobin cycling, the consulting team, though originally engaged to develop a performance measurement system, recommended a joint modeling project to develop a System Dynamics model to explain and eliminate the observed oscillations.

The purpose of the model was to explore the relationship between periodic Hgb cycling and ESA therapy and identify interventions to dampen the cycling.

Details of the model building process are described in (Rogers, Gallaher, and Hocum). The model building process led us on an exceptional journey which led to dramatic improvements in patient care, despite our initial lack of subject matter expertise. The reader is encouraged to review the incremental steps of model construction.

The model is based upon the process of erythropoiesis – the clinical term for the supply chain that continuously refreshes the supply of the body's red blood cells (RBC's) as they expire. Hemoglobin is a measure of RBCs in circulation – both mature RBC and newly formed RBCs, called reticulocytes. Figure 5 portrays the process as found in any standard hematology text (see Kaushansky et al).

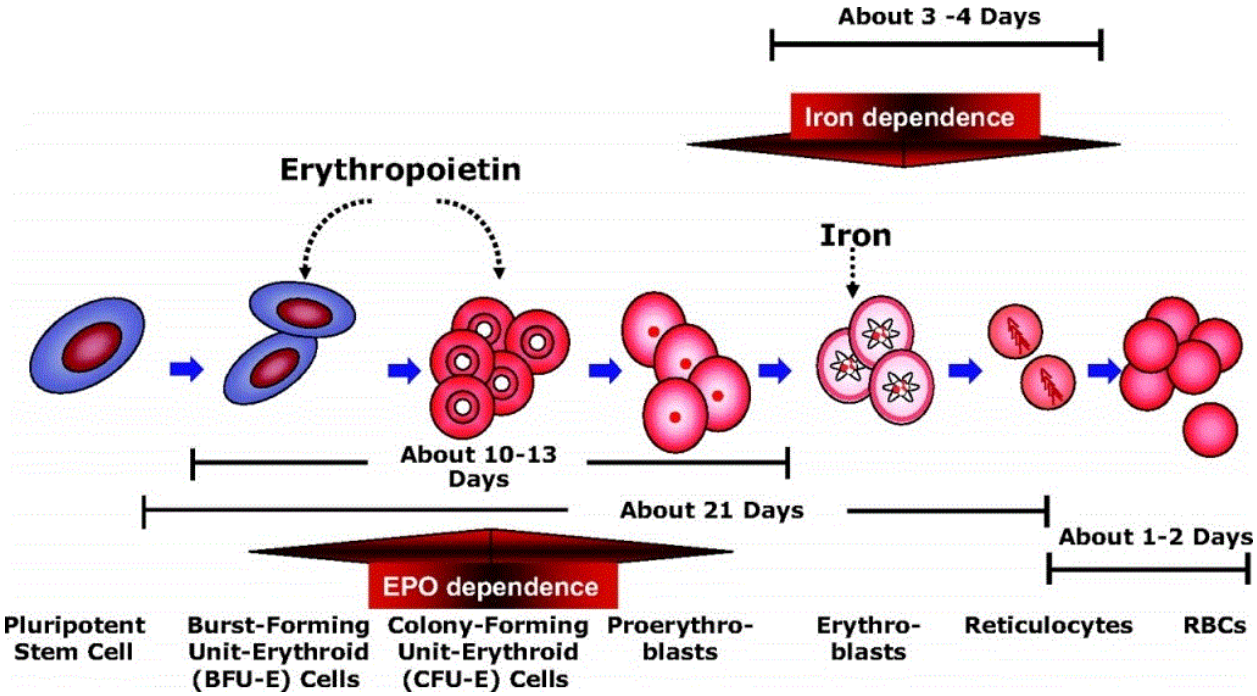

Figure 5. Erythropoiesis.

The important message in the diagram is that RBCs develop in stages in a process requiring 21-25 days. Increases in RBCs, as measured by increases in Hgb, resulting from EPO (ESA) administration will not be observed for more than two weeks. Coupled with the knowledge that RBC response to ESA administration is not only delayed, but nonlinear in both dose magnitude and frequency of administration, we have a classic situation leading to overshoot and undershoot of Hgb levels, a situation highly amenable to System Dynamics modeling.

Through many iterations over a several months we developed a functioning stock and flow model. Figure 6 provides a conceptual overview.

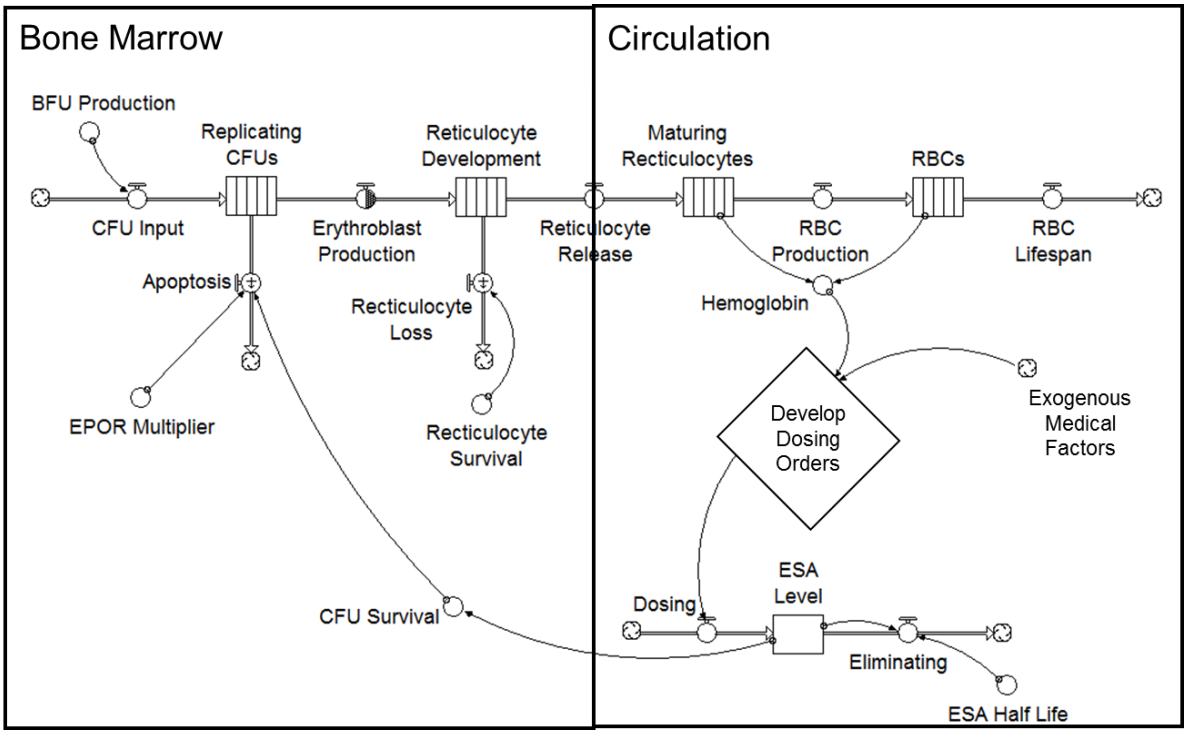

Figure 6. Conceptual Overview of the Model. (Rogers, Gallaher, and Hocum).

The model has two compartments. The Bone Marrow, where erythropoiesis unfolds, includes all of the progenitor and for precursor cell types indicated in figure 5. The circulating blood includes reticulocytes and RBCs, giving rise the Hgb measurements.

In contrast to figure 5, the model assumes only the CFU cell type is responsive to ESAs. The effect of ESAs is to prevent cell apoptosis or programmed cell death. Thus ESAs stimulate the eventual increase in RBCs by allowing more CFU cells to survive. CFU cell types undergo proliferation for 12 days in this model, dividing at intervals of 24 hours. The outflow, Erythroblast Production, contains 2^{12} times are many cells as the inflow CFU Input, less the total number of cells destroyed by apoptosis, as moderated by ESA levels.

Reticulocyte Development has a duration of 6 days. This stock represents all proerythroblast and erythroblast cells indicated in figure 5. At this stage several changes to the cell occur, the most notable being incorporation of iron, “hemoglobinization” and enucleation – the expulsion of the cell nucleus. (RBCs have no nucleus, which is why they do not replicate but expire at the end of their lifespan.) If iron bioavailability is not adequate, not all reticulocytes survive.

Maturing Reticulocytes are assumed to develop in RBCs in a 2 day period. RBCs exist in circulation in healthy patients for about 120 days. The lifespan of RBCs among HD patients is typically ranges from 60 to 90 days.

Model Parameters

We included five parameters in this model: BFU Production, CFU Survival, EPOR Multiplier, Reticulocyte Survival, and RBC Lifespan. Each of the model parameters was designed to correspond to a biophysical process occurring within the erythropoietic process.

To develop an understanding of why model parameters have specified ranges, we explain below how a truncated Monte Carlo simulation process was used to determine a useful set of model parameter values. Here, we describe the parameters.

BFU Production. For reasons to be described below was assumed to be some value between 5e+7 and 1e+9 per day.

CFU Survival. This parameter was selected from a range of 20% to 80% of a subpopulation of the CFU cells. Cells marked for survival develop EPO receptors on the cell surface. If EPO is present it binds to the EPO receptor and initiates a series of intracellular events that protect the cell from programmed cell death (apoptosis).

EPOR Multiplier. This parameter relates to an intracellular process which occurs in erythropoiesis. When EPO binds to an EPO receptor on the cell surface that sets up a cascade of events within the cell. The effect is to multiply the cell sparing affects by some value between 1 and 10.

Cell sparing in the model occurs then based upon the fraction of cell surface EPO receptor cells bound and the magnitude of the subsequent intracellular processes.

Reticulocyte Survival. This parameter was selected from a range of 20% to 80%.

RBC Lifespan. This parameter was assumed to have a range of 40 to 100 days.

As we explain below, a given set of model parameter values constitute a response profile of an individual to the presence of ESAs. For an individual patient, when each of the parameters is set to a specific value within its respective range, a simulated specific pattern of RBC production will occur over time in response to ESA dosing.

Model Boundary

After an exploration of the literature describing the relationship between erythropoietin and hemoglobin, we chose the boundary of the model to include only a part of the ESA-dependent stages of RBC development and the successive stages of erythropoiesis which lead to RBC creation. The ESA dependent stages we chose to include in the model are the stages in which ESA sensitivity is at a maximum.

There are important exclusions from the model boundary which we list here. The model assumes:

Iron Sufficiency: The patient to be modeled has adequate iron stores, having a transferrin saturation lab of 20% or more.

B12 and Folate Sufficiency: the patient to be modeled has adequate B12 and Folate stores. These affect cell division and replication, inadequate stores lead to compromised RBC production.

Stable Medical Condition: The patient's medical condition is relatively stable, currently unaffected by infection (which sequesters iron making it unavailable for erythropoiesis) and free from internal bleeding.

Blood Sampling for Hgb Measurement: The hemoglobin blood draw is always obtained at the conclusion of a hemodialysis session, after excess fluids have been removed, avoiding a laboratory distortion known as hemodilution.

IV Only: The ESA is administered intravenously, not subcutaneously.

Compliance: The recommended dosing regimen in terms of the amount and frequency of the drug to be administered will be precisely followed.

Thus, in comparison to the complexity of real world erythropoiesis the model is quite simple, simulating only the effect of ESAs on RBC creation and assuming all other factors of RBC production are operating normally. Though the model has limitations, pilot studies indicated it captured the dynamics with sufficient resolution to be clinically useful.

Referring to figure 6, the model requires the clinician to confirm the dose recommendations. As we describe below, the scope of factors included in this decision increased over time as we gained experience in using the model. These decisions involved real-world adjustments to variables outside the boundary of the model such as iron administration, or interventions to address detected inflammation or GI bleeding.

How the Model Was Used to Develop Individualized Dosing Regimens

To describe the behavior of the model, we next to explain how the model was used in two distinct phases.

In the **descriptive phase** we entered historical ESA doses and resulting Hgb levels from a prior period. We sought a set of parameter values such that known historical ESA doses produced the known historical Hgb levels. This was accomplished using a Monte Carlo strategy consisting of, typically, 100 simulations. In each simulation the model generated a set of random initial parameter values, drawn from a range of values known to be feasible based on current understanding of erythropoiesis. For each known (historical) Hgb value, the model accumulated the squared difference between the clinical value and the simulated value. After all the simulations were complete, the sets of random parameter values and their associated MSE values were exported to Excel. The data were sorted to find one or more parameter sets that yielded a minimum Mean Squared Error (MSE) of simulated hemoglobin values in comparison to the historical hemoglobin values.

The output of the descriptive phase is a set of parameter values which we regarded as an individual patient's response profile to the drug. We note that this solution to the matching problem is not unique. There may be other sets of parameter values which also describe the patient's response profile.

In a successive **prescriptive phase**, we assume that the patient's response to ESAs will, in the immediate future, be the same as their response in the immediate past, provided the patient's medical condition has not changed.

To execute the prescriptive phase, the patient's model is initialized with parameter values identified in the descriptive phase. By trial and error, constant weekly dosing regimens were simulated to find a weekly dosing regimen which stabilizes the patient's simulated hemoglobin at a desired target level. We call this the weekly therapeutic dose (WTD). In most cases, the WTD so identified was different from any of the available vial sizes.

As shown in table 2, the drug is only available in seven discrete vial sizes: 25, 40, 60, 100, 150, 200, and 300 mcg. Because the WTD we obtained as an output of the prescriptive phase was a continuous variable, as a final step we titrated the available vial sizes, scheduling a combination of various vial sizes to be administered at frequencies which would deliver an effective dose equivalent to the WTD.

As an example, if the WTD determined for an individual patient was 35 mcg per week, we used the patient-calibrated model to experiment with various combinations of standard vial sizes to arrive at a recommended prescription. In this example, that recommendation might be something like "*to achieve an equivalent effect of 35 mcg per week, give 25mcg in week one followed by 40mcg in weeks two and three and repeat three weeks cycle: 25, 40, 40.*" It was our experience that we could always find a combination of standard vial sizes which produce a simulated projected hemoglobin pattern which identically matched the simulated hemoglobin pattern over time in response to administration of the any "non-standard" WTD.

In the analysis of the model's behavior we discuss next, we refer only to the WTD.

Behavior of the Model with Respect to the Standard Protocol and a new Model-Based Protocol

With this background in mind we can now turn to an exploration of the model's behavior in response to the dosing protocol of record.

Consider a patient for whom historical ESA and hemoglobin data has been processed in the descriptive phase. A set of parameter values, the patient's response profile, is available to simulate how the patient will respond to any dosing regimen. In particular, we can simulate how the patient would be expected to respond to ESA dosing as defined by the standard protocol described in table 2.

We also can readily determine the patient's WTD to stabilize Hgb value at any desired target level.

Using this information we present nine cases to help answer three questions for each case:

- When simulating the standard protocol, does the model replicate the often observed hemoglobin cycling? If so, under what conditions?

- Does the model allow us to determine a dosing regimen, a so-called "model based protocol", which stabilizes hemoglobin at a desired level?

- Does the model allow a quality comparisons between a standard protocol and the model based protocol?

The nine cases we consider are shown in table 3:

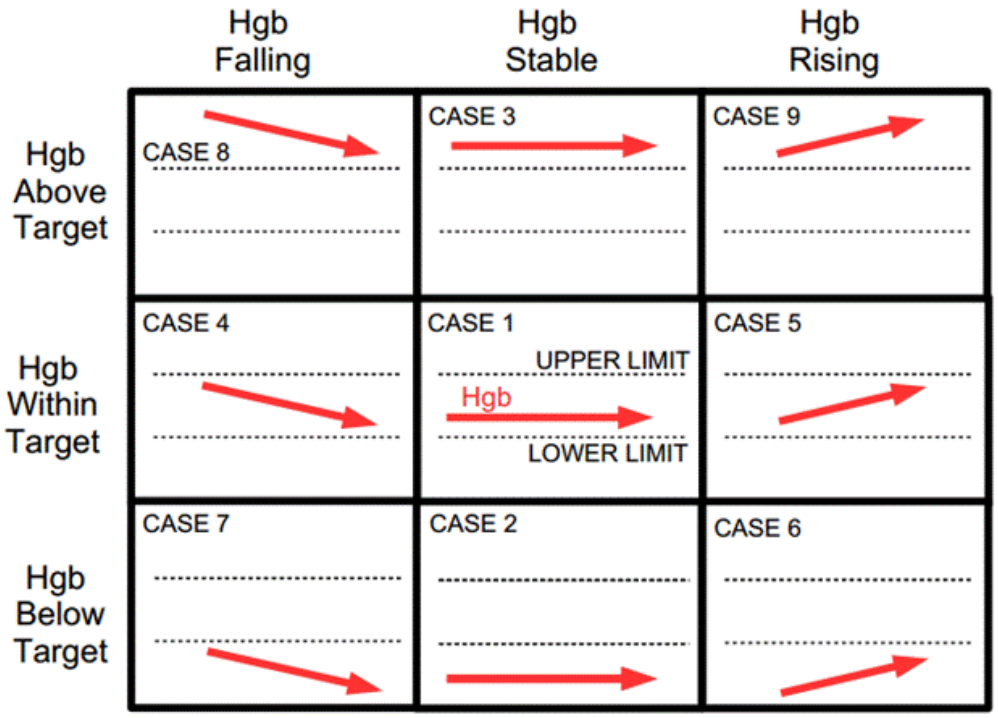

Table 3. Nine Cases for Comparison of the Standard Protocol to the Model Based Protocol.

For each case we show the results of two simulations. First (Part A) a simulation of the patient's response to the ESA dose determined by the Standard Protocol, and second (Part B) a simulation of the patient's response to the WTD.

These nine simulations were performed using the same patient model. Parameter values we obtained from the descriptive phase for this patient are shown in table 3. The WTD for all cases except Case 6 and Case 7 had been determined to be 20 mcg per week. The WTD for this patient for Case 6 and Case 7, using a slightly modified set of parameter values to allow the Hgb level to drop sufficiently low for testing, had been determined to be 50 mcg per week

Parameter	Values for Cases 1-5, 8, 9	Values fir Cases 6 and 7
BFU Input	6.5×10^8	5.5×10^8
CFU Survival	0.41	0.41
Reticulocyte Survival	0.46	0.46
EPOR Multiplier	2.45	2.45
RBC Life Span	65	65

Table 4. Model Parameter Values Used for Testing Cases 1-9.

The results of simulating the standard protocol as compared to the model based protocol for cases 1-9 are presented in the appendix.

We summarize the main conclusions of the analysis here:

- The standard protocol more often than not leads to oscillation. The standard protocol stabilized Hgb values only when Hgb values were already stable.

- The WTD derived from the simulation returns the patient to the precise target range in every case, after a delay.

- The primary reason Hgb cycling occurs is that the current protocol does not consider the delay between dose administration and observable results.

- If the clinician is only reviewing Hgb values for a one or two month period, the oscillation is imperceptible because the period of the oscillation ranges from 100 to 220 days. A behavior over time chart of sufficient temporal duration is necessary to observe what is happening with the patient.

The Model's Scope of Application within MCDS

In the previous section we described the behavior of the model for a specific patient. Our understanding of the model's behavior advanced through several stages of development. In this section we trace a pathway we followed in order to convince ourselves of the model's utility in treating anemia among HD patients for the entire MCDS patient population.

We exercised great skepticism in the beginning. We reviewed two or more years of longitudinal data for each of 50 patients at the DCF attended to by the physician assistant on the modeling team to assess their compliance with the restrictions we had placed upon the boundary of the model. We developed detailed BOTs, an effort in and of itself that was quite revealing. In addition to patterns of Hgb oscillation, the charts also revealed inconsistencies in iron maintenance therapy and recurrent patterns of hospitalizations. The BOT concept which the modelers introduced to the clinicians eventually became a critically important clinical document which has since been institutionalized.

We selected 12 patients from the group of 50 as candidates for modeling.

Three members of the modeling team each modeled the 12 patients and compared results. The three sets of recommendations turned out to be quite consistent. Based upon these, the authorized physician assistant selected a recommended dosing regimen. Weekly hemoglobin measurements were taken over a 12 week period to confirm the response matched the projections of the model. We found that the actual hemoglobin levels matched the projections of the model.

Figure 7 illustrates a typical outcome we experienced in applying the model based protocol, not just for the 12 patients described above but for all of the patients we eventually came to include in the scope of application throughout MCDS.

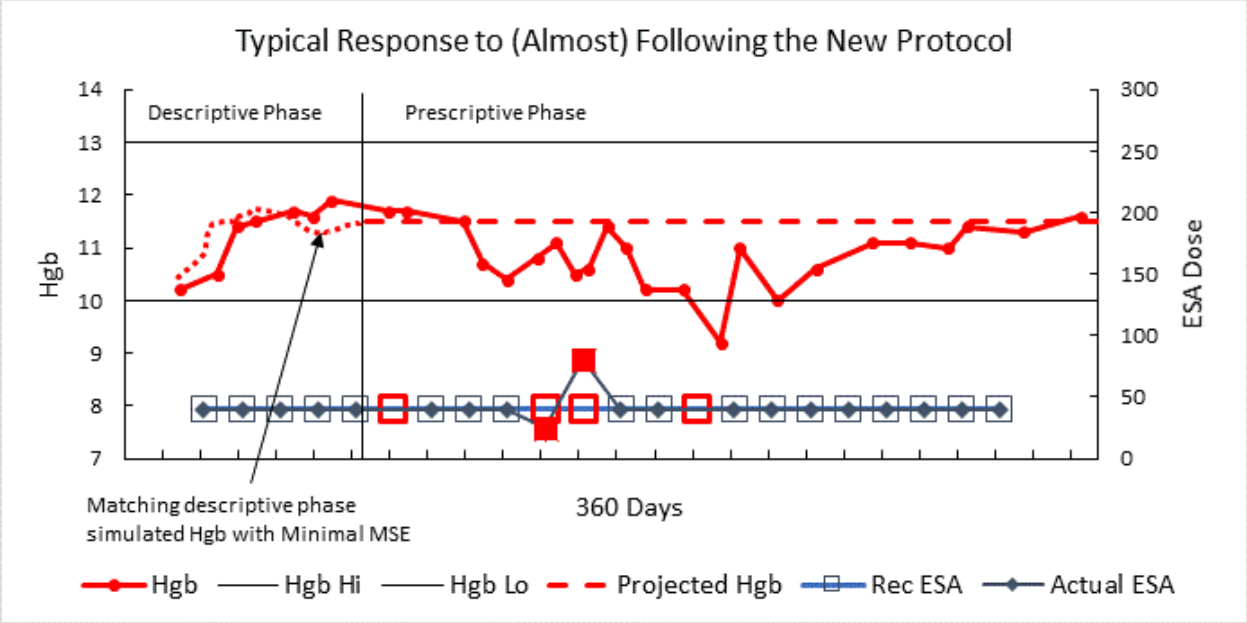

Figure7. Example of Patient Response to Recommended ESA, Including Dose Misadministration.

We expanded the initial set of patients to include most of the initially reviewed 50 patients. (While we were testing the model for the initial 12 patients, the physician assistant of the modeling team had addressed some of the exclusions we had observed earlier, the primary issue being inconsistent iron maintenance.) The majority of the 50 patients were now eligible for modeling, the main exclusions being either severely compromised medical conditions, or lack of available data due to recent admission to hemodialysis therapy.

We modeled these 50 patients and begin to outline a process for model based anemia management: secure and cleanse the most recent data, identify the patient response profile in the descriptive phase, identify the patient's WTD and equivalent titrations of available vial sizes, review dosing recommendations with the prescribing authority, order and administer the prescription, capture weekly data to confirm adherence to the recommended dosing regimen and Hgb conformance to the model's projection, review and discuss among the modeling team, and identify any required corrective actions.

This process generated requirements for what would eventually become a web-based application to manage all the information accruing for the scope of patients included. The process as we followed also became the coaching and education template we would use in the rollout the anemia management protocol to other MCDS DCFs.

We reported our early successes to the division chair, requesting that we expand the scope to include more patients from other DCFs within MCDS. In response, the division chair requested that we first identify "patients for whom the model did not work" and provide the reasons why.

We did find 18 patients for whom actual Hgb in the observation period did not match the model's projections. We found that 13 of the 18 patients had dosing variances from the model based dosing recommendations (similar to the example in Figure 7) and four of the patients had emergent medical conditions. The reasons for the one remaining patient's variance from the projection remained a mystery at the time. Based upon these confidence-building results as to the usefulness of the model, the division chair approved our request for expansion.

We then began a process of including all of the patients at all of the other DCFs with the MCDS system – approximately 650 patients at 15 different locations. The vast majority of the required data resided in a central database. There were however some exceptions which required a weekly manual creation and management of some missing data.

We enrolled all patients in the system over a six month period. Between 2009 and 2015, when the modeling team transferred operational support to Mayo Clinic, over 1000 patients had been processed using the original model without modification. The purpose of the model was to develop individualized ESA prescriptions for hemodialysis patients. The structure of the model allowed us to extend its application to all patients in the system.

A New and Different Policy for the Anemia Management for Hemodialysis Patients at MCDS

Insights from the modeling process together with the proven results which have accrued over time have brought about significant policy changes in both perspectives and practice. In this section we describe changes to the anemia management policy and note significant differences from the past.

In the following section we will discuss how policy resistance was addressed.

The modeling process revealed a powerful insight which in hindsight it is startlingly obvious: *for medically stable patients, a stable and consistent ESA dose produces a stable and consistent Hgb response*. A classic System Dynamics AHA!

This fact is not always been obvious. Fishbane (2005) on Hgb Cycling reports "the cause of hemoglobin cycling appears to be multifactorial. We found changes in rHuEPO [ESA] dose to be the most important driver, associated with hemoglobin excursions in approximately 80% of cases." In the past, dosing adjustments were made based upon concurrent Hgb conformance

to a target range, apparently unaware of how delayed feedback caused additional and unnecessary dosing adjustments, which drove cycling.

In the new policy, identification and maintenance of a stable dose is the priority. Adjustment of the ESA dosing level in less than 4 to 6 weeks is strongly discouraged.

The new policy is informed by the effect of inherent delays in erythropoiesis. It recognizes that the time between dose administration and observance of the resulting RBCs can be up to three weeks in duration. In addition to the implications this has for scheduling dosing adjustments, this delay also implies that historical data in the form of a BOT is essential to understanding the patient's condition. In the past, clinical information systems presented only current data, with historical data available as an option. The new policy requires that historical data be presented up front. We recommend maintaining a customizable BOT chart spanning at least two years as a standard clinical document.

In the past, the phrase "EPO resistance" was used to describe patients who seemed not to respond to ESA therapy. The modeling process revealed that even if adequate ESA doses are administered, iron deficiency will interfere with erythropoiesis. If the timing of iron bioavailability in erythropoiesis is not understood, the clinician may erroneously attribute lower than expected hemoglobin values to EPO resistance. We have observed situations in which the ESA dosing levels were increased to overcome "EPO resistance" when in fact the issue was iron deficiency. The new policy insists that adequate iron stores be maintained at all times.

Similar requirements apply to bioavailability of vitamin B12 and folate. Vitamin B12 and folate are required for proper cell division upstream of the proliferation of the CFU colonies. Deficiencies can also render ESA therapy apparently ineffective. Macrocytic anemia produces red blood cells which are abnormally large. This results from improper cell division early in the erythropoietic process, which can occur with vitamin B12 and folate deficiencies.

Therefore, the new policy requires that before administering ESA therapy, the clinician must ensure that the patient is iron replete, free from infection, has adequate B12 and folate stores, and is not suffering from internal bleeding.

Hemodialysis quality management reporting agencies require quarterly reports of the percentage of patients who are iron replete. Examination of the BOTs for some patients seemed to indicate that iron deficiency was discovered only after obtaining the required quarterly lab measurements, as evidenced by quarterly courses of iron supplements once the deficiency was observed. In the new policy, iron maintenance is recognized as a continuous process aimed at maintaining a constant supply of iron for erythropoiesis.

After a patient's Hgb level has stabilized, the new policy recommends careful observation of small variations in Hgb levels. These are signals to potentially changing medical conditions that were previously lost in the noise of Hgb oscillation - signals reporting the condition of the patient. A decrease from 11.5 to 11.2 over one week's time, for example, could be a signal that

the patient is developing infection or there might be bleeding internally. In the past, these signals were imperceptible.

The goal of the new policy is to do much more than understand what dosing is required to ensure a patient's Hgb level is within a desired target range. The goal of the new policy is to understand what is happening with the patient. The new policy allows for improved quality of care at a lower cost.

Anemia Management Policy Resistance and Remedies

In hindsight we realize there was little resistance to implementation. The modeling project was undertaken in 1Q08 and complete by the end of 2Q08. By the end of 4Q08, two pilot studies had been conducted, a detailed start to finish modeling process was in play, and a web-based information management application was up and running. Organization-wide enrollment of 650 patients was complete by the end of the second quarter of 2009. Though it did not seem like it at that time, we now realize that actually was a rapid deployment of a radically different process!

This is not to say that there were large numbers of people involved in the deployment – there weren't. There were several constraining factors which could have extinguished the project, but we enjoyed having several critical assets which served to overcome them all. First was the enthusiasm and commitment of the modeling team which was continually reinforced by the power of the System Dynamics modeling process, the second critical asset. Third, we had open minded subject matter expertise available to inform model construction, coupled with the fourth asset, data availability combined with expert data management and programming skills. Finally, the supervisory environment encouraged our pursuit of the model based process improvement project with zero micromanagement.

The mild resistance we did experience is common to the obstacles experienced in the implementation of any new process within the operations of a complex organization. For example: practitioners were not accustomed to interpreting BOT charts; awareness of the dynamics generated by delayed nonlinear feedback needed to be taught and nurtured; some recommended prescriptions seemed misguided - why decrease the dose of a patient with Hgb within the target range, but for another patient with Hgb also in the target range increase their dose? We used the model and the tracking tools we had implemented to explain the rationale of what at first seemed counterintuitive to the clinical team.

There were a few prescribing practitioners who continued to use the then current protocol, not because they were actively resisting the new one, more likely they were simply unaware. Since the patients under their care were also enrolled in the system we were to track their data and construct their BOT charts. Over a period of a few months the typical oscillations associated with the current protocol presented themselves in contrast to other patients who presented

stable Hgb values. The nursing staff who supported these practitioners were was extremely helpful in building awareness and encouraging adoption of the new protocol.

By the end of 2Q10, the new anemia management protocol was in play throughout the organization.

We used three main avenues to overcome the obstacles to implementation: active executive sponsorship, operational facilitation, and active education and coaching.

Active Executive Sponsorship. Once his confidence in the model was firmly established, the division chair became quite engaged in the project. He took extraordinary measures to champion the project among the entire medical direction staff of the Mayo Clinic Department Nephrology. With only minimal support from the modeling team, he developed and delivered an hour-long "grand rounds" presentation which fully described not only the benefits of the emerging anemia management protocol, but also the System Dynamics of why it worked. In that presentation, he clearly explained how RBC supply chain management is the same process used by grocery stores to maintain adequate stocks of Rice Krispies on their shelves!

Following that, in November 2010, he presented the "Mayo Clinic Anemia Management System" publicly at a National American Society of Nephrology conference to an audience of over 100 practitioners, a presentation we have frequently referenced here.

Operational Facilitation. The data management procedures for collecting, cleansing, generating, analyzing, and reporting were peculiar to Systems Thinking and System Dynamics. To get the new system up and running, the modeling team chose to design, implement, and operate the new information management system as part of the project rather than tossing it over the wall to the I/T department. This created a rapid application development scenario in which successive iterations of the information system could evolve without delay.

Active Education Coaching. The three person modeling team developed a weekly schedule of site visits and web meetings to provide education for the patient facing clinical support staff. A typical agenda for these meetings consisted of tracking the progress of previously modeled patients, reviewing new recommendations and their rationale, discussing exceptional patient situations, and designing corrective actions and interventions. The cumulative effect over time was to create a staff proficient in using the new anemia management protocol who, in turn provide support and coaching to medical directors.

Cost Reductions from the New Policy

Recall that at the beginning of the project, with respect to the target range for Hgb of 10-13, 34% of MCDS hemodialysis patients had mean Hgb levels above 13, 59% had levels within the target of 10 to 13, and 7% had levels below 10. After rollout of the new process in 2Q09, only 11% of patients had Hgb levels above 13, 80% had levels within the target range and 9% had levels below 10.0 (McCarthy.)

This was a significant improvement which continued over the successive years.

Though cost reduction was not an objective of the study, we did realize significant reductions in anemia management costs. Referring back to the available vial sizes in table one, the use of the three largest vial sizes was all but curtailed, not because it was the goal but because those dose levels were no longer required to stabilize Hgb values.

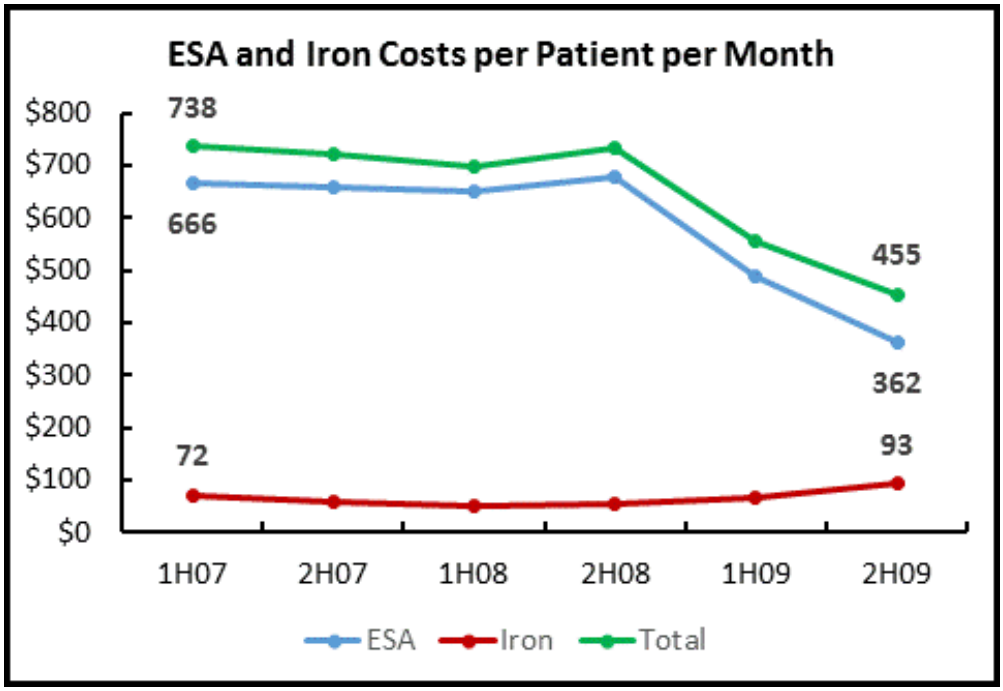

Figure 8. Reduced Cost of Anemia Management Injectables After Implementation of the Model Based Protocol in 2008. (McCarthy)

A net reduction of $283 per patient per month in anemia management drug costs was observed for 350 MCDS patients, producing an annual savings of $1.3M per year. If we extrapolate this figure to the full set of 650 patients we were serving, savings amount to as much as $2.4M million per year.

Limitations of the Current Model and Possible Extensions to Improve Its Usefulness

The model we have described has many limitations but has proven to be quite useful for almost eight years of clinical application. In this section we describe how an improved model addressing some of those limitations might lead to even better outcomes.

Administrative and Outcome Tracking Improvements. The model-supported process improvement project we initiated in 2008 was focused upon a single purpose: to explore the relationship between periodic Hgb cycling and ESA therapy and identify interventions to dampen the cycling.

We did not anticipate how valuable it is to achieve and sustain individualized Hgb levels in terms of overall patient care. Stable Hgb levels opened a new window into the patient's

underlying condition. We did not realize that this improved care would lead to significant reductions in hospitalizations as reported in (Rogers, Gallaher, and Hocum). We did not anticipate the extent to which improved care would most likely improve patient well-being and survival. Finally, we did not realize that clinical staff productivity concerning anemia management tasks would improve by orders of magnitude.

Each of those improvements is a direct outcome of applying Systems Thinking and System Dynamics to this problem, but we did not prepare to measure those improvements, unexpected as they were.

An improved process deployment project would measure initial baselines for each of those measures: patient well-being, patient survival, hospitalization rates, staff productivity, ESA therapy effectiveness, and overall ESA costs (including order rates and safety stocks). Data collection routines should be updated to include tracing those measures over time. The model should be updated to include cost and productivity metrics.

Patient Specific Biometrics. As noted above, the window into the patient's well-being created by the ability to maintain stable Hgb levels enabled significant improvements in the quality of care. Occult bleeding was exposed, infections were detected early, and other changes in the patient's medical condition became more visible to the clinician. Improvements to the model which increase its sensitivity to minor changes in Hgb levels might improve its usefulness in monitoring the patient's underlying medical condition. One way to accomplish this might be to incorporate patient specific data rather than using "standard patient" values. For example, in the current model, the estimated volume of distribution for the ESA is fixed at 7% of total body weight, which is assumed to be 70 kg. Sensitivity analysis with respect to patient specific biometrics remains to be performed.

Subcutaneous Administration. Many patients currently receive ESA doses subcutaneously but the current model only considers intravenous administration. Subcutaneous administration involves differences in absorption, distribution, metabolism, and elimination which in turn affects drug concentrations. Different concentrations of the drug change the survival rates of CFU cells which eventually affects RBC counts and Hgb levels. Inclusion of subcutaneous administration would also be helpful in model confidence building among clinicians who use and prefer that route.

Administration of IV Iron. Bailie (2015) writes "Intravenous (IV) iron is required for optimal management of the anemia in the majority of hemodialysis (HD) patients. While the IV iron prescription has increased over time, *the best dosing strategy is unknown and any effect of IV iron on survival is unclear* … [studies show] … increased risks of hospitalization and mortality with increased dosages of IV iron…In light of these associations, a well-powered clinical trial to evaluate the safety of different IV iron-dosing strategies in HD patients is urgently needed. (Italics mine)"

The proper administration of iron whether in supplemental or intravenous form has been a controversial and unresolved topic of discussion for more than 10 years. This model needs to be extended to include iron dynamics.

We are seeking sponsorship for a project which would make these model extensions to create a simulation model that would be useful to conducting such a well-powered clinical trial to identify safe and effective iron management policies.

Endogenous Erythropoietin and Extensions to Chronic Kidney Disease (CKD). The current model assumes that the residual kidney function of ESRD precludes the production of endogenous erythropoietin. In fact, ESRD patients with polycystic kidney disease do produce endogenous erythropoietin. This did not present a problem, the current model simply determined the level of "complementary ESA" which would be required to stabilize Hgb at a target level.

If however the current model was extended to include the dynamics of endogenous erythropoietin, it might be of use in monitoring the rate of kidney function decline in stages of CKD preceding ESRD. By monitoring the rate at which "complementary ESA" must be increased over time to maintain a constant Hgb level, we might gain insights into observing and slowing the rate of kidney function decline.

Variable Cell Replication Times and Progenitor Cell Self-renewal. Dingli, et.al. (2007) and Demin et.al. (2010) propose models of erythropoiesis which differ significantly from the current model. They explore the consequences of increasingly shorter cell replication rates among increasingly mature RBC progenitor cells, and the fact that BFU cells have the ability to self-renew. The current model assumes a cell replication rate of one day for all cell types in the erythropoietic supply chain and no cells have the ability to self-renew. Incorporating these the dynamics would allow for more accurate estimates of the number of mitotic events that occur from stem cells to red blood cells, the rate of replication of each cell type, and the numbers of cell types present in each stage of development in steady sate conditions among other descriptive facts.

The goal of updating the model this way would not be to get better at modeling the world. The goal would be to expose new and different parts of the world that we desperately need to understand. Cancer is uncontrolled cell replication. Improvements to the current model which incorporate these ideas could improve the usefulness of the model in understanding how to interact with the dynamics of cell division and proliferation in healthy and disease states.

Other Improvements. We have shown both in concept and application that even simple biophysical system dynamics models can be of great value in improving the quality of healthcare and reducing costs. Clinicians who have a systems physiology perspective are far more qualified than the authors to conceive of new and powerful applications. It is our hope that the presentation of this material captures the imagination of clinical practitioners in search of improved protocols to treat issues arising from complex biophysical dynamics such as those we have discussed here.

Discussion

ESA therapy for the treatment of anemia among hemodialysis patients is common. This paper has presented Hgb cycling as an important problem associated with ESA therapy. We described the structure and behavior of a model to identify the causes of hemoglobin cycling, a model which also can be used to identify dosing regimens which eliminate cycling.

An unintended and highly beneficial consequence of stabilizing hemoglobin values involves the ability to interpret small changes in individual patient Hgb levels, variations previously lost in the noise of Hgb cycling, as indicators into the patient's well-being. These indicators allow for early detection of emergent issues and improved quality of care. We have also shown that the new approach has also produced significant reductions in costs of anemia management injectables.

We have described how a new process for anemia management was implemented in a complex organization, tools and techniques we used to overcome implementation barriers, and suggested several improvements which could be made to the model to improve future applications. Some of the applications we identified implied extensions to other fields of clinical care, such as cancer.

We have also identified several improvements that could be made to the current model which would improve its usefulness in a variety of settings.

We offer these observations in hindsight concerning the power the System Dynamics methodology demonstrated to guide this project:

- The standard protocol dosing regimen was based upon an individual patient's two most recent Hgb levels which had become the clinician's range of reference. Actual Hgb oscillations with periods ranging from 100 to 200 days were imperceptible through such a narrow window. The simple task of drawing an individual's BOT clearly revealed the nature of the problem the model needed to address. The first BOT's produced created many AHA moments for clinicians.
- Though the problem surfaced in the nephrology department, the necessary insights for its solution resided in the hematology department. Crossing the interdepartmental boundary and engaging hematology subject matter experts very quickly revealed the dynamics of the underlying process and key model parameters that were required.
- The client members of the modeling team had no previous experience with System Dynamics. An introduction to stock and flow thinking, including simple examples of how stock and flow structures give rise to complex dynamic behavior patterns enabled them to productively participate in, or even occasionally lead, the model building process.
- One client team member has remarked that System Dynamics has "changed his perspective about everything".

- The modelers had little previous experience with either nephrology or hematology. The successive steps in the modeling process, such as in Sterman (2000), were sufficient to raise the right questions and produce the right answers to equip the modelers with the required subject matter expertise.
- The modeling team included a pharmacokinetic and pharmacodynamic modeling subject matter expert who brought a keen awareness of the scope of issues to consider with respect to "what the drug does to the body and what the body does to the drug". His insights were critical to establishing a laser focus on the purpose of the model as well as defining a highly functional model boundary.
- The sequence of stock and flow structures which evolved during the course of the project were powerful communication tools, enabling the joint modeling team to effectively and efficiently address critical assumptions and avoid falling victims to common misperceptions about ESAs.
- The modeling process guided us in the creation of a model which matched its purpose of both explaining and damping Hgb oscillations. The model became the engine to feed an information management system reporting both individualized and rolled up performance information, variances from targeted performance, and corrective action plans. This system enabled remarkable improvements in staff productivity with respect to anemia management tasks.
- At the conclusion of the process the modeling team had acquired deep operational understanding of the dynamics of erythropoiesis and the dosing regimens to achieve stable Hgb levels in a desired target range. This understanding became a critical resource which facilitated organization-wide implementation to achieve significant performance improvements for MCDS.

Future Work

We believe that this application of biophysical system dynamics merely scratches the surface of the potential applications which must be pursued in the future. After presenting this material at the 29th International Conference of the System Dynamics Society in 2011, we convened a group of system dynamics practitioners to ask for their perspective of what other applications would be possible. Within one hour's time they produced a list of over a dozen potential application areas including 50 topics. The major areas are listed in Table 4.

Application Areas suggested by SD Practitioners	
Immunodynamics	Body fluid electrolytes
Drug delivery systems	Chronic disease progression
Pain management	Cancers/autoimmune
Individual psychiatric interventions	Alternative and complimentary medicines
Antimicrobial resistance	Receptor dynamics
Physiology of sleep disorders	Addiction physiology
Stress response	Body fluid electrolytes

Table 4. Potential Inside- the-Skin Dynamic Modeling Areas of Application

Exploring any of these areas would be more than an academic pursuit. Each involves large numbers of real patients facing real difficulties being treated by real clinicians who are often following protocols of care based on poorly understood physiological phenomena.

Following disciplined principles of System Dynamics applied to inside the skin dynamics presents the opportunity to understand and implement real solutions.

Our future work envisions developing a management infrastructure that can rationalize, fund, and execute a well-designed portfolio of modeling projects to bring the underlying dynamics of areas like these to the light of day.

We hope that our ESRD example has begun to persuade the reader to consider the potential System Dynamics has to revolutionize all of medicine in areas like these and others.

References

Bailie, G., Larkina, M., Goodkin, D., Li, Y., Pisoni, R., Bieber, B., Mason, M., Tong, L., Locatelli, F., Marshall, M., Inaba, M., Robinson, B. Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality. Kidney International (2015) 87, 162-168.

Billett HH. Hemoglobin and Hematocrit. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 151. Available from: https://www.ncbi.nlm.nih.gov/books/NBK259/.

Demin, I., Crauste, F., Gandrillon, O., Volpert, V. 2010. A multi-scale model of erythropoiesis. Journal of Biological Dynamics, 4:1, 59-70, DOI: 10.1080/17513750902777642

Dingli, D., Traulsen, A., and Pacheco, J.M., 2007. Compartmental architecture and dynamics of hematopoiesis. PLoS ONE 2, e345.

Elliot, S.G., Foote, M., Molineux, G. (editors) Erythropoietin, Erythropoietic Factors, and Erythropoiesis; Molecular, Cellular, Preclinical, and Clinical Biology, 2nd edition. Birkhauser Publishing, Basel, 2009.

Eschbach, J., Egrie, J., Downing M., Browne, J., and Adamson, J. Correction of the Anemia of End-stage Renal Disease with Recombinant Human Erythropoietin: Results of a Combined Phase I and II Two Clinical Trial. N Engl J Med 1987; 316:73-8.

Fishbane, S., and Berns, J.S., 2005. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int 68, 1337-43.

Gross, H., and Lodish, H. Cellular Trafficking and Degradation of Erythropoietin and Novel Erythropoiesis Simulating Protein (NESP). J. Biol. Chem. 281: 2024-2032, 2006.

Kalantar-Zadeh**,** Kamyar. History of Erythropoiesis-Stimulating Agents, the Development of Biosimilars, and the Future of Anemia Treatment in Nephrology. Am J Nephrol 2017; 45:235-247.

Kaushansky, K., Lichtman, M., Prchal, J., Levi M., Press, O., Burns, L., Caligiuri, M., 2016. Williams Hematology, 9th Edition. McGraw-Hill, New York.

Luksenburg, Harvey. Safety Concerns Associated with Aranesp (darbepoetin alfa) Amgen, Inc. and Procrit (epoetin alfa) Ortho Biotech, L.P., for the Treatment of Anemia Associated with Cancer Chemotherapy. FDA Briefing Document May 4, 2004.

McCarthy, J. The Mayo Clinic Anemia Management System (MCAMS) Improves Achievement of Target Hemoglobin (Hgb) Values and Decreases High Hgb Values in Chronic Hemodialysis (CHD) Patients. 2010. Presentation. The American Society of Nephrology Conference. Denver, CO.

Rogers, J., Gallaher, E., and Hocum, C. Individualized Medicine and Biophysical System Dynamics: An Example from Clinical Practice in End Stage Renal Disease. 2011. Presentation. The 29th International Conference of the System Dynamics Society. Washington, DC.

Sterman, J.D., 2002. Business Dynamics: Systems Thinking and Modeling for a Complex World. McGraw-Hill, New York.

United States Renal Data System. 2016 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016.

Yang, W., Israni, R.K. et al., Hemoglobin Variability and Mortality in ESRD. J Amer Soc. Nephrology 18: 3164-3170, 2007.