USER EDUCATION MATERIALS:
How Do Strategic Anemia Advisor and Smart Anemia Manager Work?

Strategic Anemia Advisor

BACKGROUND

What is Strategic Anemia Advisor? Strategic Anemia Advisor (SAA) is an reference tool that personalizes ESA dosing. Its inputs are the patient's past ESA doses and hemoglobin levels, as well as a the target hemoglobin range for that patient. The target hemoglobin range can be set at the organization level, the clinic level, or the patient level. The output of SAA is a dose recommendation.

What is the purpose of SAA?
The purpose of Strategic Anemia Advisor (SAA) is to issue recommendations for ESA dosing. SAA is meant to be used for obtaining dosage recommendations only. Providers are solely responsible for reviewing all dosage recommendations before prescribing a dose for a patient. SAA is purely a reference tool and does not replace any clinical protocol or provider judgement. There may be additional clinical factors that affect patients' ESA responsiveness (such as iron levels, chronic infections, etc.), and users should consider all such factors along with SAA's recommendations when making clinical decisions. Dosis does not provide medical advice or make clinical, medical or other professional decisions.

Who is the intended user of SAA?
The intended users are anemia managers within clinics. This may include physicians, nurses, nurse practitioners, physician assistants, or any other qualified healthcare designated by a clinic to manage anemia.

What inputs used to generate the recommendations?
The three inputs SAA requires in order to issue recommendations are: a) previous Erythropoiesis Stimulating Agent (ESA) doses, b) previous hemoglobin lab values, and c) hemoglobin target range for each patient. You may recognize these as the same inputs that you are accustomed to taking into account when independently making ESA dosing decisions.

Where does the rationale for the recommendations come from?
The rationale underlying our recommendations, in the form of the mathematical equations that relate the inputs to the output, is available in published literature as well as in our patent (US Patent # 9852267). It is further explained below, in the section "How does SAA work?"

ERYTHROPOIESIS-STIMULATING AGENTS (ESAs)

- ESAs are synthetic forms of erythropoietin, a hormone naturally produced by kidneys to stimulate the production of red blood cells (RBCs). When patients experience kidney failure, erythropoietin is no longer naturally made in sufficient quantities, leading the chronic anemia. ESAs are used to boost RBC production and treat this condition.

- High doses of ESAs may increase risk of adverse cardiovascular events. KDIGO and KDOQI both caution against rapid dose escalation.
- The goal of ESAs is to use the minimum amount of ESA necessary to prevent blood transfusions.

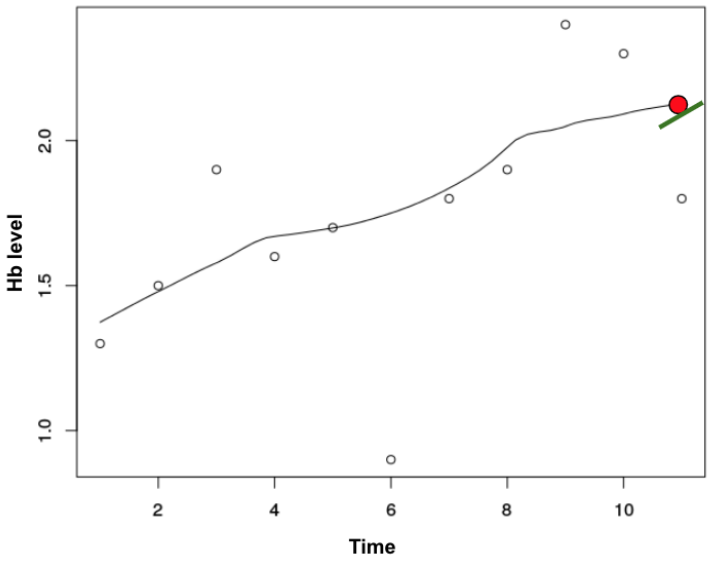
HOW DOES SAA WORK

High-level overview: SAA takes into account a patient's past hemoglobin levels and ESA doses, and the specified hemoglobin target range to determine the patient's unique response to ESA. It then predicts that patient's hemoglobin level four months out, and outputs a dose recommendation to keep the patient within target range, using the optimal amount of ESA for that particular patient.

The steps SAA uses to arrive at a dose recommendation are as follows:

1. **SAA receives inputs from clinics:**
    a. **Hemoglobin Target Range:** The desired upper and lower bounds the clinic would like to keep patients' hemoglobin levels within (in g/dL).
    b. **Up to 3 Months of Historical Hemoglobin Values**: All of the available hemoglobin values for a patient within the last 3 months (in g/dL)
    c. **Up to 3 Months of Historical ESA Received:** All of the administered ESA for a patient within the last 3 months (in IU for Epogen and mcg for Aranesp and Mircera)

2. **SAA calculates four values from received inputs:** Hemoglobin Target, Smoothed Hemoglobin, Hemoglobin Rate of Change, ESA Received.
    a. **Hemoglobin Target:** The midpoint of the provided range. For example, if a target range of 10-11 g/dL is given, the Hemoglobin Target is set to 10.5 g/dL.
    b. **Smoothed Hemoglobin:** Using the historical hemoglobin values provided, we use a technique called Lowess data smoothing to fit to the past hemoglobin levels. The hemoglobin value is determined at the last point of the model equation and we call that point the "Smoothed Hemoglobin." It is indicated as the red point in the graph below.



c. **Hemoglobin Rate of Change:** The hemoglobin rate of change is calculated by determining the rate of change at the Smoothed Hemoglobin point of the model equation. It is indicated by the green line in the graph above.
d. **ESA Received:** The weekly average ESA dose received is calculated from one week prior to the current Hemoglobin measurement back to the week of the previous Hemoglobin measurement. The time span must include at least two weeks of dose data for Epogen and Aranesp and four weeks for Mircera.
e. More information on step 2 can be found the patent, column 20, line 39-51.

3. **SAA determines how a patient's hemoglobin levels would change over the next 4 months based on 5 possible dose response categories**
    a. SAA uses the Smoothed Hemoglobin and Hemoglobin Rate of Change in the 5 possible dose response categories to predict the patient's hemoglobin levels over the next four months. The 5 possible dose response categories cover dose-response profiles from extreme hyper-responder (smallest ESA dose change required) to extreme hypo-responder (largest ESA dose change required).[1]

4. **In each dose response category, SAA chooses the optimal dose to keep the patient at the Hemoglobin Target**
    a. In each dose response category, SAA tests a wide range of ESA doses and compares the predicted hemoglobin results to the Hemoglobin Target.
    b. SAA chooses the ESA dose that minimizes the difference between the predicted hemoglobin and the Hemoglobin Target in each of the 5 possible dose response categories.
    c. The results of this step are 5 dose-response-category-specific optimal ESA doses.
    d. The exact calculations for steps 3 and 4 can be found in the patent, column 20, line 51-58, columns 21 and 22 lines 1-68, and column 23, lines 1-14.

5. **SAA weighs the 5 dose-response specific optimal ESA doses.**
    a. Using the ESA Received, SAA determines the weight of each of the 5 dose response categories to estimate the patient's ESA responsiveness.[2]
    b. More information on this step can be found in the Appendix. The exact calculations for step 5 can be found in the patent, column 23, lines 15-63.

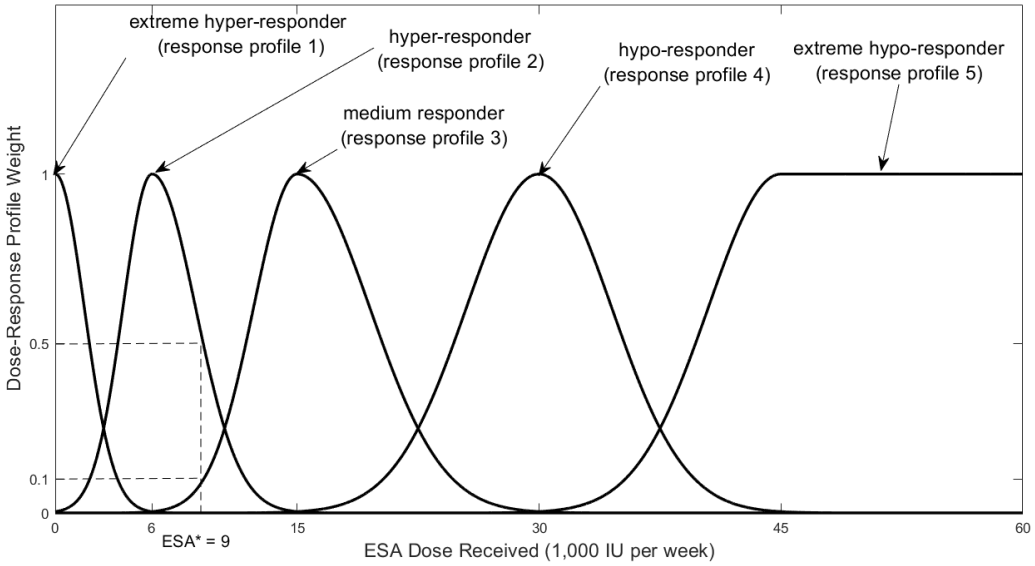
6. **SAA determines final dose recommendation**
    a. SAA uses the weighted average of the 5 dose-response specific optimal ESA doses and rounds it to the closest dispensable ESA amount, based on the clinic's specific formulary.
    b. More information about this step can be found in the Appendix. The exact calculations for step 6 can be found in the patent, column 23, lines 15-63.

[1] Source: Article 7 in Published Literature section (https://www.ncbi.nlm.nih.gov/pubmed/21941178)
[2] Source: Article 9 in Published Literature section (https://www.ncbi.nlm.nih.gov/pubmed/19115195)

Appendix

Determining the weight of each drug response profile

For an individual patient, the importance weight of the 5 dose-response specific optimal ESA doses is determined by matching the patient's current ESA Dose Received to each of the 5 dose-response profiles. The graph below contains the 5 dose-response profiles and the weight of each profile (y-axis) for a given amount of ESA (x-axis). The graph also contains an example of a patient whose ESA Received is 9,000 IU of Epogen per week, displayed as ESA*= 9 on the x-axis. It is determined where x=9 intersects with any of the dose response profiles.The y-value at the point of intersection is the weight respective dose-response profile. In this case, the weight of Dose Response Profile 2 is 0.5 and the weight of Dose Response Profile 3 is .1. The rest of the dose response profiles have a weight of 0.[3]



Determining the final dose recommendation

The patient-specific optimal ESA dose recommendation is determined by adding the product of weight of each dose response profile and the dose-response specific optimal ESA doses and dividing by the sum of the weights of each dose response profile. The equation is outlined below, where W represents the weight of a specific dose response profile and ESA represents the optimal ESA dose of a dose response profile.

$$ESA_{RawRecommendedDose} = \frac{W_1 ESA_1 + W_2 ESA_2 + W_3 ESA_3 + W_4 ESA_4 + W_5 ESA_5}{W_1 + W_2 + W_3 + W_4 + W_5}$$

[3] Source: Article 9 in Published Literature section (https://www.ncbi.nlm.nih.gov/pubmed/19115195)

Published Literature

The research team behind SAA is based at the University of Louisville, and has published extensively on the technical and clinical steps taken to build and validate SAA. Those publications can be accessed below.

Clinical Publications

1. Gaweda, Adam & A. Jacobs, Alfred & Aronoff, George & Brier, Michael. (2018). *Individualized anemia management in a dialysis facility – long-term utility as a single-center quality improvement experience.* Clinical Nephrology. 90. 10.5414/CN109499. (https://www.ncbi.nlm.nih.gov/pubmed/30049300)

2. Brier, M.E. and A.E. Gaweda, *Artificial intelligence for optimal anemia management in end-stage renal disease.* Kidney Int, 2016. **90**(2): p. 259-61. (https://www.ncbi.nlm.nih.gov/pubmed/27418093)

3. Akabua, E., et al., *Individualized model discovery: the case of anemia patients.* Comput Methods Programs Biomed, 2015. **118**(1): p. 23-33. (https://www.ncbi.nlm.nih.gov/pubmed/25459523)

4. Gaweda, A.E., et al., *Individualized anemia management reduces hemoglobin variability in hemodialysis patients.* J Am Soc Nephrol, 2014. **25**(1): p. 159-66. (https://www.ncbi.nlm.nih.gov/pubmed/24029429)

5. Brier, M.E., et al., *Randomized trial of model predictive control for improved anemia management.* Clin J Am Soc Nephrol, 2010. **5**(5): p. 814-20. (https://www.ncbi.nlm.nih.gov/pubmed/20185598)

6. Gaweda, A.E., et al., *Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response.* Clin J Am Soc Nephrol, 2010. **5**(4): p. 576-81. (https://www.ncbi.nlm.nih.gov/pubmed/20110344)

Technical Publications

7. Brier, M.E. and A.E. Gaweda, *Predictive modeling for improved anemia management in dialysis patients.* Curr Opin Nephrol Hypertens, 2011. **20**(6): p. 573-6. (https://www.ncbi.nlm.nih.gov/pubmed/21941178)

8. Gaweda, A.E., et al., *Determining optimum hemoglobin sampling for anemia management from every-treatment data.* Clin J Am Soc Nephrol, 2010. **5**(11): p. 1939-45. (https://www.ncbi.nlm.nih.gov/pubmed/20671221)

9. Gaweda, A.E., A.A. Jacobs, and M.E. Brier, *Application of fuzzy logic to predicting erythropoietic response in hemodialysis patients.* Int J Artif Organs, 2008. **31**(12): p. 1035-42. (https://www.ncbi.nlm.nih.gov/pubmed/19115195)

10. Gaweda, A.E., et al., *Model predictive control of erythropoietin administration in the anemia of ESRD.* Am J Kidney Dis, 2008. **51**(1): p. 71-9. (https://www.ncbi.nlm.nih.gov/pubmed/18155535)

11. Gaweda, A.E., et al., *Individualization of pharmacological anemia management using reinforcement learning.* Neural Netw, 2005. **18**(5-6): p. 826-34. (https://www.ncbi.nlm.nih.gov/pubmed/16109475)

12. Gaweda, A.E., et al., *Pharmacodynamic population analysis in chronic renal failure using artificial neural networks--a comparative study.* Neural Netw, 2003. **16**(5-6): p. 841-5. (https://www.ncbi.nlm.nih.gov/pubmed/12850042)

13. Gaweda el al. *Using clinical information in goal-oriented learning*. IEEE Eng Med Biol Mag. 2007 Mar-Apr;26(2):27-36 (https://www.ncbi.nlm.nih.gov/pubmed/17441606)

The Patent

The patent that includes a detailed explanation of all that calculations within SAA can be found here.

The relevant sections cited above have been excerpted below:

Step 2: "the input device receives a Hbtarget value (target hemoglobin level (g/dL)), a Hbk value (Hb level (g/dL) computed from Hb data over time using lowess smoothing or another suitable smoothing method with a 28 day window), a ΔHbk value (Hb rate of change (g/dL per day) computed from Hb data over time using lowess smoothing or another suitable smoothing method with a 28 day window), and an Epok value, which corresponds to the Epo dose previously received (Epo dose received (e.g., 1000 Units per week) or computed from Epo data over time as an average weekly Epo dose received over the preceding 28 days, if the previously-prescribed dose is not available."

(column 20, line 39-51)

Steps 3 and 4: "Also shown are five dosing regimen program modules ("i"=5), which are understood to be stored in the data storage device. The dosing regimen program modules include instructions for causing the processing device to determine an Epok+1,i value (recommended Epo dose (e.g., 1000 Units per week) for each of the "i" dosing regimens, the details of which are described below."

(column 20, line 51-58)

"each of the "i" dosing regimen program modules includes: a dose-response model module for causing the processing device to determine a Hbk+1 value and a ΔHbk+1 value (i.e., a predicted response) for a subject with a respective Epo sensitivity profile based on the Hbk value, the ΔHbk value, and a proposed Epok+1 value; and an optimization algorithm module for causing the processing device to determine the optimal value Epok+1,i* value using the Hbtarget value, and given the Epok value, the Hbk+1 value and the ΔHbk+1 value, and then iteratively providing the proposed Epok+1 value to the dose-response module and re-determining the proposed Epok+1 value until the proposed Epok+1 values converge to the optimal value Epok+1,i*, which is the value at which the objective function provided below in Equation (6) achieves minimum subject to optimization constraints.

In the exemplary dosing regimen program module 900, the dose-response model is substantially according to the function:

$$\begin{bmatrix} \frac{dHb}{dt} \\ \frac{d\Delta Hb}{dt} \end{bmatrix} = \begin{bmatrix} \frac{-2}{T_i} & \frac{1}{T_i^2} \\ 1 & 0 \end{bmatrix} \begin{bmatrix} Hb \\ \Delta Hb \end{bmatrix} + \begin{bmatrix} \frac{K_i}{T_i^2} \\ 0 \end{bmatrix} Epo \qquad (4)$$

where:
Ki—erythropoietic response (1,000 Units Epo per 1 g/dL Hb change);
Ti—time constant;

Epo—dose (1,000 Units);
Hb—hemoglobin level (g/dL);
ΔHb—hemoglobin rate of change (g/dL per day);

where:
Ki and Ti are mechanistic parameters describing sensitivity (K) and dynamics (T) of the red blood cell production process;
K is physiologically related to red cell production rate;
T is physiologically related to mean red blood cell lifespan; and

where:
a discrete time grey-box model describing Hb response to Epo can be derived by sampling Equation (4) every Ts days

$$\begin{bmatrix} Hb_{k+1} \\ \Delta Hb_{k+1} \end{bmatrix} = \begin{bmatrix} \theta_{i,1} & \theta_{i,2} \\ \theta_{i,2} & \theta_{i,4} \end{bmatrix} \begin{bmatrix} Hb_k \\ \Delta Hb_k \end{bmatrix} + \begin{bmatrix} \theta_{i,5} \\ \theta_{i,6} \end{bmatrix} Epo_{k+1} \quad (5)$$

where:
k—time step
θi=[θi,1, θi,2, θi,3, θi,4, θi,5, θi,6]—parameter vector derived from Ki and Ti by sampling Equation (4) every Ts days; and

wherein the optimization algorithm is substantially according to the objective function:

$$OFV = \sum_{k_p=1}^{H_p} \left(Hb_{target} - Hb_{k_p}\right)^2 + \lambda_i \sum_{k_c=1}^{H_c} \Delta Epo_{k_c}^2 \quad (6)$$

where:
kp, kc—time steps (weeks);
Hp—prediction horizon (weeks);
Hc—control horizon (weeks);
λi—dose change suppression (non-dimensional);
Hbkp—hemoglobin at step kp;
ΔEpokc—change in dose from step kc-1 to kc; and
subject to constraints:
0≦Epo≦90,000 units per week
0≦Hb≦20 g/dL
−0.5<ΔHb<0.5 g/dL per week
where: ΔHb=Hbkp−Hbkp-1

Equation (4) above is a continuous time equation that describes the dynamic behavior of Hb and the Hb rate of change (ΔHb) in response to an Epo dose, given a fixed Epo sensitivity profile i described by two parameters: Ki, or the erythropoietic response which represents the magnitude of Hb increase

(decrease) in steady-state after the Epo dose has been increased (or decreased) by 1,000 Units; and Ti, or the time constant that is mathematically related to the time required for Hb to achieve the steady-state after the Epo dose has been increased (or decreased). In some embodiments, Equation (1) is used as the Dose-Response Model to calculate the Hbk+1 and ΔHbk+1 values from the Hbk and ΔHbk, and to also calculate the Epok value.

Equation (6), on the other hand, describes the objective function to be minimized by Epok+1,i*. The first right-hand-side term of this equation sums the squared difference between Hbtarget and Hb predicted by the Dose-Response Model (Equation 1) at time steps kp, where kp changes from 1 through prediction horizon Hp. The second right-hand term sums the squared amounts of Epo dose adjustments at time step kc, where kc changes from 1 through control horizon Hc. In this regard, the first term thereby represents the tracking properties of the controller, i.e. how well the measured Hb is maintained close to target, while the second term represents robustness of the controller, i.e. how well the controller ignores random changes in measured Hb. The balance between tracking and robustness is determined by the parameter λi.

In the embodiment of the exemplary dosing regimen program module whose parameters are shown above, the sampling time of 7 days was selected based on an optimal frequency of Hb observation, while the values of the erythropoietic response parameter (K) for Dose-Response Models 1 through 5 were selected to cover a maximum possible range of Epo doses that can be given to a subject, as regulated by NKF-K/DOQI guidelines and the product label. The time constant parameter for all the models was selected to represent the average RBC lifespan typical for the hemodialysis patient population of 90 days. The controller parameters (Hp, Hc, and λ1 through λ5) were optimized to achieve time to reach Hb steady-state not greater than 12 weeks in response to a 1,000 Unit change in Epo dose and to miminize Epo dose changes in response to random noise in Hb measurement. Of course, for a particular application, the dosing regimen program module parameters can further be adapted or changed as desired without departing from the spirit and scope of the subject matter described herein.

(column 20, line 51-58, columns 21 and 22 lines 1-68, and column 23, lines 1-14)

Steps 5 and 6: “in the exemplary dose selection algorithm module 1000 there are 5 dosing regimens (“i”=5) and the dosing selection algorithm module determines the Eponext value substantially according to the equation (function):

$$Epo_{k+1} = \frac{w_{R1}Epo^{*}_{k+1,1} + w_{R2}Epo^{*}_{k+1,2} + w_{R3}Epo^{*}_{k+1,3} + w_{R4}Epo^{*}_{k+1,4} + w_{R5}Epo^{*}_{k+1,5}}{w_{R1} + w_{R2} + w_{R3} + w_{R4} + w_{R5}}. \quad (7)$$

The weighting values are fuzzy membership functions according to the following:
wR1=fMF(Epok, μ1, s1l, s1r) μ1=0 s1l=1.0 s1r=0.9*(Hbtarget−Hb0)
wR2=fMF(Epok, μ2, s2l, s2r) μ2=3*(Hbtarget−Hb0) s2l=s1r s2r=1.35*(Hbtarget−Hb0)
wR3=fMF(Epok, μ3, s3l, s3r) μ3=7.5*(Hbtarget−Hb0) s3l=s2r s3r=2.25*(Hbtarget−Hb0)
wR4=fMF(Epok, μ4, s4l, s4r) μ4=15*(Hbtarget−Hb0) s4l=s3r s4r=s4l
wR5=fMF(Epok, μ5, s5l, s5r) μ5=22.5*(Hbtarget−Hb0) s5l=s4r s5r=100.0

where fMF is a fuzzy membership function substantially according to the equation:

$$f_{MF}(x, \mu, s_l, s_r) = \begin{cases} \exp\left(-\frac{(x-\mu)^2}{s_l^2}\right) & x < \mu \\ 1 & x = \mu \\ \exp\left(-\frac{(x-\mu)^2}{s_r^2}\right) & x > \mu \end{cases} \quad (8)$$

and Hb0 is baseline hemoglobin, which is the hemoglobin level before first administration of Epo.

In Equation (8) above, the parameter μ represents the center of the fuzzy membership function and the parameters sl and sr represent the left and right spread of the membership function, respectively. In some embodiments, the centers (i.e., where the membership achieves the maximum value of 1.0) were chosen to represent the most typical Epo dose value received by the subjects belonging to the specific sensitivity profile, while the spreads were chosen to achieve the overlap between the neighboring membership functions at the value of 0.25.

(column 23, lines 15-63)

Smart Anemia Manager

BACKGROUND

What is Smart Anemia Manager? Smart Anemia Manager (SAM) is an reference tool that personalizes ESA dosing. Its inputs are the patient's past ESA doses and hemoglobin levels, as well as a the target hemoglobin range for that patient. The target hemoglobin range can be set at the organization level, the clinic level, or the patient level. The output of SAM is a dose recommendation.

What is the purpose of SAM?
The purpose of Smart Anemia Manager (SAM) is to issue recommendations for ESA dosing. SAM is meant to be used for obtaining dosage recommendations only. Providers are solely responsible for reviewing all dosage recommendations before prescribing a dose for a patient. SAM is purely a reference tool and does not replace any clinical protocol or provider judgement. There may be additional clinical factors that affect patients' ESA responsiveness (such as iron levels, chronic infections, etc.), and users should consider all such factors along with SAM's recommendations when making clinical decisions. Dosis does not provide medical advice or make clinical, medical or other professional decisions.

Who is the intended user of SAM?
The intended users are anemia managers within clinics. This may include physicians, nurses, nurse practitioners, physician assistants, or any other qualified healthcare designated by a clinic to manage anemia.

What inputs are used to generate the recommendations?
The following inputs are used in SAM in order to issue recommendations are: a) previous Erythropoiesis Stimulating Agent (ESA) doses, b) previous hemoglobin lab values, c) hemoglobin target range for each patient. You may recognize these as the same inputs that you are accustomed to taking into account when independently making ESA dosing decisions.

Where does the rationale for the recommendations come from?
The rationale underlying our recommendations, in the form of the mathematical equations that relate the inputs to the output, is available in published literature as well as in our patent (US Patent # 9852267). It is further explained below, in the section "How does SAM work?"

ERYTHROPOIESIS-STIMULATING AGENTS (ESAs)

- ESAs are synthetic forms of erythropoietin, a hormone naturally produced by kidneys to stimulate the production of red blood cells (RBCs). When patients experience kidney failure, erythropoietin is no longer naturally made in sufficient quantities, leading the chronic anemia. ESAs are used to boost RBC production and treat this condition.
- High doses of ESAs may increase risk of adverse cardiovascular events. KDIGO and KDOQI both caution against rapid dose escalation.
- The goal of ESAs is to use the minimum amount of ESA necessary to prevent blood transfusions.

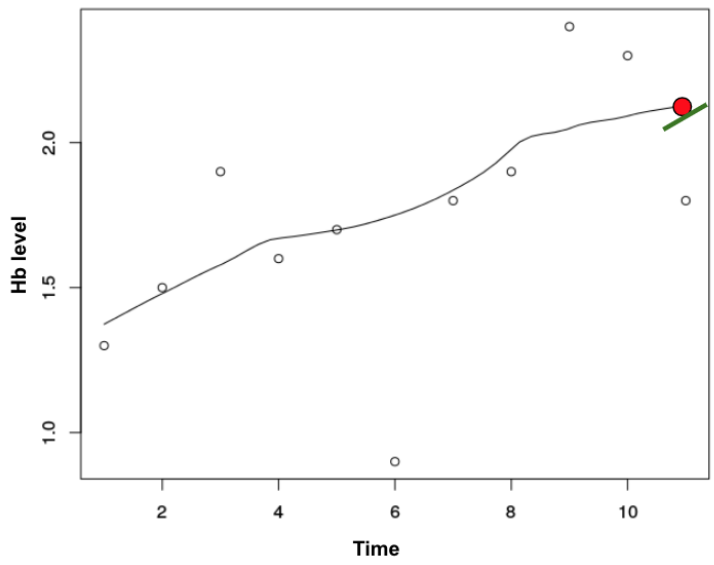
HOW DOES SAM WORK

High-level overview: SAM takes into account a patient's past hemoglobin levels and ESA doses, and the specified hemoglobin target range to determine the patient's unique response to ESA. It then predicts that patient's hemoglobin level four months out, and outputs a dose recommendation to keep the patient within target range, using the optimal amount of ESA for that particular patient.

The steps SAM uses to arrive at a dose recommendation are as follows:

1. **SAM receives inputs from clinics:**
    a. **Hemoglobin Target Range:** The desired upper and lower bounds the clinic would like to keep patients' hemoglobin levels within (in g/dL).
    b. **Up to 3 Months of Historical Hemoglobin Values**: All of the available hemoglobin values for a patient within the last 3 months (in g/dL)
    c. **Up to 3 Months of Historical ESA Received:** All of the administered ESA for a patient within the last 3 months (in IU for Epogen and mcg for Aranesp and Mircera)

2. **SAM calculates four values from received inputs:** Hemoglobin Target, Smoothed Hemoglobin, Hemoglobin Rate of Change, ESA Received.
    a. **Hemoglobin Target:** The midpoint of the provided range. For example, if a target range of 10-11 g/dL is given, the Hemoglobin Target is set to 10.5 g/dL.
    b. **Smoothed Hemoglobin:** Using the historical hemoglobin values provided, we use a technique called Lowess data smoothing to fit to the past hemoglobin levels. The hemoglobin value is determined at the last point of the model equation and we call that point the "Smoothed Hemoglobin." It is indicated as the red point in the graph below.



    c. **Hemoglobin Rate of Change:** The hemoglobin rate of change is calculated by determining the rate of change at the Smoothed Hemoglobin point of the model equation. It is indicated by the green line in the graph above.
    d. **ESA Received:** The weekly average ESA dose received is calculated from one week prior

to the current Hemoglobin measurement back to the week of the previous Hemoglobin measurement. The time span must include at least two weeks of dose data for Epogen and Aranesp and four weeks for Mircera.

e. More information on step 2 can be found the patent, column 20, line 39-51.

3. SAM determines how a patient's hemoglobin levels would change over the next 4 months based on 5 possible dose response categories

a. SAM uses the Smoothed Hemoglobin and Hemoglobin Rate of Change in the 5 possible dose response categories to predict the patient's hemoglobin levels over the next four months. The 5 possible dose response categories cover dose-response profiles from extreme hyper-responder (smallest ESA dose change required) to extreme hypo-responder (largest ESA dose change required).[4]

4. In each dose response category, SAM chooses the optimal dose to keep the patient at the Hemoglobin Target

a. In each dose response category, SAM tests a wide range of ESA doses and compares the predicted hemoglobin results to the Hemoglobin Target.
b. SAM chooses the ESA dose that minimizes the difference between the predicted hemoglobin and the Hemoglobin Target in each of the 5 possible dose response categories.
c. The results of this step are 5 dose-response-category-specific optimal ESA doses.
d. The exact calculations for steps 3 and 4 can be found in the patent, column 20, line 51-58, columns 21 and 22 lines 1-68, and column 23, lines 1-14.

5. SAM weighs the 5 dose-response specific optimal ESA doses.

a. Using the ESA Received, SAM determines the weight of each of the 5 dose response categories to estimate the patient's ESA responsiveness.[5]
b. More information on this step can be found in the Appendix. The exact calculations for step 5 can be found in the patent, column 23, lines 15-63.

6. SAM determines final dose recommendation

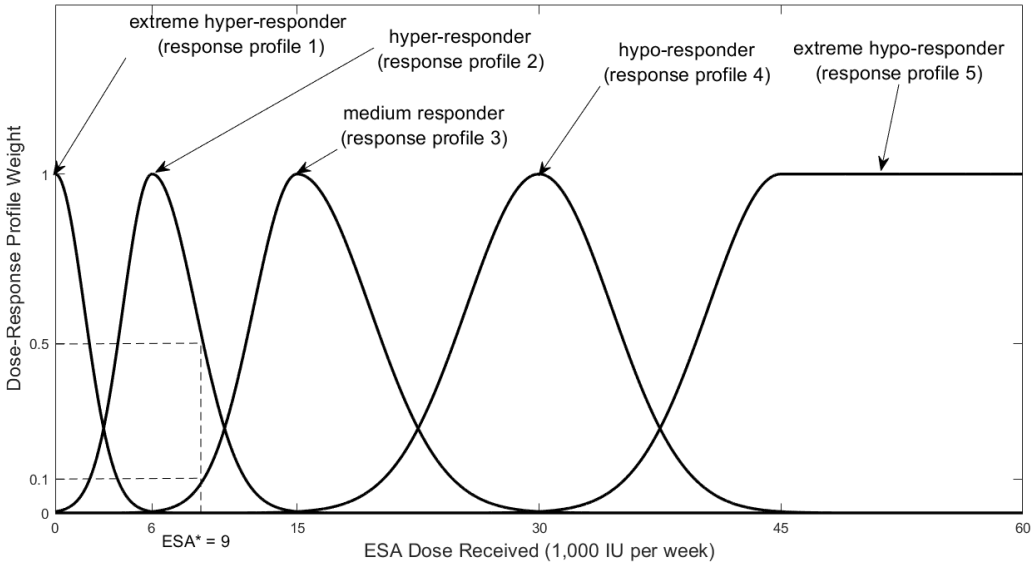
a. SAM uses the weighted average of the 5 dose-response specific optimal ESA doses and rounds it to the closest dispensable ESA amount, based on the clinic's specific formulary.
b. More information about this step can be found in the Appendix. The exact calculations for step 6 can be found in the patent, column 23, lines 15-63.

[4] Source: Article 7 in Published Literature section (https://www.ncbi.nlm.nih.gov/pubmed/21941178)
[5] Source: Article 9 in Published Literature section (https://www.ncbi.nlm.nih.gov/pubmed/19115195)

Appendix

Determining the weight of each drug response profile

For an individual patient, the importance weight of the 5 dose-response specific optimal ESA doses is determined by matching the patient's current ESA Dose Received to each of the 5 dose-response profiles. The graph below contains the 5 dose-response profiles and the weight of each profile (y-axis) for a given amount of ESA (x-axis). The graph also contains an example of a patient whose ESA Received is 9,000 IU of Epogen per week, displayed as ESA*= 9 on the x-axis. It is determined where x=9 intersects with any of the dose response profiles.The y-value at the point of intersection is the weight respective dose-response profile. In this case, the weight of Dose Response Profile 2 is 0.5 and the weight of Dose Response Profile 3 is .1. The rest of the dose response profiles have a weight of 0.[6]



Determining the final dose recommendation

The patient-specific optimal ESA dose recommendation is determined by adding the product of weight of each dose response profile and the dose-response specific optimal ESA doses and dividing by the sum of the weights of each dose response profile. The equation is outlined below, where W represents the weight of a specific dose response profile and ESA represents the optimal ESA dose of a dose response profile.

$$ESA_{RawRecommendedDose} = \frac{W_1 ESA_1 + W_2 ESA_2 + W_3 ESA_3 + W_4 ESA_4 + W_5 ESA_5}{W_1 + W_2 + W_3 + W_4 + W_5}$$

[6] Source: Article 9 in Published Literature section (https://www.ncbi.nlm.nih.gov/pubmed/19115195)

Published Literature

The research team behind SAM is based at the University of Louisville, and has published extensively on the technical and clinical steps taken to build and validate SAM. Those publications can be accessed below.

Clinical Publications

1. Gaweda, Adam & A. Jacobs, Alfred & Aronoff, George & Brier, Michael. (2018). *Individualized anemia management in a dialysis facility – long-term utility as a single-center quality improvement experience.* Clinical Nephrology. 90. 10.5414/CN109499. (https://www.ncbi.nlm.nih.gov/pubmed/30049300)

2. Brier, M.E. and A.E. Gaweda, *Artificial intelligence for optimal anemia management in end-stage renal disease.* Kidney Int, 2016. **90**(2): p. 259-61. (https://www.ncbi.nlm.nih.gov/pubmed/27418093)

3. Akabua, E., et al., *Individualized model discovery: the case of anemia patients.* Comput Methods Programs Biomed, 2015. **118**(1): p. 23-33. (https://www.ncbi.nlm.nih.gov/pubmed/25459523)

4. Gaweda, A.E., et al., *Individualized anemia management reduces hemoglobin variability in hemodialysis patients.* J Am Soc Nephrol, 2014. **25**(1): p. 159-66. (https://www.ncbi.nlm.nih.gov/pubmed/24029429)

5. Brier, M.E., et al., *Randomized trial of model predictive control for improved anemia management.* Clin J Am Soc Nephrol, 2010. **5**(5): p. 814-20. (https://www.ncbi.nlm.nih.gov/pubmed/20185598)

6. Gaweda, A.E., et al., *Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response.* Clin J Am Soc Nephrol, 2010. **5**(4): p. 576-81. (https://www.ncbi.nlm.nih.gov/pubmed/20110344)

Technical Publications

7. Brier, M.E. and A.E. Gaweda, *Predictive modeling for improved anemia management in dialysis patients.* Curr Opin Nephrol Hypertens, 2011. **20**(6): p. 573-6. (https://www.ncbi.nlm.nih.gov/pubmed/21941178)

8. Gaweda, A.E., et al., *Determining optimum hemoglobin sampling for anemia management from every-treatment data.* Clin J Am Soc Nephrol, 2010. **5**(11): p. 1939-45. (https://www.ncbi.nlm.nih.gov/pubmed/20671221)

9. Gaweda, A.E., A.A. Jacobs, and M.E. Brier, *Application of fuzzy logic to predicting erythropoietic response in hemodialysis patients.* Int J Artif Organs, 2008. **31**(12): p. 1035-42. (https://www.ncbi.nlm.nih.gov/pubmed/19115195)

10. Gaweda, A.E., et al., *Model predictive control of erythropoietin administration in the anemia of ESRD.* Am J Kidney Dis, 2008. **51**(1): p. 71-9. (https://www.ncbi.nlm.nih.gov/pubmed/18155535)

11. Gaweda, A.E., et al., *Individualization of pharmacological anemia management using reinforcement learning.* Neural Netw, 2005. **18**(5-6): p. 826-34. (https://www.ncbi.nlm.nih.gov/pubmed/16109475)

12. Gaweda, A.E., et al., *Pharmacodynamic population analysis in chronic renal failure using artificial neural networks--a comparative study.* Neural Netw, 2003. **16**(5-6): p. 841-5. (https://www.ncbi.nlm.nih.gov/pubmed/12850042)

13. Gaweda el al. *Using clinical information in goal-oriented learning*. IEEE Eng Med Biol Mag. 2007 Mar-Apr;26(2):27-36 (https://www.ncbi.nlm.nih.gov/pubmed/17441606)

The Patent

The patent that includes a detailed explanation of all that calculations within SAM can be found here.

The relevant sections cited above have been excerpted below:

Step 2: "the input device receives a Hbtarget value (target hemoglobin level (g/dL)), a Hbk value (Hb level (g/dL) computed from Hb data over time using lowess smoothing or another suitable smoothing method with a 28 day window), a ΔHbk value (Hb rate of change (g/dL per day) computed from Hb data over time using lowess smoothing or another suitable smoothing method with a 28 day window), and an Epok value, which corresponds to the Epo dose previously received (Epo dose received (e.g., 1000 Units per week) or computed from Epo data over time as an average weekly Epo dose received over the preceding 28 days, if the previously-prescribed dose is not available."

(column 20, line 39-51)

Steps 3 and 4: "Also shown are five dosing regimen program modules ("i"=5), which are understood to be stored in the data storage device. The dosing regimen program modules include instructions for causing the processing device to determine an Epok+1,i value (recommended Epo dose (e.g., 1000 Units per week) for each of the "i" dosing regimens, the details of which are described below."

(column 20, line 51-58)

"each of the "i" dosing regimen program modules includes: a dose-response model module for causing the processing device to determine a Hbk+1 value and a ΔHbk+1 value (i.e., a predicted response) for a subject with a respective Epo sensitivity profile based on the Hbk value, the ΔHbk value, and a proposed Epok+1 value; and an optimization algorithm module for causing the processing device to determine the optimal value Epok+1,i* value using the Hbtarget value, and given the Epok value, the Hbk+1 value and the ΔHbk+1 value, and then iteratively providing the proposed Epok+1 value to the dose-response module and re-determining the proposed Epok+1 value until the proposed Epok+1 values converge to the optimal value Epok+1,i*, which is the value at which the objective function provided below in Equation (6) achieves minimum subject to optimization constraints.

In the exemplary dosing regimen program module 900, the dose-response model is substantially according to the function:

$$\begin{bmatrix} \frac{dHb}{dt} \\ \frac{d\Delta Hb}{dt} \end{bmatrix} = \begin{bmatrix} \frac{-2}{T_i} & \frac{1}{T_i^2} \\ 1 & 0 \end{bmatrix} \begin{bmatrix} Hb \\ \Delta Hb \end{bmatrix} + \begin{bmatrix} \frac{K_i}{T_i^2} \\ 0 \end{bmatrix} Epo \qquad (4)$$

where:
Ki—erythropoietic response (1,000 Units Epo per 1 g/dL Hb change);
Ti—time constant;

Epo—dose (1,000 Units);
Hb—hemoglobin level (g/dL);
ΔHb—hemoglobin rate of change (g/dL per day);

where:
Ki and Ti are mechanistic parameters describing sensitivity (K) and dynamics (T) of the red blood cell production process;
K is physiologically related to red cell production rate;
T is physiologically related to mean red blood cell lifespan; and

where:
a discrete time grey-box model describing Hb response to Epo can be derived by sampling Equation (4) every Ts days

$$\begin{bmatrix} Hb_{k+1} \\ \Delta Hb_{k+1} \end{bmatrix} = \begin{bmatrix} \theta_{i,1} & \theta_{i,2} \\ \theta_{i,2} & \theta_{i,4} \end{bmatrix} \begin{bmatrix} Hb_k \\ \Delta Hb_k \end{bmatrix} + \begin{bmatrix} \theta_{i,5} \\ \theta_{i,6} \end{bmatrix} Epo_{k+1} \quad (5)$$

where:
k—time step
θi=[θi,1, θi,2, θi,3, θi,4, θi,5, θi,6]—parameter vector derived from Ki and Ti by sampling Equation (4) every Ts days; and

wherein the optimization algorithm is substantially according to the objective function:

$$OFV = \sum_{k_p=1}^{H_p} \left(Hb_{target} - Hb_{k_p}\right)^2 + \lambda_i \sum_{k_c=1}^{H_c} \Delta Epo_{k_c}^2 \quad (6)$$

where:
kp, kc—time steps (weeks);
Hp—prediction horizon (weeks);
Hc—control horizon (weeks);
λi—dose change suppression (non-dimensional);
Hbkp—hemoglobin at step kp;
ΔEpokc—change in dose from step kc-1 to kc; and
subject to constraints:
0≦Epo≦90,000 units per week
0≦Hb≦20 g/dL
−0.5<ΔHb<0.5 g/dL per week
where: ΔHb=Hbkp−Hbkp-1

Equation (4) above is a continuous time equation that describes the dynamic behavior of Hb and the Hb rate of change (ΔHb) in response to an Epo dose, given a fixed Epo sensitivity profile i described by two parameters: Ki, or the erythropoietic response which represents the magnitude of Hb increase

(decrease) in steady-state after the Epo dose has been increased (or decreased) by 1,000 Units; and Ti, or the time constant that is mathematically related to the time required for Hb to achieve the steady-state after the Epo dose has been increased (or decreased). In some embodiments, Equation (1) is used as the Dose-Response Model to calculate the Hbk+1 and ΔHbk+1 values from the Hbk and ΔHbk, and to also calculate the Epok value.

Equation (6), on the other hand, describes the objective function to be minimized by Epok+1,i*. The first right-hand-side term of this equation sums the squared difference between Hbtarget and Hb predicted by the Dose-Response Model (Equation 1) at time steps kp, where kp changes from 1 through prediction horizon Hp. The second right-hand term sums the squared amounts of Epo dose adjustments at time step kc, where kc changes from 1 through control horizon Hc. In this regard, the first term thereby represents the tracking properties of the controller, i.e. how well the measured Hb is maintained close to target, while the second term represents robustness of the controller, i.e. how well the controller ignores random changes in measured Hb. The balance between tracking and robustness is determined by the parameter λi.

In the embodiment of the exemplary dosing regimen program module whose parameters are shown above, the sampling time of 7 days was selected based on an optimal frequency of Hb observation, while the values of the erythropoietic response parameter (K) for Dose-Response Models 1 through 5 were selected to cover a maximum possible range of Epo doses that can be given to a subject, as regulated by NKF-K/DOQI guidelines and the product label. The time constant parameter for all the models was selected to represent the average RBC lifespan typical for the hemodialysis patient population of 90 days. The controller parameters (Hp, Hc, and λ1 through λ5) were optimized to achieve time to reach Hb steady-state not greater than 12 weeks in response to a 1,000 Unit change in Epo dose and to miminize Epo dose changes in response to random noise in Hb measurement. Of course, for a particular application, the dosing regimen program module parameters can further be adapted or changed as desired without departing from the spirit and scope of the subject matter described herein.

(column 20, line 51-58, columns 21 and 22 lines 1-68, and column 23, lines 1-14)

Steps 5 and 6: “in the exemplary dose selection algorithm module 1000 there are 5 dosing regimens (“i”=5) and the dosing selection algorithm module determines the Eponext value substantially according to the equation (function):

$$Epo_{k+1} = \frac{w_{R1}Epo^{*}_{k+1,1} + w_{R2}Epo^{*}_{k+1,2} + w_{R3}Epo^{*}_{k+1,3} + w_{R4}Epo^{*}_{k+1,4} + w_{R5}Epo^{*}_{k+1,5}}{w_{R1} + w_{R2} + w_{R3} + w_{R4} + w_{R5}}. \quad (7)$$

The weighting values are fuzzy membership functions according to the following:
wR1=fMF(Epok, μ1, s1l, s1r) μ1=0 s1l=1.0 s1r=0.9*(Hbtarget−Hb0)
wR2=fMF(Epok, μ2, s2l, s2r) μ2=3*(Hbtarget−Hb0) s2l=s1r s2r=1.35*(Hbtarget−Hb0)
wR3=fMF(Epok, μ3, s3l, s3r) μ3=7.5*(Hbtarget−Hb0) s3l=s2r s3r=2.25*(Hbtarget−Hb0)
wR4=fMF(Epok, μ4, s4l, s4r) μ4=15*(Hbtarget−Hb0) s4l=s3r s4r=s4l
wR5=fMF(Epok, μ5, s5l, s5r) μ5=22.5*(Hbtarget−Hb0) s5l=s4r s5r=100.0

where fMF is a fuzzy membership function substantially according to the equation:

$$f_{MF}(x, \mu, s_l, s_r) = \begin{cases} \exp\left(-\frac{(x-\mu)^2}{s_l^2}\right) & x < \mu \\ 1 & x = \mu \\ \exp\left(-\frac{(x-\mu)^2}{s_r^2}\right) & x > \mu \end{cases} \quad (8)$$

and Hb0 is baseline hemoglobin, which is the hemoglobin level before first administration of Epo.

In Equation (8) above, the parameter μ represents the center of the fuzzy membership function and the parameters sl and sr represent the left and right spread of the membership function, respectively. In some embodiments, the centers (i.e., where the membership achieves the maximum value of 1.0) were chosen to represent the most typical Epo dose value received by the subjects belonging to the specific sensitivity profile, while the spreads were chosen to achieve the overlap between the neighboring membership functions at the value of 0.25.

(column 23, lines 15-63)