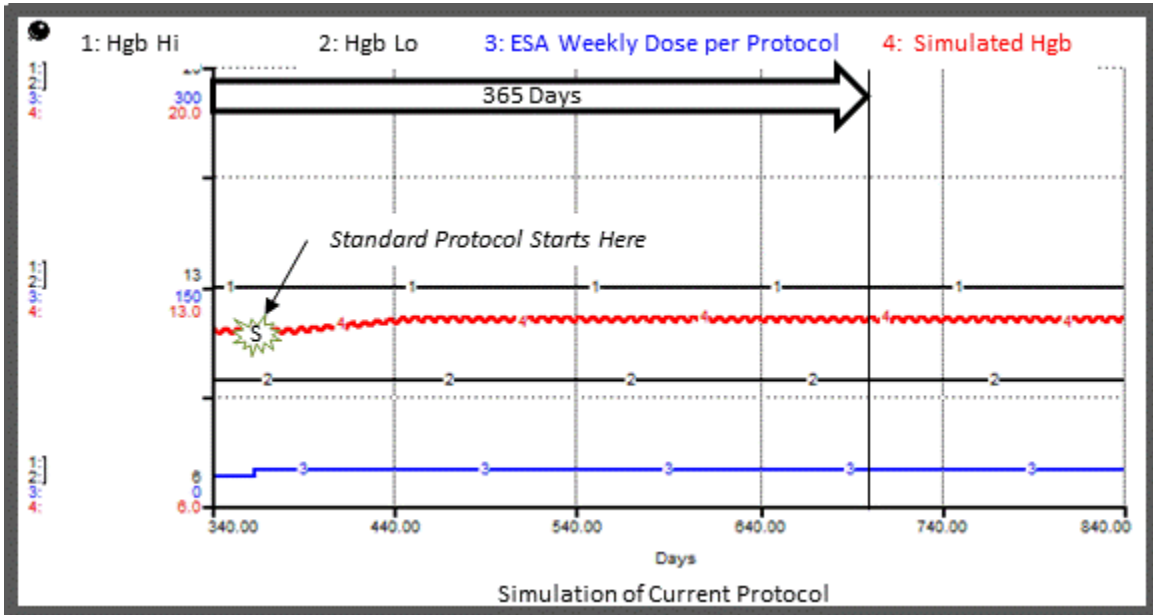


An Individualized ESA Dosing Regimen for Hemodialysis Patients
To Stabilize Hemoglobin Levels in a Target Range

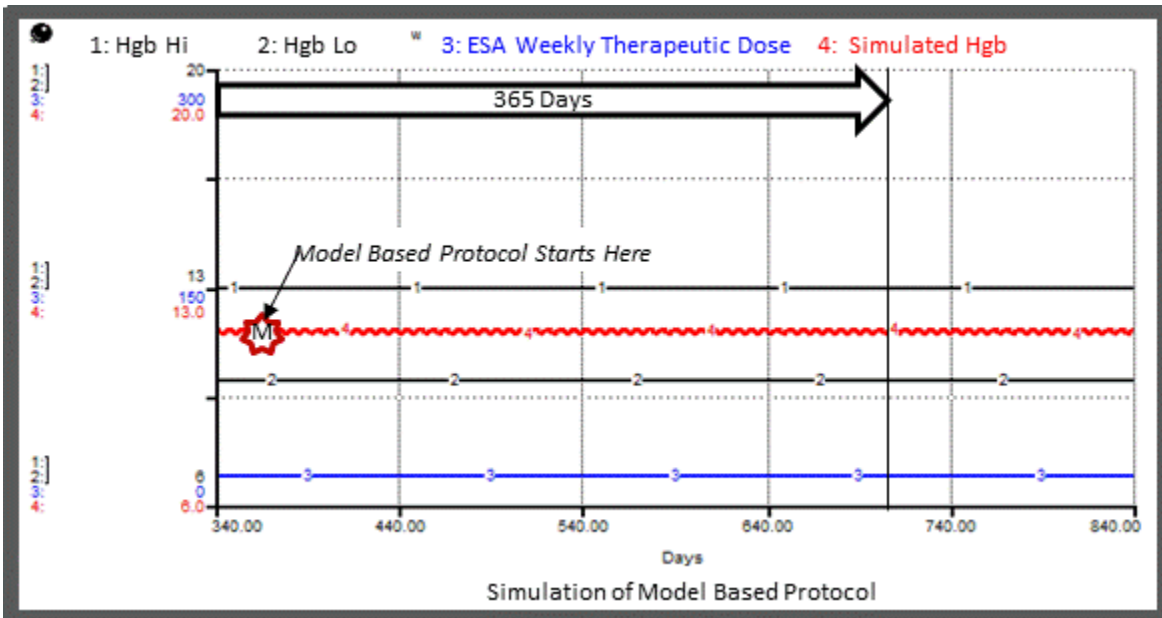
Appendix 1. Simulations of the Standard and Model Based Protocols

Case 1A: HGB is Stable and in Target Range – Standard Protocol:



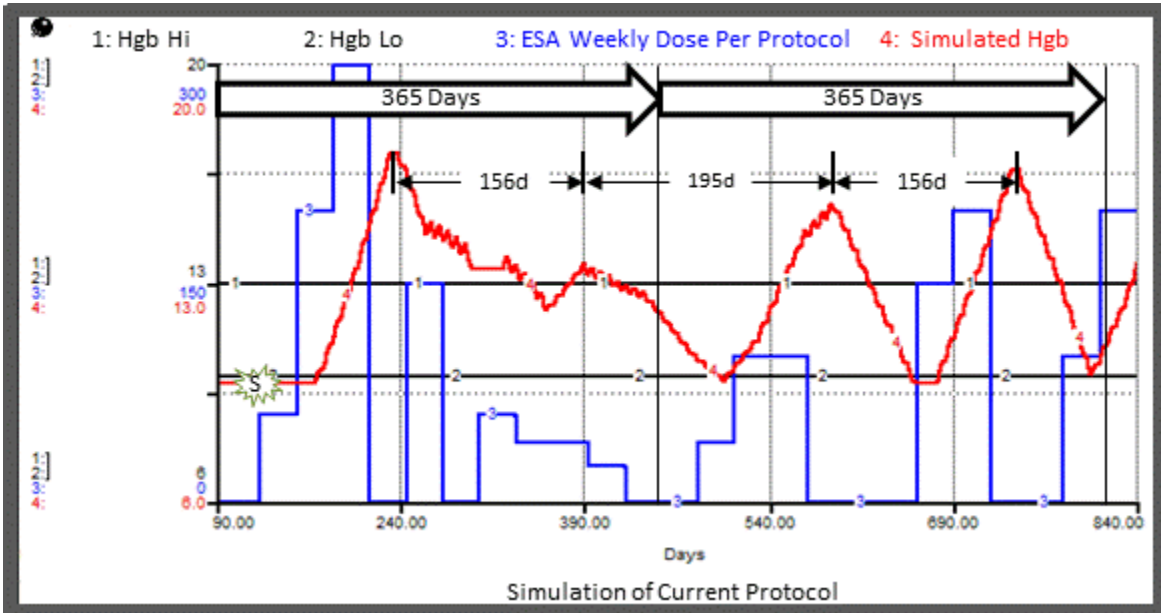
At day 340 Hgb was 11.5 with dose of 20mcg per week. Standard Protocol is initiated at day 360. This requires changing to a vial size of 25 mcg, which stabilizes Hgb at 12.0 with no further changes required.

Case 1B: HGB is Stable and in Target Range – Model Based Protocol



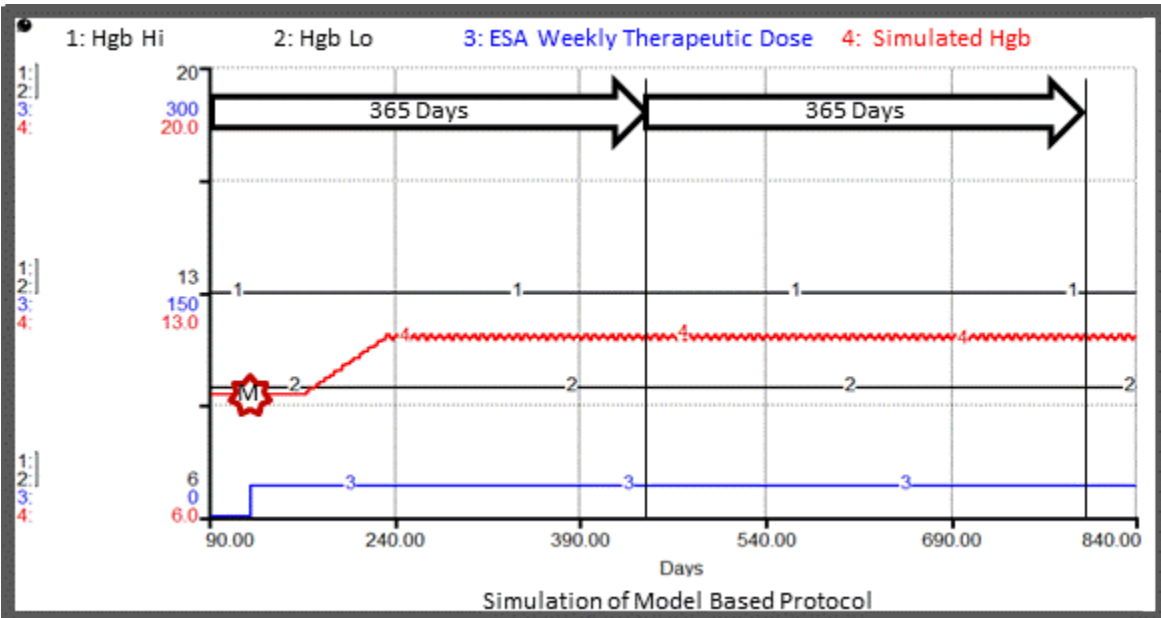
At day 340 Hgb was 11.5 with a dose of 20 mcg per week. Applying the Model Based Protocol at day 360, the previously determined WTD of 20 mcg per week is initiated. This weekly dose stabilizes Hgb at 11.5, exactly in the center of the target range. As described, the WTD of 20 mcg/week requires titration of available vial sizes to deliver the equivalent dose. The results of those titrations are not shown here.

Case 2A: HGB is Stable but Below Target Range – Standard Protocol



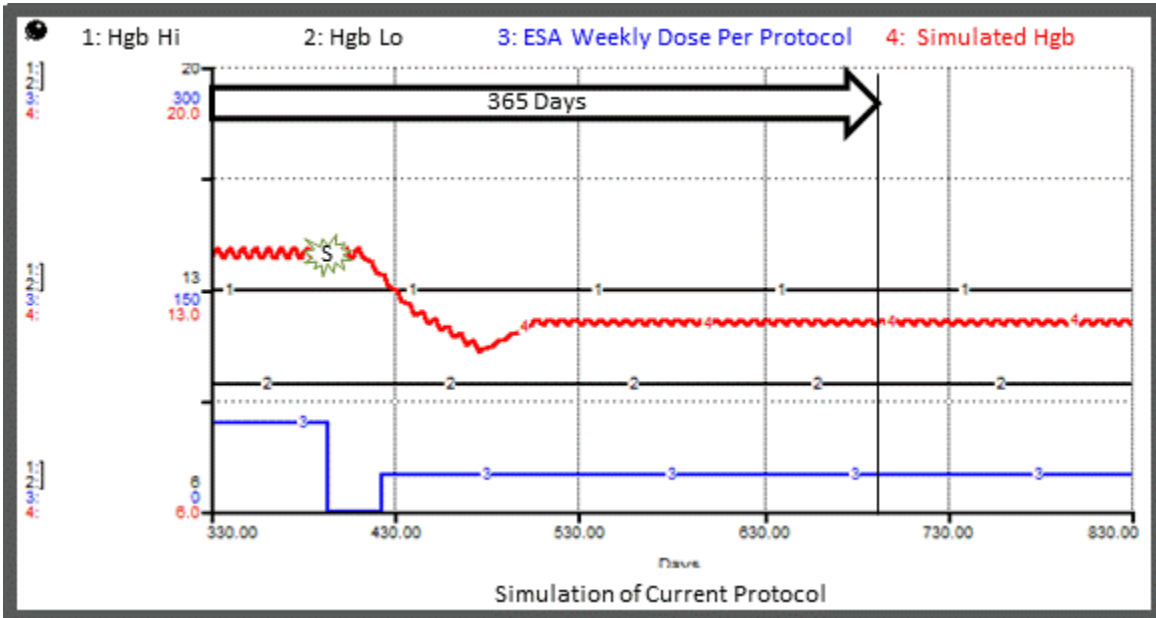
At day 90, Hgb is stable at 9.8, below the target range. Based upon monthly Hgb lab measurements, the Standard Protocol is initiated at day 120. Following the protocol leads to periodic oscillation with excursions above the desired upper limit.

Case 2B: HGB is Stable but Below Target Range – Model Based Protocol



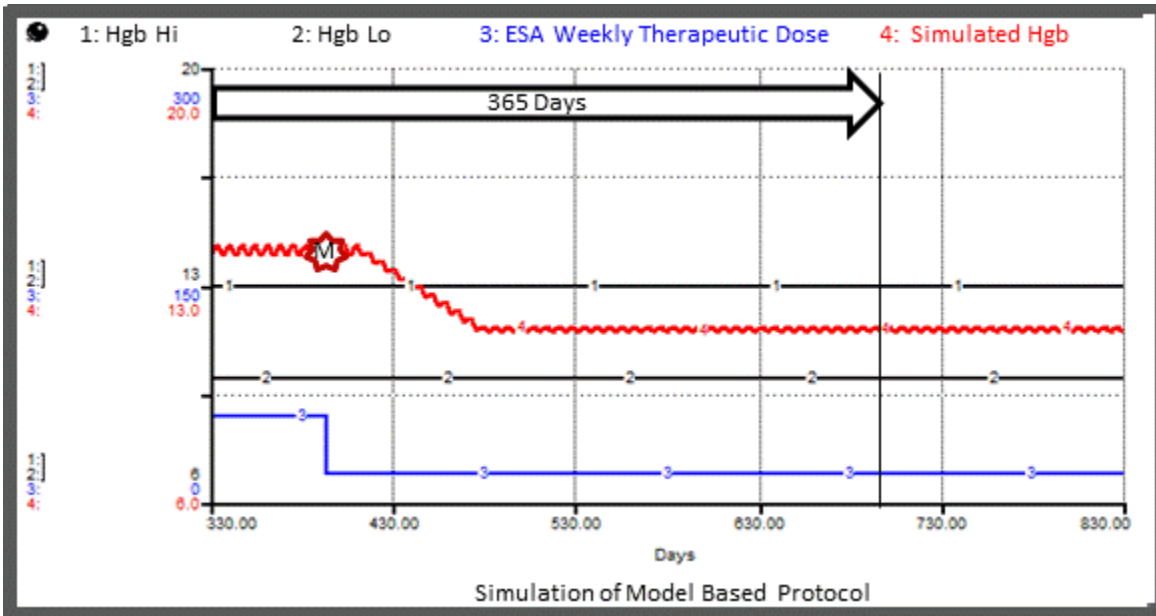
Hgb is stable at 9.8 from day 90 to day 120, below the target range. The Model Based WTD is administered at day 120, Hgb rises and stabilizes at 11.5.

Case 3A: HGB is Stable but Above Target Range – Standard Protocol



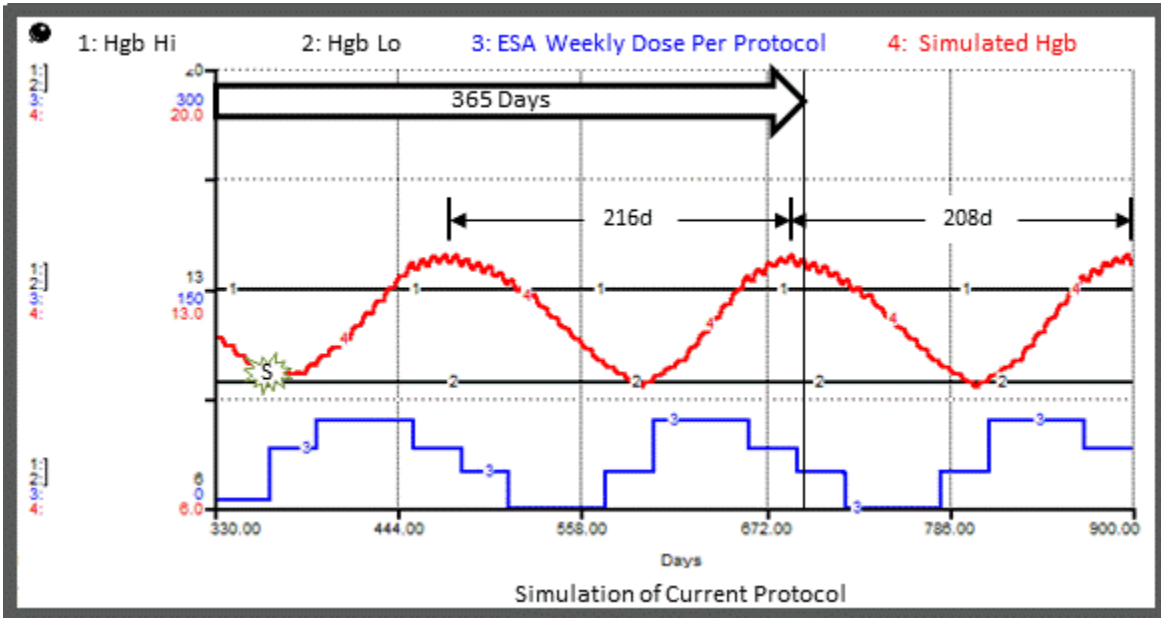
At day 90, Hgb is stable at 14.1, above the target range. Based upon monthly Hgb lab measurements, the Standard Protocol is initiated at day 360. Following the protocol stabilizes and maintains Hgb at 12.0.

Case 3B: HGB is Stable but Above Target Range – Model Based Protocol



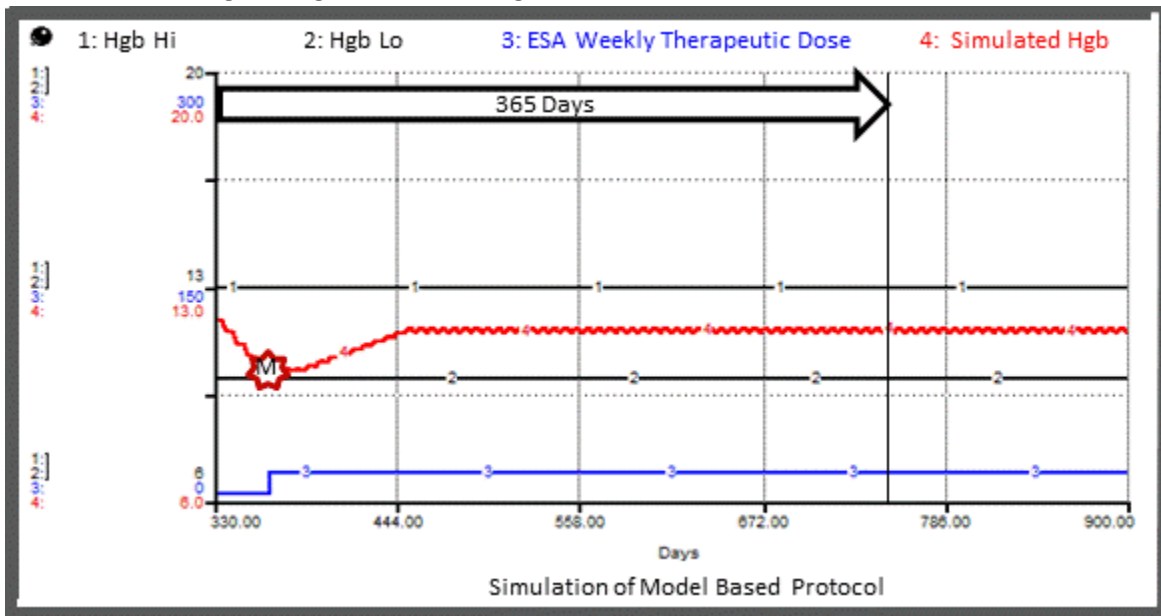
At day 90, Hgb is stable at 14.1, above the target range. Based upon monthly Hgb lab measurements, the Model Based Protocol is initialized at day 360. Following the protocol stabilizes and maintains Hgb at 11.5.

Case 4A: HGB is in Target Range but Decreasing – Standard Protocol



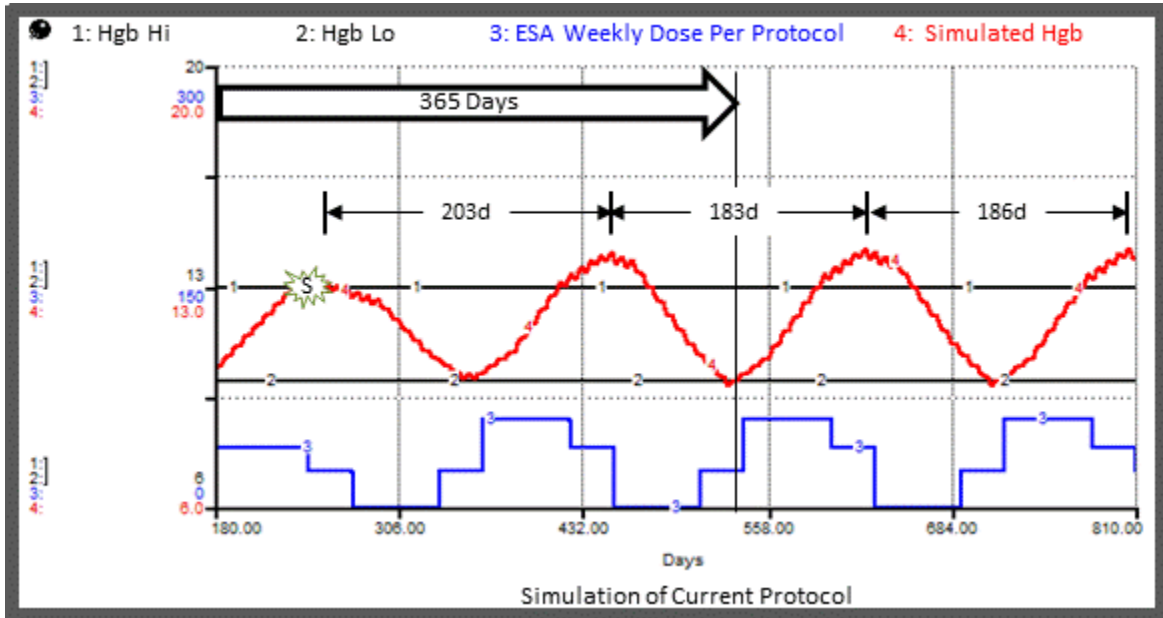
Hgb is in target range but decreasing at Day 330. The Standard Protocol is initiated at day 360. Following protocol leads to periodic oscillations with excursions above the desired upper limit.

Case 4B: HGB is in Target Range but Decreasing – Model Based Protocol



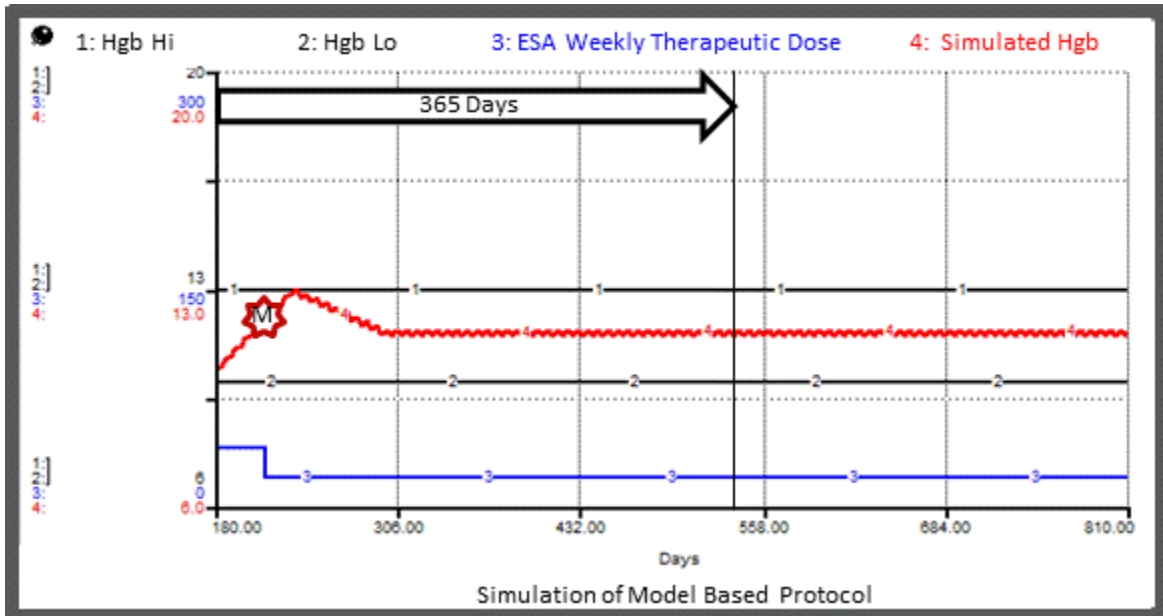
Hgb is in target range but decreasing at Day 330. The Model Based Protocol is initiated at day 360. Following protocol leads stabilizes Hgb at 11.5, the center of the target range.

Case 5A: HGB is in Target Range but Increasing - Standard Protocol



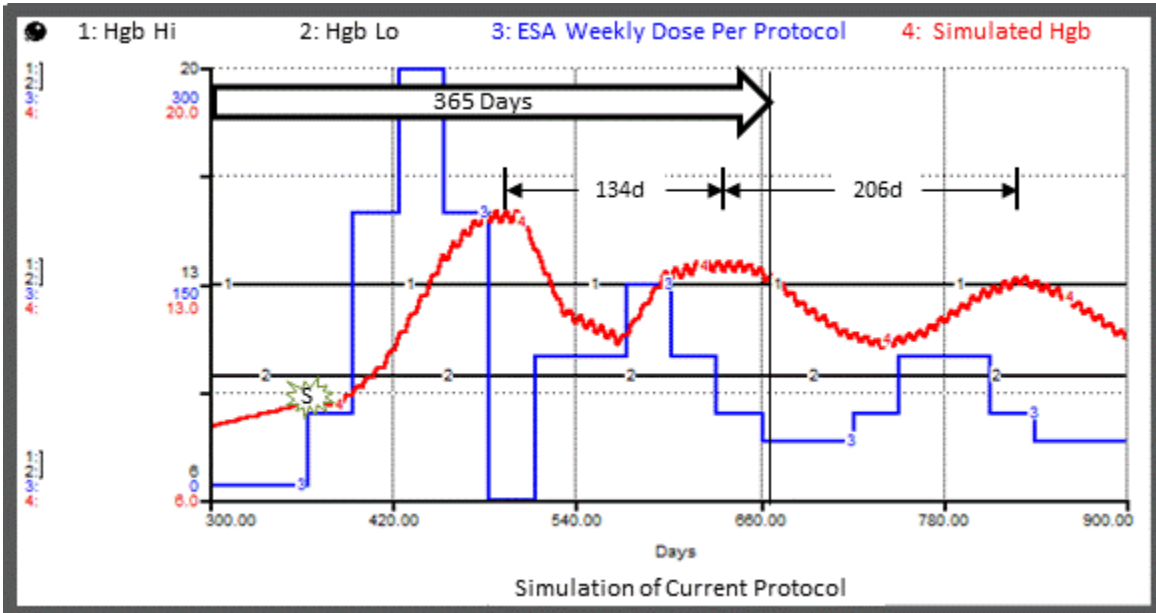
Hgb is in target range but has increased to 12.1 from day 180 to 12.9 at day 210. Standard Protocol is initiated at day 210 which leads to oscillation with excursions above the desired upper limit.

Case 5B: HGB is in Target Range but Increasing – Model Based Protocol



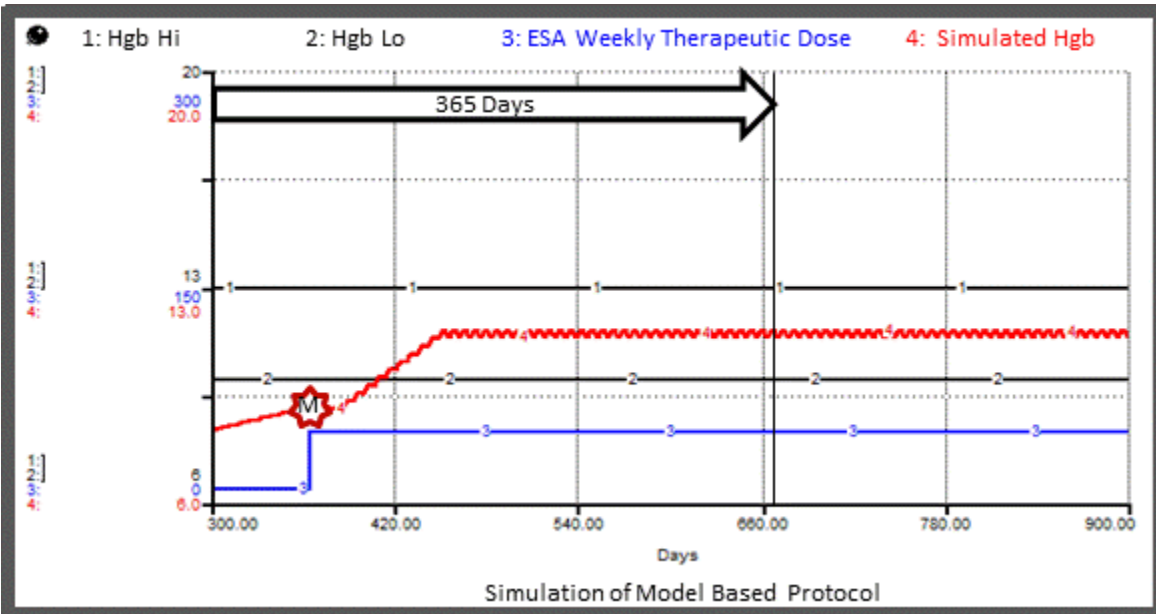
Hgb is in target range but has increased to 12.1 from day 180 to 12.9 at day 210. Model Based Protocol is initiated at day 210 which stabilized Hgb at 11.5, the center of the target range.

Case 6A: HGB is Below Target Range but Increasing –Standard Protocol



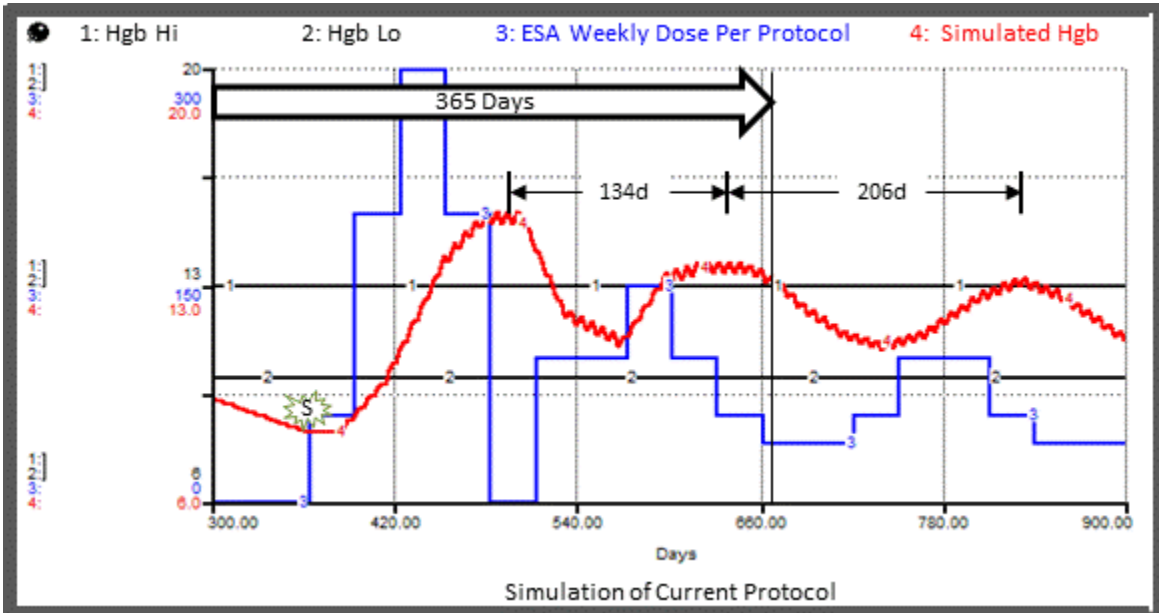
Hgb is below target range but has increased from 8.3 at day 300 to 9.1 at day 360. Standard Protocol is initiated at day 360 which leads to oscillation. By day 900, oscillation amplitude appears to be diminishing, suggesting Hgb might stabilize to a value in the target range in less than 200 more days.

Case 6B: HGB is Below Target Range but Increasing - Model Based Protocol



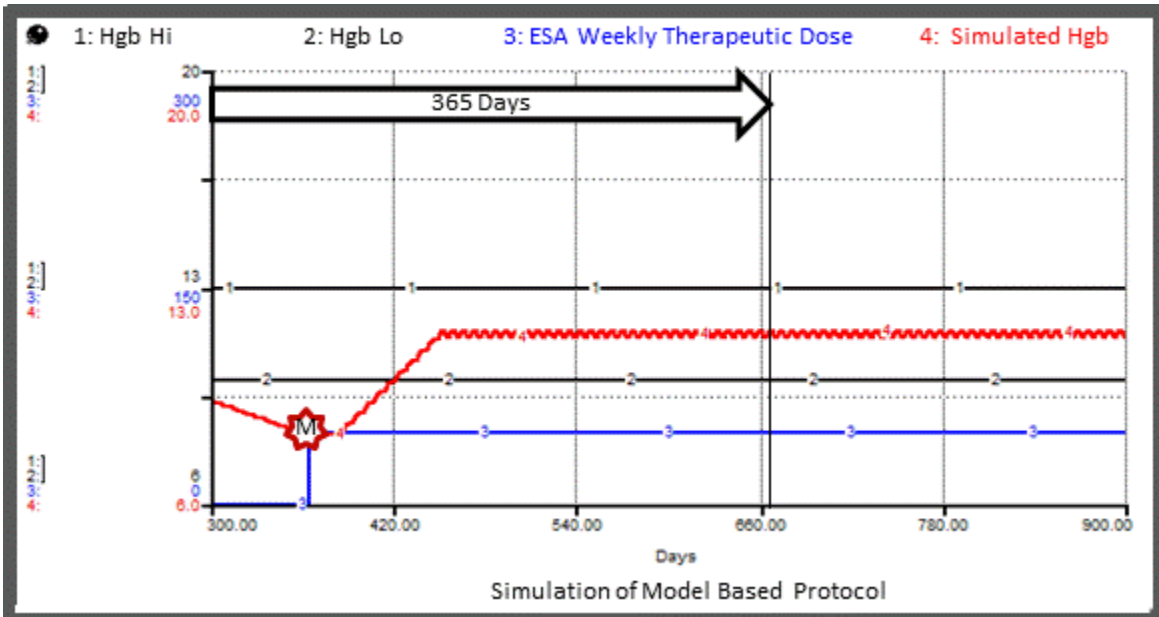
Hgb is below target range but has increased from 8.3 at day 300 to 9.1 at day 360. Model Based Protocol is initiated at day 360. This stabilizes Hgb at 11.5 within 90 days.

Case 7A: HGB is Below Target Range and Decreasing – Standard Protocol



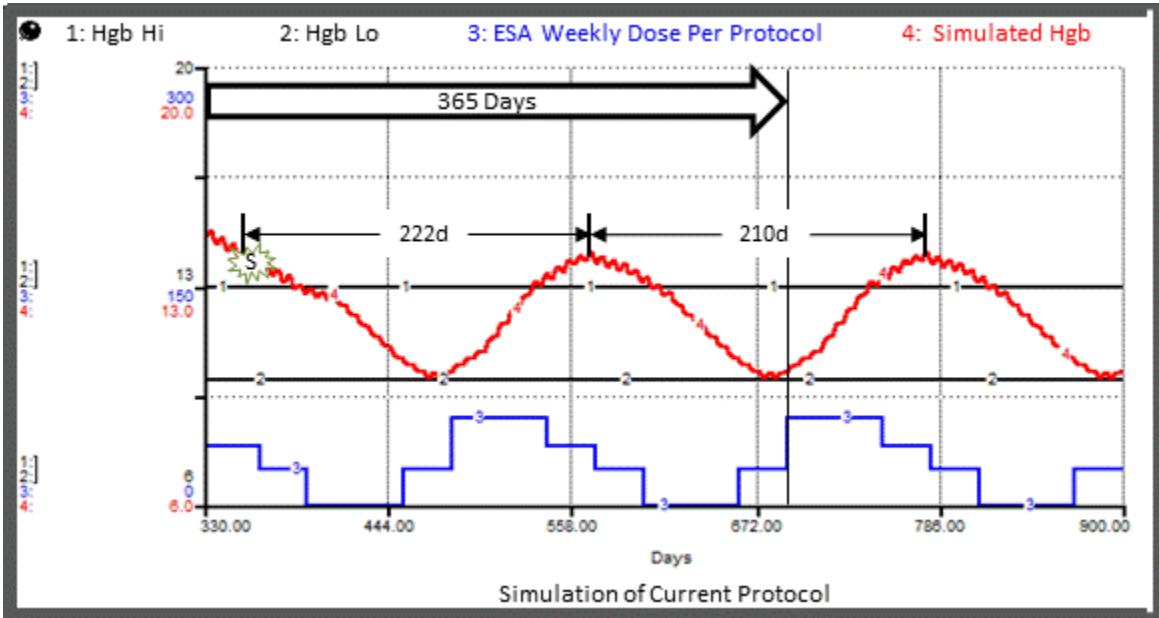
Hgb is below target range and has decreased from 9.4 at day 300 to 8.3 at day 360. Standard Protocol is initiated at day 360 which leads to oscillation. By day 900, oscillation amplitude appears to be diminishing, suggesting Hgb might stabilize to a value in the target range in less than 200 more days. Note this behavior is identical to Case 6A.

Case 7B: HGB is Below Target Range and Decreasing – Model Based Protocol



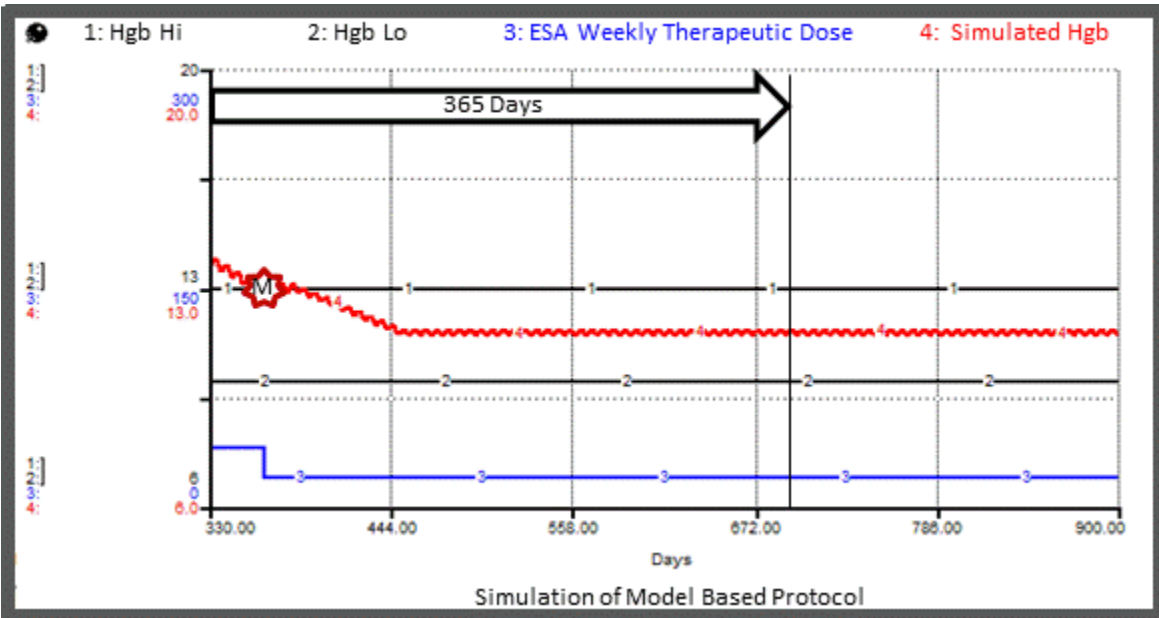
Hgb is below target range and has decreased from 9.4 at day 300 to 8.3 at day 360. Model Based Protocol is initiated at day 360. This stabilizes Hgb at 11.5 within 90 days.

Case 8A: HGB is Above Target Range but Decreasing – Standard Protocol



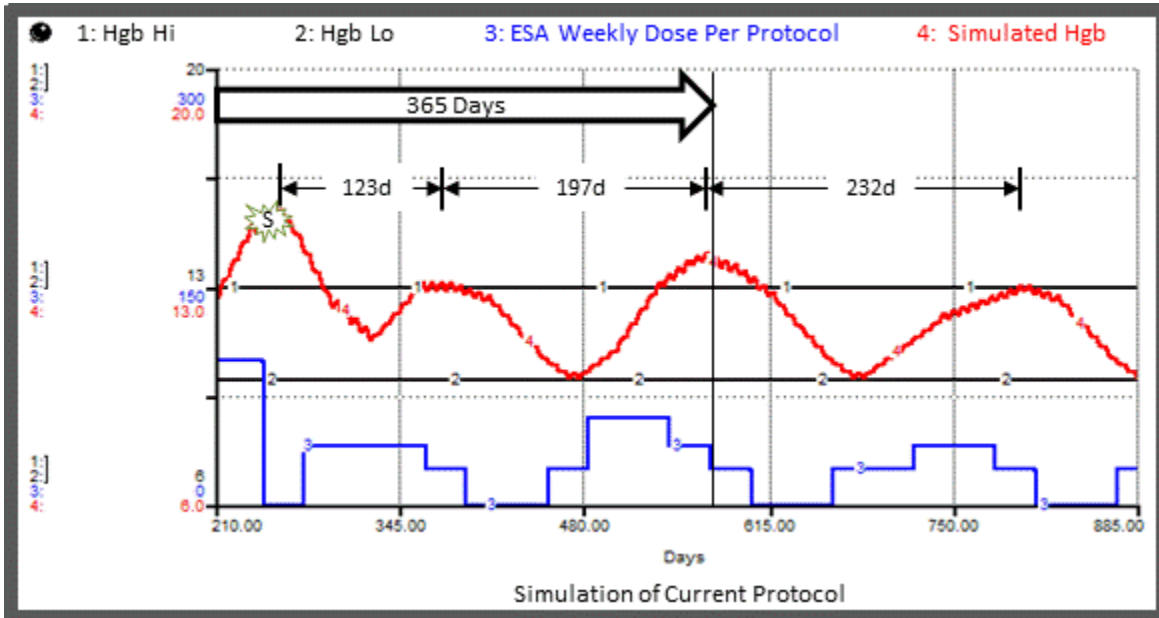
Hgb is above target range but has decreased from 14.1 at day 330 to 13.6 at day 360. Standard Protocol is initiated at day 360 which leads to oscillation with excursions above the desired upper limit.

Case 8B: HGB is Above Target Range but Decreasing – Model Based Protocol



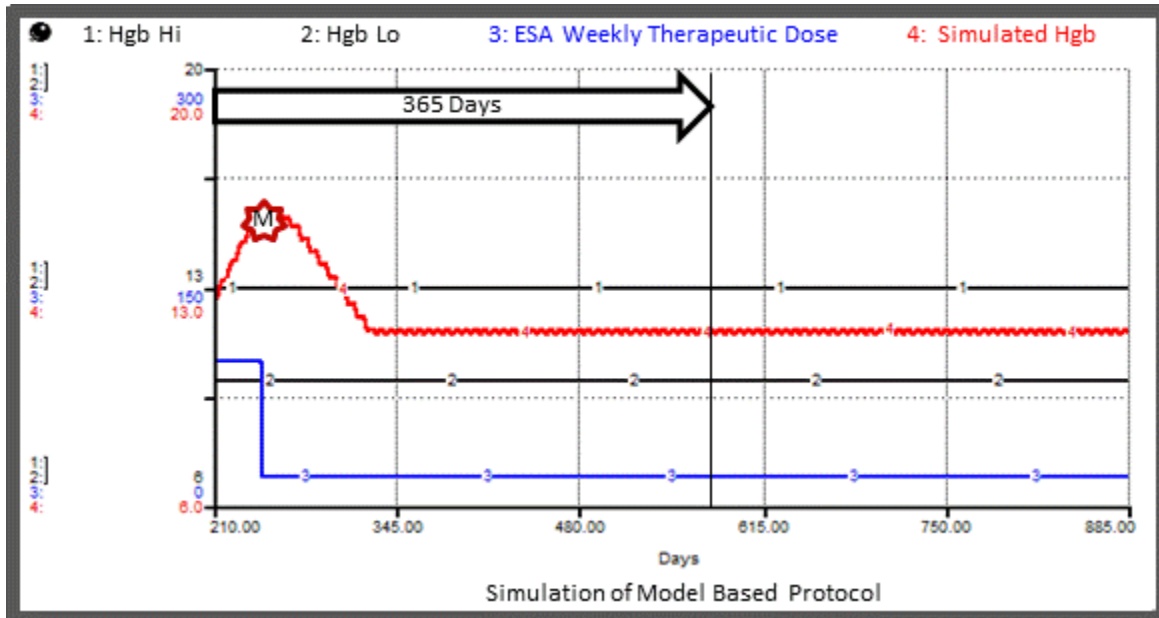
Hgb is above target range but has decreased from 14.1 at day 330 to 13.6 at day 360. Model Based Protocol is initiated at day 360 which stabilizes Hgb at 11.5 within 90 days.

Case 9A: HGB is Above Target Range and Increasing – Standard Protocol



Hgb is above target range and has increased from 13.1 at day 210 to 15.1 at day 240. Standard Protocol is initiated at day 240 which leads to oscillation with one excursions above the desired upper limit 320 days later.

Case 9B: HGB is Above Target Range and Increasing – Model Based Protocol



Hgb is above target range and has increased from 13.1 at day 210 to 15.1 at day 240. Model Based Protocol is initiated at day 240 which stabilizes Hgb at 11.5 within 90 days.