Washington State Health Care Authority

REPORT TO THE LEGISLATURE

Bleeding Disorder Collaborative for Care

Final Report

Engrossed Second Substitute Senate Bill 6052; Chapter 4; Laws of 2015; Section 213(1)(gg)

October 25, 2019

Bleeding Disorder Collaborative for Care

Washington State Health Care Authority
Clinical Quality and Care Transformation
P.O. Box 45502
Olympia, WA 98504
Phone: (360-725-0473
Fax: (360) 586-9551
www.hca.wa.gov

Table of Contents

Executive Summary

Bleeding disorders are a group of medical conditions that interfere with a patient's ability to stop bleeding. Hemophilia is one of the most well-known bleeding disorders, because it can result in frequent — sometimes serious — bleeding episodes. To prevent emergency bleeding episodes, patients receive medication, called "factor", to replace a protein missing from the patients' blood. Due to the amount of medication that patients use and the cost of these medications, managing hemophilia effectively requires considerable health care resources.

Beginning with the 2015-2017 biennial state operating budget in Engrossed Substitute Senate Bill 6052 (2015), the Washington State Legislature directed the Health Care Authority (HCA) to convene the Bleeding Disorder Collaborative for Care (Collaborative).

HCA previously reported on the Collaborative's efforts by publishing the Bleeding Disorder Collaborative for Care: Fiscal Year 2016 Progress Report. In this final report, we:

- Summarize the Collaborative's hemophilia treatment clinical trial, its results, and how it might inform evidence-based clinical practices and efforts to reduce health care costs;
- Describe potential fiscal implications of the clinical trial through a cost-benefit analysis; and
- Discuss the presentation of the clinical trial results at the May 2019 symposium to disseminate evidence-based practices for managing hemophilia.

HCA contracted with Bloodworks Northwest to conduct the Collaborative's clinical trial that evaluated factor dosing calculations using ideal body weight (IBW) instead of actual body weight (ABW). The finding that overweight and obese hemophilia A patients might need less factor, based on their IBW instead of their ABW, may prove useful to researchers and practicing clinicians.

- Researchers have an opportunity to replicate or build upon the Collaborative's clinical trial and contribute more to hemophilia's emerging clinical practice guidelines.
- Practicing clinicians are now able to use the results of the clinical trial to help personalize hemophilia treatment regimens, which could reduce health care costs without negatively affecting patient health outcomes.

With the publication of this report, the work of the Collaborative is now complete.

Background

Bleeding disorders are a group of medical conditions that interfere with patients' abilities to stop bleeding, of which hemophilia is one of the best known. Some of the most serious bleeds that hemophilia patients experience occur inside the body. Individuals with hemophilia may spontaneously bleed into their brain, joints, muscles, and other tissues, often creating life-threatening emergencies. Chronic bleeding episodes eventually can cause irreversible damage to joints, leading to early arthritis and disability.

Hemophilia is a rare, life-long, inherited medical condition that typically affects males. Deficiencies in specific factors (proteins), which help to form blood clots, cause the disease. The two most common forms of hemophilia are types A and B, which differ by the deficient blood factor:

- Hemophilia A occurs in about one per 5,000 male births.
- Hemophilia B occurs in about one per 30,000 male births.

Standard treatment for patients with severe hemophilia involves preventative use of intravenous (IV) infusions of factor drugs or concentrates — either recombinant (genetically engineered) or extracted from blood plasma.

Managing hemophilia effectively to prevent emergency bleeding episodes requires considerable health care resources. Depending on the prescribed treatment regimen and the characteristics of the patient's body, patients may use factor at different rates, sometimes requiring frequent infusions — up to several times per week. According to a 2015 estimate, the national average factor cost for a hemophilia patient exceeded $270,000 per year.[1]

Budget Proviso

The Washington State Legislature directed the Health Care Authority (HCA) in the 2015-2017 and 2017-2019 biennial state operating budgets[2,3,4] to convene the Bleeding Disorder Collaborative for Care (Collaborative). In addition to HCA, the following organizations participated in the Collaborative:

- Bleeding Disorder Foundation of Washington;[5]
- Oregon Health & Science University;[6]
- Sacred Heart Children's Hospital;[7]
- Seattle Children's Hospital;[8] and

[1] Miracle of Hemophilia Drugs Comes at a Steep Price, from www.npr.org/sections/health-shots/2018/03/05/589469361/miracle-of-hemophilia-drugs-comes-at-a-steep-price, accessed on August 2, 2019.
[2] Engrossed Substitute Senate Bill 6052; Chapter 4 Laws of 2015; Section 213(1)(gg), from lawfilesext.leg.wa.gov/biennium/2015-16/Pdf/Bills/Session%20Laws/Senate/6052-S.SL.pdf, accessed on July 26, 2019.
[3] Second Engrossed Substitute House Bill 2376; Chapter 36; Laws of 2016; Section 213(1)(nn), from lawfilesext.leg.wa.gov/biennium/2015-16/Pdf/Bills/Session%20Laws/House/2376-S.SL.pdf, accessed on July 26, 2019.
[4] Substitute Senate Bill 5883; Chapter 1; Laws of 2017; Third Special Session; Section 1213(1)(ll), from leap.leg.wa.gov/leap/budget/lbns/1710mni5883-S.SL.pdf, accessed on July 26, 2019.
[5] Bleeding Disorder Foundation of Washington, from: www.bdfwa.org/, accessed on July 26, 2019.
[6] Oregon Health & Science University, from www.ohsu.edu/, accessed on July 26, 2019.
[7] Sacred Heart Children's Hospital, from washington.providence.org/locations-directory/s/sacred-heart-childrens-hospital, accessed on July 13, 2019.
[8] Seattle Children's Hospital, from www.seattlechildrens.org/,

- Washington Center for Bleeding Disorders.[9]

The budget proviso directed the Collaborative to:

- Identify and develop evidence-based practices to improve the care of patients with bleeding disorders (including hemophilia), focusing on health care cost reduction;
- Make recommendations for distributing evidence-based practices; and
- Assist HCA to develop a cost-benefit analysis, based on the evidence-based practices the Collaborative identified. [10]

The budget proviso also directed HCA to report to the Governor and the Legislature on the Collaborative's work by September 1, 2016.

Reports to the Legislature

HCA satisfied this legislative reporting requirement by publishing the Bleeding Disorder Collaborative for Care: Fiscal Year 2016 Progress Report[11]. That report detailed the Collaborative's efforts through June 2016, which included:

- Developing strategies to complete the tasks outlined in the budget proviso;
- Evaluating existing hemophilia treatment guidelines and best practices; and
- Initiating a plan to conduct a clinical trial for hemophilia treatment to investigate weight-based factor dosing strategies as a method to reduce health care costs.

In the 2016 progress report, HCA indicated that the delivery date of the final report depended on the conclusion of the clinical trial to fulfill some of the Collaborative's objectives. We anticipated the clinical trial would conclude in time to submit the final report during 2018. However, the clinical trial took more time, and the researchers presented the results of the clinical trial at the Hemostasis and Thrombosis Research Society[12] 2019 Scientific Symposium in May 2019.

[9] Washington Center for Bleeding Disorders, from www.bloodworksnw.org/medical-services/wa-center-for-bleeding-disorders, accessed on July 13, 2019.
[10] Bleeding Disorder Collaborative for Care, from www.hca.wa.gov/about-hca/clinical-collaboration-and-initiatives/bleeding-disorder-collaborative-care, accessed on July 11, 2019.
[11] Bleeding Disorder Collaborative for Care: Fiscal Year 2016 Progress Report, from www.hca.wa.gov/assets/program/essb-6052.pdf, accessed on July 11, 2019.
[12] "Hemostasis" means the stopping of a flow of blood. "Thrombosis" means the clotting of the blood in a part of the circulatory system. For information about the Hemostasis and Thrombosis Research Society, see www.htrs.org/HTRS/about-us, accessed on July 26, 2019.

Hemophilia Treatment Clinical Trial

Literature Review

In 2016, the Collaborative began a process to identify and develop evidence-based practices with a review of current evidence in several areas of hemophilia management. The Collaborative engaged the Medicaid Evidence-based Decisions (MED) project from Oregon Health & Science University's Center for Evidence-based Policy to evaluate existing hemophilia treatment options, guidelines, and best practices. MED focused specifically on weight-based dosing, use of ultrasound, use of factor replacement therapy in a home care services setting, and special needs for the Washington Apple Health (Medicaid) populations. MED provided the following reports for the Collaborative:

- Weight-based Dosing Strategies for Factor Replacement Therapy in Hemophilia A and B;[13]
- Use of Ultrasound to Diagnose Hemarthrosis[14] and Monitor Joint Health in Hemophilia;[15]
- Home Care Services and Utilization Management for Appropriate Use of Factor Replacement Therapy in Patients with Hemophilia;[16]
- Addressing the Needs of Members with Hemophilia in Medicaid Managed Care: Issues and Implications for Health Plans;[17] and
- Interventions for Hemophilia A and B: Clinical Practice Guidelines and Cost-effectiveness.[18,19]

After reviewing the studies, the Collaborative determined that it would pursue a clinical trial to develop more evidence about weight-based dosing. The Collaborative selected weight-based

[13] Weight-based Dosing Strategies for Factor Replacement Therapy in Hemophilia A and B, from centerforevidencebasedpolicy.org/wp-content/uploads/2018/11/Hemophilia_Dosing_Final_3-17-16.pdf, accessed on July 26, 2019.
[14] Hemarthrosis is a term that refers to bleeding into a joint.
[15] Use of Ultrasound to Diagnose Hemarthrosis and Monitor Joint Health in Hemophilia, from centerforevidencebasedpolicy.org/wp-content/uploads/2018/11/Hemophilia_Ultrasound_Final_3-17-16.pdf, accessed on July 26, 2019.
[16] Home Care Services and Utilization Management for Appropriate Use of Factor Replacement Therapy in Patients with Hemophilia, from centerforevidencebasedpolicy.org/wp-content/uploads/2018/11/Hemophilia_Home-Care_Final_3-17-16.pdf, accessed on July 26, 2019.
[17] Addressing the Needs of Members with Hemophilia in Medicaid Managed Care: Issues and Implications for Health Plans, from www.hca.wa.gov/assets/program/bdc_MHPA_hemophilia_issue_brief_082113.pdf, accessed on July 26, 2019.
[18] Interventions for Hemophilia A and B: Clinical Practice Guidelines and Cost-effectiveness, from www.hca.wa.gov/assets/program/bdc_med_report_draft.pdf, accessed on July 26, 2019.
[19] Interventions for Hemophilia A and B: Clinical Practice Guidelines and Cost-effectiveness, from www.hca.wa.gov/assets/program/bdc-hemophilia-guidelines-slides-160720.pdf, accessed on July 26, 2019.

dosing, because the evidence suggested that it could have the greatest potential for health care cost reduction, while maintaining positive therapeutic outcomes.

Current hemophilia treatment protocols calculate the dose of factor on the patient's actual body weight (ABW). However:

- Factor circulates in the patient's blood plasma, with only minimal amounts of factor entering the patient's adipose (fat) tissue; and
- Although plasma volume increases with body mass, it increases less than proportionally.

The current hemophilia treatment standard that bases a patient's dose on ABW might result in excess factor use and unnecessary health care costs. If patients can receive less factor without significantly increasing their risk for bleeding episodes, then it might be possible to reduce health care costs without compromising health care outcomes.

Weight-based dosing strategies align with the Australian treatment guidelines, which MED found to have the best evaluation standards overall among the treatment guidelines they reviewed. The guidelines for hemophilia A management in Australia recommend that medical providers base factor dosing in obese patients on ideal body weight (IBW) rather than on ABW.[20]

MED's literature searches did not find any studies with strong evidence about dosing based on IBW versus ABW. However, they did find small, limited studies on the subject. While these studies had encouraging results, MED reported the need for additional, more robust research. [21]

Clinical Trial Design

HCA contracted with Bloodworks Northwest (Bloodworks)[22] to coordinate and conduct a randomized clinical trial with a larger sample size and more rigorous study design. The clinical trial's objective was to determine whether IBW-based factor dosing would result in adequate factor levels in overweight and obese patients with hemophilia A.

From March 2016 to January 2017, the Collaborative designed the clinical trial, which included the following elements:

- Inclusion and exclusion criteria for acceptance in the clinical trial;
- The target number of patients to recruit to have a sufficient sample size for this analysis;
- Measure definitions and calculations to determine outcomes;
- Protocols for collecting and testing blood samples;

[20] Guidelines for the management of haemophilia in Australia, guideline 2.7.13, page 36, from www.blood.gov.au/system/files/HaemophiliaGuidelines-interactive-updated-260317v2.pdf, accessed on July 26, 2019.
[21] Weight-based Dosing Strategies for Factor Replacement Therapy in Hemophilia A and B, page 4, from centerforevidencebasedpolicy.org/wp-content/uploads/2018/11/Hemophilia_Dosing_Final_3-17-16.pdf, accessed on July 26, 2019.
[22] Bloodworks Northwest, from www.bloodworksnw.org/, accessed on 26 July 2019.

- Statistical methods for evaluating outcomes;
- Documentation, including consent forms and communications; and
- Institutional Review Board approval to ensure the clinical trial design was ethical.

After receiving Institutional Review Board approval, Bloodworks began the Collaborative's clinical trial. Between January 2017 and December 2018, patients from the following treatment centers participated in the clinical trial:

- Washington Center for Bleeding Disorders;
- Oregon Health & Science University;
- Seattle Children's Hospital; and
- Providence Sacred Heart Children's Hospital.

During the clinical trial, patients were able to continue using their current factor products and received both ABW-based factor dosing and IBW-based factor dosing at separate times. To learn more about the design of the clinical trial, please review the Methods section in Appendix A.

Clinical Trial Results and Conclusions

Sixteen participants, age 12 to 53 years (median 21.5 years) with overweight or obese body mass indices (BMIs) of 25.6 to 41.8 (median BMI 31.3), agreed to participate in the Collaborative's clinical trial. Each participant received doses of their factor product using ABW- and IBW-based calculations. Researchers measured how well patients recovered their factor levels by comparing the actual amount of factor in their blood to the amount they targeted with their dosing to prevent bleeds.

- After receiving ABW-based factor doses, nearly all participants had more factor in their blood than necessary, ranging from 10 percent to 96 percent more than target levels. Any factor amount greater than the target level is not clinically appropriate and does not produce better health outcomes for the patients.
- After receiving IBW-based factor doses, nearly all participants had factor levels ranging between 10 percent less than target levels (less than expected) and 37 percent more than target levels (more than expected).[23]

Researchers reviewed characteristics of the patients and their factor products for their potential effects on the trial's outcomes. Age, factor concentrate brand, degree of obesity, and height did not appear to influence these results.

These results indicate that:

- ABW-based factor dosing can produce clinically inappropriate levels of factor in hemophilia A patients; and

[23] The clinical trial did not evaluate whether factor levels 10 percent or less than target levels resulted in an increased risk of bleeding. This evaluation would require another study.

- IBW-based factor dosing might be sufficient to achieve appropriate factor levels in some hemophilia A patients.

Potential Fiscal Implications

The results of this clinical trial suggest that overweight or obese Apple Health clients with hemophilia A might be able to transition from ABW- to IBW-based factor dosing, when clinically appropriate. As a result, these patients would use less factor, which could reduce costs to Apple Health.

To estimate the potential cost reduction, we began by identifying Apple Health clients with the following characteristics, per their paid health care billing (claims or encounter) data during calendar year 2018:

- Age 12 years or older;
- A hemophilia A diagnosis; and
- At least two anti-hemophilia drug claims.

Ninety-five Apple Health clients met these criteria during calendar year 2018. Thirty-seven (or 38.9 percent) of those clients had information in their paid billing data about their BMIs. Of those 37 clients:

- Fourteen (37.8 percent) had normal BMIs; and
- Twenty-three (62.2 percent) had overweight or obese BMIs.[24]

The proportion of the 37 clients with overweight or obese BMIs (62.2 percent) matches a 2017 Centers for Disease Control and Prevention estimate for Washington State.[25]

Analysis results suggested that ABW factor dosing required about 6.7 percent more factor per billing, compared to IBW factor dosing. A 6.7 percent reduction in factor use among the 95 Apple Health clients during calendar year 2018 would have reduced costs for their anti-hemophilia drugs by about $1.7 million. In this estimate, we assume that the IBW-based dosing would occur at the same frequency as the ABW-based dosing. We advise caution in interpreting or applying the results of this cost-benefit analysis, due to our assumptions in the analysis and limitations of the clinical trial results.

[24] ProviderOne Operational Data Store, data pulled in May 2019.
[25] Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition, Physical Activity, and Obesity. Data, Trend and Maps. From www.cdc.gov/nccdphp/dnpao/data-trends-maps/index.html, accessed June 12, 2019.

Evidence-Based Clinical Guidelines

Although reducing the factor dosing for patients with hemophilia A and higher BMIs could result in cost savings, dosing decisions should be personalized for the needs of the patient. Evidence-based clinical guidelines can be helpful to medical providers calculating their patients' appropriate factor doses.

HCA reported in 2016 that MED's evaluation of clinical guidelines indicated that Australia's guidelines[26] had the best evaluation standards among the guidelines MED reviewed. Since then, Australia's National Blood Authority has updated its guidelines slightly to reflect new findings.[27] However, Australia's guidelines for using IBW-based dosing for patients with hemophilia A remain unchanged.

The results of the Collaborative's clinical trial appear to support Australia's clinical guidelines. To begin sharing information about the Collaborative's clinical trial, the researchers gave a poster presentation at the Hemostasis and Thrombosis Research Society 2019 Scientific Symposium on May 11, 2019.[28] The researchers plan to publish the Collaborative's clinical trial results by the year 2020.

HCA encourages medical practitioners to watch for new studies, guidelines, and recommendations that inform and reflect emerging best practices. One example is a randomized clinical trial occurring in Pittsburgh, Pennsylvania, which seeks to determine whether IBW is more accurate than ABW in calculating hemophilia A factor dosing in adults.[29] When we reported about the Pittsburgh clinical trial in our 2016 report, the estimated completion date was August 2017. However, as with the Collaborative's clinical trial, the completion date is now later—June 2020.

In spite of challenges in conducting rigorous studies to inform hemophilia treatment guidelines, best practices continue to evolve.

---

[26] Guidelines for the management of haemophilia in Australia, from www.blood.gov.au/haemophilia-guidelines, accessed on July 26, 2019.
[27] Revision register for the Guidelines for the management of haemophilia in Australia, from www.blood.gov.au/system/files/Revision-register-Guidelines-for-the-management-of-the-haemophilia-in-Australia.pdf, accessed on July 26, 2019.
[28] HTRS/NASTH 2019 Scientific Symposium Poster Presentations, from www.eventscribe.com/2019/HTRS/posteragenda.asp?pfp=posters&h=Poster Presentations, accessed on August 19, 2019.
[29] Weight-based Dosing in Hemophilia A, from clinicaltrials.gov/ct2/show/NCT02586012, accessed on July 26, 2019.

Conclusion

The Collaborative contributed to the field of hemophilia treatment and completed its legislative mandate by:

- Contracting with Bloodworks to create original research in alternative approaches to managing factor use in overweight and obese patients with hemophilia A;
- Assisting HCA in performing a cost-benefit analysis, based on the clinical trial results; and
- Disseminating the clinical research findings at a symposium featuring hemophilia topics.

The finding that overweight and obese hemophilia A patients might need less factor, based on their IBW instead of their ABW, may prove useful to researchers and practicing clinicians as they continue to inform their practices with emerging research.

- Researchers have an opportunity to replicate or build upon the Collaborative's clinical trial and contribute more to hemophilia's emerging clinical practice guidelines.
- Practicing clinicians are now able to use the results of the clinical trial to help personalize hemophilia treatment regimens, which could reduce health care costs without negatively affecting patient health outcomes.

The budget proviso that created and funded the Collaborative expired on June 30, 2019. With the publication of this report, the work of the Collaborative is now complete.

Appendix A: Comparison of Ideal versus Actual Body Weight Factor Dosing in Hemophilia A

Below is an abstract of the clinical trial that researchers presented at the Hemostasis and Thrombosis Research Society 2019 Scientific Symposium in May 2019.

Blair, Amanda MD[1], Felgenhauer, Judy MD[2], Recht, Michael MD, PhD[3], Kruse-Jarres, Rebecca MD, MPH [4].

[1]Seattle Children's Hospital, University of Washington Medical Center, Seattle, WA. [2]Providence Sacred Heart Children's Hospital, Spokane, WA. [3]Oregon Health & Science University, Portland, OR. [4]Washington Center for Bleeding Disorders, Seattle, WA.

Background

Hemophilia A is an X-linked genetic disorder resulting in bleeding due to factor VIII deficiency. Prophylactic administration of factor concentrate several times a week to prevent bleeding is standard of care [Manco-Johnson, et al, NEJM 2007]. Factor dose is based on a patient's actual body weight (ABW), and factor circulates in the plasma with minimal distribution into the adipose tissue. Although plasma volume increases with body mass, it is not proportional. The current standard of calculating a patient's dose on ABW may overestimate the appropriate factor dose and lead to unnecessary health care cost. We sought to evaluate if factor dosing based on ideal body weight (IBW) would result in adequate factor levels in overweight and obese patients.

Objectives

To compare the pharmacokinetics (PK) of ideal versus actual body weight dosing of factor concentrate in overweight and obese (BMI ≥25) participants with hemophilia A.

Methods

Overweight or obese participants (based on calculated BMI (age 20 years and older) or by the McLaren method (ages 12- 19 years)) age 12 and up diagnosed with any severity of hemophilia A were enrolled in a randomized, prospective, multicenter, open-label, crossover study comparing the pharmacokinetics of ideal vs. actual body weight factor dosing. Participants underwent pharmacokinetic testing following a 50 unit/kg (+/-20 percent) factor dose based on ABW and IBW, the order determined by randomization. Participants used their personal brand of factor. Standard and extended half-life products were included.

Results

Sixteen participants, age 12 to 53 years (median 21.5 years) and BMI of 25.6 to 41.8 (median 31.3) underwent PK testing following an ABW and IBW-based factor dose. Participants dosed based on

ABW (Figure 1) achieved 140 percent of expected recovery on average (range 83 percent to 196 percent). One participant receiving ABW based dosing achieved lower recovery than expected. All others had peak recovery 10-96 percent above expected (average 44 percent).

Figure 1: Actual Body Weight Dosing

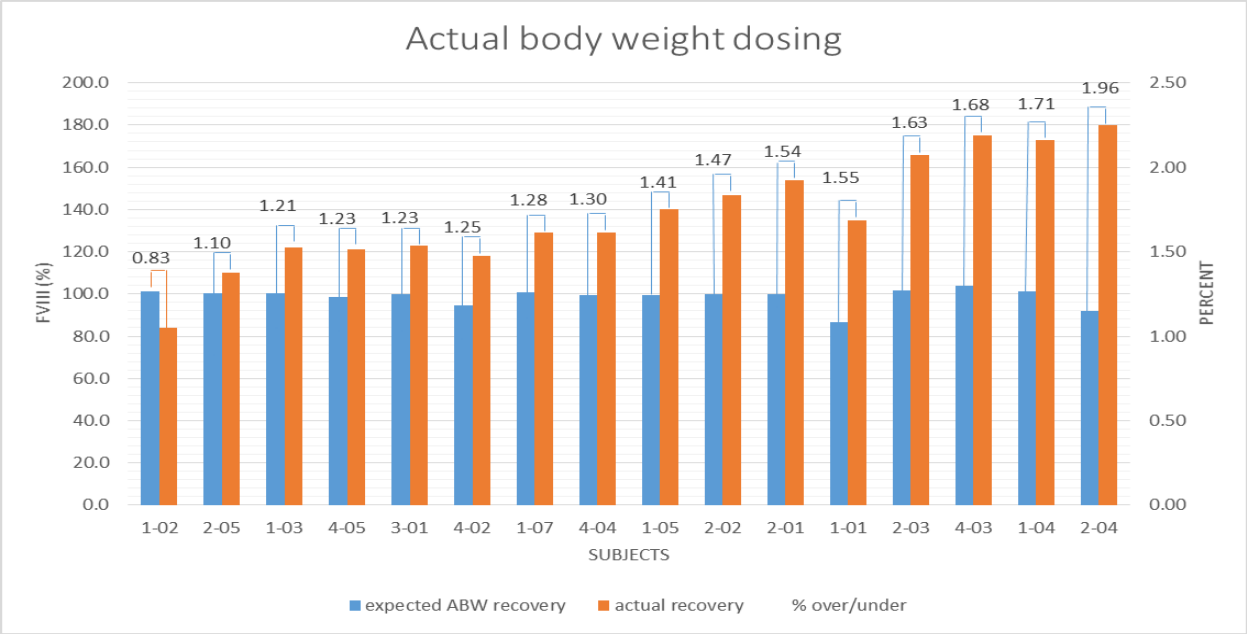
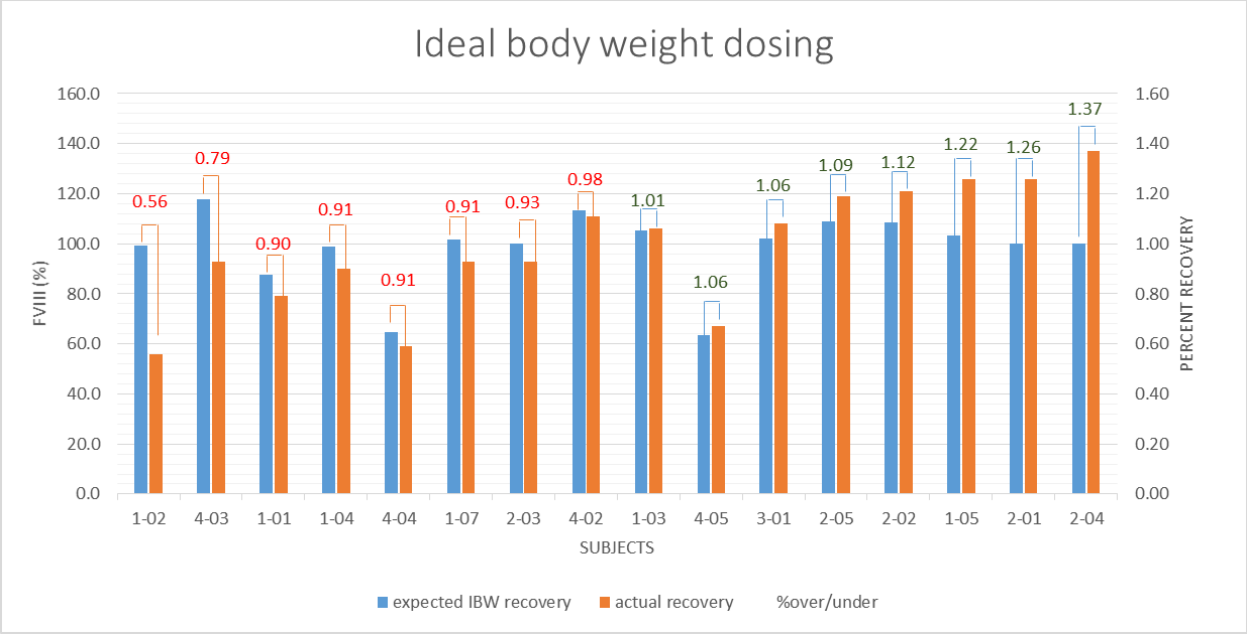


Figure 2: Ideal Body Weight Dosing



Participants dosed based on IBW (Figure 2) achieved 100 percent of their expected recovery on average (range 56 percent to 137 percent). Eight of 16 patients (50 percent) did not achieve expected recovery. Six of these by less than 10 percent. Two subjects achieved only 56 percent and

79 percent expected recovery. The remaining eight subjects achieved higher recovery than expected. Age, brand of factor concentrate, degree of obesity and height did not appear to impact these results.

Conclusions

This study shows that ABW factor dosing for overweight and obese patients leads to higher than desired peak factor VIII levels, which may lead to unnecessary healthcare costs. When IBW dosing was used, 50 percent of patients achieve a recovery less than expected, but most by less than 10 percent. Based on these results, factor dosing based on IBW may be sufficient to achieve desired peak factor VIII levels. We propose further study of an IBW dosing strategy to determine if the factor levels achieved provide adequate hemostasis.

Other

Funded by the Washington State Health Care Authority.