Executive Summary

Bleeding disorders, such as hemophilia A and B, are among the most costly and challenging medical conditions to manage for health care payers.

Engrossed Substitute Senate Bill 6052, Chapter 4, Laws of 2015 directs the Health Care Authority (HCA) to convene a Bleeding Disorder Collaborative for Care (Collaborative) to:

- Identify and develop evidence-based practices to improve care to patients with bleeding disorders with specific attention to health care cost reduction;
- Make recommendations regarding the dissemination of the evidence-based practices to relevant health care professionals; and
- Assist the Health Care Authority in the development of a cost-benefit analysis based on the evidence-based practices identified.

The Collaborative began meeting in December 2015 and has completed its initial research—a review of existing literature on guidelines and best practices for the care and costs associated with hemophilia. This review found a lack of comparative effectiveness studies and limited research and policy on which to develop evidence-based practices.

As a result, the Collaborative elected to pursue a clinical trial.

The results of this trial will not be available until approximately June 2017. Consequently, the Collaborative plans to deliver two reports to the Legislature:

- This report, to be delivered in September 2016, describing the research findings from the literature review of best practices and guidelines, and the plan and progress to date on the clinical trial; and
- A second report, with an anticipated delivery date in 2018, sharing the findings of the clinical trial, and—depending on the results—proposed evidence-based guidelines, implementation strategies, and a cost-effective analysis to model project savings with use of the evidence-based practices.

Background

Bleeding disorders, such as hemophilia A and B, are life-long, genetic medical conditions that require special care needs and appropriate case management to ensure patient health and quality of life. Given the complex and unique nature of these diseases, patients with bleeding disorders are high utilizers of health care resources, making bleeding disorders among the most costly and challenging medical conditions to manage for health care payers across the globe. Additionally, there is significant variation between patients with bleeding disorders. Clinical factors related to bleeding disorders, such as the severity of hemophilia or the presence of inhibitors—antibodies that prevent clotting factor from functioning—are associated with drastically higher costs for treatment and case management than other conditions.

Hemophilia—a disorder in which the blood does not clot properly—is treated by administering clotting factor concentrates made from either human blood plasma or recombinant (genetically engineered) clotting factor. Clotting factor costs are the primary driver in the overall expense of treating bleeding disorders. The amount of clotting factor patients need varies dramatically between individuals, constituting up to 94% of spending for individuals with severe cases.[1]

To give an approximation of the health care costs associated with hemophilia, the Health Care Authority (HCA) estimates that it spent $73.7 million from fiscal year (FY) 2014 to FY 2015 for a total of 372 hemophilia patients—with an average per-patient cost of $99,050 per year. Given the complexity of hemophilia, there have been few options for management strategies and policies to address the high cost of care for hemophilia patients.

Overview of ESSB 6052, Subsection 213 (1)(gg)

The Washington State Legislature created the Bleeding Disorder Collaborative for Care through Engrossed Substitute Senate Bill 6052 (Chapter 4, Laws of 2015), Section 213(1)(gg). ESSB 6052 directs HCA to convene a two-year Bleeding Disorder Collaborative to:

1. Identify and develop evidence-based practices to improve care to patients with bleeding disorders with specific attention to health care cost reduction. To the extent that evidence-based practices are unavailable, the collaborative shall research and create the practices or compile the necessary information. In the event that research on evidence is incomplete, the collaborative may consider research-based practices or emerging best practices;

2. Make recommendations regarding the dissemination of the evidence-based practices to relevant health care professionals and support service providers and propose options for incorporating evidence-based practices into their treatment regimens; and

3. Assist the authority in the development of a cost-benefit analysis regarding the

[1] Journal of Medical Economics. Burden of illness: direct and indirect costs among persons with hemophilia A in the United States. March 9, 2015.

use of evidence-based practices for specific populations in state-purchased health care programs."

ESSB 6052 directs HCA to provide the Governor and the Legislature with a report on September 1, 2016 summarizing "the evidence-based practices that have been developed, the clinical and fiscal implications of their implementation, and a strategy for disseminating the practices and incorporating their use among health care professionals in various state-financed health care programs."

Since the work of the Collaborative will not be completed by the mandated report due date—September 1, 2016—the Collaborative is submitting an additional report in 2018 when its work is complete.

This first report to the Governor and the Legislature will serve as a progress report on the accomplishments to date. This progress report includes sections on:

- The progress of the Collaborative on the strategies to complete the tasks outlined in the budget proviso,
- The findings from the MED literature reviews and guideline evaluations for developing evidence-based practices,
- A progress report on the clinical research being conducted by the Collaborative to address evidence gaps in the medical literature, and
- An estimate for the delivery of the final report following the completion of the research project and the development of the evidence-based practices

HCA will produce an additional report—the final report—which will fulfill the requirements outlined in the budget proviso. The final report will summarize "the evidence-based practices that have been developed, the clinical and fiscal implications of their implementation, and a strategy for disseminating the practices and incorporating their use among health care professionals in various state-financed health care programs." The delivery date for the final report depends on the conclusion of the clinical trial. HCA anticipates that the final report will be delivered in 2018.

Bleeding Disorder Collaborative for Care

The Collaborative is a two-year funded project that began on July 1, 2015 and ends June 30, 2017. The Collaborative first met on December 16, 2015.

As mandated by the legislature, the Collaborative will:

- Identify and develop evidence-based practices to improve care to patients with bleeding disorders with specific attention to health care cost reduction;
- Make recommendations regarding the dissemination of the evidence-based practices to relevant health care professionals; and
- Assist HCA in the development of a cost-benefit analysis based on the evidence-based practices identified.

The Collaborative adopted the following strategies:

- Compile, analyze, and review medical evidence related to bleeding disorder treatments,
- Prioritize recommendations from a thorough review of existing medical literature,
- Develop a new research project(s) to address gaps in existing evidence base,
- Identify methods for optimizing clotting factor use,
- Create Medicaid and HCA cost-benefit analysis based on the outputs of the Collaborative, and
- Develop practical options for incorporating identified evidence-based practices into health care treatment regimens.

The Bleeding Disorder Collaborative charter was finalized and approved in January 2016. (See Appendix A for the complete charter.)

Members

Following the requirements outlined in ESSB 6052 for Collaborative membership, HCA recruited three representatives from HCA, three representatives from the largest organization in Washington representing patients with bleeding disorders (the Bleeding Disorders Foundation of Washington), two representatives from state-designated Bleeding Disorder Centers of Excellence, and three representatives from federally funded Hemophilia Treatment Centers based in Washington.

The members of the Collaborative are:

- **Collaborative Chair:** Rebecca Kruse-Jarres (Washington Center for Bleeding Disorders)
- **HCA Sponsor:** Dan Lessler (HCA)
- Donna Sullivan (HCA)

- Lisa Humphrey (HCA)
- Stephanie Simpson (Bleeding Disorders Foundation of Washington)
- Heidi Forrester (Bleeding Disorders Foundation of Washington)
- Michael Birmingham (Bleeding Disorders Foundation of Washington)
- Mike Recht (Oregon Health & Science University)
- Dana Matthews (Seattle Children's Hospital)
- Amanda Blair (Seattle Children's Hospital)
- Judy L. Felgenhauer (Sacred Health Children's Hospital)

Work Plan

The Collaborative developed two separate tracks to accomplish its mission.

- **Track 1**: Review the available literature on guidelines and best practices for the care and costs associated with hemophilia. These will be used to develop evidence-based practices to disseminate to health care providers.

- **Track 2:** Generate evidence on different management strategies or policies when there is no existing evidence that can be used to develop evidence-based practices aimed at reducing health care costs.

This report includes the findings from Track 1, an update on the Collaborative's progress on developing a clinical trial (Track 2), and details about its plans moving forward with this work.

Review of Existing Guidelines and Best Practices

The Collaborative began its work on the first track by defining the scope and focus of its literature searches. The group developed a series of Key Questions to discover evidence-based guidelines and identify gaps in the medical literature.

HCA enlisted the Medicaid Evidence-based Decisions Project (MED) from the Center for Evidence-based Policy at Oregon Health & Science University to perform an evaluation of the existing evidence based on the Key Questions. The evaluation reports summarize existing best practices in treating hemophilia and identify areas where the evidence is lacking.

In March 2016, MED delivered three individual reviews on areas that hold great potential for health care cost reduction where evidence is lacking or nonexistent:

- Weight-based Dosing Strategies for Factor Replacement Therapy in Hemophilia A and B,
- Use of Ultrasound to Diagnose Hemarthrosis and Monitor Join Health in Hemophilia, and
- Home Care Services and Utilization Management for Appropriate Use of Factor Replacement Therapy in Patients with Hemophilia.

In addition, MED submitted a clinical brief from the Medicaid Health Plans of America Center for Best Practices titled *Addressing the Needs of Members with Hemophilia in Medicaid Managed Care: Issues and Implications for Health Plans*.

In June 2016, MED delivered the second major report, *Interventions for Hemophilia A and B: Clinical Practice Guidelines and Cost-effectiveness*. The goal of the report was to identify clinical practice guidelines on drug interventions for hemophilia A and B and to conduct a review for estimates on the cost and cost-effectiveness of those interventions.

Evidence-Based Practices for Health Care Cost Reduction

In each area of study, the researchers found a lack of comparative effectiveness studies and limited research and policy in these specific areas. The following pages summarize their findings.

Weight-based Dosing Strategies

Key Questions

1. What is the comparative effectiveness and cost-effectiveness of factor dosing based on ideal body weight (IBW) versus actual body weight (ABW)?

2. Does the comparative effectiveness of factor dosing based on ideal body weight vary by:
   a. Patient characteristics (age, ethnicity, hemophilia type, presence of inhibitors)
   b. Prophylactic use vs on-demand use
   c. Type of factor replacement

Findings

Clinical Practice Guidelines

MED identified hemophilia treatment guidelines from the United States, United Kingdom, Italy, Australia, and the World Federation of Hemophilia. All but one of the identified treatment guidelines recommend using a patient's actual body weight to calculate the factor replacement dose. Australia's treatment guidelines, still in draft form, recommend factor dosing of obese patients based on ideal body weight.

Evidence

MED staff "did not identify any randomized control trials or systematic reviews on the comparative effectiveness of dosing factor replacement based on ABW or IBW. One very small observational study of 6 patients concluded that a strategy based on IBW would result in a reduction in

prophylactic[2] factor usage of almost 50% over 3 months and generated significant cost savings. The long-term effect of this strategy has not been evaluated, however." A randomized control trial is now in progress, with an estimated completion date of August 2017. (See Appendix B for the complete MED report on weight-based dosing strategies.)

Since the Collaborative believes this dosing strategy could be a viable option for an evidence-based practice, it elected to conduct a clinical trial on this subject to generate additional evidence.

Use of Ultrasound in Hemophilia

Key Questions

1. What is the comparative effectiveness and cost-effectiveness of ultrasound vs usual care or MRI to diagnose acute hemarthrosis[3]?
2. What is the comparative effectiveness and cost-effectiveness of ultrasound vs usual care or MRI to assess joint health longitudinally?
3. Does the effectiveness of ultrasound in the management of hemophilia vary by:
   a. Patient characteristics?
   b. Presence of degenerative joint changes?
   c. History of prior joint bleeding?
   d. Severity and location of acute join bleeds?
   e. Operator experience?

Findings

Evidence

MED did not find any systematic reviews or randomized controlled trials of the use of ultrasound in patients with hemophilia A or B. Three observational trials on the effectiveness of ultrasound to assess joint health were identified, but no studies were identified that study the effectiveness of ultrasound to diagnose hemarthrosis or assess effectiveness by patient characteristics and other factors. One small (n=31) cost-effectiveness analysis was identified but this study only evaluated the cost of diagnosing arthropathy (disease or condition of the joint) and not the cost of management of hemophilia; it does not provide information on longer term cost-effectiveness. (See Appendix C for the complete MED report on the use of ultrasound in hemophilia.)

The Collaborative believes that this could be a potential area to improve patient care and reduce health care costs, but more evidence is necessary.

[2] Intended to prevent disease.

[3] Hermarthrosis, or bleeding in a joint, is the most common type of bleeding episode. According to the MED report, "bleeding may occur as the result of a trauma, but spontaneous bleeding may also occur in severe disease. Hermarthrosis causes pain and may be physically debilitating. Once a joint has been damaged by hermarthrosis, it is more susceptible to recurrent bleeding and is referred to as a "target joint."

Home Management Strategies

Key Questions

1. What is the comparative effectiveness and cost-effectiveness of continuous or episodic home nursing care for patients with hemophilia?
2. What is the comparative effectiveness and cost-effectiveness of episodic multidisciplinary home care team visits for patients with hemophilia?
3. What strategies or pathways have been described for utilization management of factor replacement for patients with hemophilia?

Findings

Evidence

MED did not find any studies addressing the comparative effectiveness or cost-effectiveness of different strategies for providing home health services for patients with hemophilia. Researchers also found no studies comparing the effectiveness or cost-effectiveness of episodic multidisciplinary home care team visits to typical care for patients with hemophilia.

The World Federation of Hemophilia guidelines recommend home management for people with hemophilia "where appropriate and possible." Factor replacement in the home setting is considered the standard of care in patients with hemophilia based on reports of improved quality of life and community integration for both children and adults. (See Appendix D for the complete MED report on home management strategies.)

The Collaborative believes that this could be a potential area to improve patient care and reduce health care costs, but more evidence is necessary.

Evidence-based Guidelines for Hemophilia A & B

Key Questions

1. What are the clinical practice guidelines of the interventions of therapeutic agents for hemophilia A or B?
2. What are the estimated direct and indirect medical costs, non-medical costs, and cost-effectiveness associated with the interventions of therapeutic agents for hemophilia A or B?

Findings

Clinical Practice Guidelines

MED identified four relevant guidelines published within the last five years for inclusion in the report. Three of the guidelines were determined to be of poor methodologic quality. The draft of the National Blood Authority (NBA) of Australia, produced by the Australian Haemophilia Centre Directors' Organization, was reviewed and determined to be of fair methodologic quality.

All four guidelines are vast and comprehensive in their recommendations on appropriate care of patients with hemophilia. They all recommend prophylaxis—action taken to prevent disease—to protect bone health and avoid disability from joint destruction. Guidelines from the Nordic countries, United Kingdom, and Australian recommend the use of recombinant factor products over plasma-derived products. The WFH guidelines support recombinant or viral-inactivated plasma-derived products. (See Appendix E for the complete MED report on evidence-based guidelines for hemophilia A & B.)

Clinical Research

To accomplish the second track, HCA entered into a contract with Bloodworks Northwest to coordinate and conduct a clinical trial. Bloodworks Northwest will subcontract with the other partner organizations of the Collaborative, whose members are representatives and coordinators of their respective institutions. The institutions are the identified Bleeding Disorder Centers of Excellence (the Washington Center for Bleeding Disorders and Oregon Health & Science University) and the identified Hemophilia Treatment Centers (Seattle Children's Hospital and Sacred Heart Children's Hospital).

The contract between HCA and Bloodworks Northwest outlines the timeline for the Collaborative's clinical trial, including milestones and deliverables, until its anticipated completion in June 2017. The research results, analysis, and outputs—scheduled to be delivered by April 30, 2017—will be used to develop evidence-based practices. A cost-effectiveness analysis will also be developed, based on the agreed-upon evidence-based practices, as a way to estimate the potential savings in health care costs to state-purchased health care programs in Washington.

Upon review of the research findings, the Collaborative decided to further investigate weight-based dosing strategies as a method of reducing health care costs. The Collaborative proposes a clinical trial to dose overweight and obese patients by their ideal body weight (IBW) rather than actual body weight (ABW). This method could prevent overdosing patients with factor due to weight-based dosing, thereby reducing the amount of factor administered to patients and billed to payers.

The primary outcomes of the research project are:

- Comparing the recovery to a 50 units/kg (±20%) dose of factor VIII (FVIII) concentrate in participants age 12 and older (age ≥12) with hemophilia A when calculated on ABW versus IBW, and
- Determining the likelihood of under-dosing when using IBW or over-dosing with ABW.

The research project will also assess a number of secondary outcomes, including determining the effect on half-life and pharmacokinetic[4] differences of hemophilia severity between patients receiving half-life versus extended half-life products and between overweight and obese patients.

The study is designed to be a randomized, prospective, multi-center, open-label, cross-over study conducted at four centers in the Pacific Northwest:

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

16 patients from these centers will be recruited to participate in the study and will be enrolled if they meet the inclusion criteria:

- At least 12 years of age
- Diagnosis of hemophilia A
- Male
- Able and willing to comply with the testing schedule
- Having either an overweight or obese body mass index (BMI), using the Centers for Disease Control and Prevention (CDC) definitions by age

Patients who meet the inclusion criteria will be randomized to receive either the dosing by ideal body weight first or actual body weight first. They will have labs drawn to measure pharmacokinetics of the factor administered, and will then cross-over to the other dosing strategy with parallel lab draws.

Progress Update

The Collaborative approved the protocol for the clinical trial on June 15, 2016. The participating centers are now working on next steps, including budgeting and development of the forms that will be used to conduct and complete the trial.

[4] Pharmacokinetics is sometimes described as what the body does to a drug. It refers to the movement of a drug into, through and out of the body, including the time it takes for the body to absorb it, and how it is distributed, metabolized, and excreted.

Timeline for Final Report

The research portion of the Bleeding Disorder Collaborative is expected to be completed by April 30, 2017 and a final report is due to HCA by June 30, 2017.

Depending on the results of this clinical trial and the adoption of new dosing strategies state-wide, the state could potentially see savings related to reducing the amount of factor product being administered under state-purchased health plans. A cost-effectiveness analysis will be constructed and completed to estimate the amount of savings the State might realize.

Additionally, the Collaborative will need to decide how the clinical research will be incorporated within the developed evidence-based practices and develop strategies for the implementation of evidence-based guidelines. As these two goals of the Bleeding Disorder Collaborative are dependent upon the completion of the clinical research, it is difficult to project when the final report will be completed to the Governor and the Legislature. Currently, the Collaborative estimates delivery in 2018 depending on how patient enrollment and data collection and analysis progress during the next year.

Looking Forward

The Collaborative is looking forward to FY 2017 for a number of significant milestones. Activities planned for FY 2017 include:

- Conducting the clinical research project,
- Developing evidence-based practices,
- Determining a plan for dissemination of evidence-based practices across Washington, and
- Construction of the cost-effectiveness analysis to model the project savings the State may realize with these evidence-based practices.

The Collaborative will provide a final report to the Governor and the Legislature upon completion of these activities.