

Bleeding Disorder Collaborative for Care

Fiscal Year 2016 Progress Report

September, 2016

Engrossed Substitute Senate Bill 6052

Chapter 4, Laws of 2015



Bleeding Disorder Collaborative for Care Fiscal Year 2016 Progress Report



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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 Joint 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



prophylactic² 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 hemarthrosis³?
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 joint 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 Hemarthrosis, 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. Hemarthrosis causes pain and may be physically debilitating. Once a joint has been damaged by hemarthrosis, 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 ($\pm 20\%$) dose of factor VIII (FVIII) concentrate in participants age 12 and older ($\text{age} \geq 12$) 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 pharmacokinetic⁴ 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.

Bleeding Disorder Collaborative for Care Charter

January 14, 2016

COLLABORATIVE CHAIR: Rebecca Kruse-Jarres, MD, MPH

HCA SPONSOR: Dan Lessler, Chief Medical Officer

SUPPORT STAFF: TBD

MEMBERS:

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Hemophilia treatment centers:

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Amanda Blair (Seattle Children's Hospital) blairA@uthscsa.edu

Judy L. Felgenhauer, MD (Sacred Heart Children's Hospital) Judy.Felgenhauer@providence.org

Others as needed with expertise to assist collaboration

AUTHORITY

Engrossed Substitute Senate Bill 6052, Chapter 4, Laws of 2015, 2015-2017 Operating Budget, Section 213, 1 (gg)(i) page 91

Overview

Purpose

To create a ***Bleeding Disorder Collaborative for Care*** tasked with identifying and developing evidence based practices related to bleeding disorders for dissemination to health care providers

Scope

As mandated by the legislature, the collaborative will 1) Identify and develop evidence-based practices to improve care to patients with bleeding disorders with specific attention to health care cost reduction, 2) Make recommendations regarding the dissemination of the evidence-based practices, and 3) Assist the Health Care Authority in the development of a cost-benefit analysis based on the evidence based practices identified.

Goals, Objectives, and Strategies

Goal

Improve care to patients with bleeding disorders

Objectives

- Identify evidence based methods to improve treatments with special attention to improving the health care quality and value;
- Create recommendations regarding the dissemination of the evidence-based practices to relevant health care professionals and support service providers; and
- Develop a cost-benefit analysis regarding the use of evidence-based practices for specific populations in state-purchased health care programs.

Strategies

- Develop new research project(s) to address gaps in existing evidence base;
- Identify methods for optimizing clotting factor use;
- Compile, analyze, and review medical evidence related to bleeding disorder treatments;
- Prioritize recommendations from thorough review of existing medical literature;
- Create Medicaid (PEB?) 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

Authority and Milestones

Funding Authority

- HCA has the funding authority for this project. No additional funds are required.

Project Oversight Authority

- The Chair of the Bleeding Disorder Collaborative. Dan Lessler, as HCA Sponsor, will report to the HCA Executive Leadership Team as needed.

Major Milestones

Date	Topic	Documents	Outcomes	Notes
October 2015	Purpose and Scope	Budget Proviso Legislation Page 91	Agree on scope Agree on committee membership, strategies, and roles/responsibilities Identify key questions for literature review	
November/Dec 2015	Research	Information on critical gaps in research	Agree on research topics, participants, lead organization, budget allocations, & contracts	
April 2016	Review Current Guidelines and Tools	Presentation of analysis/literature review evidence-based practices to improve care to patients with bleeding disorders with specific attention to health care cost reduction	Review currently available evidence Identify evidence based practices recommendations to be included in legislative report	

June 2016 or later	Cost Benefit Analysis	Evidence based practice recommendations (agreed on by the collaborative in May)	Discussion of analysis Process for or actual ranking of guidelines and tools	
July/August 2016	Legislative Report		Receive final approval by Collaborative and complete state agency review process for legislative reports	Need to identify due date to OFM

Organization

Roles and Responsibilities

Who	Does What
Health Care Authority	<ul style="list-style-type: none"> • Provide 3 collaborative members • Help select the research projects for funding • Oversee funding streams, budgets, and contracts • Develop of a cost-benefit analysis • Report to the legislature by September 1, 2016 • Commit necessary HCA resources for the project
Bleeding Disorders Foundation of Washington	<ul style="list-style-type: none"> • Provide 3 collaborative members • Help select the research projects for funding • Oversight to guarantee the mission of this project
Bleeding Disorder Centers of Excellence	<ul style="list-style-type: none"> • Provide 2 collaborative members • Propose research to be done • Conduct research/collect data • WCBD will be the data coordinating center and assure the individual research projects stay on their timeline

Hemophilia Treatment Centers	<ul style="list-style-type: none"> • Provide 2 collaborative members • Propose research to be done • Conduct research/collect data
Chair (s)	<ul style="list-style-type: none"> • Lead collaborative meetings • Commit resources for the project • Ensure leaders of associated function commit resources for the project • Hold the Collaborative or its delegates responsible for achieving improvements • Ensure leaders of associated functions commit resources necessary to execute implementation plans
Project Manager	<ul style="list-style-type: none"> • Ensures success of collaborative meetings • Responsible for ensuring that targets and milestones are met • Develop and maintain detailed project plan and schedule • Manage all contracting obligations and oversight • Ensure clear and consistent communication within collaborative • Coordinate all stakeholders needs and expectations • Track budget expenditures • Identify and obtain needed resources (equipment, expertise, staffing, etc)
Administrative Support	<ul style="list-style-type: none"> • Coordinate meeting logistics • Ensure adherence to public meeting requirements and reasonable accommodations • Take meeting minutes/action items
Research Role 1 – WCBD?	<ul style="list-style-type: none"> • Design, organize, and manage all aspects of new research inquiry related to bleeding disorder treatment. Develop protocol and take lead for all new research data collection and analysis. Subcontracts to participating HTC?
Research Role 2 – MED?	<ul style="list-style-type: none"> • Compile and analyze existing body of evidence related to bleeding disorder treatment. Present synthesis to Bleeding Disorder Collaborative for review
Collaborative Members	<ul style="list-style-type: none"> • Attend collaborative meetings and subgroups as needed • Work together as a team to reach goals and objectives • Demonstrate respect for differing viewpoints • Support the process by asking questions and making suggestions • Volunteer for tasks to achieve continuing success in the collaborative • Assist HCA in the development of a cost-benefit analysis

Critical Success Factors (Risks)

1. Outstanding Questions:
 - Can indirects be waived? State limit on indirect costs?
 - Delegation of roles/responsibilities?
2. Adherence to open public meeting rules
3. Timelines are short and not flexible
4. Workgroup resource limitations
 - Workgroup members are not compensated
5. Recommendations for state financed health programs
 - Implementation funding not provided
 - Implementation not required by law for all payers
 - Best practice implementation requires participation of providers
 - Best practice implementation may be seen as a guideline, not a mandate

Assumptions

Bleeding Disorder Collaborative for Care will not be funded beyond June 2017

Participating Organizations

Bleeding Disorders Foundation of Washington (BDFW)
Health Care Authority (HCA)
Oregon Health Science University (OHSU)
Sacred Heart Children's Hospital
Seattle Children's Hospital (SCH)
Washington Center for Bleeding Disorders (WCBD)

Revision History

VERSION	DATE	DESCRIPTION OF REVISIONS
Draft 1.0	8/11/15	
Draft 1.1	8/17/15	Addressed outstanding questions
Draft 1.2	10/7/15	Included Mike Recht's recommendations, added members and email addresses
Draft 1.3	12/29/15	Added Rebecca Kruse-Jarres as Chair Removed example budget from Budget section and provided dates for SFY16 and SFY17
Draft 1.4	1/11/16	Revised date of Cost Benefit Analysis to "June 2016 or later" under Major Milestones
Draft 1.5	1/14/16	Removed Budget section



***Weight-based Dosing Strategies
for Factor Replacement Therapy in
Hemophilia A and B***

Participant Request

March 2016

**Center for Evidence-based Policy
Medicaid Evidence-based Decisions Project (MED)**

Oregon Health & Science University
3030 SW Moody, Suite 250
Mailstop MDYCEBP
Portland, OR 97201
Phone: 503.494.2182
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Objective

To summarize the evidence on comparative effectiveness and costs of factor replacement dosing strategies based on ideal body weight (IDW), rather than actual body weight (ABW).

Background

Hemophilia is an inherited clotting disorder characterized by recurrent bleeding episodes. The most common types of hemophilia are hemophilia A, also known as factor VIII deficiency, and hemophilia B, or factor IX deficiency. Both are X-linked inherited disorders that manifest in male children of carrier females. Hemophilia A is the more common type, occurring in about 1 in 5,000 live male births, compared to hemophilia B, which occurs in about 1 in 30,000 live male births (Hoots & Shapiro, 2016). Hemophilia is classified as mild, moderate, or severe based on factor activity level. Those with severe hemophilia are more likely to have spontaneous bleeding and be younger when they experience their first bleeding episode. Hemophilia A is more likely to be severe than is hemophilia B (Hoots & Shapiro, 2016).

Hemophilia is an inherited clotting disorder characterized by recurrent bleeding episodes. The most common types of hemophilia are hemophilia A, also known as factor VIII deficiency, and hemophilia B, or factor IX deficiency. Both are X-linked inherited disorders that manifest in male children of carrier females. Hemophilia A is the more common type, occurring in about 1 in 5,000 live male births, compared to hemophilia B, which occurs in about 1 in 30,000 live male births (Hoots & Shapiro, 2016). Hemophilia is classified as mild, moderate, or severe based on factor activity level. Those with severe hemophilia are more likely to have spontaneous bleeding and be younger when they experience their first bleeding episode. Hemophilia A is more likely to be severe than is hemophilia B (Hoots & Shapiro, 2016).

Factor Replacement Therapy

Factor VIII and IX products are used to treat hemophilia A and B, respectively. Factor products are derived from human plasma or produced from cell lines (recombinant products). Factor replacement is used to treat acute bleeding episodes, or as prophylaxis to prevent bleeding. Prophylactic factor replacement therapy is further classified as primary, secondary, tertiary, or intermittent (periodic) (Table 1) (Srivastava et al., 2013). The goal of prophylaxis is to prevent bleeding and to preserve normal musculoskeletal function.

Table 1. Description of Factor Replacement Therapy Protocols

Protocol	When Initiated
Episodic treatment	At the time of clinically evident bleeding; to treat pain and serious bleeding
Primary prophylaxis	Before second joint bleed, in the absence of documented joint disease
Secondary prophylaxis	After second joint bleed and before onset of joint disease
Tertiary prophylaxis	After onset of joint disease
Intermittent prophylaxis	Given to prevent bleeding for periods not exceeding 45 weeks in a year

Source: Adapted from Srivastava et al., 2013

Dosing of factor replacement is based on the patient's weight. For example, the dose of Factor VIII is calculated by multiplying the patient's weight in kilograms by the factor level in IU/dl desired, multiplied by 0.5. The factor IX dose is calculated by multiplying the patient's weight in kilograms by the factor level desired. The factor level desired varies based on duration of treatment and type of hemorrhage (Srivastava et al., 2013). The effectiveness of factor replacement therapy is assessed by measuring factor levels, with the target plasma level based on observations of better outcomes in patients with mild hemophilia.

Because factor dosing is based on patient weight, overweight and obese patients receive a higher dose compared to patients of similar height who are not overweight. However, since fatty tissues contains less blood volume than muscle of the same weight, dosing factor based on the patient's weight overestimates total blood volume (Wong et al., 2011). If dosing is based on IDW, rather than ABW, this could reduce the amount of factor used without increasing risk of bleeding or other adverse events.

A 2005 survey found that 34.5% of adults with hemophilia ages 20 and older in the United States were overweight and 23.5% were obese (Wong et al., 2011). The same survey found that 16.4% of children with hemophilia were overweight, compared to 13.7% in the general population. A more recent study from the Netherlands found an increase in obesity that paralleled that of the general population. Inactivity may contribute to obesity in patients with hemophilia, and hemophilia care guidelines stress the importance of promoting safe exercise and good nutrition (Srivastava et al., 2013). In addition to higher factor usage, obesity puts more pressure on joints and can contribute to bleeding into joints and arthropathy (Wong et al., 2011).

PICO and Key Questions

Populations

- Adults or children with hemophilia A or B receiving factor replacement treatment

Interventions

- Factor dosing based on IBW

Comparator

- Factor dosing based on ABW

Outcomes

- Pharmacokinetic measurements
- Total factor use
- Long-term joint outcomes (arthropathy)
- Cardiovascular events
- Cost-effectiveness

Key Questions

1. What is the comparative effectiveness and cost-effectiveness of factor dosing based on IBW versus ABW?
2. Does the comparative effectiveness of factor dosing based on IBW vary by:
 - a. Patient characteristics (age, ethnicity, hemophilia type, presence of inhibitors)
 - b. Prophylactic use vs on-demand use
 - c. Type of factor replacement

Methods

To identify evidence and clinical practice guidelines, Center for Evidence-based Policy (Center) staff searched Medicaid Evidence-based Decision Project core sources and Ovid MEDLINE® using terms for factor replacement and dosing (Appendix A). Center staff also searched reference lists of included review articles and Google Scholar for articles citing included and/or relevant studies.

Findings

Clinical Practice Guidelines

Center staff identified hemophilia treatment guidelines from the United States, United Kingdom, Italy, and Australia (Australian Haemophilia Centre Directors' Organisation, 2016; Collins et al., 2013; National Hemophilia Foundation, 2015; Rocino et al., 2014). With one exception, these guidelines recommend using the patient's ABW to calculate factor

replacement dose and do not address different factor dosing strategies based on ABW versus IBW.

Australian guidelines, still in draft form, differ from the World Federation of Hemophilia guidelines and others in that they recommend factor dosing of obese patients based on IBW (Australian Haemophilia Centre Directors' Organisation, 2016). The final guidelines are expected to be released by June 30, 2016. The citation for this recommendation is an observational study of only six patients, discussed below (Graham & Jaworski, 2014).

Evidence

Searches did not identify systematic reviews or randomized controlled trials (RCTs) comparing dosing strategies based on actual versus ideal body weight. Center staff identified only uncontrolled observational studies addressing the key questions.

A study of six obese patients with hemophilia A (5 of whom had severe disease) used IBW rather than ABW to calculate dose of their usual factor VIII replacement prophylaxis (Graham & Jaworski, 2014). This regimen resulted in a mean 48.9% reduction in factor product usage over 3 months compared to ABW-based dosing. This translated to an annual mean savings of \$133,000 per patient, based on average wholesale price. The regimen was not associated with an increase in bleeding frequency or other adverse events during the study period. Despite the positive results, caution should be taken with the findings of this study. There were only six patients in the sample, which limits both the results and generalizability of the study. Additionally, no control group was used, which may significantly bias the findings by inflating the results in a positive direction. Further research should be done to replicate these findings in a larger sample with a more rigorous study design.

Three pharmacokinetic studies by the same author have found that dosing based on BMI resulted in higher factor VIII recovery levels in overweight patients (Henrard & Hermans, 2015; Henrard, Speybroeck, & Hermans, 2011, 2013). An analysis of data from eight pharmaceutical industry-sponsored RCTs examined the effect of being overweight or underweight on factor VIII recovery in 201 adults with hemophilia A (Henrard et al., 2013). Less than 5% of patients were underweight, 25.9% were overweight, and 17.4% were obese. In a regression analysis, BMI was the strongest predictor of Factor VIII recovery (citation). The researchers concluded that the assumed standard rise of 2%/IU in factor VIII /kg infused dose does not apply to those with a BMI in either underweight or obese BMI categories, and recommended that IBW be used to calculate dosing in underweight and overweight patients. Median factor recovery was 1.60, 2.14, and 2.70 IU⁻¹ dL⁻¹ IU kg⁻¹, respectively, for those with BMI below 20.3, 20.3 to 29.5, and 29.6 or more. A more recent study (Henrard & Hermans, 2015) used the same methods to examine the impact of being overweight on factor VIII dosing among 66 children with hemophilia A, and found a similar relationship between BMI and factor VIII recovery.

A recent pharmacoeconomic analysis used chart review data from the entire hemophilia population living in Mississippi to identify children ages 2 to 18 years on factor prophylaxis who exceeded their IBW (n = 20) (Majumdar et al., 2011). The analysis concluded that an IBW dosing strategy would result in a projected monthly cost savings of over \$120,000 if 20 overweight/obese pediatric patients were dosed at their IBW. This translated to nearly \$1.5 million per year. The study's authors did not address whether an ABW-based dosing strategy should be used in overweight/obese patients, but rather highlighted the importance of obesity prevention in patients with hemophilia.

Trial in Progress

A Phase 2 [RCT](#) to assess whether IBW is more accurate than ABW in calculating factor VIII dosing in adults is in progress, with an estimated completion date of August 2017.

Conclusions and Limitations

Center staff did not identify any RCTs or systematic reviews on the comparative effectiveness of dosing factor replacement based on ABW or IBW. One very small observational study concluded that a strategy based on IBW would result in a reduction in prophylactic factor usage of almost 50% over 3 months, and generate significant cost savings. The long-term effect of this strategy has not been evaluated, however. A trial in progress will evaluate this question. Obesity prevention and treatment efforts aimed at patients with hemophilia may lead to reduced factor usage even if an IBW strategy were not implemented, and may also lead to better general health outcomes and quality of life for patients.

Appendix A: Search Strategy

Database: Ovid MEDLINE(R) without Revisions <1996 to February Week 4 2016>

- 1 exp Factor VIII/ or factor replacement.mp.
- 2 weight-based dosing.mp.
- 3 1 and 2
- 4 Factor VIII/ad [Administration & Dosage]
- 5 Factor IX/ad [Administration & Dosage]
- 6 4 or 5
- 7 limit 6 to (english language and humans)
- 8 limit 7 to (meta analysis or systematic reviews)

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About the Center for Evidence-based Policy and the Medicaid Evidence-based Decisions Project

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The Medicaid Evidence-based Decisions Project (MED) is housed at the Center. Its mission is to create an effective collaboration among Medicaid programs and their state partners for the purpose of making high-quality evidence analysis available to support benefit design and coverage decisions made by state programs. Further information about the MED Project and the Center is available at www.ohsu.edu/policycenter.

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***Use of Ultrasound to Diagnose
Hemarthrosis and Monitor Joint
Health in Hemophilia***

Participant Request

March 2016

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Objective

To summarize the current evidence on effectiveness and costs of using ultrasound in the management of hemophilia A and B.

Background

Hemophilia is an inherited clotting disorder characterized by recurrent bleeding episodes. The most common types of hemophilia are hemophilia A, also known as factor VIII deficiency, and hemophilia B, or factor IX deficiency. Both are X-linked inherited disorders that manifest in male children of carrier females. Hemophilia A is the more common type, occurring in about 1 in 5,000 live male births, compared to hemophilia B, which occurs in about 1 in 30,000 live male births (Hoots & Shapiro, 2016). Hemophilia is classified as mild, moderate, or severe based on factor activity level. Those with severe hemophilia are more likely to have spontaneous bleeding and be younger when they experience their first bleeding episode. Hemophilia A is more likely to be severe than is hemophilia B (Hoots & Shapiro, 2016).

Bleeding can occur at any site, but hemarthrosis, or bleeding into a joint, is the most common manifestation, accounting for about 80% of bleeding episodes in ambulatory patients (Hoots & Shapiro, 2016). Bleeding may occur as the result of a trauma, but spontaneous bleeding may also occur in severe disease. Hemarthrosis causes pain and may be physically debilitating. Once a joint has been damaged by hemarthrosis, it is more susceptible to recurrent bleeding and is referred to as a “target joint.” Advanced joint degeneration, or hemophilic arthropathy, may develop over time with recurrent hemarthroses. Therefore, the goals of therapy are prevention, early diagnosis, and prompt treatment of hemarthroses to preserve joints.

Diagnosis of hemarthrosis is usually made based on clinical findings of pain and reduced mobility. Magnetic resonance imaging (MRI) is the most accurate method for diagnosing hemarthrosis (Khan et al., 2010). Although MRI is the “gold standard” for diagnosis of joint bleeding, its routine use is not practical due to lack of widespread availability, time requirements, need for sedation in young children, and expense. Ultrasound has been proposed as a quicker, simpler, and less costly imaging technique for the diagnosis of hemarthrosis.

Various scoring systems are used to assess hemophilic arthropathy based on radiologic and/or clinical findings. These systems are not sensitive to early joint changes, however, and may underestimate the severity of joint damage (Di Minno et al., 2013). Ultrasound may be an option to detect early changes and guide treatment.

PICO and Key Questions

Populations

- Adults or children with hemophilia A or B

Interventions

- Use of ultrasound for diagnosis of acute hemarthrosis or routine assessment of joint health

Comparator

- Usual care (clinical assessment, goniometry, patient questionnaires)
- MRI

Outcomes

- Long-term joint outcomes (arthropathy)
- Change in management
- Total factor use
- Diagnostic accuracy or time to diagnosis
- Cost-effectiveness

Key Questions

1. What is the comparative effectiveness and cost-effectiveness of ultrasound vs usual care or MRI to diagnose acute hemarthrosis?
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 joint bleeds?
 - e. Operator experience?

Methods

Center for Evidence-based Policy (Center) staff searched Medicaid Evidence-based Decision Project core sources and Ovid MEDLINE® using terms for hemophilia and ultrasound (Appendix A).

Findings

Center staff identified no systematic reviews or randomized controlled trials of the use of ultrasound in patients with hemophilia A or B. Three observational studies (Di Minno et al., 2013; Doria et al., 2015; Sierra Aisa et al., 2014) and one cost effectiveness analysis (Khan et al., 2010) were identified and used to address the key questions for this report.

Effectiveness of Ultrasound to Diagnose Hemarthrosis

We identified no studies comparing clinical examination to ultrasound for diagnosing hemarthrosis. One prospective cohort study compared ultrasound to MRI for diagnosis of joint lesions in 61 patients with hemophilia in two regions of Spain (Sierra Aisa et al., 2014). All patients had a physical examination, but only those with severe disease (n = 30) underwent MRI and ultrasound scans. There was good agreement (Kappa=1.0) between MRI and ultrasound in cases of observed bleeding. Hemarthrosis was detected in 100% of severe cases with both MRI and ultrasound (Sierra Aisa et al., 2014). The authors received editorial support from Dr. Blanca Piedrafita of Medical Statistics Counseling, which was funded by Pfizer. However, they reported no significant conflicts of interest that would potentially bias their findings.

Effectiveness of Ultrasound to Assess Joint Health

A prospective cohort study compared ultrasound to MRI to detect joint changes in asymptomatic patients with severe hemophilia (Di Minno et al., 2013). The cohort was small, consisting of 20 boys. In evaluations by blinded assessors, MRI and ultrasound scores correlated significantly for effusion (r = 0.819, P = 0.002), synovial hypertrophy (r = 0.633, P = 0.036), and cartilage erosion (r = 0.734, P = 0.010) (Di Minno et al., 2013). The researchers concluded that ultrasound was able to identify early-onset subclinical joint alterations. Because this study did not include an assessment of symptomatic joints, it does not provide evidence on the comparison of ultrasound to clinical findings. The authors noted no significant conflicts of interest.

The study by Sierra Aisa and colleagues discussed above (Sierra Aisa et al., 2014) also compared ultrasound to MRI for assessment of arthropathy in patients with severe hemophilia. Ultrasound assessment was not statistically significantly different than MRI for detecting the presence of synovial hyperplasia and erosion of margins. For detection of bone cysts or cartilage loss, however, MRI had better accuracy.

A small observational study included imaging of ankles (n = 34) or knees (n = 25) of boys with hemophilia ages 5 to 17 years in Canada and India (Doria et al., 2015). Ultrasound was sensitive and had good agreement with MRI when performed by experienced radiologists. For this study, financial support was provided by Bayer Healthcare Canada. The authors did not list conflicts of interest.

Effectiveness by Patient Characteristics and Other Factors

We identified no direct evidence addressing this key question. Observational studies discussed above found that ultrasound was comparable to MRI in detecting acute joint bleeding in patients with severe hemophilia (Sierra Aisa et al., 2014), and in detecting subclinical arthropathy in children with severe hemophilia A (Di Minno et al., 2013).

Cost Effectiveness of Ultrasound

A cost effectiveness analysis published in 2010 examined different imaging strategies for the diagnosis of hemophilic arthropathy in children (Khan et al., 2010). The study's objective was to compare costs and effectiveness of usual care (physiotherapy and radiography) to usual care plus ultrasound. This was a small study of only 31 patients that used retrospective data from medical records at a single center in Canada. The researchers found that the strategy including ultrasound was more costly, but increased diagnostic effectiveness compared to usual care. Because this analysis considered only the cost of diagnosing arthropathy and not the cost of management of hemophilia, or variations in treatment as a result of different diagnostic strategies, it does not provide information on longer term cost effectiveness.

Conclusions and Limitations

Observational studies have shown that there is good agreement between ultrasound and MRI for detecting acute bleeds and assessing joint damage in adults and children with hemophilia. However, no studies compared outcomes of treatment in patients assessed with ultrasound, usual care, or other imaging techniques. Clinical practice guidelines do not address the routine use of ultrasound in diagnosing hemoarthroses or monitoring joint health in patients with hemophilia. In part because hemophilia is a relatively rare disorder, studies are small and the evidence base is limited. Longer-term, prospective studies are needed to evaluate the place of ultrasound in the management of hemophilia.

Appendix A: Search Strategy

Database: Ovid MEDLINE(R) <1946 to February Week 4 2016>

- 1 hemophilia.mp. or exp Hemophilia A/
- 2 exp Hemophilia B/
- 3 exp Ultrasonography/ or ultrasonography.mp.
- 4 *Ultrasonography/
- 5 *Magnetic Resonance Imaging/
- 6 exp Hemarthrosis/di [Diagnosis]
- 7 1 or 2 or 6
- 8 3 or 4 or 5
- 9 7 and 8
- 10 limit 9 to (english language and humans)
- 11 limit 10 to yr="2010 -Current"

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***Home Care Services and
Utilization Management for
Appropriate Use of Factor
Replacement Therapy in Patients
with Hemophilia***

Participant Request

March 2016

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Objectives

- To summarize the evidence for the effectiveness and cost effectiveness of different home-care services for patients with hemophilia
- To describe utilization management options for the appropriate use of factor replacement therapy in patients with hemophilia

Key Findings

- Home-based factor replacement is recommended as the standard of care for patients with hemophilia
- There is no comparative evidence on different home management strategies for patients with hemophilia
- Pharmacy and utilization management options are available to manage costs associated with factor replacement therapy, without decreasing quality of care

Background

Hemophilia is an inherited clotting disorder characterized by recurrent bleeding episodes. The most common types of hemophilia are hemophilia A, also known as factor VIII deficiency, and hemophilia B, or factor IX deficiency. Both are X-linked inherited disorders that manifest in male children of carrier females. Hemophilia A is the more common type, occurring in about 1 in 5,000 live male births, compared to hemophilia B, which occurs in about 1 in 30,000 live male births (Hoots & Shapiro, 2016a). Hemophilia is classified as mild, moderate, or severe based on factor activity level. Those with severe hemophilia are more likely to have spontaneous bleeding and be younger when they experience their first bleeding episode. Hemophilia A is more likely to be severe than is hemophilia B (Hoots & Shapiro, 2016a).

Factor Replacement Therapy

Factor VIII and IX products are used to treat hemophilia A and B, respectively. Factor products are derived from human plasma or produced from cell lines (recombinant products). Factor replacement is used to treat acute bleeding episodes, or as prophylaxis to prevent bleeding. Prophylactic factor replacement therapy is further classified as primary, secondary, tertiary, or intermittent (periodic) (Table 1) (Srivastava et al., 2013). The goal of prophylaxis is to prevent bleeding and to preserve normal musculoskeletal function. Clinical practice guidelines recommend tailoring prophylactic treatment as much as possible (Srivastava et al., 2013).

Table 1. Description of Factor Replacement Therapy Protocols

Protocol	When Initiated
Episodic treatment	At the time of clinically evident bleeding; to treat pain and serious bleeding
Primary prophylaxis	Before second joint bleed, in the absence of documented joint disease
Secondary prophylaxis	After second joint bleed and before onset of joint disease
Tertiary prophylaxis	After onset of joint disease
Intermittent prophylaxis	Given to prevent bleeding for periods not exceeding 45 weeks in a year

Source: Adapted from Srivastava et al., 2013

Factor replacement prophylaxis is the standard of care for children with severe hemophilia (Srivastava et al., 2013), and has been shown in randomized controlled trials to improve outcomes (Aronstam et al., 1976; Astermark et al., 1999; Feldman et al., 2006; Fischer et al., 2002; Gringeri et al., 2011; Manco-Johnson et al., 2007). However, prophylaxis requires more factor usage and is about three times more costly than episodic treatment (Medicaid Health Plans of America, 2013). In settings with significant resource constraints, lower doses of prophylaxis given more frequently may be an effective option (Srivastava et al., 2013). In very young children, one option is to start prophylaxis frequency at once a week and increase depending on bleeding and venous access.

About 30 percent of patients with hemophilia will develop inhibitors at some point (Hoots & Shapiro, 2016b). The cost of treatment for these patients may be up to four times higher than for those without inhibitors (Medicaid Health Plans of America, 2013).

Hemophilia Treatment Centers

In 1975, Congress authorized the creation of a network of comprehensive, multidisciplinary Hemophilia Treatment Centers (HTCs). These HTCs focus on preventive services, education, and family support, and include a team of providers including hematologists, pediatricians, nurses, social workers, physical therapists, orthopedists, and dentists. Today, about 70% of the approximately 20,000 individuals with hemophilia in the United States receive care at a HTC (National Hemophilia Foundation, 2015).

The Veterans Health Care Act of 1992 designated federally-funded HTCs as covered entities eligible to participate in the 340B Drug Pricing Program. About 100 of the 141 HTCs in the United States have elected to participate in the 340B Program. Under federal grant requirements, all revenues from the 340B program must be invested back into patient services, care coordination, research and other programs that directly benefit patients (National Hemophilia Foundation, 2015).

Home Infusion

Prior to establishment of HTC, most bleeding episodes were treated in hospitals or emergency departments. Between 1990 and 2010, the number of patients with hemophilia on a home therapy program increased 37%, from 4,442 to 6,166. In 2010, 77% of patients with severe hemophilia, 51% of those with moderate hemophilia, and 21% of those with mild hemophilia used home infusion therapy (Baker et al., 2013). Patients using home infusion receive education, monitoring, and support through a HTC (Teitel et al., 2004). Most HTCs include integrated pharmacy services and provide for or arrange infusion services (Medicaid Health Plans of America, 2013).

PICO and Key Questions

Populations

- Adults or children with hemophilia A or B

Interventions

- Continuous or episodic home nursing
- Multidisciplinary home care team visits

Comparator

- Usual care

Outcomes

- Joint bleeding
- Change in management
- Total factor use
- Hospital admission or readmission
- Physical function
- Quality of life

Key Questions

1. What is the effectiveness and cost-effectiveness of continuous or episodic home nursing care for patients with hemophilia?
2. What is the 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?

Methods

Center for Evidence-based Policy (Center) staff searched Medicaid Evidence-based Decision Project core sources for evidence and guidelines on home-based services for hemophilia (See Appendix A for search strategy). Center staff also conducted internet searches using terms for hemophilia, factor replacement, Medicaid, and utilization management to identify additional information on utilization management for factor replacement therapy.

Findings

Comparative Effectiveness and Cost Effectiveness of Home Nursing

Center staff identified no studies addressing the comparative effectiveness or cost effectiveness of different strategies for providing home health services for patients with hemophilia, and no studies evaluating the effectiveness or cost effectiveness of episodic multidisciplinary home care team visits versus usual care for patients with hemophilia.

Clinical Practice Guidelines on Home Factor Administration

The World Federation of Hemophilia (WFH) guidelines recommend home management for people with hemophilia “where appropriate and possible” (Srivastava et al., 2013). They specify that home factor replacement treatment must be supervised closely by the comprehensive care team and should only be initiated after adequate education and training. The recommendations do not address details of home nursing or team care such as frequency of episodic visits, however.

A frequently cited source for recommendations regarding home treatment is a narrative review published in 2004 (Teitel et al., 2004). This was not a systematic review; authors did not assess the methodological quality of included studies, report a literature search strategy, or specify study inclusion and exclusion criteria. The researchers summarized early studies demonstrating quality of life benefits for home treatment. These studies found that children on home treatment experienced decreased hospitalization and time lost from school, better integration with peer groups, and less pain (Ekert, Moorehead, & Williamson, 1981; Lazerson, 1972; Levine & Britten, 1973; Rabiner & Telfer, 1970). Studies of home treatment also reported positive effects on family life, including less tension and greater flexibility in arranging family activities (Ekert et al., 1981; Rizza & Spooner, 1977; Wincott, 1977). Adult men reported better quality of life as well, including greater feelings of self-sufficiency and self-confidence, and less negative emotions such as fear, anger, and depression (Ingram et al., 1979; Rabiner, Telfer, & Fajardo, 1972; Rizza & Spooner, 1977). Men also experienced less work absenteeism and more employment stability (Szucs et al., 1998).

Utilization Management of Factor Replacement for Patients with Hemophilia

The Medicaid Health Plans of America has published an [issue brief](#) on hemophilia treatment in Medicaid Managed Care (Medicaid Health Plans of America, 2013). This report provides an overview of issues related to Medicaid plan members with hemophilia, including considerations for cost management and pharmacy management. Recommendations related to cost management are excerpted below.

- Work with state policy leaders to develop an effective purchasing strategy for factor under Medicaid (either through a 340b or with sufficient rebates)
- Monitor factor costs to identify the most cost effective purchasing route
- Ensure that factor dosing is within recommended parameters and generates the appropriate clinical response for preventive and acute care (assay management)
- Ensure that pharmacy benefit managers or specialty pharmacy providers carry out the full scope of required factor management services, patient education, home care services and medical waste management
- Prevent wasted factor by ensuring appropriate pharmacy management and developing protocols for the number of doses kept in the patient homes
- Prevent acute or catastrophically expensive complications by coordinating with hospitals and other providers to plan for elective and emergency conditions
- Monitor and evaluate the total cost of care, including inpatient and emergency services, to evaluate use of avoidable acute care

Conclusions and Limitations

Center staff identified no evidence on the comparative effectiveness of different home care strategies (continuous vs episodic nursing care, team visits) for patients with hemophilia. 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. Guidelines recommend home administration but are silent on the specific aspects and details of home nursing or multidisciplinary support strategies.

Appendix A: Search Strategy

Database: Ovid MEDLINE(R) <1946 to February Week 4 2016>

1 hemophilia.mp. or exp Hemophilia A/

2 hemophilia b.mp. or exp Hemophilia B/

3 exp Factor VIII/ or factor replacement.mp.

4 factor ix.mp. or exp Factor IX/

5 1 or 2 or 3 or 4

6 exp Home Nursing/

7 exp Home Care Services/ or home-based services.mp.

8 6 or 7

9 5 and 8

10 limit 9 to (english language and humans)

11 limit 10 to yr="2002 -Current"

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About the Center for Evidence-based Policy and the Medicaid Evidence-based Decisions Project

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring diverse and relevant perspectives are considered, and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

The Medicaid Evidence-based Decisions Project (MED) is housed at the Center. Its mission is to create an effective collaboration among Medicaid programs and their state partners for the purpose of making high-quality evidence analysis available to support benefit design and coverage decisions made by state programs. Further information about the MED Project and the Center is available at www.ohsu.edu/policycenter.

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***Interventions for Hemophilia A and B:
Clinical Practice Guidelines and
Cost-effectiveness***

**A Report for the Washington State Bleeding Disorder
Collaborative for Care**

June 2016

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Objectives

The goal of this report is to identify clinical practice guidelines on drug interventions for hemophilia A and B and conduct a review for estimates on the cost and cost-effectiveness of those interventions. This report is prepared for the Washington State Bleeding Disorder Collaborative of Care.

Key Findings

Clinical Practice Guidelines

- The search for clinical practice guidelines identified four relevant documents from the Australian Haemophilia Centre Directors' Organisation (Australian Haemophilia Centre Directors' Organisation, 2016), the Nordic Hemophilia Council (Nordic Hemophilia Council guideline working group, 2015), the United Kingdom Haemophilia Centre Doctors Organization (Collins et al., 2013), and the World Federation of Hemophilia (Srivastava et al., 2013).
- Three were of poor methodologic quality (Collins et al., 2013; Nordic Hemophilia Council guideline working group, 2015; Srivastava et al., 2013) for absence of clearly defined evidence process, method for translating evidence to recommendations, and editorial independence. One was of fair methodologic quality (Australian Haemophilia Centre Directors' Organisation, 2016), which heavily relied on the World Federation of Hemophilia (WFH) guideline for evidence. They had fair-quality methods of translating evidence to recommendations and reporting of conflicts of interest.
- The United Kingdom, Nordic, and Australia guidelines recommend recombinant factors over plasma-derived. The World Federation of Hemophilia recommends both viral-eradicated plasma-derived and recombinant factors.
- Prophylaxis is recommended by all identified guidelines and should begin by age three and the second clinical bleeding episode. All identified guidelines were consistent in stating an array of options for prophylaxis regimens exist and protocols may vary within and across countries.
- All identified guidelines support the use of either rFVIIa or aPCC for bleeding episodes in patients with inhibitors.

Evidence on Estimates of Direct and Indirect Medical Costs and Cost-effectiveness

- The evidence search did not identify any estimates of cost or outcomes comparing specific clotting factor preparations.
- Estimates of cost and cost-effectiveness for prophylaxis compared to on-demand therapy vary widely depending on the methods used in the analyses.

- The evidence search identified one fair methodologic quality systematic review on economics analyses analyzing the use of bypass agents (i.e. aPCC, rFVIIa) to treat mild to moderate bleeding episodes in patients with hemophilia complicated by inhibitors.
- Estimates of total direct costs to treat a single mild to moderate bleeding episode in a patient with hemophilia complicated by inhibitors (typically treated in the home setting) ranged from \$11,485 to \$49,010 for aPCC and \$9,078 to \$49,507 for rFVIIa (using 2010 United States [U.S.] dollars). Estimates of efficacy were frequently based on industry-funded studies using higher efficacy estimates and lower doses for their products (typically based on estimates from single arm clinical trials). Findings from head-to-head trials did not support superior efficacy for either product (i.e. aPCC and rFVIIa). The authors called for additional head-to-head clinical trials of rFVIIa and aPCC to better elucidate the ideal dosing regimen, clinical efficacy, and potential that the medications may be synergistic or have differences in treatment effects among subgroups of patients.

Background

Hemophilia A and B are X-linked inherited disorders of bleeding that disproportionately impact males. The prevalence of hemophilia A is 1 in 5,000 males who are born, while hemophilia B is rarer, at 1 in 30,000 males. The majority of cases arise in families with a known hemophilia history (Peyvandi, Garagiola, & Young, 2016). Individuals may produce insufficient quantities of or dysfunctional factor VIII (hemophilia A) or IX (hemophilia B). Based on the activity of their factors, individuals with hemophilia can be categorized into mild, moderate, or severe disease (Table 1). Individuals with severe disease, constituting over 50% of patients with hemophilia, can experience bleeding episodes after minimal trauma or can have spontaneous (atraumatic) bleeds.

Children with severe hemophilia may experience their first bleeding episode by 6 to 8 months of life as their activity levels increase. Morbidity and mortality arise from bleeding complications. Individuals with hemophilia may spontaneously bleed into their brain, joints, head and neck tissues, or deep muscles creating life threatening emergencies or progressive, repeated destruction of joint cartilage leading to early arthritis and disability.

Table 1: Categories of Hemophilia by Factor Activity

Severity	Factor Activity Level
Mild	0.05 to 0.4 IU/ml (5 to 40% of normal)
Moderate	0.01 to 0.05 IU/ml (1 to 5%)
Severe	0.01 IU/ml (1% or less)

Treatments for hemophilia constituted derivatives from human blood until the 1990s when the first recombinant product was produced. Table 2 provides a list of potential drug interventions for individuals with hemophilia. Agents vary by origin (i.e. human, porcine, or recombinant) but have similar pharmacokinetics (Carcao, 2014). Newer recombinant agents in clinical trials currently may provide lengthened factor half-life in the patient’s circulation (e.g. through PEGylation, fusing to IgG or albumin) and thus alter current prophylaxis recommendations (Carcao, 2014; Peyvandi et al., 2016).

Prophylactic use of Clotting Factor Concentrates

Prophylactic use of clotting factor concentrates (CFCs) started in Sweden in 1958 after clinicians observed that patients with moderate hemophilia were less likely to experience spontaneous bleeds and maintained joint function longer than those with severe disease (Fischer et al., 2013). The rationale behind prophylaxis is to maintain higher circulating factor levels continuously as opposed to providing factors only on-demand for use at the time of a bleed.

Primary prophylaxis begins early in life, prior to the onset of joint disease, while secondary prophylaxis may be initiated or continued in those with joint disease. Prophylaxis regimens vary by dose and frequency based on the specific half-life of each agent (Peyvandi et al., 2016).

Table 2. Therapeutic Agents for Hemophilia A or B

Drug Name	Type	Brand Names
Factor VIII Agents		
Antihemophilic Factor	Human	Hemofil M, Koate-DVI Monoclote-P
Antihemophilic Factor	Recombinant	Eloctate Helixate FS Kogenate FS Novoeight Nuwiq Recombinate Refacto
Antihemophilic Factor	Recombinant Porcine	Obizur
Antihemophilic Factor Plasma/Albumin Free Method (rAHF PFM)	Recombinant	Advate
Antihemophilic Factor Platelet Activating Factor (rAHF PAF)	Recombinant	Xyntha
Antihemophilic Factor/Von-Willebrand Factor Complex	Human	Alphanate Humate-P

		Wilate
Factor IX Agents		
Factor IX	Human	AlphaNine SD Mononine
Factor IX	Recombinant	Alprolix BeneFIX Ixinity Rixubis
Prothrombin Complex Concentrates (PCC)		
3-factor Prothrombin Complex Concentrate (factor IX, prothrombin (factor II), factor X ,low levels of factor VII)	Human	Bebulin Bebulin Vapor Heated (VH) Profilnine Profilnine Solvent/Detergent treated (SD)
4-factor Prothrombin Complex Concentrate (factor II, VII, IX, X)	Human	Kcentra
Bypass Agents		
Activated Prothrombin Complex Concentrate (aPCC: non-activated factors II, IX, X and activated VII)	Human	FEIBA
Factor VIIa (rVIIa)	Recombinant	NovoSeven RT

Inhibitors

Inhibitors are an uncommon but serious complication for individuals with hemophilia. The development of inhibitors often occurs within the first 30 days after initial receipt of a factor concentrate (Peyvandi et al., 2016). Estimates for inhibitor prevalence range from 3.6% to 32% (Matino, Makris, Dwan, D'Amico, & Iorio, 2015). Depending on the response of the inhibitor, treatments may consist of higher doses of CFCs for those with low-responding inhibitors or require the use of bypass agents for high-responding cases. Bypass agents support clot formation by going downstream in the clotting cascade, passed the factor VIII or XI step (which is blocked by the inhibitor). Immune tolerance induction (ITI) is a treatment option for patients with inhibitors. The aim of ITI is to eliminate or reduce the activity of the inhibitor. Protocols for ITI utilize high doses of CFCs, with associated cost implications. However, this report focuses on specific drug agents and does not include cost or cost-effectiveness evidence for ITI specifically.

Future Directions for Hemophilia Treatments

In addition to research on extending the half-life of CFCs, other clinical trials are investigating novel methods to promote clotting through synthetic antibody production and alternate pathways. Gene replacement therapy, holding a potential curative intervention for individuals

with hemophilia, may not be too far off. As of 2016, six clinical trials are in process, many still in recruitment phases, investigating the use of gene therapy for hemophilia B. While a 2014 Cochrane review did not identify any RCTs on gene therapy, the authors highlighted the need for long-term safety evaluations and provided a review on the current status of research in this developing field (Sharma, Easow Mathew, Sriganesh, Neely, & Kalipatnapu, 2014).

PICO and Key Questions

PICO

Population(s)

- Adult outpatients with hemophilia A or B
- Pediatric outpatients with hemophilia A or B

Interventions

- See list of interventions in Table 2 above

Comparators

- Usual care, other active interventions

Outcomes

- Direct and indirect economic costs; cost-effectiveness

Key Questions

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

Methods

Center for Evidence-based Policy (Center) staff conducted a full search of the Medicaid Evidence-based Decisions Project (MED) core guidelines sources to identify clinical practice guidelines using the intervention terms listed in Table 2, as well as hemophilia A and hemophilia B. Searches of core sources were limited to citations published after January 1, 2006. Lateral searches (i.e. cited by) and reference list screening was conducted on eligible documents.

Center staff performed a full Ovid MEDLINE® search for systematic reviews on direct and indirect economic costs, and cost-effectiveness of interventions listed in Table 2 for hemophilia A and hemophilia B. The full search strategy can be found in Appendix A. Searches were limited

to systematic reviews, meta-analyses, and technology assessments published in English in the past 10 years (January 1, 2006 to April 20, 2016).

Center staff searched for clinical practice guidelines published in the last five years using the sources listed in Appendix A.

Exclusion Criteria

The following exclusion criteria were applied when reviewing search results. We excluded the study if the population, intervention, comparator, or outcome was not relevant to the project scope; the study design was ecological, qualitative or a narrative review; non-comparative; duplicative; or it was not published in English.

Clinical practice guidelines were excluded if they were not relevant to project scope or published in English.

Quality Assessment

Two Center staff reviewers independently evaluated the methodologic quality of the included systematic reviews and clinical practice guidelines for this report using a quality assessment process highlighted in Appendix B. The two reviewers compared and discussed the quality assessments, and when consensus was not reached, a third reviewer was involved to settle disagreement. It is important to note that Center staff only assessed the methodologic quality of the systematic reviews and did not assess the quality (risk of bias) of the individual studies included in each review or the evidence that was considered within clinical practice guidelines.

Findings

Search Results

Clinical Practice Guidelines

Center staff identified four guidelines on hemophilia treatment. Using the quality assessment process detailed in Appendix B, three of the guidelines were found to be of poor methodologic quality; often for lacking information on methods of identifying evidence, absence of clear methods for developing recommendations, failure to disclose funding sources or competing interests of authors (Collins et al., 2013; Nordic Hemophilia Council guideline working group, 2015; Srivastava et al., 2013). The National Blood Authority (NBA) of Australia released their draft guideline to public comment in late 2015 and anticipates releasing the final in June 2016. The draft document was reviewed and found to be of fair methodologic quality (Australian Haemophilia Centre Directors' Organisation, 2016).

The Australia document, produced by the Australian Haemophilia Centre Directors' Organization, reviewed the 2012 WFH guideline and adapted recommendations to the Australian setting and conducted evidence searches for areas needing further research (Australian Haemophilia Centre Directors' Organisation, 2016). Many of the recommendations from the WFH and Australia guidelines align. Center staff included the Australia guideline in summary below, but recommendations may change when the final document is released later in 2016.

The 2010 guideline from the United Kingdom Haemophilia Centre Doctors Organization (UK) is specific to patients with congenital hemophilia with inhibitors (Collins et al., 2013). The 2012 WFH guideline uses 2011 Oxford Center for Evidence-based Medicine levels of evidence for practice statements only (Srivastava et al., 2013). The 2015 Nordic Hemophilia Guidelines (Nordic) were produced in conjunction with Nordic national patient organizations (Nordic Hemophilia Council guideline working group, 2015).

All clinical practice guidelines are vast and comprehensive in their recommendations on appropriate care of patients with hemophilia. Center staff summarized guidelines where they make specific recommendations on agents listed in Table 2.

Evidence

A two tier Ovid MEDLINE® search strategy was performed (Appendix A). The first tier limited results to systematic reviews, meta-analyses, literature reviews, and technical reports related to costs and cost-effectiveness (n = 32), while the second tier removed the limitation on type of publication (n = 58). For tier one, 28 citations were excluded based on title and abstract screening. Staff reviewed reference lists of included studies. Ultimately, staff identified four studies, three older studies (Knight, Dano, & Kennedy-Martin, 2009; Lyseng-Williamson & Plosker, 2007; Stephens, Joshi, Sumner, & Botteman, 2007) were included in the most recent publication (Hay & Zhou, 2011b). All identified systematic reviews addressed economic analyses comparing bypass agents (i.e. aPCC, rFVIIa) for mild to moderate hemophilia bleeds in patients with inhibitors.

Of note, Hay and Zhou (2010) published a letter to the editor regarding Knight's 2009 systematic review calling attention to industry influence, and repetitive use of models containing base case efficacy rates favoring rFVIIa that were based on single arm clinical trials (Hay & Zhou, 2010).

Baghaipour and Steen Carlsson (2015) subsequently published a narrative review, which included three trials published following the 2011 systematic review by Hay and Zhou (2010). Staff summarized the interval studies below given the paucity of data and the time since

completion of the systematic review (Baghaipour & Steen Carlsson, 2015). Additionally, all interval studies were identified through the tier two search strategy.

The MED core evidence sources search identified several relevant articles. One, a review article discussing variation in economic evaluations of prophylaxis with CFCs, provided useful background, analysis, and reflection upon needed research in the field (Miners, 2013) and is described below. The second provides estimates of cost and outcomes proposed from the use of a proposed treatment protocol for patients with hemophilia A complicated by inhibitors, also reviewed below (Bonnet et al., 2011).

Others, while outside the scope of this report or not meeting strict inclusion criteria, are included below for context. Two Cochrane reviews evaluating efficacy, not costs, are reviewed below as well (Iorio, Marchesini, Marcucci, Stobart, & Chan, 2011; Matino et al., 2015). The MED core evidence sources also identified a large multinational review of outcomes and costs comparing intermediate dose to high dose prophylaxis from the Netherlands and Sweden (Fischer et al., 2013), which is included given a paucity of findings relating to prophylaxis costs.

Summary of Clinical Practice Guidelines

Hemostatic Agents

The WFH guideline states that viral-inactivated plasma derived or recombinant concentrates are preferred to cryoprecipitate or fresh frozen plasma. They do not preferentially recommend recombinant over viral-inactivated factor products, stating the choice is up to local authorities. The WFH mentions a recombinant product, pending clinical trials, may replace porcine plasma derived factor VIII.

The Australian and UK guidelines recommend recombinant factors as first line treatment over plasma derived products. The rationale behind this decision is the potential (albeit with a low likelihood) for plasma based agents to spread infectious or prion diseases and the availability of recombinant products in these countries. The Nordic guideline recommends the use of recombinant over plasma derived products when available, without explanation.

The use of prothrombin complex concentrates (PCCs) includes other clotting factors (II, VII, and X), which may be activated and could increase the risk of thromboembolism. For patients with hemophilia B, factor IX replacement is recommended over PCC and in Australia, rIX is available and is the recommended product for bleeding with PCCs only used in emergency situations. This is consistent with the WFH recommendations, although they do not state a preference for plasma or recombinant preparations of factor IX.

Prophylaxis

The Nordic guideline recommend prophylaxis begin before age one, but also includes language similar to the WFH and Australian guidelines, which recommend primary prophylaxis begin before age three and the “second clinically evident large joint bleed” (Australian Haemophilia Centre Directors' Organisation, 2016, p. 21; Nordic Hemophilia Council guideline working group, 2015, p. 35).

The WFH, Australia, and Nordic guidelines mention two established protocols with long-term data for prophylaxis, the Malmo (Lee et al., 1998) and Utrecht (Blanchette, 2010) protocols, but mention that different protocols are followed within countries, and the optimal regimen “remains to be defined” and should be individualized as possible.

Malmo protocol: 25 to 40 IU/kg per dose three times a week (hemophilia A), twice a week (hemophilia B)

Utrecht protocol: 15 to 30 IU/kg per dose three times a week (hemophilia A), twice a week (hemophilia B)

In addition, the Nordic guideline recommends two more options for individuals with hemophilia A, the pharmacokinetic Swedish option (which can be reduced from high dosing in eligible patients) and the Candia dose, which up-titrates the dose based on bleeding frequency.

Inhibitors

Guidelines recommend consultation with a hemophilia treatment center when managing bleeding in a patient with an inhibitor. Low responding inhibitors may be treated with a higher dose of factor, while high responding inhibitors, but with low titers, may be treated similarly. Patients with high responding inhibitors and high titres may require bypass agents (i.e. rFVIIa, aPCC).

The WFH and Australia guideline state that the efficacy of two doses of rFVIIa and one dose of aPCC is “essentially equivalent” (Australian Haemophilia Centre Directors' Organisation, 2016, p. 84; Srivastava et al., 2013, p. 60). They also mention that some patients may respond better to one agent over the other and recommend an individualized approach.

The Nordic guideline recommends either rFVIIa (90 to 120 μ g/kg every 2 to 3 hours) or aPCC (50 to 100IU/kg every 6 to 12h) for bleeding in patients with high responding inhibitors.

The UK guideline lists a single dose of aPCC (50 to 100 μ k/kg), single high dose of rFVIIa (270ug/kg), or 1 to 3 standard doses of rFVIIa (90 μ g/kg) as treatment options for early

hemarthroses in patients with high responding inhibitors. For non-joint bleeds, aPCC or rFVIIa are treatment options.

Discussion of Costs in Guidelines

The available guidelines reported mixed results regarding the cost-effectiveness of prophylaxis. The Nordic guideline suggests that prophylaxis may be more clinically effective than on-demand treatment, but at a greater financial cost (Nordic Hemophilia Council guideline working group, 2015). The WFH states that prophylaxis may be cost-effective over the long-term via avoided costs from managing joint damage and possible improvements in quality of life.

For older children who have hemophilia A, the Nordic guideline suggests the cost-benefit ratio of prophylaxis treatment may be maximized using daily FVIII injections (specified as 10 to 20 IU/kg).

Summary of Evidence Findings

Systematic Review of Bypass Agents: aPCC compared to rFVIIa

Hay and Zhou reviewed 11 studies and converted estimates to a cost per bleeding episode in 2010 U.S. dollars (Hay & Zhou, 2011b). Nine studies were industry funded comparative economic estimates of treating a single bleeding episode; eight took a cost-minimization approach. Two studies were longitudinal cost-effectiveness studies over a 1-year timeframe or lifetime and were evaluated separately from the other studies.

Estimates of total direct costs for a single mild to moderate bleeding episode for a patient with inhibitors typically treated in the home setting (in 2010 U.S. dollars) ranged from \$11,485 to \$49,010 for aPCC, \$9,078 to \$49,507 for rFVIIa.

The authors highlight that all industry-funded studies used higher efficacy estimates and lower doses for their products (typically based on estimates from single arm clinical trials), whereas available head-to-head trials between aPCC and rFVIIa did not support superior efficacy for either product. Seven trials used nearly identical decision models with minor modifications to address country-specific features. The authors emphasize that estimates of cost-effectiveness or cost-minimization hinge on efficacy and dosing assumptions and call for further head-to-head clinical trials to address efficacy and dosing estimates (Hay & Zhou, 2011b, p. 524):

The cost-effectiveness analyses of these bypass agents have only obfuscated the current clinical uncertainties under a patina of complex mathematical models. The results of these models are driven by favorable selection of baseline clinical parameters for each of the bypass agents. Until head-to-head clinical trials of rFVIIa and aPCC clearly resolve the underlying clinical efficacy and dosing differences, including the possibility that

medications may be synergistic and have heterogeneous treatment efficacy response, cost-effectiveness analysis will confuse rather than clarify the underlying clinical decisions (p. 524).

Review of Cost Comparisons for Prophylaxis Compared to On-Demand Therapy

Miners reviewed the literature on costs and outcomes for prophylaxis compared to on-demand treatment (Miners, 2013). His review article compares and contrasts findings while offering explanations for the wide variety of cost estimates observed in 10 studies (five utilized a cost-utility analysis approach, four a cost-effectiveness analysis, and one a cost-benefit approach).

Cost effectiveness estimates spanned the full range of potential outcomes with reported positive net benefits to treatment with prophylaxis through incremental cost-effectiveness ratios of over €1 million per additional quality-adjusted life-year (QALY). A typical willingness to pay threshold to determine if an intervention is cost-effective is US\$50,000 per QALY gained.

Poorly described on-demand treatment protocols for models, failure to describe or inconsistent unit costs for CFCs, time horizons ranging from 6 months to 70 years, and failure to adhere to published standards on economic analyses are all given as reasons for limited accuracy and utility of this body of evidence.

Recent Economic Analyses on Bypass Agents

Baghaipour and Carlsson (2015), as part of the Advanced International Hemophilia course in Sweden, performed a PubMed literature review and published the work as a narrative review. Their literature review included the three trials identified above. Cost perspectives (e.g., third party payers, national health systems) and setting (e.g., at home use, in hospital use) varied across trials and prevented synthesis of cost estimates.

Their literature search identified three trials (Hay & Zhou, 2011a; Jimenez-Yuste, Nunez, Romero, Montoro, & Espinos, 2013; Salaj et al., 2012) published after the search date of Hay and Zhou's 2011 systematic review. All were identified in the tier two search.

Two studies used a decision analytic model (Hay & Zhou, 2011a; Jimenez-Yuste et al., 2013), while Salaj and colleagues used retrospective analysis to guide their efficacy rates. Only Hay and Zhou presumed equal efficacy for aPCC and rFVIIa based on a concurrent Cochrane review, while the remaining two used higher efficacy rates for rFVIIa. Additionally, Hay and Zhou was the only trial to provide the mean number of doses required to address a mild-to-moderate bleed (rFVIIa = 3; aPCC = 2).

When the efficacy of rFVIIa was greater than that for aPCC (both trials used >90% efficacy for rFVIIa and ~60% efficacy for aPCC), rFVIIa was found to provide the best value for money

(Jimenez-Yuste et al., 2013; Salaj et al., 2012). When their efficacy was equal (at 85%), aPCC provided the best value for money. Their review did not standardize costs to a single denomination across trials complicating comparisons.

Estimates of Costs from Proposed Treatment Protocol for Hemophilia A with Inhibitors

Bonnet and colleagues convened an expert panel and using a modified Delphi process, they developed a proposed treatment protocol for individuals with severe hemophilia A complicated by high-titer inhibitors (Bonnet et al., 2011). The panel also provided estimates on effectiveness to inform the cost effectiveness model of adhering or not adhering to the proposed protocol.

Adhering to their proposed model increased the number of patients with improved clinical symptoms by 72 hours (74.4% vs. 56.7%), with fewer patients requiring sequential therapy (25.6% vs. 43.3%), and a lower average cost (\$87,436 vs. \$92,604 based on 2008 Medicare Part B payment limits) regardless of which bypass agent was initially started.

Multinational Report on Costs – Intermediate vs High Dose Prophylaxis

The search strategy identified a large multinational review of outcomes and costs comparing intermediate dose to high-dose prophylaxis from the Netherlands and Sweden (Fischer et al., 2013). While the study did not meet strict inclusion criteria, it is described here given the paucity of findings relating to prophylaxis costs.

Sweden and the Netherlands opted to implement different national prophylaxis protocols (high-dose and intermediate-dose, respectively) in the 1960s. In their retrospective analysis, Fischer and colleagues (2013) capitalized on this natural experiment to analyze costs and outcomes for a birth cohort of 128 individuals with hemophilia without inhibitors born between 1970 and 1994, and receiving care at one of three hemophilia treatment centers. While protocols changed over time, the total amount of CFCs used still differs by country. The authors report that as of 2013, a Dutch citizen with hemophilia A used 3 x 1000 IU of FVIII/week compared to 3 x 1500 to 2000IU every other day for an adult in Sweden (Fischer et al., 2013).

Clinical joint status was the primary outcome and was prospectively assessed using the Hemophilia Joint Health Score (HJHS) by trained physiotherapists. Secondary outcomes included annual number of joint bleeds, self-reported activities, and quality of life. The authors calculated direct (factor concentrate and other medical) and indirect costs (days of work lost) for both cohorts (Fischer et al., 2013).

At a median age of 24 years, more of the high-dose prophylaxis cohort remained free of significant arthropathy compared to the intermediate dose cohort (89% vs. 54%, $p < 0.01$). Mean annual costs were estimated at US\$179,600 for Dutch patients compared to \$297,900 for

Swedish patients based on 2010 exchange rates. Nearly all of the difference in cost estimates is attributed to greater factor consumption in the high prophylaxis group. A limitation of this evaluation was that prophylaxis initiation occurred at a statistically significantly later age among the Dutch compared to Swedish patients (Median age 1.8 vs. 0.6 years, [p<0.01]), after the onset of joint bleeding (Fischer et al., 2013).

Cochrane Review on Efficacy of Prophylaxis versus On-demand Dosing

In a systematic review of studies comparing prophylactic use of CFCs to on-demand dosing and the impact on bleeding episodes, Iorio and colleagues identified six studies consisting of 142 participants with hemophilia (Iorio et al., 2011). Each eligible trial used a different intervention and the authors were unable to calculate pooled outcome estimates with the exception of two meta-analyses on effectiveness of three-times-a-week prophylaxis vs. on-demand in children (these were presented with caveats about their limitations). They found a pooled rate ratio of 0.30 (95% CI 0.12 to 0.76) for all bleeding episodes and 0.22 (95% CI 0.08 to 0.63) for joint bleeding, both significantly favored prophylaxis. However, these meta-analyses revealed significant statistical heterogeneity (Chi-square = 196.78, p<0.0001 and I² = 99% and Chi-square = 63.31, p<0.0001 and I² = 98%), indicating that combining these data in an overall analysis was likely inappropriate. Included trials also varied by participant age (i.e. trial 1 enrolled only children under 30 months, trial 2 enrolled children up to 7 years of age), which may explain some of the variation between the study outcomes.

Two studies investigated differing prophylaxis regimens. They did not identify statistically significant differences in bleeding episodes. The authors reported non-statistically significant increases in infections for patients receiving prophylaxis, as they require the placement and use of long-term venous access. Inhibitor occurrences were also not statistically significantly different for prophylaxis patients compared to those receiving on-demand CFCs.

While costs were outside the scope of this Cochrane review, the authors reported for standard prophylaxis of factor VII concentrate that the mean difference in monthly CFC usage was 5.27 x1000 IUs (95% CI 4.23 to 6.32) greater for participants receiving prophylaxis.

Cochrane Review on Efficacy of Agents for Patients with Inhibitors – rFVIIa vs. Plasma-derived Concentrates)

Matino and colleagues updated a 2010 systematic review of trials investigating the effectiveness of rVIIa or plasma-derived concentrates (PCC or aPCC). The authors reviewed the two trials eligible for analysis, containing a total of 69 individuals with hemophilia complicated by inhibitors. Both included trials were reported by the authors as at high risk of bias. The authors were unable to perform a meta-analysis based on insufficient outcome reporting in each trial. They analyzed additional data provided by the authors using a marginal probability of

success approach. Their analysis found that available trials did not demonstrate superiority of one method or another (i.e. rFVIIA and aPCC).

Summary and Limitations

The available clinical practice guidelines support the use of recombinant factor products over plasma derived in Nordic countries, the United Kingdom, and Australia. The WFH supports recombinant or viral-inactivated plasma derived products. Prophylaxis is supported by all clinical practice guidelines to protect bone health and avoid disability from joint destruction.

Evidence on costs of treatments for hemophilia hinge on estimates of efficacy and dosing that vary from study to study. The current evidence search did not identify any cost estimates for preparations of clotting factors aside from two agents for patients with inhibitors (rFVIIa and aPCC). As the available evidence and guidelines indicate that these two options have essentially similar efficacy, the use of cost minimization approaches may be most useful, but are lacking. A 2011 systematic review found that aPCC may provide better value for money when used first for mild-to-moderate bleeds in patients with inhibitors. Several authors highlight the limitations of available economic analyses. Specifically, estimates are likely biased by choice of efficacy rates and factor doses, which may favor particular types of products in industry-sponsored studies.

Conclusion

Estimates of cost and cost-effectiveness for treatments for hemophilia are limited by a paucity of head-to-head clinical trials on CFCs and bypass agents. Hemophilia is a rare condition with significant morbidity and mortality from bleeding complications. Future treatments for hemophilia, including the potential for gene therapy, are likely to increase intervention costs, but may have long-term safety benefits that reduce costs from complications, surgeries, hospitalizations, or improve quality of life.

Appendix A: Methods

MED Core Evidence Sources

1. Cochrane Library
2. BMJ Clinical Evidence
3. National Institute for Health and Care Excellence (NICE)
4. BlueCross and BlueShield Center for Clinical Effectiveness (CCE)
5. Hayes, Inc.
6. Veterans Administration TA and ESP programs
7. Canadian Agency for Drugs and Technologies in Health (CADTH)
8. Washington State Health Technology Assessment Program
9. United States Preventive Services Task Force (USPSTF)
10. Agency for Healthcare Research and Quality (AHRQ)
11. Tufts Cost Effectiveness Analysis

MED Core Guidelines Sources

1. Australian Government National Health and Medical Research Council (NHMRC)
2. Centers for Disease Control and Prevention (CDC) – Community Preventive Services
3. Institute for Clinical Systems Improvement (ICSI)
4. National Guidelines Clearinghouse
5. NICE
6. New Zealand Guidelines Group
7. Scottish Intercollegiate Guidelines Network (SIGN)
8. USPSTF
9. Veterans Administration/Department of Defense (VA/DOD)
10. World Federation of Hemophilia
11. National Hemophilia Foundation for all Bleeding Disorders
12. Nordic Hemophilia Council
13. National Blood Authority Australia

Search Strategy

Database: Ovid MEDLINE(R) <1946 to April 2016>

- 1 Antihemophilic Factor.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (335)

2 RAHF-PFM.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (20)

3 (3-factor Prothrombin Complex Concentrate or PCC).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (6273)

4 4-factor Prothrombin Complex Concentrate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (17)

5 Factor VIIa.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4463)

6 Hemofil M.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (27)

7 Koate-DVI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4)

8 Monoclote-P.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (13)

9 Eloctate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3)

10 Helixate FS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3)

- 11 Kogenate FS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (23)
- 12 Novoeight.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5)
- 13 Nuwiiq.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1)
- 14 Recombinate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (79)
- 15 Refacto.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (44)
- 16 Obizur.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1)
- 17 Advate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (56)
- 18 Xyntha.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5)
- 19 Alphanate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (14)

- 20 Humate-P.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (43)
- 21 Wilate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (18)
- 22 AlphaNine SD.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5)
- 23 Mononine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (26)
- 24 Alprolix.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1)
- 25 BeneFIX.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (22)
- 26 Ixinity.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)
- 27 Rixubis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4)
- 28 Bebulin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (11)

- 29 Bebulin VH.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2)
- 30 Profilnine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (15)
- 31 Profilnine SD.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (9)
- 32 Kcentra.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (9)
- 33 FEIBA.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (306)
- 34 NovoSeven RT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4)
- 35 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (11511)
- 36 (Hemophilia A or Hemophilia B or Haemophilia A or Haemophilia B).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (20927)
- 37 (Factor VIII or Factor IX or FVIII or FVIX).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (24801)
- 38 36 or 37 (35537)

39 35 and 38 (2076)

40 (cost* or saving* or economi* or return on investment or return-on-investment or ROI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (646959)

41 39 and 40 (181)

42 limit 41 to yr="2006 -Current" (94)

43 limit 42 to english language (90)

44 limit 43 to (meta analysis or "review" or systematic reviews or technical report) (32) (Tier 1)

45 43 not 44 (58) (Tier 2)

Appendix B: Quality Assessment

Staff assessed the methodological quality of the included systematic reviews using standard instruments developed and adapted by the Medicaid Evidence-based Decisions Project (MED) that are modifications of the systems in use by the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) (Guyatt et al., 2008; National Institute for Health and Care Excellence (NICE), 2009; Scottish Intercollegiate Guidelines Network (SIGN), 2009). Two experienced staff raters independently assessed all studies. In cases where there was not agreement about the quality of a study, a third rater resolved the disagreement.

Each rater assigned the study a rating of good, fair, or poor, based on its adherence to recommended methods and potential for biases. In brief, good-quality systematic reviews include a clearly-focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to select studies for inclusion (e.g., randomized controlled trials) and assess study quality, and assessment of similarities between studies to determine if combining them is appropriate for evidence synthesis. Fair-quality systematic reviews have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. Poor-quality systematic reviews have clear flaws that could introduce significant bias.

Center staff also assigned quality rating to clinical practice guidelines. Good quality clinical practice guidelines provide methods of a systematic literature search to inform recommendations. The underlying evidence is rated based on methodologic quality, and there is an explicit link between the evidence and recommendations. In addition, good quality guidelines have editorial independence from any funding source, they relevant stakeholders are represented, and recommendations are unambiguous. Fair-quality clinical practice guidelines have incomplete information about methods that might mask important limitations. Poor-quality clinical practice guidelines have clear flaws that could introduce bias.

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