Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value

Public Meeting – March 29, 2017

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

WIFI: Marriott_CONF
Password: NECEPAC

Welcome and Introduction

- **Why are we here today?**

- Innovation promising substantial benefits to patients and their families

  "He's wild. He's probably sometimes the roughest of them all. He leads a totally normal life. He plays T-ball. He'll start soccer in the fall. He runs and jumps and wrestles with his brothers."

  -- STAT, 2018

Welcome and Introduction

- **Why are we here today?**

- In 2015 alone, Medicaid paid about $353 million for prescriptions for the most commonly prescribed blood-clotting medication for hemophilia – a 273% increase from 2011.

  -- Kaiser Health News, 2018

- "Generally speaking, the price of hemophilia drugs rise as rival drugs hit the market."

  -- Kaiser Health News, 2018

- Patients with hemophilia, particularly inhibitor patients, are consistently worried about the cost of treatment.

  -- Hemophilia Federation of America and National Hemophilia Foundation

Welcome and Introduction

- **Why are we here today?**
  - Treatments with new mechanisms of action often raise questions about appropriate use, cost
  - Need for objective evaluation and public discussion of the evidence on effectiveness and value
  - **Goal**: Accelerate the transition to a sustainable health care system in which all patients are guaranteed access to innovative, high-value care

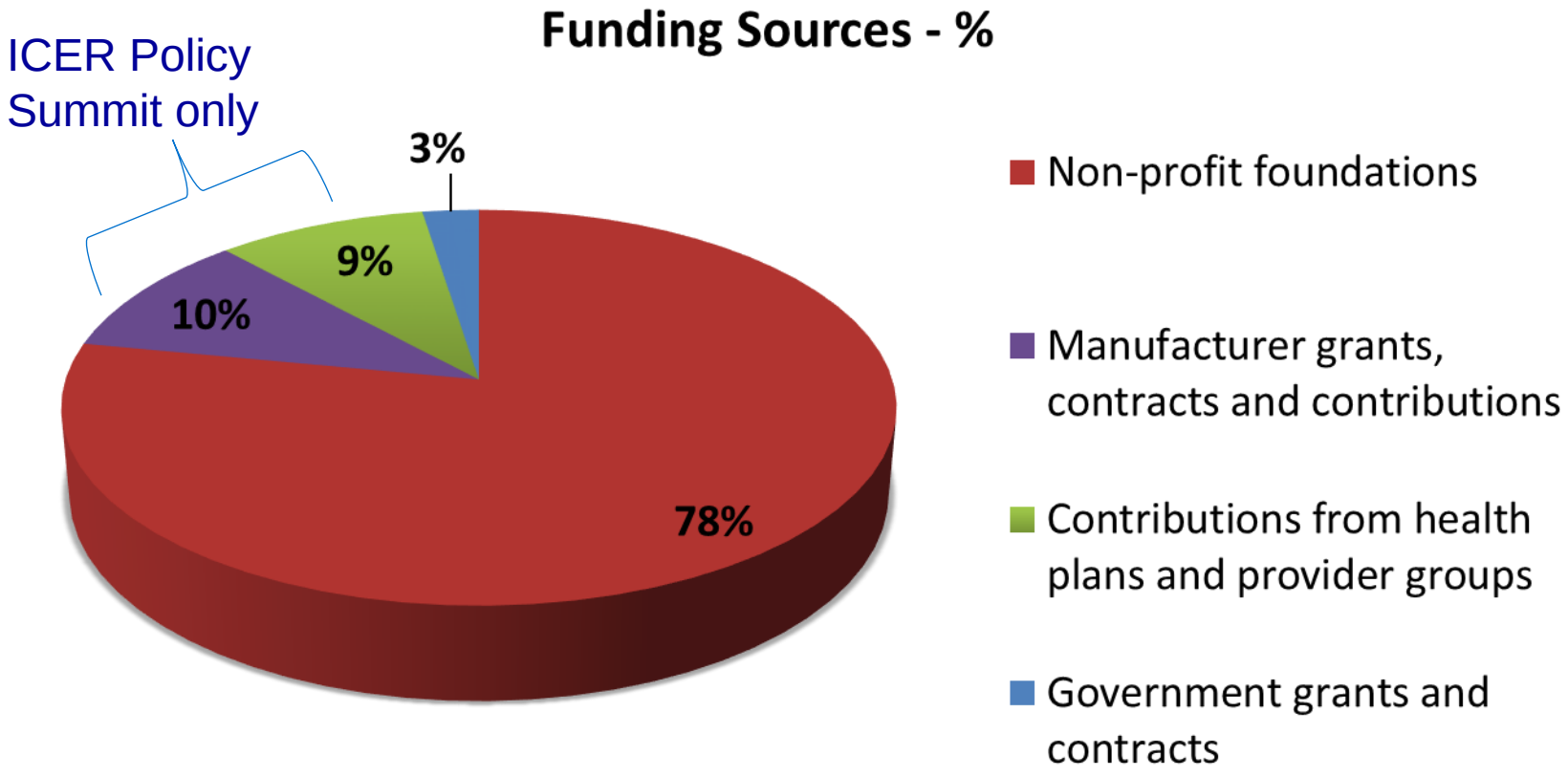
Welcome and Introduction

- New England Comparative Effectiveness Public Advisory Council (CEPAC)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2018

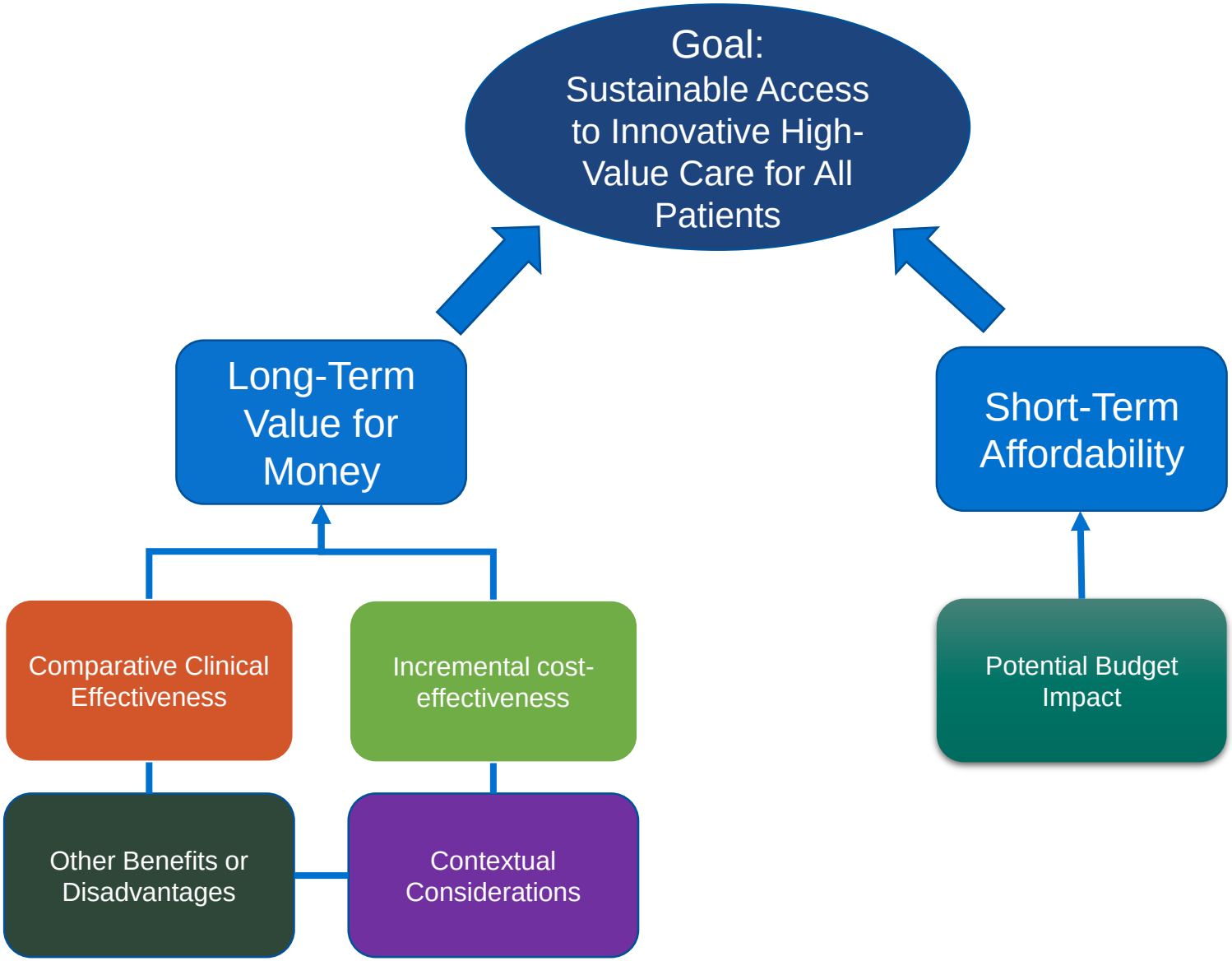
ICER Policy Summit only



Welcome and Introduction

How was the ICER report on emicizumab for treating patients with inhibitors developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Expert report reviewers
  - Margaret V. Ragni, MD, MPH
  - Steven Pipe, MD
  - Mark Skinner, JD
- How is the evidence report structured to support CEPAC voting and policy discussion?


Goal:
Sustainable Access to Innovative High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Agenda

10:00am: Welcome and Opening Remarks

10:15 am: Presentation of the Evidence

Evidence Review: David Rind, MD, MSc

Cost Effectiveness: Gregory Guzauskas, MSPH, PhD
Lotte Steuten, MSc, PhD, University of Washington

11:15 am: Manufacturer Public Comment and Discussion

11:45 am: Public Comments and Discussion

12:15 pm: Lunch

1:00 pm: CEPAC Deliberation and Votes

2:00 pm: Policy Roundtable

3:30 pm: Reflections and Wrap Up

4:00 pm: Meeting Adjourned

Evidence Review

David Rind, MD

Chief Medical Officer

ICER

INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

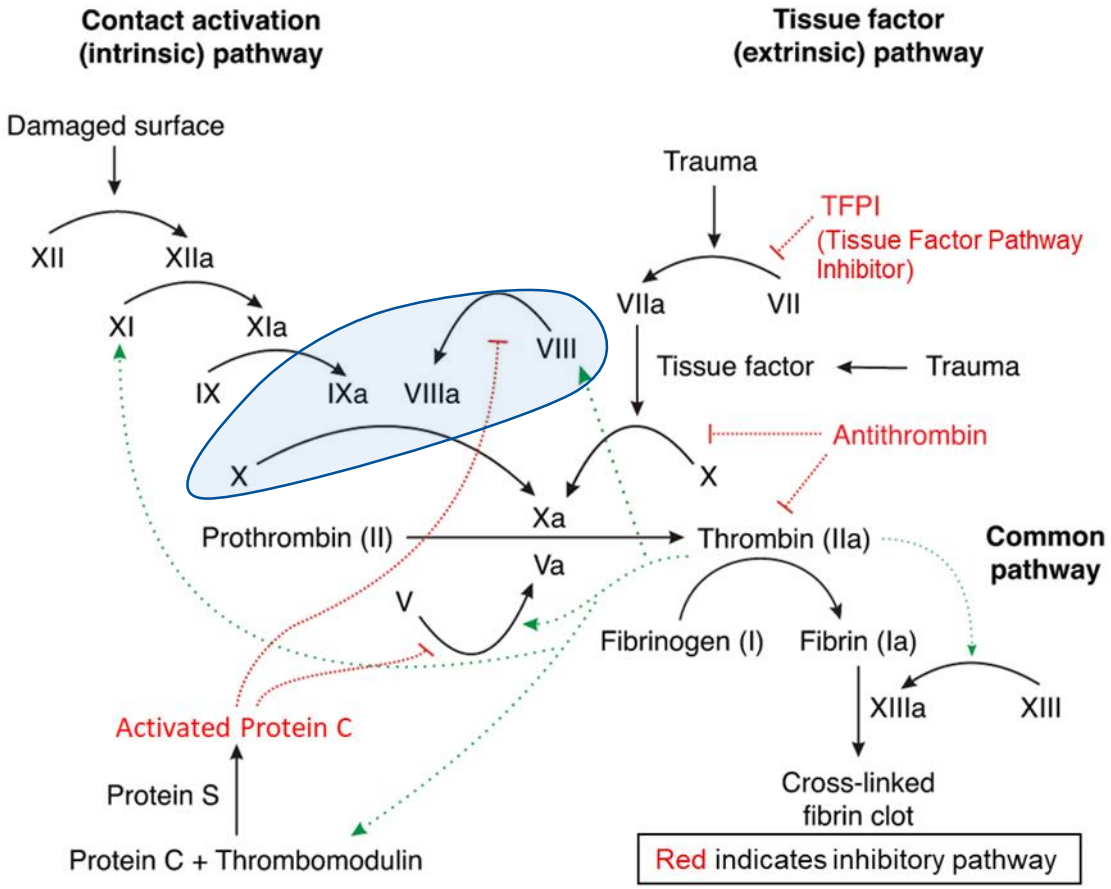
Key review team members:

- Foluso Agboola, MBBS, MPH
- Alexandra Ellis, MSc, AM
- Aqsa Mugal, BA

Disclosures:

We have no conflicts of interest relevant to this report.

Topic in Context



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Hemophilia A

- Deficiency in factor VIII
- Increased tendency to bleed
- X-linked recessive (1/5000 male births)
- Risk for life-threatening bleeding
- Bleeds into joints and muscles
- Joint bleeds lead to further bleeding and progressive joint damage

Prophylaxis

- Factor VIII for home treatment of bleeds became available in the 1970s
- Use of factor VIII infusions for prophylaxis became routine in severe hemophilia A by the early-to-mid 2000s
- Randomized trials demonstrated efficacy by the mid-to-late 2000s

Factor VIII Inhibitors

- Occur in about one-quarter of patients with severe hemophilia A who receive FVIII
- Develop early on (before 10 or 20 doses)
- Can often be eradicated with immune tolerance induction (ITI)
- People with high levels of inhibitors can’t use FVIII for bleeding or prophylaxis

Bypassing Agents

- “Bypass” the gap in the clotting cascade
  - Activated prothrombin complex concentrate (aPCC; FEIBA™, Shire)
  - Recombinant activated factor VII (rFVIIa; NovoSeven®, NovoNordisk)
- Used both to treat acute bleeding and for prophylaxis (FDA indication only for aPCC)

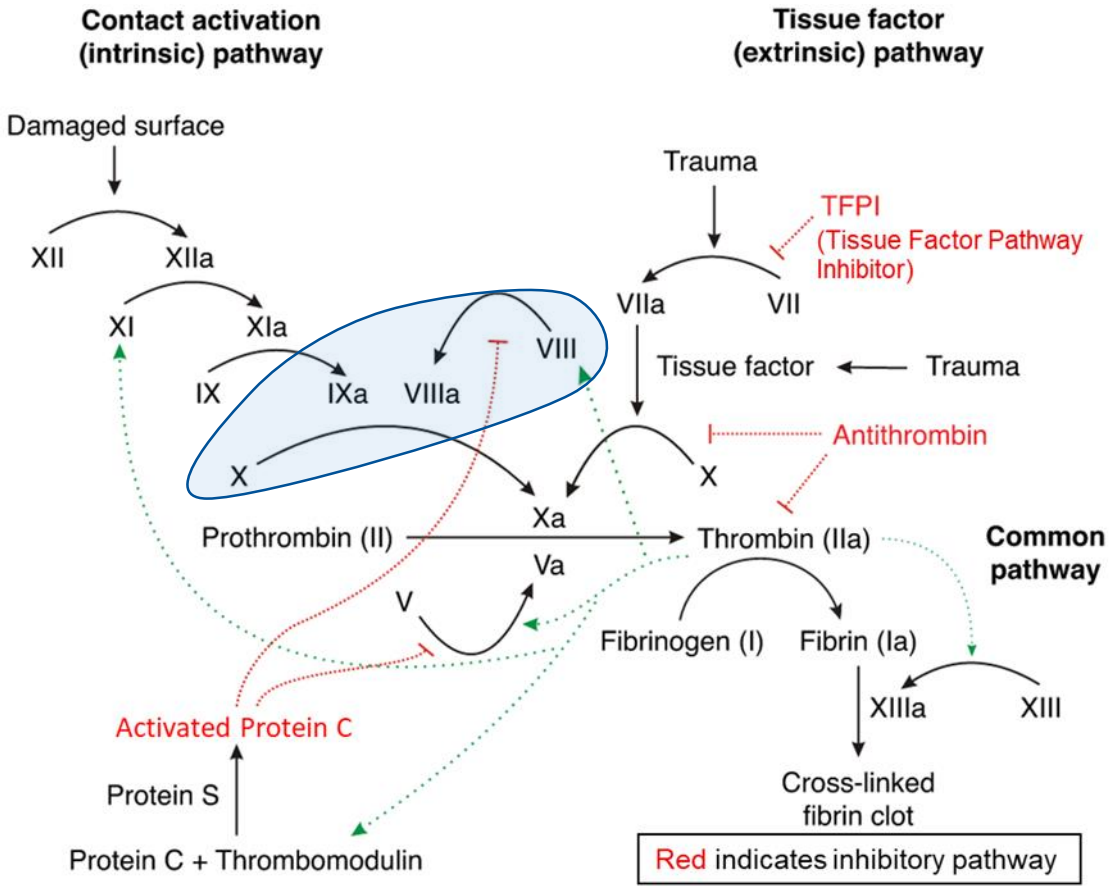
Prophylaxis

- Burdensome
  - Factors are administered intravenously
  - Must be given frequently
    - Multiple times per week
    - Even more frequent with BPAs
  - Venous access can be difficult in young children
  - Elderly patients and those who develop arthropathy may find self-administration difficult
  - Adherence is a substantial problem

Potential Patient and Caregiver Restrictions

	Bleeding Risk	Near Specialized Care	Accessibility of Factor	Flexible Time
Caregiver Career		✕		✕
Patient Career	✕	✕	✕	✕
Education		✕	✕	✕
Location of Residence		✕	✕	
Recreation	✕	✕	✕	

Topic in Context



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Emicizumab (Hemlibra®, Genentech)

- Bispecific antibody bridging aFIX and FX
- Weekly subcutaneous injection
- Used only for prophylaxis

Scope of the Review

- **Population**: Adults and children with hemophilia A with inhibitors who will not be treated with ITI or for whom ITI has been unsuccessful
- **Intervention**: Prophylaxis with emicizumab
- **Comparators**: No prophylaxis; prophylaxis with bypassing agents

(Note, all patients get bypassing agents for acute bleeding)

Two Trials of Emicizumab

HAVEN 1 trial

- Ages 12 to 75
- Open label trial/study
- Randomized (2:1) comparison between emicizumab and no prophylaxis in patients with no prior prophylaxis
  - N = 53 (35:18)
- Emicizumab in patients with prior BPA prophylaxis
  - N = 49

HAVEN 2 trial

- Age less than 12 (up to 17 if < 40 kg)
- Ongoing single-arm study (N = 23, 57)
- Patients required prior treatment with BPAs

What did the trials show?

Outcome	Comparator ABR (average # bleeds/year)	Intervention ABR (average # bleeds/year)	RR
RCT: HAVEN 1	*No prophylaxis*	*Emicizumab*	
Treated Bleeds	23.3	2.9	0.13
All Bleeds	28.3	5.5	0.20
BPAs vs. Emicizumab			
Observational: HAVEN 1	*BPAs*	*Emicizumab*	
Treated Bleeds (24 weeks)	15.7	3.3	0.21
Treated Bleeds (55 Weeks)	15.7	2.1	0.13
Observational: HAVEN 2	*BPAs*	*Emicizumab*	
Treated bleeds	17.2	0.2	0.01

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Children with no bleeds (HAVEN 2)

	Number of Patients with Zero Bleeds (%)
Number of Patients Included in Analysis	57
Treated Bleeds	54 (94.7)
All Bleeds (Treated + Untreated)	37 (64.9)
Treated Spontaneous Bleeds	56 (98.2)
Treated Joint Bleeds	56 (98.2)
Treated Target Joint Bleeds	57 (100)

Comparing with BPAs

- Likely to be adherence issues prior to the new intervention in the HAVEN trials
  - Thus, pre-post analysis likely biased
- Prior RCTs
  - Bleeding outcomes not perfectly comparable
  - Of three trials of BPAs, best risk reduction was in the PROOF trial:
    - RR (of medians) vs. no prophylaxis: 0.28

Quality of Life

- Emicizumab improved QOL compared with no prophylaxis (HAVEN 1) or baseline (HAVEN 2)
- Emicizumab improved caregiver burden and appeared to improve attendance at day care, school, or work
- In three trials, BPAs did not result in statistically significant improvement in QOL

Harms with emicizumab

- Injection site reactions (15-17%)
- HAVEN 1 events:
  - Thrombotic microangiopathy (3 patients)
  - Cavernous sinus thrombosis (1 patient)
  - Skin necrosis and superficial thrombophlebitis (1 patient)
  - Occurred with high doses of aPCC
- Boxed warning on label
- No similar events seen in HAVEN 2

Controversies and Uncertainties

- Lack of long term safety data
- Safety in clinical settings that affect or require coagulation
- Observational data comparing with BPAs
- No data on reduced joint damage or reduced mortality

Other Benefits and Contextual Considerations

- Enhanced career and education choices
- Reduced burden of therapy (patient and caregiver)
- Past iatrogenic harm to this group of patients

Public Comments Received

- Should have compared to BPAs based on HAVEN 1 intra-patient comparison
- Long-term safety of emicizumab not known relative to aPCC
- Inadequate comparative evidence for aPCC
- No high quality evidence that aPCC and rFVIIa equivalent for prophylaxis

Summary

- Some concerns about safety remain
- Efficacy is much greater than no prophylaxis
- Efficacy appears to be much greater than BPA prophylaxis and much less burdensome
- Emicizumab vs. no prophylaxis:
  - 12 and older: “A”
  - Under 12: “B+”
- Emicizumab vs. BPAs:
  - 12 and older: “B+”
  - Under 12: “B+”

Cost-Effectiveness

Greg Guzauskas, MSPH, PhD

Lotte Steuten, MSc, PhD

University of Washington

Department of Pharmacy

Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute

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Disclosures:

We have no conflicts of interest relevant to this report.

Objective

To estimate the cost-effectiveness of emicizumab as prophylactic therapy for hemophilia A patients with inhibitors to factor VIII, using a decision analytic model

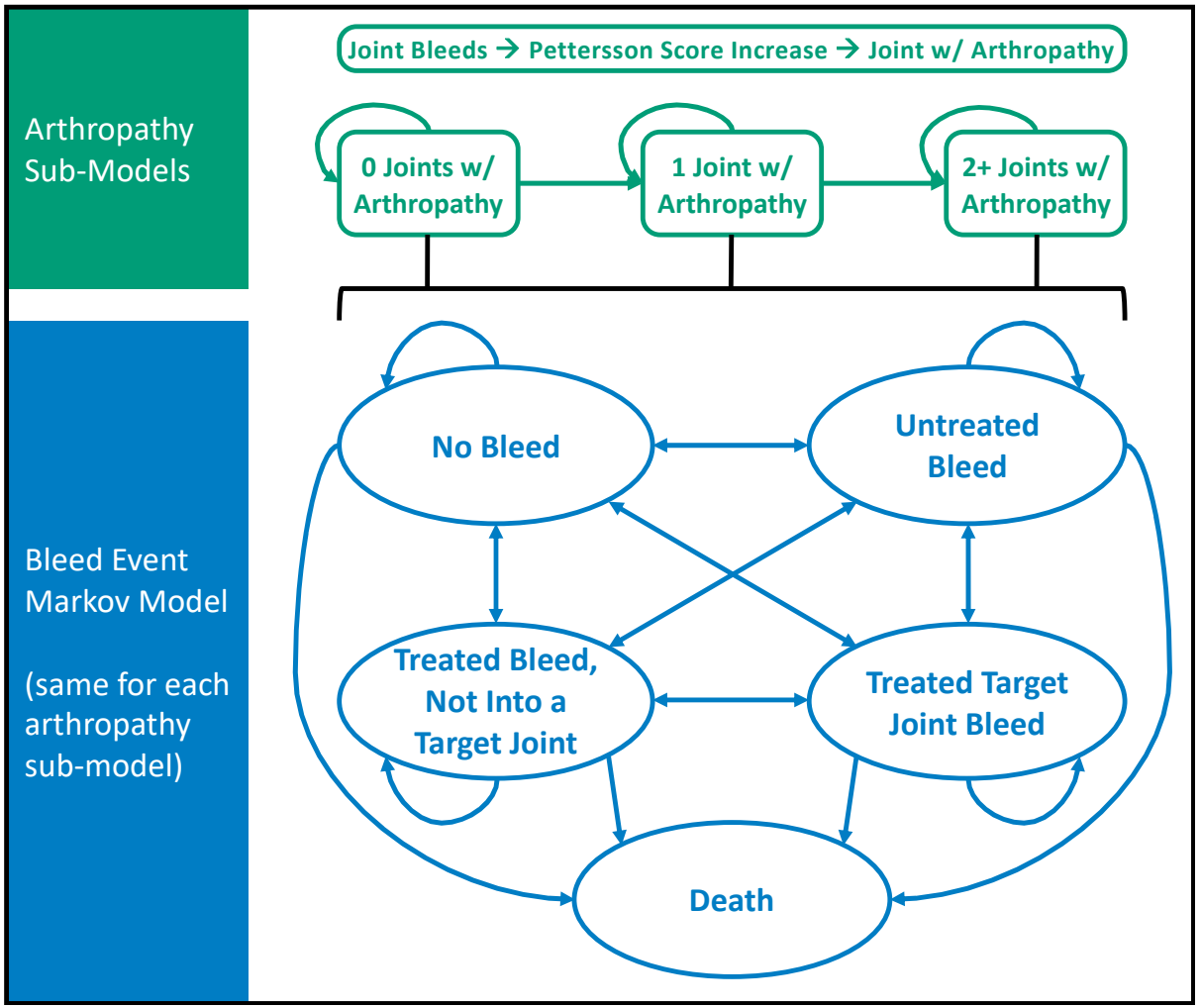
Methods in Brief

Methods Overview

- **Comparators**: Emicizumab, BPA prophylaxis, No prophylaxis
- **Populations**: Children <12 years, adults ≥12 years
- **Model**: Markov model
- **Setting**: United States
- **Perspective**: Payer
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: Weekly

- **Primary Outcomes:**
  - Lifetime cost
  - Quality adjusted life-years gained
  - Bleed events
  - Incremental cost-effectiveness ratios
    - (cost per quality-adjusted life year gained)

Model Schematic

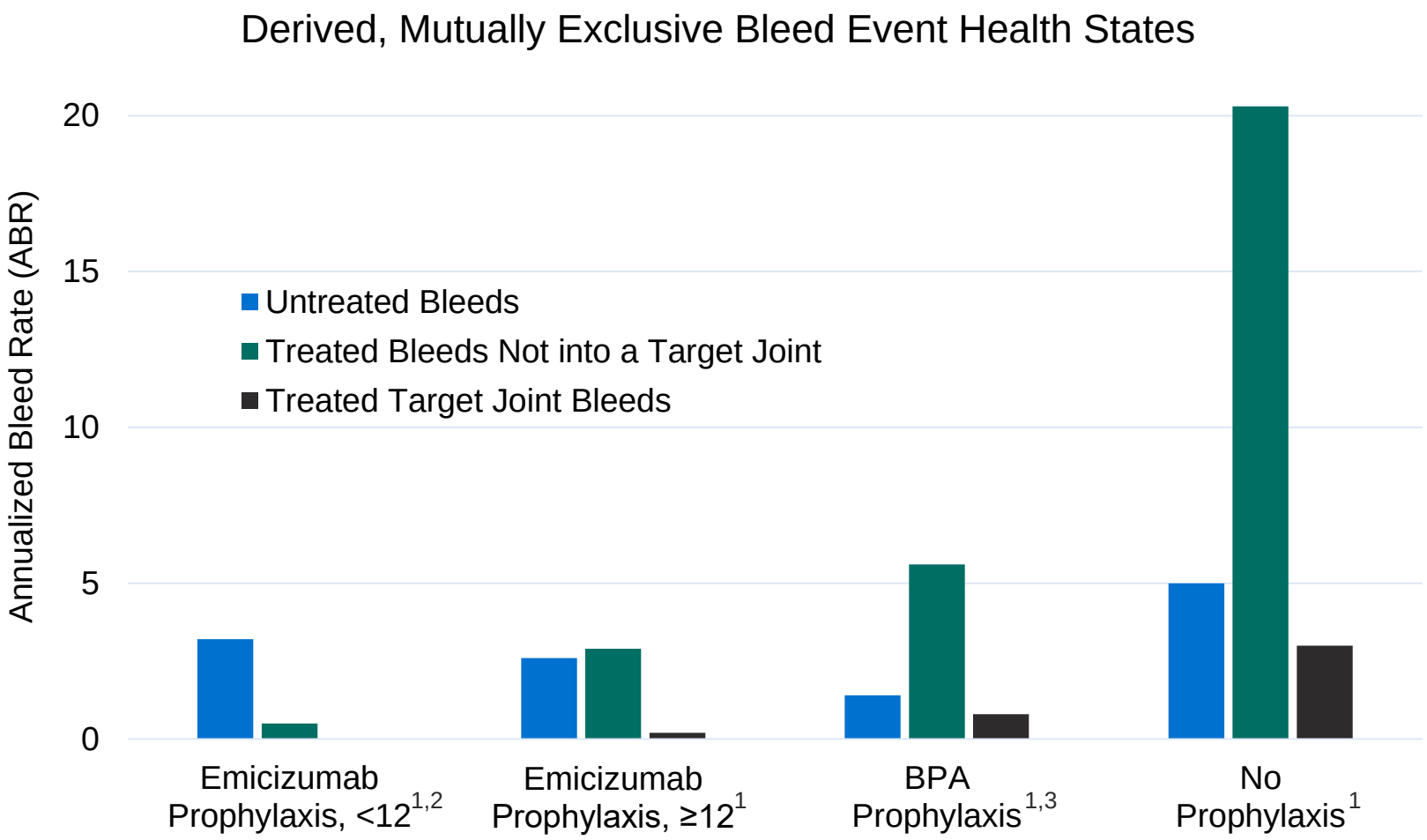


Key Model Assumptions

- Bleed event rates are equivalent regardless of arthropathy severity.
- Bleed rates transition from HAVEN 2 to HAVEN 1 estimates once patient turns 12.
- Two-day bleed disutilities, followed by an average of bleed and no bleed utility for remaining 5 days of each weekly cycle.
- Treatment adherence was assumed to be 100% for emicizumab prophylaxis and 88% for BPA prophylaxis.[1]
- No mortality difference among comparators.

1. Antunes SV, et al. Haemophilia. 2014;20(1):65-72.

Primary Clinical Inputs



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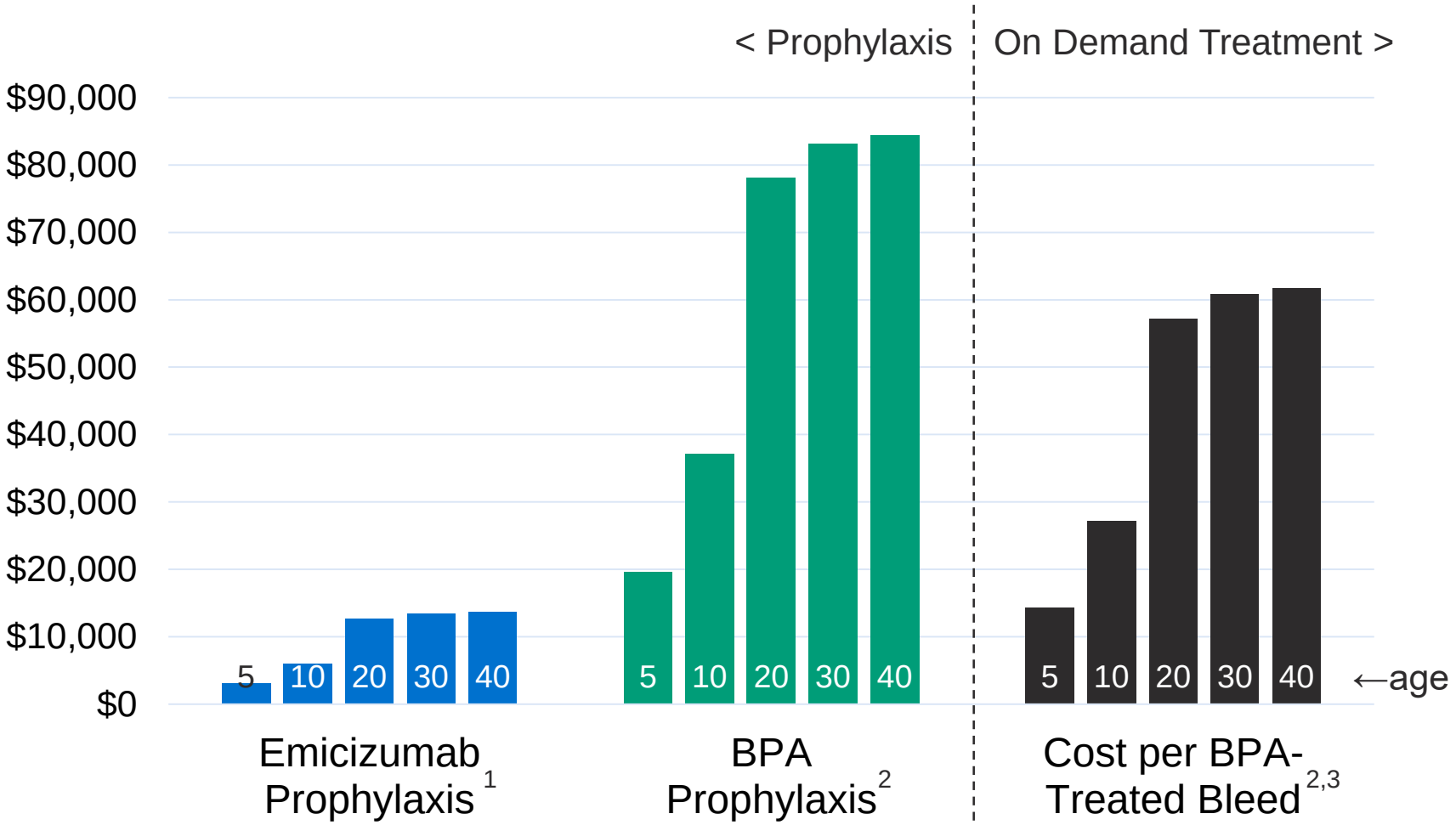
Modeled Weekly Drug Costs at Various Ages



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1. Red Book Online® Search. Truven Health Analytics; 2017.
2. Medicare Part B Drug Average Sales Price. 2017.
3. Derived from on demand treatment results of the HAVEN 1 trial.

Health State Utilities

Parameter	Value
Utility: hemophilia A with inhibitors, no bleed[1]	0.82
Utility: hemophilia A with inhibitors, treated bleed not into a target joint[1]	0.66
Utility: hemophilia A with inhibitors, target joint bleed[2]	0.54
Utility: arthropathy by Pettersson Score (PS)[3]	
• PS 0-4	0.82
• PS 4-12	0.81
• PS 13-21	0.77
• PS 22-39	0.74
• PS 40-78	0.72
Disutility: orthopedic surgery[4]	-0.39

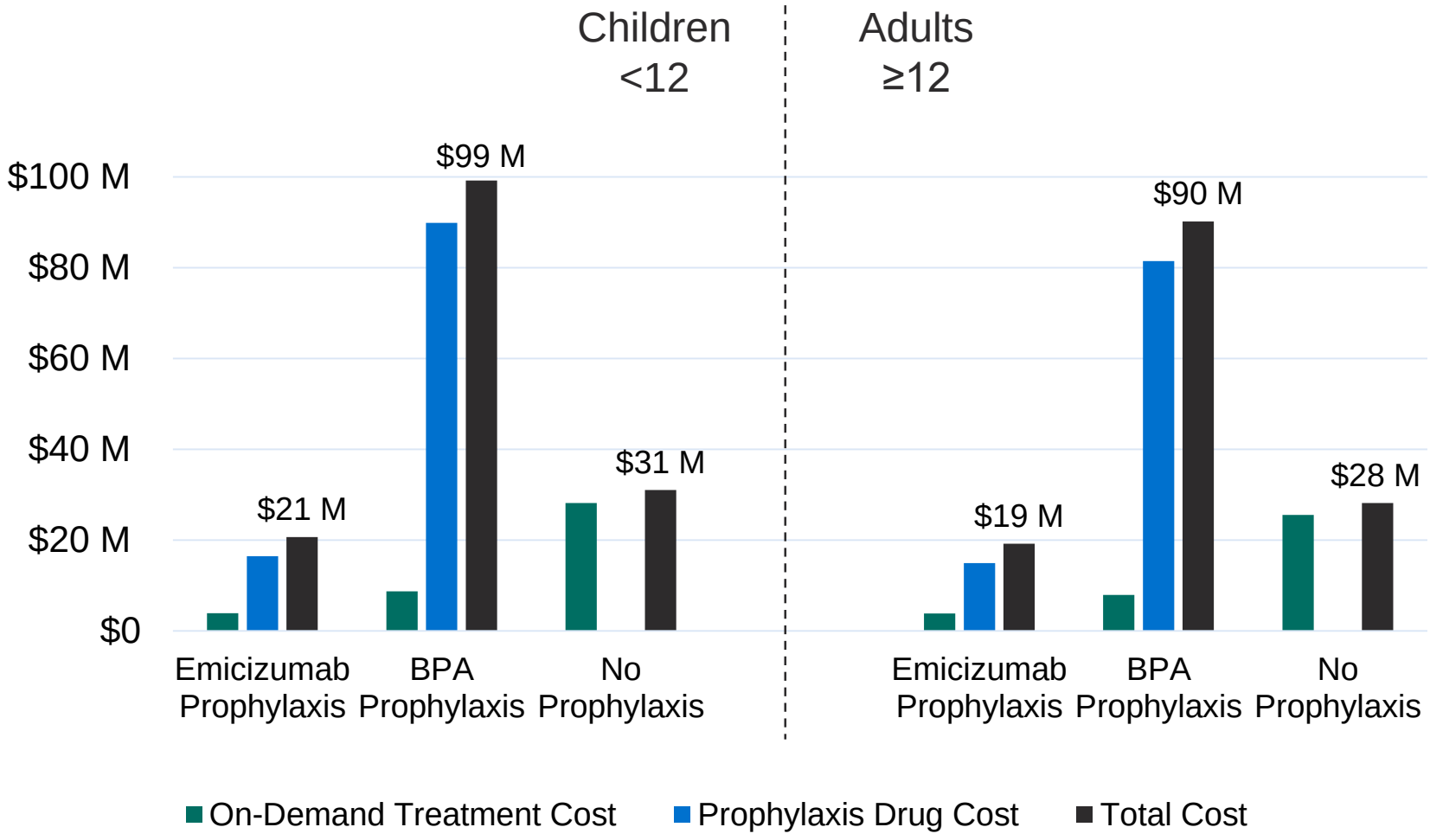
1. Neufeld EJ, et al. Value In Health. 2012;15(6):916-925.
2. Mazza G, et al. Value In Health. 2016;19(7):A593.
3. Fischer K, et al. Haemophilia. 2016;22(6):833-840.
4. Ballal RD, et al. Current Medical Research And Opinion. 2008;24(3):753-768.

Results

Lifetime Health Outcomes

Treatment	Total Bleed Events	QALYs	Life Years
Children <12 Years of Age			
Emicizumab Prophylaxis	176	22.8	28.1
BPA Prophylaxis	392	22.4	
No Prophylaxis	1267	20.4	
Adults ≥12 Years of Age			
Emicizumab Prophylaxis	107	15.4	21.3
BPA Prophylaxis	221	15.2	
No Prophylaxis	713	14.5	

Lifetime Costs



Overall Incremental Results

Comparison	Incremental Bleeds	Incremental QALYs	Incremental Cost	ICER*
Children <12 Years of Age				
Emicizumab vs. No Prophylaxis	-1091	2.4	-$10 M	Dominant
Emicizumab vs. BPA Prophylaxis	-217	0.4	-$79 M	Dominant
Adults ≥12 Years of Age				
Emicizumab vs. No Prophylaxis	-606	0.9	-$9 M	Dominant
Emicizumab vs. BPA Prophylaxis	-114	0.2	-$71 M	Dominant

*incremental cost-effectiveness ratio = incremental cost / incremental QALYs

Probabilistic Sensitivity Analysis

	Proportion of Simulations That Were…	
	Dominant	Cost-Effective
Children <12 Years of Age		
vs. BPA Prophylaxis	81%	100%
vs. No Prophylaxis	86%	~93%
Adults ≥12 Years of Age		
vs. BPA Prophylaxis	97%	100%
vs. No Prophylaxis	91%	~96%

Scenario Analyses

Emicizumab prophylaxis was cost-saving in all scenario analyses:

- Varied age at model entry
- Reduced mortality resulting from lower ABR
- Increased bleed rates in patients with arthropathy
- Varied proportion of patients able to use aPCC on demand when treated with emicizumab
- Explored whether childhood ABR (from HAVEN 2) persists into adulthood

BPA-Favoring Scenario

- **BPA prophylaxis comparator:**
  - Prophylaxis and on demand treatment with lower cost aPCC only.
- **Emicizumab comparator:**
  - On demand treatment for bleeds with more costly rFVIIa only.
  - Bleed event rates equivalent to all bleeds from HAVEN 1 (adults) and HAVEN 2 (children).
- **As in base case:**
  - Lifetime emicizumab adherence was 100% and lifetime BPA prophylaxis adherence was 88% (applied to drug cost only).
  - Used same rate of adverse thrombotic events in patients getting emicizumab even though they were no longer receiving aPCC for acute bleeds.
- Reduced the disutility of bleed events.

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- Reduced the disutility of bleed events.

Result: Emicizumab still dominant versus BPA prophylaxis

Limitations

- Modeled lifetime outcomes derived from short-term trial outcomes.
- Lack of long-term data on the development of arthropathy by treatment strategy.
- Prophylaxis adherence is based on clinical trial data, which is likely higher than real world adherence.

Comments Received

- Consistent sources for drug price must be used to ensure fair and balanced comparisons.

- Evaluation should compare emicizumab to aPCC and rFVIIa as separate BPA comparator arms rather than combining them together as a single BPA arm.

Summary

- Lower cost, more effective: Emicizumab is a dominant treatment strategy compared to no prophylaxis and BPA prophylaxis.

- Results were robust to all sensitivity and scenario analysis variation.

- Our findings are primarily driven by a reduction in lifetime bleed events and their associated costs.

Backup Slides

Overall Approach

- Developed a *de novo* decision model based on HAVEN 1&2 and other published sources

- The model considers two age groups:
  - patients <12 years old (based on HAVEN 2, modeled age = **7 years**)
  - patients ≥12 years old (based on HAVEN 1, modeled age = **37 years**)

- The model compares emicizumab to:
  1. prophylaxis with bypassing agents (BPAs)
     - recombinant FVIIa (NovoSeven®; Novo Nordisk)
     - activated prothrombin complex concentrate (aPCC [FEIBA®; Shire])
  2. no prophylaxis

- For all 3 comparators, patients may be treated with BPAs when they bleed.

Parameters: Drug Regimen & Costs

	Emicizumab	rFVIIa	aPCC
Prophylaxis Dosing	3.0 mg/kg weekly 4 weeks, then 1.5 mg/kg weekly	90 mcg/kg daily	85 units/kg every other day
Bleed Event On Demand Dosing	N/A	90 mcg/kg every 2-6 hours	50-100 units/kg every 6-12 hours
Cost Unit	1.5 mg	1 mcg	1 IU
WAC per Unit[1]	$148.80	$2.16	$2.16
ASP per Unit[2]	N/A	$2.00	$1.94
ASP Discount from WAC	N/A	7%	10%

ASP: average sales price, WAC: wholesale acquisition cost
WAC as of November 6th, 2017

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1. Red Book Online® Search. Truven Health Analytics; 2017.
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Other Healthcare Utilization Costs

	Emicizumab and BPA Prophylaxis	No Prophylaxis
Per-bleed non-pharmacy costs (weekly)[1]		
Age 6-18 years	$747	$3,081
Age 19-44 years	$4,490	$4,490
Age > 45 years	$6,689	$6,689
Arthropathy surgery cost[2]	$45,286	

1. Shrestha A, et al. Haemophilia. 2017;23(4):E267-E275.
2. Earnshaw S, et al. Haemophilia. 2015;21(3):310-319.

Arthropathy Modeling

- Starting distribution of prevalent arthropathy joints based on HAVEN 1&2.[1,2] For 0, 1, and 2+ "Joint with Arthropathy" sub-models:
  - 30%/21%/49% for adults, 75%/10%/15% for children.

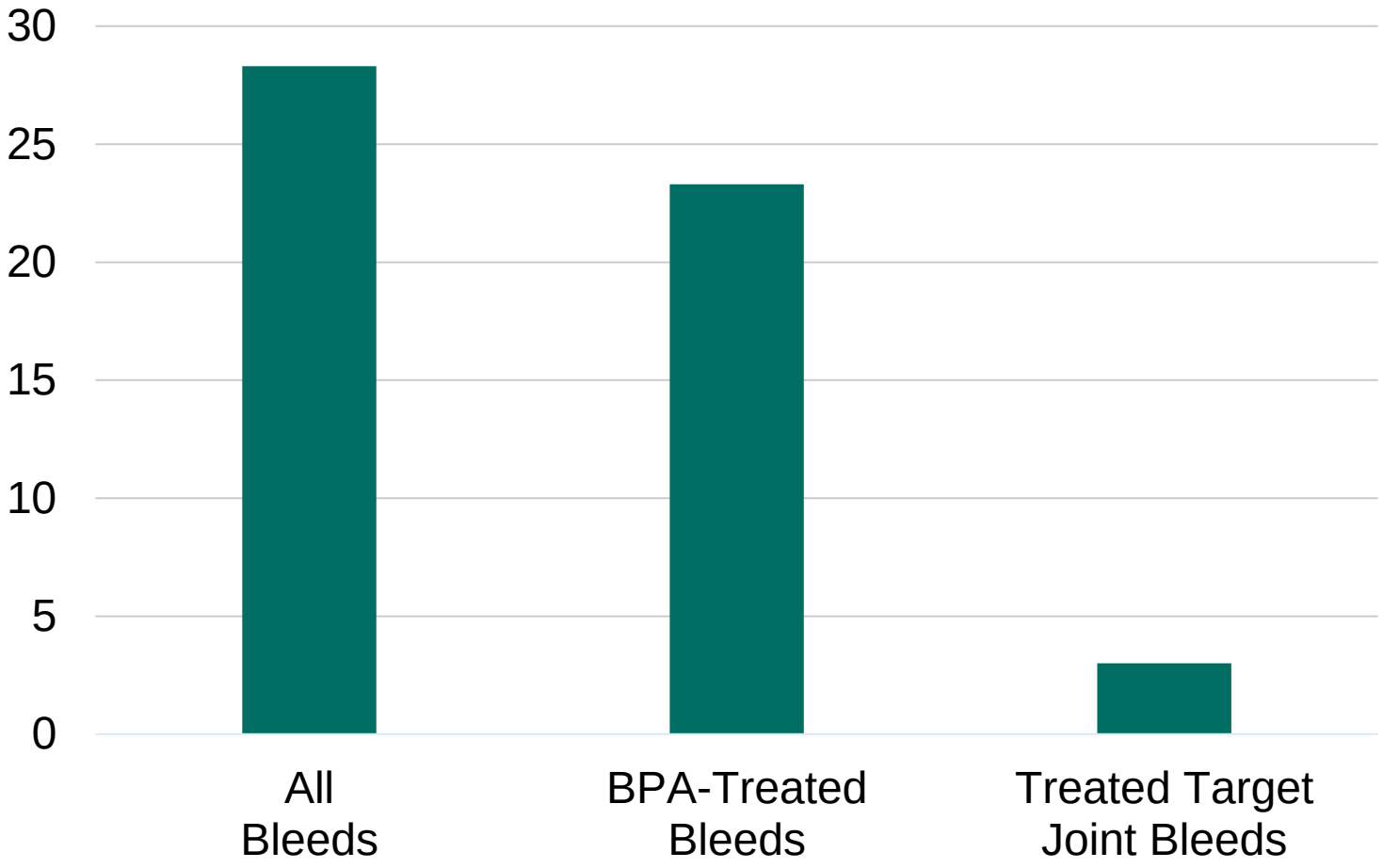
- New arthropathy development and joint replacement surgery are driven by increases in the Pettersson Score (PS), a validated radiological scoring system assessing the sum per patient of the total osteochondral changes in knees, elbows and ankles.[3]
  - A one point increase in the Pettersson score per 12.6 joint bleeds, on average (95% CI: 11.1 –14.7).[4]

- PS threshold for clinically-relevant damage requiring surgery = 28.[5]

1. Oldenburg J, et al. New England Journal of Medicine. 2017;377(9):809-818.
2. Young G, et al. HAVEN 2 Updated Analysis. American Society Of Hematology. 2017.
3. Pettersson H, et al. Acta Paediatrica Scandinavica. 1981;70(4):565-570.
4. Fischer K, et al. Acta Radiologica. 2002;43(5):528-532.
5. Earnshaw S, et al. Haemophilia. 2015;21(3):310-319.

Deriving Mutually Exclusive Bleed Health States for Markov Model

HAVEN 1 Annualized Bleed Rates (ABR): **No Prophylaxis**[1]



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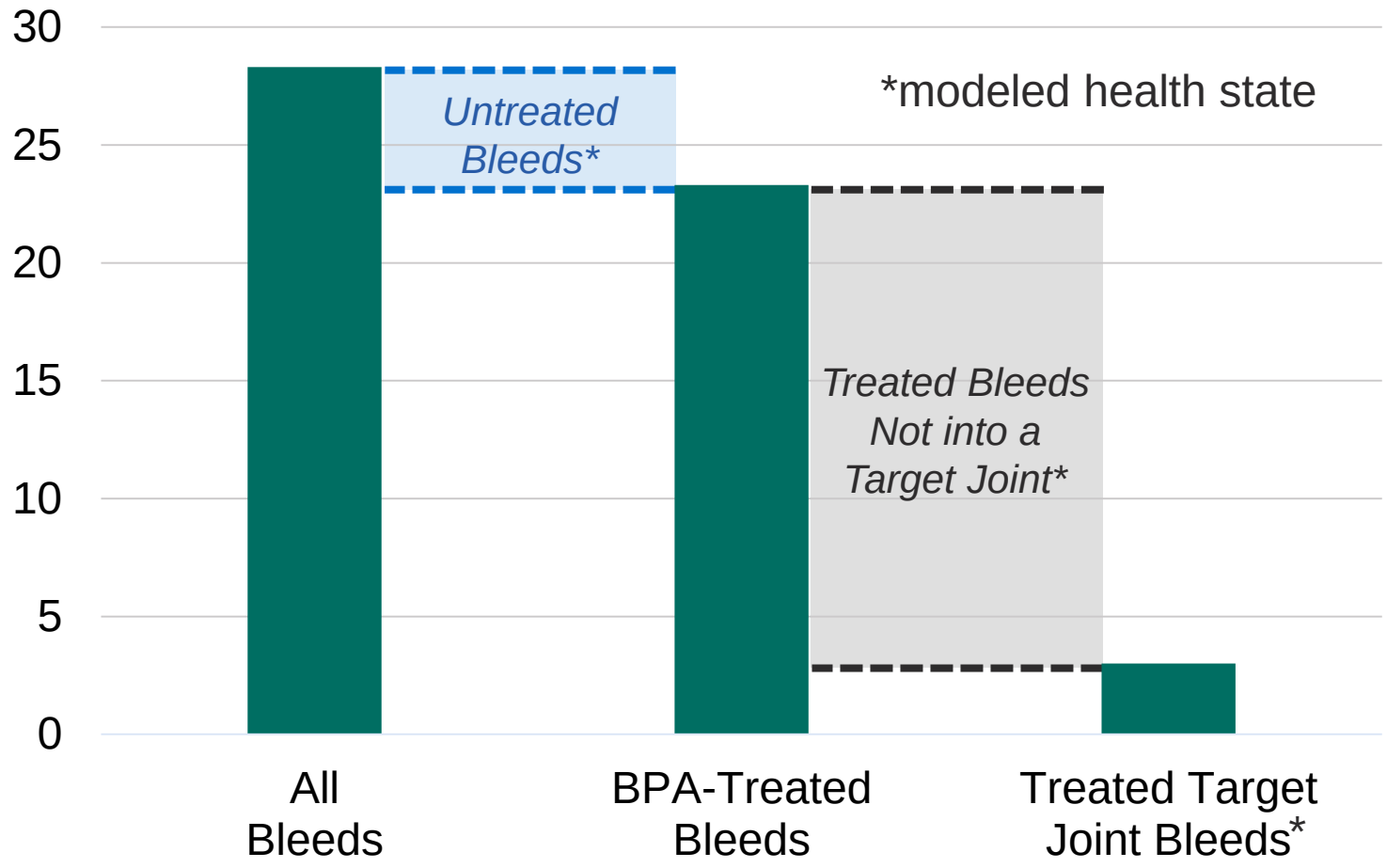

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Manufacturer Public Comment and Discussion

Speakers

Name	Title	Company
Susan Begelman, MD	Vice President Rare Disease and Neuroscience Medical Unit - US Medical Affairs	Genentech
Kathleen Gondek, PhD	Global Head of Outcomes Research and Epidemiology	Shire

Public Comment and Discussion

Johanna Gray,
Federal Policy Advisor; National Hemophilia Federation (NHF)
Senior Vice President; CRD Associates

Conflicts of interest:

- Employee of NHF, NHF receives funding from individuals, philanthropic foundations, drug/biotech manufacturers, specialty pharmacies
  - Including Shire, Novo Nordisk, Genentech

Miriam Goldstein
Associate Director, Policy
Hemophilia Federation of America (HFA)

Conflicts of interest:

- Employee of HFA, HFA receives funding from individuals, philanthropic foundations, drug/biotech manufacturers, specialty pharmacies
  - Including Shire, Novo Nordisk, Genentech, Alnylam

- Ms. Goldstein is the mother of two adult sons with hemophilia.

Lunch

Meeting will resume at 1:00 pm

Voting Questions

WIFI: Marriott_CONF
Password: NECEPAC

Kendall Square in Cambridge was almost named headquarters to which of the following major American institutions, creating its reputation as a technology hub?

A. Bell Telephone Company in 1883
B. IBM in 1924
C. NASA in 1963
D. AOL in 1983

Patient population for all questions

Patients with hemophilia A with inhibitors to factor VIII who will not be treated with immune tolerance induction (ITI) or for whom ITI has been unsuccessful. When necessary, age ranges are specified in voting questions.

1a. For patients under 12 years of age: Is the evidence adequate to demonstrate that prophylactic emicizumab provides a net health benefit compared with no prophylactic therapy?

A. Yes

B. No

1b. For patients 12 years of age and older: Is the evidence adequate to demonstrate that prophylactic emicizumab provides a net health benefit compared with no prophylactic therapy?

A. Yes

B. No

2a. For patients under 12 years of age: Is the evidence adequate to demonstrate that prophylactic emicizumab provides net health benefits compared with prophylactic therapy with bypassing agents (BPAs)?

A. Yes

B. No

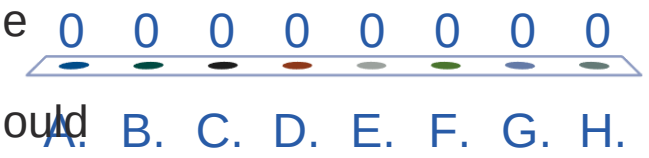
2b. For patients 12 years of age and older: Is the evidence adequate to demonstrate that prophylactic emicizumab provides net health benefits compared with prophylactic therapy with bypassing agents (BPAs)?

A. Yes

B. No

3. When compared to prophylactic therapy with BPAs, does emicizumab offer one or more of the following “other benefits”? (select all that apply)

A. Offers reduced complexity that will significantly improve patient outcomes.
B. Reduces important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.
C. Significantly reduces caregiver or broader family burden.
D. Offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
E. Has a significant impact on improving patients’ ability to return to work and/or their overall productivity.
F. Has a significant positive impact outside the family, including on schools and/or communities.
G. Has a significant impact on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
H. Includes other important benefits or disadvantages that should have an important role in judgments of the value of this intervention: _____



4. Are any of the following contextual consideration important in assessing emicizumab's long-term value for money? (select all that apply)

A. Intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.

B. Intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

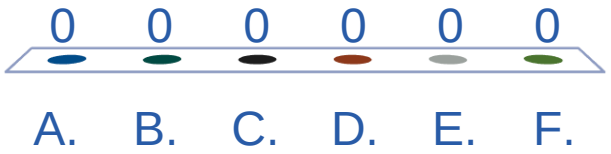
C. First intervention to offer any improvement for patients with this condition.

D. Compared to prophylactic therapy with BPAs, there is significant uncertainty about the long-term risk of serious side effects of this intervention.

E. Compared to prophylactic therapy with BPAs, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.

F. There are additional contextual considerations that should have an important role in judgments of the value of this intervention:

_____.



Policy Roundtable

Policy Roundtable Participants

Policy Roundtable	
Susan Begelman, MD Vice President, US Medical Affairs Genentech	**Stephen Pipe, MD** Professor of Pediatrics and Communicable Diseases, Professor of Pathology, University of Michigan
Kathleen Gondek, PHD Global Head of Outcomes Research and Epidemiology, Shire	**Margaret V. Ragni, MD, MPH** Professor of Medicine, Division of Hematology/Oncology, University of Pittsburgh; Director, Hemophilia Center of Western PA
Tom Kowalski, RPH Clinical Pharmacy Director, Blue Cross Blue Shield Massachusetts	**Mark W. Skinner, JD** President and CEO, Institute for Policy Advancement; President, World Federation of Hemophilia USA
Herman Kranc, RPH Manager-Integrated Care Connecticut Department of Social Services	**Sonji Wilkes, BA** Associate Director of Advocacy, Hemophilia Federation of America

CEPAC Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on/about April 20
  - Includes description of CEPAC votes, deliberation; policy roundtable discussion
- Materials available at:

  https://icer-review.org/topic/hemophilia-a/

Adjourn