SYLLABUS AND COURSE GUIDE

One Size Does Not Fit All: Using Population Pharmacokinetics for Tailored Hemophilia Care

A Free, 90-Minute CME/CNE/CPE/MIPS/ABIM MOC Live and On-Demand Activity **Premiere Date: Tuesday, March 3, 2020** 12:00 PM - 1:30 PM ET (live)

Credit Expiration Date: Wednesday, March 3, 2021

On the Web: http://bit.ly/TV-108

LIVE FACULTY: Miguel A. Escobar, MD; Mark T. Reding, MD MODERATOR: Alfonso Iorio, MD, PhD, FRCP(C)

Take advantage of our LIVE Q&A segment during this webcast!

During the webcast **type a question in the box under the presentation Email** your question or comment: **questions@cmeoutfitters.com**

All other questions: Call CME Outfitters at 877.CME.PROS

This continuing education activity is provided by



INFORMATION FOR PARTICIPANTS

Statement of Need

In order to prevent and treat bleeding in patients with hemophilia A, the activity of the replaced clotting factor VIII must reach or exceed a target level over a period of time. Pharmacokinetic (PK) measures are therefore used to determine the dosing regimen of the different factor VIII replacement products. Recently, extended half-life recombinant factor VIII products with improved PK profiles have been approved and these reduce treatment burden and improve treatment adherence.

In this CME Outfitters live and on-demand webcast, renowned hematologists will discuss the clinical significance of the results of the head-to-head comparison study of PK profiles of extended half life factor VIII products including the application of population PK models and shared decision-making (SDM) to provide personalized hemophilia A therapy.

Learning Objectives

At the end of this CE activity, participants should be able to:

- Summarize the comparative PK data and the clinical significance of popPK studies on factor VIII replacement therapies.
- Apply popPK models to determine individualized dosing regiments for patients with hemophilia A.
- Integrate approaches for SDM to develop patient-centered, PK-based treatment plans for patients with hemophilia A.

The following learning objectives pertain only to those requesting CNE or CPE credit:

- Summarize the comparative PK data and the clinical significance of popPK studies on factor VIII replacement therapies.
- Explain popPK models that can determine individualized dosing regimens for patients with hemophilia A.
- Describe approaches for SDM to develop patient-centered, PK-based treatment plans for patients with hemophilia A.

Target Audience

Hematologists, physician assistants, nurse practitioners, nurses, and clinical pharmacists.

Financial Support

Supported by an educational grant from Bayer HealthCare Pharmaceuticals, Inc.

CREDIT INFORMATION

CME Credit (Physicians)

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Note to Nurse Practitioners: Nurse practitioners can apply for AMA PRA Category 1 Credit[™] through the American Academy of Nurse Practitioners (AANP). AANP will accept AMA PRA Category 1 Credit[™] from organizations accredited by the Accreditation Council for Continuing Medical Education. Nurse practitioners can also apply for credit through their state boards.

CPE Credit (Pharmacists)

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Universal Activity Number: Live: 0376-0000-20-002-L01-P; Enduring: 0376-0000-20-002-H01-P Type: knowledge-based

ABIM/MOC Credit:

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Learning Formats:

Live activity Enduring Material

Royal College MOC:

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

MIPS Improvement Activity:

This activity counts towards MIPS Improvement Activity requirements under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Clinicians should submit their improvement activities by attestation via the CMS Quality Payment Program website.

CREDIT REQUIREMENTS

Post-tests, credit request forms, and activity evaluations must be completed online (requires free account activation), and participants can print their certificate or statement of credit immediately (75% pass rate required). This website supports all browsers except Internet Explorer for Mac. For complete technical requirements and privacy policy, visit https://www.cmeoutfitters.com/privacy-and-confidentiality-policy.

There is no fee for participation in this activity. The estimated time for completion is 90 minutes. Questions? Please call 877.CME.PROS.

FACULTY BIOS & DISCLOSURES

Alfonso Iorio, MD, PhD, FRCP(C) (Moderator)

Department of Health Research Methods, Evidence and Impact, McMaster University, Canada

Prof. lorio is a Professor in the Department of Health Research Methods, Evidence, and Impact at McMaster University Canada, where he holds the McMaster – Bayer Endowed Research Chair in Clinical Epidemiology of Congenital Bleeding Disorders. He is the Director of the Health Information Research Unit (HiRU) and of the Hamilton-Niagara Hemophilia Program. He received his medical and PhD degrees from the University of Perugia, Italy.

He is the Principal Investigator of the Web Application for Population Pharmacokinetic in Hemophilia (WAPPS) project, co-investigator of the Patient Reported Outcomes, Burden, and Experiences (PROBE), and chair of the Canadian Bleeding Disorders Registry (CBDR). He is an associate editor for bleeding disorders of the Cochrane Collaboration, Thrombosis Research, and serves on the Editorial Boards of numerous journals including the *Journal of Thrombosis and Haemostasis*, and *Haemophilia*. Prof. Iorio's current interests include internet-based knowledge dissemination, systematic review and meta-analysis methodology, and risk prediction and stratification. He has published over 200 peer reviewed publications.

Miguel A. Escobar, MD

Dr. Escobar is Professor of Internal Medicine and Pediatrics, and Director of the Gulf States Hemophilia and Thrombophilia Center at the University of Texas Health Science Center and the McGovern Medical School in Houston, Texas. He is also the Director of the Clinical Research Center at the University and the Medication, Therapy and Wellness Center at the Memorial Hermann Hospital in Houston.

Dr. Escobar received his MD from the Universidad Libre in Cali, Colombia and completed his residency in Internal Medicine at the University of Connecticut and his fellowship in hematology/oncology at the University of North Carolina at Chapel Hill.

Dr. Escobar has been involved in many clinical studies, resulting in a range of publications and is a member of several professional organisations. His main research interests are in haemophilia, congenital and acquired inhibitors, and other coagulation deficiencies.

Mark T. Reding, MD

Dr. Reding is Director of the Center for Bleeding and Clotting Disorders at the University of Minnesota Medical Center and an Associate Professor of Medicine in the Division of Hematology, Oncology, and Transplantation at the University of Minnesota in Minneapolis, Minnesota. He is also an attending physician on the Inpatient Hematology Consult Service and the Outpatient Hematology Clinic.

Dr. Reding earned his medical degree at the University of Minnesota Medical School and completed an internal medicine residency at the University of Minnesota. He was a chief resident in internal medicine at the Minneapolis VA Medical Center and completed a hematology/ oncology fellowship at the University of Minnesota.

Dr. Reding is a recipient of the Outstanding Clinical Mentor Award from the Division of Hematology, Oncology, and Transplantation at the University of Minnesota; the Clinical Excellence Award from the Department of Medicine at the University of Minnesota, and the Clinical Instructor of the Year Award from the Department of Physician Assistant Studies at Augsburg University in Minneapolis.

In addition to clinical and teaching duties, Dr. Reding has laboratory research experience investigating the mechanisms of the immune response to factor VIII and has served as principle investigator of many clinical trials in hemophilia. He is a frequent lecturer both nationally and internationally.

Disclosure of Relevant Financial Relationships with Commercial Interests

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Dr. lorio reports that he receives research support from his institution, McMaster University through project-based funding via research or service agreements from Bayer Inc.; F. Hoffmann-La Roche Ltd; Novo Nordisk; Octapharma; Pfizer Inc.; and Takeda Pharmaceutical Company Limited.

Dr. Escobar reports his institution, The University of Texas, participates in research sponsored by American Thrombosis and Hemostasis Network (ATHN); Novo Nordisk; OPKO Biologics; Pfizer Inc; Sanofi; Takeda Pharmaceuticals U.S.A., Inc.; and UniQure. He serves on the advisory committee for Genentech, Inc./Roche; National Hemophilia Foundation (NHF); Novo Nordisk; Sanofi; Takeda Pharmaceuticals U.S.A., Inc.; and UniQure. He serves on the advisory committee for Genentech, Inc./Roche; National Hemophilia Foundation (NHF); Novo Nordisk; Sanofi; Takeda Pharmaceuticals U.S.A., Inc.; and UniQure. He serves on the advisory committee for Genentech, Inc.; Novo Nordisk; Pfizer Inc.; Takeda Pharmaceuticals U.S.A., Inc.; U.S. Food and Drug Administration. (FDA)

Dr. Reding reports he receives research support from Bayer Corporation and BioMarin. He serves on the advisory committee for Bayer Corporation; Genentech, Inc.; Novo Nordisk; Sanofi Genzyme and Takeda Pharmaceuticals U.S.A., Inc.

Howard Bliwise, MD (peer reviewer) has no disclosures to report.

Mae Ochoa, RPh (peer reviewer) has no disclosures to report.

Kavitha Ramachandran, PhD (planning committee) has no disclosures to report.

Evan Luberger (planning committee) has no disclosures to report.

Jan Perez (planning committee) has no disclosures to report.

Sharon Tordoff (planning committee) has no disclosures to report.

Disclosures were obtained from the CME Outfitters, LLC staff: No disclosures to report.

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Activity Slides

The slides that are presented in this activity will be available to download and print out at the CME Outfitters website: **www.cmeoutfitters.com**. Activity slides may also be obtained via fax or email by calling **877.CME.PROS**.



CME Outfitters, LLC, is the accredited provider for this continuing education activity.

CME Outfitters, LLC, gratefully acknowledges educational grants from Bayer HealthCare Pharmaceuticals, Inc. in support of this CME/CE activity. The course guide for this activity includes slides, disclosures of faculty financial relationships, and biographical profiles.

View and/or print the course guide from the *Materials* tab underneath the video box.

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Please be sure to indicate the media format utilized and the date of participation when completing the online evaluation.

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any use not approved by the FDA) of products or devices.



Alfonso Iorio, MD, PhD, FRCP(C)

Professor, Department of Health Research Methods, Evidence, and Impact (HEI), Bayer Endowed Chair for Clinical Epidemiology and Bleeding Disorders, McMaster University Hamilton, ON, Canada

Alfonso Iorio, MD, PhD, FRCP(C) Disclosures

• *Research/Grants:* Bayer Inc.; F. Hoffmann-La Roche Ltd; Novo Nordisk; Octapharma; Pfizer Inc.; and Takeda Pharmaceutical Company Limited.



Miguel A. Escobar, MD

Professor of Medicine and Pedatrics University of Texas Health Science Center at Houston-McGovern Medical School and University of Texas M.D. Anderson Cancer Center Medical Director, Gulf States Hemophilia & Thrombophilia Center Houston, TX

Miguel A. Escobar, MD

Disclosures

- Research/Grants: American Thrombosis and Hemostasis Network (ATHN); Novo Nordisk; OPKO Biologics; Pfizer Inc; Sanofi; Takeda Pharmaceuticals U.S.A., Inc.; UniQure
- Consultant: Genentech, Inc.; Novo Nordisk; Pfizer Inc.; Takeda Pharmaceuticals U.S.A., Inc.; U.S. Food and Drug Administration (FDA)
- Advisory Board: Genentech, Inc./Roche; National Hemophilia Foundation (NHF); Novo Nordisk; Sanofi; Takeda Pharmaceuticals U.S.A., Inc.



Mark T. Reding, MD

Associate Professor of Medicine Division of Hematology, Oncology and Transplantation Director, Center for Bleeding and Clotting Disorders University of Minnesota Medical Center Minneapolis, MN

Mark T. Reding, MD Disclosures

- *Research/Grants:* Bayer Corporation; BioMarin
- Advisory Board: Bayer Corporation; Genentech, Inc.; Novo Nordisk; Sanofi Genzyme and Takeda Pharmaceuticals U.S.A., Inc.



Summarize the comparative PK data and the clinical significance of popPK studies on factor VIII replacement therapies.

Hemophilia: Overview

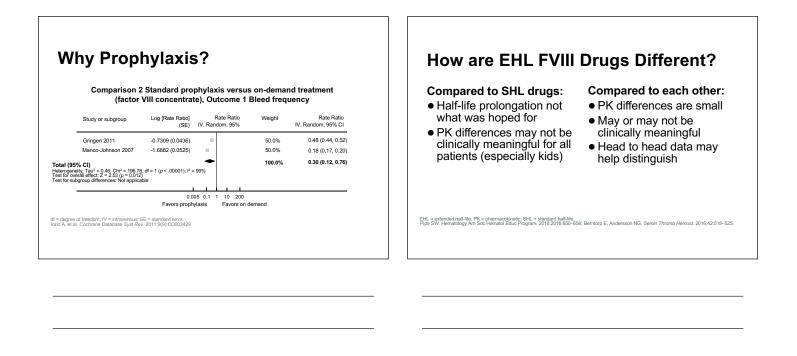
- Hemophilia refers to deficiencies of factors VIII and IX
- Both are due to mutations in the genes encoding factor VIII (hemophilia A) or factor IX (hemophilia B)
- Both are inherited in an X-linked recessive pattern • 30% of patients have no family history
- Heterozygous females (i.e. carriers) can be symptomatic
 Females can be asymptomatic carriers, or when symptomatic, mild (most often) or moderate (very rare) hemophilia patients, depending on their factor level.

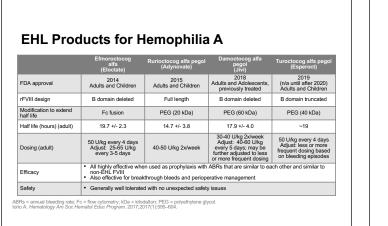
Centers for Disease Control and Prevention. 2019. https://www.cdc.gov/ncbddd/hemophilia/data.html.

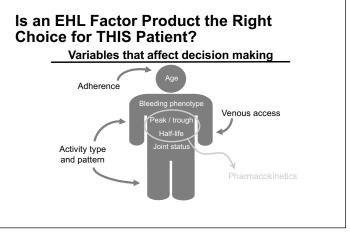
Hemophilia: Overview

- •The prevalence (per 100,000 males) of hemophilia is
 - •17.1 cases for all severities of hemophilia A,
 - 6.0 cases for severe hemophilia A
 - 3.8 cases for all severities of hemophilia B
 - 1.1 cases for severe hemophilia B

Iorio A, et al. Ann Intern Med. 2019;171:1-8.

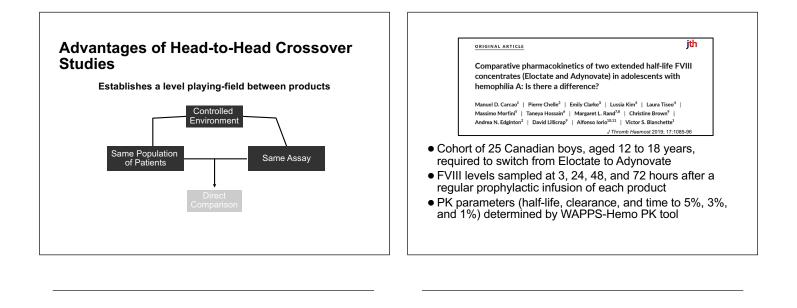


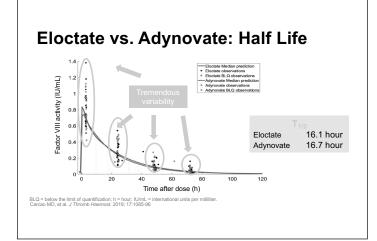


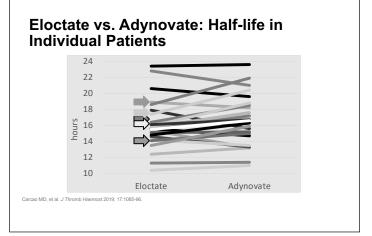


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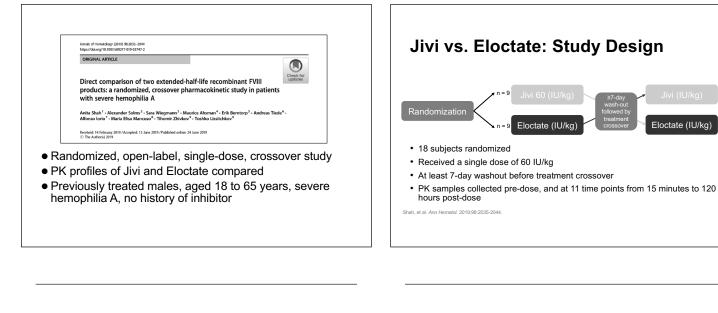
Application of PK in Hemophilia
Management Prevention of bleeding during surgery Prophylaxis Guide tapering of ITI treatment and
assessment of response Variability in PK among different individual Variability in PK among different individual Variability in PK in the same individual over
time and across different concentrates Variability of Network face Program. 2012/01/1306-064.

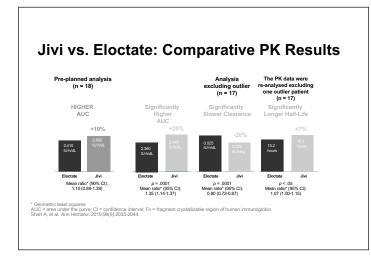


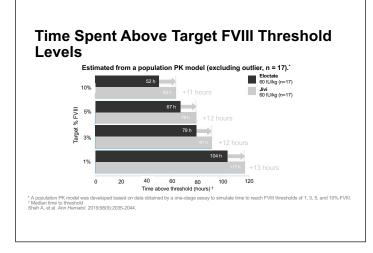




Eloctate vs. Adynovate: Half-life in Eloctate vs. Adynovate: Results **Individual Patients** 24 • All 9 blood group O subjects had half-lives shorter than the median • Among the 8 subjects with the shortest half-life, 7 were blood group O 22 • No subject had a long half-life with one product and a short half-life 20 with the other, or vice versa 18 JOULS • Conclusions: 16 Eloctate and Adynovate have almost identical PK parameters (in adolescents aged 12 to 18 years)
When switching from one to another, no change in prophylaxis regimen is 14 12 needed 10 Eloctate Adynovate Carcao MD, et al. J Thromb Haemost. 2019;17:1085-1096. ao MD, et al. J Thromb Haer ost 2019; 17: Can







Eloctate (IU/kg)

Jivi vs. Eloctate – Conclusions

- Jivi had a superior PK profile compared to Eloctate
- Real-world data needed to determine whether these PK advantages provide additional bleed protection

Extended Half-life FVIIIs: Are They All the Same?



Annual Transmission A

Study 2: Eloctate vs. Adynova an observed crossover stud

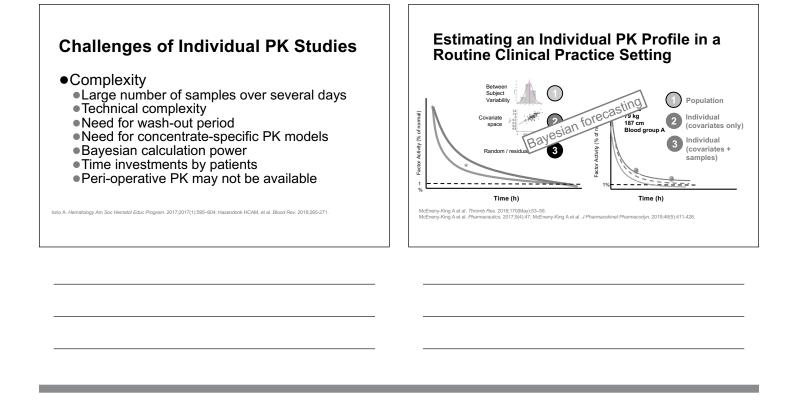


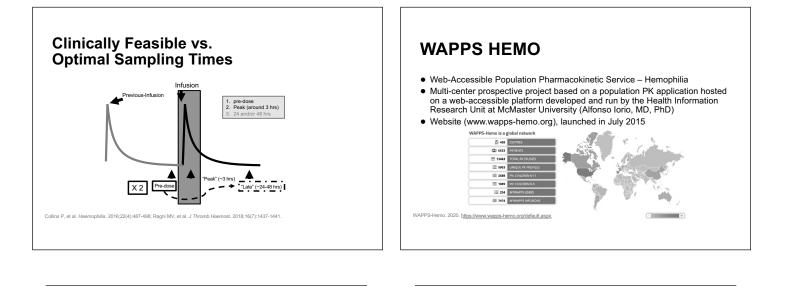
Apply popPK models to determine individualized dosing regimens for patients with hemophilia A.

Advantages of Tailored Dosing

- •Reduction of factor administration
- •Financial impact to health system
- •FVIII/FIX levels are based on peaks and troughs and not IVR
- Maximize efficacy

IVR = in vivo recovery. Iorio A. Hematology Am Soc Hematol Educ Program. 2017;2017(1):595–604; Hazendonk HCAM, et al. Blood Rev. 2018;265-271





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Integrate approaches for SDM to develop patient-centered, PK-based treatment plans for patients with hemophilia A.

NHF-McMaster recommendations Panel Questions

- Q1: Should integrated care versus non-integrated care be used for people with hemophilia?
 - . In people with hemophilia with inhibitors, and those at high risk for inhibitor
 - In popule with intertophila terms and a set of the se

Q2: For individuals with hemophilia, should a hematologist, a specialized hemophilia nurse, a physical therapist, a social worker, or round-the-clock access to a specialized coagulation laboratory be part of the integrated care team, versus an integrated care team with a lesser complement? A hematologist, a specialized hemophilia nurse, a physical therapist, a social worker, and round-the-clock access to a specialized coagulation laboratory should be part of the integrated care team over an integrated care team previous that does not a specialized to be integrated care team over an integrated

be part of the integrated care team, over an integrated care team that does not include all these components; conditional

NHF = National Hemophilia Foundation. Pai M, et al. Haemophilia. 2016;22 Suppl 3:6-16.

Principles of SDM

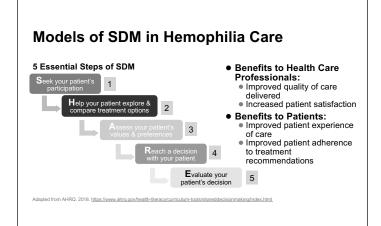
Shared decision making (SDM) has been defined as: "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences.3

SDM = shared decision-making. Elwyn G, et al. BMJ. 2010;341:c5146.

Principles of SDM

- Patient-centered care
 - Recognizes and respects patient values
 - Helps patients understand their medical condition and potential outcomes
 - •Helps patients understand the risks, benefits. and alternative options for treatment
 - Engages patients in the decision-making process

rry MJ, Edgman-Levitan S. New Engl J Med. 2012;366(9):780–781



Importance of Patient Education

- •HTCs
- Local hemophilia chapters
- National Hemophilia Foundation (NHF)
- Hemophilia Foundation of America (HFA)
- World Federation of Hemophilia (WFH)
- Other organizations

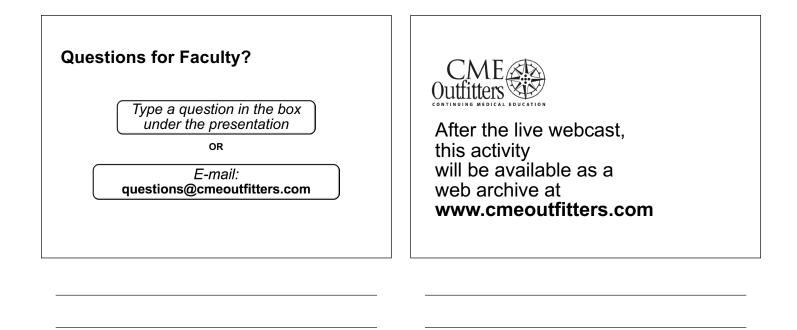
SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Implement strategies for SDM in clinical practice
- Translate data from head-to-head comparative studies on EHL products in the management of patients with hemophilia
- Adopt a popPK approach to simplify and tailor treatment in practice

Additional Resources

Visit **www.cmeoutfitters.com** for clinical information and certified educational activities





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3 Things to Do

- Actively participate in the meeting by responding to questions and/or asking the faculty questions (It's ok if you miss answering a question or get them wrong, you can still claim MOC)
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- 3. Be sure to fill in your **ABP ID number** and **DOB** (MM/DD) on the evaluation, so we can submit your credit to ABIM.



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How to Claim this Activity as a CME for MIPS Improvement Activity

- Actively participate by responding to questions and/or asking the faculty questions
- Complete activity posttest and evaluation at the link provided
- Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation.
- Complete the follow-up survey from CME Outfitters in approximately 3 months

CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity.

CME for MIPS

Attendance Form for Groups

Please complete and FAX to 614.929.3600

Other: _____

Other: _____

Activity Title and Faculty:

One Size Does Not Fit All: Using Population Pharmacokinetics for Tailored Hemophilia Care

with Alfonso Iorio, MD, PhD, FRCP(C) (Moderator); Miguel A. Escobar, MD; Mark T. Reding, MD

Site/Institution Name:							
□ Office-based □ Hospital Practice Setting: □ Large Group Practice (more tha	ital 🔲 Clinic e than 5) 🛄 Other:		Managed Care		re	□ Small Group Practice (less than 5)	
Address:							
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	MD	DO	PA	NP	RN	Pharm	Other:
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	MD	DO	PA	NP	RN	Pharm	Other:
	MD	DO	PA	NP	RN	Pharm	Other:

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PA

PA

NP

NP

RN

RN

Pharm

Pharm

MD

MD

DO

DO