




ORIGINAL ARTICLE

Focusing in on use of pharmacokinetic profiles in routine hemophilia care

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Abstract

Background: Emergence of population pharmacokinetic models for prediction of individual pharmacokinetic (PK) profiles facilitates individualization of prescribed prophylactic therapy for patients with hemophilia A and B and may have a favorable impact on clinical outcomes and annual factor utilization. How providers approach the integration and application of these data into routine clinical practice is not clear.

Objective: To explore the potential application of and barriers to incorporating PK profiles into current hemophilia prophylaxis decision making.

Methods: A facilitated group discussion of hematologists practicing within the federally-supported United States Hemophilia Treatment Center Network was conducted. Separately, a group of parents of patients with severe hemophilia less than 18 years of age participated in a focus group on individualizing prophylactic factor regimens with the use of PK data.

Results: Physician participants constructed a conceptual model for factors that determined their selection of hemophilia prophylaxis. These factors clustered in five groupings. When charged with creating a prophylaxis regimen for a specific clinical case including PK data, eight of nine providers generated a unique regimen. Parent focus group supported PK data use as they preferred data driven treatment decisions.

Conclusions: Clinician application of PK data for prophylaxis decision making is heterogeneous. Prospective evaluation of the use of PK-tailored prophylaxis in routine care and its impact on patient outcomes is needed. Parents perceived that, while obtaining blood draws could be challenging, images of factor activity decay informed their decisions about physical activity timing and provided an opportunity for partnership and shared decision making with their provider.

KEYWORDS

hemophilia A, hemophilia B, individualized medicine, pharmacokinetics, prophylaxis

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Essentials

- Integration of pharmacokinetic (PK) data into decision making for hemophilia prophylaxis is gaining momentum.
- Focus groups explored approaches to obtaining and applying PK data in the clinical setting.
- Conceptual model for prescribed prophylaxis highlights why experts' regimens vary despite PK data.
- Impact of PK-tailored prophylaxis on clinical and patient reported outcomes must be established.

1 | INTRODUCTION

The success of prophylactic infusion of factor concentrate to reduce bleed events and improve the quality of life for adults and children with severe hemophilia is well established^{1,2}; however, the optimal dosing and infusion frequency to reduce bleed risk and enable participation in routine daily and physical activities is debated.^{3,4} Emergence of population pharmacokinetic (PopPK) models for prediction of individual pharmacokinetic (PK) profiles may enable individualization of prescribed prophylactic therapy for patients with hemophilia A and B.⁵⁻⁷ More recently, integration of PK data into decision making for prescribed prophylaxis is gaining momentum, in particular to support successful transition between conventional and extended half-life (EHL) factor concentrate prophylaxis regimens.^{8,9} This practice reflects the ability to use PopPK models to estimate an individual patient's PK profile with a limited number of post-infusion blood samples in the setting of new factor concentrates which have unique PK profiles.^{6,10-13} The enthusiasm for considering PK data in medical decision making has resulted in a need to understand how providers should approach the integration and application of these data. Specific PK parameters which are felt to be critical for effective prophylaxis tailoring by treating physicians have not been delineated. Half-life, estimated terminal half-life, clearance, target trough, time within a target factor activity window or perhaps some algorithmic approach to integrating several of these parameters along with clinical variables may support decision making for an individual's optimal prophylaxis regimen.

Little has been published about how to integrate PK data into routine clinical practice; no standard approach has achieved consensus. Product-specific PK-driven study designs suggest incorporation of PK data may have a favorable impact on clinical outcomes and annual factor utilization.¹⁴⁻¹⁸ Unfortunately, these studies fail to address both the practical implementation of PK-guided therapy for the majority of patients who may benefit from the addition of PK profiling into their clinical management as well as the barriers to the execution of a PK profile in routine practice. The availability of PopPK models to both support data analysis for clinicians and produce clinically-relevant outputs for providers and patients may facilitate integration of these data into clinical practice.^{5,7} Recently, practice recommendations from the ISTH SSC on Factor VIII/IX (FVIII/FIX) addressing the use of PopPK for estimation and interpretation of PK profiles for individuals with hemophilia A or B, including timing for post-infusion blood samples, have been published.⁸ To

better understand the potential use of and barriers to using PopPK modeling with limited post-infusion factor level measurements in current clinical practice we engaged two focus groups, one of hemophilia providers and the second of patients/parents. The aim of these groups was to explore: (i) a list of attributes that influence clinicians when selecting the dose and infusion frequency of a factor replacement prophylaxis regimen, (ii) elements that influence provider decision making as to whether or not to obtain PK data for a specific patient, (iii) how providers use post-infusion samples or PK data to inform their decision making when prescribing factor prophylaxis, and (iv) patient/parent beliefs about factors, including PK data, that influence selection and adherence to a factor replacement dose and infusion frequency for prophylaxis.

2 | METHODS

2.1 | Physician focus group

A facilitated group discussion of nine hematologists with specialization and practice focus in hemophilia was conducted. Each provider practiced within the federally supported United States Hemophilia Treatment Center Network (USHTCN). Eight of the 11 Centers for Disease Control hemophilia regions were represented, highlighting the geographic diversity of participants. The 90-minute focus group was led by an external moderator and was structured in four units. Participants first completed a short, written questionnaire that included background characteristics, description of their individual current use of post-infusion blood samples to create or refine a prophylaxis regimen for patients with hemophilia A or B. Participants then created a list of factors that influenced their individual decision making when selecting a replacement product, dose, and infusion frequency for hemophilia prophylaxis. The moderator facilitated further idea generation among the group using a structured set of questions to enrich the list of factors impacting decision making around prophylaxis, including situations that could support or impede the collection and use of PK data. Collectively, participants agreed on the factors impacting provider prophylaxis decision making, then placed these factors into a hierarchical framework. Focus group participants did not specifically rank the relative importance of each item. The final section of the focus group explored how participants used PK data when available. A sample clinical scenario was provided. PK data for a patient trialing an EHL factor concentrate were presented in a stepwise fashion to learn how

each provider's empiric prophylaxis regimen changed with provision of additional PK information and which PK elements study participants found to be the most clinically useful. The clinical case used for unit 4 is described below. This same case was then re-circulated to each participant individually 11 months later to investigate potential change in decision-making for prophylaxis; participants were not provided with their previous response to the clinical case.

2.1.1 | Clinical case

Patient is a 17-year-old male with severe FVIII deficiency presently on prophylaxis with a conventional factor concentrate dosed at 25 IU/kg every other day. He enjoys sports, playing soccer and basketball a few times per month, depending on the time of year. He also works with the school trainer for general fitness. He notes he gets a little "bruised up" with team sports sometimes, but he doesn't infuse additional factor when this occurs. He typically infuses his prophylaxis doses in the afternoon. He reports one joint bleed in the past 12 months when he rolled his ankle playing basketball. He has no target joints and reports 0-1 hemarthroses annually over the past several years. He reports 85%-90% adherence to his every other day infusion regimen. He has no plans to change his current level of physical activity. He has heard about EHL factor concentrates and is curious whether they would be beneficial for him.

2.2 | Patient/parent focus group

Patients with severe hemophilia (if greater than 18 years of age) and parents of patients with severe hemophilia less than 18 years of age cared for at the Boston Children's Hospital/Boston Hemophilia Center were invited to participate in a focus group on individualizing prophylactic factor regimens for patients with hemophilia including the possible addition of PK data. Per institutional policy, invitations describing the opportunity to participate in this focus group were mailed by U.S. Postal Service to parents of patients less than 18 years of age and directly to patients aged 18-30 years old. Despite positive attendance responses from both parents and young adults, ultimately five parents of adolescents with severe FVIII deficiency on prophylaxis participated in the focus group. Group discussion elicited key drivers of prophylaxis regimen adherence and interest in use of PK data to inform decision making. The team at Boston Children's Hospital/Boston Hemophilia Center has begun to routinely discuss the opportunity for individual PK profile generation and the potential utility of this approach for tailoring prophylaxis during annual comprehensive visit education discussions. Each participant demonstrated familiarity with the concept of PK-tailored prophylaxis and contributed to the discussion.

3 | RESULTS

3.1 | Physician focus group participants

The initial survey of physician-participants revealed that each had been practicing as a hemophilia specialist for at least 5 years with

the majority (78%) practicing in this capacity for more than 10 years. Most participants reported caring for more than 60 patients with severe hemophilia A per year. Participants were evenly divided between those that cared for pediatric hemophilia patients only and those that managed both pediatric and adult hemophilia patients. None of the participants cared exclusively for adult hemophilia patients.

Participants identified a number of factors that entered into their decision making about selecting and adjusting a patient's prophylaxis regimen (Figure 1). Unanimous consensus of elements that impact provider decision making about prescribed prophylaxis was achieved by the focus group; however, specific ranking of each of these elements was not pursued. Key drivers that emerged from group discussion included quality of venous access, physical activity level, joint health status, and willingness of patient/family to adhere to the prescribed regimen. Focus group participants expressed that the limited number of blood draws needed for PopPK analysis, at most only one additional blood draw beyond routine practice, was not a barrier from a payor perspective. At the start of the focus group all participants endorsed use of factor activity levels to influence their prescribed prophylaxis regimens; however, a uniform approach was not applied to all patients (Figure 2). Participants described that generally a factor level would be drawn for patients as part of their annual comprehensive clinic visit to confirm whether or not the desired trough level was being achieved. For patients changing factor products it was more likely that additional levels such as a peak and a trough or other selected time points for PK analysis would be obtained. A few participants noted that obtaining multiple post-infusion factor levels for PK profiling was used primarily in the perioperative setting or for patients with either recurrent bleed events or aspirations of participating in physically demanding activities. Participants also discussed factors that impacted their likelihood of attempting a PK-tailored approach (Table 1). During the discussion, the heterogeneity in clinical practice was attributed to a number of factors: (i) increase in the total post-infusion samples providers decided to obtain for patients on EHL products compared to those on standard factor concentrates, (ii) the introduction of WAPPS-Hemo (availability of PopPK model for the clinician), (iii) recent individual practice decision to routinely check at least one factor level for every patient to learn something about their current prophylaxis regimen, and (iv) differential application of requirement for PK studies for specific groups of patients such as the "bleeding patient" or "peri-procedure patient."

Following the presentation of the patient scenario described in Section 2, a short preformulated list of management options was presented to the participants. Each was asked to select all of the options they would present to the patient. Sixty-seven percent selected "consider change to an EHL product using post-infusion blood samples to inform regimen." Other participants felt that prior to considering a product change, more information about the patient's factor coverage on his current product was an important first step. Fifty-five percent selected "obtain post-infusion blood samples on

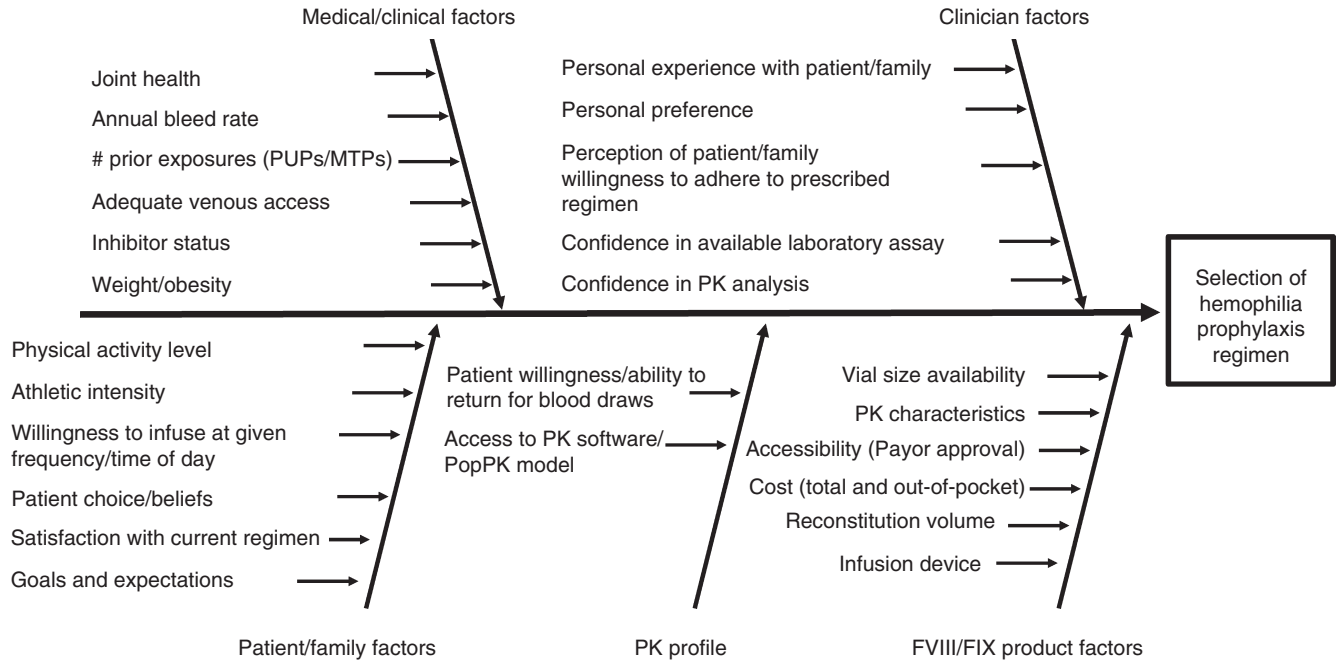


FIGURE 1 Conceptual model of prophylaxis regimen determination for a patient with severe hemophilia. PK, pharmacokinetics; PopPK, population pharmacokinetics

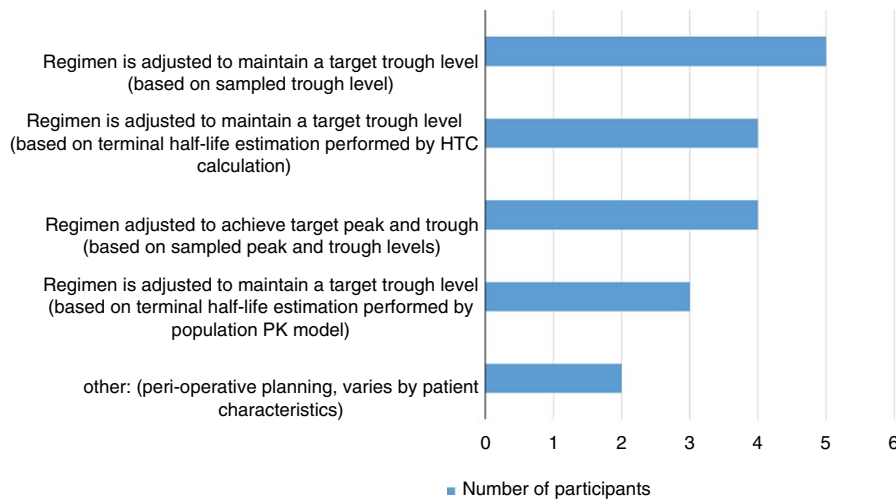


FIGURE 2 Use of post-infusion sampling and PopPK profile by hemophilia providers in the clinical setting. HTC, hemophilia treatment center; PK, pharmacokinetics; PopPK, population pharmacokinetics

patient's current factor product to learn more about his current factor coverage." Fewer participants (44%), favored "continue on current regimen with routine follow-up" or "consider change to an EHL product starting with label recommended dosing" (22%). The physician group was then provided the patient's FVIII levels following an infusion of an EHL factor concentrate dosed at 33 IU/kg. Additional PK data (analysis by WAPPS-Hemo⁵) were supplied to participants in a stepwise fashion (Figure 3), to learn how provider prescribing decisions are informed by or changed with: (i) post-infusion levels, (ii) visual presentation of PK-profile (factor activity decay curve), and (iii) reported time to FVIII activities levels of 0.05, 0.02, and 0.01 IU/ml.

Each participant generated a different planned prophylaxis regimen based on the data presented. No participants changed their planned prophylaxis regimen upon receiving additional PK data, thus, it was difficult to elucidate which PK information may have impacted an individual participant's prescribed prophylaxis regimen. On resurvey with the same case nearly a year later, participants' report of planned prophylaxis regimens demonstrated greater homogeneity; however, a broad range of infusion frequencies persisted (Table 2). Participants tended toward more frequent dosing to improve trough levels even higher than 0.01 IU/ml and more frequent peak levels to provide higher FVIII levels during activity on their follow-up planned prophylaxis regimens.

TABLE 1 Factors that impact the likelihood of provider attempt at PK-tailored approach

Contributing factors	Impact on provider considerations
Activity/athletic level	If frequency or intensity of athletic activity is high, more likely to prompt factor levels and consideration of a PK tailored approach
Adherence to current prophylaxis regimen	If poorly adherent to regimen, less likely to attempt to obtain post-infusion samples and tailor regimen based on PK profile
Belief in target factor level	Since “true ideal target levels” have not yet been identified for individual patients or for safety with activities or athletics, utility of PK-tailored prophylaxis regimens in improving patient outcomes is unclear
Confidence in PK analysis	Insufficient understanding or confidence in the assumptions and reliability of the PK analysis may limit its routine clinical use
Frequency of bleed events (not related to adherence)	Frequent bleed episodes are more likely to prompt factor levels and consideration of a PK tailored approach
Patient distance from HTC (or acceptable blood draw facility)	Longer distance from HTC, less likely to try to obtain >1 post-infusion blood sample
Patient/parent preference	Patients/parents may have a fixed decision on the maximum number of weekly prophylaxis doses irrespective of other factors
Variability in laboratory assays	If providers do not believe assay results are reliable, use of raw results or results from population-based modeling may not be applied clinically
Venous access	If access is poor, unlikely to obtain additional factor levels or support PK tailored dosing approach

HTC, hemophilia treatment center; PK, pharmacokinetics.

In contrast to the static data presented as part of the case scenario, participants shared that a clinically useful PopPK platform application needs to enable providers to modify the planned dose and infusion interval and visualize the resultant change in the estimated factor decay curve in order to support provider use of PK data in tailoring prophylaxis regimens for individual patients. Participants also requested display of the total weekly dose (IU) consumed by different dose and infusion interval combinations. The capability of selecting irregular infusion intervals to estimate twice weekly dosing, for example, was emphasized. Participants desired the ability to save and print individual patient PK profiles, so that the illustration of the estimated factor coverage with different doses and infusion frequencies could be used for patient

encounters to support patient education and rationale for prophylaxis regimen selection.

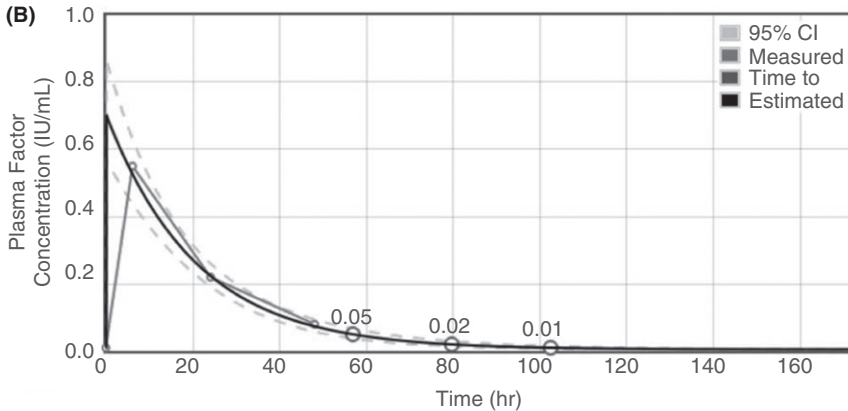
3.2 | Parent focus group participants

Parents of adolescent males with severe FVIII deficiency believed that adherence to hemophilia prophylaxis was necessary for: (i) maintaining a healthy lifestyle and (ii) reducing the risk of spontaneous and traumatic bleeding events. Collectively, participants agreed that prophylaxis was an important “health habit.” Based on their own experiences, their perception of their sons’ experiences, and previous discussions with other parents and individuals with severe hemophilia, focus group participants felt that struggles with adherence

(A)

	Pre	4-h post	24-h post	48-h post
FVIII activity	1%	55%	22%	8%

(B)



(C)

Parameter	Conservative estimate	Balanced estimated	Optimistic estimate
Time (h) to:			
0.05 IU/mL	50.25	57.00	63.50
0.02 IU/mL	69.75	79.75	89.50
0.01 IU/mL	89.75	102.50	115.75
half-life (h)	12.25	14.50	16.50

FIGURE 3 Stepwise presentation of PK-related data for clinical case. (A) Post-infusion levels following single 33 IU/kg dose of extended half-life factor concentrate, (B) visual presentation of PK-profile (decay curve), (C) time to 0.05, 0.02, 0.01 IU/ml FVIII activity levels. PK, pharmacokinetics

TABLE 2 Physician focus group participants' reported planned prophylaxis regimen based on patient scenario and PK data presented at focus group and then at follow-up timepoint

Planned prophylaxis regimen individually reported during focus group	Planned prophylaxis regimen individually reported at 11-month follow-up	Reported elements influencing prescribed prophylaxis regimen at 11-month follow-up
<ol style="list-style-type: none"> 33 IU/kg every 48 h 50 IU/kg twice weekly Start with label indicated dose rounded to closest available vial 25 IU/kg every 72 h or 35 IU/kg twice weekly 50 IU/kg every 3 d 50 IU/kg twice weekly 33 IU/kg every 4 d 33 IU/kg/50 IU/kg twice weekly Continue with previous [standard] factor regimen, 25 IU/kg every other day 	<ol style="list-style-type: none"> 33 IU/kg every 48 h 25 IU/kg every 3 d 33 IU/kg every 3 d 33 IU/kg every 3 d 40 IU/kg every 3 d 33 IU/kg every 3 d 33 IU/kg every 4 d 33 IU/kg twice weekly 50 IU/kg twice weekly 	<ol style="list-style-type: none"> Patient reported activity level (n = 9) PK data (n = 7) Patient reported bleeding history (n = 5) Physician desire for higher troughs given physical activity (n = 5) Minimize frequency of infusions (n = 2) Physician desire for more frequent peak levels and higher troughs given physical activity (n = 2) Patient reported adherence (n = 2) Physician desire for more frequent peak levels given physical activity (n = 1) Cost of prophylaxis regimen (n = 1) Current state of joints (n = 1) Patient age (n = 1)

PK, pharmacokinetics.

to prescribed prophylaxis could be attributed to the existence of: (i) competing priorities deemed more essential than prophylaxis infusion which resulted in either forgetting to infuse or deliberately choosing not to infuse, (ii) a sense of safety in delaying an infusion if previously this had not resulted in a bleed event (learned boundaries of how to stretch time between prophylaxis doses), and (iii) collective family stress and anxiety if the child was fearful or combative

with infusions. Participants favored an approach of using a PK profile to inform decision making around prophylaxis, endorsing a preference for their sons' medical care to be "driven by data." The graphical representation of factor activity decay helped them (and they perceived helped their sons as well) to develop a rough "mental map" of factor activity levels over time which informed decisions about choice of physical activities or the perceived need for preemptive

factor infusion in the setting of real or potential injury. Parents also reported that having these data presented to them facilitated a feeling of partnership and shared decision making rather than simply having a treatment regimen dictated to them. They asserted that for many parents, and adolescent/young adult males, this was important for patient acceptance and adherence. While these data were thought to be useful, participants did comment on the challenge of obtaining post-infusion blood draws, particularly if additional visits to the hemophilia treatment center (HTC) or a laboratory were required. Some individuals who lived close to the HTC noted this was a limited challenge, although it could still prove difficult to coordinate with work and school schedules. Those who lived further from the HTC (but still within about an hour's drive) noted that the timing of blood draws and the extra drive time required additional dedication. The group noted that modifying a prophylaxis regimen or switching factor products, even incorporating PK data, required careful consideration and repeated family discussions before committing to a change. Participants questioned decisions around the "right" trough level, bleed risk relative to factor levels particularly with regard to adolescent/young adult activities, and reliability of factor level estimates based on PopPK analysis. The consensus of this parent focus group was that following a regimen or product change, close interval follow-up with their hemophilia team for reevaluation of changes in bleed symptoms and quality of life assessment was critical to determine the success and appropriateness of the new regimen.

4 | DISCUSSION

Tools supporting PK-tailored prophylaxis are becoming more readily accessible to hemophilia clinicians. Both the frequency with which clinicians obtain PK data and how patients are selected for a PK-tailored approach are variable. As providers gain experience with opportunities for integration of PopPK models into their clinical practice, we anticipate use will become more consistent among patients. Beyond targeting the traditional trough of 1% or minimizing factor concentrate utilized per week, use of PK profiles offers the ability to target alternate trough levels with less trial and error and to inform factor activity levels at the time of athletic activities or other activities that may pose an increased bleed risk. An individual's PK profile may highlight the importance of timing prophylactic factor infusions in the afternoon prior to a sports event, for example, rather than always insisting on first morning infusions.

Clinician interpretation and application of PK data into prophylaxis decision making is inconsistent, as evidenced by the variability of initial prophylaxis regimens provided by the physician focus group participants following a simple clinical scenario with PK data. This variability is likely related to the numerous factors that must be considered when crafting a patient's prophylaxis regimen as highlighted in our conceptual model. Each experienced hemophilia provider implicitly weighed these variables differently when considering the case. It is interesting that despite the addition of PK data in different

formats, participants did not change their initial planned prophylaxis regimen, suggesting that the PK data, at that point, did not strongly influence their decision making. Rather, participants relied more on their experience to determine their plan for prophylaxis given the scenario. On re-challenge with the same patient case nearly a year later most providers proposed a different prophylaxis regimen than they had at the original focus group highlighting a change in decision making due to either increased familiarity with interpreting and incorporating PK data or a general shift in how they weighted elements of the conceptual model, or potentially both. Notably, the planned prophylaxis regimens became more consistent among providers, even though responses were not shared among participants.

Prospective collection of physician decision making which integrates PK data for hemophilia prophylaxis and the correlation between use of PK-tailored prophylaxis and patient outcomes is needed. Demonstration of improved clinical and patient reported outcomes using PK-tailored prophylaxis will help clinicians and patients weigh the clinical benefit of this approach against the inconvenience of post-infusion blood draws. The time required for providers to input a patient's data into a PopPK model, generate simulated, tailored prophylaxis dosing regimens, and discuss management options with a patient/family is not presently reimbursed by most payors. As use of PK profiles become more widely adopted, continued support for Hemophilia Treatment Center care models or specific reimbursement will be necessary to support this personalized care. Although the parent focus group highlighted the potential interest and benefit of PK data to improve an individual's understanding of his hemophilia, additional education provided by comprehensive hemophilia clinic visits and educational programming through Hemophilia Treatment Centers and patient-focused organizations will be needed to facilitate patient and parent engagement.

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AUTHOR CONTRIBUTIONS

SE Croteau contributed to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. MU Callaghan contributed to analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. J Davis contributed to analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. AL Dunn contributed to analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. M Guerrero contributed to analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. O. Khan contributed to analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. EJ Neufeld contributed to analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. LJ Raffini contributed to analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. M Recht contributed to, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. M Wang contributed to analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval. A Iorio contributed to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval.

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