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ORIGINAL ARTICLE

# Pharmacokinetic-tailored approach to hemophilia prophylaxis: Medical decision making and outcomes

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## Abstract

**Background:** Clinical application of population pharmacokinetics (popPK) is of increasing interest to patients with hemophilia, providers, and payers. Routine use of popPK profiles in factor replacement prophylaxis decision making has the potential to maintain or improve efficacy and reduce product consumption.

**Aim:** To investigate the feasibility of implementation and longitudinal assessment of pharmacokinetic (PK)-tailored prophylaxis in routine clinical practice for hemophilia A and to describe factors that influence decision making for prescribed hemophilia prophylaxis.

**Methods:** This longitudinal, multicenter, prospective feasibility study of children and adults with hemophilia A without inhibitors used the Web Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo) to generate PK profiles. Assessments over 12 weeks captured data on prescribed prophylaxis, popPK tool use, provider decision making, and patient-reported outcomes.

**Results:** Eighteen participants aged 6 to 39 years enrolled; half used extended half-life concentrates. Patient interest in their PK centered on general curiosity followed by a desire for participation in physical activity and decrease in infusion frequency. Providers used the WAPPS clinical calculator feature to simulate prophylaxis regimens under different dose, infusion, and trough conditions. Most targeted troughs were 1 to 3 IU/dL. The feasibility assessment demonstrated challenges with patient recruitment; however, the majority of participants successfully completed study assessments meeting feasibility targets.

**Conclusion:** A larger-scale study powered to evaluate the impact of PK-tailored prophylaxis on clinical and patient-reported outcomes is feasible with study design modifications to support increased recruitment rate. Shared decision making incorporating patient and provider goals is important and facilitated by regimen simulations with the clinical calculator.

**KEYWORDS**

decision making, factor VIII, feasibility studies, half-life, hemophilia A, pharmacokinetics

**Essentials**

- This study assesses the feasibility of implementing pharmacokinetic (PK)-tailored prophylaxis in routine clinical practice for hemophilia A and capturing longitudinal assessment of patient-reported outcomes.
- Motivations for obtaining PK profiles varied between patients and providers.
- Provider simulation of prophylaxis regimens with Web Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo) clinical calculator supported clinical decision making and led to modification of prescribed infusion frequency rather than dose to achieve prophylaxis target levels.
- The visual outputs from WAPPS-Hemo facilitated provider communication of PK results and joint decision making for patient-tailored prophylaxis regimens.

## 1 | INTRODUCTION

Individual pharmacokinetic (PK) profiles based on population PK (popPK) modeling are not yet routinely employed by US hemophilia treatment centers (HTCs); however, the potential benefit of this patient-specific information to improve prophylaxis efficacy and reduce factor product consumption has gained awareness among patients, providers, and payers.[1–4] Prophylaxis with factor concentrate is standard care for both adult and pediatric patients but is costly and challenging due to the frequency of intravenous infusions required.[5] Broad interpatient variability in clearance; increased interest in physical activity and sports participation; and the introduction of modified, extended half-life (EHL) factor concentrates impact the clinical utility of the traditional empiric approach to prophylaxis dosing.[6–8]

Knowledge of a patient's PK profile may inform and help to individually tailor his or her prophylactic factor replacement regimen and thereby reduce the risk of longitudinal joint health concerns, pain management issues, and lost productivity compared to simply adjusting the prescribed prophylaxis based on bleed events.[4,9] A prospective, randomized study comparing prophylaxis to episodic factor replacement demonstrated that as few as 1 to 2 bleeds were sufficient to be associated with radiographic joint changes.[10] The duration of time individuals spend with factor levels <1 IU/dL weekly correlates with an increased risk of bleed events (hemarthrosis and total bleeds).[11] Additionally, the physical demands placed on an individual through sports, physical activity, or job requirements may increase bleed risk using an empiric approach to prophylaxis.[7,12] Individuals with faster clearance of exogenous factor replacement are at particular risk of being inadequately dosed by use of an empiric regimen based on mean adult PK data and potentially suffer preventable bleed events. Thus, understanding the impact of dose and infusion frequency on an individual patient's factor levels over time as well as patient adherence are key for a successful (minimal bleeding) prophylaxis regimen.

The application of Bayesian analytics to create popPK models in hemophilia established that a limited number of well-timed blood samples for PK analysis could yield similar output to full 11-sample PK curves,[13,14] thus circumventing the impractical, sample intensive, model-independent strategy, designed for clinical trial use and evaluation of the bioequivalence among clotting factor concentrates.[15] Access to Web-based tools such as the Web Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo, www.wapps-hemo.org) has enabled hemophilia providers to apply a popPK approach in their practices.[1,16] WAPPS-Hemo has constructed specific models for most commercially available factor VIII (FVIII) (and factor IX) factor brands as well as a generic model capable of PK estimation for factor concentrate brands not included in the modeling data set.[17] Fat-free body mass, age, and factor brand have been found to significantly affect PK parameters and are included as covariates. The WAPPS-Hemo data set has incorporated individuals spanning a broad age and weight continuum.[17,18] The WAPPS-Hemo output for providers includes an estimate of the patient half-life for a given factor concentrate and estimated time to 5, 3, and 1 IU/dL factor activity levels. An interactive clinical calculator allows providers to simulate serial decay curves for a patient's prophylaxis regimen by manipulating a combination of dose, infusion frequency, and target trough level.

Although gaining momentum in the United States, the use of popPK has been applied more systematically in other regions such as Canada and the United Kingdom.[19–21] Provider uncertainty about how to incorporate this type of data into their established prescribing practices and the limited data demonstrating an impact on hemophilia health outcomes and economics in a routine care setting are barriers to the use of PK profiles in clinical practice.[22] The time and inconvenience of an extra laboratory visit or two and the time needed for PK data entry, interpretation, and explanation may also impede both provider and patient interest in pursuing a PK-tailored approach. This study aimed to assess the feasibility of implementing PK-tailored prophylaxis in routine clinical practice for hemophilia A and capturing a longitudinal assessment of patient-reported adherence, outcomes, and quality-of-life (QoL) factors. We also assessed provider use of the patient's PK profile and factors that contributed to clinical decision making for prescribed hemophilia prophylaxis.

## 2 | METHODS

This multicenter, longitudinal, prospective feasibility study of PK-tailored prophylaxis regimens in adults and children with hemophilia A was conducted in accordance with the ethical principles described in the Declaration of Helsinki and with institutional review board approval at each of the 5 participating HTCs. Written informed consent was obtained from all participants. HTCs were selected for study participation to incorporate diversity of geography, HTC size, patient age, and providers. The eligible patient population included individuals that were ≥6 years old, baseline FVIII activity <5 IU/dL, and willing to initiate prophylaxis (if on demand) or to consider a change to their current prophylaxis regimen or factor product. Participants were excluded if they had ongoing regular use of >1 factor concentrate concomitantly (ie, use of both EHL and standard half-life [SHL] factor concentrates), use of nonfactor products for prophylaxis, a positive inhibitor titer (>0.6 BU/mL), or a known congenital bleeding disorder other than moderate or severe hemophilia A.

Feasibility was assessed by participant recruitment, success of PK profile creation, rate of completion of longitudinal assessments, and participant maintenance of an infusion and bleed log. As this was a feasibility study, no formal sample size calculation was undertaken; however, feasibility criteria were established (Table 1) to assess for a minimally acceptable completion rate for key elements in the study to facilitate development of a powered, prospective clinical study of PK-tailored prophylaxis. Study team assessment of barriers to study execution were collected. Clinical data and patient-reported outcomes including adherence to the prescribed prophylaxis regimen, reported physical activity, and QoL questionnaires were captured in the Research Electronic Data Capture (REDCap) platform.[23] Assessments were completed at baseline, week 4, and week 12 following PK assessment. Clinical research coordinators or investigators completed verbal data collection with participants as well as medical record review to obtain the longitudinal clinical data elements for this study. These elements included participant's factor replacement regimen before and after PK profile generation, inhibitor history, bleed history, reported participation in regular physical activity (defined as equivalent of at least 30 minutes of sustained exercise/sport 3 times per week), presence of target joints (joint with ≥4 bleeds in the past 6 months). Participants and providers were also asked to select all statements that contributed to their interest in a PK profile. Options provided were developed from previously reported studies and focus groups; an option to contribute additional considerations was provided.[2,22] Patients were also asked longitudinally to quantify the number of missed or delayed prophylactic factor infusions as well as to complete a short assessment of adherence to prescribed prophylaxis using a 5-item Likert scale anchored by *always* and *never*. Patients were permitted to use handwritten or electronic tools for logging bleeds and infusions depending on their current habits and preferences. Hemophilia-specific Quality of Life (Haem-A-QoL, >18-years-old) and Canadian Hemophilia Outcomes–Kids Life Assessment Tool (CHO-KLAT, 6 years old to <18 years old) were used to test feasibility of longitudinal QoL assessments in this study.[24–27] WAPPS-Hemo was used by each site to generate PK profiles for participants and to collect data on how providers used the clinical calculator when formulating their plan for prescribed prophylaxis. Variables required for PK profile generation in WAPPS-Hemo included both patient covariates (age, weight, height, baseline FVIII activity) and infusion and laboratory details (factor product brand, date and time of factor concentrate infusion, total units of factor concentrate infused, infusion duration, date and time of pre- or postinfusion FVIII activity levels, assayed FVIII activities, assay methodology used).[28] Key considerations that impacted decision making for prescribed prophylaxis were collected as well as the changes in physician plan for prescribed prophylaxis following PK profile generation.

Descriptive statistics were used to report participant and prophylaxis regimen characteristics, provider use of the PK profile and WAPPS-Hemo interactive clinical calculator for regimen simulation, and measures of study feasibility. Patterns of treatment regimen parameter selection (dose, infusion frequency and target trough) using the clinical calculator were also reported using descriptive statistics.

**TABLE 1** Feasibility assessment

| Feasibility criteria | Result, n (%) | Feasibility assessment |
|---|---|---|
| ≥80% of sites met accrual goal | 1/5 (20) | Amber |
| ≥80% of target accrual achieved | 18/25 (72) | Amber |
| ≥80% of participants had PK profile generated using WAPPS-Hemo | 16/18 (89) | Green |
| ≥90% of participants completed all longitudinal clinical assessments | 15/16 (94) | Green |
| ≥90% of participants completed all longitudinal patient reported outcome questionnaires | 13/16 (81) | Amber |
| ≥80% of participants maintained infusion and bleed logs for the duration of the study | 9/16 (56) | Amber |

*Note:* Green, feasibility target met; amber, feasibility target not met but likely achievable with study design modification.

## 3 | RESULTS

### 3.1 | Assessment of feasibility

Target enrollment for each site was 5 patients. Sites were open for patient enrollment for an average of 5.2 months (range, 2-8 months), and 18 patients were enrolled. One site exceeded accrual goal, 2 sites enrolled 4 patients, 1 site enrolled 3 patients, and 1 center was not able to enroll any patients. Barriers to timely enrollment included distance from the HTC interfering with patient willingness to return for blood draws, lack of patient interest in their PK information, and licensure of emicizumab as an alternative prophylaxis agent in this

**TABLE 2** Characteristics of study population

| Participant characteristics | Median (range) or frequency (%) |
|---|---|
| Demographics | Median (range) |
| Age, y | 13 (6-39) |
| Weight, kg | 49, (19.6-106) |
| Participation in regular physical activity (equivalent of at least 30 min of sustained exercise/sports 3 times per wk) | Patients, n (%) 13 (87) |
| Cardiovascular exercise | 8 (53) |
| Organized school or community sports teams | 7 (47) |
| Weight lifting or toning | 4 (27) |
| Active target joints (joint with 4 + bleeds in the past 6 months) | 7 (47) |
| Ankle | 4 (27) |
| Elbow | 3 (20) |
| Knee | 2 (13) |
| Hip | 1 (7) |
| Shoulder | 1 (7) |

patient population. Table 1 presents the results of the feasibility assessment.

All but 2 patients successfully completed postinfusion blood sampling for popPK analysis. One patient could not be reached to complete baseline clinical assessment and questionnaires following generation of the PK profile. In total, 15 patients completed the longitudinal clinical assessments. All completed the week 4 clinical follow-up; 1 did not complete the week 12 clinical follow-up. Thirteen patients successfully completed all of the longitudinal QoL questionnaires. Participants variably reported maintaining an infusion and bleed log over the course of their 12 weeks of study participation. At the week 4 assessment, 69% reported maintaining logs; by week 12, this had decreased to 56%.

## 3.2 | Participant characteristics

Of the 18 eligible patients enrolled, 15 participants fulfilled both PK profile generation and completion of baseline clinical data for analysis (Table 2). All patients had severe hemophilia A with a reported baseline FVIII activity <1 IU/dL. All but 1 patient was on a continuous prophylaxis regimen at the time of enrollment. A history of any positive titer inhibitor was reported in 28% of patients. Two of these patients had spontaneously resolving low-titer inhibitors; the remaining 3 had completed an immune tolerance induction regimen. At baseline assessment, nearly all patients (87%) reported regular participation in physical activity. Seven patients (47%) reported at least 1 active target joint. Seven patients (47%) had a PK estimate for an EHL factor concentrate, and the remainder were for an SHL product.

## 3.3 | Application of WAPPS-Hemo in clinical practice

All participants reported an interest in their individualized PK profile and specifically a desire to better understand changes in their factor levels over time to support participation in physical activities, a general interest in how their factor levels change over time after factor infusion, and an interest in decreasing the frequency of infusions needed for successful prophylaxis (Figure 1). Most providers (67%) ascribed patients' interest in PK to a general interest about how their factor activity levels changed over time; however, the majority also identified that multiple factors contributed to a participant's interest in an individual PK profile. Providers reported a general interest in better

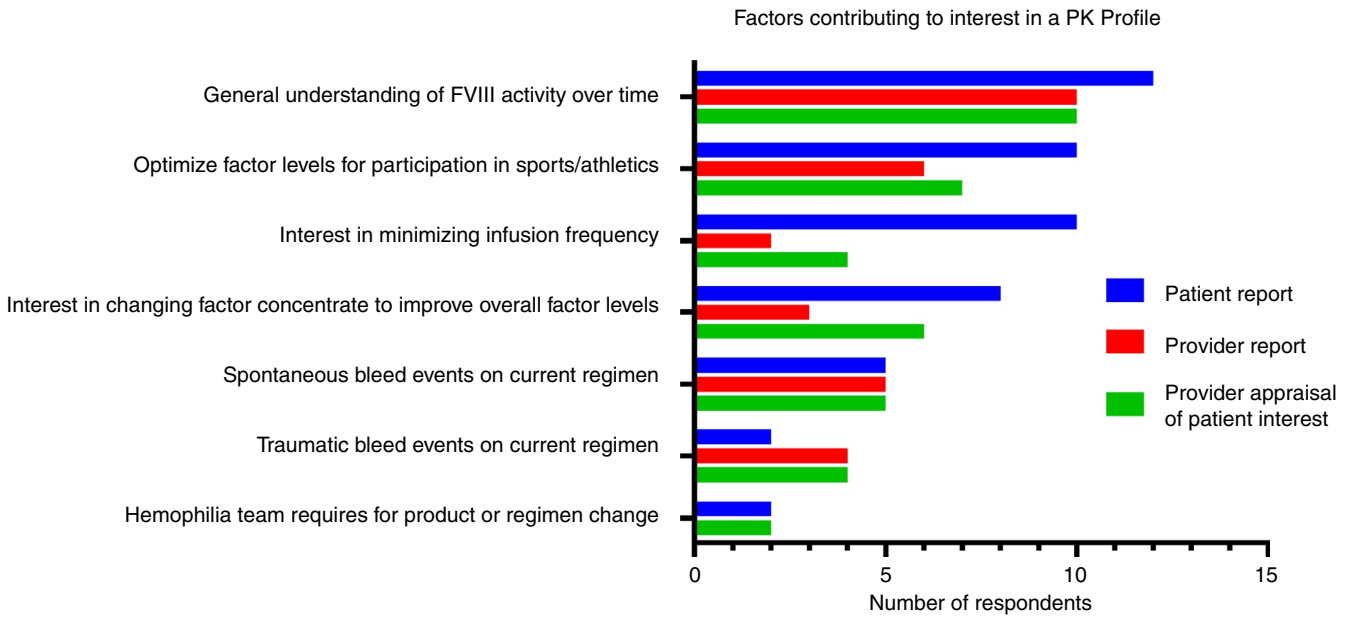


**FIGURE 1** Patient and provider reported factors contributing to their interest in a PK profile. FVIII, factor VIII; PK, pharmacokinetics.

understanding a patient's change in factor activity levels over time as their primary interest in obtaining an individualized PK profile for an enrolled patient.

Providers reported that they found the information provided by WAPPS-Hemo useful in planning a patient's prescribed prophylaxis regimen 87% of the time. The WAPPS-Hemo data outputs selected by providers as the most valuable in aiding decision making varied by patient. The most commonly favored outputs were report of time to 5, 3, and 1 IU/dL and use of the WAPPS clinical calculator. These were selected among the top 3 outputs by 80% and 53% of provider respondents, respectively. Providers endorsed a number of factors that contributed to their decision making with regard to prophylactic factor replacement summarized in Table 3. Key factors influencing decision making for prescribed prophylaxis were a desire to minimize time spent with FVIII activity <1 IU/dL or an alternate target trough level and to decrease bleeding symptoms (Figure 2).

**TABLE 3** Provider decision making for hemophilia A PK-tailored prophylaxis

| Provider response | Respondents, n (%) |
|---|---|
| Which of the following factors contributed to your decision making for this patient's prophylaxis regimen? | |
| Desire to minimize time spent at FVIII activity levels <1% per wk | 10 (67) |
| Desire to minimize time spent below a specific trough level per wk | 7 (47) |
| Reduce frequency of bleeding symptoms | 7 (47) |
| Patient/Parent preference | 6 (40) |
| Facilitate participation in sports/physical activity | 6 (40) |
| Desire to minimize number of factor infusions per wk | 4 (27) |
| Venous access issues | 2 (13%) |
| Cost of factor replacement regimen overall | 1 (7%) |
| Desire to minimize amount (IU) of factor used per week | 0 |
| History of or anticipated patient adherence to prescribed prophylaxis | 0 |
| Cost of factor replacement regimen to patient | 0 |

Abbreviations: FVIII, factor VIII; PK, pharmacokinetics.

Usage of the WAPPS clinical calculator to simulate prophylaxis regimens varied for individual patients and among providers. The WAPPS clinical calculator was used for 15 participants to simulate prophylaxis regimens under different conditions. The mean number of calculator entries (regimen simulations) per patient was 5.3 (standard deviation [SD] ±4.1). The majority (80%) of regimen simulations in the clinical calculator had a specific factor dose entered by the provider with variable request for calculation of either the infusion interval needed to achieve the provider-entered target trough level or for the estimated trough factor activity achieved by an infusion interval entered by the provider. The most common combination of inputs into the clinical calculator was factor dose and infusion interval, with request for calculation of the trough factor activity level achieved by that regimen (53%). The median dose entered into the calculator was 47.2 IU/kg (SD ±13.8). The infusion frequencies entered ranged from daily to weekly. Although the mode of infusion frequency entered was every other day, just over half of infusion frequencies trialed were for every 72 hours or less frequent. Trough levels targeted for prophylaxis simulation using the clinical calculator ranged from 1 to 10 IU/dL, with 2 IU/dL being the most frequently requested. Following the generation

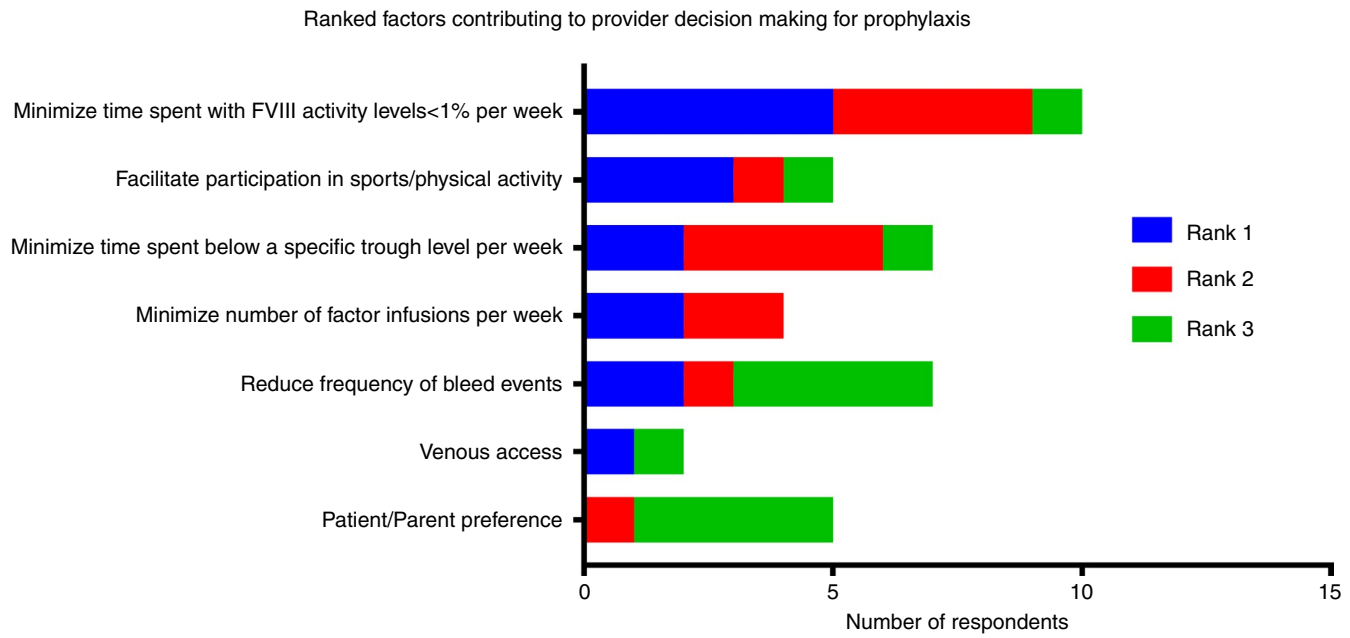


**FIGURE 2** Rank of provider-reported factors contributing to their decision making for prophylaxis. FVIII, factor VIII.

and review of a PK profile and opportunity to use the clinical calculator, 9 patients (60%) had no change in their planned prescribed prophylaxis, 1 initiated prophylaxis, 3 patients increased the frequency of their infusions, and 2 patients decreased the frequency of their infusions. Overall IU/kg/dose remained constant for individual patients despite modifications of infusion frequency. Ultimately, 1 patient transitioned to emicizumab prophylaxis during the follow-up portion of the study; however, the remainder of patients did not have additional changes made to their prescribed prophylaxis regimens during the study.

## 4 | CONCLUSIONS

Our feasibility assessment suggests that, while a larger-scale study powered to evaluate the impact of PK-tailored prophylaxis on clinical and patent reported outcomes is achievable, modification to the study design is needed to attain target enrollment. The most commonly reported reasons for patients declining to participate included challenges in returning for postinfusion blood sampling and interest in switching to emicizumab as an alternate option for prophylaxis. Providing more specific strategies to HTCs about how to overcome perceived challenges with the typical minimum of 2 postinfusion blood samples may facilitate capture of additional participants. The increasing use of emicizumab remains a hurdle to further investigation of how PK information can be integrated into hemophilia management to improve outcomes. While new therapies are a welcomed addition to our therapeutic armamentarium, with one advantage being the possibility of a lower interpatient variability and consequent less need for tailoring treatment, improved understanding of the application of PK data remains of value for those individuals choosing to remain on factor concentrates and for patients globally where emicizumab is not yet available. Since many of the principles of integrating PK data into clinical practice extend to both hemophilia A as well as hemophilia B expanding inclusion criteria to incorporate the hemophilia B population eligible for prophylaxis would be beneficial for successful recruitment of a larger study as well as to broaden the scope of applicability of PK profiles. Other elements of this study including PK profile generation by WAPPS-Hemo, use of the WAPPS clinical calculator by providers, and use of REDCap for clinical data and patient QoL tools used for data collection, were successfully implemented with acceptable completion rates and will be a useful framework for future studies in PK-tailored prophylaxis.

This study has contributed to our understanding, from both a provider and a patient perspective, of how to incorporate individualized PK data into medical decision making for hemophilia A prophylaxis. In general, the population recruited for this study were young patients with hemophilia A, including children and younger adults. This may reflect the participating HTC composition or provider practice, or could reflect more interest in PK among younger patients. Also, younger children generally have more pristine joints and on average more rapid clearance, likely incentivizing both parents and providers to be additionally cautious with prophylaxis decisions.

Motivations for interest in PK studies varied between patients and providers. While participants consistently noted general interest in understanding the FVIII activity levels over time, there was also strong interest in optimizing levels for sports and athletic pursuits as well as minimizing infusion frequency. Providers also selected interest in a general understanding as their primary interest and highlighted their interest in optimizing factor levels for physical activity and improved bleed control. Providers seemed to underestimate patient interest in reducing infusion frequency but ranked minimizing time spent with FVIII activity levels <1 IU/dL as a priority. Our study participants reported either active target joints or regular participation in physical activity or, in some cases, both. A desire to better understand one's own rate of FVIII activity decay in either of these cases makes sense and provides a motivation for participating in a study such as this. Individuals without bleeding symptoms on prophylaxis may also benefit from having a PK profile. These patients potentially need even fewer infusions or lower factor dosing to provide adequate prophylaxis; however, engaging them in the extra steps needed for PK profile may be difficult without clear demonstration of potential benefit.

Providers interacted with the WAPPS clinical calculator for almost all patients, exploring opportunities for modifying dose, infusion frequency, and trough. Typically, providers were interested in the estimation of trough levels for a predetermined factor dose and infusion frequency. Trough levels can be challenging to measure given the requirement for specific timing of blood draw and assay limitations at the lower range of FVIII activity. Estimation of the trough as a target for adequate prophylaxis seems to be valuable to providers in their decision making. The target troughs estimated were predominantly in the 1 to 3 IU/dL range, with most prescribed prophylaxis regimens consistent with a planned trough level of 2 IU/dL. This target likely reflects provider understanding that PK profiles are an estimate and provides a gentle buffer to minimize actual time <1 IU/dL. Despite a frequently reported goal of reducing factor infusion frequency, most participants did not end up changing their prescribed prophylaxis regimen, remaining on every-other-day infusions. While previously providers may have empirically trialed a less frequent infusion regimen or attempted to obtain a specifically timed lab draw at 48 or 72 hours after infusion, this practice may have increased the bleed risk of the patient or added the burden of a specific laboratory visit. The outputs from WAPPS-Hemo facilitates provider communication of a patient's options for prophylaxis including visual materials to assist in collaborative decision making. When there is a clinical need for choosing a higher target trough, the value of PK-informed tailoring is even more evident, as empirical estimation of the dose needed to achieve targets different from 1 IU/dL is very imprecise.

While individual patient PK profiles seem to be increasingly weighed in decision making for hemophilia prophylaxis regimens, it is not the only consideration. It is critical for patients, providers, and other stakeholders to appreciate that although PK profiles may offer important information about an individual patient, there are numerous clinical factors that contribute to successful prophylaxis. Further

demonstration of the impact of the added patient and provider efforts to generate and analyze PK data on clinical and patient-reported outcome in clinical practice is needed. Data from this feasibility study will provide baseline data to inform power calculations for a prospective study as well as the number of HTCs needed to achieve target enrollment. Prospective evaluation of whether use of popPK profiles change factor concentrate use, reduce annualized bleed rates, and improve patient assessment of disease burden is important so that we do not unnecessarily add complexity to prescribed prophylaxis without adding clinical value. Additional assessment of patient characteristics and motivations for participating in PK studies may add clarity regarding patient subgroups that may particularly benefit from use of popPK in clinical practice and help HTCs understand how to best guide application of popPK into their routine practice. For a prospective interventional study, incorporation of a patient-facing tool for estimating blood factor activity levels (myWAPPS, www.myWAPPS.org), as a companion application to the WAPPS-Hemo–generated popPK profiles, may provide an educational element for patients and further support adherence to prophylaxis through the ability to individually tailor infusion timing based on estimated factor levels and activity-based bleed risk assessment.

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SEC has participated as a consultant for Bayer, Bioverativ, CSL-Behring, Genentech, Novo Nordisk, Octapharma, Shire, and her institution receives research funding from Genentech, Novo Nordisk, Pfizer, and Spark Therapeutics; APW has participated as a consultant for Novo Nordisk, Octapharma, Shire, Bayer, Biomarin, and UniQure; OK reports consulting fees or honoraria from Bayer, Shire, Octapharma, and Pfizer, outside the submitted work; KMH has no conflicts of interest to disclose; AJB speaker honorarium from Novo Nordisk; SL reports participation on steering committee for UniQure; CHTY speaker honorarium from CSL Behring; AI reports institutional project based funding via research or service agreements with Bayer, CSL, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, and Takeda.

## AUTHOR CONTRIBUTIONS

SEC contributed to concept and design, data collection, analysis and interpretation of data, critical writing and revising the intellectual content, and final approval. APW, OK, CHTY, KH, AJB, SL, and AI contributed to data collection and interpretation, revising the intellectual content, and final approval.

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