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Population Pharmacokinetics of Plasma-Derived Factor X Using Clotting and Chromogenic Assays: A WAPPS-Hemo Model

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ABSTRACT

Background: Hereditary factor X (FX) deficiency is a rare autosomal recessive bleeding disorder for which individualized pharmacokinetic (PK) assessment can support optimized prophylactic management. The WAPPS-Hemo platform enables population pharmacokinetic (PopPK) individualized PK predictions based on sparse sampling.

Aim: To develop and evaluate a PopPK model for Coagdex, a FX concentrate, using manufacturer-provided PK data for its implementation on the WAPPS-Hemo platform.

Methods: Model development followed the standard PopPK modelling approach (structural, compartmental and variance partitioning steps and goodness of fit assessments). Covariates tested were age, body weight, height, fat-free mass, sex and assay type. Predictive evaluation was performed through Visual Predictive Checks (pcVPC) and Limited Sampling Analysis (LSA). LSA strategies were evaluated using dosing and sampling scenarios consistent with recommended treatment regimens for plasma-derived FX (pdFX) concentrate.

Results: A two-compartment model accounting for between-occasion and between-subject variability with fat-free mass and assay-type as main covariates was selected. Evaluation showed good predictive capabilities.

Conclusion: We have developed a PopPK model to support WAPPS-Hemo individualized prophylaxis in FX deficiency using sparse PK data. Prospective PK data collected through the WAPPS-Hemo database will be used to further characterize Factor X PK and enhance patient care.

1 | Introduction

Hereditary factor X deficiency (HFXD) is a rare autosomal recessive bleeding disorder, with population estimates suggesting it affects roughly one in half a million to one million individuals, more prevalent in populations for which consanguinity is more common [1, 2].

FX plays a central role in thrombin generation, and reduced levels or dysfunction of the protein lead to impaired coagulation and a wide spectrum of bleeding manifestations. A high-purity plasma-derived factor X concentrate (pdFX) became available in the United States in 2015 and in Europe the following year, providing a single-factor replacement option for on-demand treatment, perioperative management, routine prophylaxis, and control of bleeding episodes in patients with inherited FX deficiency [3–5].

Clinically, FX deficiency produces a bleeding profile that overlaps with haemophilia A and B, with recurrent haemorrhages involving joints, muscles, and mucosal tissues. FX deficient patients

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are among the most severely affected within the spectrum of rare bleeding disorders, and in the severe form of this deficiency, life-threatening manifestations such as gastrointestinal bleeding, umbilical stump bleeding, and intracranial haemorrhage may occur.

Unlike X-linked haemophilia A or B, FX deficiency affects males and females equally. Women may experience additional gynaecologic and obstetric complications, including heavy menstrual bleeding and postpartum haemorrhage, which contribute substantially to disease burden [3].

Prophylaxis aims to maintain FX activity above a protective level, often cited as at least 5 IU/dL, to reduce bleeding risk and improve long-term outcomes [4, 6, 7]. Individual pharmacokinetic (PK) assessment can guide dose personalization by identifying patient-specific differences in clearance, half-life, and distribution of FX in the body. However, in haemophilia, traditional PK studies typically require multiple strategically timed post-infusion samples to adequately characterize both the distribution and elimination phases. Although such studies can provide robust individual PK profiles, the need for repeated blood draws and coordinated clinic visits may be burdensome in routine clinical practice, particularly for paediatric patients and their caregivers. PopPK approaches provide a practical alternative, allowing reliable estimation of individual PK parameters from sparse sampling, especially when combined with Bayesian forecasting.

The Web-Accessible Population Pharmacokinetic Service—Haemophilia (WAPPS-Hemo) was established to support individualized PK-guided therapy across treatment centres worldwide [8]. It currently serves >800 haemophilia treatment centres worldwide and >16,000 patients, with >36,000 individual PK profiles estimated and >200,000 records of home-based patient's self-reported concentrate infusions. The database enables the development and validation of PopPK models for any coagulation factor concentrates [9]. These models, built using nonlinear mixed-effects methods and Bayesian forecasting, allow clinicians to generate individualized PK profiles based on a few post-infusion samples.

Extending the WAPPS-Hemo framework to FX deficiency, where real-world PK data remain extremely limited, is an important next step. Developing a PopPK model for FX concentrate would facilitate personalized prophylaxis, strengthen the evidence base for FX pharmacology, and help harmonize care for this rare disorder globally.

This manuscript presents the development of a PopPK model for plasma-derived factor X using manufacturer-sourced PK data and describes its evaluation through a prediction-corrected visual predictive check (pcVPC) to assess the model's predictive performance and a Limited Sampling Analysis (LSA) to determine the optimal sparse sampling strategies. These assessments provide a comprehensive evaluation of model suitability for individualized Bayesian forecasting [10] and support implementation of the factor X population PK model within the WAPPS-Hemo platform, which accommodates factor-specific population PK models and is not limited to FVIII and FIX concentrates (e.g., plasminogen) [11].

2 | Materials and Methods

2.1 | Data

The dataset combined two phase III, open-label, multicentre studies—TEN01 and TEN02 (NCT00930176, NCT01721681)—which evaluated the safety and efficacy of Coagadex in adults and paediatric patients with HFXD [3, 4]. Participants in both studies had FX activity levels below 5% and a clinical history indicating the need for replacement therapy. HFXD was classified as moderate in 1 paediatric and 2 adult participants and as severe in 8 paediatric and 14 adult participants. Characteristics of both studies are summarized in Table 1. Key exclusion criteria included the presence of FX inhibitors, clinically significant comorbidities such as liver or renal disease or other coagulopathies/thrombophilias, active bleeding at the time of PK assessment, known hypersensitivity to FX concentrate, and recent participation in another clinical trial.

The adult study [3] enrolled 16 participants and included matched concentration–time profiles for both clotting and chromogenic assays. Each participant received a single dose at two visits approximately six months apart, with 12 blood draws yielding 12 concentration measures per visit and assay type (clotting and chromogenic), except for one patient who did not complete the second visit (Figure 1, top panel). The paediatric study [4] included nine children assessed with a clotting assay. Each child contributed PK data from five visits, except two who completed two full visit cycles. Predose samples were collected at visits 1 and 5. Two post-infusion concentrations were obtained at visits 1 and 2, and one post-infusion concentration at each subsequent visit (visits 3–5), yielding five post-infusion concentrations per child (or ten for the two patients with duplicate cycles; Figure 1, bottom panel).

Body weight and height values of patients from the paediatric study from visits 2, 3 and 4 were determined based on the linear interpolation method using values from visits 1 and 5. Although paediatric growth may occur nonlinearly, the approximately six-month interval between visits 1 and 5 supported the use of linear interpolation as a reasonable approximation. Two patients (from each adult and paediatric studies) had their height values imputed based on age, weight and sex from the National Health and Nutrition Examination Survey (NHANES) data [12].

Agreement between clotting- and chromogenic-assay type concentrations in the adult study was assessed using both Bland–Altman and Passing–Bablok methods.

2.2 | Model Development

The PopPK model was built employing non-linear mixed effects modelling methodology and was implemented on NONMEM and PDxPop (v7.4 and v5.3, respectively; ICON Development Solutions, Ellicott City, MD, USA) using the first order conditional estimation with interaction (FOCEI) method with the LAPLACIAN option. Graphical analysis was conducted in R (R Core Team, 2025, v 4.4.1) using the RStudio IDE (Posit team, 2025, v2024.4.2.764). Samples that were below the limit of quantification (BLQ) were handled using the M3 method [13].

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TABLE 1 | Studies on plasma-derived FX.

	TEN 01 Study—adolescent and adult	TEN02 study –paediatric <12 years of age
Phase of study	Phase III	Phase III
Indication	HFXD	HFXD
No. of subjects	16 adults 2/16 (FX:C 1–5 IU/dL) 14B/16 (FX:C <1 IU/dL)	9 children 1/9 (FX:C 1–5 IU/dL) 8/9 (FX:C <1 IU/dL)
Dose, route	25 IU/kg, IV bolus	50 IU/kg, IV bolus
Duration	6 months	6 months
Assay types	Clotting and chromogenic	Clotting
No. observations	12 per subject, 2 visits (baseline and end of study)	5 to 10 visits per subject
LLOQ	1 IU/dL	1 IU/dL
Sampling	Predose, 0.25, 0.5, 1, 3, 6, 24, 48, 72, 96, 120 and 144h	Predose, 48/72 h, day 9–28, day 29–42, 6 months
Covariates	Height, body weight, age, sex, ethnicity, race, severity	Height, body weight, age, sex, ethnicity, race, severity
Results	• Plasma FX:C and FX:Ag reached a peak at 0.4–0.5 h. • Mean peak plasma FX:C levels were 50 and 56 IU/dL for clotting and chromogenic assays respectively. • A biphasic decay in plasma FX:C was observed over the course of 144-h	• Trough FX:C levels remained >5 IU/dL for all subjects after the last dose adjustment study visit. • Mean incremental recovery was significantly lower for younger (0–5 years) vs older (6–11 years) subjects: 1.53 vs 1.91 IU/dL per IU/kg, respectively (p = 0.001).

The methodology for model development was implemented in line with the model-building WAPPS-Hemo standard protocol [9]. Succinctly, the modelling process started by exploring structural 1-, 2- and 3-compartment models while accounting for between-subject and between-occasion variability [14]. Patient-specific endogenous baseline factor activity level was directly incorporated into the model as provided in the data set. Residual unexplained variability was explored in the form of additive and/or proportional specifications. Covariate relationships that would account for the broad age range in the data set involved age (years), body weight (kg), height (cm), fat-free mass (FFM; kg), sex (0 for males and 1 for females) and assay type (0 for clotting and 1 for chromogenic). FFM was derived using the method in Al-Sallami et al. for females and males, which incorporates maturation effects in children and converges to the established adult FFM model at older ages [15].

Model development relied on comparison of PopPK model selection measures, such as Akaike and Bayes information criteria (AIC and BIC) for the base model's structure and the objective function value (OFV) for the testing of covariates and the correlation between PK parameters (central clearance and volume of distribution). An OFV decrease higher than 3.84 when testing for a single model parameter was deemed significant at a 5% level (under the Chi-Squared distribution with one degree of freedom). Further criteria for model selection involved η-shrinkage and graphical goodness of fit analyses using conditional-weighted residuals as well as population and individual predictions and predicted random effects (predicted η's). The estimated sampling variability of the parameter estimates informing the reported relative standard errors (RSEs%) and confidence intervals (CIs) was obtained under the non-parametric bootstrap resampling method with 1000 replicates.

2.3 | Assessment of Predictive Performance

The model's predictive performance was evaluated through a prediction-corrected Visual Predictive Check (pcVPC) and a Limited Sampling Analysis (LSA), the same evaluation methods that are employed for the factor VIII and IX PopPK models deployed in WAPPS-Hemo [10]. The prediction-corrected visual predictive check (pcVPC) was implemented to assess the extent to which the model can recreate the central tendency and variability of the observed data [16]. The model was used to generate 1000 predictions on simulated factor activity levels vs. time which were visually compared with the observed data using the median, the 10th and 90th percentiles, overlaid by the corresponding 90% prediction intervals

The LSA was conducted by simulating PK observations and covariates to evaluate the model in relation to its ability to predict PK outcomes (terminal half-life, central clearance and volume and time to 3% and 2% thresholds) under limited sampling conditions and to highlight those that provide the most accurate and precise estimates [17]. The simulated PK observations from a virtual population of 1000 individuals followed a rich sampling design per subject receiving the recommended dose of 25 IU/kg/week with 12 sampling times, including predose [7]. This reference data set was used to select subsets of subject-specific time points, which represented sparse sampling designs and individual PK parameters were estimated using Bayesian

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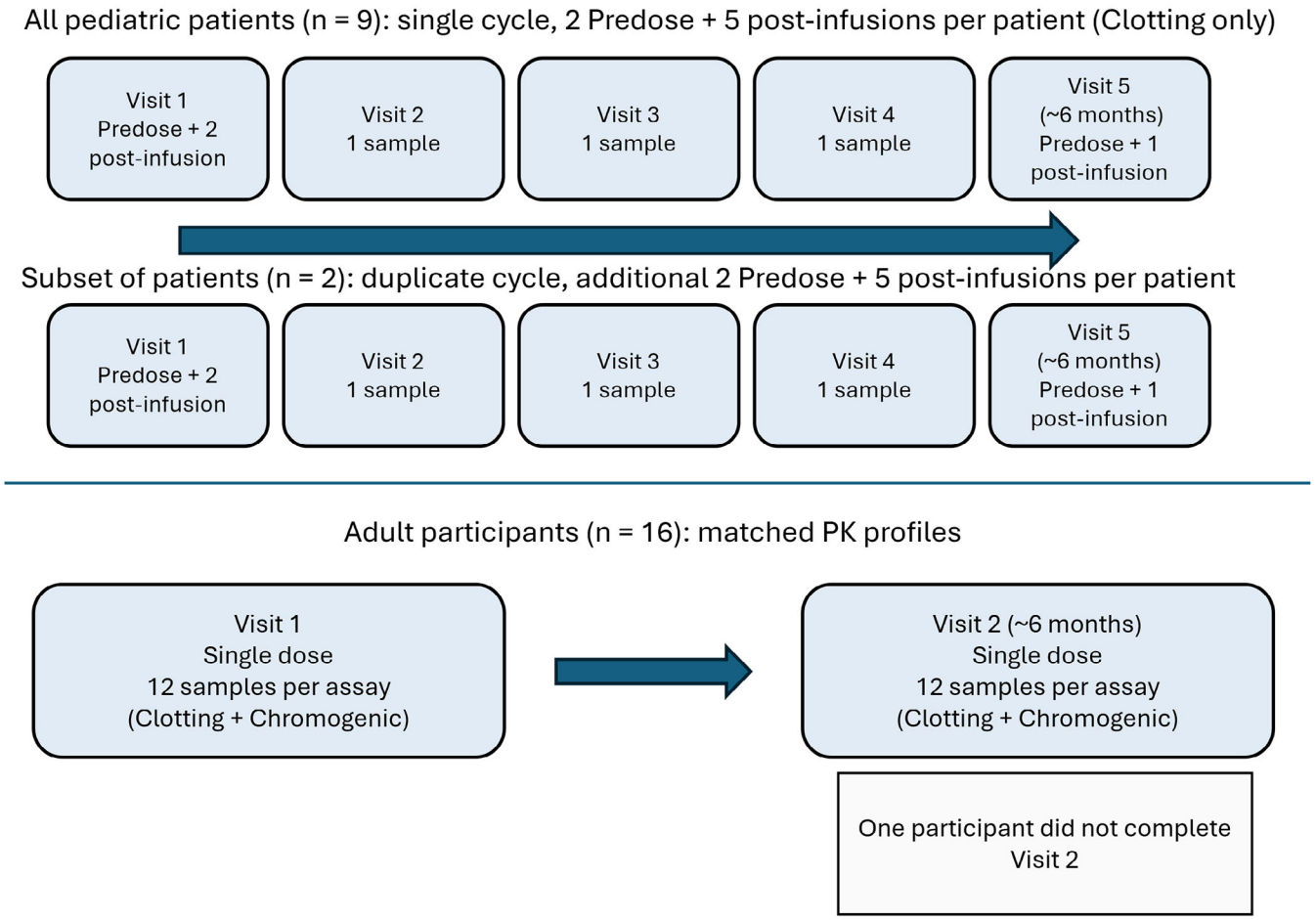

FIGURE 1 | Flowchart of the paediatric and adult clinical studies (TEN02 and TEN01), including PK sampling schedules.

forecasting. Relative errors (REs) were calculated by comparing these estimates with reference values. RE distributions were assessed using boxplots and summary statistics, where bias was defined as the median RE and variability as half the interquartile range (IQR/2).

3 | Results

3.1 | Data

There was a total of 25 patients across ages 1.8 to 58 years, from which 15 were female (5/9 patients in the paediatric study, ages < 12 years; 10/16 patients in the adult study, ages 12 to 58 years). Summary statistics of subject characteristics by age group (at the time of the first visit) are presented in Table 2 and their distributions as well as pair-wise Spearman correlations and scatterplots in Figure 2.

A total of 409 clotting- and 330 chromogenic-assay FX concentrations were analyzed and are shown in Figure 2, including 22 paediatric predose clotting-assay samples. Only 4 chromogenic measurements fell below the limit of quantification (LLOQ = 1 IU/dL), and none of the clotting assay values were BLQ. Each occasion—defined as the concentration–time sequence immediately following a dose—varied by participant, with adults contributing 2–4 occasions and children 3–8 occasions (median: 4). Sampling density ranged from 1 to 11 post-infusion concentrations per occasion, with an overall median of 11.

The Bland–Altman analysis showed close overall agreement between clotting- and chromogenic-assay concentrations, with only about 4% of paired results falling outside the limits of agreement and a mean difference indicating a modest systematic offset between assays. Passing–Bablok regression supported this interpretation, as the intercept suggested no meaningful constant bias, whereas the slope indicated a significant proportional bias. Taken together, as shown in Figure 3, these findings showed that although the two assay types were generally aligned, a consistent proportional difference existed and was addressed in the subsequent modelling.

3.2 | Model Development

Several pharmacokinetic models were evaluated to identify the one that best described the FX concentration data (Table S1). A two-compartment model provided the best overall fit. Allowing pharmacokinetic parameters such as clearance (CL) and central volume of distribution (V1), to vary between patients (between-subject variability, BSV) improved model performance. Allowing clearance to vary between visits (between-occasion variability,

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TABLE 2 | Summary of patient characteristics.

	Statistic	Age (years)	Height[a] (cm)	Body weight (kg)	Fat-free mass (kg)	Dose/kg[b] (IU/kg)
Adults	N	16.0	16.0	16.0	16.0	16.0
	Mean	27.1	162.7	66.6	43.9	24.5
	SD	15.1	10.3	18.4	9.8	1.8
	CV%	55.7	6.3	27.7	22.3	7.5
	Median	20.0	161.5	65.0	42.6	23.9
	Min	12.0	151.0	41.0	28.5	23.5
	Max	58.0	182.0	118.6	61.0	30.1
Children	N	9.0	9.0	9.0	9.0	9.0
	Mean	7.2	120.7	26.6	16.7	48.1
	SD	4.4	29.0	15.4	9.1	3.6
	CV%	61.8	24.0	58.0	54.4	7.5
	Median	8.6	132.0	18.7	13.6	49.7
	Min	1.8	84.0	10.9	7.1	38.8
	Max	11.9	157.0	46.4	28.9	50.1

Abbreviations: CV%: coefficient of variation; Max: Maximum; Min: minimum; N: number of patients; SD: standard deviation.

[a]Two values were imputed.

[b]Based on dose given at the initial visit.

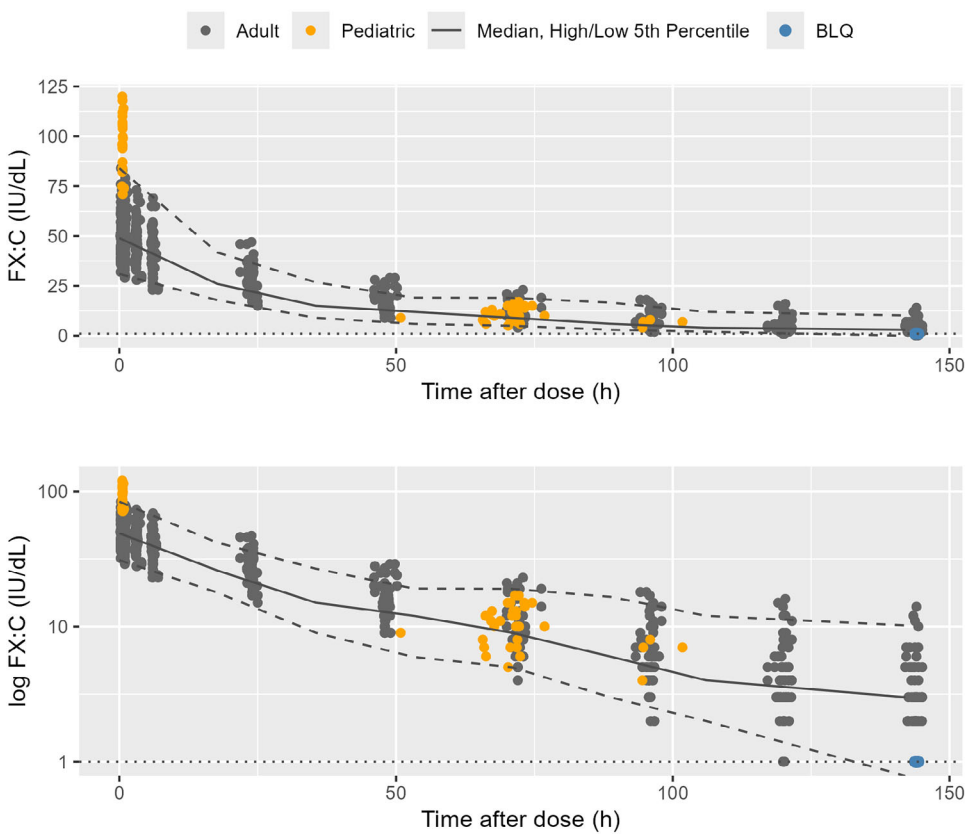

FIGURE 2 | Post-infusion concentrations by adult and paediatric study on a linear (upper) and semi-log (lower) scale. Horizontal dashed line indicates LLOQ = 1 IU/L.

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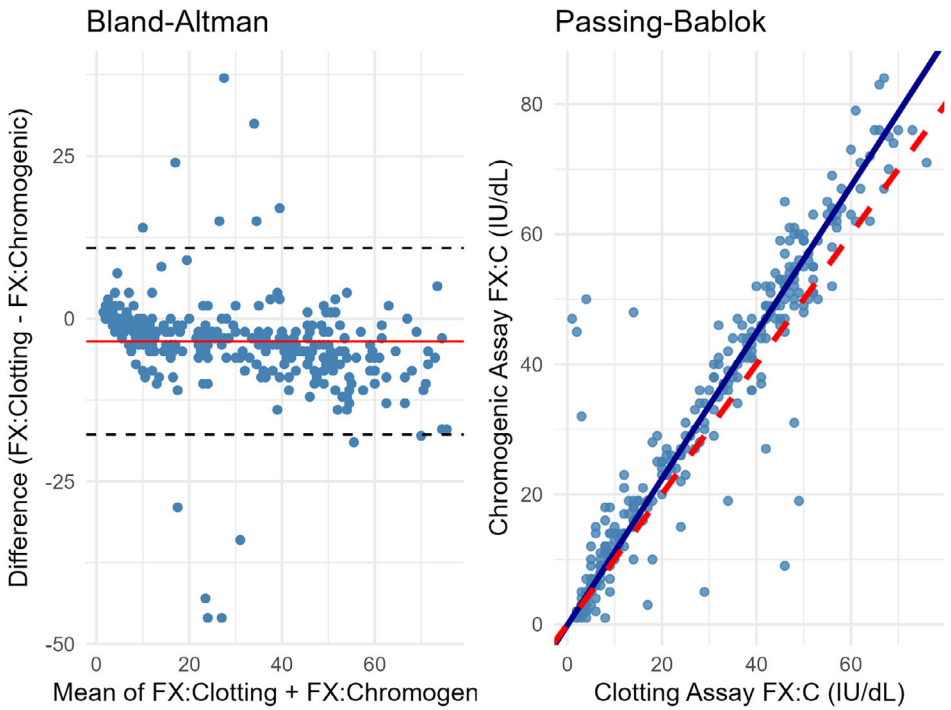

FIGURE 3 | Agreement between clotting and chromogenic concentrations via Bland-Altman (left) and Passing-Bablok regression (right).

BOV) further improved the fit. The final model adequately described the observed data and was selected for covariate analysis.

Assessment of potential covariates (Table S2 and Table S3) resulted in fat-free mass (FFM) having the strongest influence on FX PK, significantly improving the precision of both CL and V1 estimates. Because FFM inherently captures the effects of height, weight, age, and sex, it was selected as the primary covariate. To ensure that the model reliably extrapolates to younger patients, the peripheral volume (V2) was also allometrically scaled to FFM. Since preliminary assessment of the relationship between measurements obtained with clotting and chromogenic assays showed strong agreement (Figure 2), assay type was incorporated as a covariate on dose in the PopPK model, which enabled the inclusion of a larger data set comprising both chromogenic and clotting measurements. Further, a correlation term between CL and V1 resulted highly significant. Table 3 presents the parameter estimates with their bootstrap-based relative standard error (RSE%) and 95% confidence interval (CI).

Residual-based standard goodness of fit assessment and diagnostics on predicted random effects resulted in a satisfactory alignment with the distributional assumptions of the model and a strong association between observed and individual predictions ($R^2 = 97\%$, supplemental Figures S1–S3).

3.3 | Assessment of Predictive Performance

3.3.1 | Prediction-Corrected Visual Predictive Check

The pcVPC in Figure 4 shows good agreement between observations and simulations: the observed median remains within the 90% prediction interval, and the observed fifth and 95th percentiles align well with their simulated bands, indicating that both central tendency and variability are well captured.

3.3.2 | Limited Sampling Analysis

Prediction accuracy and precision for the sparse sampling scenarios are shown in Figure 5 via comparative boxplots of the relative errors (REs) for terminal half-life, clearance, central volume, and the times to reach the 3% and 2% concentration thresholds. The simulated scenarios included various 3- and 2-sample designs, both with and without a predose measurement and a preceding dose (detailed information by sampling design regarding the medians, first and third quartiles is available on the Table S4).

4 | Discussion

We have developed, validated and implemented in WAPPS-Hemo a PopPK model for FX concentrate offering the opportunity for individualized prophylaxis to FX deficiency patients.

Model-based geometric means of terminal half-life, C_{max}, CL and Vss were generally consistent with those reported by a published non-compartmental analysis (NCA) on the TEN01 study data set in adults [3]. For the clotting assay: terminal half-life was 26.6 h, C_{max} was 77.1 IU dL^{-1}, CL was 1.6 mL h^{-1} $kg^{-1}$and Vss was 60.8 mL kg^{-1} (vs. terminal half-life: 30.3 h, C_{max}: 50.4 IU dL^{-1}, CL: 1.35 mL h^{-1} $kg^{-1}$and Vd_{ss}: 56.3 mL kg^{-1}). For the chromogenic assay: terminal half-life was 31.3 h, C_{max} was 56.1 IU dL^{-1}, CL was 1.35 mL h^{-1} $kg^{-1}$and Vss was 60.1 mL kg^{-1} (vs. terminal half-life: 33.8 h, C_{max}: 56.3 IU dL^{-1}, CL: 1.17 mL h^{-1} $kg^{-1}$and Vd_{ss}:

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TABLE 3 | PopPK model parameter estimates.

Parameter (unit)	Estimate	RSE%	95% CI lower bound	95% CI upper bound
		Structural model		
CL_{pop} (dL/h)	0.008	3.1	0.007	0.008
$V1_{pop}$ (dL)	0.285	2.4	0.272	0.299
Q_{pop} (dL/h)	0.011	41.8	0.004	0.024
$V2_{pop}$ (dL)	0.044	16.0	0.031	0.059
		Covariate effects		
FFM effect on CL	0.723	8.3	0.570	0.814
FFM effect on V1	0.900	4.6	0.808	0.966
FFM effect on V2	1.000	—	—	—
ASSAY effect on Dose	0.066	16.0	0.046	0.086
		Between subject variability		
CV% of CL [Shrinkage %]	15.11 [4.61]	11.7	0.110	0.179
Cor CL, V1	0.751	15.2	0.473	0.922
CV% of V [Shrinkage %]	12.00 [3.59]	16.5	0.078	0.156
		Between occasion variability		
CV% of CL	10.10	13.4	0.074	0.126
		Residual variability		
CV% of proportional RUV [Shrinkage %]	10.76 [7.11]	5.4	0.096	0.118
SD of additive RUV (IU/L) [Shrinkage %]	0.473 [7.11]	23.5	0.244	0.659

Abbreviations: Assay = 0 if clotting, 1 if chromogenic; CI: confidence interval; CV%: coefficient of variation; RSE%: 100% x SE/Estimate; SD: standard deviation.

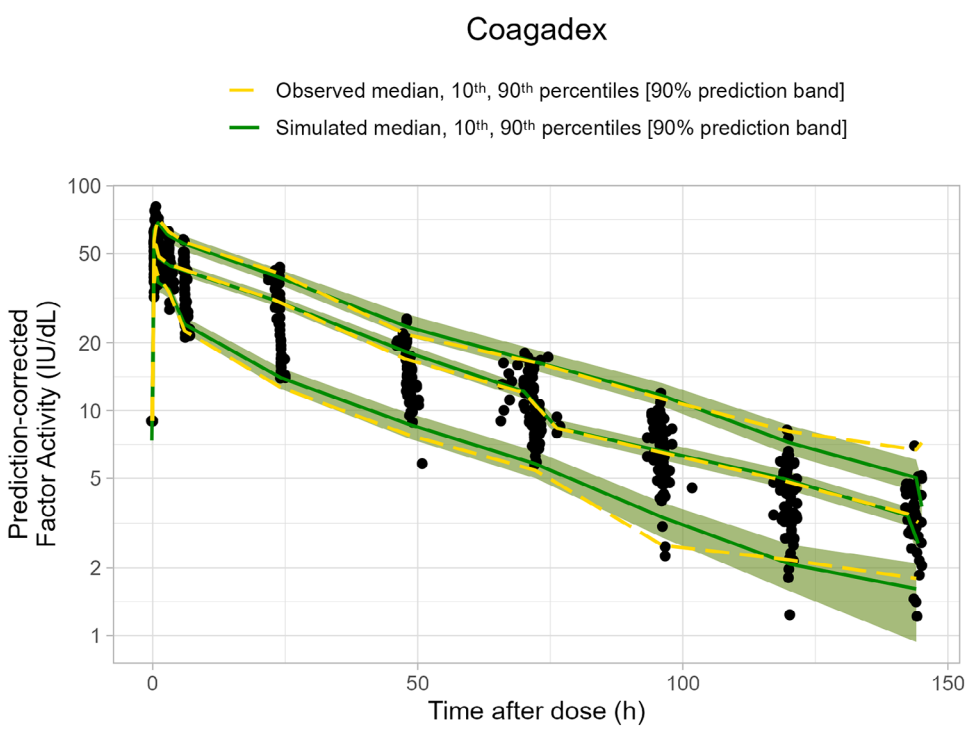

FIGURE 4 | Prediction-corrected visual predictive check (pcVPC) for FX PopPK model on the semi-log scale.

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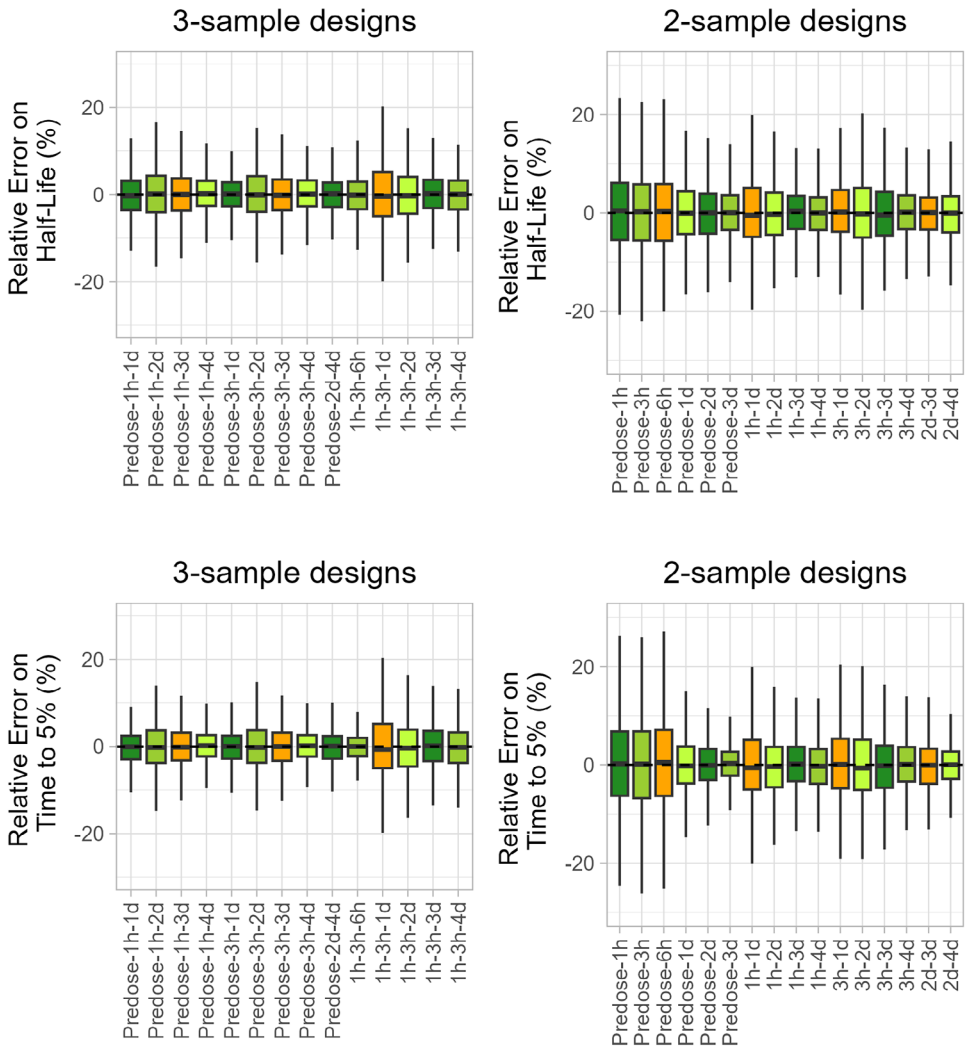

FIGURE 5 | LSA for FX PopPK model.

54.5 mL kg^{-1}). Differences are expected due to methodological discrepancies between NCA and model-based estimation.

Beyond confirming FX PK with a different approach, this work enables predictive modelling to support individualized treatment. Specifically, we used the same modelling approach perfected by our group for FVIII and FIX where the individual variability is incorporated to maximize the efficiency of Bayesian forecasting [10]. Another strength of our work was to incorporate children's data through allowing sparse samples into the derivation cohort, another benefit allowed by PopPK modelling.

As an effective tool to evaluate the predictive assessment of the model, the LSA showed reasonably precise and accurate individual PK predictions with only 2 to 3 samples. The flexibility that Bayesian predictions, in conjunction with this PopPK model provide, is reflected in the reduced patient burden, especially for the paediatric population. Bias was minimal for all simulated designs (median RE% values: -0.5% to 0.5%), and precision was reasonable (IQR/2 RE: 3.5% to 7%). Inclusion of a prior dose amount and a predose measurement when taking 3 samples led to better predictions, achieving a bias as low as -0.23% and a precision of ±3%.

Finally, to our knowledge this is the first and only model available to support treatment of HFXD patients. The PopPK model has been integrated into the WAPPS-Hemo platform (www.wapps-hemo.org) to support prophylactic replacement therapy for patients with FX deficiency. Users can now select the specific disease from a drop-down menu (Figure 6). When creating a new FX-deficient patient, the fields for adding or editing PK studies automatically adjust to reflect FX-specific treatment details and potentially bleeding logs. Collecting dose-response data in a rare disease population enables future refinement of FX PK and helps to optimize clinical management.

We expected limited data to constrain model development in this ultra-rare disease; however, FX time profiles proved adequate. One limitation which remains to be overcome with future data collection is the absence of records combining measurements and bleeding logs to identify a protective FX plasma level. Therefore, one may want to consider carefully calibrating treatment intensity on an individual patient base, adjusting treatment by using predicted concentration at the time of bleeding. Another limitation is the small number of patients used to estimate the model, which can be overcome in the future by updating the current model

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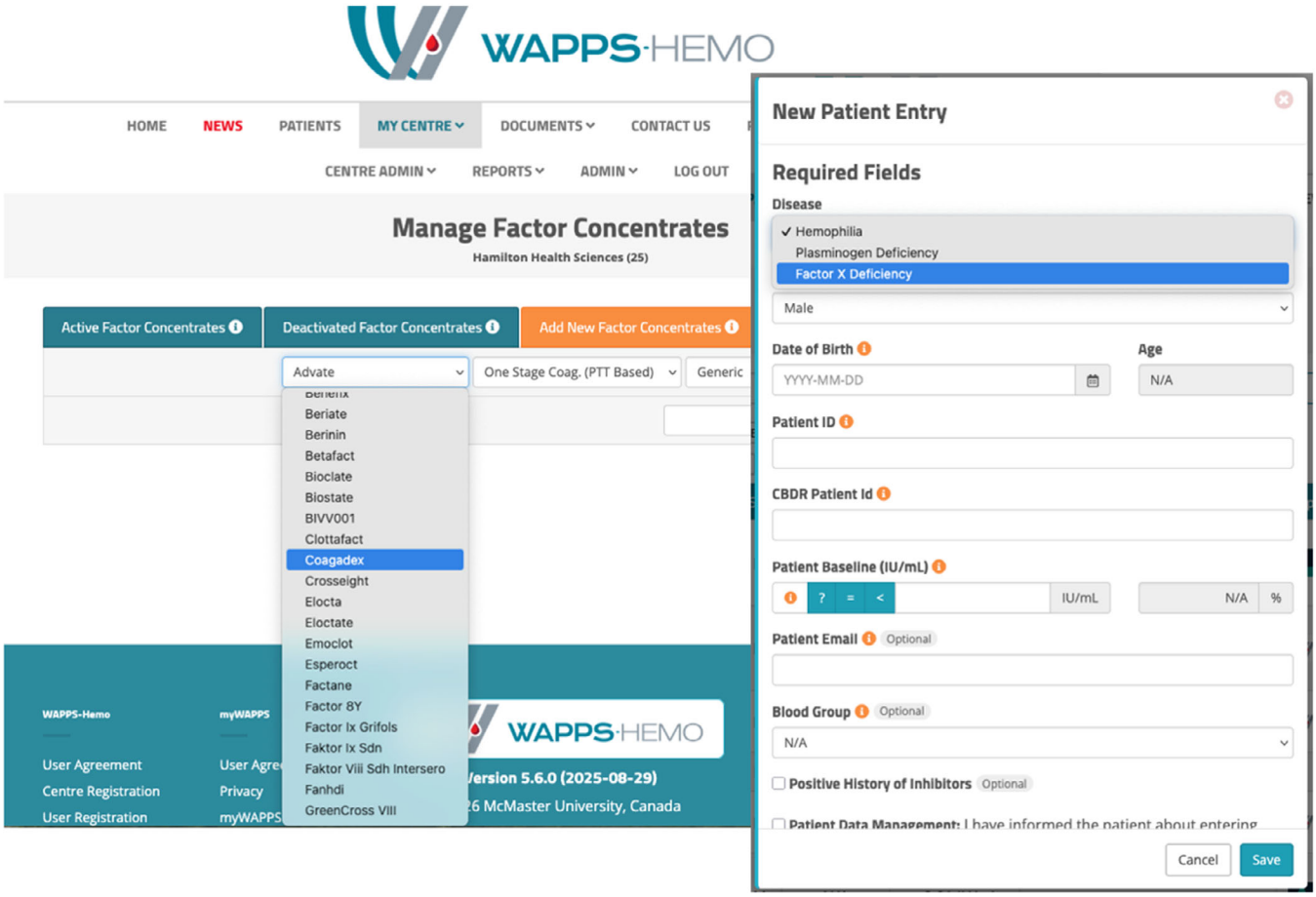

FIGURE 6 | New patient on Coagadex integration on WAPPS-Hemo platform.

using new WAPPS-Hemo data to describe more accurately the between-patient variability in the real world.

The deployment of the FX PopPK model within WAPPS-Hemo represents an important step to increase understanding and treatment of this rare disorder through the collection of real-world data. The most immediate positive implication is to support treating physicians in maintaining plasma levels at a protective level at all times and to select the optimal timing for confirmatory measurements. A second benefit is the provision of an educational tool to help physicians ensure that patients understand the variability in plasma concentrations between infusions, potentially improving treatment adherence. Patients using the myWAPPS app may gain a better understanding of expected FX plasma level variability between infusions, supporting treatment adherence and informed discussions with their healthcare providers regarding daily activities and bleed-risk management. A third potential benefit, in cases where a relationship between FX plasma levels and the occurrence of bleeding events can be established, is the optimization of treatment based on individual needs.

5 | Conclusions

This work delivers a platform-deployed PopPK tool that can be used to individualize prophylaxis for hereditary FX deficiency in routine care. By enabling Bayesian forecasting from sparse post-infusion samples, the model supports practical PK-guided dosing to help maintain protective trough activity and reduce bleeding risk without requiring intensive sampling. Implementation within WAPPS-Hemo provides clinicians with immediate access to individualized PK profiles and dosing insights and offers a mechanism to harmonize management and strengthen evidence-based treatment for this rare bleeding disorder as additional real-world data accrue.

Author Contributions

Dagmar M. Hajducek, Pierre Chelle, Manuela Scarpellini, Andrea Edginton, Alfonso Iorio contributed in the concept, design and data acquisition, drafting, critical revision, approval of final draft, agreement for accountability in ensuring that questions related to the integrity of the work are appropriately resolved.

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and dissemination of the study findings, including publication activities. The authors were responsible for the analysis and interpretation of the data, preparation of the manuscript, and the decision to submit the manuscript for publication.

Ethics Statement

The authors confirm that the research was conducted in accordance with the ethical standards of the responsible committee on human experimentation, the principles of the World Medical Association Declaration of Helsinki, and Wiley's ethical publishing policies. The study was approved by the University of Waterloo Research Ethics Board (REB Protocol #47747).

Consent

The present study involved secondary analysis of de-identified person-level data. No new data were collected, and no participants were contacted. The University of Waterloo Research Ethics Board determined that additional participant consent was not required for the current analysis.

Conflicts of Interest

Dagmar M. Hajducek, Pierre Chelle, Alfonso Iorio, Andrea Edginton have no conflicts of interest. Manuela Scarpellini is an employee at Kedrion S.p.A.

Data Availability Statement

The data underlying this study were obtained from Kedrion S.p.A. under a confidential data-sharing agreement with the University of Waterloo. The agreement does not permit the authors to share the data with third parties. Consequently, the data are not publicly available and cannot be provided by the authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Table S1: Evaluation of structural models. **Table S2**: Estimated single covariate models. **Table S3**: Estimated covariate models after including FFM on CL and V1 and FFM-allometrically scaled V2. **Table S4**: Limited sampling results. **Figure S1**: Distribution of predicted random effects on clearance and volume, ETA1 and ETA2, final model. **Figure S2**: Predicted vs. observed values on a linear (left) and semi-log (right) scale, final model. **Figure S3**: Plots of conditional weighted residuals (CWRES) for final model, final model.

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