ISTH SSC on Factor VIII and IX. Estimating and interpreting individual patients' pharmacokinetic profiles in persons with Hemophilia A or B using a population pharmacokinetic approach.

Alfonso Iorio[1,2], Victor Blanchette[3], Jan Blatny[4], Peter Collins[5], Kathelijn Fischer[6], Ellis Neufeld[7].

1 Department of Health Research, Methods, Evidence and Impact, McMaster University
2 Department of Medicine, McMaster University, Canada
3 Division of Hematology/Oncology, Hospital for Sick Children and Department of Pediatrics, University of Toronto, Ontario, Canada
4 Department of Paediatric Haematology, University Hospital Brno, Brno, Czech Republic
5 Arthur Bloom Haemophilia Centre, University Hospital of Wales, School of Medicine, Cardiff University, Cardiff, United Kingdom
6 Van Creveldkliniek, University Medical Center, Utrecht, the Netherlands
7 St Jude Children's Research Hospital, Memphis, USA

Keywords: Pharmacokinetics, Population Pharmacokinetics, factor VIII, factor IX, tailored prophylaxis, individualized prophylaxis

Word count: 1500

References: 30

Correspondence to:

Alfonso Iorio

McMaster University
1280 Main St West
Hamilton, ON L8S 4K1
Tel: +1 905 525 9140 ext 22421
Fax: +1 905-526-8447
e-mail: iorioa@mcmaster.ca

Introduction.

The ISTH SSC on Factor VIII/IX has previously issued guidelines for studies assessing the pharmacokinetics (PK) of factor concentrates [1,2].They suggested drawing 10 or 11 blood samples over a period of 32-48h or 50-72h, after infusing 25-50 or 50-75 IU/kg, respectively for factor VIII (FVIII) or factor IX (FIX), in cohorts of 12-15 patients with a crossover design. Such PK studies are not ideal for tailoring the treatment of individual patients, mostly for the requirement of several blood samples. Due to broad inter-individual variation, the individual disposition of FVIII and FIX cannot be predicted from morphometric characteristics and average PK parameters, but requires empirical assessment in each individual [3–6]. Previous guidance of this ISTH SSC described the PK methodology for the prediction of individual trough levels of FVIII [7]. The present communication, building on recent advancements in the population PK (PopPK) of FVIII and FIX [8], adds to the former documents.

PopPK models have been derived for FVIII [9–11] and FIX [8,12–14], enabling Bayesian estimation of individual PK from limited samples [15,5,6]. PopPK solutions are available to support individual forecasting for several factor concentrates [16–18]. Observing the correlation between plasma factor levels and bleeding history [3,19] has prompted a graded approach to prophylaxis, where appropriate target levels are identified for different patients, considering the variability in clinical and lifestyle characteristics [20–22]. Extended half-life (EHL) concentrates, whereas supporting more acceptable and less burdensome treatment regimens, increase the complexity of dosing optimization. A "trial-and-error" approach to identify the most appropriate regimen for each patient is less efficient for achieving and maintaining target factor levels optimized for individual patients.

The aim of this document is to provide guidance for performing, interpreting, and applying individual PopPK assessments in routine clinical practice.

Practical recommendation for a limited sampling approach to individual PK profiling.

1. **Adopt testing conditions as close as possible to routine use of the factor concentrate.**
   1.1. <u>Use any sample drawn during a routine clinical assessment</u>, including samples drawn following home infusions.
   1.2. <u>Use the first or any subsequent infusion</u> of the concentrate.
   1.3. <u>Combine time points from multiple infusions,</u> decreasing the burden of PK studies. A typical case is using two consecutive infusions where the trough of the first is used also as pre-dose for the second.
   1.4. <u>Do not perform a wash-out (box)</u> for patients on a regular treatment schedule and for whom the baseline factor level (box) is known. Performing a wash out introduces ethical and practical barriers to assess individual PK in routine clinical care, and may bias the assessment not reflecting the accumulation of clotting factor concentrate which may occur on standard prophylaxis [7,6].
   1.5. <u>Take measurements after the dose the patient is routinely treated with</u>. Individual PK assessment does not require a standardized dose, and is likely more informative when done with the dose the patient is currently using.

1.6. Give preference to sampling in "non-bleeding" conditions if assessing PK for tailoring prophylaxis. Dedicated PK models have been proposed for PK tailoring of peri-surgical treatment [23].

1.7. Repeat the PK assessment if a change in PK over time is anticipated, as in children [11] or in patients with current or past inhibitors.

2. **Select the most informative time points and record the sampling time precisely.**

2.1. For standard FVIII adopt a 2-3 samples protocol, with samples at least 12h apart in the 4-48h period (e.g. around 4-8, 16-28, 40-60); the single sample providing most information is 24h [7].

2.2. For standard FIX consider using a 2 samples protocol; 24-36h and 48-60h, at least 24h apart [8].

2.3. For EHL FVIII and FIX there have been fewer investigations performed; suggestions below are empirically derived and could change over time:

2.3.1. For EHL FVIII, add a sample at 60-84h to those indicated in 2.1.

2.3.2. For EHL FIX, add a sample at 5-14 days to those indicated in 2.2.

2.4. Consider using different time points if patient's and clinic schedules' constraints need to be accommodated, but beware that the impact of using different points is not yet well known.

2.5. Peak measurement is not required for PopPK forecasting. Peak is needed to calculate recovery (box) and might be useful for other clinical purposes.

2.6. Record the start time of the infusion and the sampling times as precisely as possible using calendar time (month, day, hours, minutes).

2.7. Include a pre-infusion sample when the patient is infused in the clinic.

2.8. Obtain from the patient and report the times and doses of the last three infusions.

2.9. Record covariates, like height (to calculate lean body weight, box); blood group, hematocrit, and von Willebrand factor antigen levels (which may influence the PK of some factor VIII concentrates) [24,25].

3. **Perform and record laboratory measurements precisely.**

3.1. Use an appropriate laboratory test. For standard FVIII and FIX concentrates, most clotting assays provide reliable results [26,27]. For EHL consider adopting appropriate tests for both routine measurements and individual PK [28]. Record the test (clotting or chromogenic, activator and standard).

3.2. Report measurement as International Units per milliliter (IU/mL). Alternative units of measure (e.g. IU/dL, or percent activity) can be converted to a common nomenclature.

3.3. Report activity levels Below Limit of Quantitation (BLQ, Box). If any of the samples have less than detectable factor activity (e.g. is reported as < 0.01 IU/mL or as value below the limit of quantification), do not discard the information, but record it as any other measurement. Ignoring data BLQ may bias the individual estimate [29,30].

4. **Adopt an optimal Bayesian estimation technique for the individual PK profiling.**

4.1. Adopt a validated modelling process. We recommend against performing in house PopPK estimation, unless specific expertise is available. Performing Bayesian estimation on limited sample requires i) a population PK model, derived and validated in a suitable population and/or published in the literature, and ii) a dedicated statistical software (e.g. Icon NONMEM, Phoenix NLME, MRC WinBUGS).

4.2. Adopt a robust PopPK solution. Dedicated solutions for individual PK profiling on limited data

are available (e.g. WAPPS-Hemo, www.wapps-hemo.org; my PKFit, www1.mypkfit.com) [16–18]. In making your choice consider the characteristics of the solution; i) output: individual PopPK profile, treatment regimen suggestion, simulation capabilities; ii) technical: documentation; measure of certainty of the prediction, handling of BLQ, active monitoring of estimates; iii) coverage: estimation for one or more specific concentrates, generic molecules; iv) flexibility: merging of multiple infusion; integration in Electronic Medical Record software; v) business model/sponsorship: for profit, not for profit, research orientation.

4.3. Seek training opportunities to improve the quality of individual PK assessment.

4.3.1. *We suggest performing or facilitating basic PK training of the clinical and laboratory staff*; this document is recommended as core content for training of those involved in performing individual PK studies.

4.3.2. *We suggest educating persons with hemophilia and their caregivers* to understand the implication of individual PK profiling in choosing their treatment regimen, the importance of matching their desired factor activity level with their schedule for physical activity, as well as how to interpret and react to intercurrent bleeding episodes.

5. **Adopt a clinical perspective in the interpretation and use of the predicted PK profile**

5.1. Use clinically meaningful PK parameters for clinical decision making**.**

5.1.1. *We recommend considering "activity over time" estimates* as the most intuitive information for building treatment regimens and for communication to patients. Time to a desired target activity level or activity level at a given time after the infusion is the most clinically relevant component of the individual PK profile, allowing health care professionals and PWH or caregivers to target any desired plasma activity level or to decide about appropriateness of timing of infusions for different levels of physical activity.

5.1.2. *Individual area under the curve, volume of distribution, terminal half-life, clearance, mean residence time in the blood or in the body* (box) may also be estimated.

5.1.3. *Choose the appropriate target activity level for each individual patient*. The advantage of individualized treatment based on PK is not limited to targeting the same trough (e.g. 0.01 IU/mL) for every patient [23].

5.2. Apply clinical judgement to assess the predicted PK profile. The Bayesian estimation of individual PK is a modeling process, combining information from limited samples with that from the underlying population. As for any modelling, the result is an approximation. When the certainty of the prediction is reported and is low, we recommend adopting conservative estimates (if available) or aiming for a target activity level slightly higher than one would.

5.3. Prospectively validate the accuracy of the prediction**.** The easiest and most reliable validation of Bayesian individual estimates is obtained by drawing new samples to verify the predicted activity(ies) at specific time point(s), e.g. before a dose (trough level) or at the time point for a critical activity level. These samples can also be used to refine the PK profile.

We believe that this guidance will facilitate better uptake of PopPK based tailoring of hemophilia treatment. Shared software solutions would also support generation of new data, further research, and eventually updates of this recommendation.

Disclosures:

References

1	Lee M, Morfini M, Schulman S, Ingerslev J. The Design and Analysis of Pharmacokinetic Studies of Coagulation Factors. *ISTH Website, Scientific and Standardization Committee Communication*. 2001. p. 1–9.

2	Morfini M, Lee M, Messori A. The design and analysis of half-life and recovery studies for factor VIII and factor IX. Factor VIII/Factor IX Scientific and Standardization Committee of the International Society for Thrombosis and Haemostasis. *Thromb Haemost* 1991; **66**: 384–6.

3	Collins PW, Fischer K, Morfini M, Blanchette VS, Bjorkman S. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. *Haemophilia* 2011; **17**: 2–10.

4	Björkman S, Folkesson A, Jönsson S. Pharmacokinetics and dose requirements of factor VIII over the age range 3–74 years. *Eur J Clin Pharmacol* 2009; **65**: 989–98.

5	McEneny-King A, Iorio A, Foster G, Edginton AN. The use of pharmacokinetics in dose individualization of factor VIII in the treatment of hemophilia A. *Expert Opin Drug Metab Toxicol* 2016; **12**: 1313–21.

6	Iorio A, McEneny-King A, Keepanasseril A, Foster G, Edginton A. What is the role for population pharmacokinetics in hemophilia? *Int J Pharmacokinet* 2017; **2**: 125–36.

7	Björkman S, Collins P. Measurement of factor VIII pharmacokinetics in routine clinical practice. *J Thromb Haemost* 2013; **11**: 180–2.

8	Brekkan A, Berntorp E, Jensen K, Nielsen EI, Jönsson S. Population pharmacokinetics of plasma-derived factor IX: procedures for dose individualization. *J Thromb Haemost* 2016; **14**: 724–32.

9	Nestorov I, Neelakantan S, Ludden TM, Li S, Jiang H, Rogge M. Population pharmacokinetics of recombinant factor VIII Fc fusion protein. *Clin Pharmacol Drug Dev* 2015; **4**: 163–74.

10	Karafoulidou A, Suarez E, Anastasopoulou I, Katsarou O, Kouramba A, Kotsi P, Zografidis A, Lukas JC. Population pharmacokinetics of recombinant factor VIII:C (ReFacto??) in adult HIV-negative and HIV-positive haemophilia patients. *Eur J Clin Pharmacol* 2009; **65**: 1121–30.

11	Bjorkman S, Oh M, Spotts G, Schroth P, Fritsch S, Ewenstein BM, Casey K, Fischer K, Blanchette VS, Collins PW. Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight. *Blood* 2012; **119**: 612–8.

12	Diao L, Li S, Ludden T, Gobburu J, Nestorov I, Jiang H. Population Pharmacokinetic Modelling of Recombinant Factor IX Fc Fusion Protein (rFIXFc) in Patients with Haemophilia B. *Clin Pharmacokinet* 2014; **53**: 467–77.

13	Collins PW, Young G, Knobe K, Karim FA, Angchaisuksiri P, Banner C, Gürsel T, Mahlangu J, Matsushita T, Mauser-Bunschoten EP, Oldenburg J, Walsh CE, Negrier C. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: A multinational randomized phase 3 trial. *Blood* 2014; **124**: 3880–6.

14   Santagostino E, Martinowitz U, Lissitchkov T, Pan-Petesch B, Hanabusa H, Oldenburg J, Boggio L, Negrier C, Pabinger I, von Depka Prondzinski M, Altisent C, Castaman G, Yamamoto K, Alvarez-Roman M-T, Voigt C, Blackman N, Jacobs I. Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. *Blood* 2016; **127**: 1761–9.

15   Sheiner LB, Beal S, Rosenberg B, Marathe V V. Forecasting individual pharmacokinetics. *Clin Pharmacol Ther* 1979; **26**: 294–305.

16   Iorio A, Keepanasseril A, Foster G, Navarro-Ruan T, McEneny-King A, Edginton AN, Thabane L. Development of a Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo): Study Protocol. *JMIR Res Protoc* JMIR Research Protocols; 2016; **5**: e239.

17   McEneny-King A, Foster G, Iorio A, Edginton AN. Data Analysis Protocol for the Development and Evaluation of Population Pharmacokinetic Models for Incorporation Into the Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo). *JMIR Res Protoc* 2016; **5**: e232.

18   Álvarez-Román MT, Fernandez-Bello I, de la Corte-Rodríguez H, Hernández-Moreno AL, Martín-Salces M, Butta-Coll N, Rivas-Pollmar MI, Rivas-Muñoz S, Jiménez-Yuste V. Experience of tailoring prophylaxis using factor VIII pharmacokinetic parameters estimated with myPKFiT ® in patients with severe haemophilia A without inhibitors. *Haemophilia* 2017; **23**: e50–4.

19   Collins PW, Blanchette VS, Fischer K, Björkman S, Oh M, Fritsch S, Schroth P, Spotts G, Astermark J, Ewenstein B. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. *J Thromb Haemost* 2009; **7**: 413–20.

20   Valentino LA, Pipe SW, Collins PW, Blanchette VS, Berntorp E, Fischer K, Ewenstein BM, Oh M, Spotts G. Association of peak factor VIII levels and area under the curve with bleeding in patients with haemophilia A on every third day pharmacokinetic-guided prophylaxis. *Haemophilia* 2016; **22**: 514–20.

21   Iorio A, Iserman E, Blanchette V, Dolan G, Escuriola Ettingshausen C, Hermans C, Negrier C, Oldenburg J, Reininger A, Rodriguez-Merchan C, Spannagl M, Valentino LA, Young G, Steinitz-Trost KN, Gringeri A. Target plasma factor levels for personalized treatment in haemophilia: a Delphi consensus statement. *Haemophilia* 2017; : 1–10.

22   Broderick CR, Herbert RD, Latimer J, Barnes C, Curtin JA, Mathieu E, Monagle P, Brown SA. Association Between Physical Activity and Risk of Bleeding in Children With Hemophilia. *JAMA* 2012; **308**: 1452–9.

23   Hazendonk H, Fijnvandraat K, Lock J, Driessens M, van der Meer F, Meijer K, Kruip M, Gorkom BL -v., Peters M, de Wildt S, Leebeek F, Cnossen M, Mathot R. A population pharmacokinetic model for perioperative dosing of factor VIII in hemophilia A patients. *Haematologica* 2016; **101**: 1159–69.

24   Hazendonk HCAM, Lock J, Mathôt RAA, Meijer K, Peters M, Laros-van Gorkom BAP, van der Meer FJM, Driessens MHE, Leebeek FWG, Fijnvandraat K, Cnossen MH. Perioperative treatment of hemophilia A patients: Blood group O patients are at risk of bleeding complications. *J Thromb Haemost* 2015; **14**: 468–78.

25   Fischer K, Pendu R, van Schooten CJ, van Dijk K, Denis C V, van den Berg HM, Lenting PJ. Models

for prediction of factor VIII half-life in severe haemophiliacs: distinct approaches for blood group O and non-O patients. *PLoS One* 2009; **4**: e6745.

26   Peyvandi F, Oldenburg J, Friedman KD. A critical appraisal of one-stage and chromogenic assays of factor VIII activity. *J Thromb Haemost* 2016; **14**: 248–61.

27   Dodt J, Hubbard AR, Wicks SJ, Gray E, Neugebauer B, Charton E, Silvester G. Potency determination of factor VIII and factor IX for new product labelling and postinfusion testing: challenges for caregivers and regulators. *Haemophilia* 2015; **21**: 543–9.

28   Iorio A, Fischer K, Blanchette V, Rangarajan S, Young G, Morfini M. Tailoring treatment of haemophilia B: accounting for the distribution and clearance of standard and extended half-life FIX concentrates. *Thromb Haemost* 2017; **117**: 1023–30.

29   Beal SL. Ways to Fit a PK Model with Some Data Below the Quantification Limit. *J Pharmacokinet Pharmacodyn* 2001; **28**: 481–504.

30   Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. *J Pharmacokinet Pharmacodyn* 2008; **35**: 401–21.

Box

Area under the curve (AUC): area beneath the activity vs. time curve; it measures the "exposure" to the concentrate.

Baseline factor level: the level of factor activity measured in plasma in absence of therapeutically administered factor concentrate. It is the level of factor activity, if any, endogenously produced by the individual. Is the factor level used to classify the patient as severe (<0.01 IU/mL). moderate (0.01 to 0.05 IU/mL) or mild (>0.05 IU/mL).

Below limit of quantitation (BLQ): indicates a measurement of factor level activity below the minimum amount detected by the laboratory assay. Most often BLQ values are reported as "undetectable", or "not measurable", or <0.01 IU/mL.

Clearance: volume of blood from which the factor activity is removed in a specified unit of time.

Half-life: The time required for the plasma activity level to decrease by half. It is qualified as **terminal** half-life when estimated on the last portion of the activity over time profile, when the elimination of the activity become constant.

Recovery: amount of factor level activity measured in the plasma as proportion of the amount of concentrate infused.

Lean Body Weight: residual body weight after subtraction of the fat component (equal or more often inferior to the body weight)

Mean residence time (MRT): the average amount of **time** that a single molecule unit of activity stays in the body or plasma

Volume of distribution: the theoretical **volume** that would be necessary to contain the total amount of a factor concentrate to generate the same activity level that it is observed in the plasma.

Wash-out: Time spent off-treatment before a conventional PK study to ensure no residual factor activity level generated by the factor concentrate is present in the blood. Usually equal or longer than 5 times the anticipated half-life. The residual measurable activity level after an appropriate wash-out is the baseline factor level.