



Review



The road to implementation of pharmacokinetic-guided dosing of factor replacement therapy in hemophilia and allied bleeding disorders. Identifying knowledge gaps by mapping barriers and facilitators

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ABSTRACT

Clinical guidelines and expert groups recommend the use of pharmacokinetic (PK)-guided dosing of factor replacement therapy for the treatment of bleeding disorders, especially for patients with hemophilia. Although PK-guided dosing is increasingly applied, it is generally not considered standard clinical practice. The aim of this scoping review is to map barriers and facilitators for the implementation of PK-guided dosing in clinical practice and to identify knowledge gaps. A literature search was performed and 110 articles were included that describe PK-guided dosing in patients with bleeding disorders, mostly hemophilia A. We defined two overarching themes, efficacy and feasibility, and discuss five topics within each theme. For each topic, barriers, facilitators and knowledge gaps were described. Although consensus was found with regard to some topics, contradicting reports were found for others, especially with respect to the efficacy of PK-guided dosing. These contradictions highlight the need for future research to elucidate current ambiguities.

1. Introduction

Patients with an inborn bleeding disorder are characterized by a deficient or dysfunctional coagulation factor. Therefore, they require factor replacement therapy either prophylactically or on demand when bleeding occurs to ensure adequate hemostasis. Targeting of specific factor trough or peak levels in the context of prophylaxis, surgery, or bleeding [1–3] is complicated by the significant inter-individual differences in the pharmacokinetics (PK) of factor concentrates. [4–6] Therefore, clinical guidelines and expert groups have recommended the use of PK-guided dosing when treating hemophilia patients with factor replacement therapy. [2,7–11] However, although PK-guided dosing is increasingly applied, [12] it is generally not considered standard clinical

practice. Two studies surveyed the application of PK when switching hemophilia patients from a standard half-life (SHL) factor concentrate to an extended half-life (EHL) factor concentrate. Full PK analysis was carried out by only 9.7% of 70 respondents within the Scientific and Standardization Committee (SSC) Factor VIII (FVIII) and Factor IX (FIX) group of the International Society of Thrombosis and Hemostasis (ISTH), and by 51% of 37 physicians from European Hemophilia Treatment Centers. [10,13] This suggests a disparity between recommendations in clinical guidelines and the actual implementation of PK-guided dosing in daily practice.

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1.1. Personalization of treatment by PK guidance

Prophylactic therapy with factor concentrates or non-factor therapies in hemophilia and factor concentrates in other allied bleeding disorders is applied to prevent (spontaneous) bleeding and resulting musculoskeletal damage. Guidelines advise that prophylaxis should be personalized. [14] This can be done classically or with PK guidance. When adjusting classically, initial doses are based on body weight. Thereafter, doses and frequency are tailored according to bleeding tendency, but also to planning of (physical) activities. Alternatively, PK-guided dosing can be applied to personalize treatment based on PK and preferably also pharmacodynamics (PD) in the near future. Preferably, as solely PK-guided dosing assumes a direct relationship between plasma factor levels and hemostasis. With PK-guided dosing different treatment options can be tested to select the most optimal regimen maintaining specific target levels at acceptable factor concentrate use. PK-guided dosing potentially reduces time spent on achieving most optimal factor levels for the individual patient. Although PK-guided dosing has mainly focused on factor concentrates, recently it has been applied to optimize non-factor therapy. Several studies have reported PK-guided dosing of emicizumab as an effective approach to optimize treatment costs and optimize vial use. [15,16]

The aim of this scoping review is to map barriers and facilitators for the clinical implementation of PK-guided dosing in bleeding disorders and to identify knowledge gaps currently hampering its widespread implementation.

2. Methods

We followed the methodology to conduct a scoping review adhering to the five stages as described by Arksey and O'Malley: 1) identification of research question; 2) identification of relevant studies; 3) study selection; 4) data charting; and 5) collation, summarization, and reporting of results. [17]

2.1. Identification of research question (1)

Following recommendations [17] to maintain a wide approach in identifying relevant research questions, the aim of the review initially included all bleeding disorders and not only focused on hemophilia. Article scope was limited based on the results of the literature search. Barriers were defined as scientific findings or practical limitations potentially impeding (or otherwise reducing interest in) the implementation of PK-guided dosing in clinical practice. Facilitators on the other hand promoted the use of PK-guided dosing as an alternative to standard dosing.

2.2. Identification and selection of studies (2–3)

An experienced librarian of the Erasmus MC performed a literature search in Embase, Medline ALL, Web of Science Core collection, Cochran and Google Scholar databases. The search strategy is included in the supplementary data. Publications were first selected by title and abstract. Two authors (M.G., A.J) then independently performed full text screening using the web-based tool Rayyan. [18] Article selection aimed to identify studies elaborating on clinical experiences and outcomes in the context of PK-guided dosing. As such, opinion papers - which are generally excluded in systematic reviews - were included in this scoping review. In contrast, clinical trials only describing the PK characteristics, safety and efficacy of novel factor concentrates were excluded as they do not describe PK guidance. Search items consisting only of an abstract (e.g. posters), were excluded as they, due to their short form, contained only limited information. The full list of exclusion conditions was as

follows: no description of PK-guidance, information already included in other publication, abstract only (posters), model development, simulation study (or otherwise no real-life patient data), no full text accessible, clinical drug trials on safety and efficacy only, use of outdated analyses (e.g. non-compartmental analysis), no bleeding disorders, wrong outcome, and duplication. Backwards citations were screened to include additional studies. Disagreements between authors were discussed until consensus was reached. An updated search was carried out in July 2022.

2.3. Data charting (4)

Included publications were charted. We identified overarching themes and grouped barriers and facilitators for the implementation of PK-guided dosing according to specific topics. The following data was extracted from articles: author, year of publication, study design and important findings and/or conclusion describing the barrier/facilitator in the investigated or described patient group.

3. Results

The PRISMA flow diagram is shown in Fig. 1. The initial search performed on July 1st, 2021 yielded 1733 publications, of which 449 duplicate records were removed, leaving a remaining 1284. An updated search at the end of July 2022 added another 189 articles resulting in a total of 1473 articles that were screened on title and abstract. A total of 262 articles were included for selection full-text analysis, from which 6 were included through backward citations. After full-text screening, a total of 110 articles were included for the analysis.

Details on the data extraction are shown in Table 1. We included two randomized controlled trials (RCT), two cross-over studies, four case reports, seven model development articles, 21 reviews, four guidelines, five expert opinion papers or surveys, two patient group discussion papers, and eight letters to the editors or short reports. The remaining articles were retrospective or prospective cohort studies. Almost all articles described PK-guided dosing of hemophilia - mainly type A and to a lesser extent also type B patients - aside from four articles describing PK-guided dosing in patients with Von Willebrand Disease (VWD). [19–22] In response to the low number of articles discussing VWD, it was decided to focus the review mainly on hemophilia. Even though the number of articles describing hemophilia B was also low, we still decided to discuss this subtype due to the similarity of the treatment with respect to hemophilia A. Two overarching themes emerged from the analysis, resulting in a grouping of articles describing the (1) efficacy and/or (2) feasibility of PK-guided dosing. Within each theme, five topics were defined for which barriers and facilitators were assessed on the basis of the included articles. Knowledge gaps were identified based on disparities between barriers and facilitators.

The following topics are discussed under the theme efficacy: 1. knowledge on endpoint to target; 2. accuracy of PK-guided dosing; 3. impact on bleeding frequency; 4. effect on infusion frequency; and 5. cost effectiveness.

With regard to feasibility, the following topics are described; 1. applicability in clinical practice; 2. Useful software tools; 3. patient involvement and 4. burdening of patients and treatment teams; 5 attainment of personalized medicine. An overview of all barriers and facilitators grouped per topic (*italic*) is provided in Fig. 2.

Theme 1: Efficacy

3.1. Knowledge on endpoint to target

3.1.1. Facilitators

Most of the literature in our search focuses on the targeting of factor

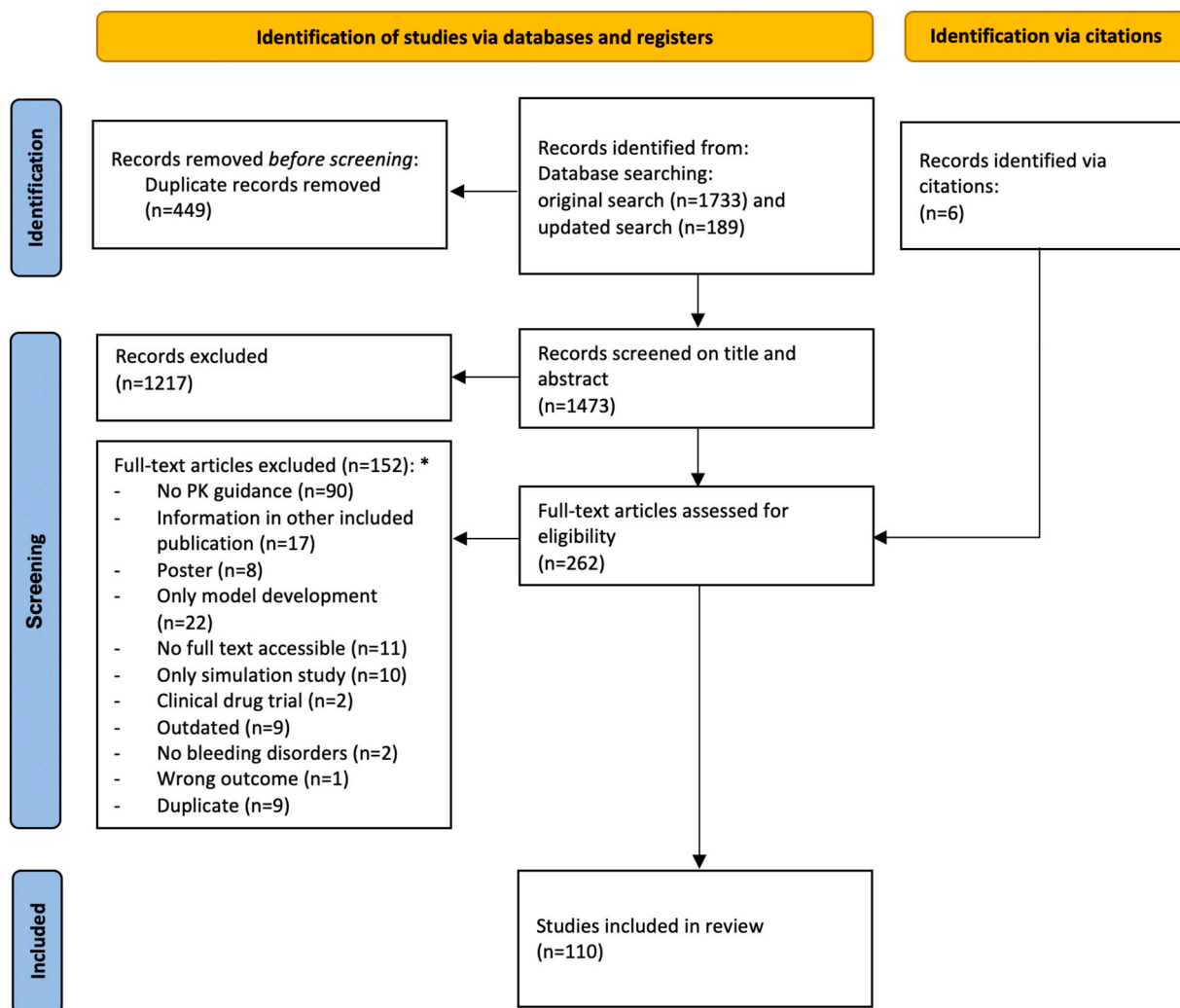


Fig. 1. PRISMA flowchart for systematic research.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: <https://doi.org/10.1136/bmj.n71>.

*Articles could have been excluded because of more than one exclusion criterium.

trough levels for prophylaxis in hemophilia A patients. Traditionally, a FVIII trough level of >1 IU/dL is advised. However, it has been demonstrated that patients with a FVIII level >1 IU/dL still present with bleeds. [23–25] In children with severe hemophilia, an increase of 1 IU/dL in FVIII trough level was associated with 2% increase in the number of children who might achieve zero bleeds. [26] Studies suggest that targeting FVIII trough levels above 10–15 IU/dL results in zero (or sparse) bleeding. [23,25–27] In a Delphi consensus, 11 experienced physicians recommended different target FVIII/FIX levels in varying situations, such as during high-risk physical activities or for patients with arthropathy. For the majority of patients, trough levels of 1–3 IU/dL were recommended. [28] Indeed, several studies have reported high efficacy of therapy using this target range. [29–31] These recommendations may be very useful in clinical practice.

Aside from FVIII trough levels, time spent above a specific FVIII level has also been associated with improved bleeding outcomes. Therefore, this parameter could be used more broadly to improve infusions timing, for example when engaging in physical activities. [9,32,33] Others have reported on additional, potentially valuable hemostatic markers that could be integrated to optimize treatment of patients with hemophilia A. Thrombin generation measurements, such as endogenous thrombin potential (ETP), may better reflect hemostatic potential and factor concentrate effects on bleeding. Importantly, associations between

thrombin generation and bleeding phenotype have been found, suggesting that the pharmacodynamics (PD) of coagulation factors may be related to thrombin generation. [34–37] Recently, PK/PD models have been developed which aim to describe this relationship. [35,38,39] Such approaches may help predict the probability of spontaneous bleeding for different dosing regimens based on different baseline ETP. [35] Finally, repeated-time-to-event (RTTE) models have been developed which associate the bleeding history with PK data, allowing for the quantification of individual bleeding risk. [40,41]

3.1.2. Barriers

Firstly, the total lack of data on appropriate FIX trough and peak levels to reduce bleeding pose a clear barrier to the implementation of PK-guided dosing in hemophilia B. It was initially expected that, similar to FVIII, trough levels of FIX would be associated with bleeding risk. However, the establishment of FIX target levels is complicated by findings that FIX binds to collagen IV in the extravascular space. Therefore, plasma FIX levels presumably do not offer a reliable relationship to hemostatic effect and depict large variation between the various FIX concentrates. Although the hemostatic effect of this binding has been described in mice, it has not yet been investigated in humans. [42–44]

Secondly, for both hemophilia A and B, it is still unknown which peak and troughs factor levels should be targeted for adequate

Table 1

Facilitators and barriers for the implementation of PK-guided dosing according to overarching theme e.g., efficacy and feasibility and specific topic.

1. Knowledge on endpoint to target					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Mingot-Castellano 2018[29]	Prospective observational case series	<u>Target level</u> of 36 severe hemophilia A patients was <u>based on personal characteristics</u> and improved clinical outcomes. Target trough level was 2% for patients with a severe bleeding phenotype (>1 bleed in previous 2 months, established arthropathy or bleeding risk associated with physical activity>1, high-risk profession), and 1% for those not presenting these characteristics.	Walsh, 2020[42]	Letter to the editor	Adequate troughs for FIX have not been determined. Although seemingly at adequate trough levels, patients on EHL FIX may still experience breakthrough bleeds. Trough levels may not directly correlate with the amount of FIX in tissues, since collagen IV binds <u>extravascular FIX</u> . Moreover, the correlation between extravascular FIX and bleeding outcomes has not been investigated in humans.
Huang, 2022[23]	Prospective interventional study	58 pediatric hemophilia A patients received individualized PK-guided prophylaxis. If the prophylaxis regimen was considered insufficient - based on a 6 monthly scoring scale including bleeding, ultrasound of joints and Hemophilia Joint Health Scores (HJHS) - the regimen would be escalated to fall into a higher trough FVIII level range. After 2 years, <u>53% of patients were on a FVIII trough level of 1-3 IU/dL. Seven patients (17%) remained at a FVIII trough level < 1 IU/dL, 9 (16%) were in trough level 3-5 IU/dL and 8 (14%) patients were in > 5 IU/dL group.</u> No bleeds were observed in the patients in the 3-5 IU/dL group during the last year of prophylaxis period.	Khayat, 2016[43]	Review	Measuring plasma FIX activity may not fully reflect the <u>hemostatic efficacy of infused FIX</u> , because of clinically significant <u>extravascular stores</u> of FIX that binds to collagen type IV. In mouse models expressing FIX variants with reduced affinity to collagen IV, hemostasis was delayed despite high FIX plasma levels. Contrastingly, On the contrary, a mouse with FIX variants with enhanced collagen affinity demonstrated prolonged hemostatic effects that persisted although FIX plasma levels were reached <1%. The role of PK-guided therapy and its relationship to clinical efficacy remains an open issue to be established.
Klamroth, 2021[24]	Prospective Phase 3 randomized trial	The PROPEL study determined impact of PK-guided prophylaxis while targeting <u>standard FVIII trough levels of 1-3% compared to elevated trough levels of 8-12%</u> in patients with severe hemophilia A. In the 95 patients who completed protocol, proportions of patients with zero total, spontaneous, and spontaneous joint bleeds in the FVIII 1- 3% vs 8-12% arms, respectively, were 40% vs 67% (p=.015), 60% vs 81% (p=0.038), and 65% vs 91% (p=0.008). Median ABR of 2.8 in the FVIII 1-3% arm was higher compared to 1.2 in the 8-12% arm.	Iorio, 2017[44]	Review	The PK of FIX is most likely represented by three compartment modeling. This implies FIX follows a complex disposition, with receptor binding or compartmentalization in some <u>extra-vascular space</u> , which may have PD and perhaps clinical relevance. About 40% of the infused FIX distributes in lymph or binds to collagen type IV in the subendothelial space.
Den Uijl, 2011[25]	Retrospective cohort	Epidemiologic evaluation of a Dutch cohort of 377 patients with hemophilia A demonstrates that a FVIII level at <u>1% may present >5 joint bleeds per year</u> , while levels <u>>10-12 % essentially have zero joint bleeds</u> .	Raymont, 2020[51]	Guideline	British guideline for children with hemophilia A and B recommends that prophylaxis regimens should <u>not be based on target peak and trough levels</u> , but to prevent bleeding for an individual.
Collins, 2011[27]	Review	Recent studies suggest that protection from joint bleeds is highly dependent on factor levels between <u>1 and 4 IU/dL</u> , but that joint bleeds still occur, although more rarely, until the factor baseline is >10-15 IU/dL.	Prijers, 2019[51]	Review	<u>Individualized target levels</u> may be needed, dependent on bleeding phenotype, daily activities and joint status.
Srivastava , 2020[2]	WFH guideline	Most clinicians prefer to target higher troughs than the traditional factor trough level ≥ 1 IU/dL (>3-5 IU/dL).	Srivastava, 2020[2]	WFH guidelines	PK focuses solely on one attribute that contributes to bleeding and <u>ignores other differences</u> between patients (e.g. sports).
Nolan, 2020[31]	Prospective extension trial	In the ASPIRE study, 110 adults and 59 children <12 years with severe hemophilia A had optimal prophylaxis (ABR < 1.0) that was individualized using PK. <u>FVIII target level was 1-3 IU/dL</u> .	Collins, 2011[27]	Review	Regimens may be better adjusted, if PK data are available that give information on <u>factor level at the time of the break-through bleeds or anticipated activity</u> .
Iorio, 2017[9]	Guideline	<u>Time at a desired factor target level</u> or level at a given time after the infusion is the most clinically relevant component of the individual PK profile, allowing healthcare professionals and persons with hemophilia or caregivers to target any desired plasma activity level or to decide on the appropriateness of timing of infusions for different levels of physical activity.	Ragni, 2021[46]	Comment	In the perioperative field of hemophilia A, there is <u>no evidence for optimal FVIII peak or trough level for surgical hemostasis</u> . Additional questions remain, for instance, are early perioperative FVIII levels a better predictor of bleeding than a postoperative range of perioperative levels? And is there a trough FVIII level that eliminates excessive postoperative bleeding, such as that known for eliminating joint bleeds with prophylaxis?
Collins, 2009[32]	Post hoc clinical trials	In 44 pediatric patients aged 1-6 years with severe hemophilia, <u>an increasing time with a FVIII <1, <2 and <5 IU/dL</u> was associated with an increased rate of bleeds and hemarthrosis. For each additional hour spent with a FVIII <1 IU d/L, ABR increased by 2.2% (CI 1.58-2.78%). Moreover, all bleeds (p = 0.01) increased as elimination half-life decreased. In 99 patients aged 10-65 years with severe hemophilia, only increasing time with a FVIII <1 IU/dL was associated with an increased rate of all bleeds and hemarthrosis. For each additional hour below 1 IU dL/1 there was a 1.4% increase in ABR (CI 0.21-2.62%).	Collins, 2011[27]	Review	Children, adolescents and adults with hemophilia cannot directly be compared because of differences in arthropathy and activities. Therefore, the <u>same factor trough levels are not clinically appropriate for all groups</u> .
Nagao, 2019[33]	Prospective cohort	Longer <u>times spent</u> >either 1% or 5% FVIII were associated with a decrease in AJBR in 39 patients with severe hemophilia A who received PK guided dosing.	Ahnström, 2004[50]	Retrospective cohort	In a retrospective cohort of 51 hemophilia A and 13 hemophilia B patients, <u>coagulation factor levels showed a very weak correlation with the incidence of joint bleeding</u> . Dosing for patients in this cohort were individualized and based on clinical outcome.
Chowdary , 2020[26]	Post hoc RCT Valentino 2012	In 66 severe and 8 moderate severe hemophilia patients (baseline FVIII <2 IU/dL) with multiple target joints who initiated tertiary prophylaxis, <u>1 IU/dL increase in FVIII trough level was associated with a 2% increase in the number of patients who achieved zero bleeds in a year</u> . Proportions of the cohort that would have been bleed free if the estimated FVIII level of 1 IU/dL was prescribed, were 40% for all bleeds, 43% for joint bleeds, and 63% for spontaneous joint bleeds. A measurable level of 1 IU/dL provided substantial benefit in the prevention of bleeds. Higher levels were associated with smaller incremental benefits. No bleeds occurred between estimated FVIII trough levels of 10 and 12 IU/dL.	Hermans, 2020[49]	Review	Optimal trough level in hemophilia patients to prevent bleeding must be determined on a <u>person-by-person basis</u> , and simply achieving a level of 1% for all patients is not appropriate.
Chowdary , 2020[26]	Post hoc RCT Valentino 2012	In 66 severe and 8 moderate severe hemophilia patients (baseline FVIII <2 IU/dL) with multiple target joints who initiated tertiary prophylaxis, <u>bleeds were also reported at high FVIII levels</u> in some patients, even outside the range of FVIII levels associated with hemophilia (0-40 IU/dL).	Chowdary, 2020[26]	Post hoc RCT Valentino 2012	In 66 severe and 8 moderate severe hemophilia patients (baseline FVIII <2 IU/dL) with multiple target joints who initiated tertiary prophylaxis, <u>bleeds were also reported at high FVIII levels</u> in some patients, even outside the range of FVIII levels associated with hemophilia (0-40 IU/dL).
Iorio, 2017[28]	Modified Delphi technique	In a <u>Delphi panel</u> , 11 hemophilia experienced health care professionals <u>defined target factor trough levels</u> in real-world settings for in use in different situations: - <1 IU/dL: if patients on this regimen do not experience bleeds - 1-3 IU/dL: as an acceptable range for most patients on prophylaxis without comorbidities, not/ limited experience with spontaneous bleeds, no repeated bleeds in the same joint and mild to moderate arthropathy, as well as a low level of physical activity. - 3-5 IU/dL: for patients during mild physical activities without activity-related bleeds, with target joints/arthropathy, patients bleeding at lower thresholds, patients with comorbidities, patients with target	Iorio, 2017[28]	Modified Delphi technique	In a Delphi panel, 11 hemophilia experienced treating health care professionals defined target factor levels in real-world settings for use in different situations. However, these levels are <u>recommendations and have never been empirically tested</u> . Moreover, the experts were <u>unable to reach consensus</u> on the following target levels: - 3-5 IU/dL: for patients following a life-threatening bleed. - 5-15 IU/dL: for patients with comorbidities - 15-30 IU/dL: during intensive sport activity - 30-50 IU/dL: for bleed treatment - 50-80 IU/dL: for high-risk activities

		<p>joint(s) or severe arthropathy.</p> <ul style="list-style-type: none"> - 5-15 IU/dL: during high-risk activities, with target joints/arthropathy, patients bleeding at lower thresholds, patients with target joint(s) or severe arthropathy presenting bleeding. - 15-30 IU/dL: late post-surgical prophylaxis after high-risk surgery, patients undergoing minor invasive procedures. - 30-50 IU/dL: Patients who had major surgery, patients who had intracranial hemorrhage. - 50-80 IU/dL: Patients undergoing minor surgery, patients who had major surgery or trauma, patients presenting with major bleeds. - >80 IU/dL: patients undergoing high-risk surgery, who had major trauma or major surgery, patients presenting life threatening bleeds. 	Preijers, 2019[45]	Review	Both prophylaxis and perioperative FVIII and FIX <u>target levels are based on expert opinion.</u>
Abrantes, 2019[41]	Model development	A repeated time-to-event model was developed in 172 patients (51 children) with a total 633 reported bleeds from the LEOPOLD and LEOPOLD-kids cohorts. Combining information about past bleeds and PK was more accurate in <u>predicting bleeding hazard compared to PK alone.</u> The model can be used for Bayesian forecasting of bleeding events.	Carcao, 2015[48]	Review	PK-guided dosing <u>does not take the patient's activity</u> patterns into consideration. Moreover, PK-guided dosing may lead to over or undertreating patients as patients may need different trough levels for successful prophylaxis.
Abrantes, 2020[40]	Post hoc analysis of clinical trials	A repeated time-to-event (RTTE) model was used to predict bleeding events in a post hoc analysis of the LEOPOLD trials. <u>Bleeds pre-study was found to be the most important predictor of individual bleeding hazard.</u> The model could also be used to predict bleeding severity. Individual bleeding hazards can be used for another approach to the <u>optimization of prophylactic treatment.</u>	Abrantes, 2019[41]	Model development	A repeated time-to-event (RTTE) model was developed on 172 patients (51 children) with a total 633 reported bleeds from LEOPOLD and LEOPOLD-kids cohorts. In virtual patients with identical characteristics and a plasma FVIII activity of 5 IU/dL, cumulative number of simulated bleeds was still highly variable at one year. The median number of bleeds was 1.53, with 40% of the patients having 1.53 - 6.17 bleeds, and 10% having more than 6.17 bleeds. Such high variability agrees with the clinical observation that patients may respond differently to identical plasma FVIII activity values, <u>thus requiring also individual FVIII trough target level.</u>
Valke, 2020[39]	Prospective cohort study	25 hemophilia A patients showed clear differences in baseline thrombin generation and plasmin generation despite having comparable FVIII activity levels. Therefore, <u>thrombin generation may be a better parameter</u> to monitor treatment in patients. Moreover, the introduction of normalized thrombin generation values makes comparisons between groups easier.			
Bukkems, 2022[38]	Model development	In 30 hemophilia A patients, similar PK profiles can exhibit different normalized thrombin potential profiles, which shows that factors other than FVIII can cause inter-individual variability in the thrombin potential. A PK/PD model was developed that describing the relationship between FVIII and thrombin/plasmin generation. <u>Adjusting FVIII replacement therapy of patients on individual FVII and thrombin/plasmin generation parameters</u> may hypothetically result in personalization of treatment with representation of bleeding phenotype.			
Delavenn e, 2020[35]	Post hoc modeling of prospective phase IIIb study	Based on bleeding result and baseline endogenous thrombin potential (ETP) of 66 adult patients with severe hemophilia, <u>probabilities of spontaneous bleedings for different dosing regimens were simulated.</u>			
Dargaud, 2018[37]	Prospective phase IIIb study	<u>Baseline mean ETP</u> was significantly lower (p=.0002) in the 7 severe hemophilia patients who experienced spontaneous bleeds versus 25 who did not. During personalized prophylaxis (n = 49), only patients with lower median trough ETP experienced spontaneous bleeds.			
Al Hawaj, 2013[34]	Prospective cohort study	In 10 severe hemophilia A patients, significant correlations were found between log FVIII and both log peak thrombin (r =0.51, p<0.001) and log thrombin generation velocity (r=0.90). Patients with a severe bleeding phenotype, defined as having one or more bleeds per month despite prophylaxis) had the lowest baseline and 48-h <u>thrombin generation and endogenous thrombin potential</u> measurements.			
Delavenn e, 2020[35]	Post hoc modeling prospective phase IIIb study	Based on 66 adult patients with severe hemophilia A, stratifying patients by baseline <u>endogenous thrombin potential (ETP)</u> level may identify 1) patients at risk of spontaneous bleeds, regardless of FVIII dosing levels, and 2) patients with unnecessary and expensive overdosing in FVIII.			
2. Accuracy of PK-guided dosing					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Lissitchkov, 2017[55]	Phase IIIb study	In 66 patients with severe hemophilia A, high FVIII trough levels of 3.4%, 4.2% and 2.7% after 2, 4 and 6 months, respectively, of Nuwiq® treatment <u>support the accuracy</u> of individual PK modeling.	Morfini, 2017[56]	Review	An appropriate <u>validation</u> procedure must assess outcomes during follow up: bleeds, consumption, quality of life, side effects. Positive outliers should decrease dosage or increase dosing interval, a choice not always well accepted by patient and doctor.
van Moort, 2021[52]	RCT	A perioperative RCT in 66 moderate-severe hemophilia A patients showed that PK-guided dosing was associated with an increased likelihood of FVIII concentration being <u>within the target</u> range compared with standard dosing (odds ratio [OR] 4.6 [95% CI 2.5–8.4]).	Zhu, 2021[63]	Retrospective study	<u>External validation</u> of the perioperative model revealed that the model did not adequately characterize the study cohort of 34 patients due to differences in patient populations (like wider body weight range, more adults, higher risk surgery).
Stemberger, 2019[53]	Prospective cohort	138 FVIII levels were measured from 25 patients with severe hemophilia A on PK-guided prophylaxis to <u>validate</u> the accuracy of population PK approach. Mean difference between predicted and observed levels was - 0.5 IU/dL (95%CI: -13.0, 11.9). The overall agreement between predictions and observations was 93%, with only 1 critical over-prediction.	Preijers, 2019[45]	Review	Suitability of a population PK model for application in dose individualization is rarely tested through an <u>external validation</u> procedure, in which real-world data (not simulated) are obtained from patients who were not used for model development. Values for covariates included in the model may not be used in clinical practice, which limits the implementation.
Bjorkman, 2010[129]	Prospective study	In 16 patients with hemophilia A, measured blood samples taken 5-17 months after PK investigation showed a median <u>absolute prediction error between 17-26%.</u>	Preijers, 2021[62]	Validation study	Using an independent dataset of 87 pediatric patients, <u>external validation</u> of a perioperative model for FVIII concentrates showed an underprediction of measured FVIII levels. Therefore, a novel model was constructed. It is important to have a validated model.

Bjorkman, 2010[129]	Prospective study	It is clear that Bayesian PK estimates based on only one sample gave a much <u>better chance to achieve a 1 IU/dL FVIII trough level</u> than using a dose based on bodyweight.	Bukkems, 2020[60]	Model development	Using an independent dataset of 43 hemophilia A patients, <u>external validation</u> of the population PK model of rFVIII-Fc (Elocta®) model showed a <u>underprediction of clearance and central distribution volume in patients <12 years</u> , because this age group was not represented in the original model. Therefore, an enriched model was constructed.
Lethagen, 2007[20]	Prospective cohort	A study aiming to assess effectiveness of Haemate® P loading dose based on individual IVR in 27 patients with VWD undergoing surgery demonstrated that the <u>IVR is constant</u> over a wide range of doses and that initial PK determinations can provide a reliable basis for serial dosing decisions. The pre- and perioperative IVRs were comparable.	Iorio, 2018[57]	Review	Because of the large variability among individuals in the population, there is a need to check if studies providing PK estimates have been performed on populations comparable to the patients we are planning to apply those results to (i.e., <u>external validity</u>).
Hajducek, 2020[54]	Simulation study	WAPPS-Hemo models were found to have <u>high predictive accuracy</u> as assessed by internal validation, supporting their ability to predict factor concentrate PK outcomes from sparse data.	Preijers, 2019[45]	Review	A population PK model can only reliably predict PK parameters and factor activity levels in patients who belong to the <u>same subpopulation</u> as used to construct the corresponding model.
Goedhart, 2021[58]	Review	A review provides a detailed overview of data used for published population PK models for FVIII and FIX concentrates, to support physicians in their choices of <u>which model best suits each patient</u> . Moreover, to enhance detailed data collection and documentation, suggestions are given for best practice.	Hazendonk, 2018[64]	Review	Bayesian adaptive dosing is only possible when population PK models are <u>representative</u> of the individual patient and her or his specific clinical setting. Models should comprise a wide variation in patient-related and circumstance-related factors. Further, to optimize current population models it is important to include often <u>underrepresented patient populations</u> , such as children and overweight/obese patients since PK parameters in these populations may differ significantly.
Iorio, 2018[57]	Review	A number of <u>methods are available for using factor levels below the limit of quantification</u> in population PK analyses.	Iorio, 2018[57]	Review	When levels <u>below limits of quantification</u> are removed from the PK modeling process, resulting half-life will be overestimated.
Collins, 2011[27]	Review	If PK is to be useful in clinical practice, then a <u>low intra-patient variation</u> across time would have to be assumed. Several studies have shown that intra-individual variance is considerably less than inter-individual in plasma derived, recombinant and B-domain deleted FVIII.	Delavenne, 2020[36]	Review	Data below the <u>limit of quantification</u> are frequent in PK studies and represent an issue for the estimation of PK parameters. Methods to handle this problem demonstrate bias.
Goedhart, 2022[61]	Simulation study	It is not necessary to take <u>potency differences</u> into account when applying PK guidance of FVIII concentrates in hemophilia A patients. However, when the patient is switched to another FVIII batch after PK-guided dosing, factor trough levels may deviate $\pm 20\%$ from calculations based on label dose.	Tardy, 2022[67]	Retrospective cohort	The terminal half-life Benefix® of 64 patients with severe hemophilia B was longer when <u>sampling times</u> were extended beyond the 72h time point as described in previous literature. Using longer sampling times will lead to more accurate PK assessment.
Morfini, 2017[56]	Review	The <u>residual FVIII/FIX</u> level present at baseline from the previous infusion undergoes a similar decay curve as the infused factor concentrate while accessing PK. Post-infusion FVIII/FIX concentrations should be adjusted according to the proportion of baseline to maximum peak using a published formula.	Morfini, 2017[56]	Review	A problem in measuring PK is the <u>residual FVIII/FIX</u> value, frequently due to a short wash out. The endogenous FVIII/IX level should be subtracted from all post-infusion points.
Chelle, 2020[59]	Model development	In model development of an extended half-life FVIII concentrate (Adynovate®), a <u>scaling factor to correct</u> the individual predicted activity for the <u>used assay</u> (OSA or CSA) led to a significant model improvement.	Bowyer, 2017[66]	Letter to the editor	As FIX:C trough levels can be used to tailor patient dosing regimens, it is important that these can be accurately determined. However, this study on extended half-life FIX products demonstrated up to <u>two-fold difference in FIX with some reagents</u> , irrespective of rFIX concentrate, a disparity which may influence clinical decisions.
Bukkems, 2020[60]	Model development	In development of the enriched rFVIII-Fc (Elocta®) model, a <u>correction factor was applied to correlate the levels of the different assays</u> (OSA and CSA). An exponential function with a parameter of 1.06 could describe the relation between the different assay methods best, which indicates that a FVIII activity measured on an OSA of 100 IU/dL on average corresponds to a FVIII activity level of 132 IU/dL measured by CSA.	Preijers, 2019[45]	Review	Discrepancies between OSA and CSA assays show that the assays are not interchangeable. Therefore, individualized dosing by MAP Bayesian estimation should only be performed with factor activity level measurements from <u>type of assay</u> that was used to construct the applied population PK model.
			Chelle, 2020[59]	Model development	Collecting no information on specific laboratory reagents used for <u>clotting assay-based measurement</u> will introduce <u>variability</u> into PK modeling.
			Ljung, 2013[65]	Review	For new factor concentrates, there will be a need for <u>guidelines on PK assessment of each factor</u> , for example, on the correct assay to use, and whether product-specific standards are required.
			Iorio, 2017[44]	Review	From the limited published data available, it has become clear that <u>accurate laboratory measurement</u> of infused factor for the EHL FIX concentrates is a serious concern, mostly due to the heterogeneity of the many commercially available aPTT reagents.
			Iorio, 2017[44]	Review	Beyond already large IIV the variability of PK can depend on the <u>PK assumptions</u> underlying the analysis, sampling times, proper management of samples below the level of quantitation (BLQ) (minimal detectable level), duration of the sampling period, estimated PK parameters, and particularly the terminal half-life.
			Iorio, 2018[57]	Review	There is robust evidence that the choice of <u>assay type</u> (i.e., OSA versus CSA), choice of <u>aPTT reagent</u> , as well as choice of reference standard (generic versus concentrate specific) <u>impacts measurement of factor levels</u> in a significant way.
			Iorio, 2018[57]	Review	We <u>do not yet know how many patients are sufficient</u> to build a predictive brand-specific population PK model best suited for Bayesian estimation.
			Iorio, 2017[9]	Guideline	The ISTH SSC on FVIII/FIX recommends to <u>prospectively validate accuracy</u> of the prediction of Bayesian individual estimation. Easiest and most reliable validation is obtained by drawing new samples to verify predicted activity or activities at specific time point(s), e.g. before a dose (trough level) or at time point for a critical activity level. These samples can also be used to refine the PK profile.
			Hazendonk, 2018[64]	Review	Prospective studies are warranted <u>validating</u> constructed population PK models.
			Delavenne, 2020[36]	Review	<u>Methodology</u> to estimate PK parameters has <u>not been defined</u> . Therefore, PK parameters of products estimated using different methods must be interpreted with caution.

3. Impact on bleeding frequency					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Mahlangu, 2014[78]	Phase III	Although superiority cannot be determined because of insufficient power, median <u>ABR</u> of severe hemophilia A patients with PK-guided prophylaxis seemed <u>lower</u> (1.6 (IQR 0.0-4.7) than in patients with standard prophylaxis (3.6 (IQR 1.9-8.4)).	Carlsson, 1997[85]	Cross-over study	In 14 severe hemophilia A patients, number of reported <u>bleedings were generally similar</u> during standard dosing and PK-guided dosing.
Nagao, 2019[33]	Prospective cohort	Both <u>ABR and AJBR tended to decrease</u> in 39 patients with severe hemophilia A after PK-guided dosing, although not statistically significant. A significant decrease of AJBR was observed after adoption of population PK based regimen in the group without end-stage arthropathy.	Nagao, 2019[33]	Prospective cohort	<u>No significant decrease of the AJBR</u> was observed after adoption of population PK based regimen in hemophilia A patients with end-stage arthropathy.
Megias-Vericat, 2019[80]	Prospective observational cohort	In 22 patients with moderate to severe hemophilia A, the significant association ($p=0.01$) that was found between <u>AJBR and a short terminal half-life (T1/2)</u> in the year before PK-guided treatment disappeared after the adoption of PK-guided dosing of prophylaxis.	Megias-Vericat, 2019[80]	Prospective observational cohort	In 22 patients with moderate to severe hemophilia A, <u>no significant difference in the AJBR and ABR</u> between a year of standard prophylaxis and a year of PK-guided treatment.
Grazzi, 2022[73]	Cross-sectional retrospective cohort study	73 hemophilia A patients receiving PK-guided prophylaxis exhibited a <u>lower ABR</u> (2.8) than ABR (3.9) of 47 patients in the non-PK-guided group ($p=0.022$). Also, number of target joints was slightly lower with a mean number of 0.5 compared to 0.9 ($p=0.036$). In a univariate regression analysis, use of PK-guided dosing was negatively associated with bleeding outcomes (beta coefficient -0.903, $p<0.05$) after controlling for treatment history and body mass index.	Grazzi, 2022[73]	Cross-sectional retrospective cohort study	A higher proportion (51.1%) of 73 hemophilia A patients in PK-guided group experienced <u>problem joints</u> compared with the proportion (42.5%) of 73 patients in non-PK-guided group ($p=0.356$).
Lissitchkov, 2017[55]	Phase IIIb study	In 66 patients with severe hemophilia A, the median <u>ABR</u> of 1.45 for all bleeds during 6-months of PK-guided prophylaxis with Nuwiq® was <u>lower</u> compared to 2.28 in a study of standard prophylaxis with Nuwiq, although a direct comparison cannot be made due to differences in study design.	Valentino, 2012[84]	RCT	1 year PK-tailored vs standard prophylaxes with FVIII <u>showed no significant differences</u> ($p=0.258$) in ABR in 66 moderate-severe hemophilia A patients (baseline FVIII level <3%). Off note, median FVIII trough levels were 3.0 IU during standard prophylaxis (56 observations in 24 subjects) and 1.0 during PK-tailored prophylaxis (52 observations in 23 subjects).
Mingot-Castellano, 2018[29]	Prospective observational case series	PK-guided dosing of 36 severe hemophilia A patients <u>significantly reduced ABR</u> from 2.2 to 1.5 ($p=0.018$) and AJBR from 1.3 to 0.7 ($p=0.012$)			
Wang, 2022[74]	Prospective cohort	In 40 patients with severe hemophilia A, a year of individualized treatment based on T1/2 significantly <u>reduced ABR</u> (from 36.54 to 4.06 ($p<0.01$)) and AJBR (from 28.36 to 2.75 ($p<0.01$))			
Tegenge, 2017[82]	Simulation study	Interindividual variability in <u>bleeding risk</u> was <u>reduced</u> using PK-guided dosing in a simulation study with verification of 31 hemophilia A patients.			
Stemberger, 2019[53]	Prospective cohort	The <u>AJBR</u> of 11 patients with severe hemophilia A <u>decreased</u> from 2.0 [IQR 0-4] during weight-based prophylaxis to 0 [IQR 0-1.6] during PK-guided treatment ($p=0.003$)			
Pasca, 2017[79]	Observational retrospective study	The <u>number of bleeds</u> in 6 pediatric hemophilia A patients (<12 years) during 6 months standard prophylaxis was 7 compared to 2 bleeds during 6 months of PK-guided prophylaxis.			
Poon, 2016[70]	Review	Individualized prophylaxis by understanding bleeding triggers and PK profiles would allow us to target appropriate trough levels that can achieve "zero bleeds".			
Pasca, 2019[81]	Letter to the editor	PK-driven prophylaxis in 12 patients with severe hemophilia A showed an <u>ABR reduction</u> in 66.7% of patients compared to previous, standard prophylaxis. ABR decreased from mean 1.9 to 1.0.			
Megias-Vericat, 2021[91]	Prospective observational cohort study	During PK-guided prophylaxis of moderate to severe hemophilia A patients compared to standard prophylaxis: - significantly <u>lower spontaneous AJBR</u> ($p=0.01$) was found in 30 patients - <u>lower spontaneous ABR</u> was reported in 9 patients ≤ 15 years ($p=0.035$). - In 21 patients aged >15 years there was a significant <u>reduction in AJBR</u> ($p=0.043$) and <u>spontaneous AJBR</u> ($p=0.016$).			
Lock, 2016[72]	Discrete choice experiment questionnaire	In a group of 133 patients or parents of young patients with hemophilia on prophylactic treatment, the most important <u>facilitators</u> for implementation of PK-guided dosing of prophylaxis were <u>reduction of risk of bleeding</u> and estimated cost reduction.			
Li, 2019[75]	Prospective cohort	In 8 Chinese boys (5-16 years) with severe hemophilia A, who spend >30h per week with a FVIII level <1IU/dL, median <u>AJBR was reduced</u> from 7.8 to 1.4 after receiving PK-tailored low dose prophylaxis. Trough level was increased from 0.37 IU/dL to 1.19 IU/dL ($p<0.05$).			
Iriuchijima, 2019[83]	Interview and retrospective study	In 29 hemophilia A patients in Japan, <u>ABR decreased from 5 to 2</u> and AJBR from 1 to 0 after implementation of PK-guided dosing of prophylaxis.			
Iorio, 2017[71]	Review	Using PK in the treatment of hemophilia will be quicker and <u>more efficient</u> than proceeding by trial and error (e.g., increasing or decreasing dose based on occurrence of bleeding events).			
Huang, 2021[76]	Prospective intervention study	Implementation of PK-guided dosing aiming trough>1 IU/dL, <u>reduced ABR</u> in 23 pediatric patients with severe hemophilia A in Beijing from 8 to 2 ($p<0.001$), AJBR from 4 to 2 ($p<.01$) and ASBR from 2 to 0 ($p<.01$). Moreover, before PK-guided adjustment, <u>longer T1/2 was found to be related to reduced ABR</u> ($r=-0.45$, $p<.05$), AJBR ($r=-0.53$, $p<.01$) and ASBR ($r=-0.41$, $p<.05$).			
Doncel, 2021[77]	Retrospective cohort study	In 60 patients with severe hemophilia A <u>total ABR significantly reduced</u> from 1.03 (62 events) before to 0.58 (35 events) after use of PK ($p=0.004$). A significant reduction in spontaneous bleeding of 73.3% ($p=0.007$) and a not significantly increase of 4.1% for traumatic bleeding was observed ($p=1.00$).			

4. Effect on infusion frequency					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Lissitchkov, 2017[55]	Phase IIIb study	Personalized prophylaxis with Nuwiq® enabled 57% of 66 severe hemophilia A patients to <u>increase dosing interval</u> from three times weekly or every other day during standard prophylaxis to <u>≤ twice weekly</u> .			
Valentino, 2012[84]	RCT	PK-tailored prophylaxis with FVIII in 66 moderate-severe hemophilia A patients resulted in <u>one infusion less</u> per week compared to standard prophylaxis. This could increase treatment adherence.			
Pasi, 2021[87]	Letter to the editor	Based on PK analysis, 44/66 (66.7%) patients with hemophilia A changed prophylactic dosing regimen. <u>Dosing frequency decreased</u> in 39/40 patients.			
Collins, 2012[86]	Review	Some older patients also have poor venous access and, because of their longer FVIII half-lives and less physically demanding lifestyles, may be adequately <u>treated less often</u> . PK studies can be very helpful in these circumstances.			
Chowdhary, 2016[88]	Summary of two IIIb studies	Patients may require an abbreviated PK study to determine their individual half-life on an extended half-life product to achieve the most benefit. The study has shown that <u>decreased frequency of infusions</u> with adequate factor trough levels is feasible, and hemophilia A patients with longer half-lives are able to take advantage of longer dosing intervals and decreased frequency of infusions.			
5. Cost effectiveness					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Lissitchkov, 2017[55]	Phase 3B study	During PK-guided dosing with Nuwiq® in 66 patients with severe hemophilia A, <u>median weekly prophylaxis dose was reduced by 7.2%</u> from 100.0 to 92.8 IU/kg compared with standard prophylaxis using 30-40 IU/kg 3 times per week.	Valentino, 2012[84]	RCT	1 year PK-tailored (FVIII trough>1 IU/dL) versus standard prophylaxis (20-40 IU/kg every other day) with FVIII (Advate) showed <u>no differences in FVIII consumption</u> in 66 patients with a baseline FVIII level <3%.
Pasca, 2017[79]	Observational retrospective study	PK-driven prophylaxis showed a total saving of 10.67% compared to standard prophylaxis (25-40 IU/kg three times per week) in six pediatric hemophilia A patients, however without significant differences (p<0.057).	van Moort, 2021[52]	RCT	A perioperative RCT in 66 moderate-severe hemophilia A patients showed <u>no differences in FVIII consumption</u> between the PK-guided dosing and standard dosing group.
Tegenge, 2017	Simulation study, with verification in 31 patients.	PK-guided dosing targeting a trough of 1 IU/dL resulted in a <u>dose sparing benefit</u> compared to standard dosing of 20-50 IU/kg three times weekly. When targeting a trough of 3-5 IU/dL, PK-guided dosing resulted in dose sparing compared to standard dosing with only 50 IU/kg.	Mingot-Castellano 2018[29]	Prospective observational case series	PK-guided dosing of 36 severe hemophilia A patients showed <u>no significant impact on mean amount of FVIII consumption</u> (p=0.737).
Iorio, 2017[71]	Review	In resource-constrained settings, PK may indicate the highest threshold that can be obtained by <u>adjusting the infusion frequency</u> of any given <u>fixed amount of factor concentrate</u> .	Wang, 2022[74]	Prospective cohort	In 40 patients with severe hemophilia A, a year of individualized treatment based on T1/2 significantly <u>increased FVIII dosage by 47%</u> (from 2540 IU/kg/year to 3736 IU/kg/year (p<0.01)).
Pasca, 2019[81]	Letter to the editor	PK-driven prophylaxis in 12 patients with severe hemophilia A showed an overall average <u>15.8% reduction in FVIII</u> concentrate consumption which leads to an equal reduction in costs, compared to standard prophylaxis with 25-50 IU/kg three times per week.	Stemberger, 2019[53]	Prospective cohort	Factor consumption of 23 patients with severe hemophilia A on <u>prophylaxis increased by 2400</u> [IQR 121-2586] IU/kg/patient/year (p=0.003) after switch to PK-guided treatment.
Mingot-Castellano, 2015[89]	Prospective observational case series	Introduction of FVIII trough level adjustment in 5 patients with severe hemophilia A <u>reduced FVIII consumption</u> by 31.3% without changes in efficacy.	Nagao, 2019[33]	Prospective cohort	Total costs of PK-guided prophylaxis of 39 severe hemophilia A patients <u>increased</u> after PK-guided dosing.
Megias-Vericat, 2019[80]	Prospective observational cohort	In 15/22 patients with moderate to severe hemophilia A, a <u>lower rFVIII consumption</u> was reported (median reduction of annual FVIII consumption: 10611 IU (IQR 6423–19001) after PK-guidance.	Megias-Vericat, 2019[80]	Prospective observational cohort	In 22 patients with moderate to severe hemophilia A, <u>no significant changes in FVIII consumption</u> were found after implementation of PK-guided dosing.
Lock, 2016[72]	Discrete choice experiment questionnaire	In a group of 133 patients or parents of young patients with hemophilia on prophylactic treatment, most important facilitators for implementation of PK-guided dosing of prophylaxis were reduction of risk of bleeding and <u>estimated cost reduction</u> .	Megias-Vericat, 2021[91]	Prospective cohort study	In 30 patients with moderate to severe hemophilia A, <u>no significant differences in the overall FVIII consumption</u> were found when standard prophylaxis was compared to PK-guided prophylaxis.
Grazzi, 2022[73]	Cross-sectional retrospective	47 patients with hemophilia A who received PK-guided dosing reported a <u>lower mean number of hematologist and nurse consultations</u> (7.1 and 5.2, respectively) than 73 patients receiving non-PK-guided dosing (10.7 and 10.3). Moreover, patients receiving PK-guided dosing were also observed to have experienced <u>fewer ward hospitalizations</u> during the 12 months prior to data collection than those receiving non-PK-guided dosing, with mean (SD) numbers of hospitalizations of 0.4 and 0.6, respectively.	Li, 2019[75]	Prospective cohort	PK was assessed in a group of Chinese boys (5-16 years) with severe hemophilia A receiving low-dose prophylaxis. Eight patients, with a FVIII level <1 IU/dL >30h per week, received PK-tailored low dose prophylaxis. The other 7 patients, who spent <30h per week with a FVIII level >1 IU/dL or with an AJBR <4 continued original prophylaxis. <u>Mean total consumption of FVIII in the PK-tailored group was higher</u> with 2401.9 ± 633.7 IU/kg/year compared to consumption in maintenance group of 1765.8 ± 902.4 IU/kg/year (p > 0.05). A more cost-effective regimen for patients in developing countries may be to <u>increase the infusion frequency</u> rather than increasing the dosage in PK-driven prophylaxis.
Iriuchijima, 2019[83]	Interview and retrospective study	In 29 patients with hemophilia A, median annual <u>drug cost decreased</u> from 14824 Japanese Yen/year before to 13749 Japanese Yen/year after PK introduction.			
Carlsson, 1998[90]	Cross-over study	Mean consumption of eight hemophilia B patients using FIX during standard dosing (20-40 IU/kg twice weekly) corresponds to a cost of \$135.400 US per patient and year. <u>Costs were lower for kinetic dosing regimens</u> (FIX trough>1 IU/dL) with dosing every 3 and 2 days, respectively, are \$77.300 US and \$60.900 US.			
Carlsson, 1997[85]	Cross-over study	In 14 severe hemophilia A patients, <u>mean FVIII consumption in 6 months was significantly decreased</u> (p<0.005) by 31% during PK-guided dosing (FVIII trough>1 IU/dL) compared to standard dosing (25-40 IU/kg three times per week). Theoretically, by reducing troughs in the PK group (2.2 IU/dL) to those of standard group (0.89 IU/dL), consumption would be reduced by 73%.			
Collins, 2011[27]	Review	Understanding the effect of PK and dosing schedules also has important implications for treating patients where <u>health care resources are limited</u> . Low-dose daily prophylactic regimen may be possible in countries where standard regimens are too expensive. In addition, more cost-effective use of health care resources is important in all countries, thus tailoring prophylaxis to the minimum effective dose is important.			

6. Applicability in clinical practice					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Pasca, 2017[79]	Observational retrospective study	Six pediatric hemophilia patients received PK-guided prophylaxis in an observational retrospective study. Its nature did not interfere with the <u>common protocol</u> of treatment applied in the center.	Srivastava, 2020	WFH guidelines	PK tailored prophylaxis <u>requires expertise</u> in interpreting results of PK.
Mingot-Castellano, 2018[29]	Prospective observational case series	36 patients with severe hemophilia A received PK-guided dosing according to <u>local guidelines and protocols</u> .	Mahlangu, 2022	State of the art	The emicizumab rollout has progressed rapidly, replacing the use of factor concentrates in patients with hemophilia A. PK of emicizumab is very predictable.
Megias-Vericat, 2021[91]	Prospective observational cohort study	This study validated the use of PK-guided dosing in 30 hemophilia A patients in <u>clinical practice</u> .			
Megias-Vericat, 2022[92]	Prospective observational cohort study	75 moderate to severe hemophilia A patients were switched under PK-guidance from SHL to EHL prophylaxis in <u>usual clinical practice</u> . No special intervention in treatment was necessary.			
Srivastava, 2020[2]	WFH guideline	For people with hemophilia A or B, prophylaxis with factor concentrates (either SHL or EHL) is <u>recommended</u> at a dose and dosing interval (dependent on PK properties of the factor concentrate) that allow them to at all times have sufficient circulating factor to prevent hemarthrosis, and spontaneous and breakthrough bleeding, based on their individual needs and lifestyles to preserve musculoskeletal function.			
Rayment, 2020[51]	Guideline	British guideline for children with hemophilia A and B <u>recommends</u> that prophylaxis regimens should be individualized, determined jointly with the patient and based on PK data, patients' activity and patient preferences.			
Ragni, 2018[10]	Communications from ISTH	In an online survey among members of the ISTH SSC FVIII and FIX interest group, <u>86% incorporated PK</u> into transition from SHL to EHL factor concentrate.	Ragni, 2018[10]	Communications from ISTH	In an online survey among members of the ISTH SSC FVIII and FIX interest group, <u>only 9.7% used PK models</u> during the transition from standard to EHL factor concentrate. Lack of time, access or resources were reasons that PK data were not used.
Preijers, 2019[95]	Case report	During a total knee replacement <u>clinical practice</u> in a patient with severe hemophilia A with morbid obesity, the patient was PK-guided dosed using ideal body weight. FVIII target levels were obtained adequately after surgery.			
McEneny-King, 2020[12]	Retrospective study	Use of WAPPS-Hemo by clinicians has increased, reflected by the <u>threefold increase</u> in number of infusions entered between October 2017 and September 2016 compared to a previous period from October 2015 through September 2016.			
Hazendonk, 2016[93]	Model development	PK-guided dosing for moderate-severe hemophilia A patients in <u>perioperative setting</u> is possible using available peri-operative population PK model. Predicted FVIII trough levels were in accordance with measured FVIII trough levels.			
Hazendonk, 2016[96]	Case report	A case study presenting a severe hemophilia A patient who underwent a renal transplantation, shows that iterative adaptive dosing by Bayesian analysis is possible and feasible for <u>major surgeries</u> .			
Iorio, 2017[9]	Guideline	The ISTH SSC on FVIII/FIX has provided <u>guidance</u> for performing, interpreting and applying individual population PK assessment routine clinical practice.			
Doncel, 2021[77]	Retrospective cohort study	In 60 patients with severe hemophilia A, FVIII <u>dose decrease of 7%</u> was observed after the use of the PK, although there was no significant difference in the dose.			
Croteau, 2018[99]	Focus group discussion	Nine hematologists specialized in hemophilia care described factors that increase likelihood of a PK tailored approach as follows: - extended-half life products and patients changing factor concentrates - high physical activity level - good adherence - belief in target level - confidence in PK analysis - frequent bleed event - acceptable patient distance from hospital	Croteau, 2018[99]	Focus group discussion	Nine hematologists specialized in hemophilia care described that the likelihood of a PK tailored approach decreased when: - poor adherence - no "true ideal target levels" have been identified - insufficient understanding or confidence in PK - longer distance from hospital - no trust in reliable assay results - poor venous access
Chaweehisal, 2022[97]	Case report	A 6-year-old boy with severe hemophilia developed a bleed in his rhabdomyosarcoma during chemotherapy despite prophylaxis. <u>After assessing the PK of FVIII, the interval was adjusted and the bleed did not recur.</u>			
McEneny-King, 2020[12]	Retrospective study	In WAPPS-Hemo, infusion data points fell both into time windows as suggested or recommended and throughout those windows. This reinforces the value of <u>flexibility in sampling time points</u> in successful execution of population PK in routine clinical practice.			
Nummi, 2022[98]	Non-interventional retrospective cohort	This <u>non-intervention study had a positive clinical experience</u> with PK-guided dosing using WAPPS-Hemo in adult hemophilia A patients.			
van der Sluis, 2022[13]	Survey	PK assessment in routine patient care was assessed in 37 European (pediatric) hematologists in a survey, <u>92% assessed PK in routine care</u> , by conducting a full PK analysis (49%) or measuring trough levels (53%) or trough and peak levels (49%). When deciding to switch a patient to an EHL therapy, 89% assessed PK and 51% carried out full PK analysis.			

7. Useful software tools					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Croteau, 2020[111]	Prospective study	Providers of hemophilia treatment centers report that they find information provided by <u>WAPPS-Hemo</u> useful in 87% of the time in planning a patient's prescribed prophylaxis regimen.	Iorio, 2017[44]	Review	The adoption of a population PK approach to individual estimation cannot happen without a collaborative approach among <u>several partners</u> .
McEneny-King, 2016[108]	Protocol article	<u>WAPPS-Hemo</u> aims at supporting clinicians assessing individual PK from only a few patient samples, thereby eliminating barriers to initiate PK-guided dosing in hemophilia. By incorporating this tool into clinical practice, clinicians can implement a personalized dosing strategy without rigorous sampling and complex calculations. Using dense data of more than 20 brands of factor concentrate, models have been developed that undergo refinement and validation.	McEneny-King, 2016[108]	Protocol article	Main risk associated with the use of WAPPS-Hemo is the possibility that the <u>specific patient is outside of the covariate space used to build the models</u> . Consequently, the PK estimations may be imprecise and could result in suboptimal treatment decisions.
Mondorf, 2019[116]	Report	<u>Smart medication™</u> is a smartphone-based software application for long-term monitoring of patients with hemophilia, which allows real-time management and surveillance of patient self-treatment, bleeding occurrence and factor concentrate usage. This could facilitate PK calculations.	Iorio, 2018[57]	Review	A practical limitation to the adoption of a population PK based tailoring approach is <u>complexity</u> of performing a post-hoc Bayesian estimation. Independent <u>interpretation and use of relevant PK outcomes</u> is beyond reach for most clinics, and there is a move towards embracing software that both calculates an individual's PK profile using Bayesian methods and allows for individualized dose regimen design
Pasca, 2017[79]	Observational retrospective study	The PK of 6 pediatric hemophilia patients was assessed by <u>myPKFIT®</u> in an observational retrospective study.	Hermans, 2020[49]	Review	A key limitation of the WAPPS-Hemo tool is the requirement for users to have a <u>basic understanding of PK</u> .
Mannucci, 2013[105]	Prospective study	A <u>dosing calculator</u> is available on the <u>Humate-P</u> web site using a patient's in vivo recovery next to baseline level, target level and body weight.	Hazendonk, 2018[64]	Review	<u>Transparency and reliability</u> of the data used to construct population models used in PK tools are of crucial importance.
McEneny-King, 2016[109]	Review	<u>myPKFIT</u> addresses the two major barriers to the uptake of a population PK approach into the clinical practice, which are the need for a dedicated population model and specialized algorithm to perform the population PK estimation.	Berntorp, 2014[102]	Review	Adoption of limited sampling strategies is limited by practitioner's <u>lack of access</u> to population PK data and simple methods for calculating dosing based on such data. Development of an easy electronically-based, "PK-calculator" would fill an important need.
Versloot, 2021[106]	Cross sectional study	Reference values of T1/2 have been established <u>and formulas</u> were derived to allow estimation of T1/2 based on patient characteristics (age, body weight/BMI, type of concentrate, inhibitory history, blood group). This formula can be used in the absence of measured data.	Preijers, 2018[117]	Cross evaluation study	<u>Three evaluated PK tools</u> (myPKFIT, WAPPS, NONMEM) produced significantly <u>different PK parameters and dosing advice</u> for 39 patients with moderate and severe hemophilia A. However, validation procedures demonstrated adequacy of the tools.
Arvanitakis, 2021[114]	non-intervention cohort study	In a study that compared PK profiles from 18 severe hemophilia patients and dosing estimations between the tools <u>myPKFIT and WAPPS-Hemo</u> , <u>tools provide similar PK outcomes with the one-stage and chromogenic assays</u> .	Arvanitakis, 2021[114]	non-intervention cohort study	In a study that compared PK profiles from 18 severe hemophilia patients and dosing estimations between the tool myPKFIT and WAPPS-Hemo, <u>tools calculate different times</u> to a specific trough level, hence providing <u>different dose estimations</u> which may have a significant impact on clinical outcome and factor consumption. We believe clinicians need to be aware of these discrepancies and take them into account while making clinical decisions, as well as closely monitoring activity levels achieved by each dosing schedule.
Ar, 2017[113]	Review	Tools to estimate individual PK parameters may change the concept of prophylaxis and increase its effectiveness by fine-tuning treatment according to the actual needs of the patient and improve quality of life by providing reasonable flexibility. Preliminary results of the studies utilizing these <u>tools imply that they improve patient engagement, ensure adequate level of factor for a safe exercise, and help providing good follow-up of care</u> .	Abdel-Rahman, 2020[103]	Software development	Successful application of PK-guided dosing to routine patient care requires: (1) comprehensive knowledge of the patient, (2) thorough understanding of pharmacological principles that drive the relationship between dose exposure (3) expertise in mathematical and PK modeling and simulation. Providers with expert knowledge of the latter often have limited involvement with patient or their primary medical team, which may <u>introduce delays in dosing solutions</u> .
Mahlangu, 2022[100]	State of the art	WAPPS-Hemo research has developed the tool <u>Calibra® to support different levels of emicizumab</u> . The tool calculates appropriate dose and suggests alternative combinations of dose and injection frequencies. In future, measurements of clotting activity after emicizumab injections could be modelled.			
Álvarez-Román, 2017[112]	Letter to the editors	27 patients with severe hemophilia A received PK-guided dosing using <u>myPKFIT®</u> that provided dosage calculations and a weekly graph. Use of myPKFIT has <u>increased the number of PK studies</u> in university hospital in Madrid. In those patients who were not adequately controlled, myPKFIT® enabled <u>rapid and easy assessment to adjust factor use and protection for bleeds</u> .			
Li, 2019[75]	Prospective cohort	<u>WinNonLin</u> software was used in a study of 15 patients with severe hemophilia A to assess PK parameters and time with FVIII level ≥ 1 IU/dL.			
Iorio, 2017[71]	Review	<u>Graphical profiles</u> provide all of the required information in a format easier to understand and communicate than any PK parameters.			
Hay, 2017[115]	Report	<u>Haemtrack</u> is an <u>electronic home treatment diary</u> for patients with inherited bleeding disorders. Such a system makes data handling and verification much easier and less labor intensive for the hemophilia center and could be used for PK guidance.			
Croteau, 2018[99]	Focus group discussion	Nine hematologists specialized in hemophilia care shared that a clinically useful population PK platform application needs to enable providers to <u>modify the planned dose and infusion interval</u> and <u>visualize</u> resultant change in estimated factor decay curve in order to support physician use of PK data in tailoring prophylaxis regimens.			
Berntorp, 2017[104]	Commentary	For implementation of PK tailored dosing in clinical routine practice, <u>practical software packages are needed, and these have been developed</u> .			
Batovora, 2022	Expert opinion	50% of the nine hemophilia experts felt that more personalized treatment to increase protection was very important, and the use of <u>telemedicine applications</u> such as Florio® HAEMO (Sobi) and myPKFIT™* (Takeda) was important/very important.			
Brekkan, 2019[107]	Simulation study	Implementation of PK-based individualization also depends on <u>software availability</u> . Several resources are available including for example WAPPS-Hemo Project, DoseMe and InsightRX.			

8. Patient involvement					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Santoro, 2013[120]	Review	<u>Good adherence</u> to a prophylactic regimen is important to success, and personalized prophylaxis can be a way to achieve adherence from patients and their families.	Grazzi, 2022[73]	Cross-sectional retrospective	A <u>similar proportion of fully adherent</u> patients was found between 47 hemophilia A patients receiving PK-guided prophylaxis (78.1%) and 73 patients on non-PK-guided prophylaxis (78.7%) (p=0.759)
Petrini, 2015[121]	Review	The ability to tailor dosing around lifestyle and physical activity is described as a motivator of <u>adherence</u> .	Mangles, 2018[123]	Letter to the editor	In a study aiming to investigate PK-guided dosing in clinical practice, 6/20 enrolled patients with hemophilia <u>withdrew</u> prior to baseline assessment. Only 2/11 recruited patients remained enrolled for ≥6 months of an expected study period of 12 months. Reasons for withdrawal were difficulties with attending appointments and no willingness or confidence to reduce FVIII dose.
Megias-Vericat, 2019[80]	Prospective observational cohort	In 4/22 patients with moderate to severe hemophilia A, <u>adherence increased</u> after PK-guided dosing and majority of patients showed a similar adherence.	Berntorp, 2016[119]	Expert opinion	The idea of individual PK for many physicians and patients alike could be a major impediment. Introducing a <u>new concept</u> to people who have lived with hemophilia for decades is similarly not easy.
Berntorp, 2016[119]	Expert opinion	Knowing an individuals' PK allows all regimens <u>options to be discussed</u> and for the hemophilia patient to choose with the physician the best regimen that is tailored truly to their needs. Tailoring prophylaxis allows the opportunity for the clinician <u>to engage actively with the patient</u> .	Croteau, 2018[99]	Focus group discussion	Five parents of adolescent patients with severe hemophilia A <u>questioned decisions on the "right" trough and reliability</u> of factor level estimated based on population PK analysis. Therefore, close follow-up was critical to determine success.
Nagao, 2019[33]	Prospective cohort	<u>Improved adherence</u> was observed in 5 severe hemophilia A patients who required shorting of infusion interval based on PK analysis, and in 19 patients who did not require a change in their prophylaxis regimens.	Adrameri na, 2022[124]	Prospective study	Previous prophylactic treatment of 17/20 hemophilia A patients was deemed insufficient based on a PK profile assessment and index joint (knees, elbow, and ankles) ultrasound scans. However, when given the choice to increase dose amount, dosing frequency or switching FVIII products, only 3/17 patients opted for an increase in dosing frequency. This was partly because <u>patients were not prepared to intensify their previous regimen</u> .
Iorio, 2017[71]	Review	Alerting functions triggered by reaching risky plasma estimated factor levels could <u>minimize the chance of skipping infusions</u> , particularly for regimens with a low frequency of infusion.			
Álvarez-Román, 2017[112]	Letter to the editors	At an educational level, myPKFIT® helped find concordance between clinicians and patients or his parents regarding dosing and schedule, as PK and weekly simulations helped foresee situations if infusions were spaced apart in time or doses increased. Graphical output, that was attractive and informative, was used as an <u>educational tool</u> . 27 patients (and parents) with severe hemophilia A benefitted from clear information in a PK-guided plan that facilitated <u>decision making</u> with the attending clinician.			
Croteau, 2020[111]	Prospective study	In this study of children and adults with hemophilia A investigating the feasibility if PK-tailored prophylaxis in clinical practice, all participants reported an interest in their individualized PK profile and specifically a desire to <u>better understand</u> changes in their factor levels over time to support participation in physical activities, a general interest in how their factor levels changed over time after factor infusion, and an interest in decreasing frequency of infusions needed for successful prophylaxis.			
Megias-Vericat, 2019[80]	Prospective observational cohort	The PK profile was used as an <u>educational tool</u> to adjust physical activity for a 16-year-old patient with severe hemophilia A.			
Jackson, 2019[118]	Case report	Knowing time to FVIII of 1% after PK assessment allowed <u>greater flexibility of exercise</u> times in a 30-year-old severe hemophilia A patient.			
Jackson, 2019[118]	Case report	Population PK modeling tools provide patient-friendly information that help the patient to <u>understand</u> the implications of various prophylactic dosing strategies, to play an <u>active part in making decisions</u> about their treatment, and to adapt their treatment appropriately in the future.			
Preijers, 2019[95]	Case report	PK-guided dosing during a total knee replacement in a patient with severe hemophilia A gave the patient more <u>confidence</u> and a sense of relief. He recommends it to any hemophilia patient undergoing surgery.			
Iriuchijima, 2019[83]	Interview and retrospective study	Results from an interview with medical staff of the largest hemophilia center in Japan show that individualized therapy is effective if: - measures are taken to understand the disease through patient guidance - data is visualized to improve patient understanding - burden of visits to the hospital is reduced to 2 samples during one visit.			
Croteau, 2018[99]	Focus group discussion	Nine hematologists specialized in hemophilia care desired to be able to save and print individual patient PK profiles, so that the illustration of estimated factor coverage with different doses and infusion frequencies could be used for patient encounters to <u>support patient education</u> and rationale for prophylaxis regimen selection.			
Croteau, 2018[99]	Focus group discussion	Five parents of adolescent patients with severe hemophilia A favored an approach of using a PK profile <u>to inform decision making</u> around prophylaxis, endorsing a preference for their sons' medical care to be "driven by data." 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. 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.			
Nummi, 2022[98]	Non-interventional retrospective cohort	In this non-intervention study, clinical experience with PK-guided dosing using WAPPS-Hemo in adult hemophilia A patients was positive, enabling <u>shared decision</u> making with patients.			
Dargaud, 2018[122]	Review	Prevention also seeks to facilitate patient's socio-professional insertion. The more a prophylaxis protocol is adapted to a specific person, the more <u>efficacious</u> it is likely to be. In addition to patient's individual needs and clinical features, the approach must also be tailored to objective laboratory results like the clotting factor concentrates PK and pharmacodynamics characteristics.			

9. Burdening of patients and treatment teams					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Stemberger, 2019[53]	Prospective cohort	Scores of hemophilia-specific <u>QoL</u> questionnaires of 11 patients with severe hemophilia A on prophylaxis <u>increased</u> with a median of 2.3 (IQR 1.1-4.3) (p=0.04) points after switching to PK-guided treatment. A change of >1 points assumed to represent a clinically relevant change.	Valentino, 2012[84]	RCT	1 year PK-tailored versus standard prophylaxis with FVIII showed <u>no differences in health-related quality of life</u> in 66 hemophilia patients with a baseline FVIII level <3%.
Croteau, 2018[99]	Focus group discussion	Nine hematologists specialized in hemophilia care expressed that the <u>limited number of blood draws</u> needed for population PK analysis was not a barrier.	Croteau, 2018[99]	Focus group discussion	Five parents of adolescent patients with severe hemophilia A commented on the <u>challenge of obtaining blood samples</u> , particularly if additional visits to the hospital were required. For patients who lived close to the hospital, it could still be difficult to coordinate sampling with work and school schedules.
Iorio, 2017[44]	Review	For a population PK approach <u>1 point in each of the 3 compartments</u> that described the PK of FIX is needed.			
Mingot-Castellano 2018[29]	Prospective observational case series	Only <u>2 samples</u> were required in 29 of 36 severe hemophilia A patients to assess PK.	Yu, 2019[128]	Simulation	Individual PK of a prior FVIII concentrate cannot be used to predict a future EHL FVIII product using the eta-method. Therefore, most individuals still need <u>PK assessment on the new factor concentrate</u> .
Morfini, 2017[56]	Review	The major advantage in population PK is that even <u>sparse samples</u> from all individuals can be combined to build the model	Srivastava, 2020[2]	WFH guidelines	PK tailored prophylaxis required patients to undergo at least a <u>minimal PK evaluation</u> .
Álvarez-Román, 2017[112]	Letter to the editors	The need for <u>only two valid samples</u> in 16/27 patients with severe hemophilia A patients to obtain PK estimations was found to be useful in improving our practice, and in avoiding the inconvenience to parents and patients related with traditional PK studies.	Ljung, 2013[65]	Review	To allow sparser sampling using the Bayesian method, new coagulation factor concentrates may each need their own population data. Thus, <u>large product-specific databases of PK parameters</u> should be gathered, although this will be demanding and difficult to achieve.
McEneny-King, 2021[125]	Simulation study	A limited sampling strategy has been identified for rFVIIIc including <u>only 2 or 3 samples</u> .	Iorio, 2018[57]	Review	Non-stable conditions will necessitate <u>reassessment of PK</u> to ensure that congruent dosing, for example PK assessment in young children is done every 2 to three years in some centers.
Bjorkman, 2010[5]	Model development	Reducing sampling schedule of rAHF-PFM (Advate®) had only minor impact on estimates of clearance and volume of distribution. Therefore, <u>limited blood sampling can be used in clinical practice</u> .	Raymont, 2020[51]	Guideline	Evidence for how frequently PK analyses should be repeated in children is not available, but a pragmatic approach would be to <u>repeat analysis</u> every 3 years or when there is a significant change in body weight or when changing products.
Iorio, 2017[9]	Guideline	To <u>lower the burden of assessing PK</u> , some practical recommendations for a limited sampling approach are as follows: - use samples drawn at routine clinical visits. - combine time points from multiple infusions (trough of first is also predose of second). - do not perform a washout.	Croteau, 2020[111]	Prospective study	In study of children and adults with hemophilia A investigating feasibility of PK-tailored prophylaxis in clinical practice, barriers to enrollment included <u>distance from the hospital</u> 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.
Iorio, 2017[71]	Review	Clinical studies reassessing individual PK after 6 to 12 months show that <u>PK profiles remain stable</u> over time.	Brekkan, 2016[127]	Model development	If model-based dose tailoring of FIX is to be used clinically, <u>sampling schedules must be practical</u> , with respect to number of samples taken and to timing of samples.
Chowdary, 2019[126]	4 clinical trials	This combined PK analysis shows that PK characteristics of N8-GP (EHL-FVIII) are consistent over time.			
10. Attainment of personalized medicine					
Facilitator			Barrier		
Author, year	Study design	Finding	Author, year	Study design	Finding
Mingot-Castellano 2018[29]	Prospective observational case series	After assessment of PK, <u>only 4 out of 36 severe hemophilia A patients maintained</u> their previous dosage.	Megías-Vericat, 2019[80]	Prospective observational cohort	In 15/22 patients with moderate to severe hemophilia A, <u>no changes in dosing regimens</u> were required after PK assessment.
Megías-Vericat, 2021[91]	Prospective observational cohort study	After assessment of PK, <u>15/30</u> moderate to severe hemophilia A patients received <u>modified dosing regimens</u> .			
Nagao, 2019[33]	Prospective cohort	23/39 severe hemophilia A patients required <u>dose adjustment</u> of their prophylaxis after PK analysis.			
Huang, 2021[76]	Prospective intervention study	In pediatric patients with severe hemophilia A in Beijing, <u>28/46 patients adjusted dosing regimens</u> after PK assessment because of trough levels <1 IU/dL or unaccepted bleeds.			
Hazendonk, 2018[64]	Review	PK-guided dosing will facilitate individualization of dosing according to <u>individual lifestyle and activities</u> .			
Bukkems, 2021[19]	Model development	A case demonstrates that according to the developed interaction VWF/FVIII population PK model, <u>higher doses than given based on clinical guidelines</u> would have been needed to achieve the target levels in a patient with von Willebrand Disease.			

PK: pharmacokinetic, FVIII: Factor FVIII, FIX: Factor IX, IU: International units, PD: pharmacodynamics, A(J)BR: Annualized joint bleeding rate, vs: versus, WFH: World Federation of Hemophilia, CI: Confidence interval, RCT: Randomized controlled trial, RTTE: Repeated time to event, ETP: Endogenous thrombin potential, OR: Odds ratio, rFVIII: recombinant Factor VIII, rFIX: recombinant FIX IVR: In vivo recovery, VWD: von Willebrand disease, OSA: One-stage assay, CSA: Chromogenic substrate assay, MAP: Maximum a posteriori, aPTT: Activated partial thromboplastin time; IIV: Interindividual variation, BLQ: Below level of quantification, VWF:RCo: von Willebrand factor Ristocetin Cofactor, IQR: inter quartile range, T1/2: terminal half-life, SD: standard deviation, ISTH: International Society of Thrombosis and Hemostasis, SSC: Scientific subcommittee, SHL: Standard half-life, EHL: Extended half-life, WAPPS-Hemo: Web Accessible Population Pharmacokinetic Service-Hemophilia.

hemostasis in perioperative settings. [45,46] Thirdly, target levels recommended by experts after Delphi consensus have not been empirically tested and consensus is still lacking in some situations. [28] Fourthly, there is growing evidence that target levels should be set individually and patient characteristics such as bleeding phenotype, physical activities, and joint status should all be taken into consideration. [2,26,27,47–51] Importantly, PK-guided dosing focuses only on factor levels, not taking individual differences in bleeding phenotype and other PD markers such as thrombin generation into account. [38,39,41] These

parameters might be able to explain discrepancies in bleeding phenotype in patients with similar FVIII/FIX levels. Although PK/PD models have been developed, they have not yet been validated or utilized in patients yet.

3.1.3. Overall knowledge gaps

Importantly, future research should focus on establishing a treatment target for hemophilia B, either based on FIX levels or bleeding risk. The main goal of future research in hemophilia A should be to allow for

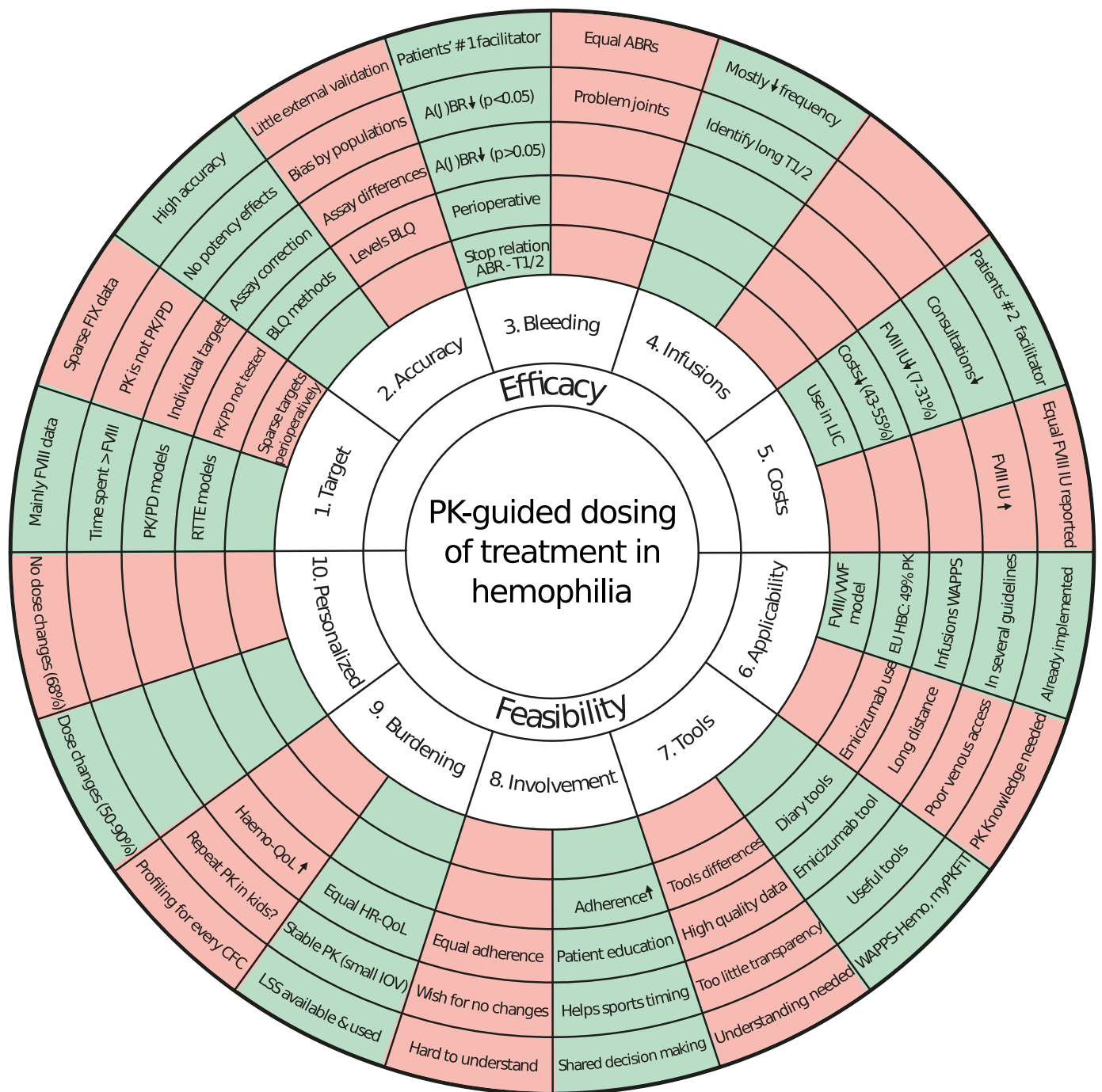


Fig. 2. Barriers and facilitators for implementation of PK-guided dosing of treatment in bleeding disorders according to overarching themes efficacy and feasibility grouped into ten common topics; five per theme.

Facilitators are displayed in green and barriers are displayed in red. See Table 1 for extensive formulation of barriers and facilitators.

A(J)BR: Annualized (joint) bleeding rate, FVIII: Factor FVIII, FIX: Factor IX, PK: Pharmacokinetics, PD: Pharmacodynamics, RTTE: Repeated time to event, IU: International Units, LSS: Limited sampling strategies, WAPPS: Web-Accessible Population Pharmacokinetic Service, EU: European Union, HBC: Hemophilia Treatment Center, BLQ: Below limit of quantification, Haemo-QoL: Hemophilia Quality of life, CFC: Clotting factor concentrate, IOV: Inter occasion variability. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

individualization of target levels not only according to patient characteristics (i.e. PK) but also based on knowledge of retrospective (break-through) bleeding events, physical activity, behavior, trauma/ impact, and arthropathy. Importantly, as an example, no studies report on target factor levels during physical activities, or other high bleeding risk states.

RTTE models may facilitate empirical selection of desired target levels. Validation of such models in prospective studies remains important. The developed PK/PD model which includes thrombin

generation measurements may be used to further explore application of PD-guided dosing in patients with hemophilia A. For instance, it may be interesting to investigate if dosing based on a combination of FVIII and thrombin potential reduces spontaneous bleeding and if the predicted bleeds are accurate, although this might be difficult due to sparsity of bleeds and low reliability of thrombin test results.

3.2. Accuracy of PK-guided dosing

3.2.1. Facilitators

An important prerequisite for the implementation of PK-guided dosing is that the available PK models are able to accurately predict observed drug levels. Implementation of PK-guided dosing in hemophilia A is supported by reports of high accuracy by several studies, whether focusing on target level attainment, error with respect to observed factor levels, or validation of models with new data from centralized data collections such as Web Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo). [52–56] Fortunately, high accuracy is also obtained using sparse sampling techniques. [55] Secondly, FVIII PK is reproducible resulting in accurate longitudinal PK assessments. [20,27] Thirdly, methods to obtain information from samples below the quantification limit exist for PK models. [57] Recently, an overview of PK models was published to support selection of the best model for the patient at hand. This aids in the selection of the appropriate model based on the similarity of the patient populations, and [58] It is also possible to correct for discrepancies between one-stage and chromogenic assay utilization by applying a correction factor in available population PK models. [59,60] Finally, the accuracy of PK predictions is not affected by potency differences between labeled and actual content of FVIII vials, which probably also applies to similar bleeding disorders [61].

3.2.2. Barriers

The most important barrier with regard to accuracy is that PK models are rarely externally validated, while studies performing such validations frequently report clinically significant biases. [9,45,56,60,62–64] Bias can for example be caused by an under-representation of specific patient sub-populations in models. [45,57,64] In addition, it can be caused by inherent differences between patient populations from varying treatment centers or countries. Other sources of bias are measurement discrepancies between results of blood samples assessed by one-stage or chromogenic assay. [45] Moreover, several studies have found that the use of certain assay reagents may result in clinically relevant discrepancies. [44,45,57,59,65,66] Another form of bias is related to cases where residual factor activity levels are unknown, which affect post infusion measurements. [36,56,57] PK assessment can also be affected by the focus on working with target levels close to the limit of quantification. [36,57] Finally, study design may also negatively impact accuracy of PK models. For example, in a retrospective study of patients receiving Benefix®, authors found that its half-life was underestimated in other studies. [67] This was attributed to the fact that in these studies the FIX sampling times did not extend beyond 72 h and thus were too short.

Importantly, it is difficult for non-professionals to detect issues related to modeling assumptions in published models. [36,44,57] For example, the patient numbers needed to construct a model are dependent on inter-, intra and residual data variability, and not ascertainable by non-experts. [57]

3.2.3. Overall knowledge gaps

Although there are many reports on factors affecting the accuracy of PK models, there is no consensus on clinically acceptable levels of error. Additionally, an important question is if the same amount of error is acceptable for all types of factor levels (trough, mid, peak). It is for example undesirable to maintain similar error thresholds for trough and peak levels (Goedhart et al., submitted).

Moreover, there should be a higher emphasis on the importance of external validation of PK models. In cases where external data is not available, internal validation methods should be applied. Unfortunately, such validation procedures are rarely performed.

The reproducibility of PK studies should also be improved in our opinion. Often, published PK studies include insufficient information to actually implement or reproduce PK models. [68,69] Directly sharing

model files and code is strongly advised. It may also be useful to improve the transparency of the patient population by for example sharing histograms depicting the distribution of patient's age, weight and other relevant markers when reporting on patient characteristics.

3.3. Impact on bleeding frequency

3.3.1. Facilitators

Compared to standard dosing, individualizing therapy by PK-guided dosing is thought to be more efficacious to prevent bleeds. [70,71] A reduction in bleeding risk was the most important facilitator for implementation of PK-guided dosing of prophylaxis according to 133 patients with hemophilia and their caregivers. [72] Indeed, several cohort studies have reported significantly lower annualized (joint) bleeding rates (A(J)BR) in patients with hemophilia A switching from weight-based to PK-guided prophylaxis. [29,53,73–77] Other studies have also found decreased ABR after implementation of PK-guided dosing, although not all studies could report on its statistical significance due to study design [55,78,79] or have not described a significant effect on ABR. [33,80–83] Moreover, one cohort study identified a significant association between AJBR and shorter FVIII half-life, that disappeared after the implementation of PK-guided dosing. [80]

3.3.2. Barriers

In contrast to previous studies which reported reductions in ABR, a randomized controlled trial (RCT) in hemophilia A patients on prophylaxis showed no such differences when comparing standard and PK-guided prophylaxis. Notably, median FVIII trough level was higher in the standard group (3.0 vs 1.0 IU/dL). [84] Likewise, a RCT in perioperative hemophilia A patients found no difference in bleeding between standard and PK-guided replacement therapy. Importantly, this RCT was not powered to detect differences in bleeding due to scarcity of perioperative bleeding in general. [52] Next, a cross-over study [85] and two cohort studies found no differences between A(J)BRs between standard and PK-guided prophylaxis. [33,80] Moreover, in a recent cross-sectional retrospective cohort study, 51% of hemophilia A patients in the PK-guided group experienced problematic joints compared to 42.5% patients in the non-PK-guided group, although this difference was not significant. [73]

3.3.3. Overall knowledge gaps

For hemophilia A, a RCT with long-term follow-up comparing standard dosing to PK-guided prophylaxis utilizing individualized target levels >1 IU/dL is needed to further investigate impacts on bleeding frequency. However, as control of bleeding is often also associated with behavior it may be difficult to independently establish outcomes. Importantly, no studies in our search report on bleeding outcomes after PK-guided dosing in hemophilia B.

3.4. Effect on infusion frequency

3.4.1. Facilitators

PK analysis may be useful to identify patients with longer factor concentrate half-lives, especially those on extended half-life factor concentrates, who are able to reduce their dose and/or dosing frequency. Of course, dose reduction lowers treatment costs. Moreover, reducing dose frequency may also be more convenient for many patients, especially for children, the elderly, and others with poor venous access. [86] In four studies, among which one RCT, dosing frequency of most patients with hemophilia A could be reduced after starting PK-guidance. [55,84,87,88] One of these studies reported that PK assessment resulted in a decreased dosing frequency in 57% of the hemophilia A patients receiving Nuwiq®. Importantly, despite decreased dosing frequency, ABR (median 0) was lower compared to ABR in the previous standard prophylaxis period (median 0.9). Moreover, comparable low ABRs were reported irrespective of dosing frequency (<2 weekly or > 2

weekly). [55]

3.4.2. Barriers

No barriers found during analysis.

3.4.3. Overall knowledge gaps

Firstly, no publications described effect of PK-guided therapy on infusion frequency in hemophilia. Secondly, only Lissitchkov reported on lower ABRs after reduction of dosing frequency. [55] Theoretically, a lower dosing frequency - with subsequently longer periods on lower factor levels - may increase the bleeding risk. In particular patients who have higher frequency of (moderate-high risk) physical activities may be at higher risk of sports-related bleeding. More research with real-world data is necessary to investigate this dilemma.

3.5. Cost effectiveness

3.5.1. Facilitators

According to hemophilia A patients and their parents, one of the most important facilitators for the implementation of PK-guided dosing is the estimated cost reduction. [72] Several cohort and cross-over studies have reported on FVIII dose reduction of around 7–31% when performing PK-guided dosing compared to standard prophylaxis. [55,79–81,83,85,89] When targeting a FVIII trough of 1 IU/dL, PK-guided dosing resulted in a dose sparing benefit compared to standard dosing (20–50 IU/kg three times per week). When increasing target trough levels towards 3–5 IU/dL, dose consumption during PK-guided dosing was only lower when compared to standard dosing following 50 IU/kg. [82] Aside from decreases in FVIII consumption, a lower mean number of (pediatric) hematologist and nurse consultations as well as hospitalizations were observed during PK-guidance. [73] Similarly for hemophilia B, one cross-over study found a cost reduction of 43–55% when switching to PK-guided dosing. [90] Importantly, dose sparing following the use of PK-guided dosing may be of special interest in resource limited countries. The most cost-effective way of increasing trough levels is often by increasing infusion frequency. [27,71]

3.5.2. Barriers

The suggestion that PK-guided dosing reduces factor consumption remains controversial. Two RCTs showed no difference in FVIII consumption when compared to standard dosing during PK-guided prophylaxis or perioperative treatment. [52,84] These results are in accordance with other cohort studies in hemophilia A that report no differences in FVIII consumption. [29,80,91] Four studies have even reported an increase in FVIII consumption after switching to PK-guided therapy. [33,53,74,75]

3.5.3. Overall knowledge gaps

Contradicting results with respect to factor consumption are probably the result of differences in standard dosing regimens and targeted trough levels under PK guidance. It is of course expected that factor consumption increases in studies where trough levels are increased after PK assessment. For example, Li et al. reported a trough level increase from 0.37 IU/dL to 1.19 ($p < 0.05$). [75]

Strikingly, no studies have taken the cost of sampling and PK calculations into account. This should be incorporated in future studies. Furthermore, cost-effectiveness of PK-guidance in hemophilia B is under-reported, with only a single study identified in our search. [90]

Theme 2: Feasibility

3.6. Applicability in clinical practice

3.6.1. Facilitators

Several guidelines recommend the use of PK-guided dosing of

prophylaxis for hemophilia A and B patients, facilitating its implementation. [2,9,10,51] Various studies have reported successful implementation of PK-guided dosing in clinical practice. The fact that PK-guided dosing is applicable in clinical practice is reflected by publications where hemophilia A patients are treated with PK-guided dosing according to local protocols without a preceding intervention study. [29,77,79,91,92] PK-guided dosing is also applicable in the surgical setting using specifically developed perioperative population PK models. [93,94] Application in this setting has also been described in case reports resulting in good hemostatic results. [95–97]

In a survey among 37 European (pediatric) hematologists, 92% answered to assess PK in routine care, and 49% conducted full PK analyses regularly for their patients. When switching patients to EHL concentrates, 89% assessed PK with 51% carrying out full PK analysis. [13] The increasing number of infusions that have been entered into the WAPPS-Hemo software also reflects a rising adoption of PK-guided dosing in clinical practice. [12] Moreover, flexibility in time points of sampling - both inside and outside recommended time windows - makes it easier to implement PK-guided dosing. [12,57] Clinical experiences with WAPPS-Hemo are positive. [98]

3.6.2. Barriers

A major barrier for implementation is the requirement of expertise in interpreting and understanding PK results. [2,99] Lack of time, access, and/or resources were the main reasons that only 9.7% of physicians in an ISTH survey performed PK analysis during the transition from SHL to EHL factor concentrates. [10] Nine hematologists described additional barriers such as low patient adherence, poor venous access, and long distances from hospital. [99] Of course, in developed countries, FVIII concentrates have been increasingly replaced by non-factor replacement therapy, such as emicizumab. Since the PK of emicizumab depicts lower variability, interest in PK-guided dosing may decrease. [100] On the other hand, patients will need replacement therapy with factor concentrates during surgical procedures or for treatment of bleeds. [2] Additionally, high costs of emicizumab hinders its use in low-income countries. A potential consequence of the increased interest in non-factor-based therapies might also be that factor concentrates become more affordable in the near future as demand decreases in high-income countries. [101] It is thus likely that factor concentrates will still be used for treatment in the future.

3.6.3. Overall knowledge gaps

Little is known about PK-guidance in clinical practice in other diseases than hemophilia.

3.7. Useful software tools

3.7.1. Facilitators

A practical limitation for the adoption of PK-guided dosing has been the complexity of model development as well as the actual implementation of Bayesian forecasting. [57,102,103] In response to this limitation, various software tools have been developed that aim to support physicians and patients with the implementation of PK-guided dosing. [75,104–107] Web-based software applications such as WAPPS-Hemo and myPKFiT™ allow physicians to obtain individualized dosing advice based on only a few patient samples. [79,108,109] Multiple studies have pointed out the importance of the availability of such tools. [104,109,110] Most of the time, information obtained from WAPPS-Hemo is deemed useful. [111] Graphics can be produced which facilitate interpretation for non-experts compared to plain PK parameters. [71,99] For patients with inadequate hemostatic control, these tools can be used for a rapid and easy assessment of the optimal dose adjustment. [112] In addition, studies looking at the implementation of these tools depict increased patient engagement, treatment personalization, and improved care follow-up have been observed. [113] Additionally, PK outcomes when comparing myPKFiT and WAPPS-Hemo

were similar. [114] For non-factor based treatment (e.g. emicizumab), online dosing tools have also been developed. [100]

Additionally, several patient diary applications, such as smart medication™ and haemtrack, have been developed that allow patients to record administered dose and bleeding events. Accurate recording is important for the evaluation of treatment efficacy and surveillance. [115,116] Such applications could also be used to alert patients when reaching risky factor levels to prevent them from missing infusions. [71]

3.7.2. Barriers

Although most of the previously mentioned tools reduce the complexity of obtaining individualized PK profiles, a basic understanding of PK is still required for their correct use. [49,103] Next, there is a lack of transparency of data used to construct PK models. [64] This can for example cause problems when PK assessments are requested for patients that are not included in the patient population used to construct the PK model. [108] Similarly, due to differences between PK models, different tools may report different PK parameters based on the same data. [114,117] There is thus a risk of obtaining unreliable results when using the incorrect tool for a specific PK assessment. It may therefore be necessary to collaborate with several experts in the PK assessment procedure in order to validate obtained results. However, the introduction of additional experts with limited involvement in the care of patient may also introduce delays. [44,103]

To move PK-guided dosing towards individualized bleeding control, high quality data collection of dose administration times and bleeding events is crucial. This issue is however rarely mentioned in the literature. Although several studies have reported on the development or availability of patient diaries, [115,116] it is unclear if they are faithfully used by the local patient population to collect such data. If the quality of home monitoring is inadequate, the use of PK for bleeding control may be severely compromised.

3.7.3. Knowledge gaps

To trust software tools, transparency of the used PK models is very important. In addition, it is important to know the reliability of infusion or bleeding data reported by patients. Finally, it is of interest to investigate if software tools actually improve treatment adherence.

3.8. Patient involvement

3.8.1. Facilitators

After PK profile assessment, it is possible to simulate several options for prophylaxis dosing schedules and to provide graphical representations of factor levels over time. Such visualizations are helpful to educate patients on the effects of changing infusion times and dose during the week. [80,83,99,112] PK analysis may also aid the patient in selecting optimal time frames for exercise. [111,118] Many studies have reported on the benefits of using PK information to facilitate shared decision making. [98,112,118,119] One case-study reported higher patient trust in bleeding management during surgery when dosing decisions were supported by PK. [95] In addition, achieving personalized prophylaxis and more closely involving the patient in their treatment choices has resulted in approved adherence in patients with hemophilia A. [33,71,80,89,120,121] It is similarly likely that more personalized treatment is more efficacious when each patient's socio-professional life is taken into account. [122]

3.8.2. Barriers

On the other hand, one cross-sectional retrospective cohort study reported no differences in adherence between hemophilia A patients receiving standard prophylaxis versus PK-guided prophylaxis. [73] Although PK studies can be used for patient education, introducing a new concept to patients who have lived with hemophilia for decades might not be easy. [119] In addition, patients may also question the reliability of PK assessment. [99] Another impediment is the

unwillingness of patients to alter doses or dosing frequency. [123,124] When given the choice, patients may prefer increasing administered dosage rather than dose frequency, although dose increases are generally a less cost-effective approach to achieve higher trough levels. [124] If patients are not open to changing dose frequency, the efficacy of PK-guided prophylaxis may be reduced.

3.8.3. Knowledge gaps

No large studies have explored patient satisfaction with regard to PK-guided treatment. It is possible that patients achieve greater benefits when better informed about how their factor levels are influenced by prophylaxis. Software tools increasingly provide real-time visualization of factor levels, which might be especially useful during sport activities. This hypothetically may result in higher patient satisfaction and independence.

3.9. Burdening of patients and treatment teams

3.9.1. Facilitators

In the past, generation of a full PK profile required many blood samples to attain acceptable accuracy. [104] However, the burden of generating PK profiles has been greatly reduced with the introduction of limited sampling methods. [5,29,44,56,99,112,125] Most models are also flexible with respect to time points at which samples can be taken, making it easier for treatment teams to schedule blood draws during routine visits. [9] Additionally, the PK of FVIII and FIX remains stable over time, meaning that a PK profile, once obtained, can be used for longer periods of time. [71,126] Interestingly, in a prospective cohort study, 11 hemophilia A patients reported higher hemophilia-specific quality of life scores after switching to PK-guided prophylaxis. [53]

3.9.2. Barriers

The most important barrier for the implementation of PK-guided dosing is that regular blood sampling may be difficult for some patients, particularly for those who live far from the hospital and those requiring multiple visits. [2,99,111,127] Similarly, in the context of novel non-factor related therapies such as emicizumab, patients may be less inclined to spend additional time on PK assessments. [99] Switching to a different drug might also require new PK evaluations. [128] In order to benefit from limited sampling strategies, a population PK model developed on a representatively sized and heterogeneous patient cohort is required for every new factor concentrate, which might not always be available. [65]

Although PK remains stable over time, it is not exactly known at what interval PK assessments should be repeated for (young) children. As PK is known to change in early life, the pragmatic approach of reassessing the PK of children every 2–3 years has been reported. [51,57]

Finally, a larger ($n = 66$) RCT found no significant difference in health-related quality of life scores between patients on PK-guided versus standard prophylaxis. [84]

3.9.3. Knowledge gaps

It is unknown how frequently PK studies should be repeated in children. Additionally, there is ambiguous reporting on the benefits of PK-guided prophylaxis on quality of life. In such studies, patients should be questioned before and after switching to personalized prophylaxis.

3.10. Attaining personalized medicine

3.10.1. Facilitators

PK-guided dosing is able to facilitate individualization of dosing according to PK, lifestyle, and activity profile. [64] Four prospective cohort studies have reported how dose adjustments were made after PK assessment in 50–89% of hemophilia A patients. [29,33,76,91]

3.10.2. Barriers

Contrastingly, one prospective study reported no change in dosing regimens after PK assessment in 68% of the hemophilia A patients. [80]

3.10.3. Knowledge gaps

Firstly, no studies report on dose adjustments in hemophilia B after PK assessment. Secondly, it would be interesting to know if patients find it more convenient to have personalized infusion times, and if confidence rises with concomitant decreases in mild physical complaints during exercise after personalization of prophylaxis by PK guidance.

4. Study limitations

The first limitation of our study is that we did not include more search terms to include all different bleeding disorders, apart from hemophilia and VWD. In the end, we decided on only focussing on hemophilia as it was the most commonly discussed in literature in the context of PK-guided dosing. Specific results found in the search with respect to other inborn bleeding disorders have been omitted. Although it is likely that there are similarities with respect to the implementation of PK-guided dosing between hemophilia and these other bleeding disorders, it is uncertain if all the discussed facilitators and barriers will be valid for all disorders.

As our goal was to evaluate facilitators and barriers in the context of regular clinical practice, another limitation was that these aspects of care may not always find their way to scientific manuscripts. For example, only a small subset of the papers involved surveys of clinical staff, which may be the best source of information with respect to our study aim. Conversely, limiting inclusions to surveys and interviews would however result in limited information and not include essential topics related to effectiveness and accuracy.

5. Conclusion and future considerations

In conclusion, this scoping review has mapped a total of ten topics describing barriers and facilitators for the implementation of PK guided dosing in clinical practice under the themes efficacy and feasibility. The contradicting results, especially with regards to the efficacy of PK-guided dosing, highlight the knowledge gaps and the necessity for more research on implementation strategies.

Practice points

- PK-guided dosing in hemophilia exhibits high accuracy, supporting broader use.
- Although targeting of FVIII trough levels of >1–3 IU/dL is recommended for the majority of hemophilia A patients, personalization of trough levels is key.
- Successful implementation of PK-guided dosing is especially facilitated by patient involvement, application of software tools, reduction of blood sampling, reduction of infusion frequency and awareness of its impact and ability to personalize treatment.
- When using software tools, a basic understanding of PK and transparency of included data to construct PK models is necessary.

Research agenda

- Research should focus on acquiring evidence on appropriate targets for preventing break-through bleeding in different scenarios (e.g. during surgery/physical exercise) and specifically for hemophilia B patients.
- Long-term randomized controlled trials are of interest during investigation of bleeding outcomes in the context of standard dosing, PK-guided dosing, or novel tools based on individual bleeding risk (e.g. repeated time-to-event models and thrombin generation tests).

- Clinically acceptable levels of prediction error should be established in order to facilitate external validation of published PK models.
- When evaluating cost-effectiveness of PK-guided dosing, additional costs of sampling and personnel should be taken into account.
- Large scale studies should be performed evaluating patient satisfaction and quality of life improvements when switching to PK-guided dosing.
- Research should explore the benefits of software tools to improve patient engagement, and what kind of information is meaningful to patients.
- More information is required on the frequency with which PK assessments should be repeated, especially in children.

Authorships

M.G. and A.J. screened all literature, performed analyses and interpretation of data and wrote the manuscript. M.H.C. conceptually designed the study and supervised the study together with R.A.A.M. All authors substantially contributed to group discussions, and critically revised the manuscript, with approval of the final draft.

Declaration of Competing Interest

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The SYMPHONY NWO-NWA consortium which aims to orchestrate personalized treatment in patients with bleeding disorders, is a unique collaboration between patients, health care professionals and translational & fundamental researchers specialized in inborn bleeding disorders, as well as experts from multiple disciplines. It aims to identify best treatment choice for each individual based on bleeding phenotype. In order to achieve this goal, work packages (WPs) have been organized according to three themes e.g. Diagnostics (WPs 3&4), Treatment (WPs 5-9) and Fundamental Research (WPs 10-12). This research received funding from the Netherlands Organization for Scientific Research (NWO) in the framework of the NWA-ORC Call grant agreement NWA.1160.18.038. Principal investigator: Dr. M.H. Cnossen. Project manager: Dr. S.H. Reitsma.

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