Clinical application of the Web-Accessible Population Pharmacokinetic Service – Hemophilia (WAPPS-Hemo): proposal for a pilot study of a population pharmacokinetic approach to tailored prophylaxis in hemophilia.

Clinical application of the Web-Accessible Population Pharmacokinetic Service – Hemophilia (WAPPS-Hemo): a pilot study of a population pharmacokinetic approach to tailored prophylaxis in hemophilia.

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TITLE: Clinical application of the Web-Accessible Population Pharmacokinetic Service – Hemophilia (WAPPS-Hemo): a pilot study of a population pharmacokinetic approach to tailored prophylaxis in hemophilia.

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Abstract

Background
A possible way to improve the global clinical benefit of hemophilia treatment could be adopting a tailored prophylaxis regimen. To execute a tailored prophylaxis treatment scheme is necessary the evaluation of pharmacokinetic (PK) parameters acquired after the infusion of clotting factor concentrates at the individual patient level. However, an individual, complete, PK study for either FVIII or FIX can be demanding and impractical. An alternative to the traditional PK studies is the population PK (popPK) approach. The Web Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo) is an independent population PK calculator developed at McMaster University by Dr. Alfonso Iorio. Sparse data from individual patients are fitted using a Bayesian iterative approach to estimate terminal half-life and times to critical concentrations and to produce an interactive graphical display of the concentration time curve.

Objective
The aim of this project is to develop a protocol for a pilot study to assess the feasibility of an interventional trial designed to test the efficacy of the PopPK approach to tailored prophylaxis in hemophilia.

Methods
Design: The proposed study is multi-centre, prospective (pre-post), open label, clinical trial. This study is designed to be primarily a feasibility study. Setting: Canadian Hemophilia Treatment Centers. Study population: In this study, we will enroll severe congenital hemophilia A and B patients (baseline factor level <1%) who have been on factor with any factor concentrate for at least 12 months and have reached a minimum of 150 exposure days. Intervention: The study intervention is the new personalized dosing recommendation based on PopPK, produced through the WAPPS-Hemo application. Feasibility Criteria for success: We'll consider the pilot study to be feasible and successful if at least 50% of enrolled patients are eligible for a regimen adjustment (switch to personalized dosing regimen); at least 75% of patients who start the new prophylaxis regimen based on the personalized dosing recommendation complete the 12 months' follow-up.

Conclusion
The goal of dose individualization for clotting factor concentrates is to improve the outcomes in severe hemophilia patients. The PopPK approach has this potential, but whether the use of PopPK will be will translate into clinically or economically meaningful changes in the practice of hemophilia care remains to be demonstrated. The pilot study described in this proposal will assess the feasibility of a full-scale interventional study designed to this purpose.

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Clinical application of the Web-Accessible Population Pharmacokinetic Service – Hemophilia (WAPPS-Hemo): a pilot study of a population pharmacokinetic approach to tailored prophylaxis in hemophilia.

Chapter 1

1.1 Background and rationale

Haemophilia A (HA) is a rare X-linked bleeding disorder with an estimated incidence of about 1 in 5000 male live births[1]. It is characterized by deficient or dysfunctional Factor VIII protein (FVIII), a clotting protein that is essential for blood coagulation. In particular, it is a cofactor to the activated Factor IX which converts Factor X in its activated form; this step is critical in the amplification phase of the coagulation cascade and the subsequent thrombin activation and fibrin formation. Hemophilia B (HB) is much less common (one in 20,000 live male births), but affected individuals share the same clinical manifestations of haemophilia A patients, because of the role that these proteins have in the coagulation system and the need for the presence of both in the development of a properly functional blood clot [1]. Therefore, people affected by HA or HB will bleed longer than healthy people. Bleeding may occur after minor trauma or even spontaneously, mostly into the joints and muscles. Life-threatening intracranial haemorrhages are also possible. The

frequency and severity of bleeding depends on the amount of residual circulating clotting factor. In the absence of preventive treatment, patients with severe haemophilia will have frequent bleeding episodes, most of which will be spontaneous[2]. Many different clinical manifestations of the disease are possible, including epistaxis, gastro-intestinal bleeding, hematuria, but spontaneous bleeding into joints and muscles is the most frequent event in patients affected by severe hemophilia[1]. The acute intra-articular bleeding is responsible for inflammation and increase in pro-inflammatory cytokines. The synovial hypertrophy makes the probability of a re-bleed higher and the repeated bleedings evolves in a chronic persistent disorder known as "hemophilic synovitis" accompanied by cartilage and bone destruction. This can result in a permanent loss of function of the affected joint.

The aim of replacement therapy, namely prophylactic intravenous of the missing factor, is to restore haemostasis and prevent bleeding[3]. Factor concentrates are available as plasma-derived human products (purified from human plasma) or recombinant products (produced by recombinant DNA technology).

Regular prophylaxis (e.g. multiple factor infusions/week) provides protection from bleeding and allows patients with severe haemophilia to lead normal lives[4].

1.2 Prophylaxis in hemophilia treatment

Replacement of the deficient coagulation protein with factor concentrates is the standard of care for hemophilia. In fact, it corrects the defect in patients with hemophilia and reduces the risks of the severe complications that can result from uncontrolled bleeding. Factor replacement therapy can be given either on an "on demand" basis to treat bleeding episodes when they occur. Alternatively, it can be administered on an "episodic" basis to reduce the possibility of bleedings at the time of high risk events, or on a regular or "prophylactic" basis to prevent bleeding[5]. Prophylaxis with clotting factor concentrates is the only effective method for avoiding joint damage in hemophilia patients, as episodic treatment has been shown to be much less effective[6]; in the absence of regular preventive treatment with coagulation factors all patients develop various degrees of joint damage and loss of function with reduced range of motion[6]. Prophylaxis is usually started in early childhood before joint disease is apparent, but the specific implementation may vary widely between countries and settings and is still a matter of debate. Specifically, there is a great variability in clinical practice among the hemophilia treatment centers about the starting time and dose, the frequency of infusions, the desired therapeutic target and stepping up and stepping down rules. Over the years, several different **schemes have** been proposed, e.g. administration of a fixed high dose every other day[7], to the escalating dose protocol [8]. In resource-poor settings very low dose

regimens have been also used[9]. The main objective of prophylaxis is to maintain the clotting factor level above a desired target of plasma activity.

Currently, it is generally accepted that the objective of prophylaxis therapy should be to keep the factor level above 1% (1 IU/dL) or more in order to prevent **bleeding**. Using PK data and patient treatment logs collected during a clinical trial, Collins et al. could demonstrate a correlation between risk of bleeding (joint bleeding and total bleeds) and estimated time patients spend with factor levels <1%[10]. Other studies have suggested that bleeding prevention is at least comparable when trough levels of coagulation factors are maintained above 1-3%[5]. The monitoring of prophylactic therapy relies on the measurements of FVIII or FIX activity in plasma samples after the i.v. infusion of the clotting factor concentrates. Physicians can compare the results to expected values based on the amount of factor injected and timing of the last infusion. Although this has been the traditional way of adjusting therapy for individual patients, there are still several issues to be considered, as detailed in the next paragraph.

1.3 Conceptual Framework

1.3.1 Dose individualization of clotting factor concentrates: role of pharmacokinetics

Hemophilic patients usually receive a dose based on their weight, but there is evidence that this approach can be suboptimal[11], and might lead to either overdosing (and consequently wastage of resources) or under dosing (potentially unsafe for patients and less effective in bleeding prevention). In fact, the results of clinical trials have shown that many hemophilia patients need to be treated with a higher or lower prophylactic dose of factor concentrate than the standard regimen doses (i.e. 20 to 50 IU/kg, generally 2 to 3 times per week) and around 30% of them can be treated with a lower dose of clotting factor or with a reduced number of infusions per week[12]. The large between-subject variability in haemophilic patients makes the 'one size fits all' dosing strategy based on body weight unsuitable in some individuals and necessitates a different approach. For these reasons, it has been suggested that a possible way to improve the global clinical benefit of hemophilia treatment could be adopting a different therapeutic strategy, based on tailored prophylaxis to individual patient characteristics.

The most important factor required to execute a tailored prophylaxis treatment scheme is the evaluation of PK parameters acquired after the infusion of clotting factor concentrates at the individual patient level. Pharmacokinetic has

been proposed to be the right tool to define the ideal prophylactic treatment,

overcoming the large inter-patient variability in post-infusion factor concentrate

levels. Therefore, a proposed strategy to improve treatment in hemophilia is to

perform individual PK studies with the rationale of using the PK profile to identify

the best regimen (i.e. combination of dose and frequency) and subsequently using

clinical criteria to confirm or modify the frequency and dosing strategy. An

individual, complete, PK study for either FVIII or FIX can be demanding and

impractical. In fact, considering the classic structural approach, 9 to 11 blood

samples are required: four must be collected in the distribution phase (0-1 h) and

five to seven in the elimination phase (3-48 h) – as previously suggested by the

relevant subcommittee of the International Society on Thrombosis and

Haemostasis[13,19]. In addition, such PK study would require a pre-infusion washout of

five half-lives (approximately 2 days for FVIII and 5 days for FIX), which can be

inappropriate in specific clinical conditions and risky to perform, particularly in

patients on primary continuous prophylaxis[14]. This has been a barrier for the routine

use of PK to be implemented in the clinical practice for treatment doses

recommendations, especially considering also the requirement for multiple blood

samples to calculate PK values[15].

1.3.2 Population pharmacokinetics

The traditional PK studies are routinely performed in a small number of individuals, require extensive blood sampling, following the drug administration and can be used to estimate the variability of the drug concentration in plasma between individuals after the administration of a specific dose[16].

The population PK approach also permits the characterisation of PK parameters using data collected from treated patients but without the extensive blood sampling from any single individual. This method requires the study of a large number of patients, but only collecting a limited number of samples from each subject[17]. From these measurements, the estimate of the central tendency values and variability (between subjects and within subject) are calculated. PopPK makes use of non-linear mixed effects regression modelling to calculate the concentrations of the drug of interest in a population of subjects, taking into account all of the known variables affecting the PK estimates[18]. Important covariates may include demographical characteristics (body weight, gender, age), genetic background (e.g. the polymorphic cytochrome P450 isoforms, blood group, ethnicity), or pathophysiological features (renal and hepatic impairment, comorbidities).

In hemophilia, the PopPK approach has permitted PK models to better incorporate between-patient variability and thus allowing to obtain individualized PK estimates using a relatively low number (2-3 samples) of post-infusion

measurements[19]. Overall, there are several advantages of using PopPK namely the cost-effectiveness of the analyses[20], the more precise estimates of the population mean and variance and the possibility to evaluate the inter-patient variability in the PK parameters, combining random and fixed effects covariates. Importantly, the PK parameters can be estimated in the target population using sparse data unlike the traditional approach in which individuals are sampled intensively.

1.3.3 The WAPPS-Hemo Service: a population pharmacokinetic calculator

The Web Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo, www.wapps-hemo.org) provides an independent, PopPK calculator for numerous factor concentrate brands. Sparse data from individual patients are fitted using a Bayesian iterative approach to estimate terminal half-life and times to critical concentrations (0.05, 0.02 and 0.01 IU/mL) and to produce an interactive graphical display of the concentration time curve[19].

WAPPS-Hemo is a user-friendly, industry independent, web-based tool to facilitate assessment of individual pharmacokinetics with a population pharmacokinetics approach (www.wapps-hemo.org). Created by Dr. Alfonso Iorio and his team at Health Information Research Unit (HIRU), McMaster University, this population pharmacokinetic Bayesian calculator provides probabilistic PK estimates

calculated based on 2-3 post–infusion samples. The system is powered with dedicated population PK models for Advate (Shire), Alprolix (Bioverativ), Novo8 (Novonordisk), BeneFIX (Pfizer), Eloctate (Bioverativ), Kogenate FS/Helixate NextGen (Bayer/CSL Behring), Emoclot (Kedrion), Nuwiq (Octapharma), Refacto AF/Xyntha (Pfizer) and Wilate (Octapharma); modeling is underway Kovaltry (Bayer) and a data transfer agreement is currently discussed with other manufacturers (all products listed are currently available in Canada). Nearly 600 individual patient kinetics (and 969 kinetic studies) from the PK phases of industry-sponsored studies have been obtained and used for modeling. Over 250 PK studies performed by independent investigators have been obtained and are currently used to externally validate and update the models. Over 300 "real world" patients have been processed through the WAPPS-Hemo website since its launch in July 2015, as part of its current intended use by hemophilia treaters in 30 centers from 17 different countries.

1.3.4 The Canadian Bleeding Disorders Registry: what it is, how it works, integration within the study

The Canadian Bleeding Disorders Registry program (CBDR, https://www.cbdr.ca) is a web-based hemophilia clinic management software with enhanced capability of data sharing across the network of users, and with two specific functionalities: a) feeding a national Canadian repository of hemophilia

treatment data and b) supporting a module dedicated to patients (MyCBDR, https://www.mycbdr.ca), which allows patients to directly record treatment and bleeding logs. The system has been recently adopted by the AHCDC (Association of Hemophilia Clinic Directors of Canada), already launched in 9 centers, and to be ideally adopted across the border. The system is hosted and maintained at McMaster University, Health Information Research Unit.

MyCBDR has been developed as a secure website for people with bleeding disorders or parents/caregivers. MyCBDR can be easily used to record home treatments and bleeds. Bleed details can be added and linked to the treatments: a body map will help patients to identify the location of the bleed and a notes field will open to write any further details that the patient would like to record. The current treatment plan details can be viewed online as well as reports of treatment and bleed histories.

The CBDR system, its management, access and operation are strictly controlled. Stringent security protocols that ensure data safety have been built into the CBDR system. These protocols control access to patients' personal data to make sure that identifying information is only accessible by the health care professionals who provide the treatment at the hemophilia center and authorised support staff. Additionally, a research oriented module (CBDR-RM) has been recently implemented to complement CBDR. CBDR-RM is an add-on infrastructure for CBDR, intended to

facilitate the management and data collection of clinical data for patients enrolled in CBDR and participating in a research study. In brief, CBDR-RM permits to design pages to collect additional information not available in CBDR in an integrated database. The information, initially available to the study organizers and participants only, can at the end of the research project be consolidated in the CBDR database and re-used as needed. CBDR-RM is already in use for other Canadian clinical studies (e.g. the"CHIC" study coordinated by Dr. Paula James, Queen's University).

Altogether the development of CBDR, MyCBDR and CBDR-RM has allowed to record, review and analyze data provided by both researchers and patients, as required for many collaborative clinical studies in the field of rare bleeding disorders. This study will make use of these features to collect the data required in this study, providing to all the Canadian Hemophilia Centers the tools to participate in the study.

1.3.5 Conclusions

The ultimate goal of dose individualization for clotting factor concentrates is to improve the outcomes in severe hemophilia patients. The PopPK approach has this potential, but whether the use of PopPK will be will translate into clinically or

economically meaningful changes in the practice of hemophilia care remains to be demonstrated. The pilot study described in this proposal will assess the feasibility of a full-scale interventional study designed to this purpose.

Chapter 2

2.1 Study design

The proposed study is a Canadian, multi-centre, pre-post, open label, clinical trial. This study is designed to be primarily a feasibility study and to determine recruitment rates, retention rates, refusal rates, adherence rates, percentage of patients eligible for a tailored prophylaxis, determine centre willingness and capacity, usability of the WAPPS-hemo software by Hemophilia Centres. Other clinically relevant outcomes (such as annual factor consumption, PK-related parameters) will only be reported descriptively and considered hypothesis generating. These data will be used to inform the planning of a larger, adequately powered clinical trial to test the intervention efficacy (cost-effectiveness, safety, predictive validity).

2.2 Hypothesis and objectives

We hypothesize that the WAPPS-hemo software will facilitate clinicians working in the hemophilia centres in recommending a tailored prophylaxis to hemophilia A and B patients and a substantial proportion of patients currently in prophylaxis will be eligible for such a treatment. It is not known how many hemophilic patients already in prophylaxis with factor concentrates might be eligible for a further optimization of the replacement therapy using a PopPK approach. Also, the acceptability of a tailored prophylaxis in this population is not known. The aim of this study is to address the potential clinical impact of the tailored prophylaxis using WAPPS-hemo by assessing the proportion of patients on prophylaxis that might benefit from a dose-individualization (tailored prophylaxis) and describe the acceptance-rate and compliance to the proposed treatment.

2.2.1 Primary objective

The primary objective of this study is to determine the proportion of patients on prophylaxis with factor concentrates who are eligible for, accept and can comply with the regimen adjustment generated with the PopPK approach for at least 12 months.

2.2.2 Secondary objectives

As ancillary and exploratory only objectives, we will describe the annual factor consumption during the study period to the previous 12 months-period, the

predictive efficiency of the probabilistic PK estimates (defined as the proportion of accurate predictions) and the estimated time spent below 1% and 5% factor activity level by patients with their prior standard prophylaxis regimen and with the suggested treatment schedule generated with WAPPS-hemo.

2.6.8 Setting

Patients will be enrolled in the participating Canadian Hemophilia Centers. The study will be coordinated at McMaster University. Centers who have declared interest in the study are Hamilton, Toronto (St Michaels), Ottawa (Adult and Pediatrics), Kingston, Montreal (Vezina), Saskatoon, Vancouver (St Paul and Pediatrics), and Calgary (Adult).

2.5 Study population and inclusion/exclusion criteria

In this study, we will enroll severe congenital hemophilia A and B patients (baseline factor level <1%) who have been on factor prophylaxis (see study definitions) with any factor concentrate for at least 12 months and have reached a minimum of 150 exposure days.

2.5.1 Inclusion criteria

• Age >6 years

- Severe haemophilia A or B

- Already on prophylaxis in the previous 12 months

- Registered on CBDR (a minimum of 12 months' log is required)

- Ability and willingness to comply with study requirements

- Signed informed consent of patient or legal tutors

2.5.2 Exclusion criteria

- Other congenital or acquired bleeding defects

- Partial success of previous ITI

- Active inhibitor or currently on ITI

2.3 Study outcomes

2.3.1 Primary outcome

The primary outcome measures is: proportion of enrolled patients that

complete the initial laboratory assessment and are eligible for tailored prophylaxis

regimen with successful follow-up at 12 months. We will express follow-up as the

percent of subjects who are successfully followed for the 12-months study period.

We will report the proportion of enrolled patients (i.e. proportion of patients that have accepted to be enrolled in the study and completed the preliminary evaluation to produce a prophylaxis regimen with WAPPS-hemo) that complete the 12-months study period under the PopPK-adjusted prophylaxis regimen over those who are not able or are not willing to implement the new prophylaxis scheme for the entire study period. All the patients that will complete the study period without stopping the new prophylaxis regimen (i.e. switch to previous or other treatment regimen for any reason) will be considered to have successfully complied with the proposed treatment scheme.

An initial number of eligible patients will be determined at the beginning of the study through chart review. Recruitment rates, retention rates, refusal rates, will also be calculated. The centre's recruitment rate will be defined as the number of eligible patients who participate at the local Hemophilia Centre over the duration of the centre's recruitment period (12 months). Total number of potential participants screened and approached, consented and enrolled will be recorded. The study recruitment rate will be defined as the mean of all the Hemophilia centres' recruitment rates and the standard error of the mean.

We will measure the number of patients that adhere to the new treatment regimen through the infusion logs registered in CBDR.

The adherence to the treatment scheme will be assessed by evaluating the weekly infusion schedule used at 1 month, 3 months, 6 months and 12 months. Patients will be considered to be adherent to the proposed regimen when at least 75% of infusion logs follow the recommendations provided via the WAPPS-hemo application (comparison between the prescribed factor and registered infusions).

2.3.2 Secondary outcome

The secondary outcome measures are the clinical outcome measures that will be used if the full study is considered feasible, specifically: annual factor consumption, annualized bleeding rate, predictive accuracy of WAPPS-Hemo. Factor consumption will be reported as before-after annualized factor usage. The amount of factor used will be assessed through CBDR. The accuracy of the predictions generated by WAPPS will be tested comparing the actual factor level with the prediction generated by the software at two different time points. During the study period, a blood sample will be drawn from patients that have switched to the personalized prophylaxis regimen on the second day after the last factor infusion and on the last day before the subsequent factor treatment. Results will be classified according to the measured factor activity in: >15%, 5-15% and <5%. The

predicted and measured factor activity will be compared and calculate the proportion of correctly classified samples.

Safety & Adverse Event reporting

The number of bleedings occurred before and after the regimen adjustment will be reported. In the full study, we aim at reporting safety in terms of ABR and compare the previous 12-month bleeds logs to the number of bleeds during the tailored prophylaxis period. All clinically relevant bleeding, or breakthrough bleedings, that requires clinical attention and or medical therapy to be resolved (additional treatment with factor concentrates) will be registered. Site of bleeding and bleeding characteristics (spontaneous vs traumatic, date, duration, severity) will be recorded and the association with clinical (bleeding logs from previous year, adherence, age, BMI, HJHS) and laboratory characteristics (inhibitor occurrence, estimated time below trough) will be explored.

Carryover effect on bleeding frequency is minimal due to factors' short half-life and absence of any effect when the molecule is not present in circulation: the effect of the treatment regimen of the previous time period on the response at the current (tailored regimen intervention) time period is limited to few days at most.

2.4 Study Intervention

Patients enrolled in the trial that are eligible to switch to the personalized dosing regimen will start intravenous injections with plasma-derived or recombinant factor concentrate with the new tailored regimen produced through the WAPPS-Hemo application. Patients will continue to use the same factor product they were using before the study period; the study intervention is the new personalized dosing recommendation based on PopPK. The use and management of central venous access devices will be left to the discretion of the managing clinician. Vials with the lyophilized FVIII and solvent are provided in the 250, 500, 1000 and 2000 IU (International Units) format and will be used to give the appropriate amount of factor choosing a vial size (one or more vials, as needed) that is as close as possible to the desired dose, but always rounding up to the nearest whole vial size and infuse the full vial.

2.6 Study definitions

2.6.1 Factor Prophylaxis

A patient will be considered to be on prophylaxis if he is receiving regular infusion of clotting factor concentrates in order to prevent bleeding.

2.6.2 Breakthrough bleedings

All clinically relevant bleeding that requires clinical attention and or medical therapy to be resolved (additional treatment with factor concentrates)

2.6.3 Exposure day

An exposure day is defined as a calendar day during which one or more infusions of factor concentrate is given.

2.6.4 Coagulation Factor Inhibitor

Neutralizing anti-FVIII or anti-FIX antibodies

2.6.5 Inhibitor development

The occurrence of a positive inhibitor titre (≥ 1.0 Bethesda Units) according to the local laboratory on at least two occasions combined with a decreased FVIII recovery (<66% of expected).

2.6.6 Active inhibitor

A positive titer (≥ 1.0 Bethesda Units) or results of the PK analysis showing a reduced expected recovery or half-life in the previous 6 months.

2.6.7 ITI (Immune Tolerance Induction)

Factor concentrates infusions at a dose 100 IU/kg at least thrice weekly aimed at inhibitor eradication.

ITI outcome will be defined as complete success, partial success or failure:

• Complete success: Negative inhibitor titer, normal FVIII recovery, normal FVIII half-life and the absence of anamnesis upon further FVIII exposure;

• Partial success: After 33 months of ITI, negative inhibitor titer, but FVIII recovery less than 66% of expected, and/or FVIII half-life < 6 hours after a 72-hour wash-out period with clinical response to FVIII therapy without an anamnestic response;

• Failure: Failure of the inhibitor to decline by 20% over any 6-month period after the first 3 months of ITI, or failure to achieve tolerance or partial response after 33 months of ITI;

Chapter 3

3.1 Study Plan

3.1.1 Recruitment and consent

Patients will be recruited from participating Haemophilia Treatment Centers in Canada. The total number of potential patients will be assessed through chart review. All consecutive patients will be approached and reason for not consenting will be recorded. The local Principal Investigator or designate (e.g., research nurse or nurse practitioner) will be responsible for identifying eligible patients for the study.

If eligible, the local Principal Investigator or designate (e.g., research nurse or nurse practitioner) will discuss the study with the parents or guardians of the patient during a routine clinic visit and obtain informed consent using the Consent Form and Patient Information Sheet. Target enrollment for the study is 124 participants. We estimate approximately 10-12 participants per Center. The study protocol and consent for the current study will be submitted for approval by Research Ethics Boards at all participating sites before the start of the study. If consent is obtained an ID will be given to each participant and used throughout the study.

Written informed consent from each participant or participant's parents or legally authorized representatives will be obtained according to local regulations to allow access to their medical records and blood collection. One copy of the form will be archived by the researcher at the participating institution, while the other will be given to the patient.

3.2 Data collection

Data will be collected using e-CRF. Relevant data that will be collected/retrieved through CBDR: Age, gender, race/ethnicity; weight, height; hemophilia type/severity; baseline factor level; Inhibitor history; Current infusion schedule, doses; Current occupation and activity level; Infusion history for the

previous twelve months: product, dose, frequency to treat bleeds requiring factor

infusions, number, type of bleed/procedure.

In particular, study measurements will include:

3.2.1 Center level

• Number of eligible patients

• Number of patients approached for the study

• Number of consented patients

• Number of patients with a completed PK study using WAPPS

• Number of patients with a regimen change proposed

• Number of patients completing one year of follow up

3.2.2 Patient level

3.2.2.1 Baseline data

• Treatment Regimen

• Annual number of bleeds (previous 12 months)

• Site distribution of joint bleeds

• Typology of bleeds (spontaneous, traumatic)

• Annual utilization of factor concentrates (previous 12 months)

• The patient will be invited to fill a PROBE questionnaire (including EQ 5D-5L)

- HJHS (Hemophilia Joint Health Score)

3.2.2.2 6 months follow-up

- Factor activity at the second day after the last factor infusion and on the last day

before the subsequent factor treatment

- Dose and time of infusion

3.2.2.3 End of study

- Treatment Regimen(s)

- Annual number of bleeds (on study)

- Site distribution of joint bleeds

- Typology of bleeds (spontaneous, traumatic)

- Annual utilization of factor concentrates (on study)

- EQ 5D-5L

- HJHS

### 3.3 Study procedures

3.3.1 General aspects

    Eligibility of hemophilia patients will be assessed at the participating

Hemophilia Centers. The Web-based Application for the Population

Pharmacokinetic Service – Hemophilia will be used to generate PK profiles for participants. Eligible patients will be enrolled in the study and the baseline data collection will be performed (see "Data collection - Baseline data" paragraph). At this time, the patient will be invited to fill in a PROBE questionnaire (including EQ 5D-5L, see http://probestudy.org/about/whatisprobe). Enrolled patients will be infused with FVIII or FIX for hemophilia A and B respectively. Patients enrolled in the study will continue to use the same clotting factor product that they have used in the previous 12 months, as per the indications of the treating physician and will be the same throughout the study period.

Patients will be seen for follow up at the local Hemophilia Center at six and twelve months. They will also have telephone follow up at one and three months to determine whether there is a failure of prophylaxis to prevent hemorrhages or if there is any other reason for the patient not to comply with the proposed treatment regimen.

The study protocol is summarized in **Figure 1**.
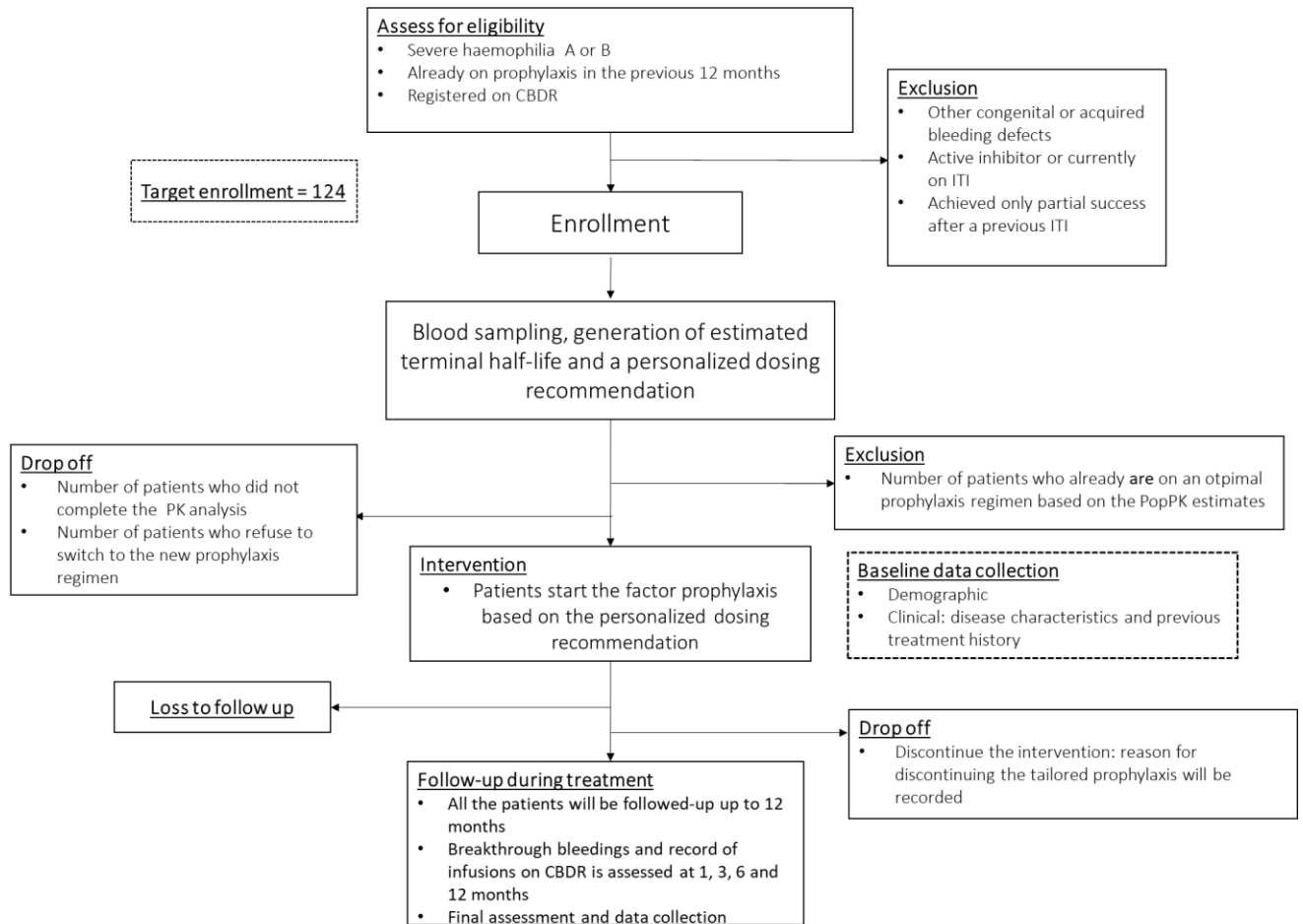
Figure 1. Flow diagram summarizing the study protocol.

3.3.2 Generation of a personalized dosing recommendation

Samples to determine factor levels will be collected following the limited

sampling approach to individual PK profiling (detailed operating procedures will be

provided). A minimum of two blood samples taken during the study period will be required for study participation.

The patient's PK measurements data will be entered into the WAPPS-Hemo software by the participating center. A personalized dosing recommendation will be produced and reviewed by experts at the coordinating center prior to dissemination to the participating clinical site. In particular, dosing strategies based on the preference of the treating physician at the relevant Hemophilia Center, will be proposed identifying a) the dose required to maintain a pre-specified factor level, given a desired frequency of infusion; or b) the frequency required to maintain a pre-specified factor level, given a desired infusion dose; or c) the possible combinations of dose and frequency suitable to maintain a pre-specified factor level. The WAPPS-hemo application will also provide an estimated time to 1% factor activity level. This will be used to predict the time a patient would spend with <1% factor activity for a given factor replacement infusion frequency. The proposed tailored regimen will be reviewed by the treating physician that will evaluate the opportunity to switch to the recommended prophylaxis regimen. The eligibility to regimen adjustment will be at the sole discretion of the treating physician who will notify in writing the coordinating Center with the decision to accept (or reject) the new regimen for each patient.

3.3.3 Tailoring procedure

1. At the baseline or subsequent visit, the treating physician will discuss with the patient the treatment goals. These can be described as reducing the infusion frequency; ensuring a specific plasma clotting factor level at pre-dose, or at the time of physical activity; a combination of the frequency and target; an intensification of treatment to reduce an excessive bleeding rate, or to accommodate a more intense program of clinical activity or active lifestyle; a de-intensification of treatment to accommodate for a switch to a more sedentary life style, etc. The treatment goal will be recorded.

2. The study investigator will decide which approach he elects to follow for each specific patient between generating an individualized treatment regimen by using the online calculator (see 3), or requesting the coordinating center to produce one or more pre-defined treatment regimens built to match the goals defined in 1). The latter will be requested via a standardized e-mail request to the study coordinator.

3. For patients with available PK assessment, the PI will access the WAPPS clinical calculator module, and will set 2 out of dose, interval and target to generate the desired treatment level. A dedicated training will be provided, and detailed documentation with worked examples will be available. Once the selected treatment regimen will have been identified, it will be saved using the ad hoc function of the

WAPPS program, printed and discussed with the patient. A new treatment plan will

be created in CBDR to document the decision.

3.3.4 Breakthrough bleeding

Breakthrough bleeding on prophylaxis will be managed as per current clinical

practice by an increase in the dose or the frequency of infusions as determined by

the treating physician. When the bleeding is controlled the patients will be

restarted on the proposed prophylaxis treatment, unless a different indication is

given by the treating physician. If the breakthrough bleeding is deemed not to be

due to non-compliance by the judgement of the treating physician an inhibitor titer

and pre-infusion trough level, and a post-infusion (30-60 minutes) recovery level

will be obtained as per current clinical practice. The bleeding episode and the

consequent variation in treatment dose/frequency will not be considered *per se* a

deviation from protocol, but only if the patient cannot resume anymore the

proposed tailored prophylaxis regimen, after the bleeding has resolved, for any

reason. The likelihood of a new inhibitor to develop in a previously treated patient

is low (<1% / year) so we don't expect it to be a relevant reason to discontinue the

proposed treatment in our study.

3.3.5 Blood sampling to assess the predictive efficacy of WAPPS-hemo

At the time of the 6 months follow-up visit, patients who have consistently switched to the new regimen will be asked to provide a baseline blood sample (taken before the factor infusion) and on the second day after the last factor infusion and on the last day before the subsequent factor treatment. Factor activity levels will be measured at the local Hemophilia Center laboratory and recorded, together with the amount of factor infused at the last injection. The timing and dose of factor will be recorded as precisely as possible and sent to the coordinating center for the analysis.

3.4 Follow up

1.   Monitoring of treatment and bleed logging. The central study staff will monitor that patient will fill out bleed and treatment logs at 1, 3, 6 and 12 months. In case the logging is suboptimal, the central study staff will notify the local investigator, who in turn will notify the patient (the central study facility is available to directly contact patients if so desired and requested by the local investigator).

2.   Clinical follow up visit will be performed at 6 months. Patients will have telephone follow up call at one and three months to determine whether there is a

failure of prophylaxis to prevent hemorrhages or if there is any other reason for the patient not to comply with the proposed treatment regimen. Samples to test the predictive efficacy of WAPPPS-hemo will be collected at the time of the 6-months clinical follow-up visit. Dose and time of infusion will need to be recorded as precisely as possible.

3.   Treatment change modifications. Any treatment change modification taken at any stage during the study will be recorded in CBDR as a regular treatment plan.

3.4.1 End-of study visit

1.   After 12 months of follow-up, or at study withdrawal (irrespective of the reason for withdrawing), the data collection phase will be completed. Any data missing in CBDR but available on any other format will be input in CBDR.

2.   The patient will be clinically reviewed, and HJHS completed (may not happen for drop outs).

3.   The patient will be invited to fill a PROBE questionnaire, inclusive of EQ5D-5L (may not happen for drop outs).

3.6 Statistical methods

3.6.1 Criteria to determine the success of the pilot study

This study is designed as a single arm, prospective trial to evaluate the feasibility of switching from a standard prophylaxis regimen to a tailored dosing strategy obtained from the WAPPS clinical module.

We'll consider the pilot study to be feasible and successful if:

- At least 50% of enrolled patients have been considered to be eligible for a regimen adjustment (switch to personalized dosing regimen).

- At least 75% of patients who start the new prophylaxis regimen based on the personalized dosing recommendation complete the 12 months' follow-up.

- Measurement of factor levels to assess the accuracy of predictions are completed by at least 90% of patients who complete the 12 months' follow-up.

3.6.2 Sample size considerations and study duration

Using a 95% CI for the proportion of eligible patients who complete the study follow-up, a margin of error (ME) of 0.1 and an expected completion rate of 80% the required sample for the pilot study would be at least 124 patients in the worst-case scenario that only 50% of them will be eligible to be started on the study intervention. We plan to keep the enrollment phase open for a maximum of 12 months. The total expected study duration is 24 months. Standard descriptive

statistics will be used to describe baseline patient characteristics. Central tendency and variability of continuous variables will be expressed as mean and standard deviation for normally distributed data or with medians and interquartile ranges for skewed data. Discrete data will be reported as absolute numbers and percentages.

3.7 Ethical aspects

This study will evaluate the feasibility of switching patients affected by hemophilia A or B to a different prophylaxis regimen. The intervention proposed is an optimized regimen of the same drug that the patient is already regularly taking as a treatment, based on factor levels collected following the limited sampling approach to individual PK profiling. The coagulation factor concentrates used in this study are all licensed and marketed products and will be used on-label. These concentrates would be prescribed regardless of whether the patient participates in the study. The new prophylaxis scheme is reviewed by an expert in the treatment of bleeding disorders and then proposed to the treating physician. Even though the possibility of a reduction in the efficacy instead of an improvement in the treatment regimen (in terms of time spent below the target trough level and therefore with an increased risk of bleeding) is conceivable, it seems to be extremely unlikely. At any

time, the treating physician can discontinue the treatment and reintroduce the previous regimen or start a different one.

The risks of carrying out such a study is, in our opinion, commensurated with the potential benefits to the hemophilia community and the society.

Many of the patients participating in this study are children, and the parents will be provided with all the relevant information about the study and offered to consent to participate in the study. It is important to consider that participation by minors could not be avoided, since appropriate treatment of children with hemophilia requires to start prophylaxis with factor concentrates in the early childhood. Also, the population that would benefit from study findings would be pediatric as well.

The other potential risk in participating in this study is mostly related to the venipuncture to draw the blood sample. Blood sampling by venipuncture might be associated with pain, bruising, hematoma formation or infection at the site of venipuncture. Since it will be performed at the Hemophilia Center, during a scheduled visit under medical supervision and in a highly specialized context it seems unlikely to us that the risk/benefit ratio would be unfavorable. Moreover, the blood sample needed for the study will be drawn during a standard venipuncture used for clinical purposes. No more than 3 ml/kg of blood will be drawn in any 24 hour period and no more than 10 ml/kg will be drawn in any 10 week period.

The protocol and consent for this study will be submitted for approval by Research Ethics Boards at all participating sites before the start of the study.

3.8 Discussion

We believe the proposed prospective design to be the most appropriate for the objectives of this study. Pilot studies can be used to assess the feasibility of large full-scale studies and offer a unique opportunity to evaluate the probability of success of the main study[21]. In particular, to provide the investigator with relevant information, the pilot study needs to mirror the main study in design. Any difference in the trial characteristics/process/execution could be potentially detrimental: the main achievement of the study is to give a genuine evaluation of the likelihood to conduct a trial that has been planned in a specific way. Therefore, our pilot study has the same design that will be implemented in the full-scale study if feasibility criteria are met.

Previously published experiences with clinical studies involving PK raise the question about the feasibility of such studies[22]. In particular, it has been shown that such studies are potentially at risk of high withdrawal rate. This can be prior to baseline assessments; prior to complete the pharmacokinetic assessments; during the follow-up period. In fact, the number of visits and difficulty attending appointments can make the trial impractical. An additional difficulty reported by

patients was the need for increased frequency of dosing. This might lead some of them to discontinuation and returning to previous or alternative regimen.

Also, patients might not feel confident remaining on the reduced dose of prophylaxis. The new dose recommendation can result in administering a lower dose; a perceived increase in bleeding can ultimately lead some patients to interrupt the proposed prophylactic regimen. On the other hand, the need for increased frequency of factor concentrate infusions – that might be proposed to target a specific trough level based on the PK study – could also represent a challenge to stay compliant with the new regimen. Once again, especially in the context of PK studies, it is important to not underestimate the role of patients' engagement during the study process and the value of good communication between researchers and patients.

In conclusion, the dose individualization of clotting factor concentrates might improve the outcomes in severe hemophilia patients. The PopPK approach has the potential to overcome limitations of traditional PK approach, however the feasibility of a full-scale interventional study in this setting needs to be assessed. The results of this study will provide the information needed to inform the planning of a larger, adequately powered clinical trial to test the intervention efficacy (cost-effectiveness, safety, predictive validity).

References

1. Mannucci P, Tuddenham E. The Hemophilias — From Royal Genes to Gene Therapy. New England Journal of Medicine. 2001;344(23):1773-1779.

2. Iorio A, Carcao M. Individualizing Factor Replacement Therapy in Severe Hemophilia. Seminars in Thrombosis and Hemostasis. 2015;41(08):864-871.

3. Berntorp E, Negrier C, Gozzi P, Blaas P, Lethagen S. Dosing regimens, FVIII levels and estimated haemostatic protection with special focus on rFVIIIFc. Haemophilia. 2016;22(3):389-396.

4. Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Cochrane Database Syst. Rev. 9(9), CD003429 (2011).

5. Coppola A, Tagliaferri A, Di Capua M, Franchini M. Prophylaxis in Children with Hemophilia: Evidence-Based Achievements, Old and New Challenges. Seminars in Thrombosis and Hemostasis. 2012;38(01):79-94.

6. Manco-Johnson M, Abshire T, Shapiro A, Riske B, Hacker M, Kilcoyne R et al. Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia. New England Journal of Medicine. 2007;357(6):535-544.

7. Petrini P, Chambost H, Nemes L. Towards the goal of prophylaxis: experience and treatment strategies from Sweden, France and Hungary. Haemophilia. 2004;10(s4):94-96.

8. Blanchette V, Manco-Johnson M, Santagostino E, Ljung R. Optimizing factor prophylaxis for the haemophilia population: where do we stand?. Haemophilia. 2004;10(s4):97-104.

9. Wu R, Luke K, Poon M, Wu X, Zhang N, Zhao L et al. Low dose secondary prophylaxis reduces joint bleeding in severe and moderate haemophilic children: a pilot study in China. Haemophilia. 2010;17(1):70-74.

10. Collins P, Björkman S, Fischer K, Blanchette V, Oh M, Schroth P et al. Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: influences of variance in pharmacokinetics and treatment regimens. Journal of Thrombosis and Haemostasis. 2010;8(2):269-275.

11. McEneny-King A, Iorio A, Foster G, Edginton A. The use of pharmacokinetics in dose individualization of factor VIII in the treatment of hemophilia A. Expert Opinion on Drug Metabolism & Toxicology. 2016;12(11):1313-1321.

12. Gringeri A, Lundin B, Von Mackensen S, Mantovani L, Mannucci P. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). Journal of Thrombosis and Haemostasis. 2011;9(4):700-710.

13. Lee M, Morfini M, Schulman S, Ingerslev J. The Design and Analysis of Pharmacokinetic Studies of Coagulation Factors. ISTH Website, Sci. Stand. Comm. Commun. 2001; 1–9.

14. Bjorkman S, Carlsson M. The pharmacokinetics of factor VIII and factor IX: methodology, pitfalls and applications. Haemophilia. 1997;3(1):1-8.

15. Morfini M. Pharmacokinetics of VWF/FVIII concentrates is a very intricate matter. Haemophilia. 2011;17(6):846-848.

16. Bjorkman S, Berntorp E. Pharmacokinetics of coagulation factors: clinical relevance for patients with haemophilia. Pharmacokinetics of Coagulation Factors. Clinical Pharmacokinetics. 2001;40(11):815-832.

17. Ette E, Williams P. Population Pharmacokinetics I: Background, Concepts, and Models. Annals of Pharmacotherapy. 2004;38(10):1702-1706.

18. Samara E, Granneman R. Role of Population Pharmacokinetics in Drug Development. Clinical Pharmacokinetics. 1997;32(4):294-312.

19. Iorio A, McEneny-King A, Keepanasseril A, Foster G, Edginton A. What is the role for population pharmacokinetics in hemophilia?. International Journal of Pharmacokinetics. 2017;2(2):125-136.

20. Samara E, Granneman R. Role of Population Pharmacokinetics in Drug Development. Clinical Pharmacokinetics. 1997;32(4):294-312.

21. Eldridge S, Bond C, Campbell M, Hopewell S, Thabane L, Lancaster G et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: using consensus methods and validation to develop a conceptual framework. Trials. 2015;16(S2).

22. Valentino L, Mamonov V, Hellmann A, Quon D, Chybicka A, Schroth P et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. Journal of Thrombosis and Haemostasis. 2012;10(3):359-367.;