A RANDOMIZED WAIT-LIST, PILOT DESIGN THESIS: Feasibility of the Web Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) Tool in Severe Hemophilia Patients Undertaking Personalized Regimen Tailoring

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by

Joseph Mussa, BSc.

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AUTHOR: Joseph Mussa, BSc.

SUPERVISOR: Dr. Alfonso Iorio

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Supervisory Committee

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Supervisory Committee

Dr. Alfonso Iorio - MD, PhD, FRCP(C) – **Supervisor** Associate Professor, Department of Health Research Methods, Evidence and Impact, Deputy Chief, Health Information Research Unit (HIRU)

Dr. Lehana Thabane – Committee Member
Professor and Associate Chair, Department of Health Research Methods, Evidence and Impact

Arun Keepanasseril – Committee Member
Research and Data Operations Lead, McMaster Hemophilia Research Group

Dr. Andrea Edington – External Reviewer
Associate Professor/Program Assessment Officer, School of Pharmacy, University of Waterloo

Dedication

First and foremost, to my family, who always pushed me to strive for more and believe in myself.

Thank you to Dr. Alfonso Iorio, Dr. Lehana Thabane and Arun Keepanasseril for their insightful comments and continued effort to help guide and develop the final thesis.

"If you think education is expensive – try ignorance". – Derek Bok

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List of Abbreviations

CBDR = Canadian Bleeding Disorders Registry
CF = Clotting Factor
CHIC = Canadian Hemophilia Carriers
CHIMPS = Canadian Hemophilia Immune-tolerance Prospective Study
DMSB = Data Monitoring Safety Board
EAHAD = European Association for Hemophilia and Allied Disorders
ECHO = Expanding Communication of Hemophilia A Outcomes
EHL = Extended Half-Life
FIX = Factor 9
FVIII = Factor 8
GEE = Generalized Estimating Equation
HA = Hemophilia A
HB = Hemophilia B
HIRU = Health Information Research Unit
QoL = Quality of Life
IIV = Inter-individual variability
IOV = Intra-occasion variability
IU = International Units
kg = kilogram
km = kilometres
mo = months
NBR = Negative Binomial Regression
ON = Ontario
PopPK = Population Pharmacokinetics
PK = Pharmacokinetics
QoL = Quality of Life
RCT = Randomized Control Trial
REB = Research Ethics Board
TBW = Total Body Weight
WAPPS-Hemo: Web Accessible Population Phar
WFH = World Federation of Hemophilia
y/o = years old

CHAPTER 1: LITERATURE REVIEW

1.1 Background and rationale

Hemophilia is an X-linked, congenital bleeding disorder that results from the deficiency of two specific coagulation factors required for clotting. Deficiencies in Factor VIII (FVIII) and Factor IX (FIX) are known as Hemophilia A (HA) and Hemophilia B (HB), respectively, and are a result of genetic mutation. It is known that this disorder affects approximately 1 in 5000 live male births with Hemophilia A representing 80-85% of Hemophilia cases.[1] HA and HB patients will bleed for longer periods of time since FVIII and FIX are essential proteins in the coagulation cascade pathway. Clotting factors work to help keep platelets together to form a clotting plug, which stop a bleed once a vessel is inflicted with damage. The process works as the Von Willebrand Factor-FVIII complex naturally circulates in the bloodstream and is activated by locally generated thrombin.[2] The activated FVIII protein then binds to FIX to form activated FX. FX then continues throughout the cascade ultimately resulting in thrombin activation and fibrin formation. With deficient and/or dysfunctional FVIII and FIX proteins, the coagulation process to form a stable hemostatic clot is halted and the need for external clotting factor concentrate to mimic these proteins becomes necessary to cease a bleed.

Hemophilia results in affected individuals bleeding for substantially longer periods of time and more easily than healthy individuals and it can be categorized into three classes – mild, moderate and severe.[3] Mild hemophilia patients may experience severe bleeding upon major surgery/trauma while moderate cases are expected to have prolonged bleeds after minor surgery/trauma. Many of the serious, fatal cases are experienced by severe

patients, who tend to have less than 1% the normal clotting factor level and experience spontaneous bleeds into their joints (commonly in the knee and elbow area) and muscles in the absence of hemostatic challenges.[1] These breakthrough bleeds put excess pressure on the joints, leading to severe pain in the targeted area. Hemophilia can become life-threatening when bleeds occur at neck, throat, gastrointestinal and/or intracranial sites which is why appropriate treatment is crucial.

1.2 Prophylaxis

The current standard of care is replacement therapy which aims to restore hemostasis and allows patients to live a normal life by intravenously administering clotting factor, often 3 times weekly, based on an individual's total body weight.[4] Treatment can either be administered episodically ("on demand"), periodically or as continuous prophylaxis (for those with severe hemophilia status) and concentrate is available as recombinant product or plasma-derived human product.[1] The availability of concentrate factor resource varies drastically around the globe and therefore a spectrum of different protocols are followed by hemophilia patients on prophylaxis.[5] Episodic treatment aims to administer treatment during the occurrence of a clinically evident bleed while periodic treatment is implemented during periods of high-risk events (i.e. sports with physical contact). Continued prophylaxis is routinely followed by severe hemophilia patients and can either be categorized as primary, secondary or tertiary. Prophylaxis for severe hemophiliacs aims to consistently prevent bleed from occurring day-to-day by keeping patients above a 1% bleed threshold and remains at the cornerstone of hemophilia care.[1] This is due to the fact that these patients experience the most symptom

burden since spontaneous, internal joints bleeds put patients at risk of musculoskeletal complications or other serious life-threatening consequences. Prophylaxis cannot reverse established joint damage, however the main aim is to decrease bleed frequency, slow progression of joint damage and ultimately improve the quality of life.[6] Primary prophylaxis is defined as regular, continuous treatment initiated in the absence of osteochondral joint disease (as determined by imaging studies/physical examination) and before the secondary clinically evidence joint bleed. Secondary prophylaxis is initiated after two or more bleeds into large joints, however before the onset of any documented joint disease. Tertiary prophylaxis is a final measure to protect the patient from the progression of musculoskeletal complications, however is initiated after the onset of joint disease.[1]

Prophylaxis is often initiated in early childhood prior to documented joint disease[6,] however the implementation and practice varies across countries and their resource constraints since treatment can be costly. In the long run, administration of prophylaxis still poses as a cost-effective solution, even for countries with significant resource constraints, since it minimizes the high costs associated with joint damage in later years of life. In developing countries with less resources, lower doses of factor concentrate given at a more frequent rate may be an effective option to minimizing complication-associated costs.[7] The aim of all prophylaxis measures is to maintain factor levels above a set 1% threshold and various dosing protocols are followed to achieve this including daily dosing, escalating dosages, fixed high doses on alternating days, etc.. Currently, there are two common protocols practiced in North America and Europe, with long term

data available, known as the Malmo protocol and Utrecht protocol.[8] The Malmo protocol recommends 25-40 IU/kg per dose, administered three times weekly for HA and twice weekly for HB. The Utrecht protocol recommends administering 15-30 IU/kg per dose, three times weekly for HA and twice weekly for HB.

Given that there is variability in practice regarding infusion frequency, desired targets, dosage amount, and optimal infusion time, many different protocols are followed even within the same country, and the optimal regimen still remains undefined. According to WFH, optimal protocols should be individualized as much as possible[1] and this is why pharmacokinetics (PK) has become a hot topic in the field. Currently, physicians aim to personalize regimens based on bleed phenotype, availability of clotting factor (CF), lifestyle, physical activity, venous access and age, however with the recent significant advancements in technology, pharmacokinetic-tailored dosing has the potential of further advancing the care of hemophilia.[9]

1.3 Threshold Maintenance

The aim of standard prophylaxis routine is to maintain trough levels above 1% in severe patients in order to prevent spontaneous bleeding.[8] The rationale behind administering doses to maintain this level stems from the observation that moderate patients who have CF levels ranging from 1-5% experience significantly less breakthrough bleeds.[6] Therefore, in order to prevent hemarthrosis and arthropathy, CF levels in patients should be kept at higher levels resembling healthy individuals. Even though much inter-patient variability exists in hemophiliacs, with some patients failing to

spontaneously bleed below a trough level of 1% while others require higher trough levels to prevent bleeds, the 1% threshold is generally agreed upon by the hemophilia community.[1] A study conducted by Collins et al. has shown a correlation between the time spent with factors below 1% and bleeding events, however others estimate this to range between 1-3%. Variable amounts of FVIII and FIX are required to maintain a desired trough level and this inter-patient variability can be attributed to a patient's dosage frequency and clearance of CF.[6] The role of pharmacokinetics is important and has the potential to increase the efficacy while reducing the cost and frequency of prophylaxis by tailoring the regimen to each patient's PK profile.[10] The Web Accessible Population Pharmacokinetics Service-Hemophilia (WAPPS-Hemo) tool provides the knowledge of the estimated CF activity during the time of a breakthrough bleeding when it occurs. This will allow providers to correlate the individual's activity threshold to the event of a bleed for each patient and allow further tailoring. This will allow for better informed decisions and treatment regimens to match the goal of each patient in their everyday life.

1.4 Conceptual Framework

1.4.1 Classical Approach to Pharmacokinetics

Currently, the standard of care is to administer a prophylaxis regimen based on patient total body weight (TBW) with adjustments made based on activity level, age, lifestyle and clinical criteria.[4] However, evidence within the literature shows that this approach may be suboptimal and can often result in underdosing or overdosing.[11]

Underdosing is particularly unsafe in the hemophilia population since it puts patients at risk of experiencing breakthrough bleeds and thus irreversible joint damage. Overdosing can lead to more infusions and a waste of CF, a high-demand resource that is relatively costly per unit. With much uncertainty regarding the optimal dose being suggested by the "one-size-fits-all" TBW model currently being practiced, a large majority of the hemophilia community believes in tailored prophylaxis to improve the care for patients. Over the years, PK has been regarded as the ideal tool to personalize an optimal dosing regimen and overcome significant inter-patient variability as a result of TBW dosing.[10] PK-tailored prophylaxis requires the assessment of PK parameters at several different times after CF infusion for each individual patient. Lacking clinical trials involving individualized PK-generation are difficult to conduct due to logistics and ethical reasons. The classical PK approach[12] requires 9-11 blood samples per patient after infusion within 48 hours.[13] In addition, conducting a study to assess PK predictability would demand a pre-infusion washout of 5 half lives. Clearance would take 2 to 5 days for FVIII and FIX, respectively, and can pose a serious risk, especially towards patients on primary prophylaxis who require infusions frequently. Reinfusing a patient before total clearance from plasma would result in accumulation of concentrate until the steady state is reached. Many HTCs also remain unwilling to undergo the complexity of calculating estimates under multicompartmental assumptions[14]. In conclusion, excessive blood sampling along with unethical washout periods has posed a barrier to PK-tailored prophylaxis and halted the progress of clinical trials until now.[13]

1.4.2 Population Pharmacokinetics (PopPK)

In contrast to traditional PK measures, PopPK offers an array of benefits to characterize PK parameters with the perspective of providing a personalized regimen.[11] Due to traditional PK requiring an extensive number of blood samples in the post-infusion period (all within 24-78 hours) for each individual, it is often only performed within a small number of individuals. Population PK is able to provide PK profiles by collecting a limited number of samples from a large cohort of treated patients. PopPK implements non-linear mixed effects to calculate estimates of central tendency values and variability of the drug concentration in the population, accounting for all known variables[15]. The model may take into account important covariates such as comorbidity, genetics (ethnicity, blood type), demographical information (age, sex, weight), etc. (**Figure 1**)

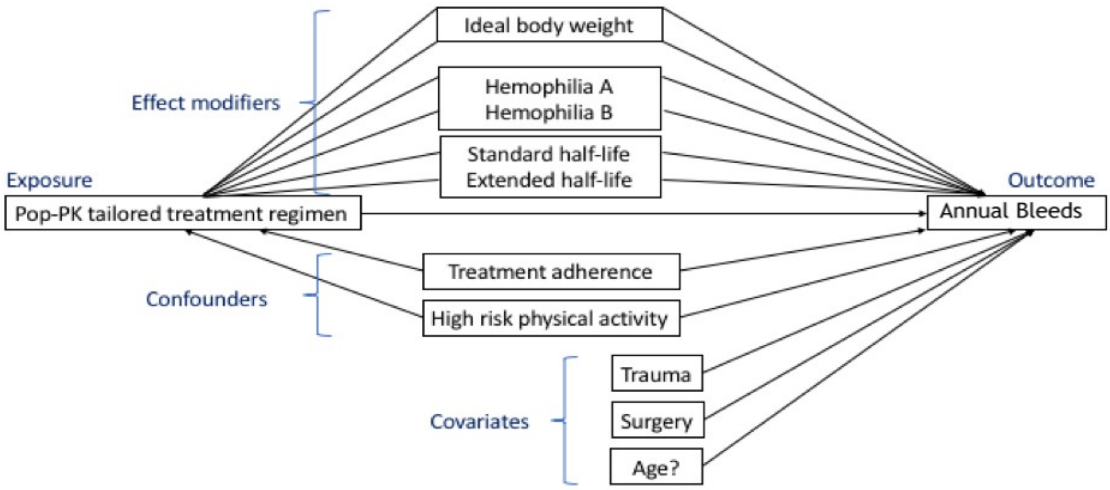


Figure 1: Association between PopPK tailoring and annualized bleed rates within hemophilia patients (non-inferior). Potential effect modifiers and confounders are also listed.

The advantage of the PopPK approach over the traditional approach revolves around the ability to obtain individual estimates using sparse data from the population mean and variance while modeling determinants of inter-patient variability.[10] Post-infusion measurements include peaks, troughs, recovery and elimination half-life to begin PK profiling and individualized dosing. Sources of variability involving PopPK estimates include: variability in PK among different individuals, among different concentrates and among the same individuals over time across different concentrates.[16] The conceptual framework for implementing a PopPK approach is based on PK parameters having large inter-individual variability (IIV) and small intra-occasion variability (IOV) (**Figure 2**).[11] Generated structured knowledge about the general shape of the PK profile for each concentrate includes relevant patient-level covariates in a multivariable regression model to factor in patient characteristics responsible for variability between individuals[16].

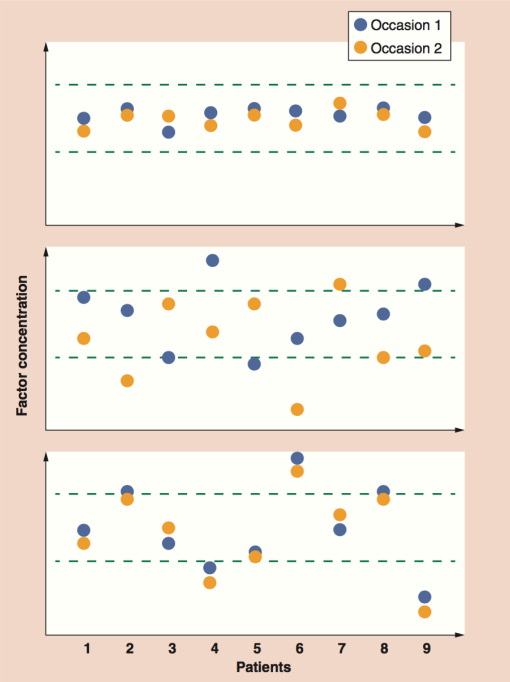
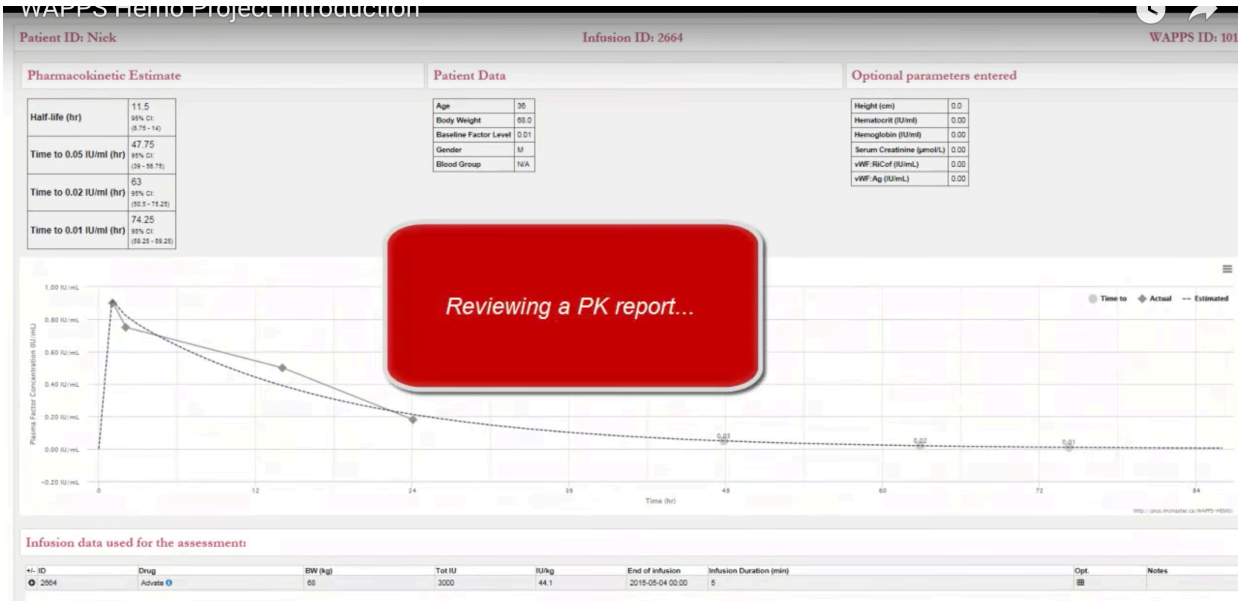


Figure 2: Graphical representation of small and large intra-occasion and inter-individual variability. Top panel shows a case with low IIV and IOV. Middle panel shows a case of both high IIV and IOV. Bottom panel shows a case of high IIV and low IOV, which is the case for factor concentrates.

(*Adopted from Iorio et al., 2017)*[11]

1.5 WAPPS-Hemo: a Bayesian PopPK calculator and its role in optimizing resource use and equitable access to treatment

The Web Accessible Population Pharmacokinetic Service-Hemophilia tool is a web based computer application that supports tailoring a personalized prophylaxis regimen by generation of a PK profile for the patient. The WAPPS calculator is the first non-industry sponsored PopPK calculator and was created by Dr. Alfonso Iorio and the Health Information Research Unit (HIRU) at McMaster University (Hamilton, ON). The calculator uses a Bayesian hierarchical approach to model the IIV in the population estimate over individual characteristics.[16] The model requires 1-3 post infusion samples which are fitted using the Bayesian approach to estimate half-life, clearance, and concentration as a function of time (i.e. time to critical concentration levels: 0.05 IU/mL, 0.02 IU/mL, 0.01 IU/mL), also represented as expected concentration at 24h, 48h and 72h, all displayed in one interactive graph (**Figure 3**).[17]



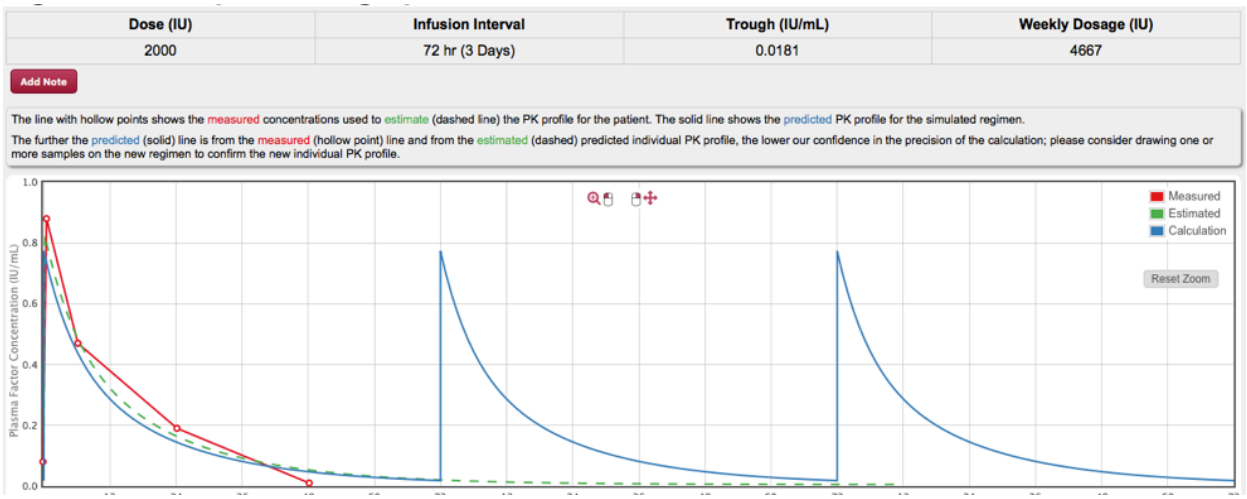


Figure 3: Individualized pharmacokinetic estimates of predicted half-life and time to critical concentrations for each patient. A visual representation of plasma factor concentration as a function of time is produced on the WAPPS-Hemo software for both the provider and patient to monitor at any point in time.

The PopPK model is currently available for standard concentrates and extended half-life products, offering high applicability to patients and providers **(Table 1).** Adoption of a PK-tailored approach has the potential to reduce costs, wasted resources, number of infusions and experienced breakthrough bleeds and arthropathy cases.[11] Prospective, randomized studies which aim to compare episodic treatment to prophylaxis have shown that permanent joint changes and damage can be caused in as little as 2-3 breakthrough bleeds experienced by the patient.[18] Replacement therapy involving factor concentrate is often expensive and in high demand with insufficient resources to meet treatment needs globally.[5] Monitoring a patient's levels and ensuring that they are always above the critical threshold should reduce the number of annual bleeds along with associated joint damage and costs.

WAPPS-Hemo will also allow physicians to monitor plasma concentration of concentrate at all times and therefore correlate breakthrough bleed events with predicted CF plasma concentration, since the critical threshold may differ for each individual.[6] Implementation of the tool can even allow for better resource use since PK profiles can help suggest the dose required to meet target levels needed to perform certain activities (i.e. sports or intense physical activity) or optimize dosages for those currently being overdosed or underdosed.[16] The patient is also expected to remain far more engaged and adhere to their regimen since WAPPS-Hemo allows the patient to have a deeper understanding of the pathophysiology of the disease.[19] The tool is also currently being developed as a mobile app and will be able to display CF levels to enable patients to make on-the-spot lifestyle choices, alert them when they are approaching critical plasma CF concentrations, enable them track their doses and remind them of upcoming doses. In conclusion, the WAPPS-Hemo computer application makes tailoring a dosing schedule based on the patient's PK, clinically-feasible for everyday use between the provider and patient. Up to date, the WAPPS-Hemo software is being used in 180 centers across 32 different countries with 2228 patients having their PK profile generated with the software (www.wapps-hemo.org). The software and its benefits continue to expand rapidly across Canada also with 335 patients registered in the software across 18 hemophilia treatment centers in Canada.

Table 1 : Current drug concentrate models available in WAPPS-Hemo

Advate	Adynovate
Afstyla	Alphanate
Alphanine	Alprolix
Benefix	Beriate
Clottafact	Elocta
Eloctate	Emoclot
Factane	Factor Ix Grifolds
Factor Vii Sdh Intersero	Fanhdi
GreenGene F	Haemoctin Sdh
Helixate	Helixate Nexgen
Humate P	Idelvion
Immunate	Kogenate
Kovaltry	Novoeight
Nuwiq	Octanine
Optiate	Recombinate
Refacto	Refacto Af
Rixubis	Wilate
Xyntha	

1.6 The Canadian Bleeding Disorders Registry (CBDR) and its role for electronic data collection in current and future hemophilia studies

CBDR is a web-based, clinical management software used for those affected by mild, moderate and severe cases of Hemophilia A and Hemophilia B in the Canadian population. The software serves as a registry to capture hemophiliac data with the capability of optimized data shared across the vast network of users. CBDR is being adopted by the Association of Hemophilia Clinic Directors of Canada and serves two purposes: 1) serving as a Canadian-wide data storage system capturing information related to hemophilia and needed to measure baseline and outcome data in the population related to the disease 2) allow patients to record and track their own data (infusion doses, frequency, time of administration, bleed logs, type of bleed, etc. in a complementary

system called MyCBDR). CBDR collects information such as: age, gender, race/ethnicity, weight, height, hemophilia severity, baseline factor levels, inhibitor history, past/current infusion schedules (factor concentrate, product dose, PK, frequency, factor concentrate), patient's occupation, physical activity levels, etc. and has already been used to store the data of over 5000 patients countrywide. The database is already rich in the Canadian setting, capturing a large percentage of the 2016 hemophilia population **(Figure 4).**

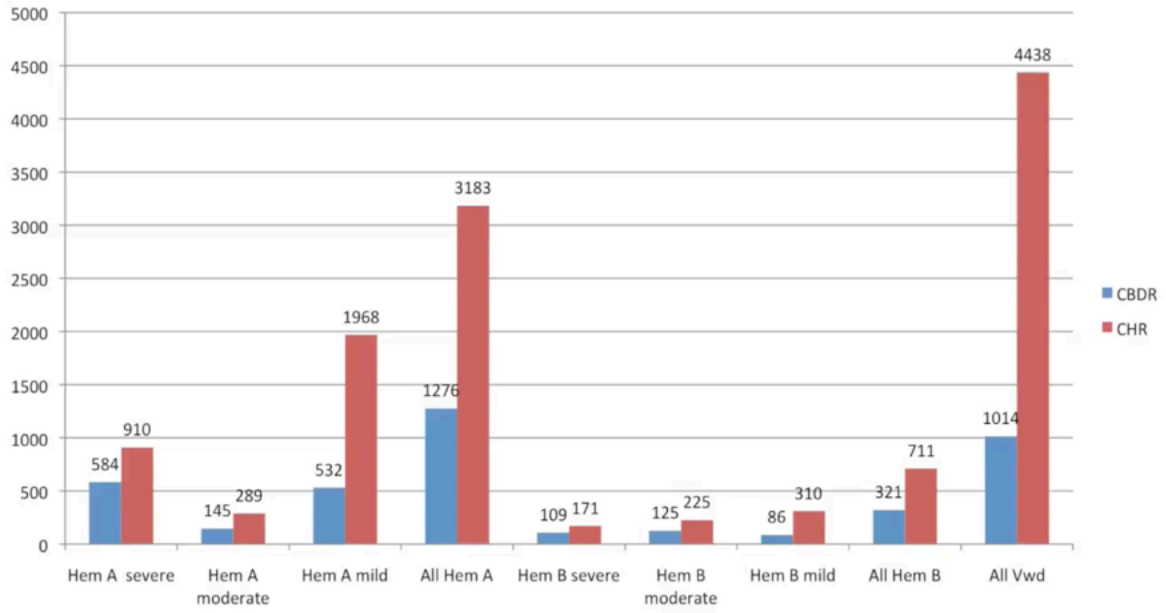


Figure 4: Comparison of enrolled patients in Canadian Hemophilia Registry (CHR) versus CBDR registry according to 2016 data.

McMaster University's own Health Information Research Unit currently hosts and maintains all of the system's data, however the registry is ready to be adopted cross-border. CBDR-RM has also been developed along with CBDR to capture outcomes that can be used to complement other hemophilia research initiatives in the near future (i.e. PROBE questionnaires, EQ 5D-5L, reason for dropoff/participant inclusion/exclusion).

CBDR-RM specifically serves two functions: 1) collecting data to ensure efficient selection and enrolment of patients matching inclusion criteria set for other future project initiatives 2) using historical/ad-hoc data collected from one study that can then be later reused for analysis in another future study. Both data repositories are tightly secured and only approved healthcare professionals and staff can access patient-level data. CBDR and CBDR-RM has already been widely implemented and used for the Canadian Hemophilia Immune-tolerance Prospective Study (CHIMPS), Expanding Communications on Hemophilia A Outcomes project (ECHO), and the Canadian Hemophilia Carriers study (CHIC). CBDR, CBDR-RM and MyCBDR offers patients and providers a comprehensive overview and collection of patient-level data that is needed for the hemophilia community. The use of these modules reduces the amount of personnel required to collect such copious amounts of data and is already used to capture a large majority of the hemophilia population in Canada. Integration with the WAPPS-Hemo software has already been completed and will allow for efficient patient recruitment along with the collection of baseline data, infusion records and outcome data in the proposed feasibility trial aimed at assessing the uptake of WAPPS-Hemo in the Canadian population. Once the study begin, the WAPPS-Hemo PK profile will become available for viewing on the CBDR software and providers and patients will be able to enter baseline data, follow-up data, outcome(s), and treatment information into CBDR and MyCBDR, respectively.

1.7 Conclusions

Prophylaxis is crucial to prevent hemarthrosis from reoccurring in hemophilia patients, as the literature indicates that the median ABR in severe Canadian hemophilia patients is approximately 8 bleeds, ranging from 3-16 bleeds annually[20]. Recurrent hemarthroses is the most commonly experienced symptom in this population, resulting in bleeds within the knees, elbows and other joints. Hemarthroses in these areas leads to progressive destruction, irreversible arthropathy, severe chronic pain and remains the major cause of morbidity for hemophiliacs[8]. Studies have demonstrated that prophylaxis is effective in preventing hemarthroses and the associated structural joint damage in Hemophilia A patients while improving their quality of life.[21] Large inter-individual variance in dose exposure to factor concentrate for each individual makes it challenging to keep patients above 1% thresholds with the TBW model and therefore pharmacokinetics offers a solution to optimizing treatment. The empiric approach of dosing by weight remains suboptimal as half life of the infused CF (with standard concentrates) can last anywhere from 6 to 18 hours depending on the patient's body[11] (**Figure 5**). Whether or not PopPK-tailored prophylaxis will be received with strong uptake and satisfaction, while also producing significant clinical and/or economical changes, remains undiscovered in the hemophilia community. A pilot study has been proposed to assess the feasibility of conducting a full randomized control trial with the WAPPS-Hemo tool compared to the standard dosing treatment (primary outcome), while also recording hemophilia-related quality of life and clinically-evident bleed events (secondary outcomes), which can later be used in a future large-scale, randomized trial of the WAPPS-intervention if deemed feasible.

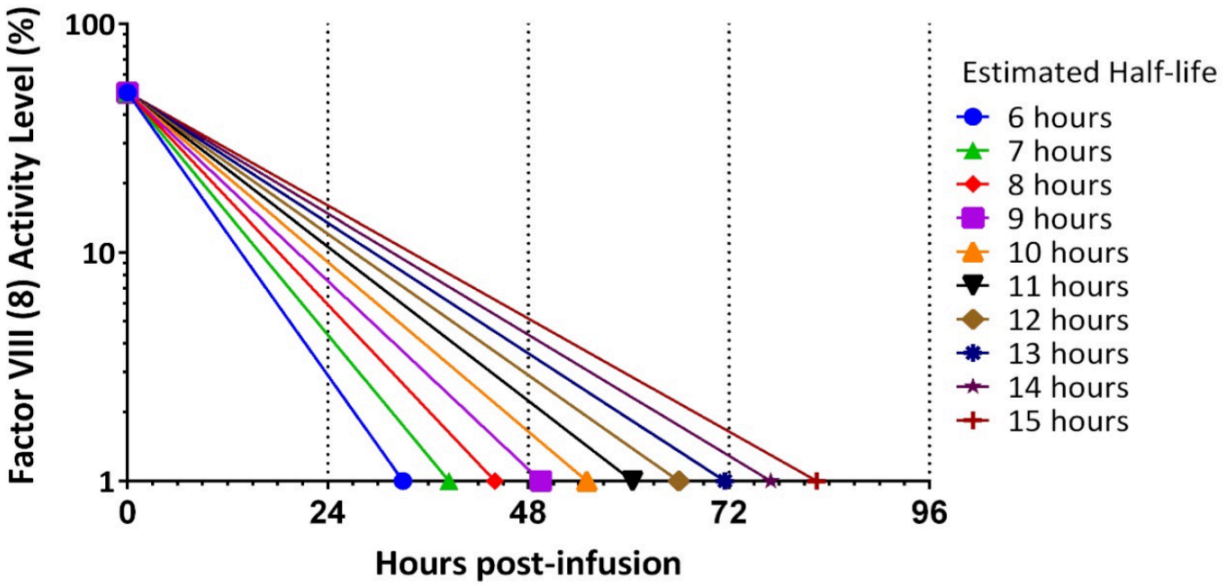


Figure 5: Graphical representation of high inter-individual variability related to drug clearance. Varying half-life of Factor VIII within the plasma of different individuals starting at identical baseline factor levels.

Chapter 2 – Methods: Participants, Interventions, Outcomes

2.1 Hypothesis and Objectives

We hypothesize that the contextual availability in Canada of both WAPPS-Hemo and CBDR will make it feasible to conduct a larger-scale randomization trial across additional patients and multicenters in Canada. Along with hypothesizing that the pilot trial will be considered feasible in Canada, we also hypothesize that the quality of life will improve and the bleed rate event will be maintained and/or reduced for those receiving the WAPPS intervention since: 1) providers can set trough levels for their patients and administer a dose and frequency to accommodate to their lifestyle and/or level of physical activity 2) plasma concentrate at the time of the bleed is recorded and can be kept above this threshold for future guidance in the patient's tailoring process. The annual bleed rate and quality of life (QoL) will be recorded in the intervention and

comparator group within the six months of the study for further analysis in the large-scale randomized control trial (RCT) if the pilot study is deemed feasible.

2.2 Trial Outcomes

2.2.1 Primary outcome: Feasibility

The primary objective of the pilot study is to determine if it is feasible to conduct a large, multicenter, randomized control trial (6 month duration) in severe Hemophilia A and Hemophilia B patients either undergoing 1) a prophylaxis regimen tailored by the PopPK calculator, WAPPS-Hemo 2) standard total body weight dosing in the absence of PK generation. The feasibility of the RCT will be assessed based on 4 pre-set measures required for success:

1) **Recruitment:** Expected minimum of **15%** (8.7% - 21.3%) of total eligible population is recruited into the study (86 patients)
2) **Enrolment**: Expected minimum of **50%** (41.1% - 58.9%)- of recruited, eligible patients are considered fully enrolled in the study (minimum of 43 patients). To be considered fully enrolled, patients must sign and return the informed consent form, complete the initial laboratory assessments and sampling, gain approval of the proposed regimen change from their hematologist, register into CBDR (if not already registered) and begin the prescribed regimen within one week of study initiation.
3) **Patient engagement**: Expected minimum of **70%** (61.9% - 78.1%) of the prescribed doses are administered to the patient and recorded in order for the

patient to be considered fully adherent to the schedule.

4) **Retain**: Expected minimum of **70%** (61.9% - 78.1%) of the enrolled patients complete the full 6-month study with "full adherence" to their prescribed regimen (loss of follow-up may be due to cross over, low adherence/regimen change, increased complications, study dropout, etc.)

The WAPPS-Hemo software is well received by clinicians in the hemophilia community and quickly expanding to patients across the globe through dissemination by the HIRU research team. It is expected that a large group of patients will be eager in joining the pilot study to have their current regimen assessed and possibly changed to fit the most appropriate regimen for their lifestyle. The above criteria aim to assess the acceptance and compliance with the WAPPS-Hemo software among providers and hemophilia patients in Canada.

2.2.2 Secondary outcomes: Annualized Bleed Rate + Hemophilia Related Quality of Life

How providers implement the WAPPS-Hemo tool and whether it can offer patients the benefit of improved health outcomes and quality of life remains to be investigated. Secondary outcomes that the pilot study will capture include ABR and QoL. Both ABR and QoL are in alignment with the patient's top priorities and have been particularly chosen in consultation with the Canadian Hemophilia Society. Demonstrating an association between WAPPS-Hemo and improved patient outcomes will help broaden its uptake and prove beneficial to the rest of the hemophilia community who remain

uncertain about the PopPK approach.

Annualized bleed rate will be calculated by dividing the number of bleed events by the number of days since the patient entered the pilot study. Being that the goal of prophylaxis is to reduce bleeds, it is evident that unexpected bleeding is an important patient outcome and is relatively easy to capture with electronic medical logs. The WAPPS-Hemo tool holds the potential to reduce the number of breakthrough bleeds that preludes arthropathy in severe patients. Assessment of bleed events will determine whether the intervention does more good than harm and can be compared between the intervention and wait-list control in a large-scale RCT if deemed feasible.

If approved to be feasible, the bleed events can also be compared in the pre-WAPPS phase and post-WAPPS phase of the waitlist group to assess the impact of the WAPPS-Hemo software on an individual level. The data monitoring safety board (DMSB) will develop a pre-set threshold of harm/feasibility, at which the study will be terminated if WAPPS-Hemo demonstrates a clinically significant increase in bleeds for patients (≥ 30% annual bleeds). This is not anticipated due to the role monitoring pharmacokinetics in adjusting an individual's dose over the bleed threshold. The trial may also be halted if the study cannot meet enrollment and/or adherence targets set for the feasibility within a reasonable time frame (as judged by assessing success at pre-stated follow-up times). The full scale RCT will aim to assess the ABR in the intervention and comparator group and subgroup analysis will be conducted for differing age (pediatric vs adult population) and product (EHL vs standard) groups.

For purposes of the pilot study, quality of life will be also measured at baseline

and study completion within both groups. Quality of life (QoL) measurements aim to assess and focus on the value of health that treatments can offer throughout the stages of chronic disease. In particular to the hemophilia population, consequences of disease can result in arthropathy, restricted physical activity, unexpected breakthrough bleeds, psychological concern of experiencing a life-threatening bleed, demand for orthopedic procedures, damage to self-esteem, etc..[22]

General questionnaires to measure QoL in studies often include the WHO-QoL and SF-36 questionnaire form, however there are only a few validated questionnaires that are specifically directed towards complications experienced by hemophilia patients. The Haemophilia Specific QoL index (Haemo-QoL) questionnaire contains 35 items with 9 dimensions aimed to assess the quality of life in pediatric and young adolescent hemophilia patients. The Haemo-QoL will be used for patients aged between 12 and 17 years old who enroll in the study. The hemophilia-specific quality of life questionnaire for adults (Haemo-QoL-A) was developed in correspondence with the Haemo-QoL tool for children and will be used to assess the QoL in those 18 years of age and older. The index contains 46 items and is divided into ten dimensions including physical health, feelings, self-perception, sports and leisure, work and school, coping, treatment, future, family planning, relationships and partners. A lower score indicates a higher QoL and each domain is ranked by the patient from a scale of 0-100 (**Table 2)**. Both tools are sensitive, validated, hemophilia-specific instruments and capture the multidimensional aspects of measuring quality of life in these patients.[22] Anemia, joint health, mode of treatment and synovectomy are all factors that can affect with quality of life in

hemophilia patients who have experienced a joint bleed.[23]

Table 2: All domains of the QoL score will be reported in the following chart format for each participant in the study. Comparisons will be drawn from the intervention and control arm to assess for improvements in Haemo-QoL and Haemo-QoL-A scores.

	Group 1 Standard of Care N = 22	Group 2 WAPPS-Hemo N = 21
Physical Health Min-Max Mean ± SD		
Feelings Min-Max Mean ± SD		
Self-perception Min-Max Mean ± SD		
Sports and leisure Min-Max Mean ± SD		
Work and school Min-Max Mean ± SD		
Coping Min-Max Mean ± SD		
Treatment Min-Max Mean ± SD		
Future Min-Max Mean ± SD		
Family Planning Min-Max Mean ± SD		
Relationships/Partners Min-Max Mean ± SD		

In the field of hemophilia treatment, and particularly when dealing with prophylaxis, cost considerations are often raised as relevant topics from the patient-perspective. Building a cost-effectiveness layer would likely make it too cumbersome for the six-month pilot study, and potentially introduce bias into the provider's dosing regimen set for the patient. Also, the price and availability of specific concentrate in Canada is subject to change over time due to the tendering based procurement process. The full-scale RCT will consider using the data collected during the pilot trial (mainly utilization of factor concentrate and impact on patient life) as the base for an indirect assessment of the impact that PK-tailoring has on the annual cost for treatment.

2.3 Trial Design

The pilot study proposed will be a Canadian, multicenter, open-label, randomized waitlist clinical trial over the duration of six months (**Figure 6)**. Patients will serve as the unit of randomization as half will receive the WAPPS-Hemo intervention at the start period of the study, while the other half will receive it after a six month wait period. The waitlist design allows for the short-term evaluation of the WAPPS-Hemo intervention's acceptability and usability for purposes of a future randomized control trial. The WAPPS-Hemo calculator is widely viewed as a beneficial tool to clinicians and the waitlist design is both fair and ethical since all patients who seek personalized prophylaxis will receive tailoring within a reasonable time frame.

Since the primary objective of the pilot study is to test the feasibility of conducting a large, randomized control trial of the WAPPS-Hemo across Canada, a randomized

waitlist design allows for two merits: 1) Recruitment efforts are maximized and made easier. Word of the WAPPS-Hemo service is expanding into the larger patient community and patients may not want to be restricted to a single intervention arm, as the classic parallel design would offer. The waitlist design faces less recruiting pressure as severe hemophilia patients are offered the opportunity to tailor and optimize their regimen through the tool. Those on waitlist will be offered a regimen tailored by the intervention after 6 months and will serve as the control group to be compared to the intervention group in Phase 1. Essentially, the waitlist patients will provide data on their standard regimen while they wait for the intervention. 2) In phase 2 of the study, the control group will then begin to use the intervention and can then be clustered with already current users of WAPPS-Hemo, in order to quickly power a larger RCT aimed at assessing the efficacy and safety of the tool. Rates of recruitment, adherence, eligibility, retention and completion, and participant refusal and reason will all be recorded in the CBDR system. The ABR will be recorded in the system also and be used as a safety measure to plan a larger RCT assessing the efficacy of the tool to its users.

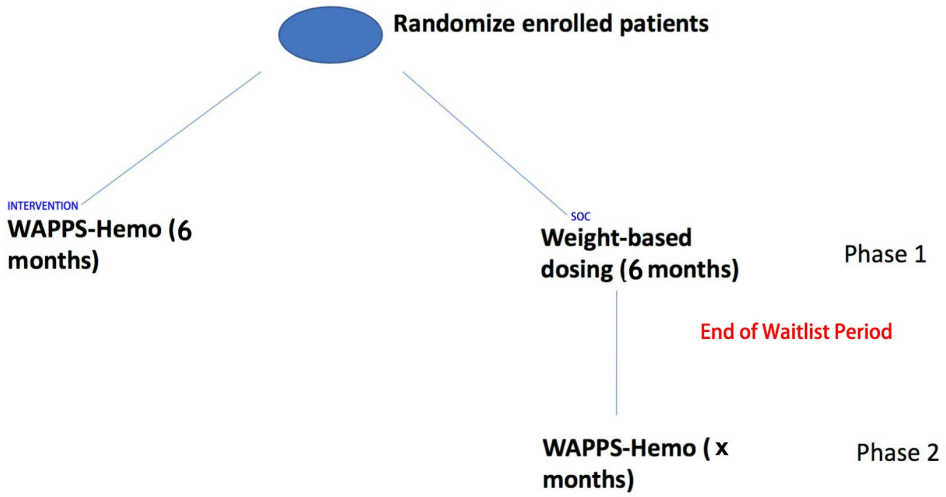


Figure 6: Basic schematic representation of the randomized registry, wait-list trial design. Phase 1 aimed to assess feasibility of WAPPS-Hemo within 6 month period. Phase 2 of larger, full-scaled RCT is conditional upon meeting feasibility requirements in Phase 1 of study design.

2.4 Study Setting

All patients who enroll in the study must be in the CBDR database and/or willing to join and willing to participate from HTCs who serve as registered users and/or co-investigators in the WAPPS-Hemo network within Canada. The retrieval of data will take place at each respective HTC and be fed into the CBDR system, however coordination of the full study will stem from McMaster University (Hamilton, ON). Currently, 18 HTC across Canada are affiliated with the network (13 co-investigation centers, 5 registered users), including some of the largest HTC's in Canada such as St. Michael's (Toronto), St. Paul's (Vancouver), Hamilton Health Sciences Corporation (Hamilton), etc.

2.5 Study Population of Interest

2.5.1 Eligibility Criteria

Inclusion:

- Severe hemophilia A and hemophilia B patients using prophylaxis (<0.01 IU)
- Age >12 years old
- Interested in receiving PK-tailored prophylaxis
- Already registered on Canadian Bleed Disorders Registry and/or willing to register onto CBDR
- Minimum of 150 exposure days
- Informed Consent
- Willingness to participate in study's protocol

2.5.2 Restriction

Exclusion:

- Other concomitant bleed disorders
- Presence of active inhibitors (FVIII and FIX)
- Currently using immune tolerance induction
- Partial success of immune tolerance induction
- History of PK estimates and tailoring

2.6 Study Intervention

All patients must be approved by their clinician to receive a change in their regular infusion schedule towards a PopPK approach, tailored by the WAPPS-Hemo tool. Throughout the study, the patient will be expected to remain on the same clotting factor concentrate (either plasma-derived or recombinant factor product) used in the pre-WAPPS phase with dose and/or frequency adjustment based on the input into the tool. All CF will be administered via intravenous injection and the use of central venous access devices will be left to the discretion of the healthcare provider (**Figure 7**).[28]

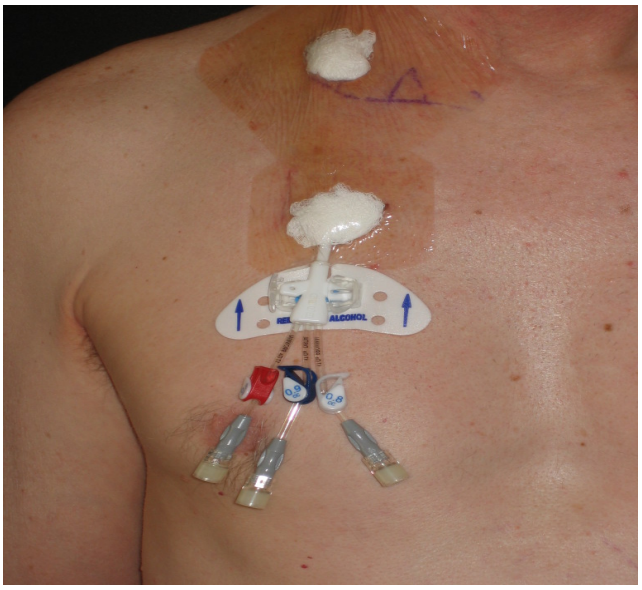


Figure 7: Real-life central venous access device on a hemophilia patient. Allows frequent infusion into large veins via small, flexible tubes.

CF should be infused by slow intravenous injection not to exceed a rate of 3mL/minute in adults or 100 units/minute in young children.[24] FVIII is used to treat Hemophilia A and vials range from 250-3000 IU (administered in 250IU, 500IU, 1000 IU, 2000IU and 3000IU vials). FIX is used to treat Hemophilia B and the vials range

from 250-2000IU. The appropriate vial size will be administered to achieve the plasma concentration target, rounding up to the nearest whole vial size. Infusion of full vials is recommended for the patient, once reconstituted, by the World Federation of Hemophilia.[1]

2.7 Required Patient Data

2.7.1 PK-Estimate Data

Providers will need to report the following patient information in order to obtain a PK estimate:

a) a patient identifier of your choice;
b) the patient month and year of birth;
c) patient gender and race;
d) patient occupation and level of physical activity
e) the patient baseline factor level;
f) a check box stating that you have informed your patient that you are using WAPPS to calculate his PK;
g) data on the infusion: concentrate name, total dose administered, body weight (kg)/height, infusion day, time, duration (if left blank, this will be assumed to be 5 minutes); and
h) any number of plasma samples, measured in your routine laboratory.

After providing blood samples at the requested times, the local HTC will measure and record factor activity levels, along with the last infused dosage and time. A 1 mL aliquot of plasma from the three time points in should be kept frozen at -80 degrees at the local center. Once the patient's information and blood samples have been submitted by the coordinating center (Appendix A), a pharmacokinetic estimate will be manually validated by a PK expert from the WAPPS research team (turnaround time is 24h or less). An inhibitor titer will be obtained with the pre-infusion sample. The provider will receive a PK estimate from the calculator which will include information pertaining to: time to 0.05 IU/ml, 0.02 IU/mL, 0.01 IU/mL, terminal half-life and plasma concentration as a function of time on an interactive PK chart. The provider can then enter 2 of the following 3 inputs to receive the third: 1) frequency per week 2) input dose 3) target plasma concentrate levels (**Figure 8**). A minimum of two post-infusion blood samples will be required to participate in the study.

Figure 8: Required input from the WAPPS-Hemo software to calculate either dosage, trough or infusion frequency in accordance with the participant's set treatment goals.

2.7.2 Post-infusion plasma sampling:

1) For Factor VIII
    a. Best Option: 4 HRS, 24 and 48 HRS.
    b. Alternative: 8 HRS, 30 HRS.
    c. Alternative: 24 HRS.
        i. Note: all times are indicative, e.g. 24 can be anytime between 18 and 30 hours. Please avoid samples taken before 4 hours unless you are mostly interested in peak concentration estimation.
2) For Factor IX
    a. Best Option: Any Time on day 2 and 3.
    b. Alternative: Two samples on any of day 2 or 3, optimally, 4 or more hours apart.
3) Long Acting Concentrates
    a. As above, but moving 24 HRS ahead for factor VIII, 48 HRS ahead for factor IX.

2.8 WAPPS-Hemo Integration

2.8.1 WAPPS-Hemo Registration

In order to begin PopPK tailoring, HTCs must become a registered user or co-investigator within the network. To become a registered user, centers must simply sign a user agreement. By becoming a co-investigator, the HTC can become part of the research

network and be involved in various research projects relating to pharmacokinetic studies. However, co-investigators may also need to obtain ethical approval to participate or sign a data transfer agreement which may prolong the registration process. The reason for making CBDR enrollment mandatory is to leverage the existing CBDR recording of baseline and outcome variables.

2.8.2 WAPPS-Hemo Assistance: Stewardship

The stewardship program was initiated in January 2018 and was created to aid HTCs in implementing the WAPPS tool. The implementation of PopPK-tailored prophylaxis currently faces two barriers: 1) uncertainty of how to incorporate PK data into current practice and recommendation of a new prophylaxis regimen, 2) lack of a user-friendly application to allow for PK-generation. The stewardship program is intended to support, education and train to accelerate the integration of the service to avoid these issues. The steward will be able to provide training with the calculator, input of data and interpretation of the estimates to staff via in-person, email/telephone, and live webinar. In addition, the steward can also assist in preparation and submission of research ethics board (REB) approval, and educate users (patients and clinicians) on the principles of population pharmacokinetics and merits of the tool. Contact Sydney MacLeod at maclesd@mcmaster.ca or wappshemo@mcmasterhkr.com or at 905-525-9140 (ext 25214) on how to get started using WAPPS-Hemo.

2.9 Study Definitions

Active Inhibitor

Antibody that attaches to FVIII or FIX and neutralizes the clotting factor. Inhibitors are an immune response to clotting factor treatment and indicated by assay/positive titer of >1 Bethesda Units.[1]

Arthropathy

Disease or abnormality of facet joints. Occurs by breakdown/wearing of cartilage between joints.

Breakthrough Bleed

Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge.[1]

Continuous Prophylaxis

Regular continuous treatment aimed to prevent spontaneous, breakthrough bleeds by keeping factor activity levels above 1% threshold. Often initiated in severe hemophilia patients and expected to continue for an indefinite time period. Divided into three categories – primary, secondary and tertiary prophylaxis.

Episodic/ "On-demand" Treatment:

Clotting factor treatment administered in the event/time that patients experience a hemarthrosis or prior to high-risk activities (i.e. physical contacts sports).

Exposure Days

A calendar day in which infusion of clotting factor occurred one or more times.

Inhibitor Development

The development of inhibitor antibodies in the patient. Usually develops after the first 5-50 infusions but can develop later in life. Detected by activated partial thromboplastin time blood test to calculate the time it takes to clot after infusion. A Bethesda assay is used to detect titer levels (low < 5 BU) and determine the level of anamnestic response (low or high responder).[1]

Immune Tolerance Induction (ITI)

High levels of clotting factor are regularly administered over a period of time in order to allow the patient's immune response to recognize and adapt. It is expected that inhibitor titre levels will drop below the limit of quantification in complete success of ITI.

Complete Success: Negative test for inhibitor detection by Bethesda assay + Low APTT test time + no anamnestic response + normal factor recovery/half-life

Partial Success: Negative test for inhibitor detection by Bethesda assay + Low APTT test time + no anamnestic response + slow factor recovery levels (66% less than expected) or <6h half-life after 72 hr washout period.

Failure: No substantial change in inhibitor titre levels + APTT test time. Failure to achieve immune tolerance or partial response after 36 months of ITI.

Joint Hemarthrosis

Bleed into joint that would prompt administration of clotting factor therapy. Clinically assessed by joint swelling, stiffness, pain and/ or limited range of motion.

Overweight/Obese

Overweight: BMI ≥ 85th percentile (age and sex deponent) in pediatric patients aged 2-19 years age; BMI ≥ 25 in adults (≥20 years)

Obese: BMI ≥ 95th percentile (age and sex dependent) in pediatric patients aged 2-19 years of age; BMI ≥ 30 in adults (≥20 years)

Race/Ethnicity

Self-report identification of the patient's social heritage. Categorized into American Indian, South Asian, East Asian, African, Naitive Hawaiin or other Pacific Island, Caucasian, Hispanic or other.

Severe Hemophilia

<1% factor activity level in plasma as determined by one-step assay or chromogenic assay. Usually experience spontaneous joint bleeds in absence of hemostatic challenge.

Target Joint

A single joint that has experienced four or more hemorrhages in the past six months.

Chapter 3: Study Plan

3.1 Participant Enrollment

The planned recruitment period for each centre is twelve months initiated at the point of first contact by the WAPPS-Hemo research team. Recruitment will take place from cooperating HTCs who are co-investigators in the WAPPS-Hemo Canadian network. The local principal investigator at each center will be responsible for identifying

patients who visit the clinic routinely and meet the inclusion criteria. The local PI can then begin to discuss the tool and its merits during the visit and offer patients the opportunity to receive personalized prophylaxis within the study's timeframe. Once the recruitment period has ended, enrolment into the study will take place within the first two weeks. If interested in the study, the patient will notify the PI and will then receive an informed consent form to fill. Both the consent form and protocol will be submitted to the research ethics board at each facility before initiation of the study. Once consent is obtained, an identification number will be assigned to the patient. Written consent forms will be obtained from the patient or his/her legal guardian if under the age of 18. The informed consent form will detail the participant's willingness to engage in the full study protocol and allow research team access to medical records and past/future bleed data. Both parties will receive copies of the consent form. The enrolment period will ensure that the following procedures have been fully completed before randomization begins: eligibility screening, obtaining informed consent from the patient, blood sampling and receiving approval from their respective clinician to undergo a regimen switch towards PopPK tailoring (**Figure 9)**.

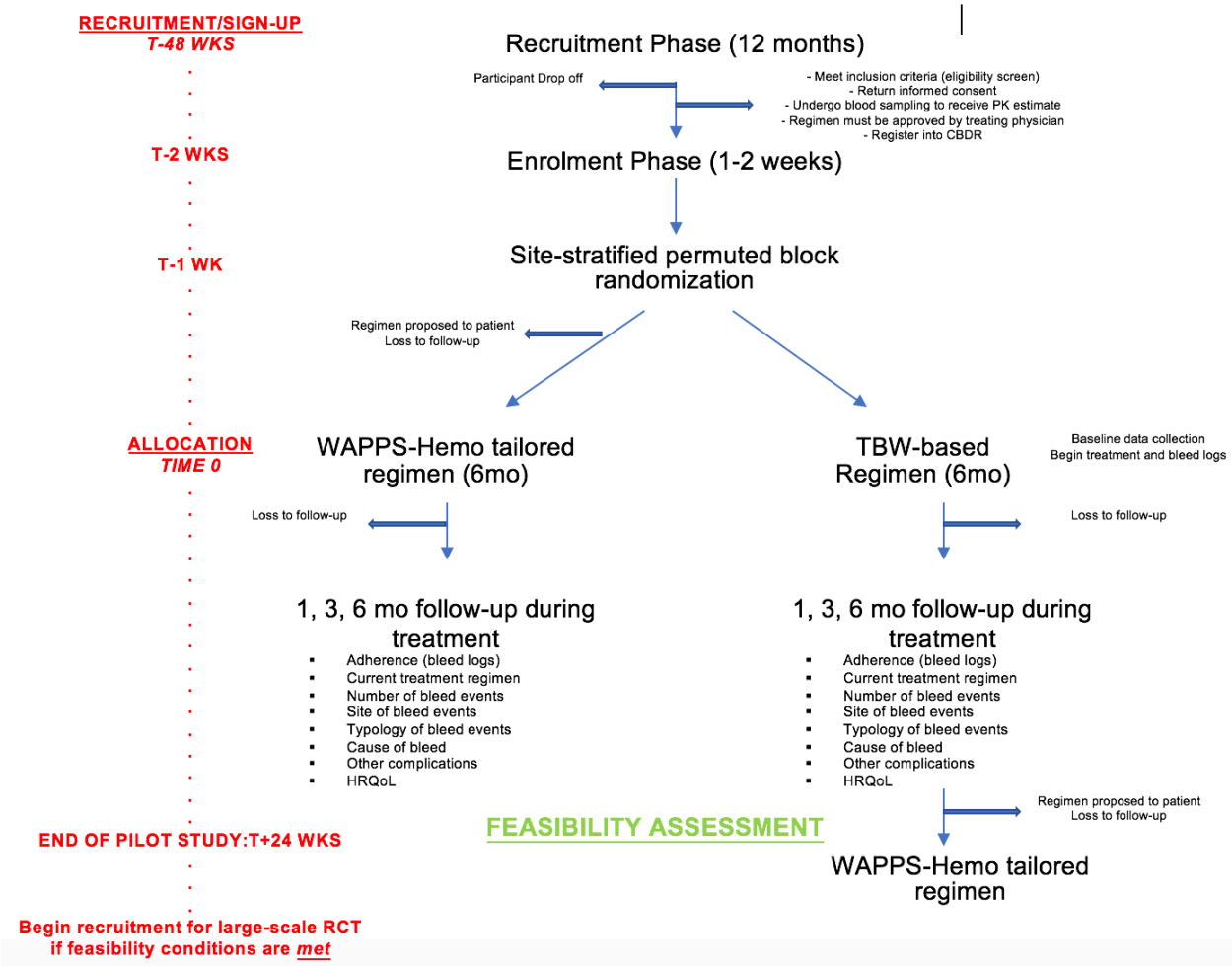


Figure 9: Comprehensive overview of the study time of the WAPPS-Hemo pilot trial.

Project Timeline

Month 1-12: Site Finalization + Patient Recruitment + Blood Sampling/PK Generation + Baseline Data Collection

Month 12-13: Patient Full Enrollment and Randomization

Month 13-18: Pilot Trial Execution

Month 18: Pilot Trial Ends

Month 19: Data Analysis

Month 20: Study report publication + Begin recruitment for full-scale RCT

Baseline assessment

Baseline demographic and clinical information will be collected by chart review and/or short interview with the participant stored in the CBDR system. This information includes:

- Age
- Gender
- Race/Ethnicity
- Weight
- Height
- Hemophilia type
- Hemophilia severity
- Baseline factor level
- Inhibitor history
- Past/present infusion schedule (product, dose, frequency)
- Occupation
- Level of physical activity
- QoL

For those who meet the eligibility criteria yet are unwilling to participate in the study or eventually decide to dropout, participant reasoning will be recorded in the CBDR-RM database to guide future research efforts. Barriers to participating in the study will also be

recorded, where applicable, and may involve issues with: patient engagement, blood sampling, data reporting and/or PK profile generation and be used to inform study investigators in planning of the large-scale RCT.

Bleed logs

Bleed logs and reported complications will be expected to be filled by the patient in MyCBDR and will be checked every three months by the study nurse.

PK estimation

Once allocation takes place, all patients will be expected to begin the assigned treatment within a one week period (turnover time for PK estimate is 24 hours). For patients in the intervention group, post-infusion sampling to produce a PK estimate will take ideally place at 4h, 24h, 48h (FVIII patients) or anytime during day 2 and 3 (FIX patients). A minimum of 2 blood samples will be required to participate in the study. Before further continuation of the WAPPS-Hemo service, it is advised that clinicians will check to confirm the plasma concentration estimate resembles the actual concentration within the patient.

3.2 Patient Monitoring and Follow up

Since a regimen switch poses a degree of novelty to the patient, some individuals may have difficulty adhering to the new infusion schedule proposed by the clinician based on the WAPPS-Hemo software. Adverse events such as increased bleeds may be a consequence of lowered adherence if the patient is experiencing difficulty adjusting,

however the provider can choose to set alerts on the application to constantly remind the patient. Although a minimum threshold of 70% adherence is required for the participants to enroll in the study, an independent DMSB will be assembled to monitor bleeds. Bleeds pose a serious risk for permanent joint damage and if the study meets a pre-set threshold of harm that is being observed in the WAPPS-Hemo group, the study will be terminated although this is not anticipated. The investigator will still regularly use every three months to review interim adherence and safety results and will be empowered to terminate the study if there is high dropout rates and/or complication (adverse event) rates.

Study Completion

Feasibility outcomes will be evaluated at baseline and subsequently every three months until study completion (6 months), with success rates defined above. If deemed feasible, the control group can begin to use the WAPPS-Hemo calculator after the wait period has ended. Patients in the intervention during phase 1 can choose to continue using the tool to tailor their prophylaxis regimen and may be contacted to participate in a larger RCT if satisfied with the tool. If deemed unfeasible, the study will be terminated and all patients will be notified for the reason being, however waitlist patients may still choose to use the WAPPS-Hemo tool at their discretion. The tasks and deadlines of the pilot trial are summarized in **Table 3 below.**

	WAPPS-HEMO FEASIBILITY STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT**	$-t_1$	**0 baseline**	t_1 *1 mo*	t_2 *3 mo*	t_3 *6 mo*	t_x
ENROLMENT:						
Eligibility screen	X					
Lab Assessment + PK generation	X					
Informed consent+ regimen approval	X					
Allocation		X				
INTERVENTIONS PK-tailored Regimen Reveal to Patient:						
Standard of Care					X	
PK tailored prophylaxis		X				
ASSESSMENTS:						
Baseline variables	X	X				
Feasibility criteria+ Bleeds		X	X	X	X	
QoL		X			X	

Table 3: Study time points and associated deliverables to be collected and/or assessed.

3.3 Required Sample Size

According to Canadian Hemophilia Registry in 2016, 1081 patients are living with severe Hemophilia within Canada[25]. Approximately 874 of all severe Hemophilia patients are aged 12 years or older and this should be a proxy for the number of patients that are taking bleeding and treatment diaries. 642 (549 A + 93 B) severe Hemophilia

patients (>12 y/o) and already registered in CBDR and currently compromise 74% of the database **(Table 4).** Approximately 75% of all severe hemophiliacs in Canada should be treated with prophylaxis on a regular basis, resulting in an estimate of 655 patients[1]. Among these patients, a pop-PK estimation has likely already been performed in ~ 10 % leaving approximately 590 eligible patients to be recruited. The proportion of the remaining 590 patients presenting other exclusion criteria is likely negligible, but we can conservatively estimate a further 2%, leading to **578 patients** as the eligible population of interest for the study.

	Under 12 y/o	**Over 12 y/o**	**% Over 12 y/o**
Hemophilia A	196	549	73.69%
Hemophilia B	32	93	74.4%
Grand Total	228	642	73.79%

Table 4: Proportion of patients in the CBDR that are eligible, in regards to age, for participation in the WAPPS-Hemo pilot trial (according to 2018 data).

The pilot study will be deemed feasible if the trial is able to recruit a minimum of 15% of the eligible population (86 patients) into the study[26] (calculations shown in **Appendix D**). Setting a 90% CI and a margin of error of 0.1, we will require a minimum sample of **43** patients (8% of the target population) to fully enroll into the study in order to meet the set statistical constraints of achieving an expected proportion of 80% of participants reaching study completion (chosen as the primary feasibility criteria to determine the sample size). Therefore, target recruitment will aim for approximately 86 patients in the unlikely, worst-case scenario that only 50% of recruited patients will be able to provide consent forms, obtain PK sampling in the 12 month recruitment phase,

register onto CBDR and gain approval from their clinician of a regimen change. The target recruitment number of 86 patients corresponds with our feasibility criteria of recruiting a minimum of 15% of the eligible population to ensure that full study adherence can be met even in the event of dropout cases.

$$\textbf{Equation 1}: m = 1.645\sqrt{\hat{\boldsymbol{p}}(\mathbf{1}-\hat{\boldsymbol{p}})/\boldsymbol{n}}$$

The hemophilia community of patients and physician is considerably committed to clinical research and we are confident that we can not only achieve this enrolment number but also exceed it.

3.4 Site-Stratified Permuted Block Randomization and Allocation Concealment

Once written consent is obtained and the patient is fully enrolled into the study, the investigator will assign the patient a unique identification number. After the enrolment period closes (2 week duration period), the research coordinator will notify the patient as to which arm of the study the patient has been allocated in. The randomization mechanism proposed implements the stratified permuted block randomization technique to improve sampling variability. Each participating HTC will serve as a stratum and randomization will take place in each of these centers independently. Using Stats Direct Statistical Analysis Software, entering a block size of 0 allows the system to generate block sizes of 3, 4 and 6 at random. Random block sizes allow for allocation concealment and the small blocking sizes will allow the treatment groups to remain similar in size. Once the block size is randomly selected, a computer generator will randomly select one

of the arrangements from all of the permutations created by the block size and this strategy will be used to randomize the patients to either the control or intervention[27]. No study personnel or investigators will be allowed access to the block randomization code to ensure that the allocation remains concealed to the study investigator during the randomization process.

Procedure:

1) Stratify the population based on each HTC site that enrolls in the study
2) Stats Direct generator randomly selects a block size
3) List all possible arrangements by block size permutation
4) Random generator selects arrangement from list
5) Repeat for the next block until all patients at the site are randomized

   Repeat the entire process (steps 1-5) for the next site

3.5 Blinding

The treatment cannot be double blinded to the patient and provider once randomization has taken place due to the nature of the intervention. If allocated into the control group, the patient will continue to use the same factor concentrate and dosing regimen as before until the wait-list period ends. If allocated into the intervention arm, the clinician and patient will discuss the patient's preferences/goals with the treatment, take post-infusion samples at the suggested time and begin tailoring immediately. Blinding of the patient and provider would also be considered unethical in this situation since it would prevent administration of time-sensitive doses (i.e. pre-operation,

involvement in heavy-contact sports, etc.). The patient and provider would be aware of a regimen change and administration of a placebo is not possible as it would involve daily injections to blind the patient. In addition, a suitable placebo cannot be expected from the pharmaceutical industry since WAPPS-Hemo is expected to reduce CF costs as a result of optimizing regimen tailoring.

3.6 Data Collection

Data will be collected continuously throughout the study, initiating at time 0 once allocation has occurred. Two types of data will be collected for the purposes of the feasibility study: site-level data and patient-level data. Site level date will include the following information from all participating hemophilia treatment centers in the study:

3.6.1 Site-level data

- Number of severe hemophilia patients registered at the site
- Proportion of severe hemophilia patients already on the CBDR system
- Number of eligible patients (meet inclusion criteria to participate in the study)
- Number of eligible patients attempted to be recruited
- Number of rejections during 12 month recruitment phase and reason
- Number of consenting patients (must sign and return informed consent form) who undergo initial laboratory assessment (blood sampling), receive PopPK estimates and receive a regimen change
- Number of patients who are approved for the regimen change by their practitioner ("FULL ENROLLMENT")

- Number of patient dropouts at 1mo, 3mo, 6mo in both study arms and reason
- Average distance (km) from patient
- Number of local, surrounding HTC
- Number of clinicians, nurses and support staff trained with the WAPPS-Hemo tool

The following information will be collected at the patient level. This data information is routinely collected on the CBDR system and will not be required for collection if already registered on CBDR.

3.6.2 Patient-level data

3.6.2.1 Baseline

- Date of birth
- Gender
- Race/ethnicity
- Blood type
- Type of mutation (as classified as EAHAD)
- Weight
- Height
- Past # of bleed events
- Site of bleeds
- Typology of bleed
- Cause of bleed
- Severity of Hemophilia

- Baseline factor level
- Past and current treatment regimen (product, dosage, frequency)
- Inhibitor history: results of any factor mutation analysis, age at inhibitor development, highest Bethesda titer and date, last titer/date, family history of inhibiters
- Occupation and level of physical activity
- QoL
- Approximate acceptable time patient is willing to wait for PopPK tailoring
- Invasive surgery: # of procedures, data and time of execution

3.6.2.2 Follow-up (1mo, 3mo) end of study (6mo)

- Adherence (bleed logs)
- Current treatment regimen
- Number of bleed events
- Site of bleed events
- Typology of bleed events
- Cause of bleed
- Other complications
- Reason for dropout
- QoL

3.6.3 CBDR Data Collection

All patients enrolling into the proposed study are expected to register on CBDR and its counterparts if they have not already registered. CBDR will allow for the pilot study to run as a randomized registry trial. Conducting the study in this manner allows for the robustness and rigor of a randomized control trial with only a proportion of the expense, time and resources required for patient recruitment. Since CBDR already contains information from a large proportion of the Canadian population (**Figure 4**), information can be used to quickly target and recruit patients who meet the eligibility criteria across coordinating HTCs with only a fraction of the personnel. Since the registry already has captured vast amounts of data from a large sample of severe hemophilia patients in Canada, CBDR is a reputable registry of real-world patients that provide adequate representativeness when generalizing our findings. However, it should be noted that randomizing patients within the registry may introduce sampling bias since individuals may have high compliance and/or adherence rates.

3.6.4 MyCBDR Data Collection

MyCBDR will be used primarily for collection of data related to treatment regimen, time of post-infusion blood samples, reporting patient complications, bleed logs and recording factor infusion times and doses. The main purpose of the software is to serve as a controlled personal health record module with easy accessibility for the patient. WAPPS-Hemo PK charts will be made viewable on the MyCBDR database for patient viewing.

3.6.5 CBDR-RM Data Collection

CBDR-RM is a research oriented module designed to complement CBDR with the collection of information that is not on the system. CBDR-RM will be used to collect the majority of center-level data, reason for participant rejection from eligible patients, QoL and approximate willingness for wait-time to receive PopPK which may later be used for future studies.

3.6.6 Post-Infusion Blood Sampling Data Collection

For those enrolled in the study, post-infusion blood samples will be collected at a convenient time for the patient (**Table 5)**. A minimum of 2 samples will be needed to generate a PK-estimate and the time of post-infusion samples will be recorded with the patient's information in MyCBDR. The participating HTC will enter the patient's data into the WAPPS-Hemo software to generate an individualized dosing regimen. The dosing strategy will be dependent on 1) input of dose and frequency to obtain a pre-specified plasma factor level 2) input of frequency and pre-specified level to obtain a dosage amount 3) input of dose and pre-specified factor level to obtain frequency of dosing. The regimen will then be reviewed by the PK expert and subsequently approved by the hematologist before applied to the patient.

Factor Replacement	Number of Post-Infusion Samples	Time (hours)	Quality of PK-estimate
8	3	4, 24, 48	Optimal
	2	8, 30	Alternative

	1	24	Alternative
9	2	Anytime after 48h and 72h	Optimal
	2	Anytime after 48h OR 72h (4h apart)	Alternative
EHL FVIII (+24h)	3	28, 48, 72	Optimal
EHL FIX (+48h)	2	Anytime after 72h and 120h	Optimal

Table 5: Optimal and alternative times for post-infusion sampling required for individual PK parameter estimates. All times are indicative. Samples should not be taken prior to four hours once infused unless the patient is mostly interested in estimating peak plasma factor concentrations.

3.7 General Study Aspects

3.7.1 Process of Pharmacokinetic Tailoring

1) Each patient's treatment goals will be discussed with their treating physician to either: reduce weekly frequency of infusions, intensify treatment to reduce breakthrough bleeds and/or accommodate certain activities or to ensure the achievement of target plasma levels.
2) The goal(s) will be recorded and the treating physician will select the goal that is most appropriate for the patient's circumstances. The physician can either choose to use the calculator himself to further adjust for the patient or use the recommended regimen generated by the PK expert. The patient's PK results will be discussed by the treating physician with one of the experts to ensure full understanding of the recommended regimen. Dedicated training will be implemented by the steward to ensure that the physician is able to understand the calculator and demonstrations will be given to illustrate the tool's functions. Once

the selected treatment regimen has been identified and agreed upon both parties, the ad-hoc function will save the program. Infusion frequency, dose and pre-set threshold levels will be saved into the integrated CBDR system. For those on the waitlist, the new regimen will be proposed to the patient once the wait period is over to ensure adherence throughout the entire study period.

3.7.2 Monitoring Harm: Breakthrough Bleeds

In the case that the patient experiences breakthrough bleeds while allocated to the intervention arm, the provider will check to confirm patient adherence to the proposed regimen. If compliance is met, the provider will then check the patient's inhibitor levels, pre-infusion trough levels and 30-60 minute post-infusion recovery levels for assessment. If the patient is considered to be fully adherent to the program with no signs of inhibitors present, the infusion dosage and/or frequency will be increased accordingly as determined by the treating physician[8]. Patients will still be considered adherent if a change in regimen is proposed in the case of a lifestyle change/increased complications, as long as the PopPK calculator is being used to tailor the adjusted treatment. If the patient can no longer adhere to the suggested treatment schedule from the WAPPS-Hemo software, the patient will be considered to be dropping out from the study. Patients will be expected to record all breakthrough bleeds and/or additional complications in the MyCBDR application. Patients will also be followed up via telephone call and information tracking record at 1mo and 3mo follow up by the study investigator.

3.7.3 Outcome Measurement

3.7.3.1 Primary outcome measurement: Study feasibility

There are four characteristics required for the completion of any successful RCT: recruitment, enrolment, engagement and ability to retain. In order to reassure successful uptake of large-scale RCT, high rates of recruitment, enrolment, regimen adherence and full study completion are expected in the pilot trial.

1) Recruitment will be defined as the number of eligible participants willing to join the study divided by the total number within the target population.

$$\text{Recruitment} = \frac{n}{N} \qquad \text{Refusal} = \frac{N-n}{N}$$

n = participants eligible and willing to participate
N = total eligible sample approached

2) Although patients may express interest in participating in the study, several tasks must be met to ensure **full enrolment** into the study. Recruits will be expected to:
    - Sign an informed consent form
    - Complete the initial laboratory assessment and post-infusion blood samples to allow for a PK-estimate to be created. 24hr turnover time from the last post-infusion blood sample and a PK expert will assign a regimen based on the baseline data, PK estimate and patient goal.
    - Approval of the suggested regimen by the patient's clinician
    - Patient must register into CBDR database if approved

Enrolment will begin once the recruitment period closes and last 1-2 weeks.

$$\text{Enrolment} = \frac{n(conditional)\ baseline}{n}$$

n (conditional) = patients that have completed objectives to fully enroll into study

3) All RCTs want to ensure that the treatment effect (i.e. bleed count as a secondary outcome in this case) are a result of the actual treatment and not a result of the patient's adherence, in order to conclude a causal association. Low adherence in either arm has the potential to harm the strength of the study and is the reason patients must meet a tight inclusion criteria, register on CBDR and are followed up. Infusion logs will be recorded in MyCBDR and detail the time of infusion and dosage. Integrating WAPPS-Hemo with CBDR will allow the patient to view their recommended dose, PK chart and even provide reminders for the patient if requested. The patient will document all of their infused doses (time of infusion will be recorded) on the MyCBDR application and adherence will be confirmed by comparing registered infusions with the prescribed factor recommended by the WAPPS-Hemo regimen.

$$\text{Adherence} = \frac{Total\ Registered\ Infusions}{Total\ Recommended\ Infusions}$$

Regimen changes will be permitted at the discretion of the clinician, if it is required to suit the patient's goals and/or serious circumstances (i.e. surgery), however must still be Pop-PK tailored.

4) Full completion of the trial will be assessed after the six month study duration. The ability to retain 70% of those initially enrolled will deem running a full-scaled RCT feasible. The larger-scaled RCT will aim to assess the efficacy of WAPPS-Hemo in reducing bleeds and annual cost of treatment.

$$\text{Ability to retain} = \frac{n(conditional)final}{n(conditional)\ baseline}$$

With 70% of patients able to adhere with the regimen and complete the full study, the uptake of running a RCT will be proven feasible and will help expand the WAPPS-Hemo service to more patients and providers.

3.7.3.2 Potential Reasons for Dropouts

- Increased complications
- Low adherence/no longer willing to follow the prescribed regimen
- Death
- Relocation
- Inhibitor development
- Comorbidity development

3.7.3.3 Secondary outcome measurement: Bleeds + QoL

Bleed rates will be recorded in MyCBDR and expected to be reported by the patients. Typology, cause and site of bleed will all be recorded and ABR will be calculated as the number of bleeds divided by the follow-uptime for the patient.

$$\text{Annual Bleed Rate} = \frac{Total\ Number\ of\ Bleeds}{\#\ of\ days\ enrolled\ in\ study} * 365$$

- Joint bleeds
- Muscle bleeds
- Life-threatening bleeds (intracranial, gastrointestinal, neck/throat)
- Mucous membranes in the mouth, gums, nose, and genitourinary tract

Hemophilia-related Quality of Life

Haemo-QoL-A

1) Physical Health (score 0-100)
2) Feelings (score 0-100)
3) Self-perception (score 0-100)
4) Sports and Leisure (score 0-100)
5) Work and School (score 0-100)
6) Coping (score 0-100)
7) Treatment (score 0-100)
8) Future (score 0-100)
9) Family Planning (score 0-100)
10) Relationships/Partners (score 0-100)

Each domain is ranked from a scale of 0-100 by the patient with a score of 0 indicating highest quality of life.[22] Descriptive statistics will be used to assess the mean score and standard deviation for the pediatric and adult group and will be compared between the intervention and comparator group. Results will be considered hypothesis generating for

the main trial to assess if the intervention does more good than harm in the quality of life domain.

Nature of Objective	Outcome Measure	Criteria for Success	Method of Analysis
Primary Feasibility: To determine if it is feasible to conduct a large, multicenter RCT with the WAPPS-Hemo tool in severe Hemophilia patients who require prophylaxis and are living in Canada. Feasibility is defined by four outcomes below and all criteria must be met.			
To determine if the feasibility trial is able to recruit a specific proportion of the population. Assessing acceptability of the WAPPS-Hemo tool in the hemophilia community.	Patient Recruitment	Overall study ≥ 15%	Descriptive statistics: percentages and confidence intervals
To determine the percentage of recruited patients who are able to fully enroll in the study. Must complete the initial laboratory assessment, provide informed consent, undergo a PK profile generation and have regimen approved by their physician.	Patient Enrolment	Overall study ≥ 50%	Descriptive statistics: percentages and confidence intervals
To determine the percentage of patients that are considered fully adherent. Fully adherent = 70% or more of prescribed doses are taken and recorded.	Treatment Adherence	Overall study ≥ 70%	Descriptive statistics: percentages and confidence intervals
To determine the percentage of patients who complete the full 6-month study.	Study completion	Overall study ≥ 70%	Descriptive statistics: percentages and confidence intervals
Secondary Outcomes (Clinical)			
To assess the safety of the WAPPS-Hemo intervention and test for an association with ABR.	Annualized Bleed Rate	Hypothesis-generating	Mann-Whitney U Test + Negative Binomial Regression (full-scale RCT)
To establish the efficacy of the WAPPS-Hemo intervention.	Haemo-QoL/Haemo-QoL-A	Hypothesis-generating	Mann-Whitney U Test + Generalized Estimating Equation Method

Figure 10: Primary and secondary outcome measures and corresponding method of analyses.

3.7.3.4 Follow Up and End of Study Visit

1) QoL will be recorded in the CBDR-RM database and will be measured at baseline and study completion. Bleeds and infusion adherence will be recorded in the MyCBDR database. The study investigator will check to see if this data is being filled into the system at 4 wk, 12 wk, and 24 wk period. If many missing values are noticed in the system at the point of checkup, the study investigator will alert

the treating physician to notify their patient. In the case that there is an increase in bleeds and/or less compliance from the patient than expected, the patient will be contacted by the physician to determine the reason for low compliance or failure of prophylaxis to prevent bleeding.

2) Modification to treatment regimen. In the case that registered infusions on MyCBDR differ from the WAPPS-Hemo recommendation for the patient, the investigator will contact the treating physician to inquire if a regimen change has been proposed by them. All modifications will be recorded into CBDR and patients will still be considered adherent if the new regimen is PopPK tailored.

3.8 Alternative Study Design

The proposed randomized waitlist design serves as the optimal design to study the feasibility of a pilot trial and also prepare for a larger, full-scale study in the near future. The design essentially serves as a randomized control trial in Phase 1 but offers the control group the intervention at a later time. RCTs are known to produce the highest quality of evidence and our randomization technique ensures equal allocation into both arms while balancing known and unknown confounders. Conducting the full study prospectively allows the investigator to avoid studying variables that may have been affected over time (i.e. CF cost) and would be distributed unequally in a before-after study. The patient can also serve as their own control in this study design once they switch to PopPK tailoring. This will allow us to observe the intra- and inter- effect of the WAPPS-Hemo tool and generate hypotheses for future studies. The WAPPS-Hemo

calculator is a sophisticated tool but yet to be validated tool to support tailoring treatment in hemophilia. Proof of its feasibility to conduct an RCT will only help expand the service to more patients and reassure the community of the benefits associated with PopPK tailoring. Pilot studies should be designed to mimic the methodology of the main study and this design is plausible for a larger-scale RCT aimed to assess the efficacy and safety of WAPPS-Hemo. Powerful feasibility and efficacy studies will aid in implementation and expansion of the WAPPS-Hemo intervention on a global scale.

3.9.1 Data Analysis

Standard descriptive statistics will be used to summarize patients characteristics and baseline variables and include central tendency and variability for continuous variables and proportions for categorical variables. Descriptive statistics will be used to assess the feasibility of the pilot trial. Data will be reported both as percentages and absolute numbers.

$$\text{Recruitment} = \frac{n}{N} \geq 15\%$$

$$\text{Enrolment} = \frac{n(conditional)\ baseline}{n} \geq 50\%$$

$$\text{Adherence} = \frac{Total\ Registered\ Infusions}{Total\ Recommended\ Infusions} \geq 70\%$$

$$\text{Ability to retain} = \frac{n(conditional) final}{n(conditional)\ baseline} \geq 70\%$$

Bleed events and QoL will be reported for the purpose of the study but will be reported descriptively and used to generate hypothesis. The main purpose of the pilot trial is to test feasibility but the larger-scale RCT be used to assess the safety and efficacy of WAPPS-Hemo. Safety will be assessed in terms of annualized bleed rates and will be analyzed using a Mann-Whitney test and negative binomial regression. A negative binomial regression (NBR) is a more complex form of statistical analysis that considers other influential variables and reports incidence rate ratios. NBR is being proposed since the data is count data that is highly skewed as the variance in bleeds are much greater than the mean within the population. Subgroup analysis will also be used to assess for changes in treatment effects within the pediatric and adult population along with patients using the standard concentrate vs EHL factor concentrate, and test for interactions between these variables and ABR in the full-scale RCT. The overall median QoL measure between both treatment arms will be compared for statistically significant differences using the Mann-Whitney test with two independent samples. Additional testing will be done using the generalized estimating equation (GEE) method to measure the efficacy of WAPPS-Hemo, with adjustment for baseline covariates and confounders.

3.9.2 Data Monitoring Safety Board

The study investigator will follow-up with patient data and ensure it is continuously monitored for safety and feasibility purposes. The formation of a DMSB is being proposed for the purpose of this pilot study since the new regimen tailored by PopPK may pose issues with adherence due to variation from the standard schedule that

patients are used to dosing. The DMSB will be expected to contain methodologists, statisticians, patient representative, senior hematologists, WAPPS-Hemo developers and PK experts to meet at pre-determined interims. All members of the DMSB will be expected to hold no conflict of interest with the WAPPS-Hemo software or pharmaceutical sponsors. Participating HTCs will appoint a local healthcare staff who will also be in contact with the study investigator via monthly conference call to provide an update on the study's progress, enrollment rates and adverse events experienced by patients at their clinic. These results will be communicated to the DMSB at each interim.

3.9.3 Research Ethics

The WAPPS-Hemo tool offers patients an opportunity to optimize their regimen based on PopPK estimates. The tool itself has been rigorously designed, validated and well received by the hemophilia community in previous versions. The current PopPK model has comprehensive, underlying data from the pharmaceutical industry and peer-reviewed literature about patient and product information. The software is already being used for tailoring in more than 2000 real-world patients around the world since its establishment in 2015. The WAPPS-Hemo intervention is known to provide the merit of personalization in their dosing and both arms of the study are being offered the opportunity to join the network of users. The intervention requires the patient to use the same factor product that they have been using throughout their life with the exception of individualized dosing being more tailored to their aims. All CF suggested by WAPPS-Hemo are licensed by the FDA and easily made available to patients by the industry.

Since hemophilia is a chronic condition, patients would be using the product regardless if enrolled into the study. The new recommendation must undergo review from two experts in order to be approved – the WAPPS-Hemo PK expert and treating physician. In the worst-case scenario that PopPK tailoring increases BT bleeds, the provider can always terminate PK-tailoring and reintroduce the prior regimen used in the pre-WAPPS phase. Patients can also choose to withdraw from the study at any point in time.

The randomization technique to determine who will receive the intervention first is an aspect of the waitlist design and is both fair and ethical for the study. All patients will be receiving the intervention (WAPPS-Hemo tailoring) within a reasonable time. If demonstration of feasibility to run an RCT is unable to be shown, the tool will still be made available to waitlist patients and the public for use at their own discretion. The full benefits of PopPK tailoring are not fully known and clinical equipoise exists between the two treatments. The ABR is relatively low in severe, Canadian hemophilia patients on prophylaxis to begin with as the literature reports a median of 6-8 bleeds per year per patient. The 6 month waitlist timeframe proposed is a short and reasonable wait period, especially for patients who will still be protected from bleeds by continuous prophylaxis by TBW dosing.

This pilot study poses minimal risk patients are expected to adhere to the same treatment product, however with implementation of a new regimen. Recruitment will be voluntary and refusal to participate will not affect the patient's level of care. Other risks that this study pose may involve the chance of pain, hematoma formation, bruising or infection at the site of venipuncture during blood sampling required for the study. This

risk is minimal since blood sampling will be conducted at the respective HTC under medical supervision by trained personnel during a schedule visit. The healthcare staff will apply firm pressure to the location of the vein for a minimum of 10 minutes to reduce the chance of experiencing a bleed during the venipuncture procedure. No more than 2mL/kg will be drawn within a 24hr period and restricted to 4mL/kg in a 30 day period, as per guidelines intended for clinical research requiring blood samples.[24] Standard precautions will be taken to reduce the chance of hypersensitivity and allergic reactions occurring. All prepared consent forms and protocols will be submitted for approval by each participating HTC before recruitment at the site begins. In our opinion, the potential benefit of conducting the pilot study outweighs the minimal risk posed by the intervention.

3.9.4 Informed Consent

Written consent will be collected from all enrolled patients. For patients under the legal age of 18, consent from a legal guardian and/or parent will be required in addition. An interpreter will be utilized to consent non-English speaking patients.

3.9.5. Protocol Amendments

The progress of the study will be discussed in monthly conference calls with the PI and staff at each participating HTC. Any serious safety or feasibility concerns will be up for discussion during the conference call and patients will be notified of any serious changes to the protocol. Modifications to any aspect of the study including eligibility

criteria, outcome measurement and data analysis will be communicated to all HTC co-investigators, patients, trial registries and research ethics boards.

3.9.6 Confidentiality

Participation records will be maintained and kept confidential by law. Each patient will be assigned an ID number and will be identified by their study ID throughout the study. Each participating HTC will keep a record base of the ID that pertains to each individual patient and this will be secured in a protected database. In order to preserve patient confidentiality, personal information of enrolled patients will be collected and stored into the secure CBDR database. CBDR is hosted at the Health Research Unit at McMaster and during the full-scale RCT, the database will be anonymized for data analysis between the intervention and control. All individuals who require access to the database will be provided with a username and password for its access. The identity of subjects will not be revealed in any study report or publication.

3.9.7 Dissemination

Feasibility results will be discussed at local, national and international conferences with the aim to improve awareness of the WAPPS-Hemo tool. The study team will also be sure to publish the results and the protocol of the pilot trial into peer-reviewed journals and seek to promote WAPPS-Hemo uptake and implementation for its growing demand within the field. Word of the WAPPS-Hemo tool and its merits is quickly spreading in the hemophilia community. Every few months, Dr. Alfonso Iorio is invited to national and international conference to present his PopPK calculator and is allowing for large

exposure to WAPPS-Hemo, demonstrated by substantial amounts of patient registrations since its launch in July 2015.

3.9.8 Associated Benefits of WAPPS-Hemo and Impact of the Study

The availability of a PopPK Bayesian calculator that is user friendly and requires a minimal draw of blood samples represents a significant advancement in the hemophilia community. Less sampling and friendly-user application interface of the tool now makes it feasible for use in everyday practice. In addition, WAPPS-Hemo has successfully been integrated with the CBDR, which contains rich data from a large number of the total hemophilia population in its database already. The increasing popularity of the tool demonstrates the high demand and acceptance from the hemophilia community with a 250% increase in registered users over the last twelve months. Patients can expect to receive the benefit of personalizing their care and contributing to the improvement of hemophilia care by their participation in the study. By adopting the tool, clinicians will also avoid complex calculations usually required for PK-tailored dosing strategies. No financial compensation will be delivered to participants or investigators as all patients are already interested in switching their regimen towards a PopPK approach and will be granted access to the tool within the timeframe of the study. Financial remuneration will be compensated to institutions for costs associated with the study such as IRB submission fees.

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Appendix A: PRE- AND POST- INFUSION DATA COLLECTION FORMS

Dear patient,
Thank you for participating in the feasibility trial of the WAPPS-Hemo study. We will be able to generate your PK and estimate the factor half-life once you provide the following information. A minimum of 2 post-infusion blood samples are required for PK generation, however 3 samples are recommended for optimal PK generation.

PRE-INFUSION DATA
Date: _____
Time: ___ HR _____ MIN
Factor Product (Label): _____
IU Label on Product Vial: _____ IU

POST-INFUSION DATA

Approximate times during the day to return to the lab for post-infusion blood sampling for optimal PK generation (Clinic hours: 8AM-9PM):

Factor VIII Day 1	Sample Draw 1 (+4h)	Sample Draw 2 (+24h)	Sample Draw 3 (+48h)
Before 11AM	3PM-6PM (Day 1)	8AM-11AM (Day 2)	8AM-11AM (Day 3)
11AM-5PM	3PM-9PM (Day 1)	11AM-5PM (Day 2)	11AM-5PM (Day 3)
6PM-9PM	8 AM (Day 2)	6PM-PM (Day 2)	6PM-9PM (Day 3)

Type of Assay: _____
Patient Weight, Height, Age: _____, _____, _____
Blood Sample 1: Date _____, Time_____, Concentration in Plasma _____ %
Blood Sample 2: Date _____, Time_____, Concentration in Plasma _____ %
Blood Sample 3: Date _____, Time_____, Concentration in Plasma _____ %

Appendix B: HC Personnel Background Questionnaire (to be completed by personnel being trained by the steward to use WAPPS-Hemo calculator)

1. What is your profession at the HTC?
   A) Administrator
   B) Nurse
   C) Hematologist/Primary Physician
   D) Other:

2. Do you have experience using a PK calculator?
   A) Yes (how long?)
   B) No

3. Do you have experience using WAPPS-Hemo specifically?
   A) Yes
   B) No

4. Do you require training from the WAPPS-Hemo steward to understand the tool and its function?
   A) Yes
   B) No

Appendix C: Minimal Blood Draw Guidelines for Clinical Research Purposes[24]

MAXIMUM ALLOWABLE TOTAL BLOOD DRAW VOLUMES (CLINICAL + RESEARCH) CONSIDERED MINIMAL RISK (adapted from (1))				
Body Weight (Kg)	**Body Weight (lbs)**	**Total blood volume (mL)**	**Maximum allowable volume (mL) in one blood draw (= 2.5% of TBV)**	**Maximum allowable volume (mL) drawn over a 30 day period (= 5% of TBV) for outpatients only *note: must occur no more than 3 consecutive months**
3	6.6	240	6	12
4	8.8	320	8	16
5	11	400	10	20
6	13.2	480	12	24
7	15.4	560	14	28
8	17.6	640	16	32
9	19.8	720	18	36
10	22	800	20	40
11-15	24-33	880-1200	22-30	44-60
16-20	35-44	1280-1600	32-40	64-80
21-25	46-55	1680-2000	42-50	64-100
26-30	57-66	2080-2400	52-60	104-120
31-35	68-77	2480-2800	62-70	124-140
36-40	79-88	2880-3200	72-80	144-160
41-45	90-99	3280-3600	82-90	164-180
46-50	101-110	3680-4000	92-100	184-200
51-55	112-121	4080-4400	102-110	204-220
56-60	123-132	4480-4800	112-120	224-240
61-65	134-143	4880-5200	122-130	244-260
68-70	145-154	5280-5600	132-140	264-280
71-75	156-185	5680-6000	142-150	284-300
76-80	167-176	6080-6400	152-160	304-360
81-85	178-187	6480-6800	162-170	324-340
86-90	189-198	6880-7200	172-180	344-360
91-95	200-209	7280-7600	182-190	364-380
96-100	211-220	7680-8000	192-200	384-400

Appendix D: Feasibility Sample Calculations + Confidence Intervals

<u>Equation 1</u>: m = 1.645 ($\sqrt{\frac{(0.8*(1-0.8))}{n}}$) → n = 43 enrolled → Recruitment goal: 86 patients

(Worst case scenario that only 50% of patients who are recruited, fully enroll into study)

m= 0.1 margin of error
1.645 = 90% CI
0.8 = proportion *expected* to complete the 6-month study (70% is lower margin of expectation)
n = ? sample size

Confidence Intervals (90%)

1) **Recruit (15%)**

   m = 1.645 ($\sqrt{\frac{(0.15*0.85)}{86}}$) = 6.3% (8.7% - 21.3%)

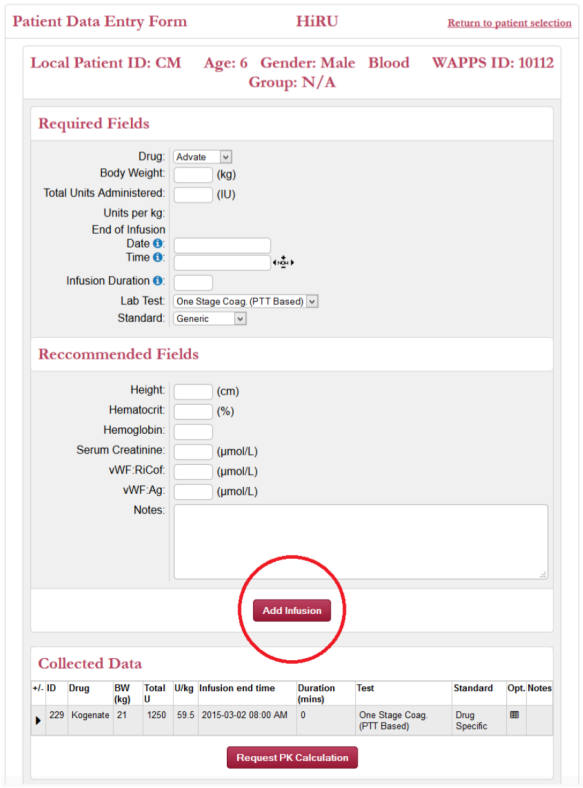
2) **Enroll (50%)**

   m = 1.645 ($\sqrt{\frac{(0.5*0.5)}{86}}$) = 8.9% (41.1% - 58.9%)

3) **Adherence/Study Completion (70%)**

   m = 1.645 ($\sqrt{\frac{(0.7*0.3)}{86}}$) = 8.1% (61.9% - 78.9%)

Appendix E: WAPPS-Hemo Patient Data Entry Form + Input Variables



Variable	Description	Units
Required variables		
CID	Patient identification number	Positive integer
OCC	Dose occasion	Positive integer
TIMEH	Time for each concentration measurement from start of bolus	Hours or fraction of hours (minimum of 4 decimal places)
AMT	Total dose	IU[a]
RATE	Rate of entry of drug: AMT/TIMEH	IU/h
DV	Plasma concentration of valid observation or BLQ[b]	IU/L
AGE	Age	Positive integer, years
BW	Weight	Positive integer, kilograms
EVID	Event identification variable	Positive integer (0=valid observation, 1= dose, 3=BLQ observation)
DOSE	AMT/BW	Positive number, IU/kg
PREDOSE	Plasma concentration at time of start of bolus	Zero or positive integer if measured, -1 if not measured (IU/L)
MDV5	Missing dependent variable	0 = valid observation; 1 = dose or BLQ observation; MDV5 = MDV when no BLQ
BASELINE	Endogenous plasma concentration	Positive integer if known, -1 if not known, IU/L
BLQ	Below limit of quantification	≤ 0 = non BLQ measurement, positive integer = BLQ value, IU/L
MDV3	Missing dependent variable	0 = valid observation or BLQ; 1 = dose; MDV3 = MDV when BLQ is present
Optional covariates		
HT	Height	Positive integer, cm[c]
VWF	von Willebrand factor	Percentage
RACE	Race	Positive integer (1=White, 2=Black, 3=…)
BTYPE	Blood type	Positive integer (1=A, 2=B, 3=AB, 4=O)
HCT	Hematocrit	Percentage

[a]IU: international unit.
[b]BLQ: below the limit of quantification.
[c]cm: centimeter.