McMaster PopPK User Manual

July 2020

Version 2.1

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1. Introduction and Intended Use

Welcome to McMaster PopPK (MacPopPK). MacPopPK is a centralized, dedicated, actively moderated database that allows participating hemophilia centres to securely input factor VIII/IX plasma levels from sparse samples and returns individual pharmacokinetic estimates (PK). These estimates are generated by an automated proprietary population PK engine and are then reviewed manually for a final validation.

The WAPPS-Hemo engine produces an individual PK profile for your patient in the form of an interactive report page that includes the data you provided, the estimated half-life, and the time to 1%, 2%, and 5% levels, respectively. You can save the report as a PDF or you can print it and share it with your patient. Furthermore, MacPopPK also offers you a clinical calculator page, which when used with the PK profile of each patient, helps you build an optimized individualized treatment regimen. It will produce a graph and calculate the weekly dose, the peak, the trough(s), and the time spent above 1%, 3%, and 15%. You can choose to have a prepared treatment regimen activated for your patient for use with the companion **myWAPPS** mobile app or other available mobile apps currently available. The patients can record their infusions and see their predicted concentrations while MacPopPK collects and makes available the patients' treatment logs.

The PK estimates we generate are highly accurate based on extensive and continued modeling of samples, currently in excess of 10,000; however, if the information inputted is inaccurate or sub-optimal, the prediction may be imprecise. We perform a manual check of all input data and all PK estimates, there are no error-free systems. For this reason, we strongly recommend that you use your own judgement when determining the appropriateness of the estimates. Ultimately, the MD or other health care professional is responsible for the use of McMaster PopPK and the information it reports. Should you have any doubt, please contact us at mcmasterpoppk@mcmasterhkr.com for further information or through our website at mcmasterpoppk.org.

2. Intended User

The intended users of the software are hemophilia specialists (MDs or other health care professionals [HCPs] under the supervision of an MD). The software will assist MDs and HCPs estimate PK data and help them prepare optimized treatment plans. The software is not intended for use by generalists or non-HCPs who lack the expertise in treating hemophilia, nor is it intended for use directly by patients or pharmaceutical companies.

3. List of Resources

WAPPS·HEMO	**WAPPS-Hemo**	[Visit Online Here](#)
WAPPS·NEWS	**WAPPS-Hemo News Site**	[Visit Online Here](#)
(Twitter)	**Follow us Twitter** *Subscribe to receive notification about new releases*	[Visit Online Here](#)
YouTube	**WAPPS-Hemo on YouTube** *Subscribe to receive notification about new releases*	[Visit Online Here](#)
myWAPPS	**myWAPPS** *the **WAPPS-Hemo** powered personal PK monitor for hemophilia patients.*	Download on the App Store Now available in the Apple Store GET IT ON Google Play Now available in Google Play
(envelope)	*email your questions and comments to us*	mcmasterpoppk@mcmasterhkr.com

4. Information Collected by MacPopPK

To obtain PK estimates from patients, you will provide:

(1) a patient identifier of your choice - This can be a code, sensible patient data (first name, last name), or a mix of both. We are approved for storing patient-sensible data and will de-identify them for modelling or research.

(2) the patient's date of birth - The precise date of birth provides more precise estimates; however, setting the day to the first of the month is acceptable if your local regulators suggest you do so.

(3) the patient baseline factor level (please check the **below threshold box** if the baseline level is below the limit of quantification at your center) - Most commonly, severe patients are reported as <0.01 IU/mL (the system will also show you the corresponding < 1%).

(4) a checkbox stating that you have informed your patient that you are inputting your patient's data into WAPPS-Hemo - Data uses are detailed in the **Terms of Use** and **Privacy Policy** https://www.mcmasterpoppk.org/UserAgreement.aspx

(5) It is strongly recommended that you provide the blood group for hemophilia A patients as this is a strong predictor for the individual's PK.

(6) For specific infusion and measurement data (PK study), you will provide:
- data on the infusion: concentrate name, total dose administered, body weight (kg only), height (cm only), infusion day, infusion time, and duration (we will assume it to be 5 minutes unless entered otherwise)
- any number of factor activity levels measured in your routine laboratory.

Please note: You can provide any number of samples, and we will do our best to produce an estimate; however, we recommend the following:

1) For Factor VIII
    a. Pre-dose measurement, then
    b. Option (1) Best: 2-4 hours, 24 +/- 4 hours, and 48 +/-6 hours.
    c. Option (2): 8 +/-2 hours, 30 +/- 4 hours.
    d. Option (3): 24 +/- 4 hours only.
        i. All times are indicative (example: 24 hours can be anytime between 18 and 30 hours). Please avoid samples taken before 4 hours unless you are primarily interested in a peak concentration estimate.
        ii. Single data points do not always allow enough precision in the estimation; therefore, the clinical calculator may not be activated for single-measurement PK studies.
        iii. When pre-dose is not available, please ensure you provide the requested information about the time and dose of the previous dose and/or the current prophylaxis regimen for the patient.
2) For Factor IX
    a. Pre-dose measurement, then
    b. Option (1) Best: Any Time on day 2 and 3.
    c. Option (2): Two samples on any of day 2 or 3 that are optimally 4 or more hours apart.
3) Long-Acting Concentrates
    a. As above, but adding a time point at 60-84 hours for factor VIII; 2-14 days for factor IX.
        i. If simpler, the time at 60-84 hours can substitute for the one at 48 (Factor VIII) and the late sample can substitute for day 3 (Factor IX).
b) The patient does not need to perform a washout and they can continue their standard prophylaxis regimen. Without a washout, we strongly recommend a pre-infusion (pre-dose) measurement be provided.
c) You can ask to estimate PK using data obtained after different infusions. You are requested to register the infusions separately, and then use the **merge** function on the website. Secondary Infusions will provide additional measurement points for the merged infusion. To be eligible for merging, Secondary Infusions must meet the following criteria:
    (1) Use the same Factor Concentrate as the Primary Infusion
    (2) Be within 48 months of the Primary Infusion if the patient is 16 or older
    (3) Be within 18 months of the Primary Infusion if the patient is younger than 16
    (4) IU/kg must be within 15% of the Primary Infusion

5. Safety Information

This section contains important safety information. You must read and understand all warnings, cautions, precautions, and the user manual before using McMaster PopPK.

Cautions

The individual pharmacokinetic reports and any other treatment regimen simulation or information provided through this website are the best estimates obtained based on MacPopPK population models and the data you provide.

Errors or imprecision in the data provided and/or the models and/or the estimation process cannot be completely excluded. Therefore, any use of the materials and/or website requires your own clinical judgment and is your sole responsibility.

If you share any materials with your patients on paper or via any dedicated website or mobile app, it is your sole responsibility to ensure your patients (or their legal custodians, where applicable) understand the materials provided and their limitations.

6. Basic Functions

6.1 Adding a Patient

Select the **Patients** tab from menu.

HOME	PATIENTS	MY CENTRE ⌄	DOCUMENTS ⌄	CONTACT US	CENTRE ADMIN ⌄

Click on the **Add Patient** button (far right of the screen)

Patient Search ⓘ [　　　　　] 🔍 Clear　Page Size [10] ⌄　　　　　　　　　　　　　Add Patient

You are presented the following frame:

New Patient Entry ⊗

Required Fields

Sex

[Male] ⌄

Date of Birth ⓘ　　　　　　　　　Age

[YYYY-MM-DD] 📅　　　　[N/A]

Patient ID ⓘ

[　　　　　　　　　　　　　　　　　　　]

Patient Baseline (IU/mL) ⓘ

[ⓘ | ? | = | < | 　　　　　 | IU/mL]　[　　　　N/A | %]

Complete the Required Fields.

Note: The Patient Baseline is the plasma factor activity level measured in absence of treatment (the one used to assign the severity of hemophilia). If the patient level is below the limit of detection of the laboratory test (usually 0.01 IU/mL or 1%), then input 0.01 (or the local limit of detection) and select the **<** symbol (see the example below).

Patient Baseline (IU/mL) ⓘ

| ⓘ | ? | = | < | | IU/mL | | | N/A | % |

Optional Fields

Patient Email ⓘ

[   ]

Blood Group ⓘ

[⌄]

☐ Positive History of Inhibitors

Cancel   **Save**

Blood Group is an optional field but consider providing it as often as you can. Reporting the patients' blood group is very important, particularly when calculating the Factor VIII PK.

Click **Save** when you are completed.

6.2 Retrieving a Patient

Select the **Patients** tab from menu.

HOME	PATIENTS	MY CENTRE ⌄	DOCUMENTS ⌄	CONTACT US	CENTRE ADMIN ⌄
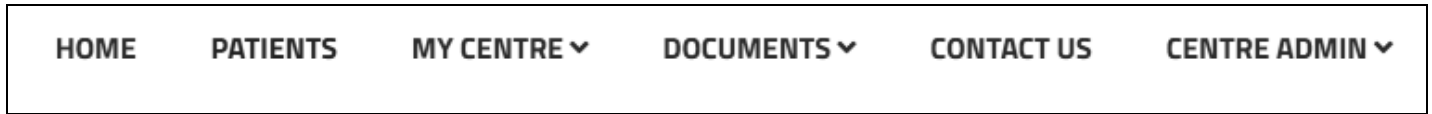
Patient Search ⓘ [ ] 🔍 Clear Page Size [10 ⌄] Add Patient

You can search for a patient by:

a) using the partial or full local patient ID.

b) manually navigating through numbered pages of local patient IDs, which can be ordered by any column by clicking on its header.

Patient Search ⓘ [ ] 🔍 Clear Page Size [10 ⌄] Add Patient

ID	Patient ID ⇕	Age ⇕	Sex ⇕	Blood Group ⇕	Patient Baseline (IU/mL) ⇕	Treatment Plan	App	Tools
31512	bobby35	37	M	N/A	< 0.01	Drug, 2000 every 2 day(s)	ꜰ	👤⁄👤×
31513	bobby36	37	M	N/A	< 0.01	Advate, 2000 every 1 day(s)	ꜰ	👤⁄👤×
31514	bobby37	38	M	N/A	< 0.01	Drug, 2000 every 2 day(s)	ꜰ	👤⁄👤×
31515	bobby38	39	M	N/A	< 0.01	Drug, 2000 every 2 day(s)	ꜰ	👤⁄👤×
31445	bobby39	39	M	N/A	< 0.01	Elocta, 2000 Mo, Th	ꜰ	👤⁄👤×
31584	bobby40	32	F	N/A	< 0.01			👤⁄👤×
31590	Bobby41	49	M	N/A	< 0.01	Eloctate, 2000 every 3 day(s)	ꜰ	👤⁄👤×
31591	Bobby42	49	M	N/A	< 0.01	Advate, 2000 Mo, We, Fr	ꜰ	👤⁄👤×
31592	Bobby43	48	M	N/A	< 0.01	Elocta, 3000 every 2 day(s)	ꜰ	👤⁄👤×
31593	Bobby44	48	M	N/A	< 0.01	Kogenate, 1500 Tu, Th, Su	ꜰ	👤⁄👤×

1 2 3 **4** 5 6 7 Add Patient

6.3   Editing a Patient

Retrieve the patient info you want to edit (see **Finding a Patient**). Click on the blue icon on the left under **Tools** (hovering over the option to **Edit** will appear).

ID	Patient ID ⬍	Age ⬍	Sex ⬍	Blood Group ⬍	Patient Baseline (IU/mL) ⬍	Treatment Plan	App	Tools
31625	TestPatient	58	M	N/A	< 0.01			👤✎ 👤✕

The screen below appears:

You cannot edit Sex or Date of Birth. If you make an error in these fields, you must delete the patient record and create a new record. *When deleting a patient record, all PK studies recorded for the patient will be lost.

Click on **Save** when you are completed.

6.4   Deleting a Patient

Retrieve the patient info you want to edit (see **Finding a Patient**). Click on the red icon on the right under Tools (hovering over the option to **Delete** will appear).

ID	Patient ID ⇕	Age ⇕	Sex ⇕	Blood Group ⇕	Patient Baseline (IU/mL) ⇕	Treatment Plan	App	Tools
31625	TestPatient	58	M	N/A	< 0.01			👤✎ 👤✕

The following warning appears:

Delete Patient Warning

Warning: Deleting this patient will remove all associated data, including PK estimates, infusion details and data collected via myWAPPS, if activated.

This action cannot be reversed. Are you sure you wish to delete this patient?

Cancel   Delete

Click on **Delete**.

6.5 Adding a PK Study

6.5.1 Adding the PK Study information

On the patient list page, click on the local **Patient ID** to open the patient record.

The following screen appears:

Click on **Add a PK Study**. The following screen will appear:

PK Study Data

Required Fields

Factor Concentrate

Please Select	⌄

Missing Factor Concentrate?

Assay Type

Chromogenic	⌄

Calibrator

Drug Specific	⌄

Height

	cm

Body Weight

	kg

Total Units Administered

	IU

Units per kg

	IU/kg

End of infusion

Date ⓘ

YYYY-MM-DD	📅

Time ⓘ

	🕐

Infusion Duration ⓘ

	min

Optional Fields

Hematocrit

	%

Hemoglobin (g/L)

	g/L

Serum Creatinine

	μmol/L

CrCl

	mL/min

Cancel   Save Infusion

You must complete all the fields.

Please note that the dropdown menu presents the concentrates active for your centre. If the concentrate you want is not in the list, click on **Missing Factor Concentrate?** A short video explains how to request having a concentrate added.

You must indicate the **Infusion Duration**. The average infusion duration is 3-5 minutes and can be entered as 0 if they <u>are</u> less than 3 minutes. If you leave the field empty, we will assume it is 5 minutes.

Among the optional fields, please provide vWF data, if available.

Click on **Save Infusion** when you are complete.

6.5.2 Adding the measurements

After the infusion information is entered, this screen will appear:

Please note that if you don't see the above screen, click on the **+/-** field to the left of the **PK Estimate** to make it appear (see below):

To proceed, click on the **Add Measurement** button. The following screen will appear:

This information must be provided for each measurement you have available for the PK study. If you have a *pre-dose* measurement, check the **Pre-dose** field. If the measurement is reported by the lab as < [value] (example: <0.01 IU/mL), please add the value and click on the **<** sign.

Please note that the measurements must be entered as IU/mL. The system translates the measurement as an approximate % after you click on **Save** (see screen below). You can use the **Notes** field to provide any information about that specific measurement.

When complete click **Save**
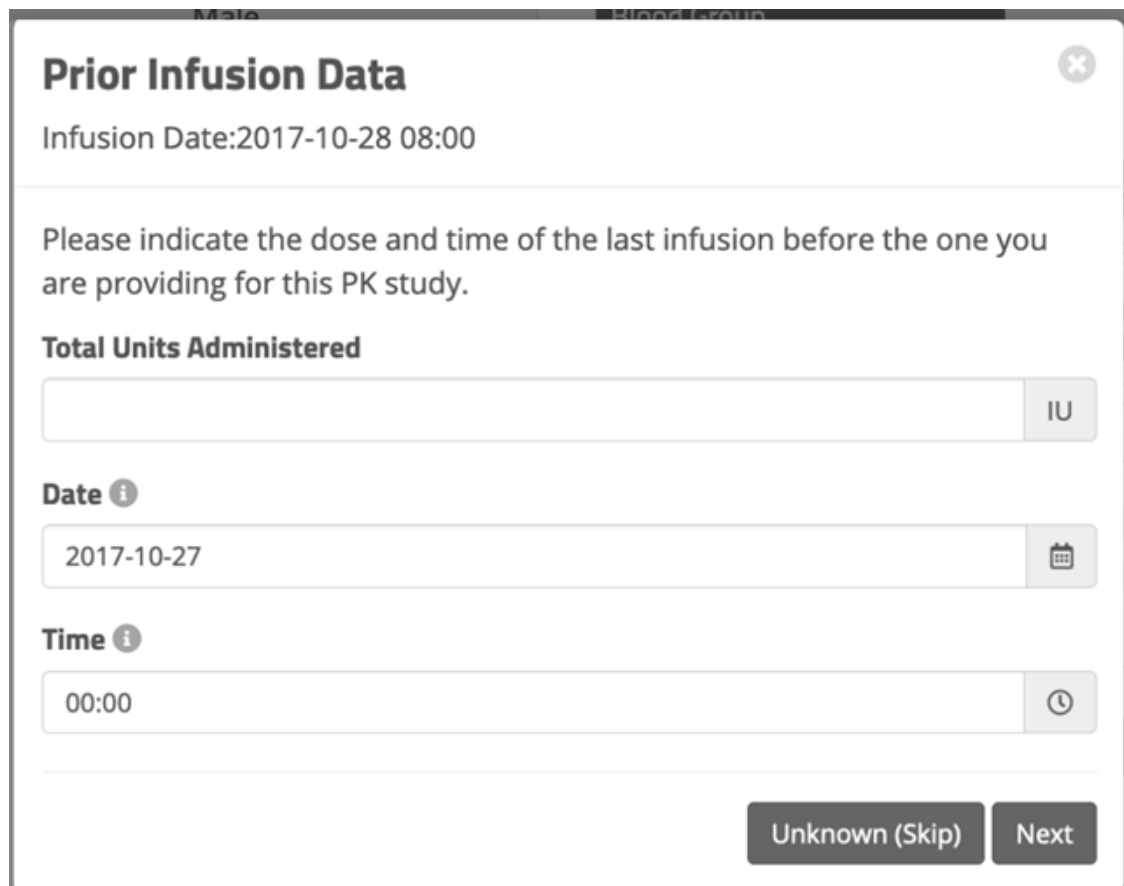
6.5.3 Adding the Previous Dose/Current Regimen Information

After all the measurements are entered, click on **Request PK**. Before being submitted, additional information will be requested (depending on the data provided as part of the PK study).

In most cases, the following screen will appear:

Provide the information you have. This is very important, particularly when a pre-dose measurement was not provided. Complete the information to the best of your knowledge (you also may need to rely on the recollection of your patient). We have verified that imprecision measurable in hours has little impact when the infusion is more than 24 hours before.

If you don't have the information, click on **Unknown (Skip)**

In most cases, you then will see the two following screens:

Treatment Plan

Infusion Date:2015-08-06 11:02

Is this prophylaxis treatment plan (stored in WAPPS and shown below) still the patient's current treatment plan?

Dose (IU)	Interval (Days)	Trough (IU/mL)	Peak (IU/mL)
3000	2.5	2.369	0.027

○ Yes
○ No

Unknown (Skip) Previous Next

Treatment Plan

Infusion Date:2017-10-28 08:00

Please input the patient treatment plan.

Infusion Interval

Regular

Days

0

Dose
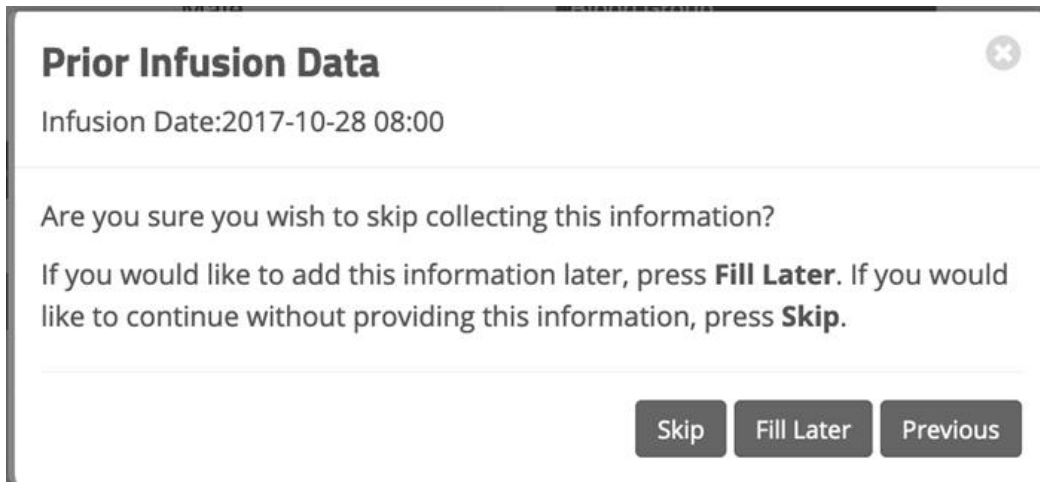
Total Units

Unknown (Skip) Previous Next

Please provide the information about the patient's current prophylaxis regimen (example: 3000 units every 3 days, or 2000 units on Monday and 3000 on Thursday, as in the following examples).

Current prophylaxis example 1:

Current prophylaxis example 2:

If you don't have the information available, click on **Unknown (Skip)**

Pressing **Unknown (Skip)** will take you to this screen where a decision must be made:
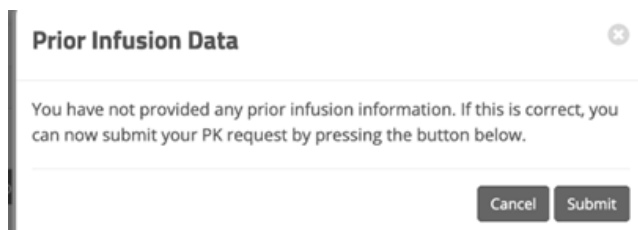

If you would like to add the information later, press **Fill Later.** If you would like to continue without providing this information, press **Skip.** You can return to the previous screen by pressing **Previous** and provide the data immediately.
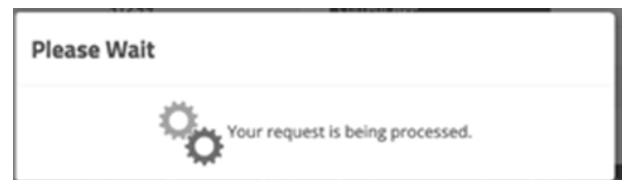
6.5.4 Requesting the PK estimate

After providing (or not providing) the previous infusion/current regimen information, **Submit** the PK request (screen below), or the PK request will be submitted automatically for estimation.
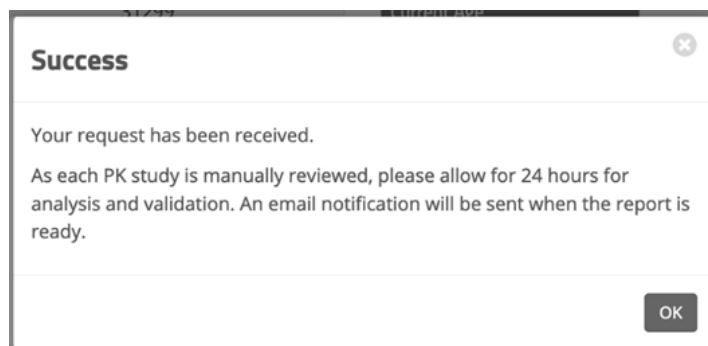

You will receive a notice that your request has been sent.

After your request is received, a confirmation is sent advising that it may take up to 24 hours to receive your PK report.

Click on **OK.**

The analysis and validation are usually completed within 24 hours and an email notification will be sent when the results are available. In the unlikely event your report is delayed, please submit a reminder with the **Send Reminder** function indicated in the screen below.

PK Studies

+/-	PK Estimate ⓘ	ID	Factor Concentrate	Age	Height (cm)	BW (kg)	LBW (kg)	Tot IU	IU/kg	End of infusion	Supplemental Info	Tools
⊖	Send Reminder	36517	Advate ⓘ	52	170	75	57	2000	26.7	2017-10-28 08:00	⊞	🔓 ▣ ✕

Sampling Date Time ⓘ	Time Elapsed (hh:mm) ⓘ	Pre-dose ⓘ	Plasma Factor Concentration ⓘ	Notes	Tools
2017-10-28 08:20	0:20		0.400 IU/mL (40.0%)		
2017-10-29 08:00	24:00		0.040 IU/mL (4.0%)		

Add an infusion   Add a Validation Set   Merge Infusions

6.6 Interpreting/Printing/Downloading a PK Profile

When a PK profile is released, an email with a link is sent to you. Clicking on the link takes you directly to the PK profile page. You can also reach the page by clicking on the **patient ID** on the list and then on **View** on the left of the PK study row (see below):

PK Studies

+/-	PK Estimate ⓘ	ID	Factor Concentrate	Age	Height (cm)	BW (kg)	LBW (kg)	Tot IU	IU/kg	End of infusion	Supplemental Info	Tools
⊕	View	30940	Humate P ⓘ	7	124	28	24	2048	73.1	2011-01-05 12:57	⊞ 💬	🔓 ▣ ✕
⊕	View	36512	Humate P ⓘ	7	124	28	22	2048	73.1	2011-01-05 12:57	⊞ 💬	🔓 ▣ ✕

Add an infusion   Add a Validation Set   Merge Infusions

The following screen will then appear:

Result Review
Hamilton Health Sciences

CONCENTRATE: Humate P
ASSAY TYPE: One Stage Coag. (PTT Based)
CALIBRATOR: Generic

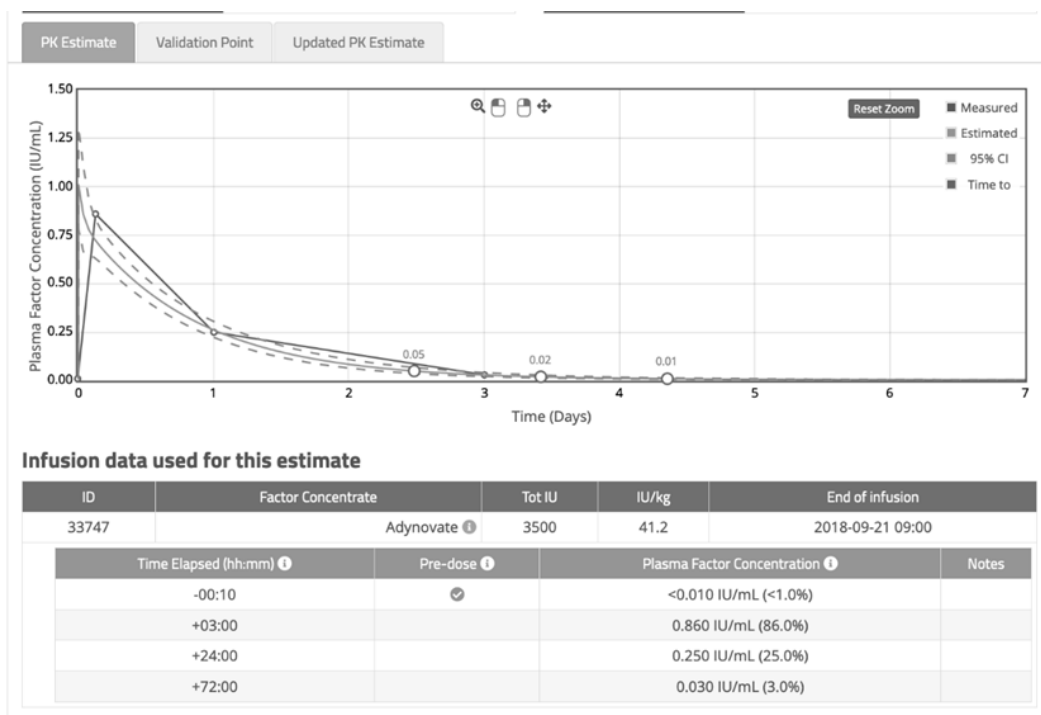← Return to patient   ⏱ Clinical Calculator   ⬇ Download as PDF

Patient Data

ID	10139	Sex	M
Patient ID	CL	Patient Baseline (IU/mL)	< 0.010
Infusion ID	30940	Blood Group	O
Current Age	16	vWF:RiCof (IU/mL)	0.00
Age at PK Study	7	vWF:Ag (IU/mL)	0.00
Body Weight (kg)	28.0	Hematocrit (IU/ml)	0.00
Height (cm)	124.0	Hemoglobin (IU/ml)	0.00
Lean Body Weight (kg)	24.46	Serum Creatinine (µmol/L)	0.00

PK Estimate   Validation Point   Updated PK Estimate

The **PK Studies** report table is populated with patient information that you provided. The **Result Review** table below is an example of the program calculated **PK Estimate**.

PK Estimate   Validation Point   Updated PK Estimate

Plasma Factor Concentration (IU/mL) vs Time (Days)

Reset Zoom ■ Measured ■ Estimated ■ 95% CI ■ Time to

Infusion data used for this estimate

ID	Factor Concentrate		Tot IU	IU/kg	End of infusion
33747		Adynovate ⓘ	3500	41.2	2018-09-21 09:00

Time Elapsed (hh:mm) ⓘ	Pre-dose ⓘ	Plasma Factor Concentration ⓘ	Notes
-00:10	✓	<0.010 IU/mL (<1.0%)	
+03:00		0.860 IU/mL (86.0%)	
+24:00		0.250 IU/mL (25.0%)	
+72:00		0.030 IU/mL (3.0%)	

This segment of the report provides an interactive graph and the source infusion data used to estimate the profile. If the estimate does not make sense, check whether the data provided are correct.

Pharmacokinetic Estimate

Please note that the **distance** between the *conservative* and the *optimistic* estimate is **directly proportional** to the uncertainty of the estimation. When the values are distant enough that the choice between a *balanced* or *conservative* estimate would result in a different clinical decision (e.g. they are more than 24 hrs apart, suggesting an infusion regime one day shorter), we recommend using the *conservative* estimate.

Parameter	Estimate (hr)		
	Conservative	Balanced	Optimistic
Time to 0.05 IU/ml	52.75	59.50	66.50
Time to 0.02 IU/ml	72.50	82.00	91.50
Time to 0.01 IU/ml	92.25	104.50	116.75
Half-life	12.50	14.25	16.00

Convert days to hours	Plasma Factor Concentration Estimate (IU/mL)		
Time (Days)	Conservative	Balanced	Optimistic
1	0.214	0.251	0.294
2	0.062	0.081	0.106
3	0.021	0.028	0.041
4	0.009	0.012	0.018
5	0.006	0.007	0.010

Disclaimer: All PK estimates generated by WAPPS, including this report, are to be used as indicated in the user agreement and at the user's sole responsibility.

Approved by Alfonso Iorio

⚕ Clinical Calculator   🖹 Download as PDF

In the previous example, the time to critical concentrations (5%, 2%, and 1%) and the concentration at various days after the infusion are presented at the bottom. The top section provides additional details. At the bottom right is the name of the individual who approved the PK estimate.

To print/save the report in PDF format, click on the **Download as PDF** icon at the top right or bottom right (see below).

← Return to patient   ⚕ Clinical Calculator   🖹 Download as PDF

Patient Data

ID	12739	Sex	M
Patient ID	MK10312	Patient Baseline (IU/mL)	< 0.010
Infusion ID	30847	Blood Group	O
Current Age	7	vWF:RiCof (IU/mL)	0.00
Age at PK Study	5	vWF:Ag (IU/mL)	0.00
Body Weight (kg)	23.4	Hematocrit (IU/ml)	0.00
Height (cm)	123.1	Hemoglobin (IU/ml)	0.00
Lean Body Weight (kg)	21.66	Serum Creatinine (µmol/L)	0.00

| PK Estimate | Validation Point | Updated PK Estimate |

The screen below will appear:
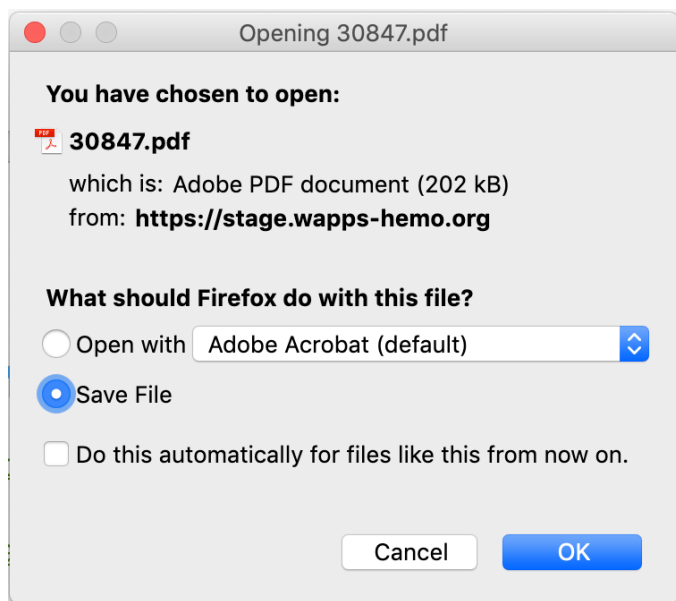
You can select **Open with Adobe Acrobat** and print, or **Save File** in a PDF format

6.7 Editing a PK Study

The information for both the infusion and the related measurements can be edited at any time. The process is different depending on the status of the PK study (see below).

To edit a PK study, click on the ✏ icon under the **Tools** header and edit the infusion or measurement data, as needed.

To edit PK studies already submitted, click the 🔓 icon. You will see a warning reminding you that any treatment regimens associated with the infusion will be deleted (see next image **Confirm Unlock**).

If you have provided previous infusion/current regimen data, you will be asked whether you want to keep or discard them. The data are shown for you in the prompt screen (see image below). If you confirm you want to proceed by clicking **Unlock**, the ✏ icon will appear, and you can edit the PK study data.

When the editing is completed, save and submit again for estimation (see **Requesting a PK**).

6.8 Merging PK Studies

The merge function allows you to estimate a PK profile using measurements obtained after different infusions. You are required to first register each infusion separately (see 4.5 **Adding a PK Study**), and then use the **Merge** function on the website. You can merge any of the PK studies recorded for the patient: those already reported (indicated by the **View** button) and those yet to be submitted (indicated by the **Request PK** button) (see example below).

Click on the **Merge Infusions** button. This field may also appear as **Merge PK Studies**.

PK Studies

+/-	PK Estimate ⓘ	ID	Factor Concentrate	Age	Height (cm)	BW (kg)	LBW (kg)	Tot IU	IU/kg	End of infusion	Supplemental Info	Tools
➕	View	30847	Kovaltry ⓘ	5	123.1	23.4	22	1000	42.7	2017-12-18 10:44	⊞	🔒 📋 ✕
➕	Request PK	34076	Kovaltry ⓘ	5	123.1	23.4	19	1000	42.7	2017-12-18 10:44	⊞	🔒 📋 ✕
➕	View	26937	Kovaltry ⓘ	5	122.5	23.2	21	500	21.6	2017-09-25 09:53	⊞	🔒 📋 ✕
➕	View	6386	Kogenate ⓘ	3	N/A	18	N/A	500	27.8	2015-11-25 10:15	⊞	🔒 📋 ✕
➕	Request PK	34077	Kogenate ⓘ	3	150	18	17	500	27.8	2015-11-25 10:15	⊞	🔒 📋 ✕

Add an infusion   Add a Validation Set   **Merge Infusions**

Select the base (primary) infusion you want to use for merging the data from other infusions then click **Next**.

Merge Infusions

Step 1: Choose the primary infusion

The primary infusion will dictate the base information to be used for the set. It also provides the criteria to which other infusions must adhere in order to be merged.

+/-		ID	Factor Concentrate	Height (cm)	BW (kg)	Tot IU	IU/kg	End of infusion	Infusion Duration (min)	Opt.	Notes
➕	○	30847	Kovaltry ⓘ	123.1	23.4	1000	42.7	2017-12-18 10:44	3	⊞	
➕	○	34076	Kovaltry ⓘ	123.1	23.4	500	21.4	2017-12-18 10:44	3	⊞	
➕	○	26937	Kovaltry ⓘ	122.5	23.2	500	21.6	2017-09-25 09:53	3	⊞	
➕	○	36519	Kovaltry ⓘ	122.5	23.2	500	21.6	2017-09-25 09:53	3	⊞	🏆
➕	○	6386	Kogenate ⓘ	N/A	18	500	27.8	2015-11-25 10:15	3	⊞	
➕	○	34077	Kogenate ⓘ	150	18	500	27.8	2015-11-25 10:15	3	⊞	

Cancel   Next

All the infusions that can be merged with your selected primary infusion will be listed. The rules are shown in the example below:

Select the one(s) you want to merge and click **Next**.

All the measurement points **scaled** to the time of the primary infusion are listed (see below). The last column on the right indicates the PK study from which the measurement was taken. At this point, you cannot choose to keep or delete measurements, but this can be completed after merging. Write down the measurement you may want to delete. Click on **Merge** to proceed.

The new infusion will be listed among the others, identified by the ⚇ icon.

PK Studies

+/-	PK Estimate ⓘ	ID	Factor Concentrate	Age	Height (cm)	BW (kg)	LBW (kg)	Tot IU	IU/kg	End of infusion	Supplemental Info		Tools		
➕	View	30847	Kovaltry ⓘ	5	123.1	23.4	22	1000	42.7	2017-12-18 10:44	▦		🔒	📋	✕
➕	Request PK	34076	Kovaltry ⓘ	5	123.1	23.4	19	500	21.4	2017-12-18 10:44	▦		✎	📋	✕
➕	View	26937	Kovaltry ⓘ	5	122.5	23.2	21	500	21.6	2017-09-25 09:53	▦		🔒	📋	✕
➖	Request PK	36519	Kovaltry ⓘ	5	122.5	23.2	21	500	21.6	2017-09-25 09:53	▦	⚇	✎	📋	✕

Sampling Date Time ⓘ	Time Elapsed (hh:mm) ⓘ	Pre-dose ⓘ	Plasma Factor Concentration ⓘ	Notes	Tools
2017-09-25 09:50	-0:03	✔	0.010 IU/mL (1.0%)		✎ ✕
2017-09-25 10:15	0:22		0.490 IU/mL (49.0%)		✎ ✕
2017-09-25 12:39	2:46		0.750 IU/mL (75.0%)		✎ ✕
2017-09-25 14:00	4:07		0.330 IU/mL (33.0%)		✎ ✕
2017-09-26 09:50	23:57		0.100 IU/mL (10.0%)		✎ ✕
2017-09-26 11:29	25:36		0.140 IU/mL (14.0%)		✎ ✕

+ Add Measurement

+/-	PK Estimate	ID	Factor Concentrate	Age	Height (cm)	BW (kg)	LBW (kg)	Tot IU	IU/kg	End of infusion	Supplemental Info	Tools		
➕	View	6386	Kogenate ⓘ	3	N/A	18	N/A	500	27.8	2015-11-25 10:15	▦	🔒	📋	✕
➕	Request PK	34077	Kogenate ⓘ	3	150	18	17	500	27.8	2015-11-25 10:15	▦	🔒	📋	✕

Add an infusion   **Add a Validation Set**   **Merge Infusions**

6.9 Deleting a PK Study

To delete a PK study, click on the **X** to the right at the end of the infusion record row.

You will be reminded that all the associated PK estimates will be deleted.
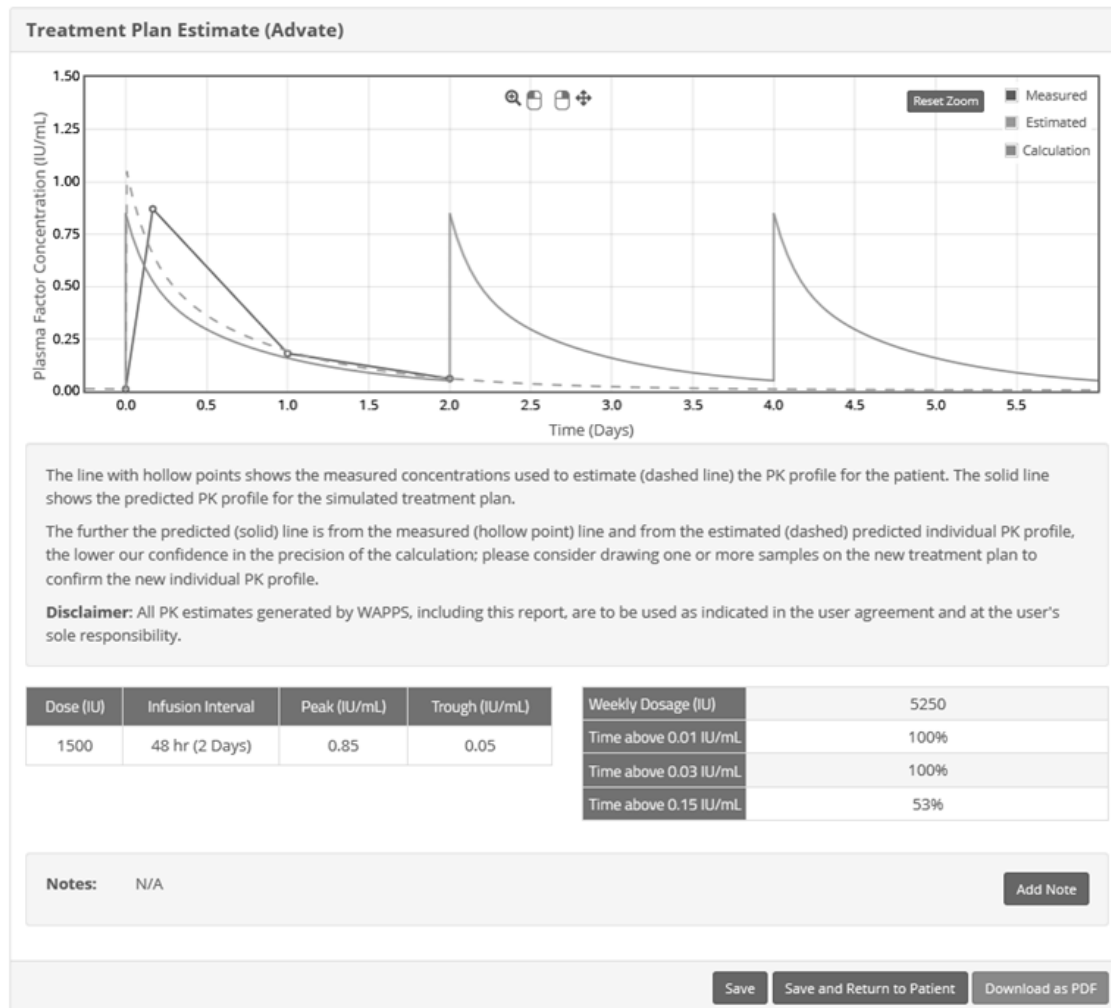
7.0 Advanced Functions

7.1 Using the Clinical Calculator

The Clinical Calculator allows you to test the factor levels obtained with different doses and intervals. When you complete 2 of the 3 input fields (dose, trough, and interval), the calculator will estimate the third for you.

Please note that the calculator shows the height and weight last recorded for the patient. If these have changed, which is typically the case with children, you must enter current information to get an accurate PK.

Note: If you have a patient who is less than one-year-old, the age will appear as 0 (zero). The Clinical Calculator will show an error message unless you change the age to 1. Only then will it provide you an accurate patient profile.

The calculator will return an interactive graph and some tables. If the graph shows an acceptable result, you can click on **Save and Return to Patient**.

Treatment Plan Estimate (Advate)

The line with hollow points shows the measured concentrations used to estimate (dashed line) the PK profile for the patient. The solid line shows the predicted PK profile for the simulated treatment plan.

The further the predicted (solid) line is from the measured (hollow point) line and from the estimated (dashed) predicted individual PK profile, the lower our confidence in the precision of the calculation; please consider drawing one or more samples on the new treatment plan to confirm the new individual PK profile.

Disclaimer: All PK estimates generated by WAPPS, including this report, are to be used as indicated in the user agreement and at the user's sole responsibility.

Dose (IU)	Infusion Interval	Peak (IU/mL)	Trough (IU/mL)
1500	48 hr (2 Days)	0.85	0.05

Weekly Dosage (IU)	5250
Time above 0.01 IU/mL	100%
Time above 0.03 IU/mL	100%
Time above 0.15 IU/mL	53%

Notes: N/A

Add Note

Save Save and Return to Patient Download as PDF

The **Saved Treatment Plans** appears. Click the button under **Current** to activate it, which will change it from **No** to **Yes**.

Saved Treatment Plans How to activate myWAPPS?

Enable App

ID	Infusion ID	Treatment Plan Estimate					Weekly Dosage (IU)	Saved	Notes	Current	Tools
		Dose (IU)	Interval (Days)	Weekdays	Trough (IU/mL)	Peak (IU/mL)	Advate 5250	2020-01-30 14:24	💬	Yes	👁✖
2424	36481	1500	2.0		0.0502	0.8478					

7.2 Activating a Patient App

The following few pages deal with the activation of a patient accessed device, designed to accompany MacPopPK. Please use the installation instructions provided by the app manufacturer or ask our help desk for assistance.

Step 1: Select the patient you want to activate for the app. In this example, it is 31263 (Test – Jivi). The absence of an icon in the **App** column indicates the patient has not yet been activated for any mobile app. If an icon exists, it indicates that they have already been activated.

Patient List

Centre: Hamilton Health Sciences

Patient Search | Page Size 10

ID	Patient ID ⬍	Age ⬍	Sex ⬍	Blood Group ⬍	Patient Baseline (IU/mL) ⬍	Treatment Plan	App	Tools
28125	MS25788	32	M	N/A	0.02	Kovaltry, 2000 Mo, Fr		👥👤
28126	DM10128	57	M	N/A	< 0.01			👥👤
31223	10348	40	M	N/A	< 0.01	Benefix, 6000 every 2 day(s)	W	👥👤
31238	9809	24	M	B+	< 0.01	Kovaltry, 2000 every 3 day(s)	W	👥👤
31239	TEST PRIOR	20	M	N/A	< 0.01	Adynovate, 2000 Mo, Fr	W	👥👤
31255	1364135	70	M	A	0.0001			👥👤
31257	Marko	31	M	N/A	< 0.01	Adynovate, 3000 every 3 day(s)	W	👥👤
31261	1360414	7	M	A	0.01			👥👤
31263	Test - JIVI	32	M	N/A	< 0.01	Jivi, 2000 every 7 day(s)		👥👤
31270	1364156	30	M	B	< 0.01	Kovaltry, 3000 every 3 day(s)	W	👥👤

1 2 3 4 5 6 **7** 8 9

Add Patient

Step 2: Access the patient record. To activate any mobile app, the patient must first have a completed treatment plan. To begin a treatment plane, click on **View** for the PK you want to use as the base for the treatment plan.

PK Studies

+/-	PK Estimate ⓘ	ID	Factor Concentrate	Age	Height (cm)	BW (kg)	LBW (kg)	Tot IU	IU/kg	End of infusion	Supplemental Info	Tools
⊕	View	33794	Jivi ⓘ	30	170	72.6	56	3000	41.3	2018-10-10 08:00	⊞	🔒📋✕
⊕	View	33795	Jivi ⓘ	30	170	72.6	56	3000	41.3	2018-10-10 08:00	⊞	🔒📋✕
⊕	View	33796	Jivi ⓘ	30	170	72.6	56	3000	41.3	2018-10-10 08:00	⊞	🔒📋✕

Add an infusion | Add a Validation Set | Merge Infusions

Saved Treatment Plans   How to activate myWAPPS?   You must select a treatment plan before enabling App access.

ID	Infusion ID	Treatment Plan Estimate	Weekly Dosage (IU)	Saved	Notes	Current	Tools

Patient Infusions

To view the patient's infusions recorded in myWAPPS, please complete the following steps.

1. Prepare a treatment plan using the clinical calculator and select as 'Current'.
2. Activate myWAPPS for the patient by clicking 'Enable App'.

Once registration is complete, any infusions recorded by the patient in myWAPPS will appear here.

Note: If the patient already has a treatment plan(s) saved, skip to **Step 6** below, otherwise a patient regimen must be created.

Step 3: In the **Result Review** page, click on the **Clinical Calculator** button.

Step 4: Select the dose and frequency you want to prescribe and click the **Calculate** button.

Step 5: If the regimen is the one you want, click on **Save** or **Save and Return to Patient**.

shows the predicted PK profile for the simulated treatment plan.

The further the predicted (solid) line is from the measured (hollow point) line and from the estimated (dashed) predicted individual PK profile, the lower our confidence in the precision of the calculation; please consider drawing one or more samples on the new treatment plan to confirm the new individual PK profile.

Disclaimer: All PK estimates generated by WAPPS, including this report, are to be used as indicated in the user agreement and at the user's sole responsibility.

Dose (IU)	Infusion Interval	Peak (IU/mL)	Trough (IU/mL)
2000	168 hr (7 Days)	0.78	0.024

Weekly Dosage (IU)	2000
Time above 0.01 IU/mL	100%
Time above 0.03 IU/mL	92%
Time above 0.15 IU/mL	44%

Notes: N/A   Add Note

Save   Save and Return to Patient   Download as PDF

Step 6: The regimen will now appear below the saved treatment plans. If there is more than one regimen, indicate the one you want the app to use by clicking on the switch under the **Current** column and changing it from **No** to **Yes**.

PK Studies

+/-	PK Estimate ⓘ	ID	Factor Concentrate	Age	Height (cm)	BW (kg)	LBW (kg)	Tot IU	IU/kg	End of infusion	Supplemental Info	Tools
⊕	View	33794	Jivi ⓘ	30	170	72.6	56	3000	41.3	2018-10-10 08:00	⊞	🔒 ▦ ×
⊕	View	33795	Jivi ⓘ	30	170	72.6	56	3000	41.3	2018-10-10 08:00	⊞	🔒 ▦ ×
⊕	View	33796	Jivi ⓘ	30	170	72.6	56	3000	41.3	2018-10-10 08:00	⊞	🔒 ▦ ×

Add an infusion   Add a Validation Set   Merge Infusions

Saved Treatment Plans   How to activate myWAPPS?   You must select a treatment plan before enabling App access.

ID	Infusion ID	Treatment Plan Estimate					Weekly Dosage (IU)	Saved	Notes	Current	Tools
		Dose (IU)	Interval (Days)	Weekdays	Trough (IU/mL)	Peak (IU/mL)	Jivi	2020-02-13 23:12	💬	No	👁×
2454	33794	2000	7.0		0.0237	0.7799	2000				

Patient Infusions

To view the patient's infusions recorded in myWAPPS, please complete the following steps.

   1 Prepare a treatment plan using the clinical calculator and select as 'Current'

Step 7: The button **Enable App** appears.

Click on **Enable App**.

Step 8: Before the patient can use the app, you must first enter the patients email address and acknowledge the declaration. When completed, click **Activate** and your part is finished. The patient will receive an activation email from MacPopPK with a link to complete the process.

Step 9: The patient will then receive an email with a link so the patient can create their own password and acknowledge their Terms of Use agreement. This is a sample of a myWapps app user and other apps will have their own customized email.
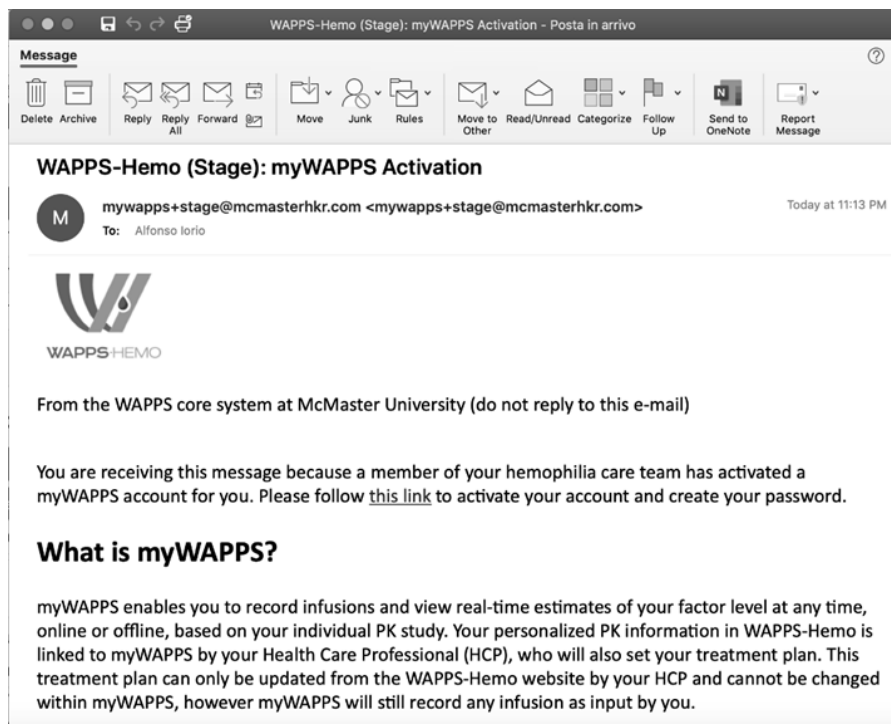
7.3 Checking the Patient Infusion Log

For patients using myWAPPS, the infusions they record in the app appear for your review (if you wish) under **Patient Infusions** on the patient page. For this patient, there are 3 pages of infusions.

Saved Treatment Plans   How to activate myWAPPS?

*********n@rogers.com

ID	Infusion ID	Treatment Plan Estimate					Weekly Dosage (IU)	Saved	Notes	Current	Tools
		Dose (IU)	Interval (Days)	Weekdays	Trough (IU/mL)	Peak (IU/mL)					
2222	3995	3000	2.0		0.0265	1.1453	Kogenate 10500	2018-09-18 10:38		Yes	👁✕

Patient Infusions

Dose (IU)	Date & Time	Factor Concentrate
3133	2018-09-22 22:15	Kogenate
3000	2018-09-25 07:00	Kogenate
3133	2018-09-27 11:36	Kogenate
3133	2018-09-29 09:33	Kogenate
3187	2018-09-30 06:23	Kogenate
3187	2018-10-02 05:40	Kogenate
3187	2018-10-04 05:50	Kogenate
3187	2018-10-06 08:18	Kogenate
3187	2018-10-08 09:59	Kogenate
3187	2018-10-09 09:59	Kogenate

1 2 3

7.4 Adding a Validation Point

On the patient page (Figure 1), click on **Add a Validation Set** button.

Figure 1

Then select the infusion you want to validate (Figure 2).

Figure 2

Add the dose and time of infusion (Figure 3) exactly as when recording a PK study, except the concentrate will be **Set** to the same as the PK study you want to validate.

Figure 3

Then add your measurement data in the same input screen used to report measurements of a PK study (Figure 4).

Figure 4

Finally, click on **Validate** to get the results (Figure 5).

Figure 5

When the results appear, the second tab, **Validation Point**, reports the values (Figure 6).

Validation Point Results

Validation Point

Time	Predicted	Prediction Interval (PI)	Observed	Absolute Difference	Observed Within PI	Clinically Relevant Difference? ⓘ	
48	0.012	0.009 - 0.017	0.014	-0.002	✓	Yes	No
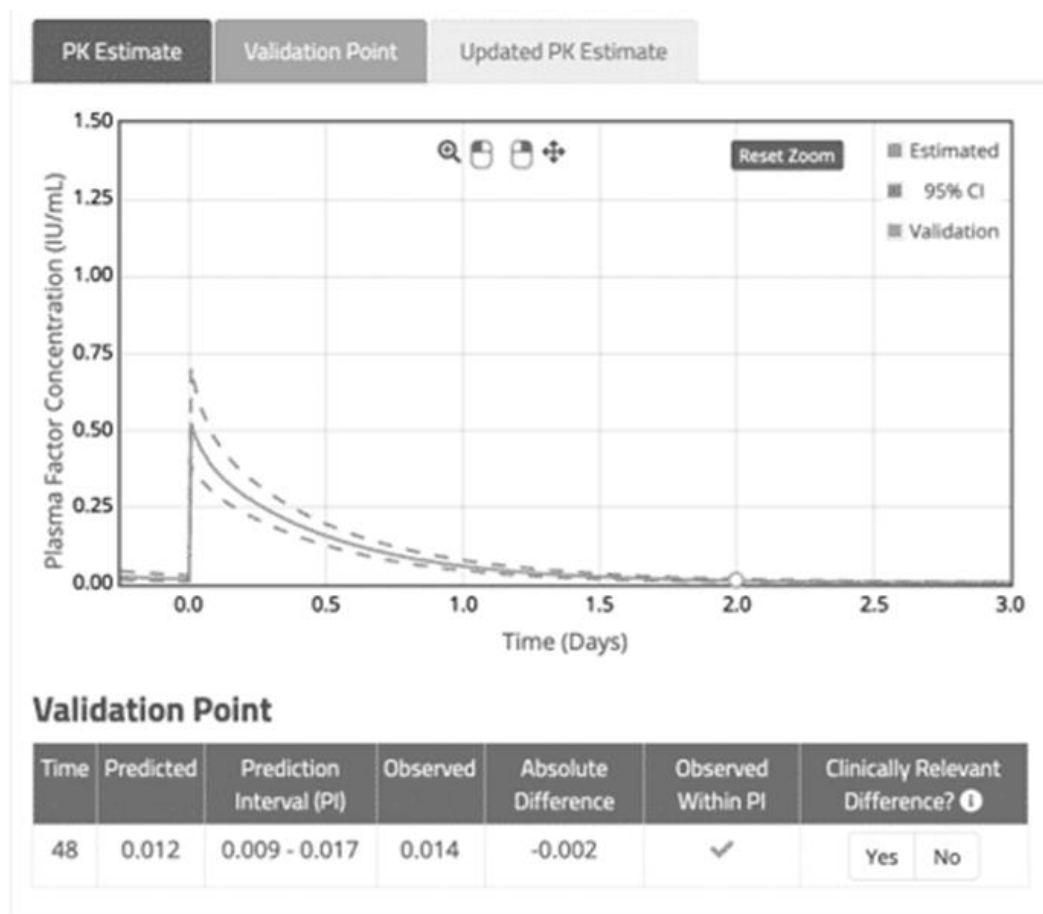
(Figure 6)

From right to left in Figure 6, you have the following information:

(1) **Time** (hrs): the time of the validation sample in hours.

(2) **Predicted** (IUmL): the predicted concentration at **time** in IU/mL.

(3) **Prediction Interval** (IUmL): the variability around the prediction (the lowest and highest likely values).

(4) **Observed** (IUmL): the measured level you have provided in IU/mL.

(5) **Absolute Difference** (IUmL): Observed – Predicted, in IU/mL.

(6) **Observed Within PI** (Predicted Interval)**:** this is automatically set to **v** if the observation falls within the prediction interval and **x** if It falls outside the prediction interval.

(7) **Clinically Relevant Difference?:** this is a question you must answer; the difference may be *statistically significant* or not (observed within predicted interval, or not), but in either case it may or may not be clinically relevant (example: leading to a change in the management of the patient). For example, would you change the dose, the infusion interval, or perform a new PK? Please select **Yes** if you judge the difference to be clinically relevant and requires you to take some action, otherwise select **No**.

   *We are asking this question to understand what hemophilia specialists, MDs or other HCPs under the supervision of an MD, consider a clinically relevant difference between a measurement and a prediction.

After your answer is submitted, you can access the **Updated PK Estimate** on the right-hand tab (Figures below).

Infusion data used for this estimate

ID	Factor Concentrate	Tot IU	IU/kg	End of infusion
30943	Advate ⓘ	500	31.3	2015-08-06 11:05

Time Elapsed (hh:mm) ⓘ	Pre-dose ⓘ	Plasma Factor Concentration ⓘ	Notes
-00:05	⊘	0.020 IU/mL (2.0%)	
+01:00		0.450 IU/mL (45.0%)	
+24:00		0.040 IU/mL (4.0%)	
+43:00		0.020 IU/mL (2.0%)	
+47:57*		0.014 IU/mL (1.4%)	
*Validation Point			
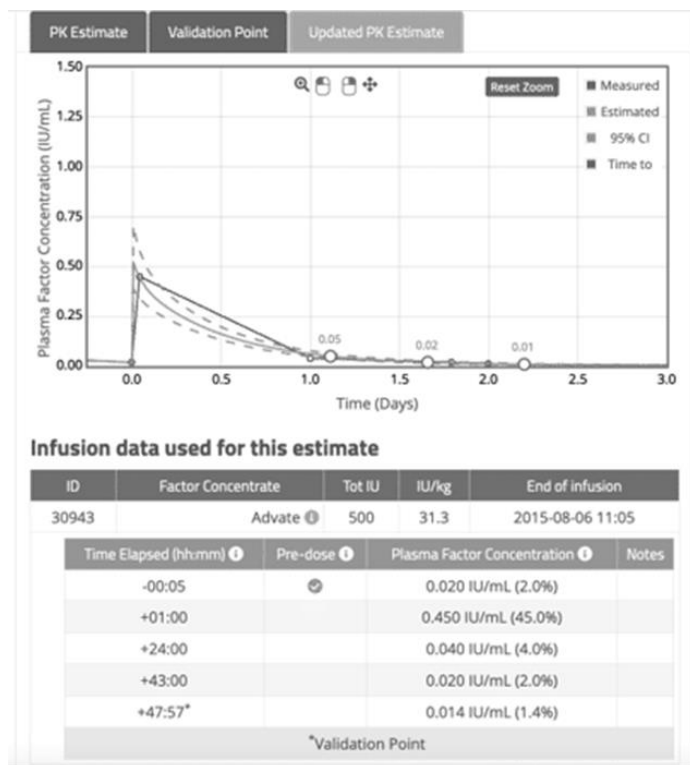
The validation point is now added to the series of measurements for the PK study. The information provided is identical to the standard PK estimate tab.

Parameter	Estimate (hr)		
	Conservative	Balanced	Optimistic
Time to 0.05 IU/ml	23.75	26.75	30.00
Time to 0.02 IU/ml	36.00	39.75	44.00
Time to 0.01 IU/ml	47.75	52.75	58.50
Half-life	7.25	8.25	9.25

Convert days to hours	Plasma Factor Concentration Estimate (IU/mL)		
Time (Days)	Conservative	Balanced	Optimistic
1	0.050	0.062	0.077
2	0.010	0.013	0.017
3	0.006	0.006	0.007

By clicking on the **PK Estimate, Validation Point,** or **Updated PK Estimate** tab, you can toggle between the original and the updated PKs.

You can also indicate whether you want to use the updated PK in the clinical calculator. There is no right or wrong PK estimate, and sometimes the updated estimate will be more precise, sometimes it will be identical, and at times you may prefer to keep using the original estimate.

The validation point function allows you to see how accurate MacPopPK is for each of your patients. We suggest you draw a blood sample when clinically assessing your patients and input it as validation point. This will confirm how precise the estimation is for that specific patient. The sum of all the individual validations provides valuable empirical information leading to an even more effective MacPopPK.

7.5 Inputting Clotting and Chromogenic PK Studies

Some centers measure plasma factor activity levels with both a clotting and a chromogenic test. If you want to submit a PK study completed with both tests, you may want to use the **Copy PK Study** function (see below).

The 📋 icon creates a copy of the PK study record. The infusion details (except the test) and measurement times will be the same as for the other test. You now must edit the infusion, change to the desired test (example either clotting or chromogenic), and edit the measurements to input the appropriate results.

8.0 Administrative Functions

8.1 Adding Users to Your Site

Note: Only users with Administrator status may add new users.

Select **My Centre** from the Menu.

Click on the **Add New Users** tab.

Enter the email address of the user you want to add.

The user will receive an email with a "click here to register" link where they can confirm their registration and choose their password.

When the user is registered, return to the **Active Users** tab and enable the user to receive results by clicking the **No** button under **Send Results** to change it to **Yes**.

To grant a user administrator access, click the **No** button under **Administrator** to change it to **Yes**.
Clicking the ⛏ icon under **Tools** will deactivate a user.

8.2 Adding a New Factor Concentrate

Under the **My Centre** tab, choose **Manage Factor Concentrates.**
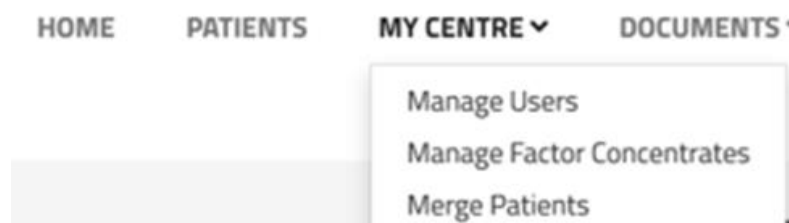
Active Factors are listed by default. To view inactive drugs, click on the **Deactivated Factor Concentrates** tab.

Click on **Add New Factor Concentrates** to add a new drug.

From the dropdown menu, choose the drug you want to activate and select **Add Factor Concentrate Specifics** to set the default lab measurement for the new concentrate. In most cases, this will be **One Stage Coag (PTT Based)** and **Generic**, which are proposed as defaults for new drugs. You can change the test when inputting an infusion.

For Coagulation Test you can choose

One stage

Two stage

Chromogenic

For Calibrator, you can choose between Generic and Drug Specific.

If you do not see the drug in the dropdown list, type it in the **Request a New Factor Concentrate** input box and we will add it for you.

We have a comprehensive list of available drugs and continue to update new models as additional concentrates become available.

If you deactivated a drug, it can be reactivated by clicking the checkmark.

Active Factor Concentrates ⓘ	Deactivated Factor Concentrates ⓘ	Add New Factor Concentrates ⓘ	
Factor Concentrate Name	Default Assay Type	Calibrator	Tools
Adynovate	One Stage Coag. (PTT Based)	Drug Specific	☑ ✓
Alphanine	One Stage Coag. (PTT Based)	Generic	☑ ✓
Crosseight	One Stage Coag. (PTT Based)	Generic	☑ ✓

When reactivated, the Default Assay Type or Calibrator can be changed by clicking on the ☑ icon.

Active Factor Concentrates ⓘ	Deactivated Factor Concentrates ⓘ	Add New Factor Concentrates ⓘ	
Factor Concentrate Name	Default Assay Type	Calibrator	Tools
Advate	One Stage Coag. (PTT Based)	Generic	☑ ⊘
Adynovate	One Stage Coag. (PTT Based)	Drug Specific	☑ ⊘

8.3 Merging Patients

This function is used if in a rare case you find yourself with duplicate patient records in MacPopPK.

Go to **My Centre/Merge Patients**

A screen showing your patients twice will appear (local ID). Select the record you want to keep on the left (primary) and the one to merge on the right (secondary).

The system will show you all the data recorded for the two patients. Select to keep any data from each of the two. When you have completed your selection, click on merge. **Beware! This operation cannot be undone.**

8.4 Request an extended PK

The MacPopPK profile report is intentionally simple and reports only the data needed for clinical practice. We can, however, provide all the PK data associated with the PK profile (AUC, clearance, volumes, etc.).

CE