Background
The potential of dose individualization using model-based therapeutic drug monitoring (TDM) is known to be challenged by high magnitudes of inter-occasion variability (IOV) [1, 2]. Currently, it is not clear which is the preferred method to individualize dosing regimens in the presence of IOV.

Objective
To compare different approaches to handle IOV in a TDM context, using a population PK model for coagulation factor VIII (FVIII) as example.

Methods
This simulation-based study consists of a chain of steps for a number of simulated scenarios, as represented below:

STEP 1
Simulation from a population pharmacokinetic model

STEP 2
Bayesian forecasting using a population pharmacokinetic model varying the number of observations (occasions) included

STEP 3
Dose calculation to reach pre-defined target [FVIII of 0.01 IU/mL at 48 h post-dose]

STEP 4
Calculation of FVIII at 48 h post-dose on next occasion using dose from step 3 and true PK parameters from step 1

STEP 5
Comparison between expected FVIII activity and target

Simulations were based on a PK model for FVIII activity following i.v. administration to hemophilia A patients [ORIG model [3]], and alternative models with none (0%) to large (50%) IOV on CL or V1 (IOV models):
- ORIG model: 2-compartment model, IVV on CL (28%) and V1 (17%, correlation CL-V 0.64), IOV on CL (13%) and V1 (10%), combined residual error (8.5%, 0.012 IU/mL)
- Simulated steady-state FVIII activity at 4, 24 and 48 h following FVIII administration of 30 IU/kg to 1000 patients on 4 occasions

Alternative models without IOV were estimated based on real or simulated data (IIV models).

The following approaches were explored to calculate the individual dose:
- Approach IV: Bayesian forecasting based on an IVV model
- Approach IOV1: Bayesian forecasting based on an IOV model; IOV etas were not included in the calculation of the individualized dose
- Approach IOV2: Bayesian forecasting based on an IOV model; IVV and IOV etas were included in the calculation of the individualized dose

All procedures were carried out in NONMEM 7.3 assisted by PsN 4.6.16 and R 3.3.1.

Results
The performance of the explored approaches to predict an individualized dose that aims to result in the target FVIII activity (0.01 IU/mL) on the next occasion is depicted in Figure 1.

In general, the individual predicted doses resulted in low bias in the predicted FVIII activity. As expected, the imprecision of the predictions increased with increasing magnitude of IOV, and IVV and IOV1 resulted in the most precise predictions.

The percent of values predicted to be below 0.0025 IU/mL (1/4 of target) and in the interval [0.0025, 0.005] IU/mL (1/4-1/2 of target) for approaches IV and IOV1 are presented in Table 1.

Table 1 – Percent of predicted FVIII trough activity values <0.0025 and [0.0025, 0.005] IU/mL when aiming at a target of 0.01 IU/mL, using information from 1 or 3 occasions to predict the subsequent occasion, according to approaches IV and IOV1 for the simulated scenarios.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>1 occasion</th>
<th>3 occasions</th>
<th>1 occasion</th>
<th>3 occasions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL IOV 15%</td>
<td>0.0025</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>V1 IOV 10%</td>
<td>0.0025</td>
<td>11.7</td>
<td>11.7</td>
<td>12.0</td>
</tr>
<tr>
<td>ORIG</td>
<td>0.0025</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>CL IOV 0%</td>
<td>0.0025</td>
<td>15.9</td>
<td>15.9</td>
<td>13.4</td>
</tr>
<tr>
<td>CL IOV 20%</td>
<td>0.0025</td>
<td>17.5</td>
<td>17.5</td>
<td>16.5</td>
</tr>
<tr>
<td>V1 IOV 50%</td>
<td>0.0025</td>
<td>28.7</td>
<td>31.1</td>
<td>24.2</td>
</tr>
<tr>
<td>CL IOV 50%</td>
<td>0.0025</td>
<td>12.9</td>
<td>14.4</td>
<td>11.6</td>
</tr>
<tr>
<td>V1 IOV 5%</td>
<td>0.0025</td>
<td>10.9</td>
<td>8.2</td>
<td>10.3</td>
</tr>
<tr>
<td>V1 IOV 20%</td>
<td>0.0025</td>
<td>5.6</td>
<td>4.6</td>
<td>5.3</td>
</tr>
<tr>
<td>V1 IOV 30%</td>
<td>0.0025</td>
<td>14.4</td>
<td>13.4</td>
<td>12.2</td>
</tr>
<tr>
<td>V1 IOV 50%</td>
<td>0.0025</td>
<td>19.9</td>
<td>19.1</td>
<td>17.1</td>
</tr>
</tbody>
</table>

In scenarios with low IOV (<20%), IVV and IOV1 had a similar performance when predicting low FVIII activity, but increasing IOV lead to a higher percent of very low values (<0.0025 IU/mL) with the IVV approach, regardless of the information content considered.

Conclusion
The IVV and IOV1 approaches showed a similar performance to individualize doses when IOV was low (<20%), and IOV1 was superior for the remaining scenarios of IOV.

If employing an IOV model in Bayesian forecasting, the IOV etas should not be used in the calculation of the individualized dose.