Bayesian forecasting utilizing bleeding information to support dose individualization of factor VIII

João A. Abrantes¹, Alexander Solms², Dirk Garmann³, Elisabet I. Nielsen¹, Siv Jönsson¹, Mats O. Karlsson¹

(¹) Uppsala Pharmacometrics Research Group, Uppsala University, Uppsala, Sweden
(²) Bayer, Berlin, Germany
(³) Bayer, Wuppertal, Germany
Haemophilia A

• Congenital X-linked bleeding disorder

• Deficiency of coagulation factor VIII (FVIII)

• Characteristic phenotype: spontaneous bleeding events
Severe haemophilia A

Endogenous plasma factor VIII activity <1 IU/dL
FVIII replacement therapy

Prophylactic administration of 15-40 IU/kg 3x week

clinical and economic burden (~ €200,000/patient/year)\(^1\)

FVIII replacement therapy

PK-guided model-based dose individualization increasingly encouraged [1,2]

FVIII replacement therapy

PK-guided model-based dose individualization increasingly encouraged [1,2]

PK-bleed-covariate model

*Dose-exposure-response relationship*

Population PK model

2-compartment model

Population PK model

(IIV on CL, V1, residual error)

CL: clearance; IIV: inter-individual variability; LBW: lean body weight; V1 and V2: central and peripheral volumes of distribution

PK-bleed-covariate model

Dose-exposure-response relationship

Bleed model
Repeated time-to-event model

\[ h(t) = 3.0 \cdot e^{-0.57 \cdot (t - 1)} \cdot \left( 1 - \frac{F_{VIII}}{F_{VIII} + I_{F50}} \right) \cdot e^n \]

Population PK model
(IIV on CL, V1, residual error)

RTTE model
(IIV on \( h(t) \))

CL: clearance; IIV: inter-individual variability; V1: central volume of distribution
PK-bleed-covariate model

*Dose-exposure-response relationship*

**Covariates**

Full random effects modeling

- Age
- Body weight, LBW, BMI
- Race
- von Willebrand factor levels
- Number of spontaneous bleeds within 12 months pre-study
- Pre-study treatment (prophylaxis/on-demand)
- Number of target joints at study start
- Study

BMI: body mass index; CL: clearance; IIV: inter-individual variability; LBW: lean body weight; V1: central volume of distribution

Use the PK-bleed-covariate model to contrast different sources of patient information in their ability to predict future occurrence of bleeds.

Wait... but why?

- Current model-based dose individualization methods are mainly PK-guided.
- Considering other sources of patients’ information may ↑ accuracy in predictions and cost-effectiveness.
**LEOPOLD I and II clinical trials**[1-3]

- 121 patients with severe haemophilia A (≥12 years)
- Prophylactic treatment with octocog alfa
- 12 months
  - 798 sparse FVIII activity observations
  - 530 bleeding events (~1% of all observed days)
  - 11 covariates
  (subset of data used to develop the PK-bleed-covariate model)
Bleeding forecasting workflow

**Bayesian forecasting + calculation of \( P_i(\text{bleeding}) \)**

### June

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- **EBEs patient \( i \):**
  - Day 1
  - Day 1, 2
  - Day 1 … \( n-1 \)

- **\( P_i(\text{bleeding}) \) patient \( i \):**
  - Day 2
  - Day 3
  - Day \( n \)

\( n \): last day of patient \( i \) in the study

\( P_i(\text{bleeding}) \): individual forecasted probability of having a bleed in the upcoming 24 h

EBEs: empirical Bayes estimates (individual parameters, eg. individual clearance or individual bleeding hazard)

\[
P_i(\text{bleeding}) = 1 - e^{-\int_{t}^{t+24h} h_i(t) \, dt}, \text{ where } t \text{ is the end of the Bayesian forecasting observation period}
\]
Bleeding forecasting workflow

Bayesian forecasting + calculation of $P_i(\text{bleeding})$

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EBEs: empirical Bayes estimates (individual parameters, eg. individual clearance or individual bleeding hazard)

$P_i(\text{bleeding}) = 1 - e^{-\int_{t}^{t+24} h_i(t) dt}$, where $t$ is the end of the Bayesian forecasting observation period

EBEs patient $i$
- Day 1
- Day 1, 2
- Day 1 … $n$-1

$P_i(\text{bleeding})$ patient $i$
- Day 2
- Day 3
- Day $n$

$n$: last day of patient $i$ in the study

$P_i(\text{bleeding})$: individual forecasted probability of having a bleed in the upcoming 24 h
# Bleeding forecasting workflow

*Bayesian forecasting + calculation of $P_i(\text{bleeding})$*

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**EBEs patient $i$**
- Day 1
- Day 1, 2
- Day 1 … $n$-1

**$P_i(\text{bleeding})$ patient $i$**
- Day 2
- Day 3
- Day $n$

$n$: last day of patient $i$ in the study

$P_i(\text{bleeding})$: individual forecasted probability of having a bleed in the upcoming 24 h

**EBEs: empirical Bayes estimates (individual parameters, eg. individual clearance or individual bleeding hazard)**

$$P_i(\text{bleeding}) = 1 - e^{-\int_t^{t+24} h_i(t) \, dt}, \text{ where } t \text{ is the end of the Bayesian forecasting observation period}$$
**Bleeding forecasting workflow**

**Bayesian forecasting + calculation of $P_i(bleeding)$**

<table>
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EBEs: empirical Bayes estimates (*individual parameters*, eg. individual clearance or individual bleeding hazard)

$P_i(bleeding) = 1 - e^{-\int_t^{t+24h} h(t) dt}$, where $t$ is the end of the Bayesian forecasting observation period

**EBEs patient $i$**
- Day 1
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**$P_i(bleeding)$ patient $i$**
- Day 2
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$n$: last day of patient $i$ in the study
Bleeding forecasting workflow

Bayesian forecasting + calculation of $P_i(bleeding)$

EBEs patient $i$
- Day 1
- Day 1, 2
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$P_i(bleeding)$ patient $i$
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$n$: last day of patient $i$ in the study

$P_i(bleeding)$: individual forecasted probability of having a bleed in the upcoming 24 h

EBEs: empirical Bayes estimates (individual parameters, eg. individual clearance or individual bleeding hazard)

$P_i(bleeding) = 1 - e^{-\int_t^{t+24h} h_i(t) dt}$, where $t$ is the end of the Bayesian forecasting observation period
Information scenarios
“PK”, “Bleed”, and “All”

<table>
<thead>
<tr>
<th>June</th>
<th>PK observations</th>
<th>Bleed observations</th>
<th>All PK, bleeding observations and covariates</th>
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<tr>
<td>M</td>
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Infusion PK PK sampling No bleed Bleed
Time-varying bleeding probabilistic forecast

Illustrative patient

| FVIII infusion | Time of bleed |

P_i(bleeding): individual forecasted probability of having a bleed in the upcoming 24 h
Predictive performance assessment

Three techniques were used

- $P_i$(bleeding) was compared with the actual occurrence or non-occurrence of a bleed on the forecasted day
  - Separation plots\[1\]
  - Receiver operating characteristic (ROC) analyses\[2\]
  - Precision-recall analyses\[3\]

$P_i$(bleeding): individual forecasted probability of having a bleed in the upcoming 24 h

### Separation plots

*Merged P_i(bleeding) data for all days for all patients*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Forecasted day</th>
<th>P_i(bleeding)</th>
<th>Bleed</th>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0.020</td>
<td>0</td>
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<td>1</td>
<td>3</td>
<td>0.075</td>
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<td>1</td>
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<td>0.051</td>
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<td>0.181</td>
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<td>4</td>
<td>0.138</td>
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<tr>
<td>3</td>
<td>n</td>
<td>0.121</td>
<td>0</td>
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</tbody>
</table>
Rows ordered according to the ascending order of $P_i$(bleeding)
Highlighted rows corresponding to days when bleeds actually occurred

<table>
<thead>
<tr>
<th>Patient</th>
<th>Forecasted day</th>
<th>( P_i ) (bleeding)</th>
<th>Bleed</th>
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<tr>
<td>1</td>
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Separation plots
Separation plots

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Low P_{i}(bleeding) vs. High P_{i}(bleeding)
Separation plots

\[ P_i(\text{bleeding}) : \text{individual forecasted probability of having a bleed in the upcoming 24 h} \]

- Low \( P_i(\text{bleeding}) \)
- High \( P_i(\text{bleeding}) \)
- bleed day
- no-bleed day

\[ \text{Ordered } P_i(\text{bleeding}) \]
Separation plots

\textbf{Bleed and All} associated with higher relative \( P_i(\text{bleeding}) \)

- Bleed days more often associated with higher \( P_i(\text{bleeding}) \) in \textbf{Bleed} and \textbf{All} than in \textbf{PK}

- PK information and covariates did not substantially improve the predictive performance

\( P_i(\text{bleeding}) \): individual forecasted probability of having a bleed in the upcoming 24 h

Separation plots showing all predicted days for all patients. Since the occurrence of bleeds was rare (~1.2% of forecasted days), vertical bars corresponding to bleed days were emphasized.
Receiver operating characteristic (ROC) analysis

**Bleeds were a main component driving the forecast of future bleeds**

![ROC Curve](image)

**True positive rate** = \( \frac{\text{true positives}}{\text{positives}} \), **false positive rate** = \( \frac{\text{false positives}}{\text{negatives}} \)

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<tr>
<th>Group</th>
<th>$AUC_{ROC}$ Value (95% CI)</th>
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<tr>
<td>PK</td>
<td>0.67 (0.65-0.69)</td>
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<td>Bleed</td>
<td>0.78 (0.76-0.80)</td>
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<tr>
<td>All</td>
<td>0.79 (0.77-0.81)</td>
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Precision-recall analysis

Bleeds were a main component driving the forecast of future bleeds

Precision = \( \frac{\text{true positives}}{\text{true positives} + \text{false positives}} \) (low precision observed for all information scenarios as expected); recall = true positive rate = \( \frac{\text{true positives}}{\text{positives}} \)
Some limitations

- Evaluation based on a subset of data used to develop the model

- Study design, for instance:
  - PK sampling times
  - Patients well protected against bleeds
An integrated PK-bleed-covariate model approach can be used to forecast the occurrence of bleeds under prophylactic treatment.

Three techniques confirmed that past bleeding information is a main component driving the forecast of future bleeds.

Further steps to optimize the proposed tool for FVIII dose adaptation are required.
Acknowledgements

Uppsala Pharmacometrics Research Group

Apotekare Gunnar Hylténs stiftelse
Bayesian forecasting utilizing bleeding information to support dose individualization of factor VIII

João A. Abrantes¹, Alexander Solms², Dirk Garmann³, Elisabet I. Nielsen¹, Siv Jönsson¹, Mats O. Karlsson¹

(1) Uppsala Pharmacometrics Research Group, Uppsala University, Uppsala, Sweden
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(3) Bayer, Wuppertal, Germany
Varying the observation period length
The longer the observation period for EBEs estimation the better

Information scenario: **Bleed**

Prediction error = \(\text{Bleed}_{\text{forecast}} - \text{Bleed}_{\text{observed}}\) where \(\text{Bleed}_{\text{forecast}}\) and \(\text{Bleed}_{\text{observed}}\) are the number of forecasted and observed bleeds during the whole individual study period. Bleeding risk was categorized as: **low risk**, if patients did not bleed during the study (\(N=33\)); **moderate risk**, 1-4 bleeds (\(N=49\)); and **high risk**, \(\geq 5\) bleeds (\(N=39\)).