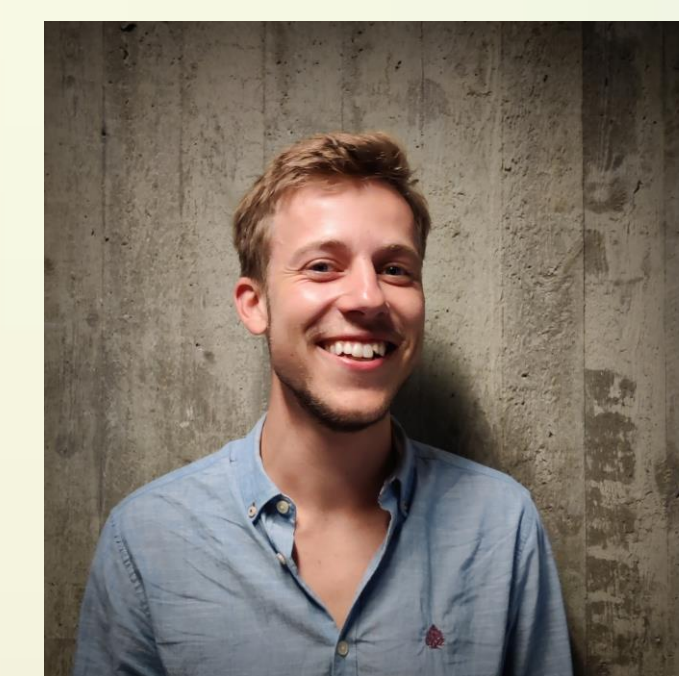




Sanquin



s.vandenberg@sanquin.nl
[linkedin.com/in/sphvandenberg](https://www.linkedin.com/in/sphvandenberg)

Pharmacokinetic model-informed precision dosing of natalizumab in Multiple Sclerosis

Stefan P. H. van den Berg^{1,2}, Alyssa A. Toorop³, Femke Hooijberg⁴, Gertjan Wolbink⁴, Nivea M.F. Voelkner^{1,2}, Liza M.Y. Gelissen³, Joep Killestein³, Zoë L. E. van Kempen³, Thomas P.C. Dorlo⁵, Theo Rispens^{1,2}

1. Department of Immunopathology, Sanquin Research Amsterdam; 2. Amsterdam Institute for Infection and Immunity, Amsterdam, The Netherlands; 3. MS Center Amsterdam, Amsterdam University Medical Center, location VUMC; 4. Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, location Reade Amsterdam; 5. Department of Pharmacy, Pharmacometrics, Uppsala University

1. Natalizumab prevents entrance to the central nervous system

Multiple Sclerosis (MS) is an auto-immune disease where immune cells target oligodendrocytes. Natalizumab (monoclonal IgG4k) binding to $\alpha 4$ -integrins prevent entrance to the central nervous system (Figure 1). An immuno-compromised central nervous system can cause virus-induced brain failure (e.g., PML). Meanwhile, the standard intravenous (i.v.) **treatment interval of 4 weeks may be excessive** for most patients. Recent studies evaluated extension of natalizumab dosing interval prospectively, maintaining high efficacy in extended dose intervals.

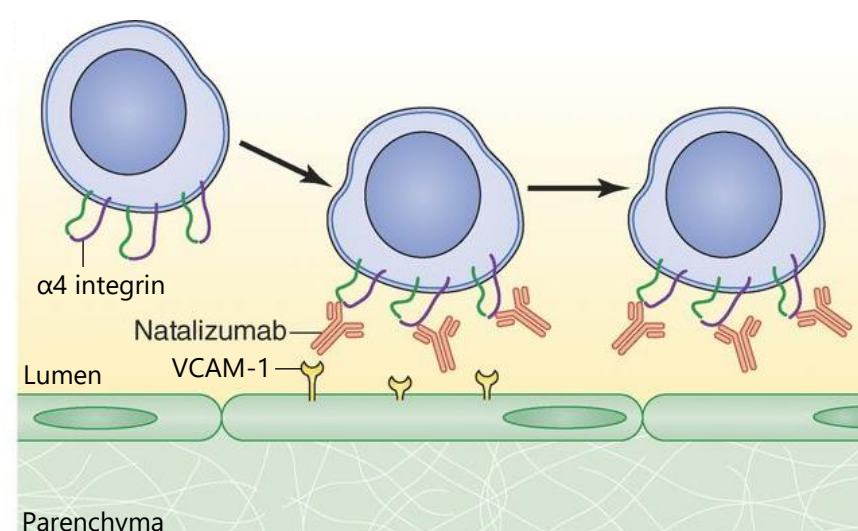


Figure 1.

The aim is to personalize dosing of natalizumab guided by a population pharmacokinetic model coupled with therapeutic drug monitoring (TDM), known as model-informed precision dosing (MIPD).



- Reduce disease burden
- Reduce excessive medical costs
- Partially restore immunosurveillance in the central nervous system

2. Stratified personalized dosing (SPD)

A previous study extended dosing intervals guided by drug concentrations to lower natalizumab exposure, further referred to as the stratified personalized dosing protocol (SPD). Individuals were included who had received treatment for at least 6 months and did not exhibit anti-drug antibodies.

Personal intervals were determined on **two 4-week interval trough samples and the target concentration (10 or 5 $\mu\text{g/mL}$)** following a decision tree (Figure 2).

Patients were monitored and re-adjustments were done if their concentrations were above 20 or below 2 $\mu\text{g/mL}$.

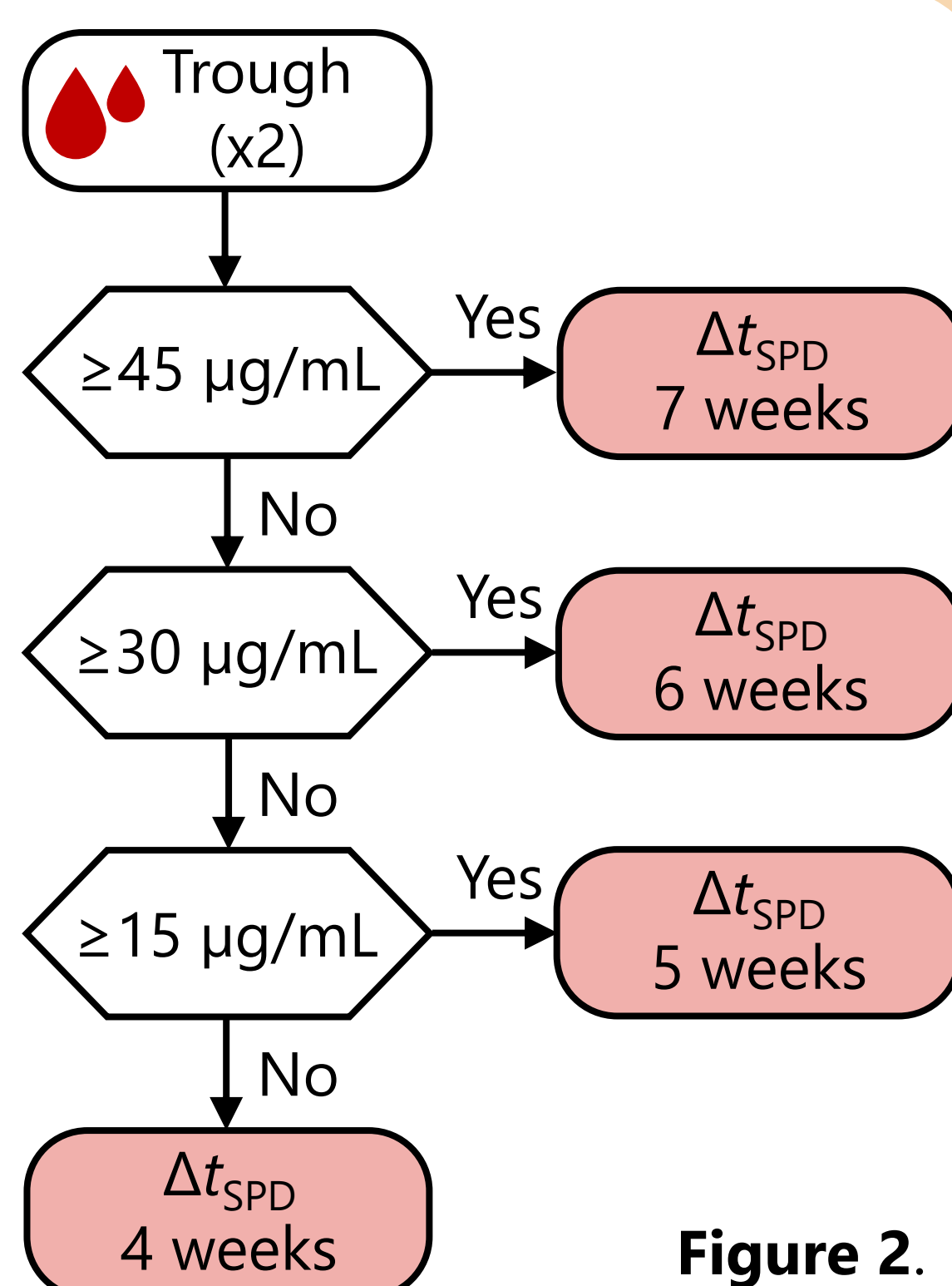


Figure 2.

3. Model-informed precision dosing (MIPD)

Here, a population PK model was developed using NONMEM® on data collected in these studies deploying the SPD protocol, **including 2523 observations of 379 patients** in 20 clinics across the Netherlands. PK of i.v. natalizumab were best described with a two compartment PK model containing both linear (first-order) and non-linear target-mediated elimination following Michaelis-Menten kinetics. Inter-individual variability was applied to linear clearance, peripheral volume and maximum elimination rate. Stepwise covariate model building identified covariates weight on clearance, and height on distribution volumes.

Individual posterior PK estimates, referred to as **empirical Bayesian estimates (EBEs)** were derived using patient height, weight and two trough concentrations at the standard dose interval (MAXEVAL=0).

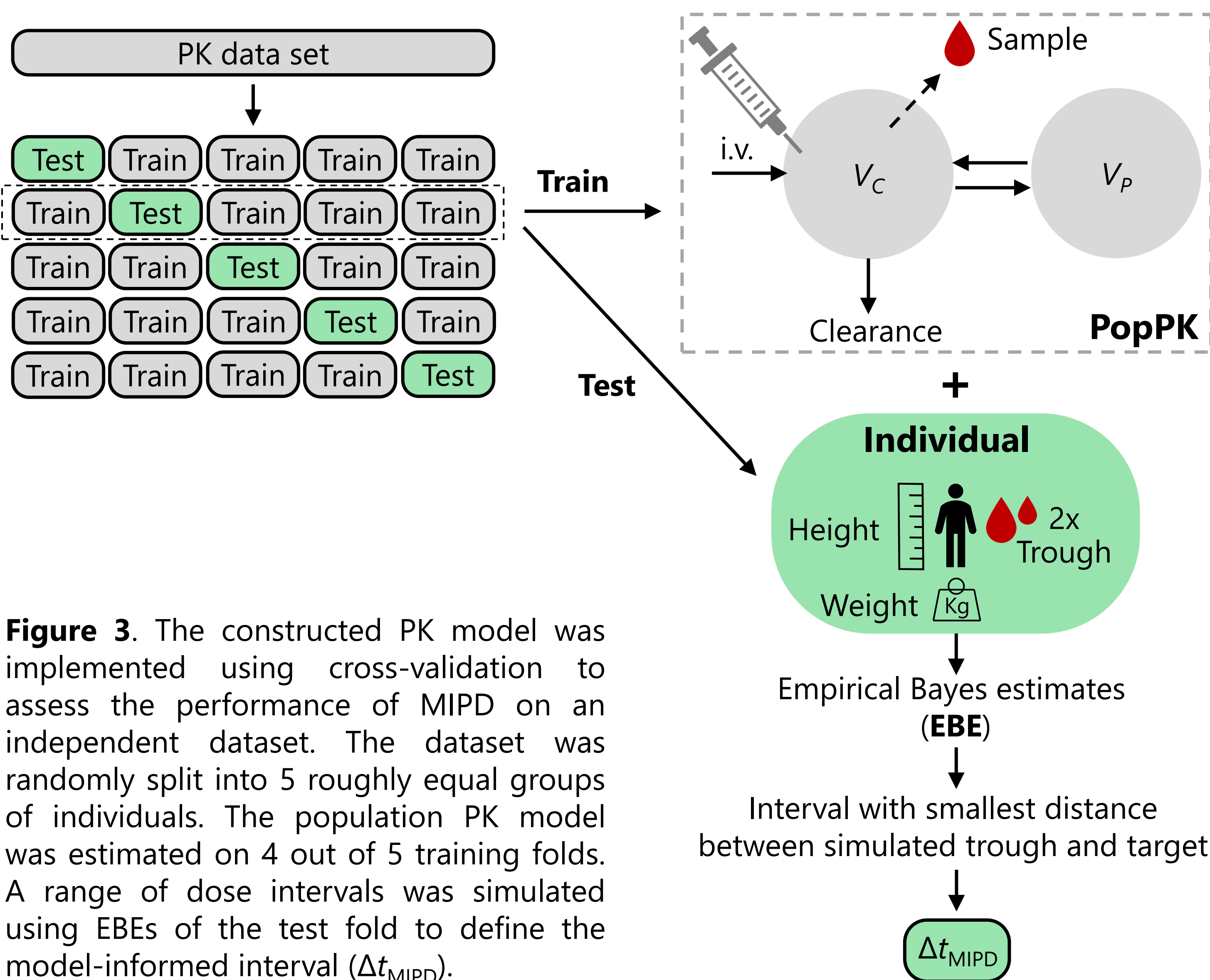
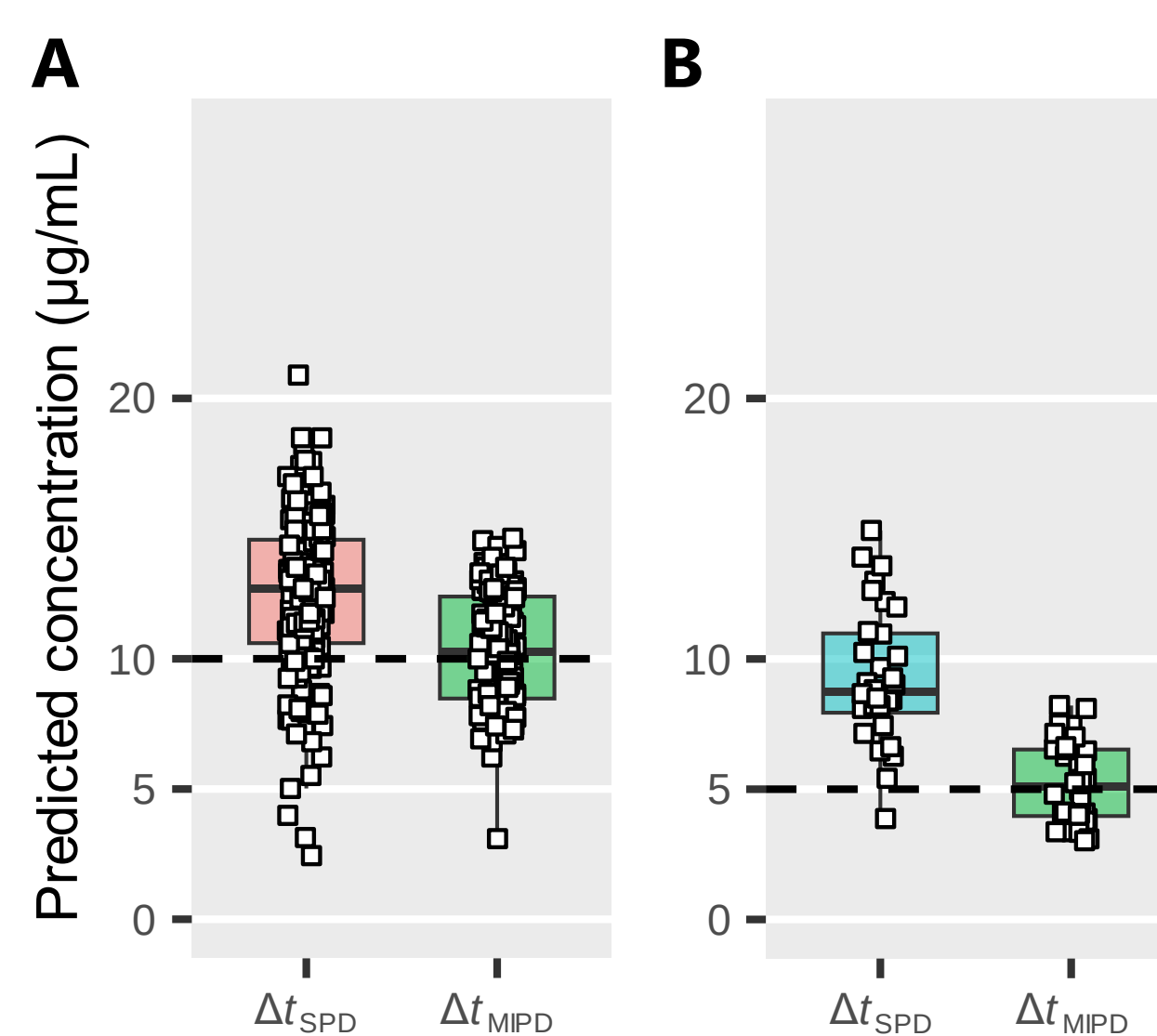


Figure 3. The constructed PK model was implemented using cross-validation to assess the performance of MIPD on an independent dataset. The dataset was randomly split into 5 roughly equal groups of individuals. The population PK model was estimated on 4 out of 5 training folds. A range of dose intervals was simulated using EBEs of the test fold to define the model-informed interval (Δt_{MIPD}).

4. MIPD has improved performance of personalized interval selection



	Target ($\mu\text{g/mL}$)	MPE (%) [95% CI]	RMSE [95% CI]
SPD	10	24.2 [19.53; 28.88]	3.92 [3.28; 4.56]
MIPD	10	3.53 [0.21; 6.85]	2.22 [1.86; 2.57]
SPD	5	85.76 [67.68; 103.85]	5 [3.24; 6.76]
MIPD	5	4.88 [-6.03; 15.79]	1.57 [1.01; 2.12]

Figure 4. Predicted trough levels for individuals both at the SPD interval (Δt_{SPD}) and the MIPD interval (Δt_{MIPD}) targeting (A) 10 or (B) 5 $\mu\text{g/mL}$ at trough. Bias and accuracy were assessed by mean percentage error (MPE) and root mean squared error (RMSE) between the predicted concentration at trough and target.

Simulations of personalized dosing with a model **improved the precision and accuracy of target attainment** compared to the SPD protocol (Figure 4).

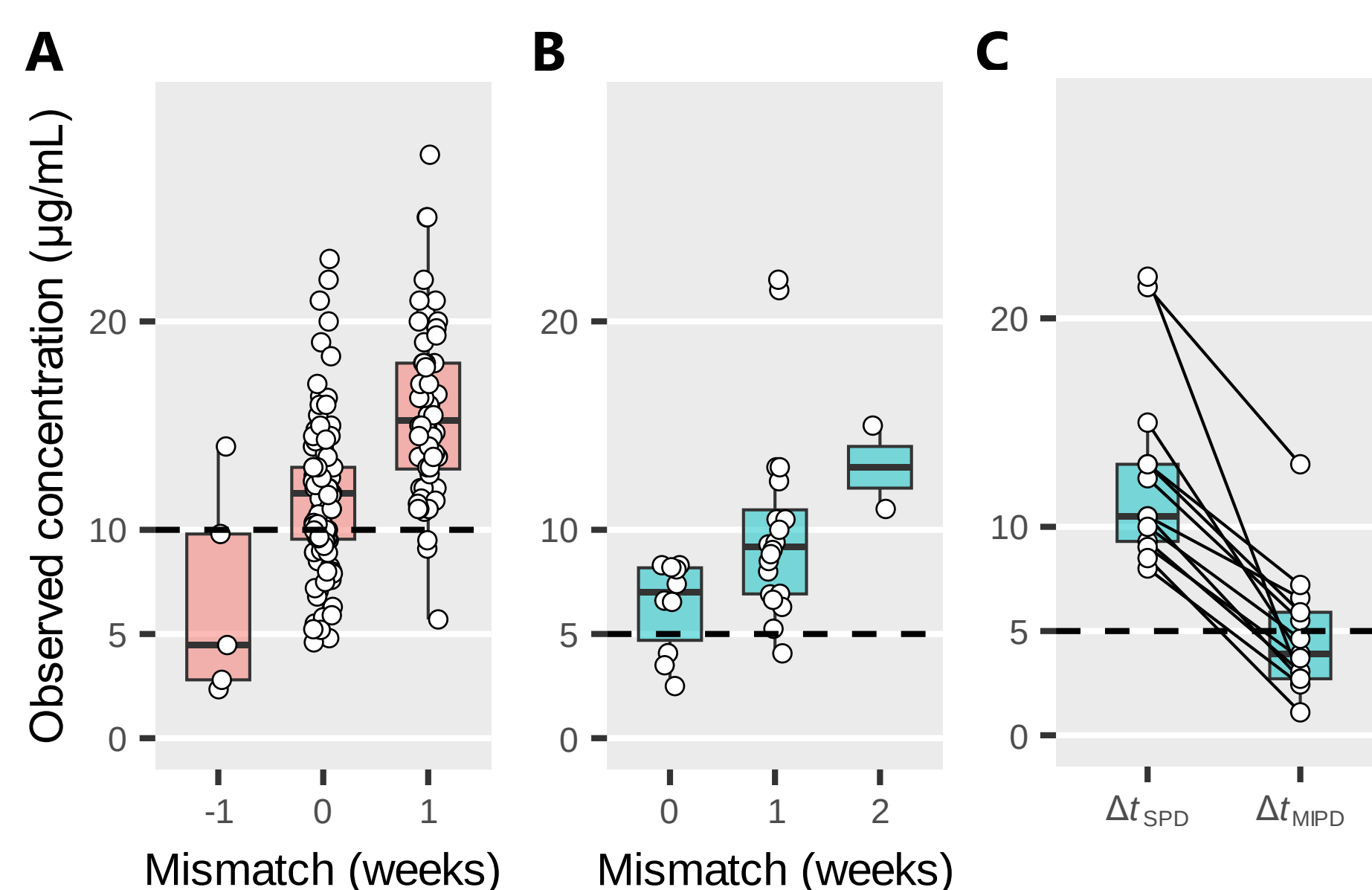


Figure 5. Trough target attainment of MIPD was examined based on a (mis)match of Δt_{MIPD} and Δt_{SPD} . Observed conc. stratified by mismatch (= $\Delta t_{\text{MIPD}} - \Delta t_{\text{SPD}}$) for (A) 10 $\mu\text{g/mL}$ and (B) 5 $\mu\text{g/mL}$ (dotted line).

(C) Individuals which were adjusted after reaching the initial SPD interval, which resulted to be the model-informed intervals.

The intervals chosen in the SPD protocol that matched with the model exhibited concentrations closer to the desired trough level, than those that mismatched, **showing improved target attainment retrospectively**.

5. Ensuring efficacy while optimizing natalizumab dosing

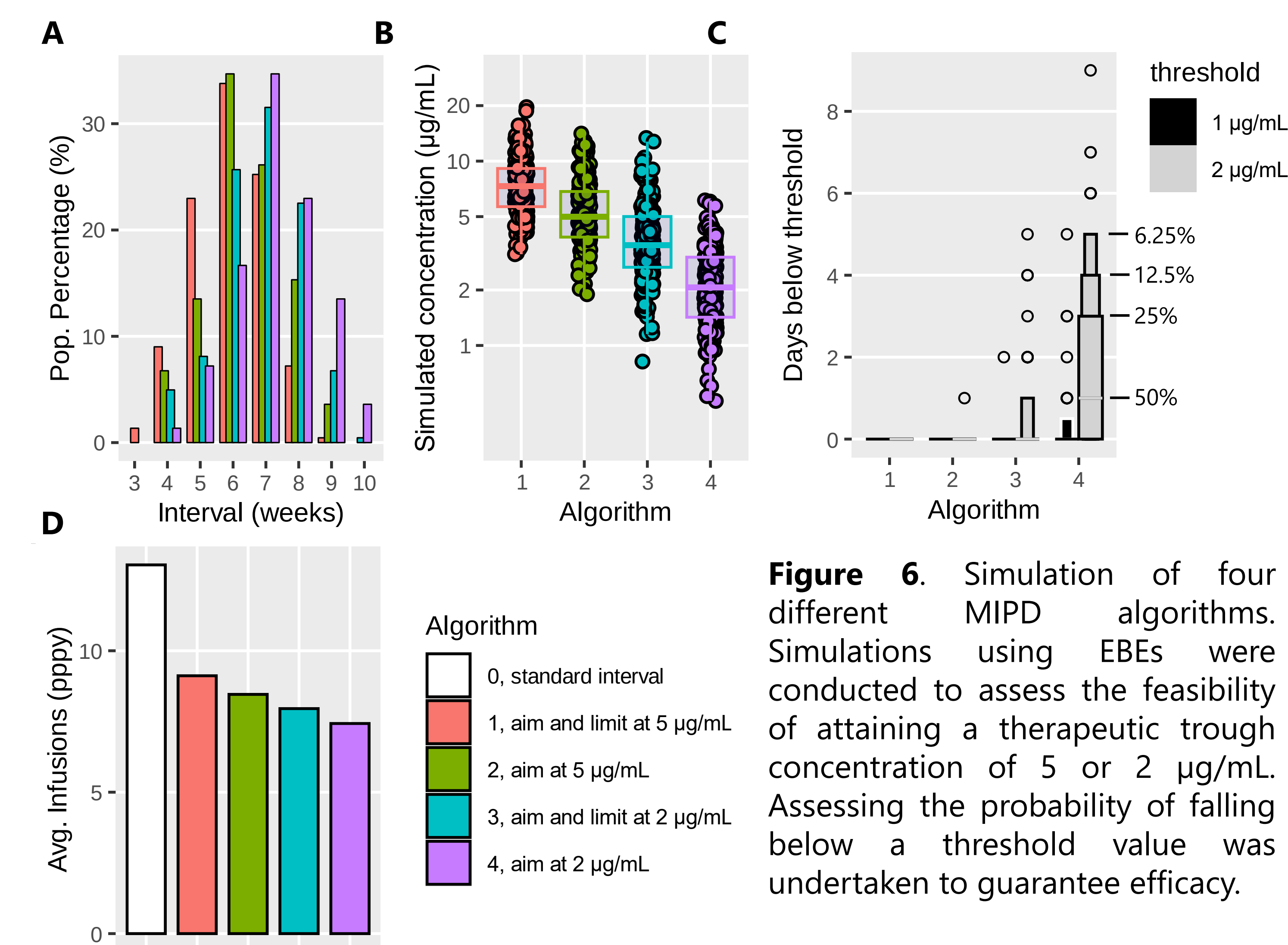


Figure 6. Simulation of four different MIPD algorithms. Simulations using EBEs were conducted to assess the feasibility of attaining a therapeutic trough concentration of 5 or 2 $\mu\text{g/mL}$. Assessing the probability of falling below a threshold value was undertaken to guarantee efficacy.

Simulation of algorithm 3 resulted in a median (IQR) trough level of 3.5 (2.65-5) $\mu\text{g/mL}$. MIPD simulations indicated an **average dose interval of 7 weeks compared to 4 weeks, reducing infusions on average per patient per year by 40%**. By using MIPD, the frequency of infusions and health care visits is lowered, reducing the drug.

6. Conclusion

Simulations of MIPD outperformed the conventional TDM-guided protocol by providing improved accuracy in selecting individual treatment intervals, resulting in more precise trough target attainment. **Simulations further indicate a preferential clinical deployment of MIPD for natalizumab in terms of healthcare and patient burden.**