

Model-informed precision dosing during infliximab induction therapy to improve long-term deep remission rates in paediatric patients with inflammatory bowel diseases

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Background

- **Higher infliximab concentrations** during induction treatment are **associated with deep remission** (combined endoscopic and corticosteroid-free clinical remission) at six months in paediatric patients with inflammatory bowel diseases (IBD)¹.
- An infliximab **concentration of 5.0 mg/L at week 12** was **previously defined** as the best target for deep remission.¹
- Under the approved weight-based dosing strategy (5 mg/kg), patients with lower bodyweight are expected to have lower infliximab trough concentration since the relationship between bodyweight and the pharmacokinetic (PK) parameters of infliximab is nonlinear.²
- **Model-informed precision dosing (MIPD)** has been advocated to appropriately account for PK variability during infliximab treatment.³

Objectives

- To develop an exposure-response model describing the relationship between infliximab trough concentration at week 12 and probability of attaining deep remission.
- To evaluate the predictive ability of samples taken at different time points using different MIPD approaches.
- To evaluate predictive ability of monitoring markers during induction towards deep remission.

Methods

Data	
Number of patients:	31 paediatric patients with IBD (aged 4 – 18 years)
Study centers:	Prospective study ¹ University Hospitals Leuven, Belgium
Dosing scheme:	Infliximab induction treatment

Exposure-Response model	
Software:	NONMEM (version. 7.5)
Model:	Logistic regression Markov models with an E _{max} function
Model validation:	Bootstrap (N=1000)

Population pharmacokinetic model identification	
Methods:	Literature searches to identify models
Model approaches:	• Single model approach • Multi-model approaches (model selection and model averaging)⁴
Weighting schemes⁴:	• Objective function values (OFV) • Adjusted Akaike information criterion (AIC) • Squared prediction errors (SSEs)
Evaluated settings:	• <i>A priori</i> prediction (only covariate data) • <i>Maximum a posteriori</i> predictions (concentrations at week 2, 4, or 6)

Predictive performance evaluations	
Accuracy:	• Relative bias (rBias) • $\pm 20\%$ rBias with a 95% confidence interval (CI) including zero was considered clinically acceptable.
Precision:	• Relative root mean square error (rRMSE) • as low as possible
Classification accuracy	• At the identified target

Monitoring marker evaluations	
Markers:	• Model-predicted exposure metrics (concentrations, AUC) • Estimated infliximab clearances • Biomarkers (serum albumin, C-reactive protein, erythrocyte sedimentation rate)
Methods:	• Receiver operating characteristic (ROC) analysis • Compared area under the ROC curve (AUROC) using Delong's method (P ≤ 0.05)

Results

- Deep remission was achieved in 18 patients (58%) at six months. A week 12 infliximab concentration of 4.3 mg/L corresponded to a 50% probability of attaining deep remission (EC₅₀: mean 4.5 [95% CI 1.1–7.4] mg/L). A trough concentration target of 7.5 mg/L, associated with 64% probability of attaining deep remission was identified as optimal (**Figure 1**).
- The performance metrics of the multi-model approaches using SSEs were better than the other weighting schemes regarding accuracy and precision (**data not shown**).
- The accuracy of the predicted week 6 infliximab trough concentration based on covariates nor the trough concentration at week 2 was clinically unacceptable (**Figure 2**).
- The accuracy of the predicted week 12 infliximab concentration based on week 6 covariates was also highly biased and imprecise. MAP prediction using the trough concentration at week 6 (*with rapid assay*) resulted in a clinically acceptable prediction of the week 12 concentration (**Figure 2**).
- Providing an additional intermediate concentration at week 4 to the trough concentration at week 2 (*without rapid assay*) improved predictions of the week 12 concentration (**Figure 2**).
- To predict the trough concentration at week 12, MAPs providing the trough concentration at week 6 had significantly higher classification accuracy than that of without (**data not shown**).
- The AUROCs of multi-model averaged predicted exposure metrics and estimated clearances at week 12 (0.738, 95% CI 0.561 – 0.915]) were not significantly different from the AUROC of the measured infliximab concentration at week 12 (0.844 [95% CI 0.680 – 1.000]) in classifying deep remission, P = 0.125.
- None of the observed biomarkers was predictive for deep remission (**data not shown**).

Conclusion

- The success rate of infliximab induction therapy in children could be **improved by measuring the infliximab concentration at week 6 using a rapid assay** and adjusting the infliximab dose on the same day using our MIPD software tool, aiming for a 7.5 mg/L infliximab concentration at week 12.
- **The infliximab clearance may be monitored** as well by sampling again at week 12/14 (**Figure 3**).
- Our MIPD software tool is freely available for stakeholders seeking to perform an innovative prospective clinic trial aiming at improved paediatric IBD care (**Figure 3**).

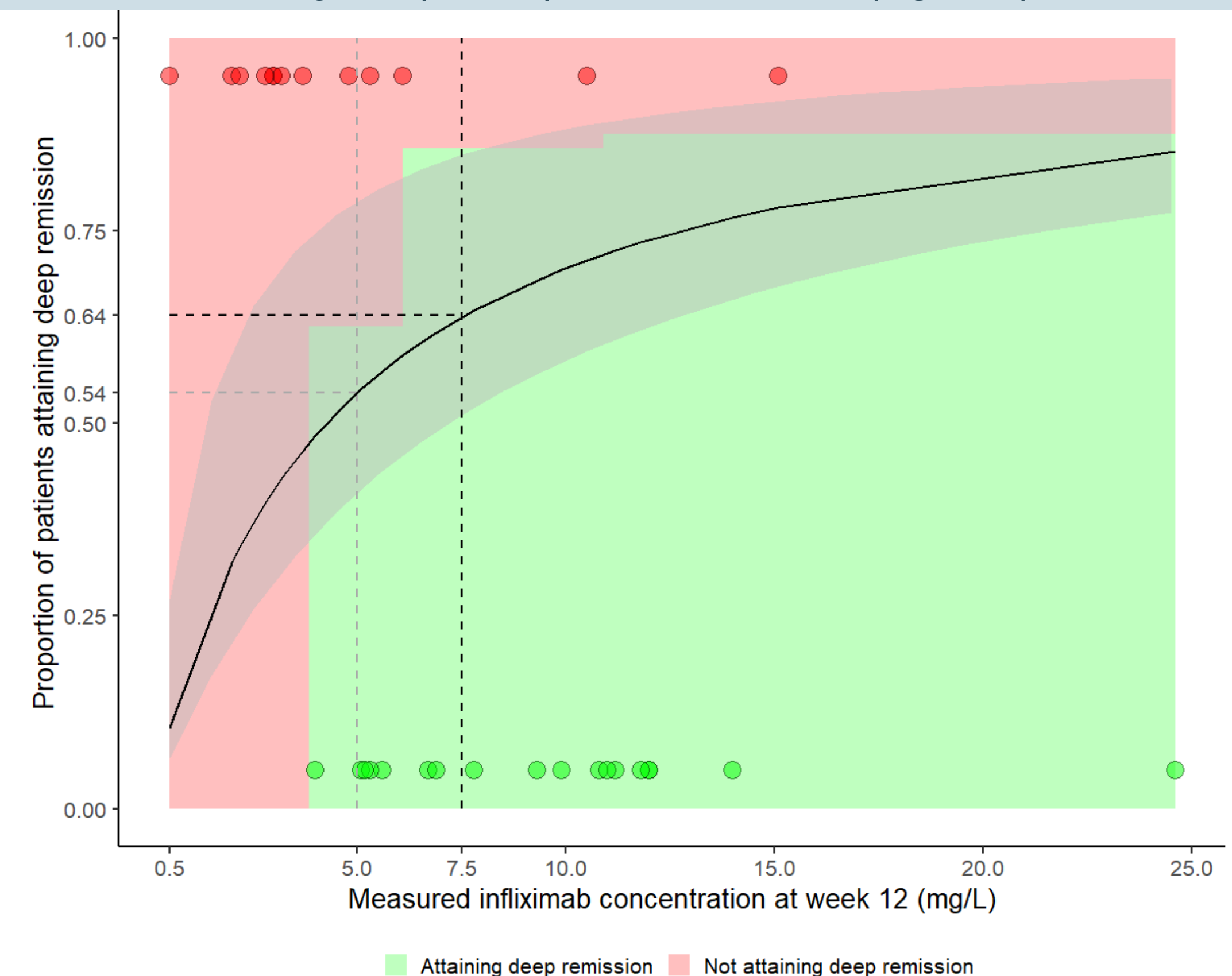


Figure 1. The goodness-of-fit plot of the logistic regression Markov exposure-response model. Observed (tiles) proportion of patients attaining (green) and not attaining (red) deep remission and predicted (solid black line) proportion of patients attaining deep remission as a function of the measured infliximab concentration at week 12 with a symmetric 95% confidence interval (grey shaded area). Circular shapes represent children attaining (green) and not attaining (red) deep remission.

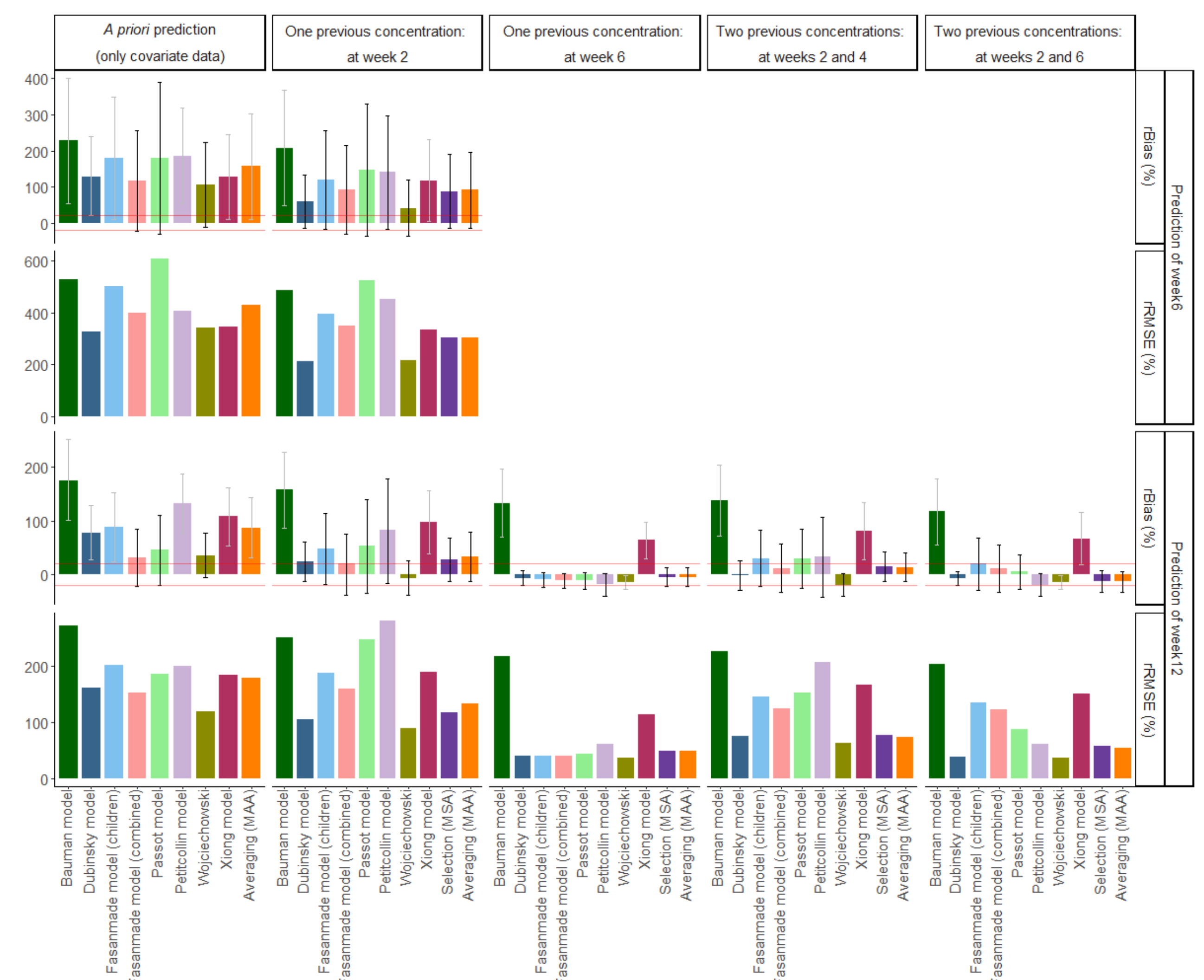


Figure 2. The predictive performance of eight single population pharmacokinetic models versus the multi-model approaches using all eight models for predicting the infliximab concentration at week 6 (top) and week 12 (bottom). Evaluated settings included *a priori* prediction (with only covariate data) and maximum *a posteriori* (MAP) prediction using covariate data and one previous concentration (at week 2, or at week 6) or two previous concentrations (at weeks 2 and 4, or at weeks 2 and 6). Whiskers indicate the 95% confidence interval (CI) of the relative bias calculated via the standard error (black whiskers indicate 95% CIs including 0). Horizontal red lines indicate the $\pm 20\%$ range of the rBias that is deemed clinically acceptable. Note: Model weights during *a priori* prediction are equal (1/number of models), precluding a model selection procedure in this setting.

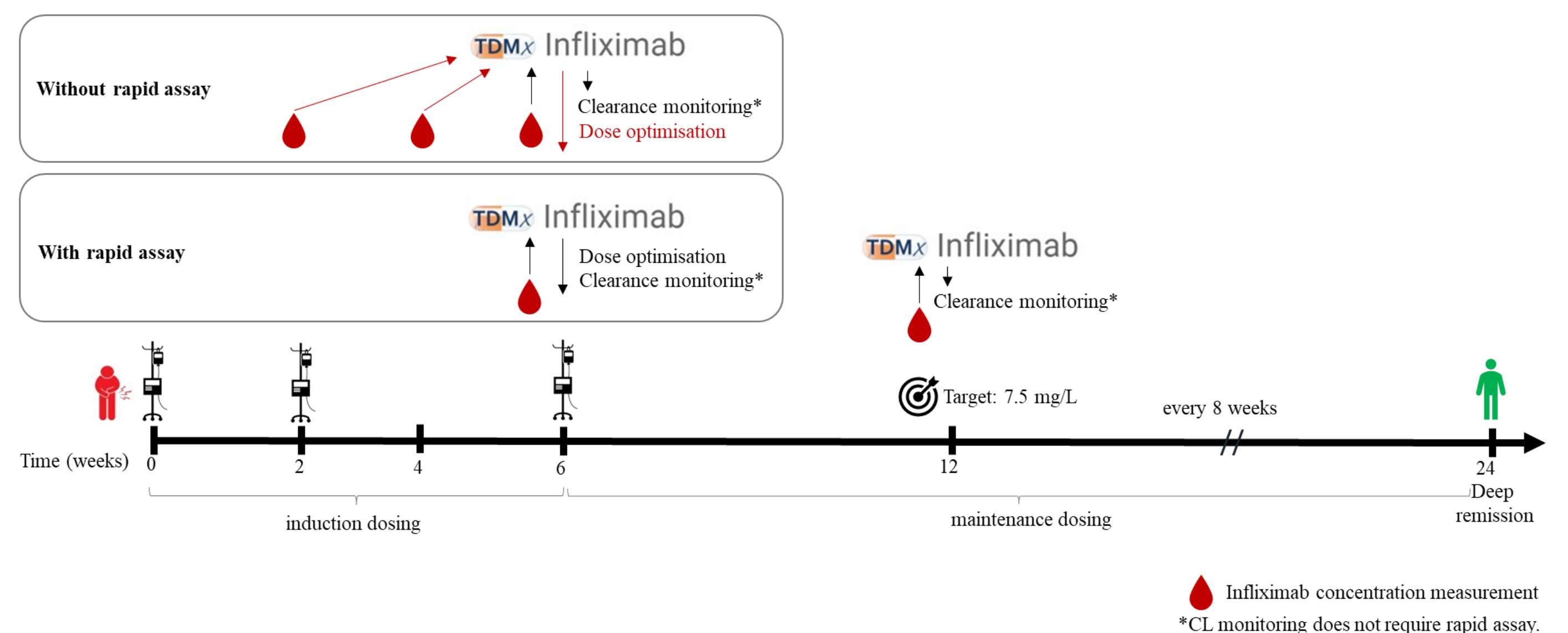


Figure 3. Suggested MIPD framework for guiding infliximab induction treatment in children with IBD.

References

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