

Optimal study design for pharmacokinetic modeling of teicoplanin in critically ill children, including those undergoing Continuous Renal Replacement Therapy



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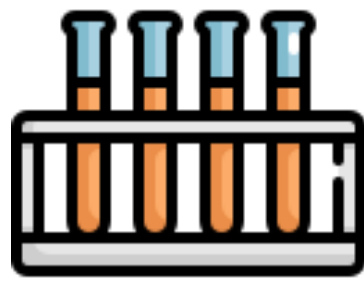
Introduction

In pharmacokinetic (PK) studies, setting the adequate number of samples and sampling times is a critical aspect for building robust population models. In pediatric patients undergoing Continuous Kidney Replacement Therapy (CKRT), the main challenge is the limited availability of subjects, further compounded by children's lower blood sampling tolerance compared to adults [1]. Additionally, the high cost of each sample poses a significant constraint.

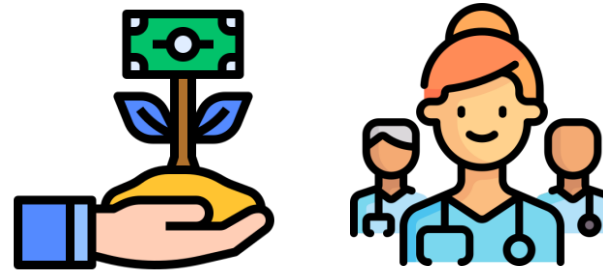
1. Scarcity of patients
(Especially with CKRT)



2. Limited blood sampling tolerance



3. Economic expense and hospital human resources



Variations in number of patients, samples per patient, or distribution of samples across different matrices (plasma, prefilter, postfilter, effluent) can significantly impact model development.

Objective: optimizing the study design to maximize efficiency while minimizing the required sample size.

Methods

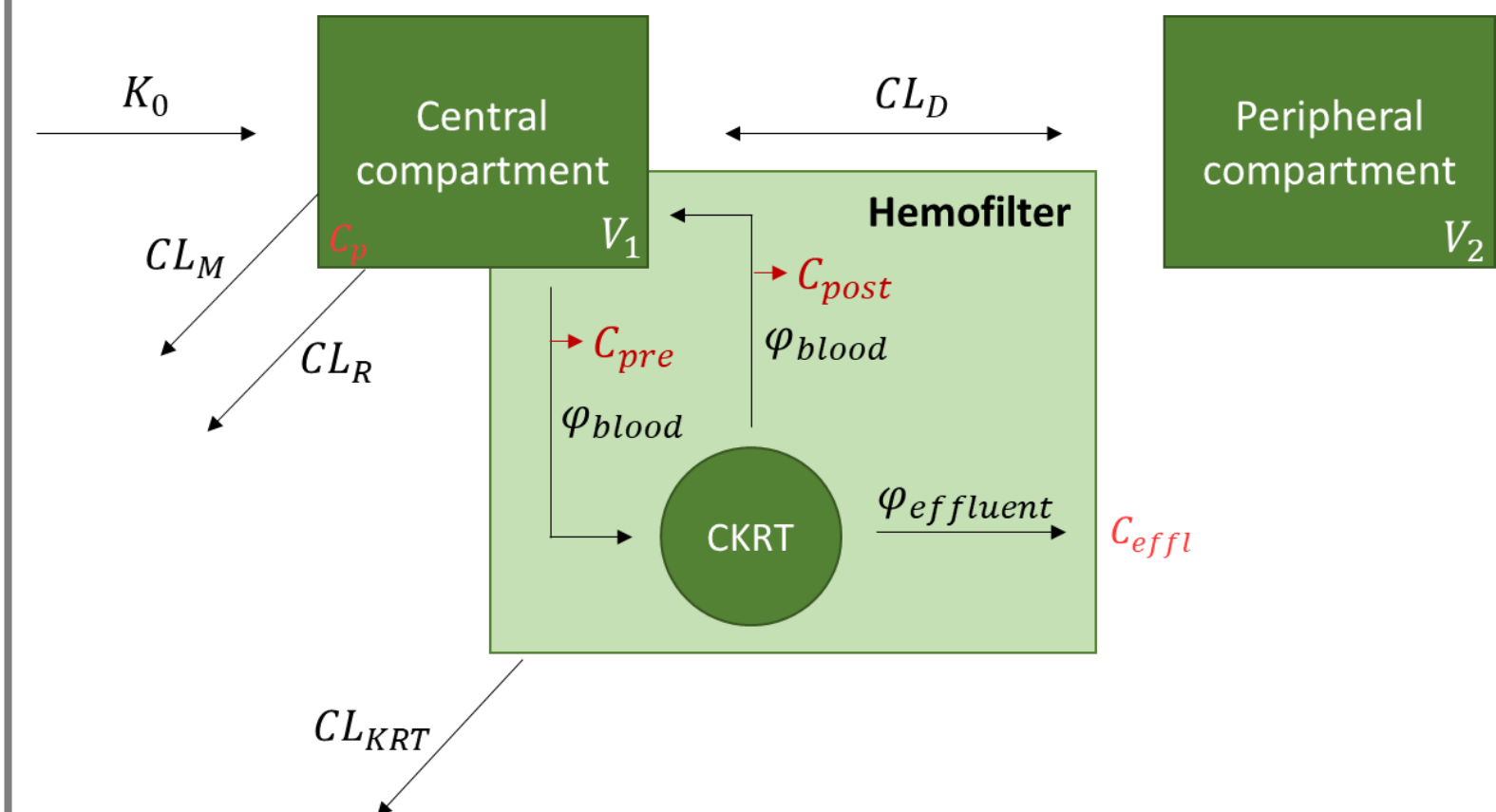


Figure 1. Model structure of the models for teicoplanin, piperacillin and meropenem in children with or without CKRT.

Based on previously developed models for teicoplanin piperacillin and meropenem (**Figure 1**) [2-4] and after some design constraints, the workflow followed in the present evaluation is represented in **Figure 2**:

1. The Fisher information matrix (**FIM**) is used to optimize number of samples and sampling times.
2. The proportion of patients in each group (with and without CKRT) is evaluated using the **FIM**.
3. Simulations and re-estimations are run with the median covariate values to validate the results from the FIM optimization. Additionally, SSEs are run with 100 databases with different covariate values to test the design sensitivity to a range of patient covariates.

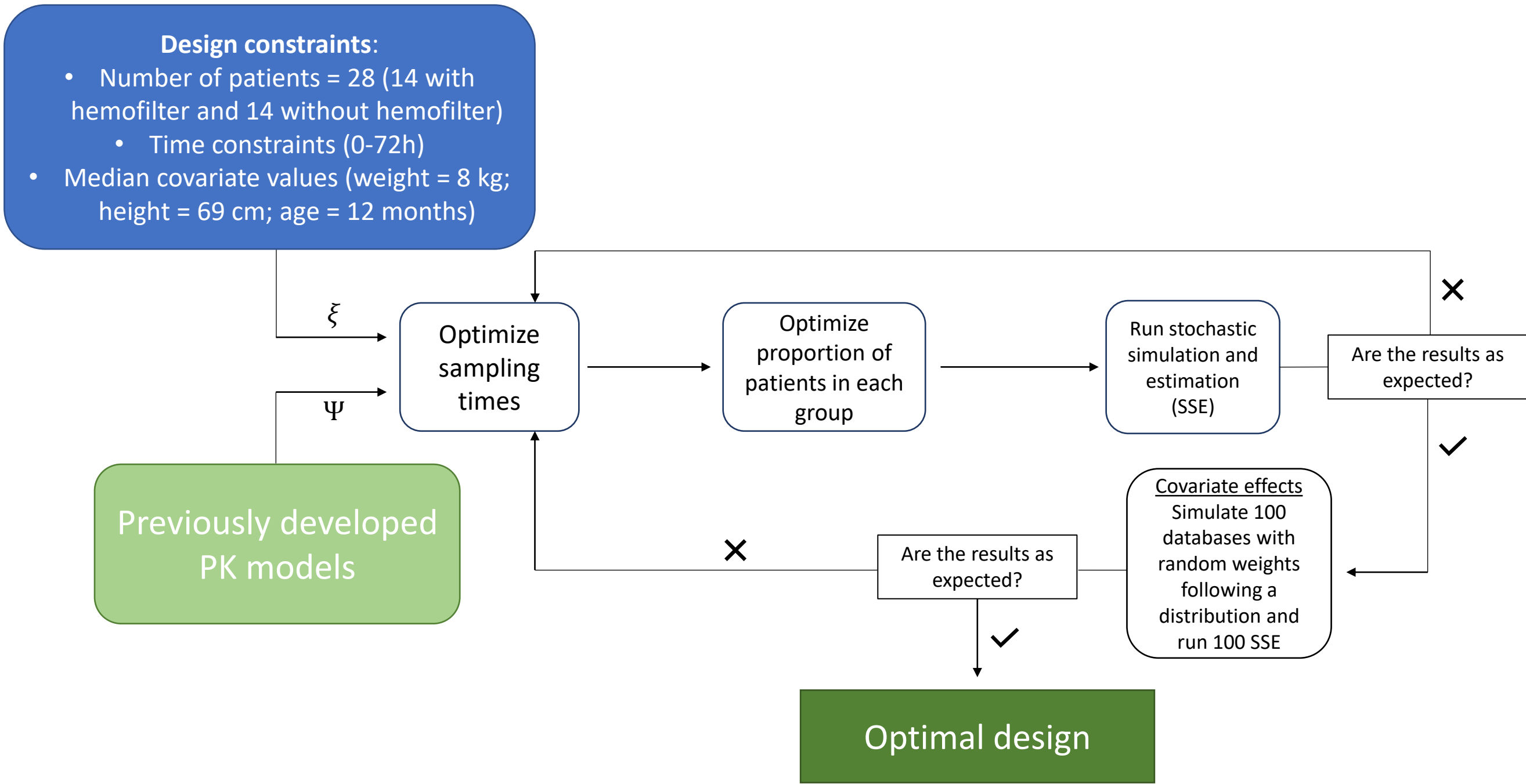


Figure 2. Design optimization workflow. NONMEM 7.5 was used for FIM optimization (\$DESIGN) and PsN was used for SSEs. Ψ , model parameters; ξ , design variables.

Results

1. Optimal sampling times after FIM optimization

Table 2. Sampling times (h) resulted from the design optimization.

		Teicoplanin	Piperacillin	Meropenem
No CKRT	Plasma	1, 6, 40	1, 3, 7, 40	1, 3, 8, 16, 28, 64
	Prefilter	6, 40	3, 7, 40	1, 3, 16, 28, 64
CKRT	Postfilter	1, 6	1,40	1, 8, 16, 28
	Effluent	1, 6, 40	1, 3, 7, 40	1, 3, 8, 16, 28, 64

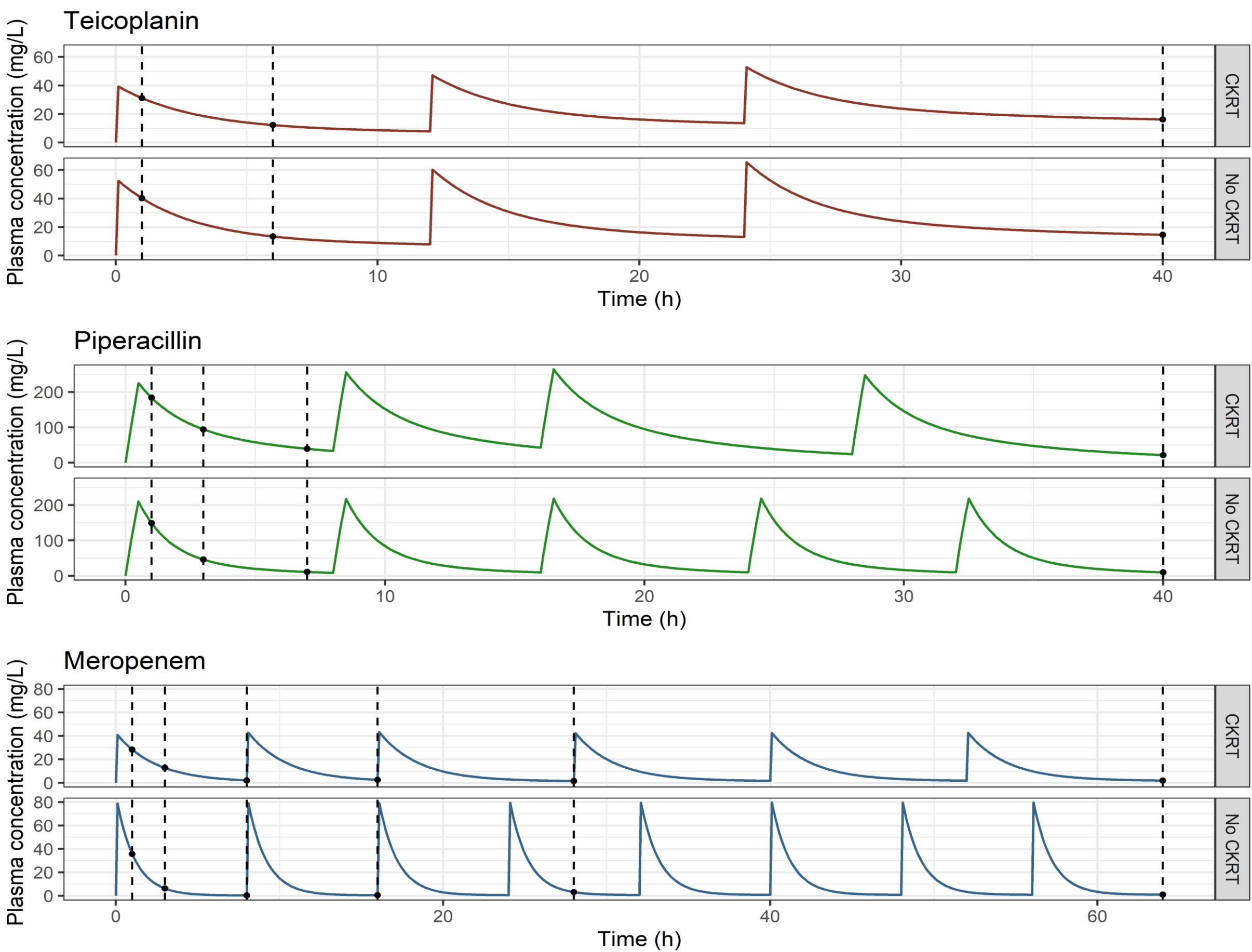


Figure 3. Solid lines represent the typical PK profile. Dashed vertical lines correspond to the optimal sampling times after FIM optimization.

2. Evaluation of proportion of patients in each group

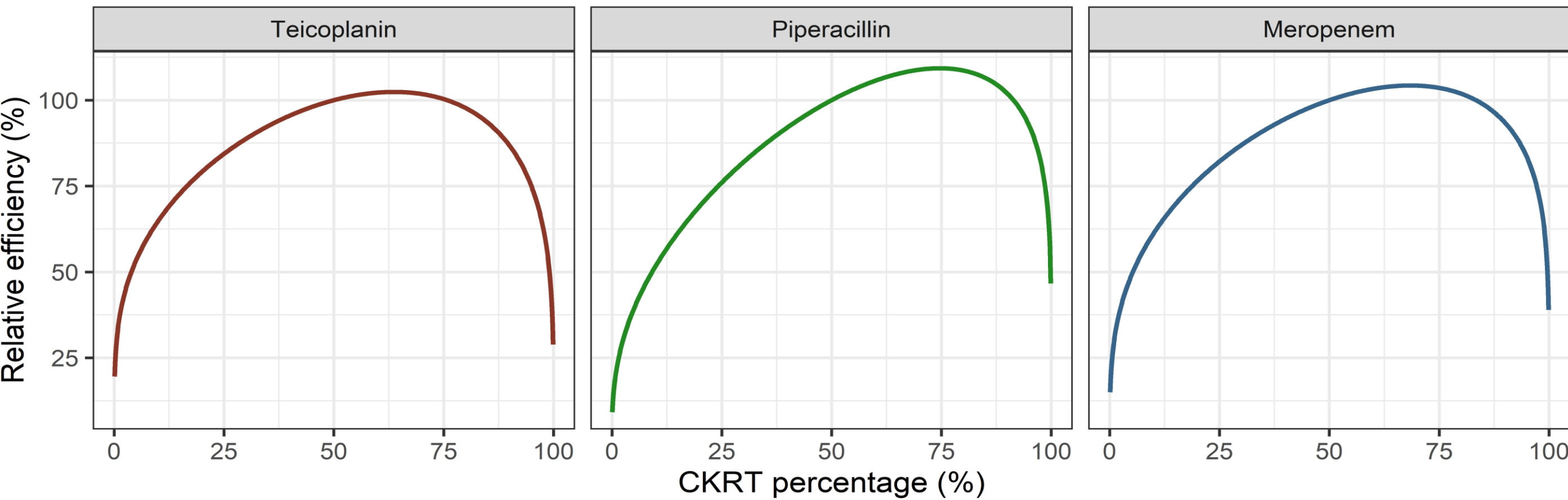


Figure 4. Relative efficiency of the different proportions of CKRT patients in the study population compared to the 50/50 proportion.

3. Design evaluation with SSEs

1. Using the typical patient with respect to covariates
2. Using different values for weight, height, age, eGFR and filter size

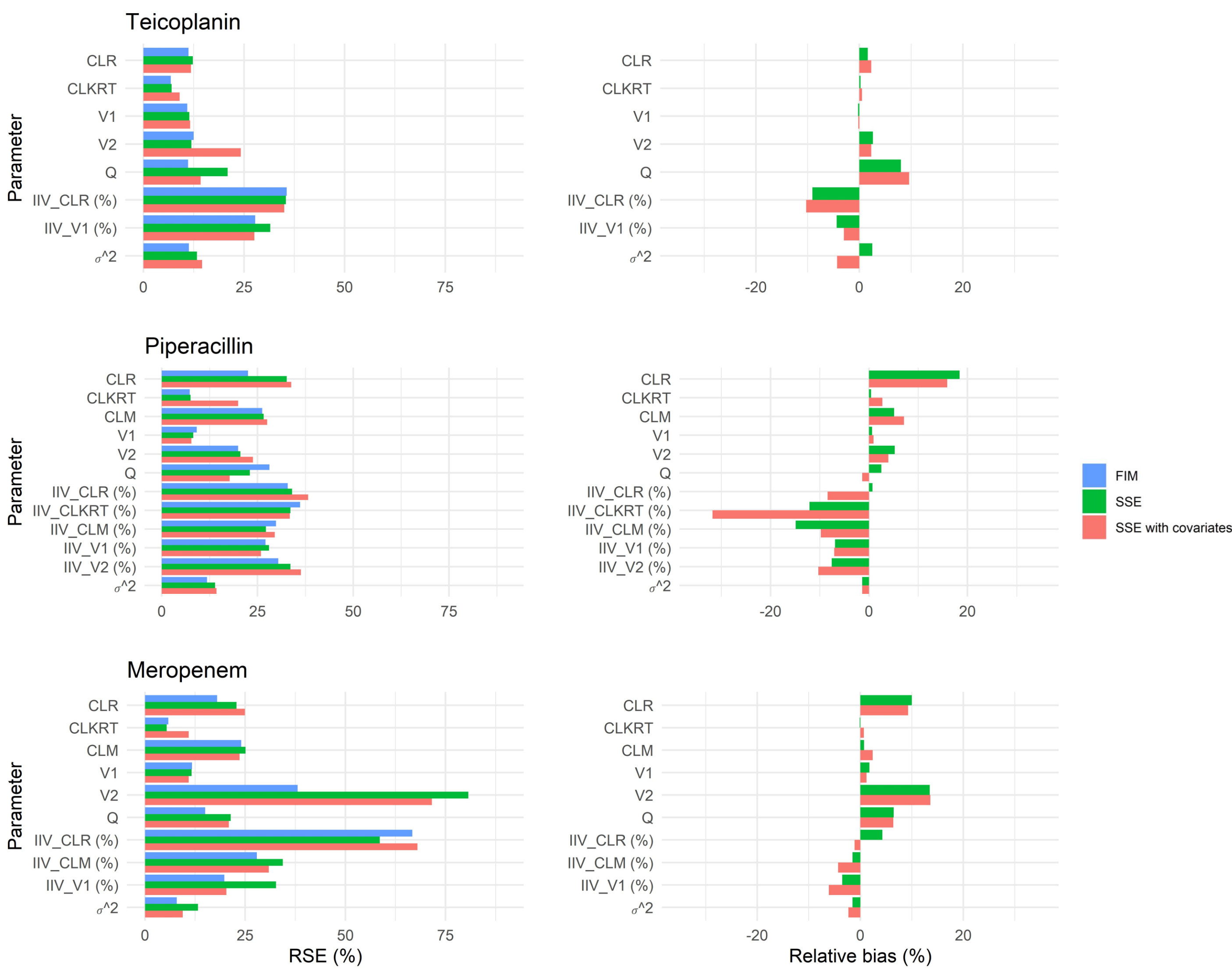


Figure 5. RSE values from FIM optimization and RSE and relative bias values after performing SSEs.

Conclusion

This work emphasizes the importance of optimizing study designs, as it facilitates the development of PK models by reducing the amount of samples needed and economic costs.

Bibliography

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