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The reference corrected VPC: A more intuitive model diagnostic

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Objective

To introduce the reference corrected visual predictive check (rcVPC), that leverages a user defined set of independent variables, for a more intuitive model diagnostic that can be used for improved communication of modeling results.

Background

The prediction corrected visual predictive check (pcVPC) is an informative model diagnostic for heterogenous studies[1]. However, a drawback with these plots is that the prediction correction often results in y-axis trends that are nonintuitive and do not translate to any meaningful aspect of the study design.

Methods

The definition of a reference dataset with user defined independent variables, e.g., covariates and dosing regimens, but otherwise with the same dimensions as the analysis dataset.

N number of simulations are conducted with this reference dataset as well as with the original analysis dataset.

The observed and simulated dependent variable are subjected to the same type of reference correction, as follow:

$$rcY_{ij}^{*} = Y_{ij} \cdot PRED_{ij,ref}/PRED_{ij}$$

$$rcY_{ij} = e^{\left(\ln\left(PRED_{ij,ref}\right) + \left(\ln\left(rcY_{ij}^{*}\right) - \ln\left(PRED_{ij,ref}\right)\right) \cdot sd(\ln(Y_{ij,ref})/sd(\ln(rcY_{ij}^{*})\right)}$$

Where rcY_{ij} is the reference corrected dependent variable, Y_{ij} is the dependent variable and $PRED_{ij}$ is the population typical prediction, each for the i^{th} individual and j^{th} observation. $Y_{ij,ref}$ and $PRED_{ij,ref}$ are the corresponding variable for the reference simulations.

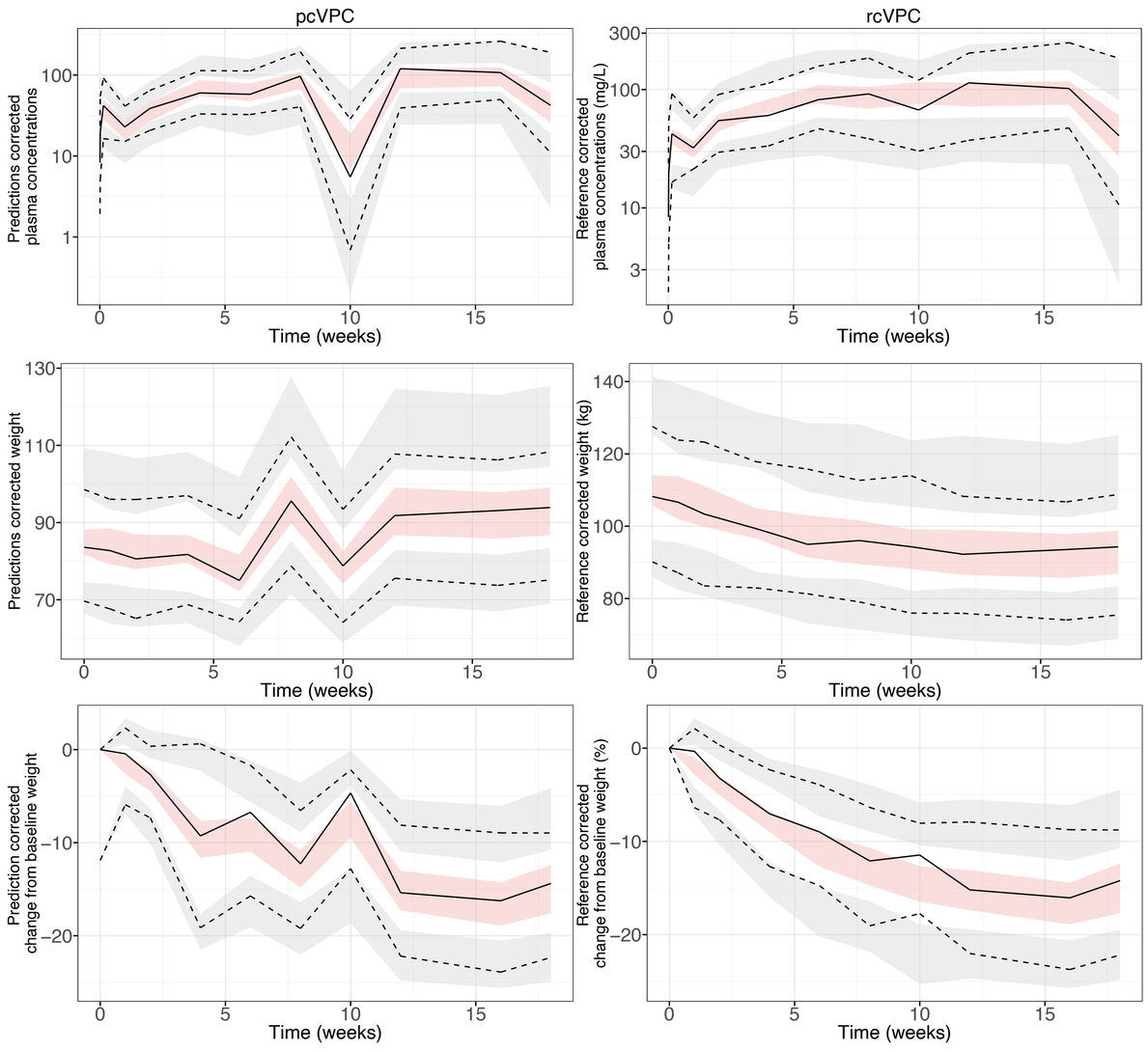

Figure 1. pcVPC and rcVPC of PK, PD and change from baseline PD data versus tme in Example I. The rcVPC dependent variables are normalized to a reference subject with ADDL=15 and AMT=600 mg, the two main features of POC-study design. The solid and dashed black lines represent the median, 5th and 95th percentiles of the corrected observations; the shaded pink and gray areas represent the 95% confidence intervals of the median, 5th and 95th percentiles predicted by the model.

Conclusions

rcVPC provides more intuitive interpretation and guidance to model development/evaluation process compared to the traditional pcVPCs.

rcVPCs can be used not only for model diagnostic purposes but as a means for efficient communication of modeling results.

The rcVPC approach was compared to pcVPCs for the real-data inspired examples shown in table 1.

Table 1. Real-data inspired examples.

Example	PK/PD	Covariates	Design
I	One compartment, Turn-over	Alometric scaling	MRD-study: 5 patient x 5 doses over 6 weeks + 4 weeks follow-up. POC-study: 20 patients x 1 dose over 16 weeks + 2 weeks follow-up.
II	Two compartement	Alometric scaling eGFR maturation Formulation on F	Five age-cohorts, 18 subjects per cohort. Opportunistic sampling from 1 to 4 samples per subject.

Results

The rcVPCs showed the model's predictive performance with a more intuitive interpretation of the y-axis scale, e.g., plasma concentrations normalized to an individual with weekly dosing of 600 mg for 16 weeks (Figure 1).

The rcVPC approach indicated the true model misspecifications more clearly when a misvspecified linear exposure-response (ER) relationship was present (Figure 2) and with the lack of an appropriate clearance maturation function (Figure 3).

In Figure 2, the improved approach was used to normalize the y-axis variable to depict the end of treatment response at week 16 versus $C_{trough\ ss}$, showcasing its use as a model diagnostic and an efficient tool for communicating the established underlying ER relationship.

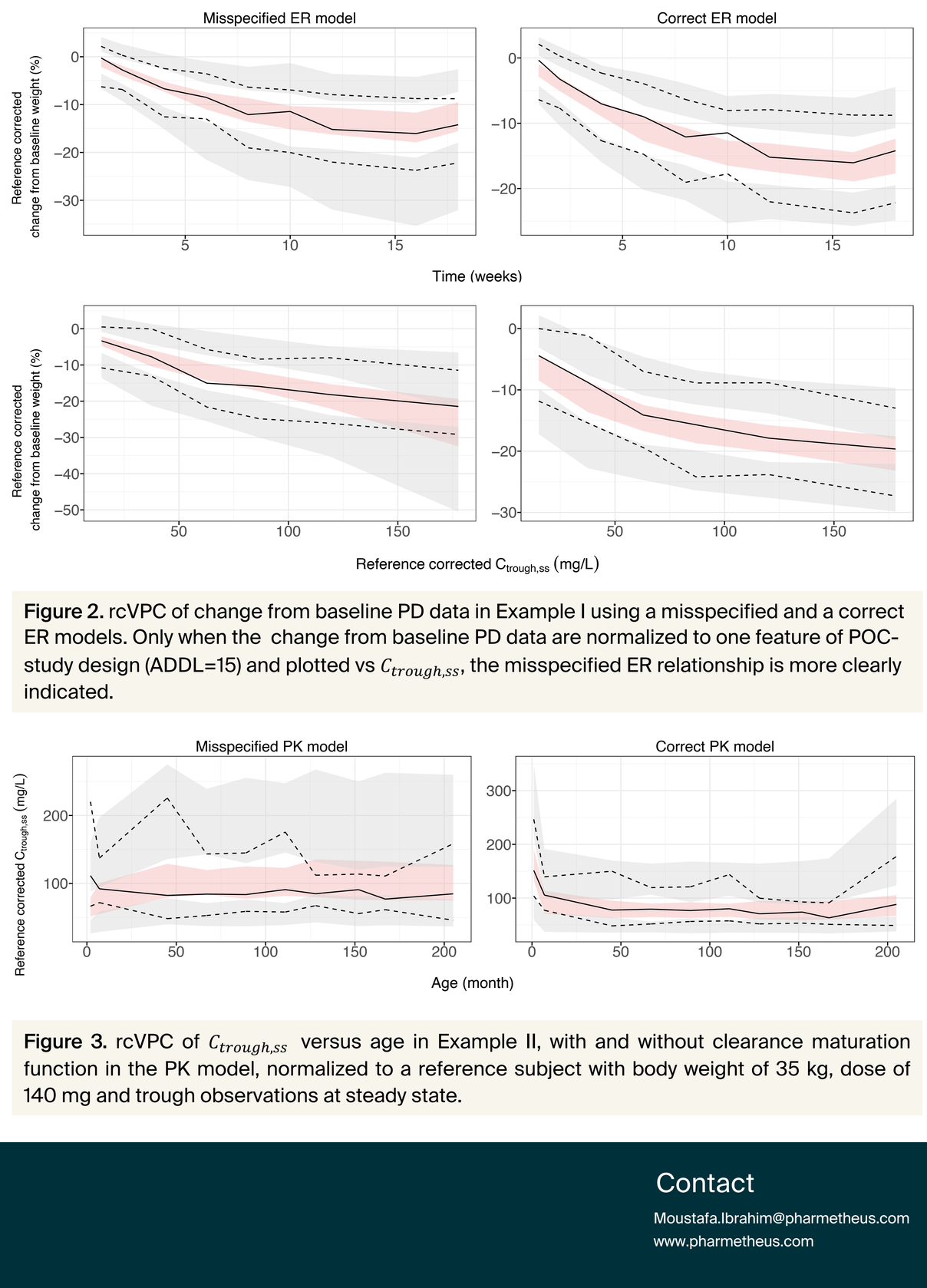

Figure 2. rcVPC of change from baseline PD data in Example I using a misspecified and a correct ER models. Only when the change from baseline PD data are normalized to one feature of POC-study design (ADDL=15) and plotted vs $C_{trough,ss}$, the misspecified ER relationship is more clearly indicated.

Figure 3. rcVPC of $C_{trough,ss}$ versus age in Example II, with and without clearance maturation function in the PK model, normalized to a reference subject with body weight of 35 kg, dose of 140 mg and trough observations at steady state.

References

1. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J. 2011 Jun;13(2):143-51.

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Supplementary material

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Plots of row data

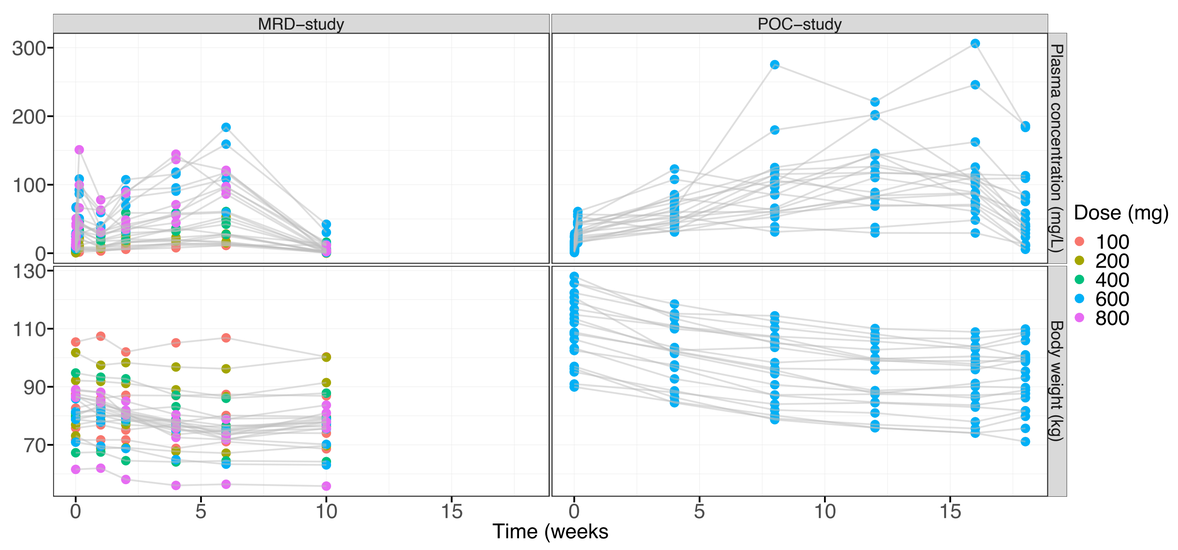

Figure S1. Time profiles of the observed PK and PD data from Example I, stratified by study and colored by dose group.

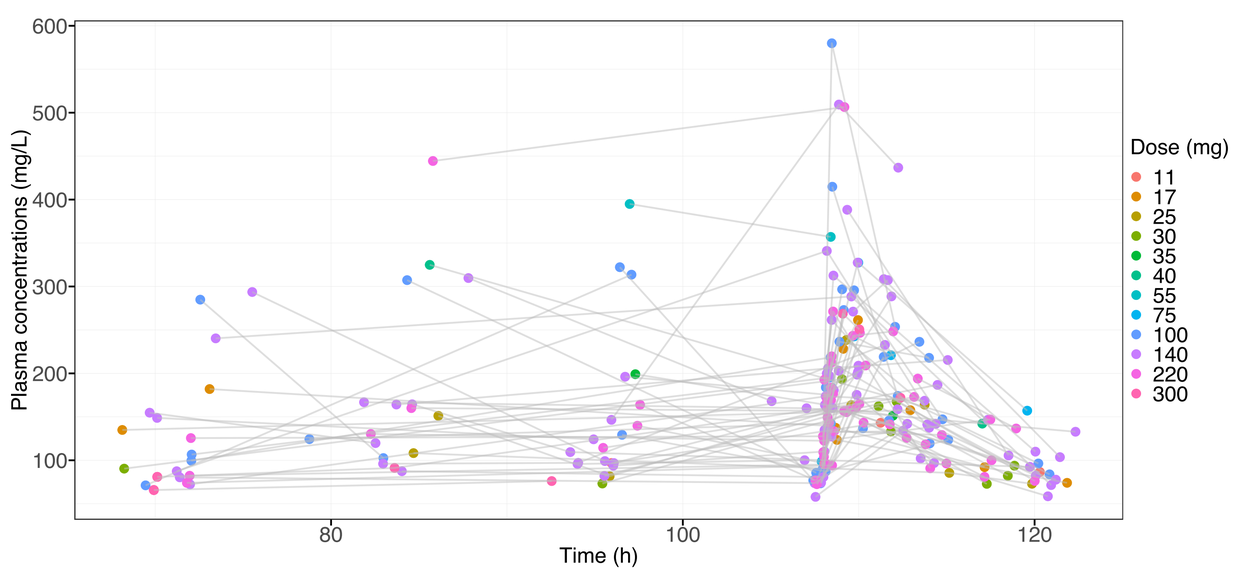

Figure S2. Time profiles of the observed PK data from Example II, colored by dose group.

Additional plots from Results

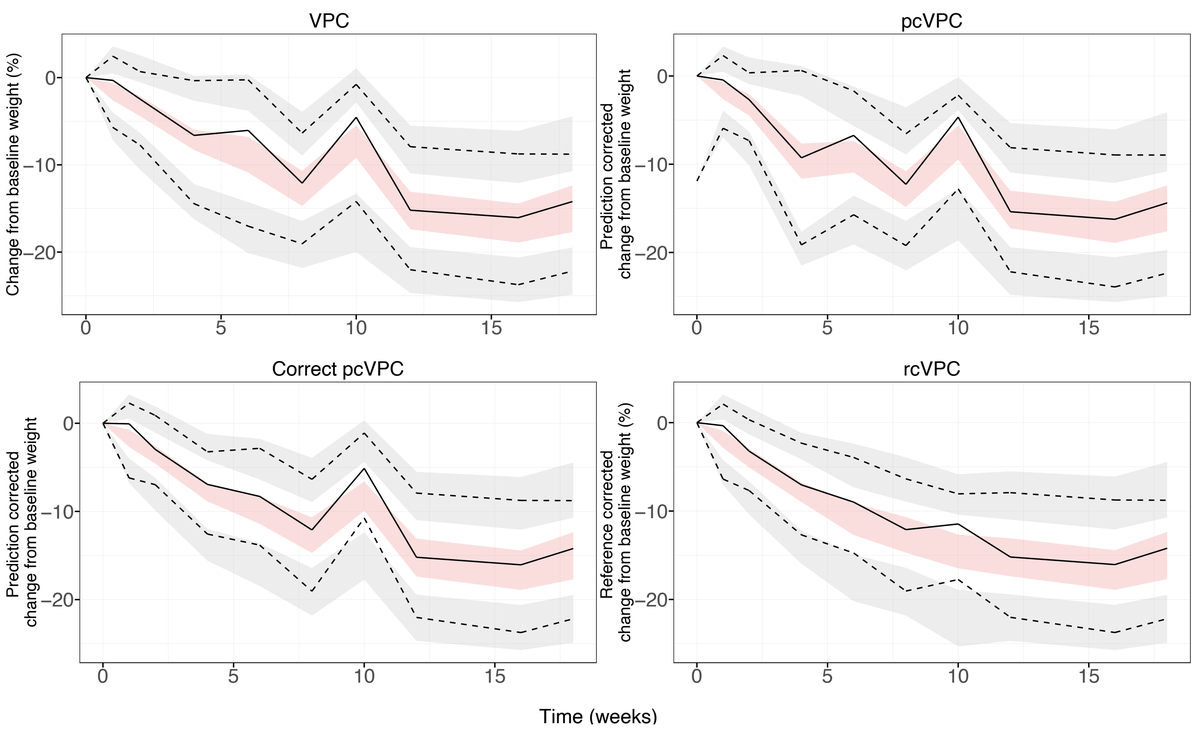

Figure S3. VPC, pcVPC and rcVPC of change from baseline PD data versus time in Example I. Standard pcVPC is produced using PRED data item outputted from NONMEM, which is the predictions of the dependent variable, not the predictions of the change from baseline dependent variable. The correct pcVPC is produced using the right predictions of the change from baseline dependent variable by fixing all OMEGAs and SIGMAs to zero. The rcVPC dependent variables are normalized to a reference subject with ADDL=15 and AMT=600 mg, the two main features of POC-study design.

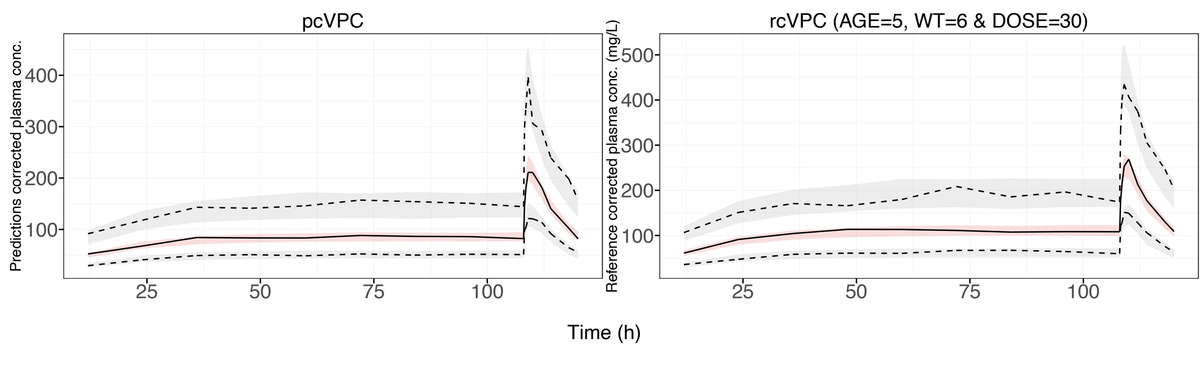

Figure S5. pcVPC and rcVPC of PK data versus time in Example II. The rcVPC dependent variables are normalized to a reference young subject with age of 5 month, body weight of 6 kg and dose of 30 mg.

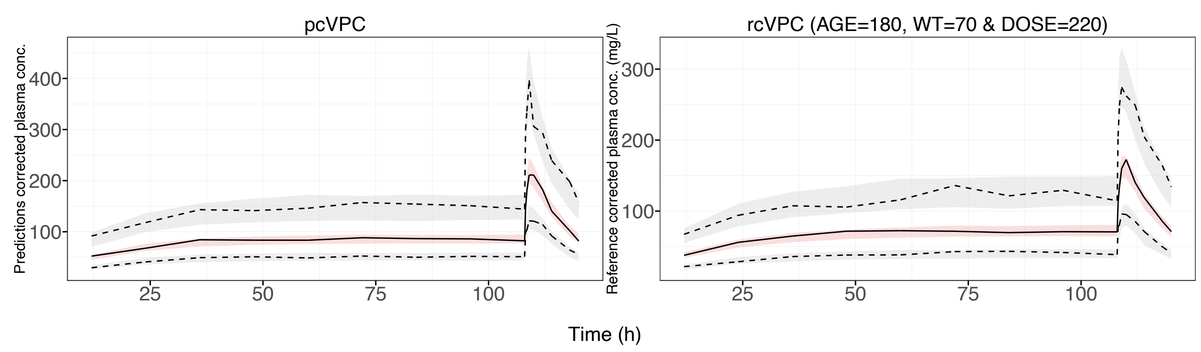

Figure S6. pcVPC and rcVPC of PK data versus time in Example II. The rcVPC dependent variables are normalized to a reference adult subject with age of 180 month, body weight of 70 kg and dose of 220 mg.

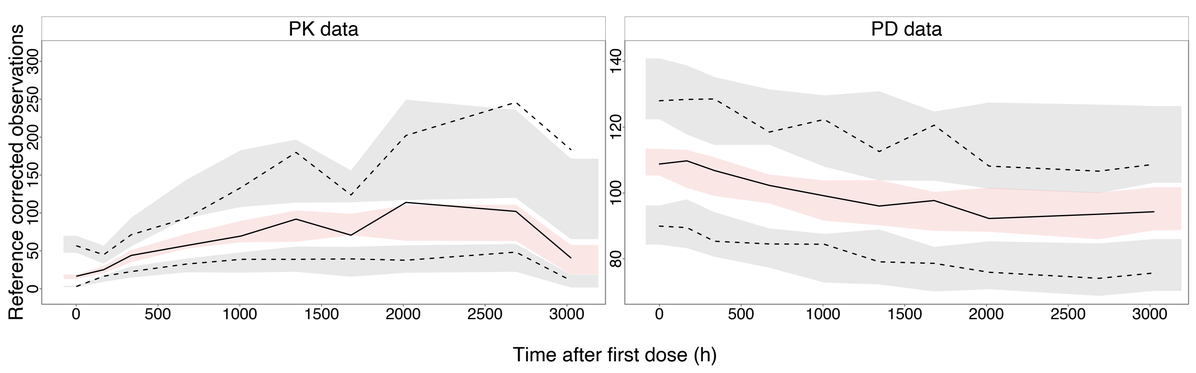

Figure S4. rcVPC of PK and PD data versus time after dose in Example I, using -refcorr argument in PSN::vpc functionality. The rcVPC dependent variables are normalized to a reference subject with ADDL=15 and AMT=600 mg, the two main features of POC-study design.

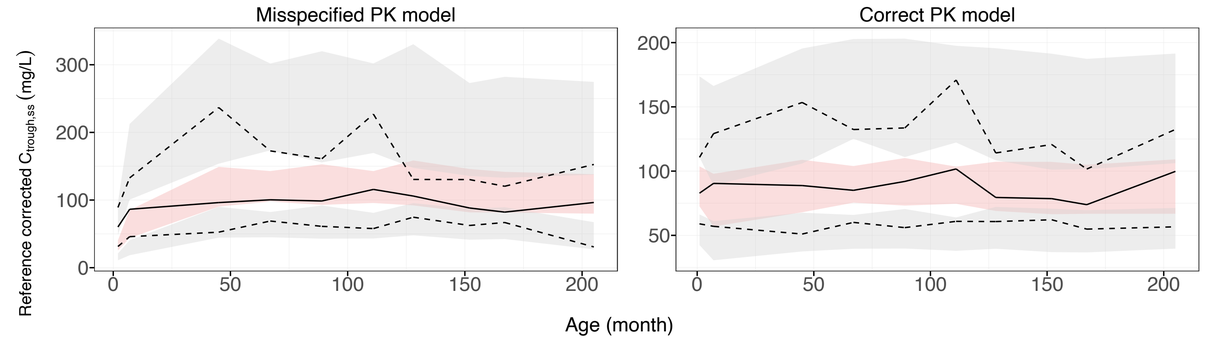

Figure S7. rcVPC of $C_{trough,ss}$ versus age in Example II, with and without clearance maturation function in the PK model, normalized to a reference subject with trough observations at steady state.