

Using Fisher Information Matrix to predict covariate effects in Forest Plots and power of their relevance



Lucie Fayette^{@ 1 2} Karl Brendel² France Mentré¹
[@]lucie.fayette@inserm.fr ¹Université Paris Cité, Inserm, IAME, F-75018 Paris, France
²Pharmacometrics, Ipsen Innovation, Les Ulis, France



CONTEXT

- Aim of pharmacokinetic (PK) and pharmacodynamic (PD) analysis: identify and quantify covariates that explain part of inter-individual variability (IIV)
- Effect of a covariate: ratio of change in the PKPD parameters and its confidence interval (CI)
 - Computed for given values or categories of the covariates and relatively to a reference value $\Rightarrow$ Forest Plot [1]
- A covariate effect is deemed
 - Statistically significant** if covariate parameter different from 0 according to Wald test at level 95%
 - Significance test on covariate parameter, using its standard error (SE)
 - Clinically relevant** if the 90% CI of the ratio outside a predetermined interval
 - Relevance test on ratio of covariate effect, using its CI
- PFIM**: 1st software (2001) evaluating design based on Fisher Information Matrix (FIM)
 - PFIM version 4.0 [2]: discrete covariates
 - Predict power of statistical significance test
 - Optimize design to achieve given confidence level [3, 4]
 - R package *PFIM6* [5] (CRAN release March 2024) does not include covariates

Objectives:

- Extend *PFIM6* to include both discrete and continuous covariates
- Explore different approaches to handle continuous covariates
- Predict CI of ratio, power of significance and relevance test

METHODS

PFIM6 extended to discrete and continuous covariates

- Ξ : population design with N subjects ξ_i : elementary design for i^{th} subject
- FIM, denoted $M_F \rightarrow$ Expectation on the joint distribution of covariates

$$M_F(\Xi, \Psi) = \sum_{i=1}^N \int M_F(\xi_i, \Psi, z_i) p_z(z_i) dz_i \approx \sum_{i=1}^N \frac{1}{S} \sum_{s=1}^S M_F(\xi_i, \Psi, z_{i,s}) \quad (1)$$

with Ψ : population parameters, z_i : vector of covariates in individual i , p_z : distribution of covariate vector

- To this end, three methods proposed + implemented in a working version of *PFIM6*
 - Using a provided sample of covariate vectors, allowing to consider correlation between them
 - Simulating covariate vectors, based on provided independent distributions
 - Simulating covariate vectors, based on a provided copula [6], allowing to consider correlation between covariates

Ratio, CI and Power computation

- Given design + covariate effects $\Rightarrow$ SE on parameters $\Rightarrow$ CI of the ratios
 - Binary covariates: ratio r_{bin} calculated for the non-reference category in relation to the reference

$$r_{bin} = e^{\beta} \quad CI(r_{bin}) = e^{\beta \pm q_{1-\alpha/2} SE_{\beta}} \quad (2)$$

with β : covariate parameter and q : quantile function of the normal distribution

- Continuous covariates: ratio r_{PX} computed for the 10th and 90th percentiles of the covariate distribution (P10 and P90) in relation to its median (MED)

$$r_{PX} = e^{\beta \times \ln(PX/MED)} \quad CI(r_{PX}) = e^{(\beta \pm q_{1-\alpha/2} SE_{\beta}) \ln(PX/MED)} \quad (3)$$

with PX : P10 or P90

- Given SE: analytical computation of power of significance and relevance tests

Simulation study - inspired by case study [7]

- PK Model
 - 1 compartment model - IV bolus - linear elimination
 - Combined error model: $y = f + (a + bf)$
 - Covariate effects:
 - 2 continuous: creatinine clearance (*CLCR*) on *Cl* and *Weight* on *V*
 - 1 discrete: *Sex* on *V*

$$\begin{cases} \ln Cl_i = \ln \mu_{Cl} + \beta_{Cl,CLCR} \ln \left(\frac{CLCR_i}{REF(CLCR)} \right) + \eta_{Cl,i} \\ \ln V_i = \ln \mu_V + \beta_{V,Weight} \ln \left(\frac{Weight_i}{REF(Weight)} \right) + \beta_{V,Sex} Sex_i + \eta_{V,i} \end{cases} \quad (4)$$

Parameter	μ_{Cl} (L/h)	μ_V (L)	ω_{Cl}	ω_V	a	b	$\beta_{Cl,CLCR}$	$\beta_{V,Weight}$	$\beta_{V,Sex}$
Value	0.43	7.13	0.30	0.24	2.39	0.08	0.87	1.0	-0.35

Table 1. Population PK parameter values used in the simulation study

- 4 different scenarios, combining

Design	IIV
Design 1: $N = 100$, 16 samplings from 0 to 24h	True Omega
Design 2: $N = 24$, 3 samplings at 1, 4 and 12h	High Omega: $2 \times \omega_{Cl}$; $2 \times \omega_V$

- Design evaluation with *PFIM*: 3 methods for handling covariates
 - Data: use the $S = 100$ covariate vectors from the original data [7]
 - Distributions: draw $S = 1000$ vectors from distribution fitted on the data
 - independent Gaussian for continuous covariates
 - Bernoulli distribution for discrete covariates
 - Copula: draw $S = 1000$ vectors from copulas fitted on the data: one for each sex (*rvinecopulib* [8])
 - Power of significance and relevance tests as a function of N
 - Simulation value of $\beta_{Cl,CLCR}$ (i.e. $r_{Cl,CLCR}(P10) = 0.63$)
 - Lower and higher values (i.e. $r_{Cl,CLCR}(P10) = 0.70$ and 0.50)
 - Simulation
 - 200 datasets - Estimation: Monolix 2023R1 [9]
 - SE calculated from the FIM computed by linearization
 - For each covariate effect
 - Significance test: Wald test at level $\alpha = 0.05$
 - Relevance test: null hypothesis rejected if the 90%CI of the ratio is outside [0.8; 1.2]
- $\Rightarrow$ Estimated CI and powers compared to PFIM's predictions

RESULTS

Forest Plots

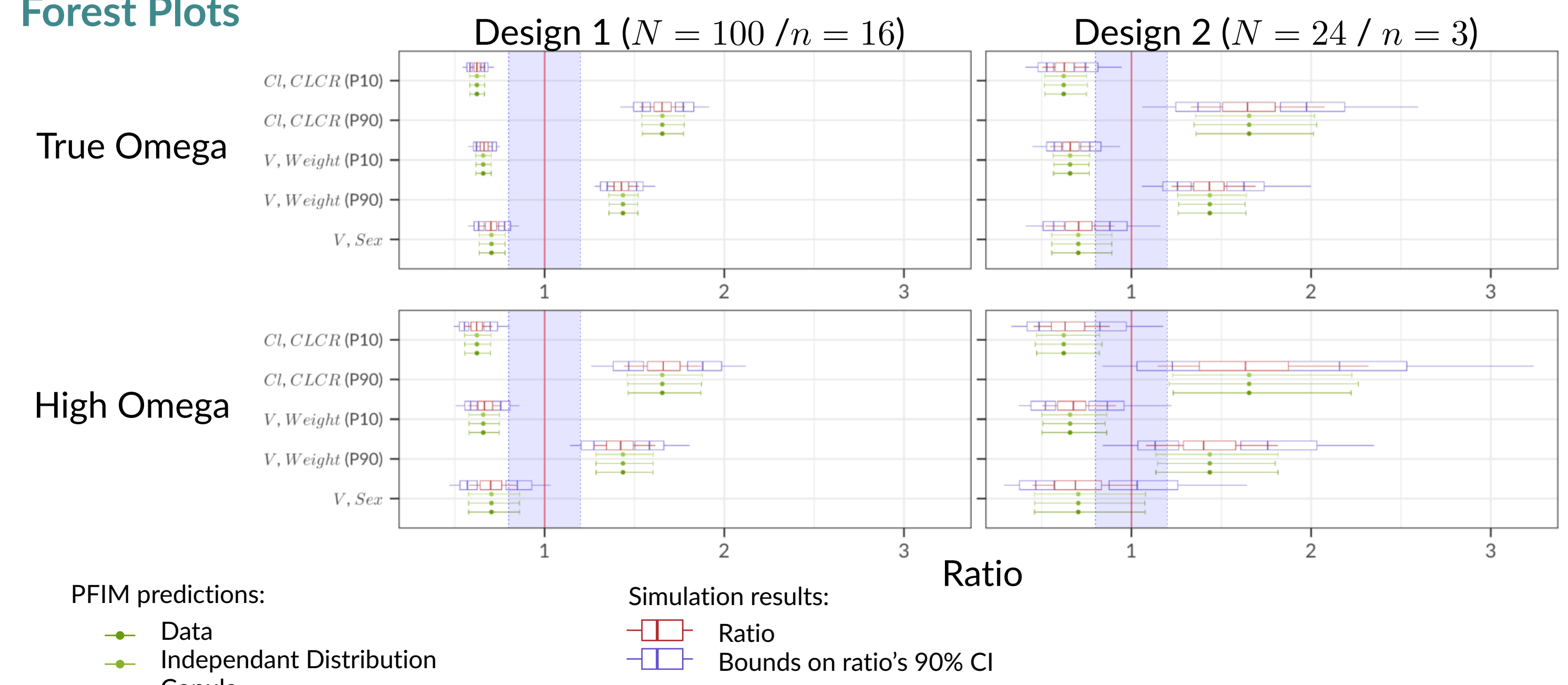


Figure 1. Forest Plot: Ratios and 90% Confidence intervals in the 4 scenarios

- The three methods for handling covariates in the FIM give similar results
- SE are overall well predicted leading to good prediction of CI of ratios
- Less subjects and sparser design raises uncertainty more than increased IIV

Power of tests

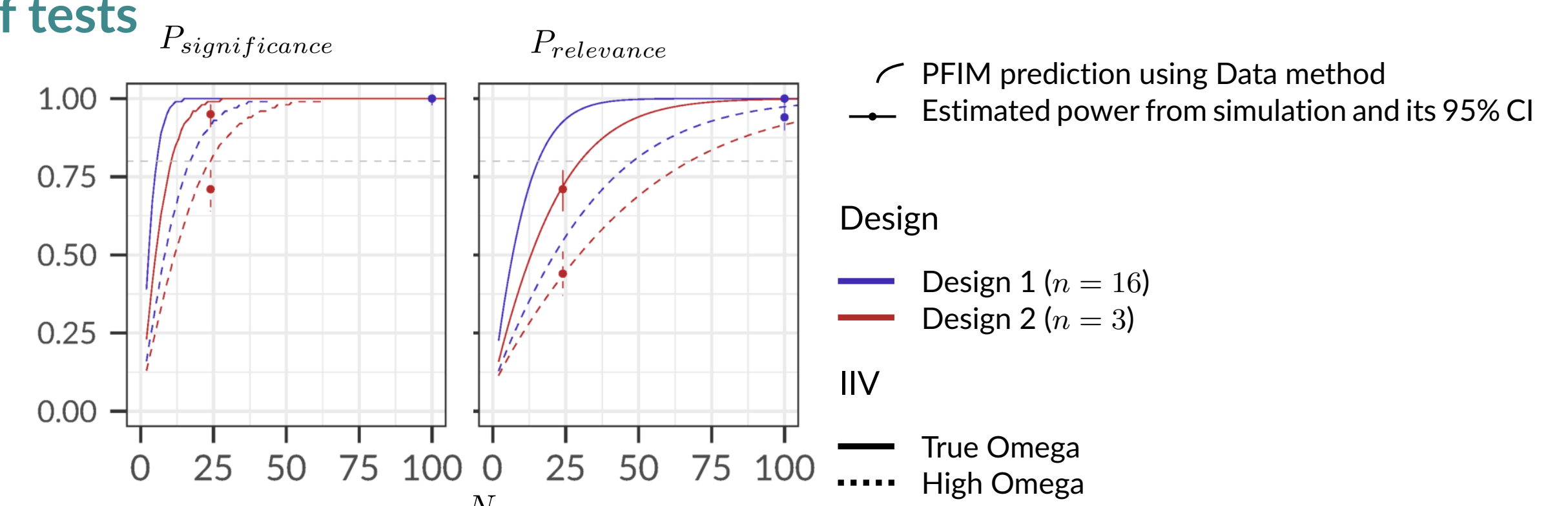


Figure 2. Power of significance test and Power of relevance test for effect of *CLCR* (P10) on *Cl*, as function of N for simulation value of $\beta_{Cl,CLCR}$ (i.e. $r_{Cl,CLCR}(P10) = 0.63$)

- Powers are overall well predicted

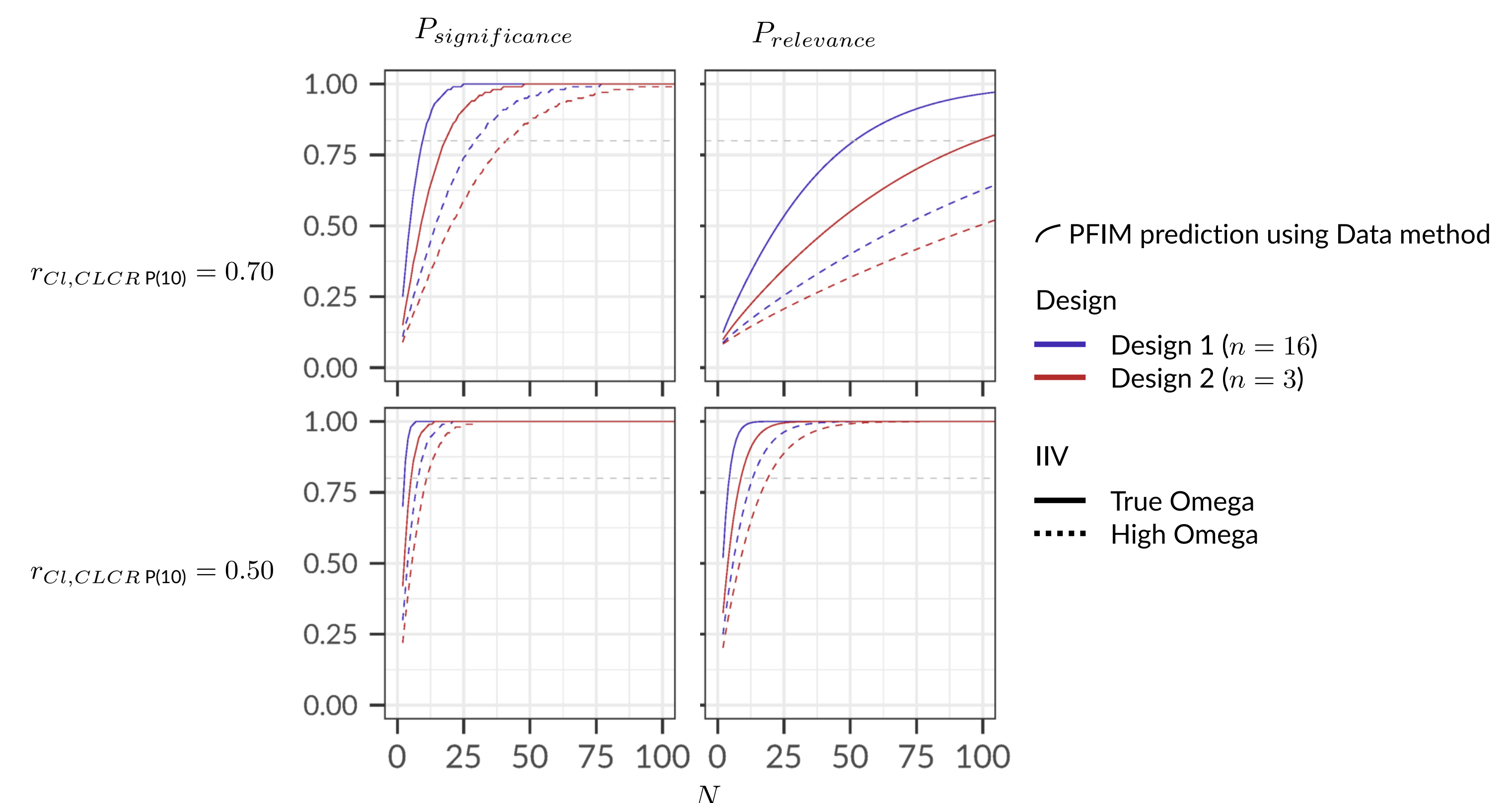


Figure 3. Power of significance test and Power of relevance test for effect of *CLCR* (P10) on *Cl*, as function of N for different values of $\beta_{Cl,CLCR}$

- The greater the effect, the higher the powers
- With sparser design the power of tests are smaller
- The higher the IIV on parameters with covariate effects, the lower the power $\Rightarrow$ A larger number of subject is needed
- Variability has a greater impact than design

Conclusions

- Asymptotic conditions + limited IIV $\Rightarrow$ PFIM accurately predicts uncertainty on covariate effects + power of both significance and relevance tests $\Rightarrow$ Influence of sample size, IIV, effect size or sampling design on power of tests
- Three methods for handling covariates in FIM computation: same results $\Rightarrow$ respective impact should be further explored in complex cases
- Promising results $\Rightarrow$ more widely implemented in the future version of PFIM
- Perspective: optimizing the distribution of covariates in clinical trials with the aim of maximizing power of relevance tests

REFERENCES

1. Marier, J.F. et al. *CPT Pharmacometrics Syst Pharmacol* (2022). 2. Dumont, C. et al. *Comput Methods Programs Biomed* (2018). 3. Retout, S. et al. *Stat Med* (2007). 4. Nguyen, T.T. et al. *Stat Med* (2012). 5. Leroux, R. et al. *PAGE* (2023). 6. Zwep, L. et al. *Int J Clin Pharmacol Ther* (2022). 7. BEGINNER'S TUTORIAL Case Study 1 <https://ctm.umaryland.edu/#/ms-pharma/model/bgt/cs>. 8. Nagler, T. et al. *R package version 0.5* (2021). 9. Monolix 2023R1, Lixoft SAS, a Simulations Plus company.

