Reduction in Interindividual Variability and Clinical Significance Ratio in Covariate Assessment

S. Willavize and J. Fiedler-Kelly

Cognigen Corporation, Buffalo, NY

INTRODUCTION

Covariate analysis has become a customary and expected part of population pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) modeling.[1] The covariate submodel describes, explains, and predicts the impact of patient characteristics on drug exposure and effects. Various criteria have been discussed for assessing the utility of a covariate. These criteria include reduction in interindividual variability (IIV)[2] and measures of the clinical importance.[3]

When we fit the covariate submodel, we are regressing the typical value of a parameter (for example, typical value of clearance [TVCL]) on a potential covariate (Z_i). Consider, for example, the following covariate submodel.

$$TVCL_i = \theta_0 + \theta_c \times Z_i$$

The probability of demonstrating that:

$$\theta_c \neq 0$$

is dependent on the following formula.

$$\frac{|\theta_c|\sqrt{CSS}}{\omega}$$

Where θ_c is the true slope, ω is the IIV (expressed as a standard deviation), and

$$CSS = \sum_{i=1}^{N}(Z_i - \bar{Z})^2$$

is the corrected sum of squares for the covariate (a measure of the diversity of the covariate in the dataset). Hence, the basic statistical properties of the covariate submodel alone indicate that the probability of detecting a covariate relationship is dependent on the true value of the slope and CSS.[4] The probability, given the data observed, of concluding that $\theta_c \neq 0$ (when, in fact, $\theta_c = 0$) is the statistical significance (p-value).

The relationship between creatinine clearance (CrCL) and drug clearance (CL) can be used as an instructive example for investigating how the statistical properties of the covariate submodel come into play in the context of a population PK model. Because there are well-defined categories of renal impairment,[5] a clinical significance ratio (CSR) can be constructed as a gauge on the clinical importance of the covariate effect. For our purposes, CSR was defined as the ratio of the population estimated typical value of CL in moderate renal dysfunction compared to normal renal function:

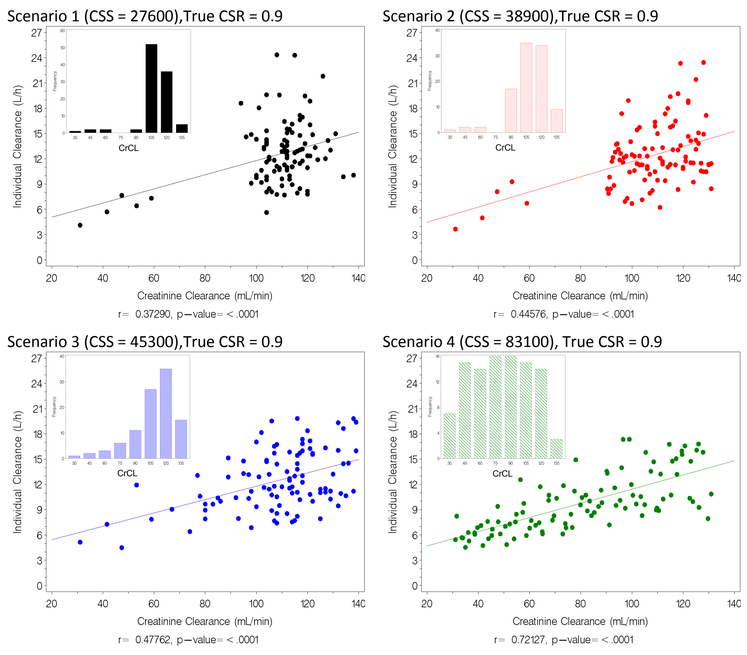
$$\frac{(TVCL\ at\ CrCL = 45)}{(TVCL\ at\ CrCL = 115)}$$

Where:

CrCL = 45 mL/min represents moderate renal dysfunction and *CrCL* = 115 mL/min represents normal renal function. A CSR value of 1 would then indicate no difference in the *TVCL* with moderate renal dysfunction and with normal renal function.

Figure 1 shows the covariate scenarios used in our simulation study. In the base model (where θ_c is assumed equal to 0), the estimated IIV encompasses all variability in TVCL; in the covariate model, θ_c explains some of the variability in TVCL and the estimated IIV should be reduced in comparison, where the greater the absolute value of the slope, the greater the reduction in IIV. The examples displayed here are for a clinical significance ratio of 0.9.

Figure 1. Relationships Between Simulated True Individual CL and CrCL for Various Scenarios in Representative Study (N = 100)



AIMS

Explore relationships among

- Clinical significance;
- Reduction in IIV; and
- Statistical significance.

OBJECTIVES

Using baseline CrCL as an example covariate, this study will investigate the

- Relationship between the CSR and reduction in IIV between base and covariate models;
- Relationship between the CSR and p-value;
- Relationship between reduction in IIV and p-value; and
- Impact of design factors, such as the number of subjects (N), number of PK samples per subject (n), and the diversity of the covariate observations (in terms of the CSS of the observed covariates) on these relationships

in the context of a population PK model.

METHODS

Data Simulation

- 1-compartment, single bolus dose PK model with first-order elimination, CL = 3 L/h, Vc = 50 L, $t_{1/2}$ = 11.6 hours, dose = 100 mg
- TVCL = θ_0 + θ_c x CrCL; θ_0 = 50 mL/min, θ_c = 0, 0.0850, 0.212 ,0.4225, 0.83 (corresponding to true CSR values of 1, 0.9, 0.8, 0.7, and 0.6, respectively)
- Baseline CrCL ranges from 30 to 140 mL/min; 4 differently distributed samples from this range of CrCL values which provide differing patterns of diversity and, hence, different values of CSS were utilized, corresponding to Scenarios 1 - 4
- R = 500 simulation replications/scenario
- N = 50, 100 simulated subjects/clinical trial
- Full-profile or sparse sampling with n = 12 or 5 samples per subject (at times t = 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 hours or t = 0, 1, 4, 12, 24 hours)
- ω_{CL} = 25 %CV, ω_{Vc} = 25 %CV (CL_i = TVCL x exp[η_{1i}], Vc_i = TVV x exp[η_{2i}]), σ = 30 %CV (proportional residual variability, variance = 0.09)
- SAS Version 9.2 was used to create the simulation data and to summarize the results

Model Estimation

- NONMEM Version 7.1.2, with first-order conditional estimation with interaction
- Base model with covariate effect at null value
- Linear covariate model:
  TVCL = THETA(1) + THETA(2) ∗ (CrCL - 80)
- Power function covariate model:
  TVCL = THETA(1) ∗ (CrCL / 80) **(THETA(2))
- Statistical significance based on p-value was computed by χ^2 (delta_MVOF, 1); where delta_MVOF is computed by difference in MVOF for base model (THETA(2) fixed at 0) versus covariate model
- Reduction in IIV was calculated as the percent reduction in the estimated IIV (expressed as standard deviation) for base model versus covariate model
- Boxplots show 25th, 50th, and 75th percentiles with whiskers for 5th and 95th percentiles and asterisks show data points outside the 90% inner range

RESULTS

Example results for sparse sampling (n = 5) and N = 100 are provided below. The percent reduction in IIV increased with increasing CSS (**Figure 2**). Percent reduction in IIV varied inversely with true CSR. For the scenarios studied here, a reduction in IIV of 5% or more was generally associated with a clinically important covariate (true CSR of 0.9 or less). When clinical significance was lacking (true CSR = 1.0), the IIV reduction was generally less than 5% and, in a small number of cases, was negative (indicating an increase in estimated IIV).

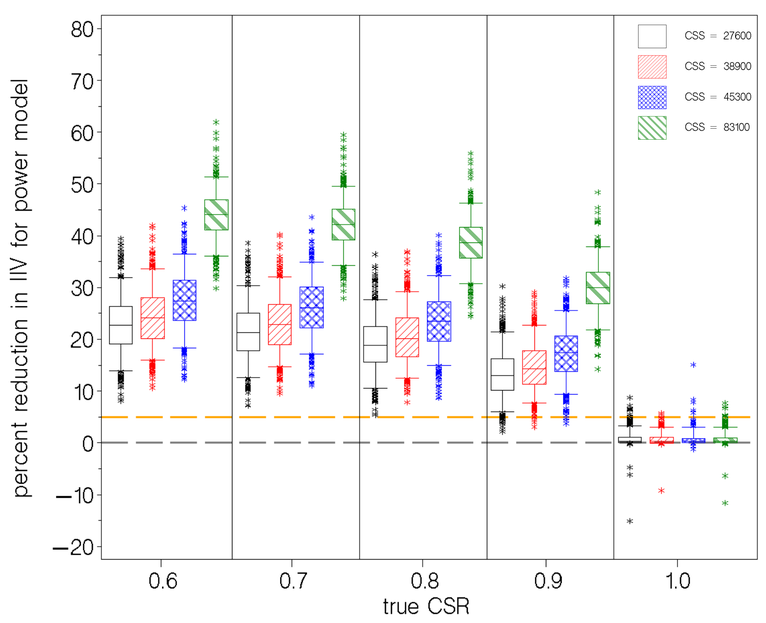
The estimated CSR (**Figure 3**) was essentially constant with increasing CSS (although its variability decreased). When the true CSR was equal to 1 (null cases), the estimated CSR was unbiased. In non-null cases, the CSR was consistently underestimated, but seemed to plateau for values of true CSR < 0.9.

As shown in **Figure 4**, p-values for the null case averaged about 0.5, as expected, while p-values for non-null cases usually indicated statistical significance (mean < 0.01 and maximum < 0.1). The results for true CSR < 0.8, which were all much less than 0.05, are not shown.

The relative standard error (%SEM) values generally decreased as true CSR decreased from 0.9 to 0.6 (**Figure 5**) and, as expected, also decreased with increasing CSS. Clinical significance was generally associated with %SEM values for the estimated covariate parameter in the 5% to 25% range, while %SEM values much higher in absolute value were seen mainly when clinical significance was lacking. Because the power coefficient parameter estimates were very small and could be positive or negative, values of %SEM for the null case (not shown) ranged much more widely with 25th and 75th percentiles of -136% and 123% for CSS = 27,600.

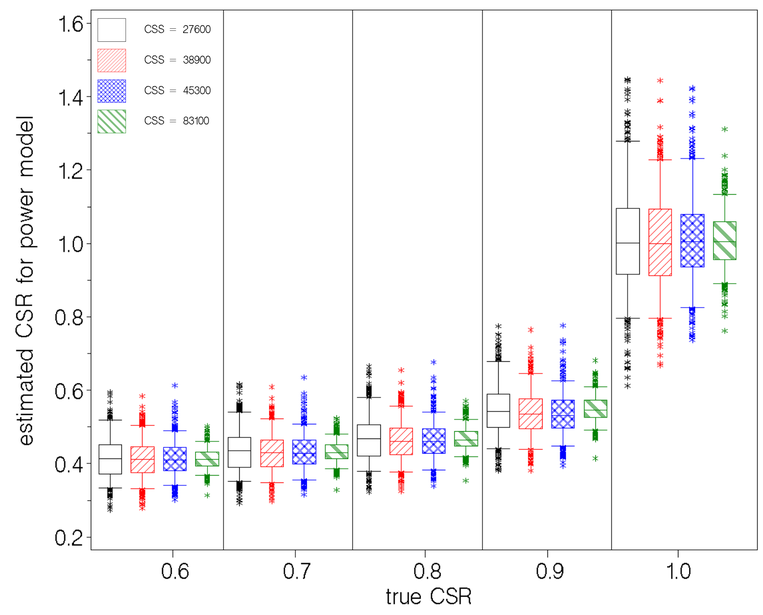
Results for N = 50 were essentially the same as those for N = 100; and results for full profile (n = 12) and sparse sampling (n = 5) were similar. The results for the linear covariate model were essentially the same as those for the power covariate model, but, as the slope increased, the linear models had more non-convergent runs than the power model. For the power covariate model with N = 100 and sparse sampling (n = 5), the number of convergent runs was 500 for all cases when true CSR > 0.6, and for true CSR = 0.6 there were at least 490 convergent of the 500 replications of each scenario.

Figure 2. Percent Reduction in Interindividual Variability for Power Covariate Model



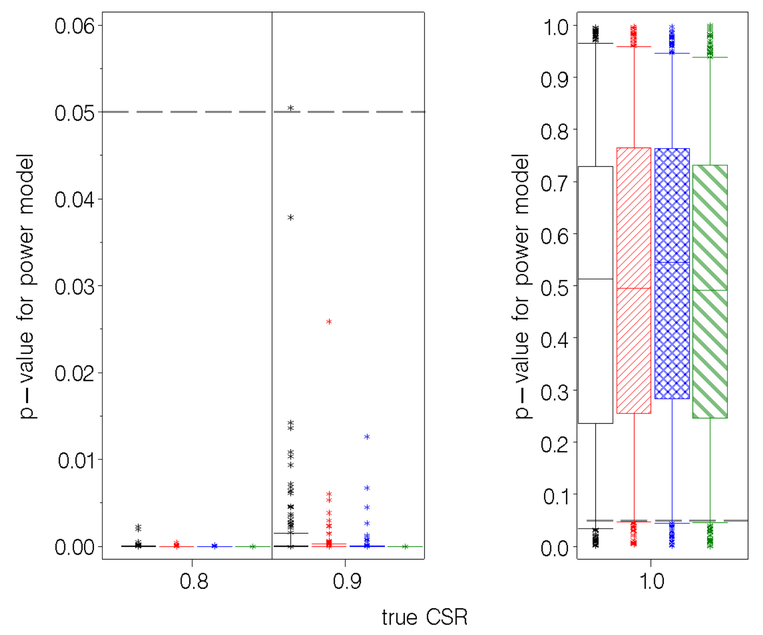
Note: N = 100, n = 5.

Figure 3. Estimated Clinical Significance Ratio for Power Covariate Model



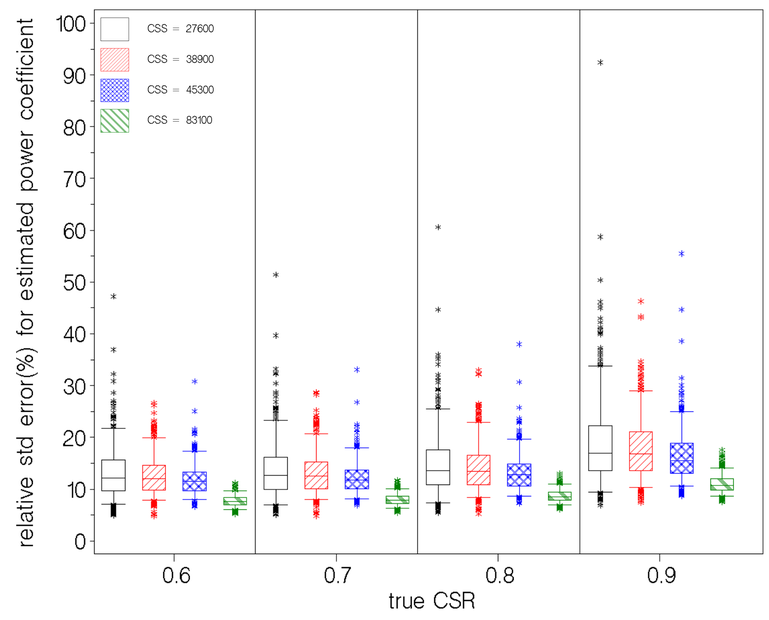
Note: N = 100, n = 5.

Figure 4. Significance Levels (p-values) for Power Covariate Model



Note: N = 100, n = 5.

Figure 5. Relative Standard Error (%SEM) Values for Power Covariate Model



Note: N = 100, n = 5.

CONCLUSIONS

- The estimated clinical significance ratio decreased with the true clinical significance ratio, indicating the presence of a covariate effect.
- In the absence of a clearly defined clinical significance function, a reduction in IIV of 5% or more, together with statistical significance, may provide an indication of the presence of a covariate effect, with the magnitude of the reduction in IIV indicative of the size of the CSR.
- As expected based on the statistical properties of the covariate submodel, higher CSS was associated with a greater reduction in %SEM for the covariate parameter. In the examples studied, higher CSS also resulted in reduced variability in the estimated CSR.
- Reduction in IIV was generally consistent with statistical significance.

REFERENCES

1. Dartois C, Brendel K, Comets E, et al. Overview of model-building strategies in population PK/PD analyses: 2002-2004 literature survey. *Br J Clin Pharmacol*. 2007;64:603-612.

2. Lagishetty CV, Vajjah P, and Duffull SB. A reduction in between subject variability is not mandatory for selecting a new covariate. *J Pharmacokinet Pharmacodyn*. 2012;39:383-392.

3. Gastonguay MR. A full model estimation approach for covariate effects: inference based on clinical importance and estimation precision. *AAPS*. 2004;6(S1):Abstract W4354.

4. Neter J, Wasserman W. *Applied Linear Statistical Models: Regression, Analysis of Variance, and Experimental Design*. Homewood, IL: Richard D. Irwin, Inc.; 1974.

5. Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling. 2010.

Willavize S, Fiedler-Kelly J. Reduction in Interindividual Variability and Clinical Significance Ratio in Covariate Assessment. American Conference on Pharmacometrics; May 12-15, 2013; Fort Lauderdale, FL.

For additional information, please contact
Susan Willavize, PhD
Cognigen Corporation
395 South Youngs Road, Buffalo, NY 14221
(716) 633-3463, ext. 252 or susan.willavize@cognigencorp.com