



Mutaz M. Jaber¹, Richard C. Brundage¹

¹Department of Experimental and Clinical Pharmacology, College of Pharmacy, Minneapolis, MN

Objective

In nonlinear mixed-effects (NLME) modeling of pharmacokinetic (PK) and pharmacodynamic (PD) data, we refer to two levels of random effects: between-subject variability (BSV), and residual unexplained variability (RUV). RUV quantifies the residual uncertainty in the model after accounting for the variability due to the structural, covariate, and BSV models. Various sources are expected to contribute to RUV; imprecision of our analytical techniques, misspecification of the PK, PD, covariate, BSV, or RUV models, errors in recording times of blood sampling or dose administration, variability in formulations, and an uncertain prior dosing history. The goal of this study was to investigate the extent to which PK and RUV model misspecification, errors in recording dosing and sampling times, and variability in drug content uniformly contribute to the estimated magnitude of RUV.

Conclusion

We assessed the contribution of hypothetical sources of variability in RUV during NLME modeling. PK and RUV model misspecifications were associated with relatively large increases in the magnitude of RUV compared to other sources for INT and SPA designs. As expected, SPA sampling has higher deviations than INT designs. The contribution of dose misspecification, and dosing and sampling time misspecifications have negligible effects on RUV. Misspecifications had little effect on the estimates of CL and Vc.

Our misspecifications were admittedly small and simulated under an assumption of a tightly controlled clinical trial. Increases in RUV may be higher in clinical settings with outpatient sampling.

We did not assess the unexplained variability in scenarios with multiple dosing, other PK/PD models, or misspecification of the covariate or BSV models

Results

The median [min, max] from the 100 runs of each scenario is reported in the figure below.

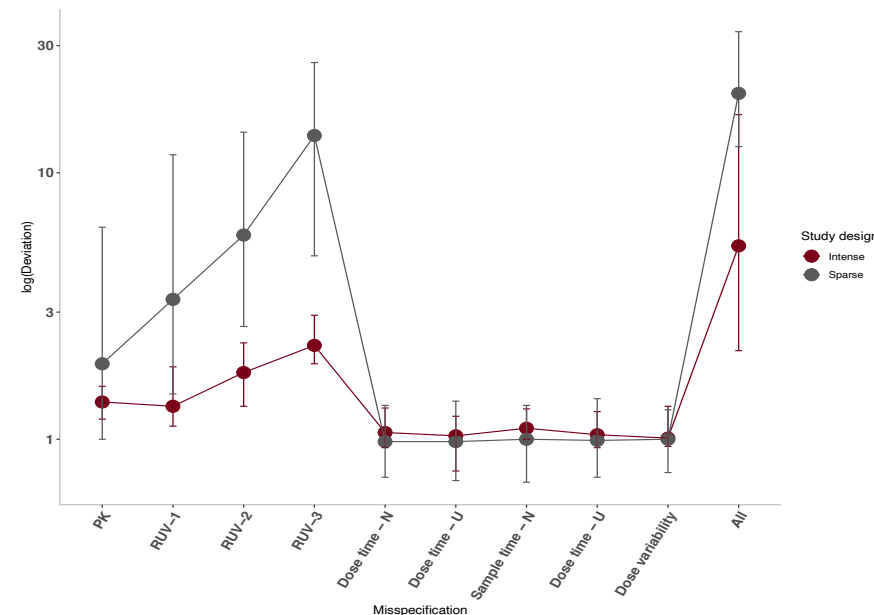


Figure. Deviation from the nominal RUV value; N presents the normal distribution; U presents the uniform distribution; RUV-n is the three levels of additive error component; All presents the additional scenario with all perturbations. Study design is color coded.

Additional info:

Mutaz M. Jaber: jaber038@umn.edu

Richard C. Brundage: brund001@umn.edu

Methods

Base model

A two-compartment model with first-order absorption and linear elimination was simulated with a fast distributive (alpha) half-life (0.28 hrs) and an extended terminal elimination (beta) half-life (12.2 hrs). PK disposition parameters included in the simulation were clearance (CL) 5.0 L/hour, central volume of distribution (Vc) 35 L, inter-compartmental clearance (Q) 50 L/hour, and peripheral volume of distribution (Vp) 50 L. The absorption rate constant (KA) was 0.7 (1/hr). All parameters were assumed to have a 30% BSV coefficient of variation (CV). The simulated dose was 120 mg. Intense (INT) and sparse (SPA) sampling designs were investigated in simulations of 100 subjects. For the intensive design, sampling times were 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours (9 samples), and at 2, 12, 24, and 48 hours (4 samples) for the sparse sampling design. A 5% proportional error model was assumed as an optimistic baseline RUV. This base model was simulated and fit 100 times.

Perturbations

The base model was perturbed in several ways to investigate changes in RUV:

- 1) PK model misspecification where the data from above were fit to a one-compartment model. New datasets were simulated as above to explore additional perturbations;
- 2) RUV model misspecification using a 5% proportional error with 0.01, 0.02, and 0.04 mg/L additive error;
- 3) Dosing time misspecification was achieved by perturbing the time of dose with either a normal distribution (mean of 0 and standard deviation of 5 minutes), or uniform distribution (between -5 and 5 minutes);
- 4) Sampling time misspecification was achieved by perturbing the time of sample using the same distributions as dose time misspecification; and
- 5) Dose variability misspecification was accomplished by corrupting the dose with a normal distribution (mean of 120 mg and standard deviation of 12 mg).

An additional scenario was simulated that included PK model misspecification, RUV misspecification with an additive component of 0.04, dose and sampling time misspecification using the specified normal distribution, and dose misspecification.

In all cases, the perturbed simulated concentrations were fit assuming the baseline nominal dose, times, and RUV.