Clarity in Reporting Parameter Variance Needed to Improve Use of Published Models for Simulation Applications

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ABSTRACT

Background: Since published pharmacokinetic and pharmacodynamic models are often used by others for the purpose of simulations, enhanced clarity in reporting and clear statements regarding assumptions will improve the reproducibility of modeling and simulation results and allow for accurate re-use of models and modeling findings.

Methods: To illustrate the importance of this issue, simulations were performed using the pharmacokinetic model for paroxetine by *Feng et. al.*[1], a manuscript that did not report which method was used for %CV calculation. This paper was selected in part because reported variability was in excess of 70 %CV for several parameters. Two simulations of 1000 individuals were performed using ω^2 parameter estimates that were calculated from the reported %CV values, one based on the method of $\%CV = 100 * \sqrt{\exp(\omega^2) - 1}$ and one based on the method of $\%CV = 100 * \sqrt{\omega^2}$. Simulations were performed using the R package *mrgsolve*.[2] Results of the simulations were then used to calculate the magnitude of between-subject variability (%CV) for each run and compare it to the original value.

Results: A 13.3-27.8% difference in %CV of the simulated distribution of the VM parameter was observed with the $\%CV = 100 * \sqrt{\omega^2}$method when the other method was assumed to be used for reporting, and a 15.6-24.5% difference was observed when the reverse was assumed. Calculated % difference increases as the true ω^2 increases, with ω^2 = 0.1 yielding a 0.81% difference and ω^2 =1.25 yielding a 46.0% difference.

Conclusions: Accurate reporting of either the variance (ω^2) estimates in parameter tables or the method used to calculate %CV is important, especially as between-subject variance estimates increase.

INTRODUCTION

Since published pharmacokinetic and pharmacodynamic models are often used by others for the purpose of simulations, clarity in reporting model parameter estimates is needed.[3,4,5] We have found a particular situation where lack of clarity is frequently observed. Pharmacokinetic parameters are typically assumed to have log-normal distributions as they are required to be positive and are often right skewed.[6,7] For instance, clearance (CL) is typically described as shown (Equation 1).

$$CL_i = \theta_1 * \exp(\eta_{1i}) \qquad (1)$$

where η_{1i} is the zero-centered, normally-distributed, random deviate that determines the difference between the i^{th} individual from the typical population clearance, θ_1. As variance parameters are reported in NONMEM®,[8] and other population analysis software, the OMEGA element (ω^2_{CL}) is a scalar, fixed-effect parameter that describes the variance of the distribution for CL_i. The relationship between the variance of η and variance of CL is described elsewhere.[9] Estimates of interindividual variability in parameters (ω^2) are often reported in the tables of manuscripts and clinical study reports as percent coefficients of variation (%CV). Two methods have been presented in the literature and on the NONMEM Users Network listserv to calculate the %CV for the ω^2 parameter estimate; these methods are presented below in Equation 2 and Equation 3.[10-13]

$$\%CV = 100 * \sqrt{\exp(\omega^2) - 1} \qquad (2)$$

$$\%CV = 100 * \sqrt{\omega^2} \qquad (3)$$

For a given ω^2 estimate, the method of Equation 2 gives a %CV value which exceeds that of the method of Equation 3. It has been suggested that when ω^2 is <30%CV the simpler method of Equation 3 can be used with reasonably small error.[8] As ω^2 increases however, the difference between the two methods increases (**Table 1**). The difference in %CV between methods exceeds 10 %CV units when the ω^2 estimate exceeds 0.5 (approximate %CV > 70%).

Table 1: Difference between resulting %CV values using the two computation methods for various values of ω^2

ω^2	%CV based on Eq. 2	%CV based on Eq. 3	Difference in %CV (Eq. 2 – Eq. 3)
0.001	3.163	3.162	0.001
0.01	10.025	10.000	0.025
0.025	15.911	15.811	0.099
0.05	22.643	22.361	0.282
0.1	32.430	31.623	0.807
0.15	40.229	38.730	1.499
0.2	47.053	44.721	2.332
0.25	53.294	50.000	3.294
0.4	70.130	63.246	6.885
0.5	80.543	70.711	9.833
0.6	90.671	77.460	13.211
0.7	100.685	83.666	17.019
0.8	110.704	89.443	21.261
1	131.083	100.000	31.083
1.25	157.808	111.803	46.005

METHODS

To give context to the frequency of equivocal reporting of ω^2 parameter estimates, we performed a survey of models (PK, PD, PBPK, mathematical) published in the journal *CPT: Pharmacometrics & Systems Pharmacology* (CPT:PSP) from the first online issue (September 2012) until December 2018. Each manuscript was examined to see whether the authors reported: 1) either the method used to compute %CV values or the ω^2 parameter estimates themselves, or 2) neither the equation used to compute %CV nor the ω^2 parameter estimates. Three time ranges were considered: 2012-2015, 2016-2017, and 2018. This choice of range and stratification was intended to give both a broad scope of the literature and a look at current practice in a core pharmacometrics journal.

To illustrate the importance of this issue, two different simulation exercises were performed using the identified models. The first exercise was performed using a model for vancomycin based on the paper by *Moore et al.*[14], which was chosen as it reported the parameter estimates and represented a first order model. For this exercise, three simulations were performed. The first simulation used the ω^2 estimates reported in the paper. The second simulation used an erroneous ω^2 value that was obtained from calculating the %CV with Eq. 3 and calculating the resulting ω^2 value with Eq. 4. The third simulation was repeated in the same way, but utilized Eq. 2 and Eq. 5.

$$\omega^2 = \ln((\frac{\%CV}{100})^2 + 1) \qquad (4)$$

$$\omega^2 = (\frac{\%CV}{100})^2 \qquad (5)$$

The second exercise was performed using a model for paroxetine by *Feng et. al.*[1], a manuscript that did not report which method was used for %CV calculation. While there are numerous examples of this scenario in the literature, this paper was selected in part because reported variability was in excess of 70 %CV for several parameters. For this exercise, two simulations of 1000 individuals were performed using ω^2 parameter estimates that were calculated from the reported %CV values, one based on Equation 4 and one based on Equation 5. Simulations were performed using the R package *mrgsolve*.[2] Results of the simulations were then used to calculate the magnitude of between-subject variability (%CV) for each run and compare it to the original value.

RESULTS

For the years 2012-2015, 30 of 55 (54.5%) manuscripts reported either the ω^2 estimate or how %CV was calculated. For the years 2016-2017, 37 of 65 (56.9%) manuscripts reported either the estimate or how %CV was calculated. For the year 2018, 13 of 19 (68.4%) manuscripts reported either the estimate or how %CV was calculated (**Figure 1**). Thus, more recent papers were more likely to have given clarity to the definition of the parameter variance, yet still nearly one-third of the manuscripts examined did not give adequate clarity or definition to use the reported model parameters accurately with certainty.

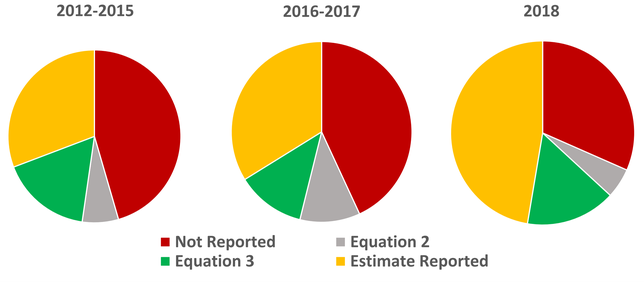

Figure 1: Percentage of papers that reported the method, the ω^2 estimate, or did not accurately report either

For the first exercise, 10,000 subjects receiving a 1500mg infusion every 12 hours were simulated. Concentration time profiles were generated for each run. The %CV was calculated using both methods and ω^2 value were then calculated using the wrong method. Estimates used were shown below (**Table 2**). There was approximately a 1.5-fold increase in the ω^2 value for CL between the two incorrect calculations leading to under or overestimation of the model (**Figure 2**).

Table 2: Estimates of random effects used for simulations

	ω^2 True Value	%CV based on Eq. 3	Incorrect Estimate using Eq. 4	%CV based on Eq. 2	Incorrect Estimate using Eq. 5
CL	0.466	68	0.382	77	0.593
V	0.109	33	0.104	34	0.116

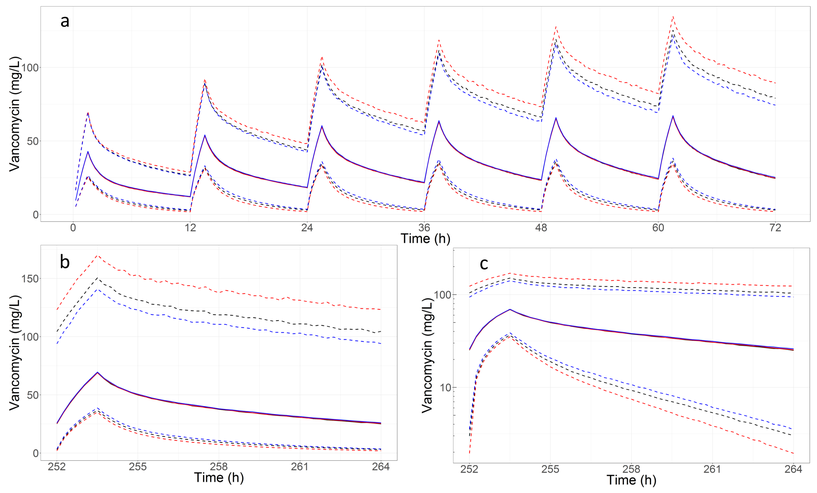

Figure 2: Concentration vs time profiles for vancomycin at a) Prior to steady state. b) Steady state. c) Steady state on a log scale. Lines represent the median, 5th and 95th percentile of concentrations for each of the three simulations. The black lines represent the simulation using the estimate reported. The blue line represents the simulation when incorrectly calculating ω^2 estimate with Eq. 4. The red line represents the simulation when incorrectly calculating ω^2 estimate from Eq. 5.

Another example of the impact of using the incorrect assumption regarding variability is provided in the table below, where differences from the true value are presented assuming simulation estimates were calculated with the incorrect assumption regarding the %CV calculation. **Table 3** demonstrates the magnitude of error that will result in simulations from a published model if the wrong equation is used to derive the ω^2 estimate from the %CV value reported in a manuscript. When the wrong assumption is used, between-subject variability in model-based simulations will be systematically under- or over-estimated. The impact of the discrepancy will increase with increasing values of the true ω^2 value.

Table 3: Magnitude of error if the inappropriate calculation is used for simulations

	Calculated %CV from simulation (calculated using Equation 3)	%CV assuming Equation 2 solution is true	% Difference in %CV†	Calculated %CV from simulation (calculated using Equation 2)	%CV assuming Equation 3 solution is true	% Difference in %CV†
VM	Pheno0=111 Pheno1=110 Pheno2=102 Pheno3=115 Pheno4=108	90	23.3 22.2 13.3 27.8 20	Pheno0=90.4 Pheno1=89.2 Pheno2=84.3 Pheno3=94.3 Pheno4=88.6	111.7	-19.1 -20.1 -24.5 -15.6 -20.7
KM	156	109	43.1	112	156	-28.2
V2	90.2	77.8	15.9	78	91.2	-14.5

†Percent Difference = ((calculated-actual)/actual))*100
Pheno0 = missing phenotype information
Pheno1 = poor metabolizers
Pheno2 = intermediate metabolizers
Pheno3 = extensive metabolizers
Pheno4 = ultra-rapid metabolizers

SUMMARY

Accurate reporting of either the variance (ω^2) estimates in parameter tables or the method used to calculate %CV is important, especially as the magnitude of between-subject variance estimates increase. Enhanced clarity in reporting and clear statements regarding assumptions will improve the reproducibility of modeling and simulation results and allow for accurate re-use of models and modeling findings.

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