Title: Confidence Intervals for Variability Estimates of Mixed-Effect Models

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Purpose: Confidence intervals (CIs) for the parameter estimates of mixed-effect models are often reported using the assumption of asymptotic normality. While this assumption is a reasonable approximation for the estimates of fixed effects and off-diagonal elements of the variance-covariance matrix, variances of the random effects are χ^2 distributed. We aim to introduce CIs for variances based on χ^2 distribution (χ^2CIs), and compare them with the asymptotically normal CIs (nCIs) and CIs obtained by bootstrap (bCIs) and simulation-estimation (sseCIs) procedures on the example of a PK model with high variability and uncertainty of the parameter estimates.

Methods: Concentrations of 50, 100, 300, or 1000 subjects were simulated from a two-compartment PK model with high inter-individual and moderate or high intra-individual variability (CV=55% for clearance (CL) and central volume (Vc), CV=100% for absorption rate constant (Ka), and CV=20% or 50% for proportional residual variability) for 2 sampling designs (4 or 6 post-dose samples) following a single oral dose. The parameters were estimated for all 16 data sets, and 95% χ^2CIs and nCIs were computed for all variance parameters. 95% bCIs and sseCIs from 1000 bootstrap or simulation-estimation samples were also computed. For each estimated variance (ω^2_{CL}, ω^2_{Vc}, ω^2_{Ka}, σ^2), normalized CIs were plotted versus relative standard error (RSE) of the estimates for all datasets and CI methods. The normalized true values were also overlaid.

Results: The degrees of freedom (df) and 100*(1-α)% χ^2CIs for an estimated parameter (ω^2) are computed as

$$df = 2/RSE^2, \text{ and } \chi^2CI= [\omega^2 * df/\chi^2_{1-\alpha/2,df} \; ; \; \omega^2 * df/\chi^2_{\alpha/2,df}].$$

χ^2CIs are always shifted up compared to nCIs, but for RSE<20%, the difference is small ($\leq$13%). For RSE>50%, the lower bound of nCIs becomes negative while it slowly approaches zero for χ^2CI. The upper bound of χ^2CIs increases steeply after RSE>60% and becomes very wide. bCIs and sseCIs were generally close to each other and were somewhere between nCIs and χ^2CIs, but both of them were sometimes inconsistently wide or narrow in relation to χ^2CIs, nCIs and each other.

Conclusions: Theoretically correct χ^2-based confidence intervals for estimates of the variance parameters were introduced. Practical applicability of these CIs needs further investigation.