Normalisation weight in a covariate function affects the relative standard error of clearance: an example with paediatric data

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INTRODUCTION

While in population models most covariates are normalized to the median value, for bodyweight (WT), normalization to 70 or 1 kg is often applied.

CONCLUSION

- Using a WT_{norm} outside the observed covariate range can result in a high RSE of the corresponding population estimate, as the obtained RSE corresponds to the RSE for an extrapolated population parameter value.
- As this RSE is not informative about the precision of the CL estimate in the studied WT range, normalizing WT on 70 kg in the paediatric population should be applied with caution.

RESEARCH QUESTIONS

1. How does normalization weight (WT_{norm}) impact the relative standard error (RSE) and bootstrap values of clearance (CL) estimates in a neonatal dataset?
2. What do the bootstrap confidence intervals (95% CIs) of typical CL predictions between 1 to 100 kg look like?
3. Does the impact of WT_{norm} on parameter uncertainty differ for different WT distributions?

METHODS

1. *Impact of WT_{norm} on RSE and bootstrap values*
   - 1-compartment PK model for phenobarbital in 53 (pre)term neonates (0.45 – 4.4 kg, gestational age: 24-42 weeks, postnatal age 0-22 days) with CL as

$$CL_i = \theta_1 * \left(\frac{WT}{WT_{norm}}\right)^{\theta_2}$$

   - WT_{norm} was set to 1 kg, 2.7 kg (median) and 70 kg
2. *Bootstrap CIs of typical CL for 1 to 100 kg*
   - For normalizations to 1, 2.7 and 70 kg, 1000 CL functions were calculated over a weight range of 1-100 kg using the bootstrap estimates of the CL and the exponent
3. *Impact of different WT distributions*
   - 250 datasets of 50 patients were sampled from three different hypothetical WT distributions with similar median WT:
     1. Lognormal distribution; median WT = 20.1 kg, SD on logscale = 0.25
     2. Uniform distribution 10 - 32 kg
     3. Uniform distribution 1 - 51 kg
   - Simulated patients receive a single dose of 10 mg/kg (sampling times of 24, 72 and 120h)
   - Datasets were fitted with WT_{norm} = 70 kg and RSE were compared

RESULTS

Table 1. *RSE [%] of CL for different WT_{norm}*

WT_{norm}	1 kg	2.7 kg (Median)	70 kg
OFV	1091	1091	1091
CL [L/h] (θ_1)*	**0.00615 (10.6%)**	**0.0119 (8.0%)**	**0.104 (48.2%)**
V [L]	2.37 (4.4%)	2.37 (4.4%)	2.37 (4.4%)
allom. exp (θ_2)	0.665 (20.3%)	0.665 (20.3%)	0.665 (20.3%)
prop. Error [%]	2.89 (23.5%)	2.89 (23.5%)	2.89 (23.5%)

** RSE [%] obtained from the bootstrap analysis (1000 runs) were 10.5%, 8.1% and 48.8% of a WT_{norm} 1 kg, 2.7 kg and 70 kg respectively*

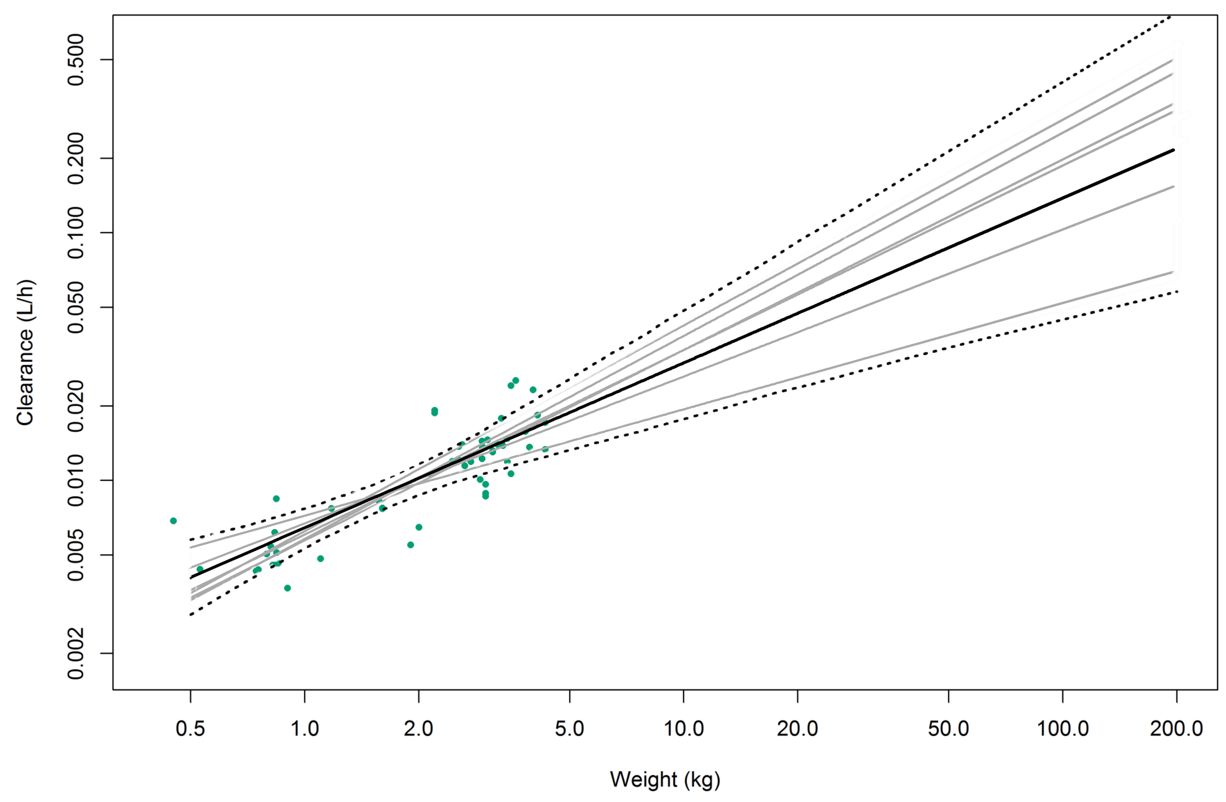

Figure 1. *Median (solid black line) and 95% confidence interval (dotted lines) of the CL function using 1000 bootstrap runs; grey lines represent a random sample of 6 functions; green dots represent observations*

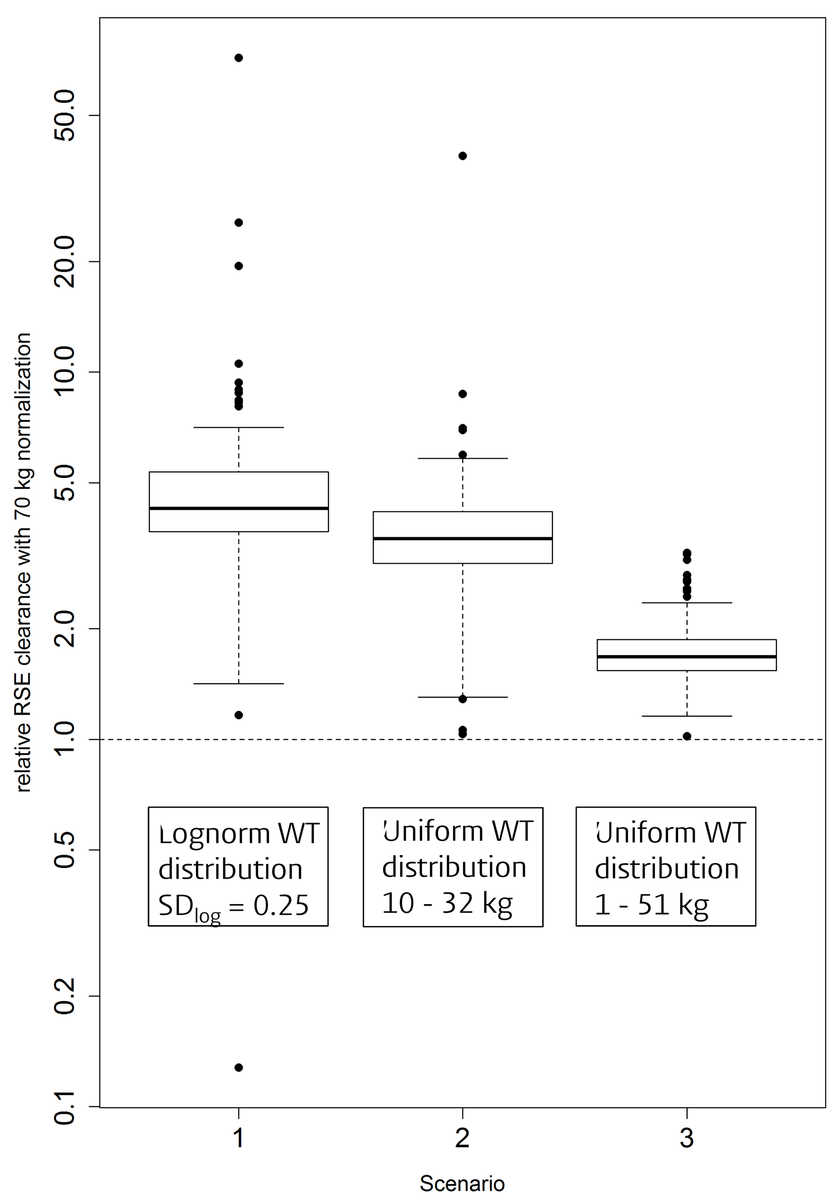

Figure 3. *Boxplots of RSE [%] on CL of 250 fitted datasets with three different WT distributions (median WT ≈ 21 kg for each of the datasets)*

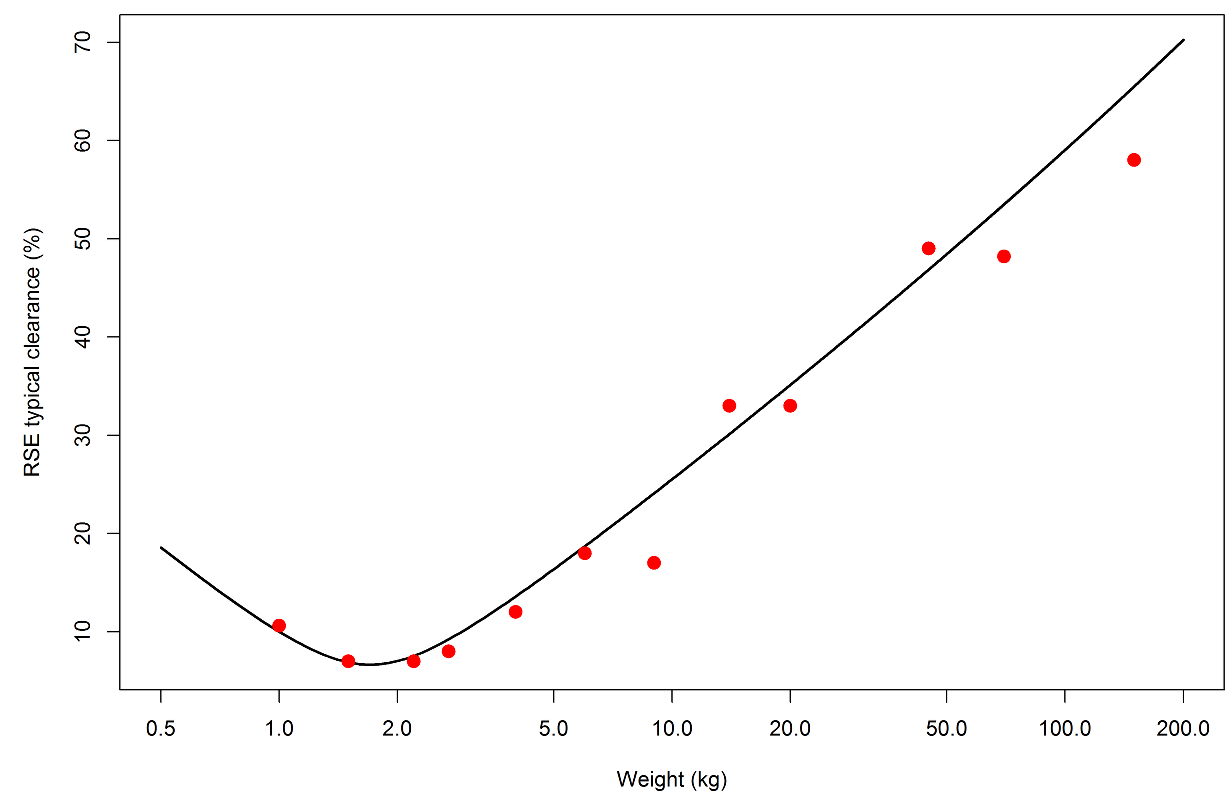

Figure 2. *RSE [%] versus WT; solid line represents the median RSE [%] obtained from 1000 bootstrap runs, red dots represent the RSE [%] obtained from the covariance step of a single NONMEM® run using the corresponding WT_{norm}*

1. *Impact of WT_{norm} on RSE and bootstrap values*
   - Only the CL estimate and the RSE of CL change with different WT_{norm} (Table 2)
   - RSE on CL is lowest when WT_{norm} is close to median WT
   - RSE estimate of bootstrap and NONMEM covariance matrix were comparable
2. *Bootstrap CIs of typical CL for 1 to 100 kg*
   - Bootstrap 95%CI of CL over a weight range of 1-100 kg (Figure 1) was independent from WT_{norm}
   - WT_{norm} does not impact the precision of the CL estimation within the studied WT range (Figure 2)
3. *Impact of different WT distributions*
   - With WT_{norm} = 70 kg RSE increases (Figure 3) when:
     – WT range decreases
     – The WT distribution is narrower

AFFILIATIONS

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