

INFLUENCE OF COVARIATE DISTRIBUTION ON MODEL PREDICTION AND EXTRAPOLATION

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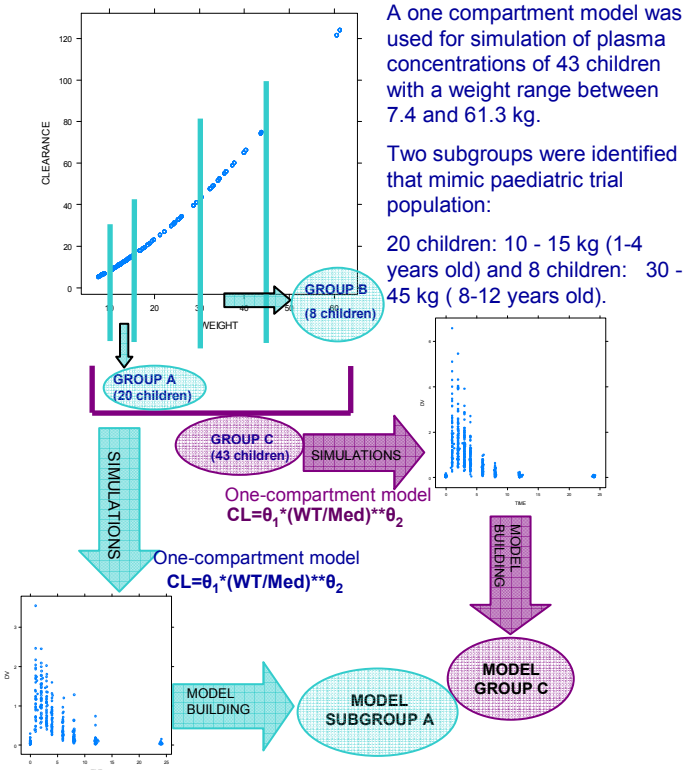
INTRODUCTION

- A good model is not only supposed to describe well the data used during model building, but also to show predictive value when making extrapolations to a different population.
- Extrapolations beyond the covariate range explored during model building are particularly important in paediatric research.
- Covariate-parameter correlations are often described using "centering" around the median or mean value. This approach is supposed to make the estimation more stable and facilitate the interpretation of the coefficients in the correlation.
- The aim of this investigation was to assess whether "centering" ensures accurate prediction of the pharmacokinetic parameters in a new population for which **covariate values occur beyond the range available for model building** and hence represents a potentially different covariate distribution.

METHODS

Different scenarios were simulated which reflect typical relationships between parameter and covariate:

$CL = \theta_1 \cdot (WT/Med)^{\theta_2}$	$\theta_2 < 1$ $\theta_2 > 1$	CL=Clearance WT=Body weight
$CL = \theta_3 + (WT/Med)^{\theta_4}$	$\theta_4 < 1$ $\theta_4 > 1$	Med=Median body weight



The PK model obtained from the analysis of all patients was used to predict pharmacokinetic parameters in each subgroup. Conversely, the PK model obtained from each subgroup was used to extrapolate parameters across populations.

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RESULTS

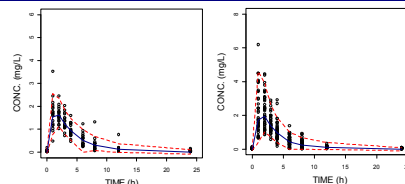


Figure 1: VPC for the PK model obtained from subgroup A (left) and group C (right), when $\theta_2 < 1$.

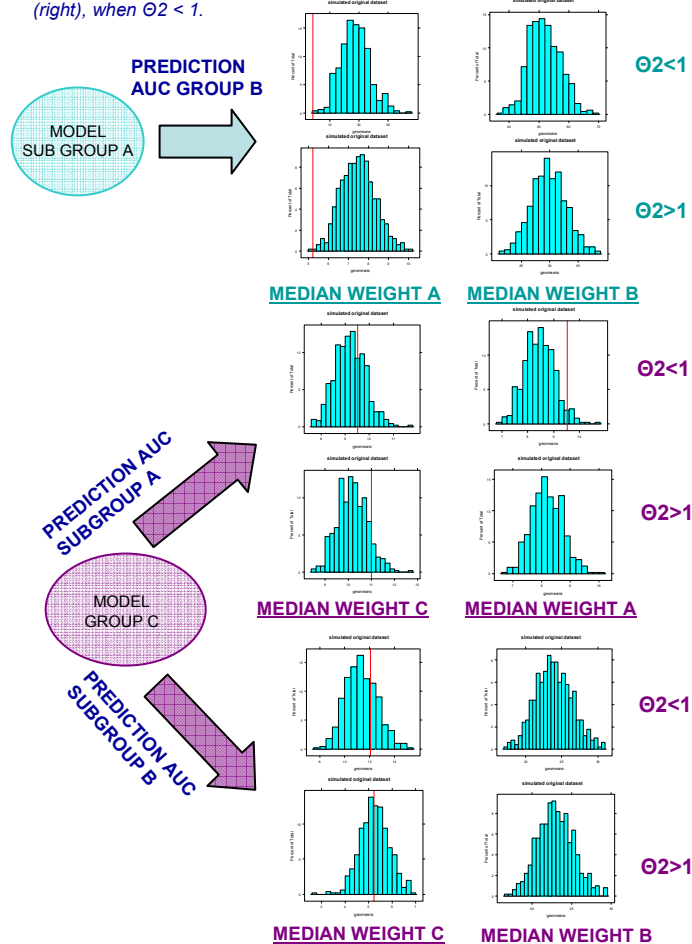


Figure 2: Histograms represent distributions of predicted AUC in each population. Simulations were performed by using the median value of WT from the original data or adapting it to reflect the WT distribution in the new population

CONCLUSIONS

- Model performance appears to be independent of the nature of the parameter-covariate correlation if predictions refer to *interpolations*.
- The value used for centering during model building must be kept even when the covariate point estimate of the population being simulated differs statistically from the original population.
- Extrapolations beyond the covariate range used during model building seem to be accurate only for linear correlations between parameter and covariate (i.e., $\theta_2 = 1$).