On multiple imputation using chained equations (MICE) and missing covariates in population pharmacokinetic analysis

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**Objectives**: To evaluate MICE\textsuperscript{1} for handling missing covariates in population pharmacokinetic analysis using stochastic simulation and estimation approach.

**Methods**: One compartment model with zero order infusion was as structural model. Weight and sex (Female=0, Male=1) variables were simulated as covariates. Clearance was a function of sex. Weights were simulated from two truncated log-normal distributions with sex-specific medians and variances as described before\textsuperscript{2}. Datasets (n=200) were simulated with each containing 200 subjects with each subject having two steady-state concentrations. From these full datasets, missing datasets with 10, 20 and 30\% missing sex covariate by three different missingness mechanisms (MCAR, MAR and MNAR) were created. Five imputed datasets for each missing dataset were created using the MICE package in R (3.2.2). The true model was fit to each dataset and results were combined. Two variations on the set of predictors for the MICE approach were tested: A) weight only, and B) weight and individual clearance (CL\textsubscript{i}). Relative standard deviation (RSE) and relative bias were calculated for each parameter. Relative bias of <5\% and <10\% for fixed and random effect parameters, respectively, was considered unbiased. A RSE of <10\% and <20\% for fixed and random effect parameters, respectively, was considered precise.

**Results**: The fixed effect parameters were above the limit (>5\%) of relative bias set a priori in the method A of MICE based imputation for data missingness level >10\%. The random effect parameter was severely biased (>50\%) in all scenarios tested with method A. The fixed and random effect parameters were within the limit of prespecified limits of relative bias and RSE for all the scenarios and missing data levels using method B and deemed acceptable.

**Conclusions**: MICE is a useful alternative to handling missing covariates in population pharmacokinetic analysis.
