Data Gaps, Model Mishaps: Quantifying the Impact of Missing Pharmacometrics Data on Pharmacodynamic Projections

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Background & Objectives

Many times, in pharmacokinetic/pharmacodynamic (PK/PD) analyses, it seems prudent to remove subjects from the PD analysis that are missing most or all corresponding PK data for fear of introducing bias in the predicted response. To determine if this fear is warranted, we wanted to determine the bias and precision of PD estimates and predictions when different levels of PK data are missing. Simulations under various scenarios were used to assess the impact of bias and precision on PD parameter estimate and at a 12-week landmark endpoint. In every simulation scenario, the percentage of PK data missing completely at random (MCAR) was increased, and the bias and precision (measured as root mean squared error [RMSE] calculated across simulation replicates) were calculated.

Methods

Main Workflow

1. **PK data were generated** with a two-compartment model with first-order absorption and covariates (sample from an NHANES database[1]) of weight (WT), estimated glomerular filtration rate (eGFR), age, and albumin were included on apparent clearance (CL/F) and/or volume (V/F) parameters. Interindividual variability (IIV) on CL/F, V/F and absorption (ka) parameters, and residual unexplained variability (RUV) were also included.
2. **Six PK datasets were generated**, each with a different proportion of subjects missing PK and determined randomly (MCAR). All patients assigned to have missing PK data were subsequently assigned typical exposure metrics conditional upon their covariate values.
3. **PD time-courses were simulated**, using an indirect response model. The drug exposure at which half of the maximum response was reached (EC50) was calculated as approximately the median area under the exposure curve (AUC) for the simulated 150 mg dose group. IIV and RUV (as a proportional effect) were included.
4. **PD parameters were estimated**, and a landmark PD endpoint (12-week change from baseline (CFB)) was determined from each of the six datasets.
5. **Relative bias and RMSE were calculated** for each of the six datasets across dose groups and simulated replicates.

Increase Interindividual Variability

- Variance on the PK parameters that included IIV were all increased proportionally by 10, 50, 200 or 300%.

Increase Residual Variability

- Residual variability in PK simulations was increased proportionally by 10, 50, 200 or 300%.

Decrease Number of Subjects

- Run PK population simulation with smaller sample sizes

Methodology is summarized in Figure 1.

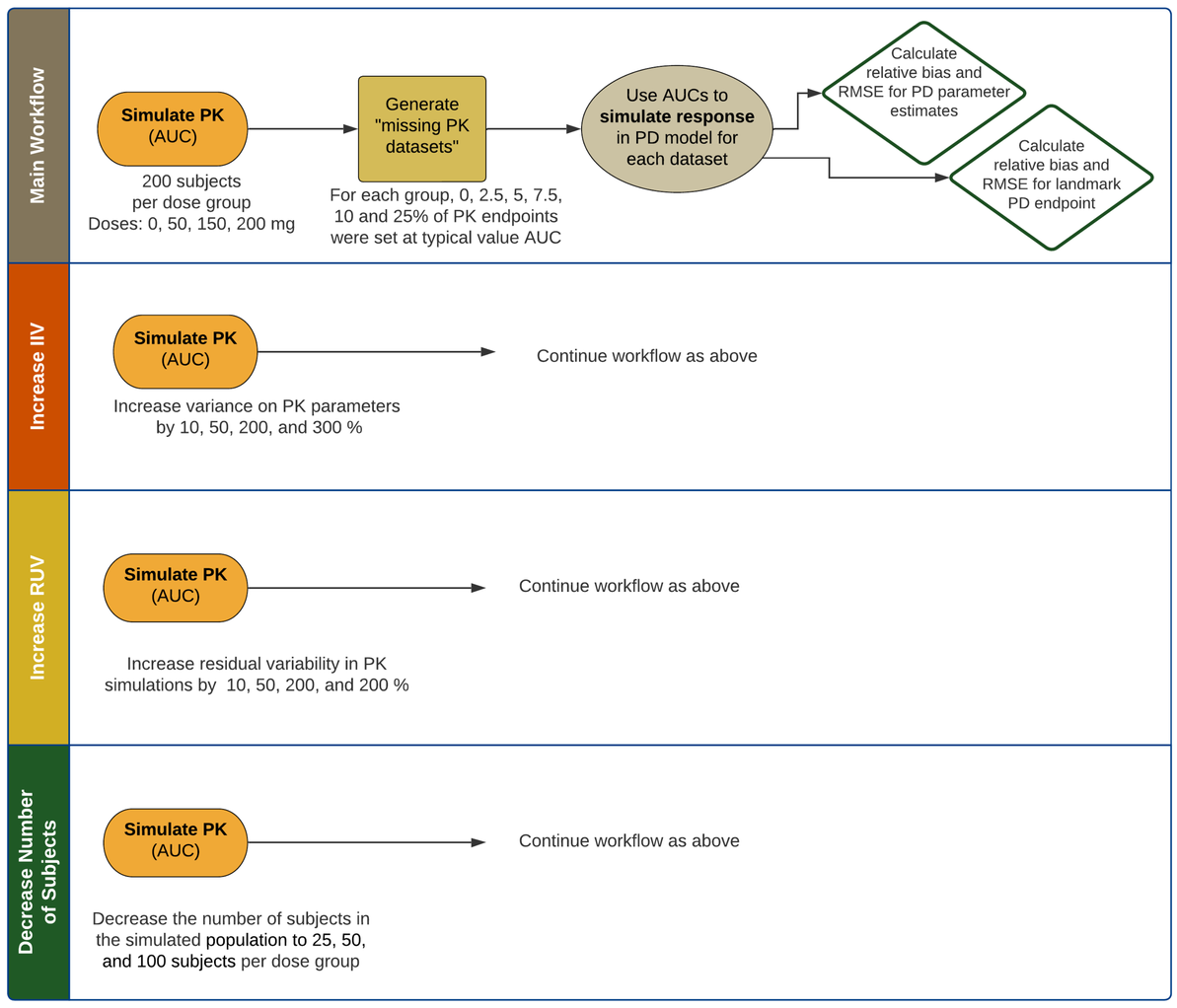

Figure 1. Summary of simulation workflows for each scenario

Conclusion

When predicting PD outcomes, imputing population-level PK estimates for subjects missing PK is an acceptable practice/approach when populations are reasonably large, simulations with a relatively large proportion of subjects' missing PK did not show a marked difference in estimated PD parameters or simulated responses. Even under conditions with large IIV or RUV in PK, the ability to estimate PD parameters or a landmark endpoint remains, in most cases, was unaffected.

In smaller populations (down to N=25), the impact on relative bias and RMSE around the landmark endpoint was minimal. Only the bias around the parameter estimates seemed to be affected by population size (the magnitude of bias increased with smaller sample size, but the median across simulations stayed the same across a range of sample sizes tested). Additional characterization of operating characteristics impacting the imputation of typical exposures for PD analyses is warranted.

Future Directions

Additional scenarios should also be evaluated. For example, when PK data are missing not completely at random, this is similar to the real-world situation when a greater proportion of PK data may be below the limit of quantification (LOQ) in groups assigned to the lower doses.

References

[1] NHANES - National Health and Nutrition Examination Survey Homepage. http://www.cdc.gov/nchs/nhanes/ (2018). Accessed: 2024.

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Results

Main Workflow

For fixed parameter estimates, the magnitude of bias was greatest for IIV on offset rate (kout; Figure 2), but there was little difference between groups (median of 0.0834 and 0.0909 for 0% and 25% missing PK, respectively). There was little difference in RMSE across different levels of missing data across all parameters (Figure 3). Any trends were likely due to the number of successful estimation runs differing across simulations with different levels of missing data. For the PD endpoint of 12-week CFB, although there was a slight trend towards an increase in mean bias with level of missingness, the magnitude of bias was very small (absolute mean of 0.0474 and 0.0501 for 0% and 25% missing PK, respectively; Figure 4). There were no trends in RMSE for the landmark endpoint (Figure 5).

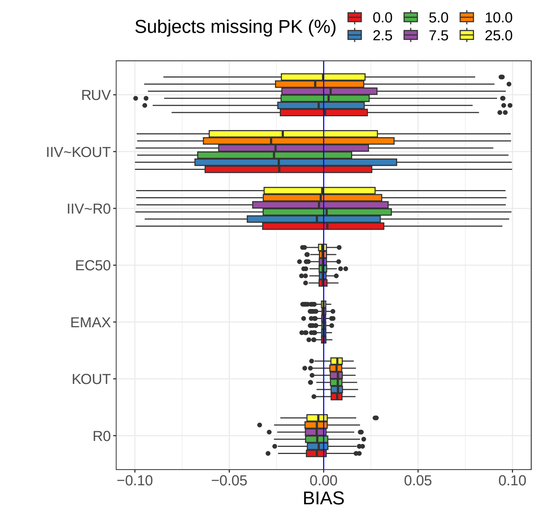

Figure 2. Bias for PD parameter estimates. Solid blue line indicates bias = 0, or perfect unity between predictions and true estimates

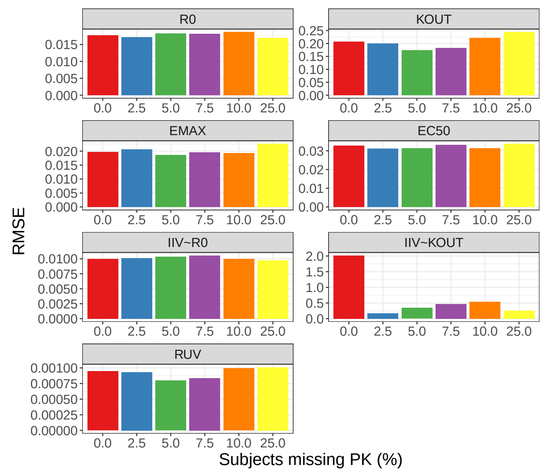

Figure 3. RMSE for PD parameter estimates

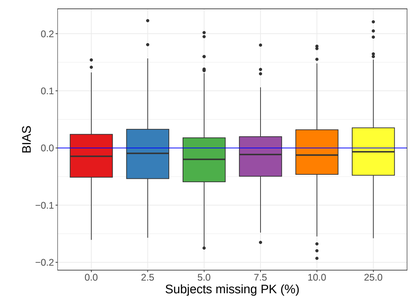

Figure 4. Bias for landmark endpoint (12 week CFB), grouped by % of subjects with missing PK data. Solid blue line indicates bias = 0, or perfect unity between predictions and true estimates

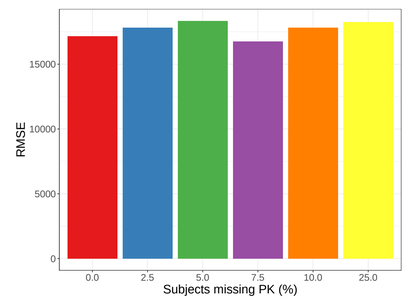

Figure 5. RMSE for landmark endpoint (12 week CFB)

Increase IIV: There was no meaningful change in bias or RMSE when IIV was increased on all PK parameters by 10, 50, 200, or 300 % (Figures 6 and 7).

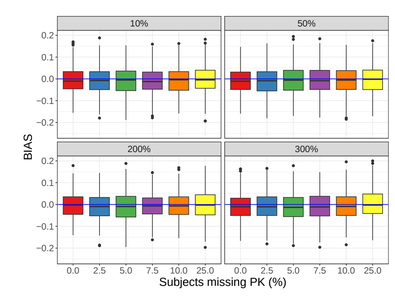

Figure 6. Bias for landmark endpoint (12 week CFB) colored by different levels of missing PK data, grouped by increasing levels of IIV. Solid blue line indicates bias = 0, or perfect unity between predictions and true estimates

Figure 7. RMSE for landmark endpoint (12 week CFB) colored by different levels of missing PK data, grouped by increasing levels of IIV

Increase RUV: There was no meaningful change in bias or RMSE when RUV (applied as proportional error model) was increased on by 10, 50, 200, or 300 % (Figures 8 and 9).

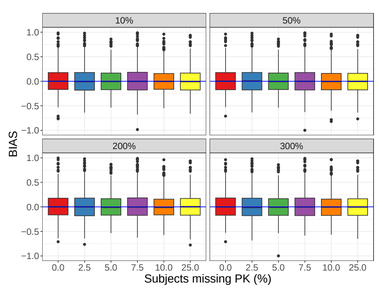

Figure 8. Bias for landmark endpoint (12 week CFB) colored by different levels of missing PK data, grouped by increasing levels of RUV. Solid blue line indicates bias = 0, or perfect unity between predictions and true estimates

Figure 9. RMSE for landmark endpoint (12 week CFB) colored by different levels of missing PK data, grouped by increasing levels of RUV

Decrease Number of Subjects: Decreasing the number of subjects in the study population had no impact on the ability to estimate a landmark PD endpoint (bias and RMSE did not change across population sizes of 25, 50, or 100; Figures 11 and 12). Only the magnitude of bias increased on the PD parameter estimates as population size decreased (Figure 10).

Figure 10. Interquartile range (IQR) for bias around parameter estimates for runs with different simulated number of subjects

Figure 11. Bias for landmark endpoint (12 week CFB) colored by different levels of missing PK data, grouped by increasing population sizes. Solid blue line indicates bias = 0, or perfect unity between predictions and true estimates

Figure 12. RMSE for landmark endpoint (12 week CFB) colored by different levels of missing PK data, grouped by increasing population sizes