Advance in Data Imputation Approach to Support BE Assessment

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day (2/2), Session 7: Quantitative Methods – Study Design, Model-integrated BE Approaches

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

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- **Background**
  - Missing data
  - Data imputation
  - Existing methods
- **Method**
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- **Performance Test**
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  - Performance evaluation
- **Case Study**
  - A hypothetic application of the Improved GSimp

Motivation

- In current practice for bioequivalence (BE) assessment, the applicant's submitted protocol should include plans to minimize missing data and prespecify statistical analysis for treating missing data (if applicable) with sufficient justifications.
- Generally, replacement of missing values using data imputation methods is not recommended.
- Under some special circumstances, data imputation methods could be potentially used to provide additional evidence to support BE assessment.
- This presentation reports a recent research study in developing a new data imputation method that could be potentially used to support BE assessment*.

* This work should not be considered as an FDA-recommended method for ANDA submission.

Background – Types of missing data

- Missing data is ubiquitous
- Commonly exists for pharmacokinetic (PK) or pharmacodynamic (PD) BE studies

- Different types of missing data
  - **MNAR**: Missing Not at Random (e.g., censoring due to detection limit)
  - **MCAR**: Missing Completely at Random
  - **MAR**: Missing at Random

Missing values in real world datasets are usually a mixture of these types

Note: It is classically assumed that all MAR values are also MCAR, and the same imputation methods for MCAR can also be used for MAR missing values [2].

[2] Lazar, Cosmin, et al. "Accounting for the multiple natures of missing values in label-free quantitative proteomics data sets to compare imputation strategies." Journal of proteome research 15.4 (2016): 1116-1125.

Background – Challenges posed by missing data

- Missing data pose challenges in BE assessment as it can:
  - Bias parameter estimations
  - Distort sample distribution
  - Impair statistical power

- Imputation is the process of replacing missing data with substituted values

- Scientifically sound imputation methods could potentially be used to support BE assessment

Background - Existing imputation methods

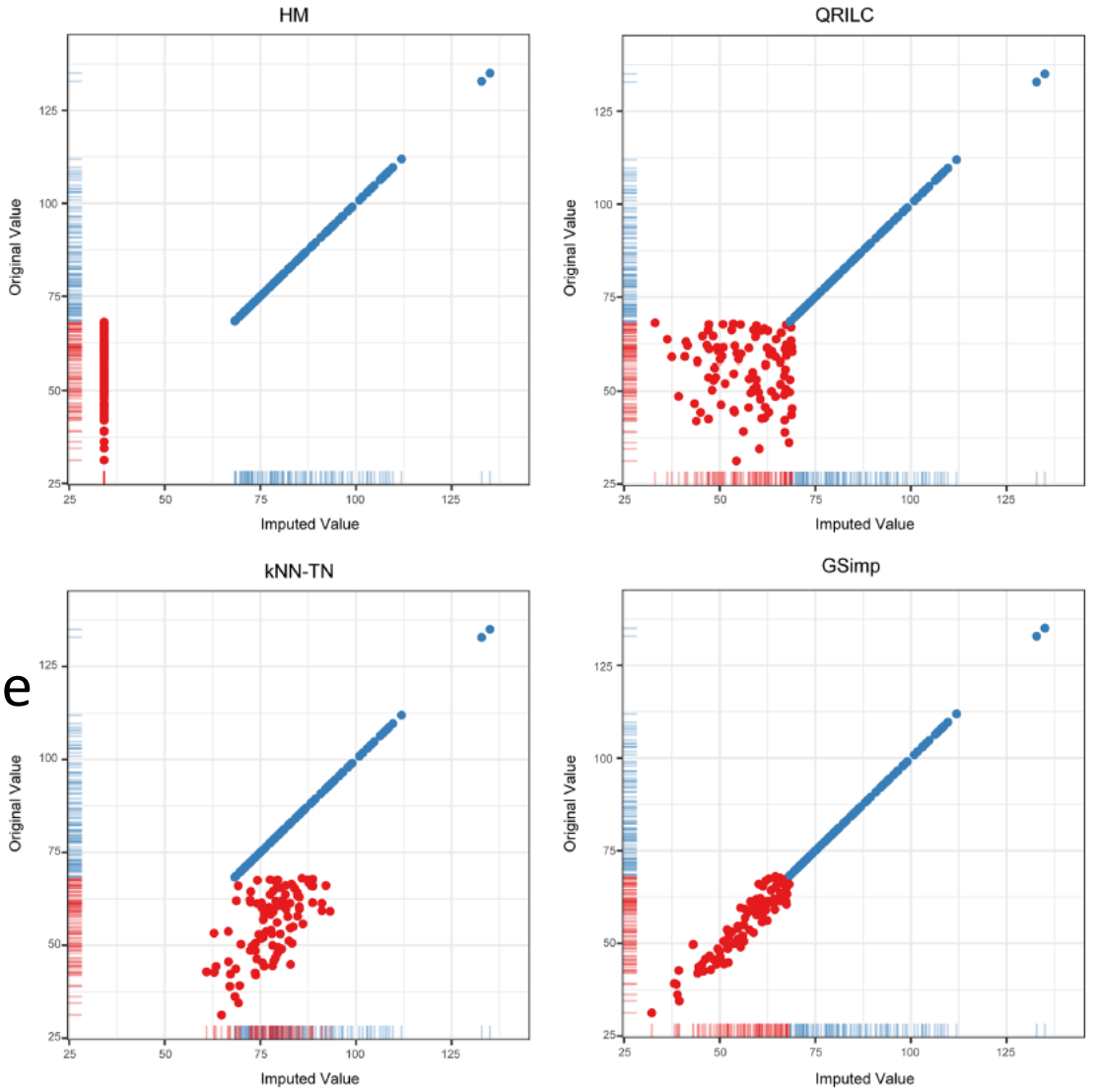
(not only for PK or PD data)

- For MNAR data:
  - Half of the minimum value (HM)
  - K-nearest neighbor truncation (trKNN)
  - Quantile regression approach for left-censored missing (QRILC)
  - **Gibbs sampler based left-censored missing value imputation approach (GSimp)**

- For MCAR/MAR data:
  - K-nearest neighbors (KNN)
  - MissForest
  - Imputation with Singular Value Decomposition (SVD)

Background - GSimp

- Best performance for MNAR [3]
- Potentially good performance to handle MCAR/MAR [4]



[3] Wei, Runmin, et al. "GSimp: A Gibbs sampler based left-censored missing value imputation approach for metabolomics studies." PLoS computational biology 14.1 (2018): e1005973.
[4] Lenz, Michael, et al. "Missing value imputation in proximity extension assay-based targeted proteomics data." Plos one 15.12 (2020): e0243487.

METHOD

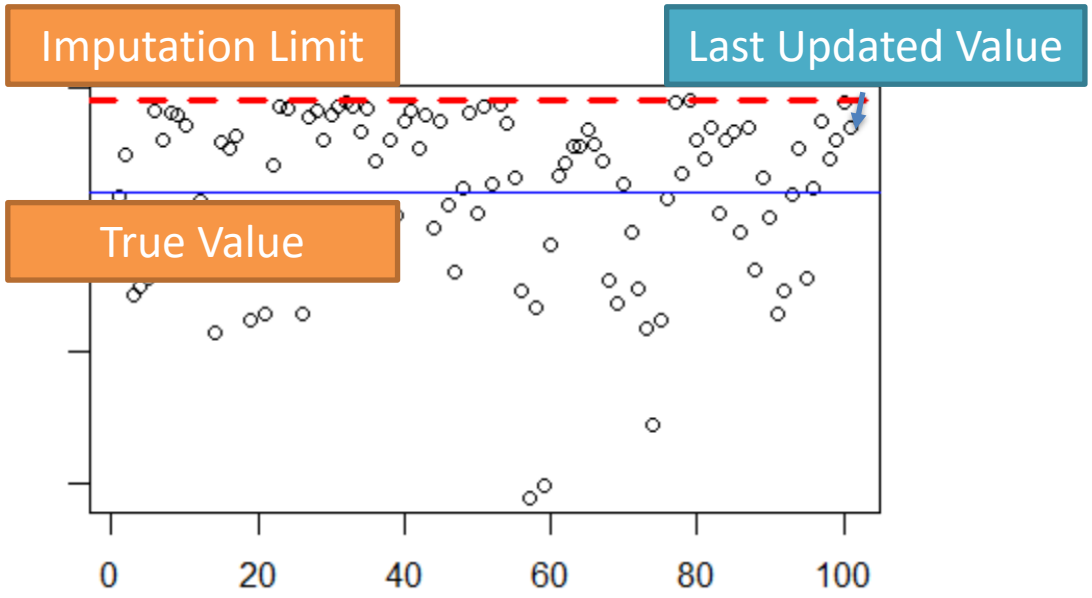
Original GSimp

Improved GSimp

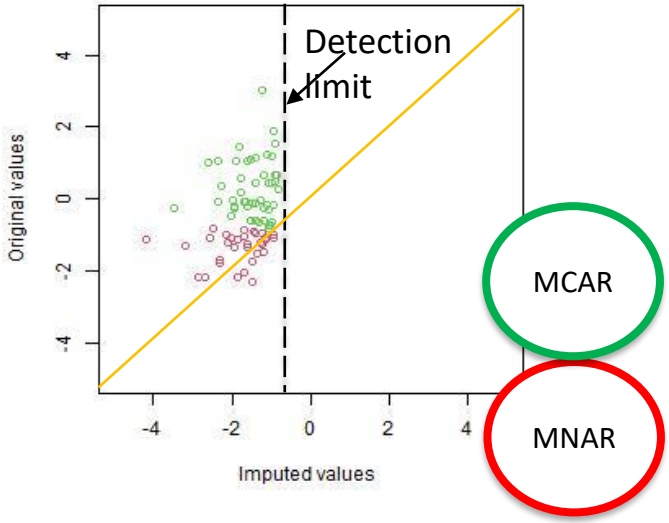
Original GSimp

Limitation 1- Potentially unstable prediction

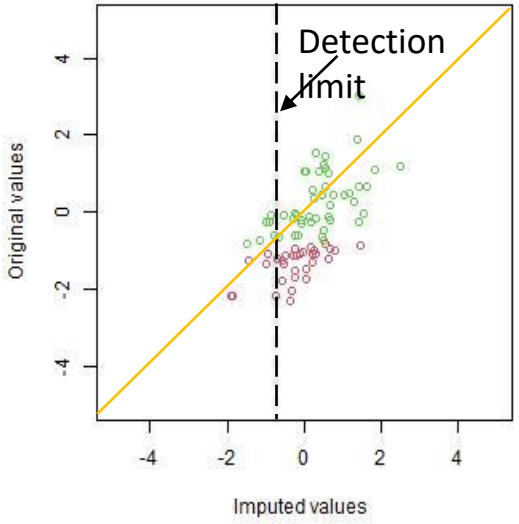
Limitation 2 - Underperforming for data with mixed MNAR and MCAR/MAR values



Original GSimp with limits



Original GSimp with no limits



Improved GSimp

- Implement probability-based prediction

  → to improve the reliability and accuracy of imputed values

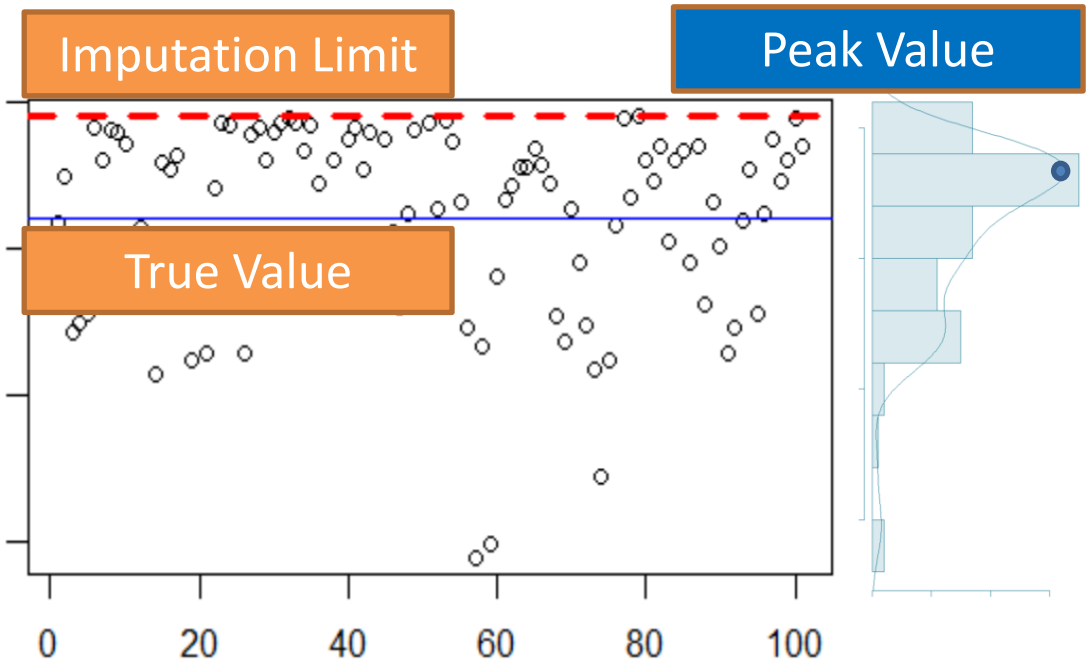
- Integrate different limits for each missing value based on its missing type

  →to extend the algorithm to mixtures of missing types

Improved GSimp – Improvement (I)

Implement probability-based prediction

Use the peak value of the estimated probability density of predicted values in all iterations as the imputed value



Case example
True value = -1.6752

Imputation Process #	Original GSimp Imputed Values	Improved GSimp Imputed Values
1	-1.7982	-1.6704
2	-1.6199	-1.6684
3	-1.8384	-1.6753
4	-1.5587	-1.6681
5	-1.7538	-1.7003
6	-1.5551	-1.6628
7	-1.6716	-1.6457

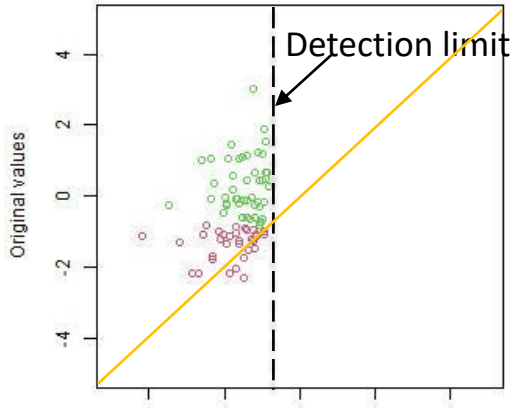
Improved GSimp – Improvement (II)

Extend to mixtures of missing types

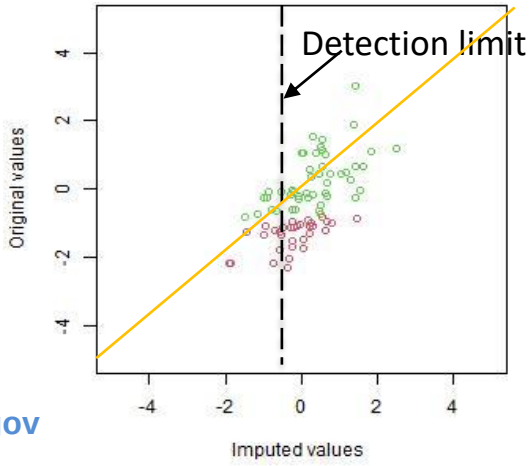
Add missing-type marks for missing values

Set up different limits for each missing value based on missing type mark

Original GSimp with limits



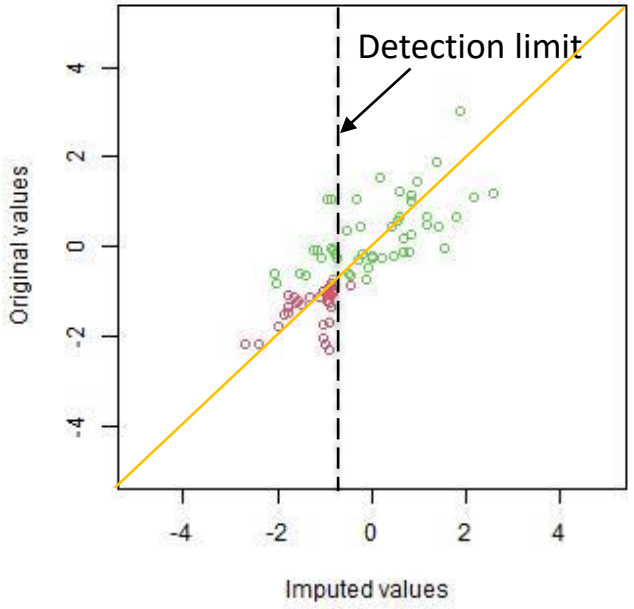
Original GSimp with no limits



MCAR

MNAR

Improved GSimp



PERFORMANCE TEST

Simulation

Performance evaluation

Simulation - Dataset

- Dataset used:

  160x76 dataset without missing values from the original GSimp paper

- Missing values were generated based on missing proportion and the ratio of MNAR type in the mixture
  - To control both the total proportion of missing values α and the MNAR ratio β in the mixture of missing types
  - Missing type mark were added for each generated missing value

Performance Metrics

- Normalized root mean square error (NRMSE)

$$\sqrt{\frac{\frac{1}{n}\sum_{i=1}^{n}\left(x_i^{imp}-x_i^{true}\right)^2}{\frac{1}{n}\sum_{i=1}^{n1}(x_i^{true}-\mu_{miss}^{true})^2}}$$

n=total number of missing values

- NRMSE – based Sum of Ranks (SOR)

$$\sum_{i=1}^{k} Rank_i(NRMSE)$$

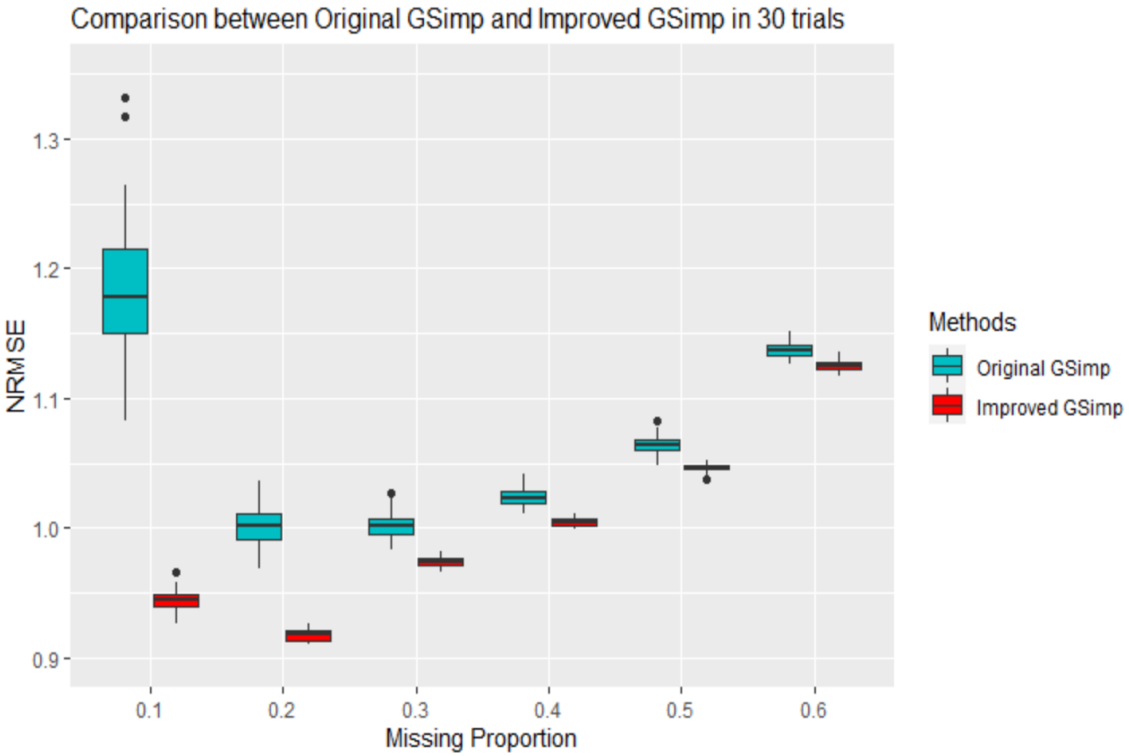
k =the number of missing variables

- Scatter plots

Performance Test 1

Compare Improved and Original GSimp with MNAR data

Paired T-test results showed that the Improved GSimp had significantly lower NRMSE than the original GSimp across all missing proportions from 0.1 to 0.6 ($p<0.001$ for all-comparisons)



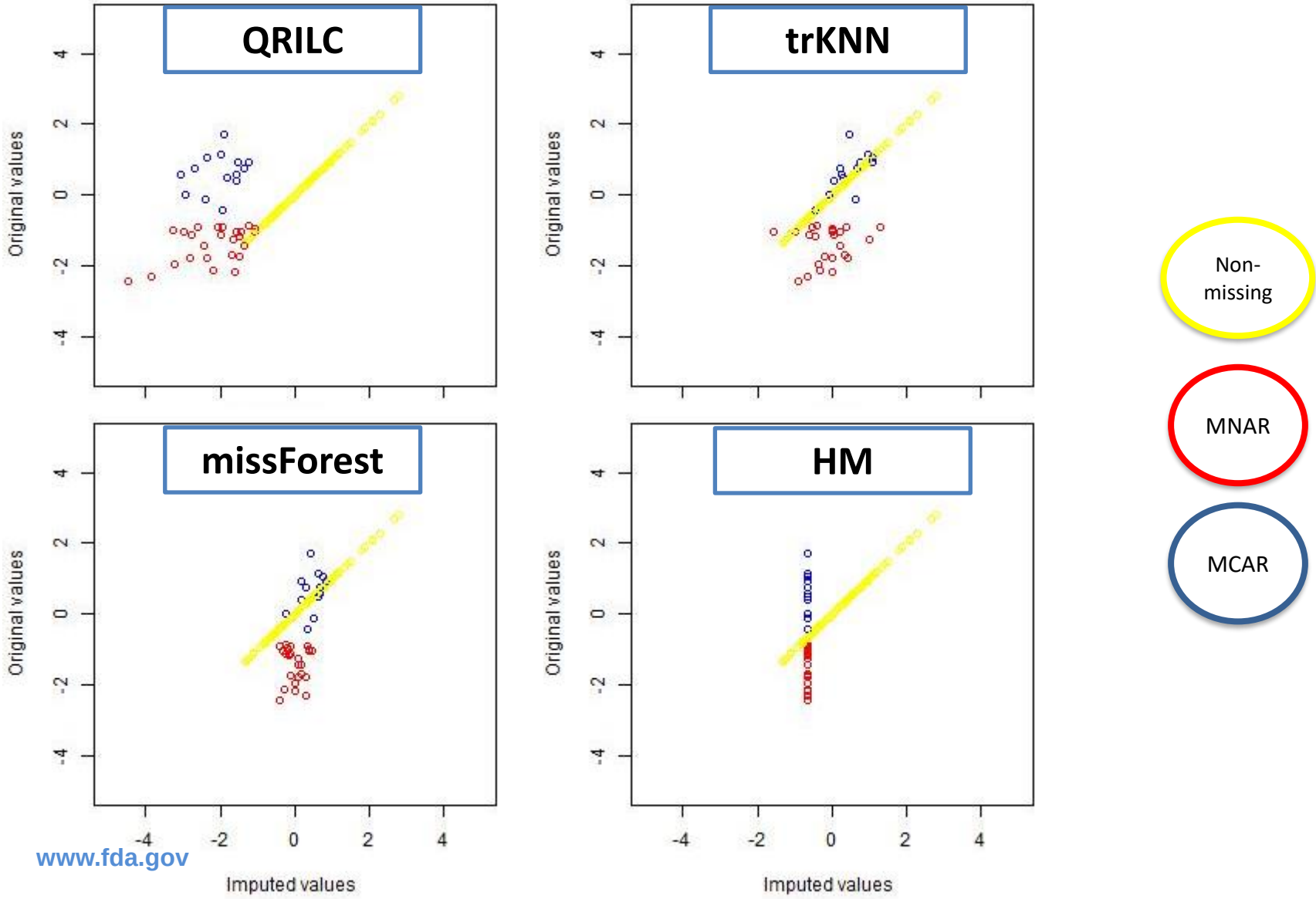
Improved GSimp always showed significant lower imputation error than the original GSimp

(Imputation Process 30 times for MNAR datasets, missing proportion from 0.1 to 0.6).

Performance Test 2

Improved GSimp vs. other methods with mixture of missing types

Case Example: Missing proportion 0.2 | MNAR 70%



Non-missing

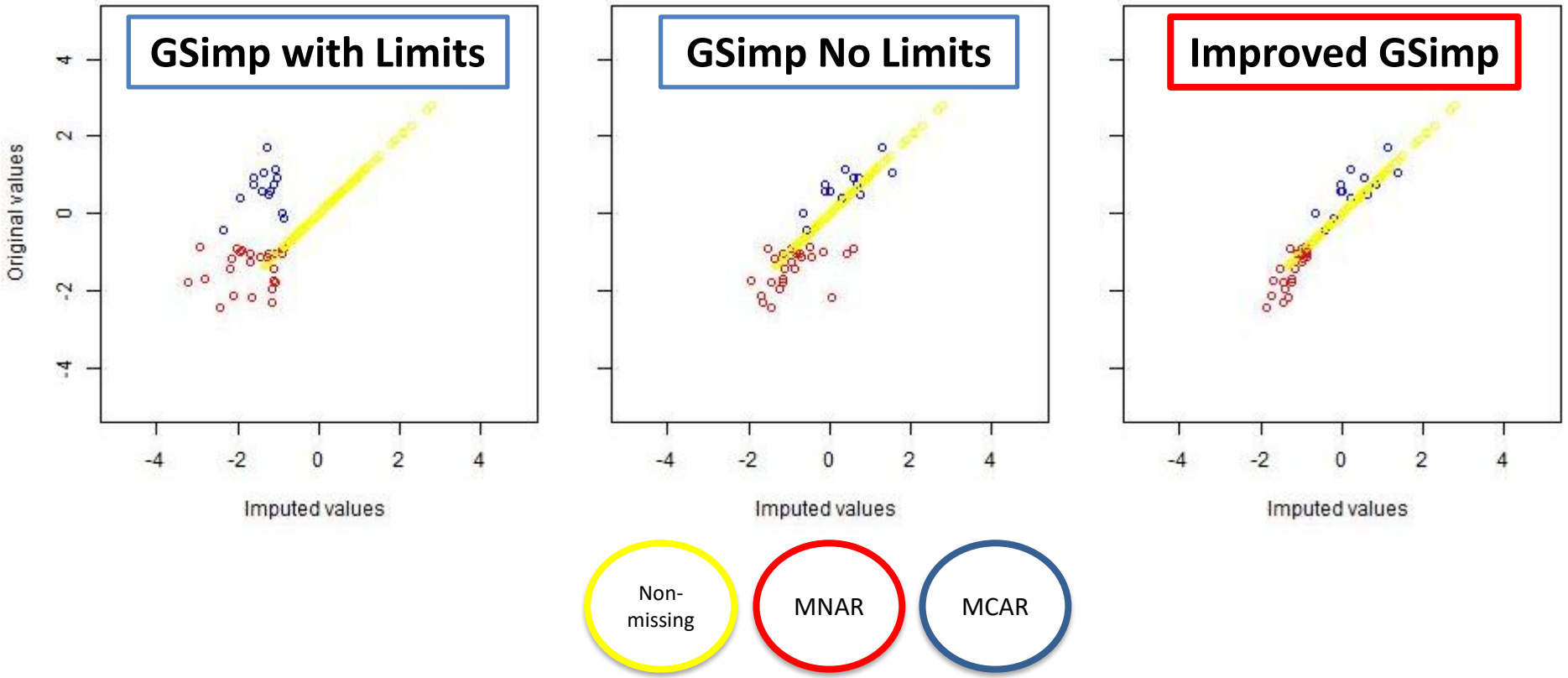
MNAR

MCAR

Performance Test 2

Improved GSimp vs. other methods with mixture of missing types

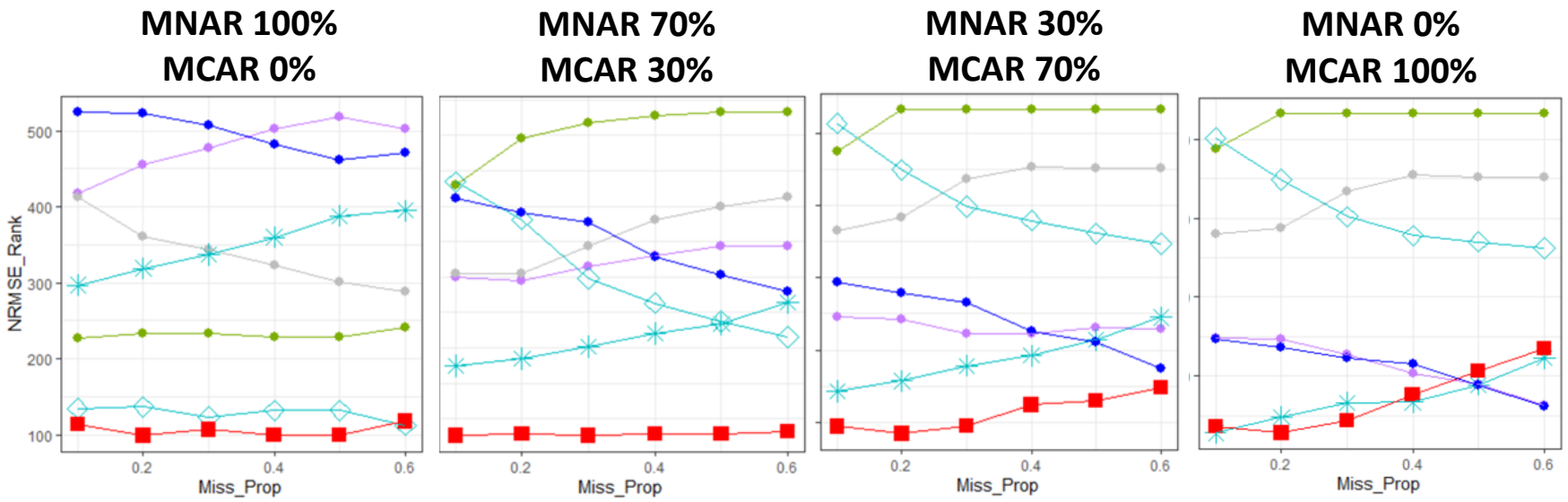
Case Example: Missing proportion 0.2 | MNAR 70%



Improved GSimp outperforms the original GSimp and other methods for MNAR and MCAR mixture dataset

Performance Test 2

Improved GSimp vs. other methods with mixture of missing types



Improved GSimp outperforms the original GSimp and other methods in most cases for MNAR, MCAR, or mixture datasets

A Hypothetic Application of the Improved GSimp

Case Example

Basic information for the case example

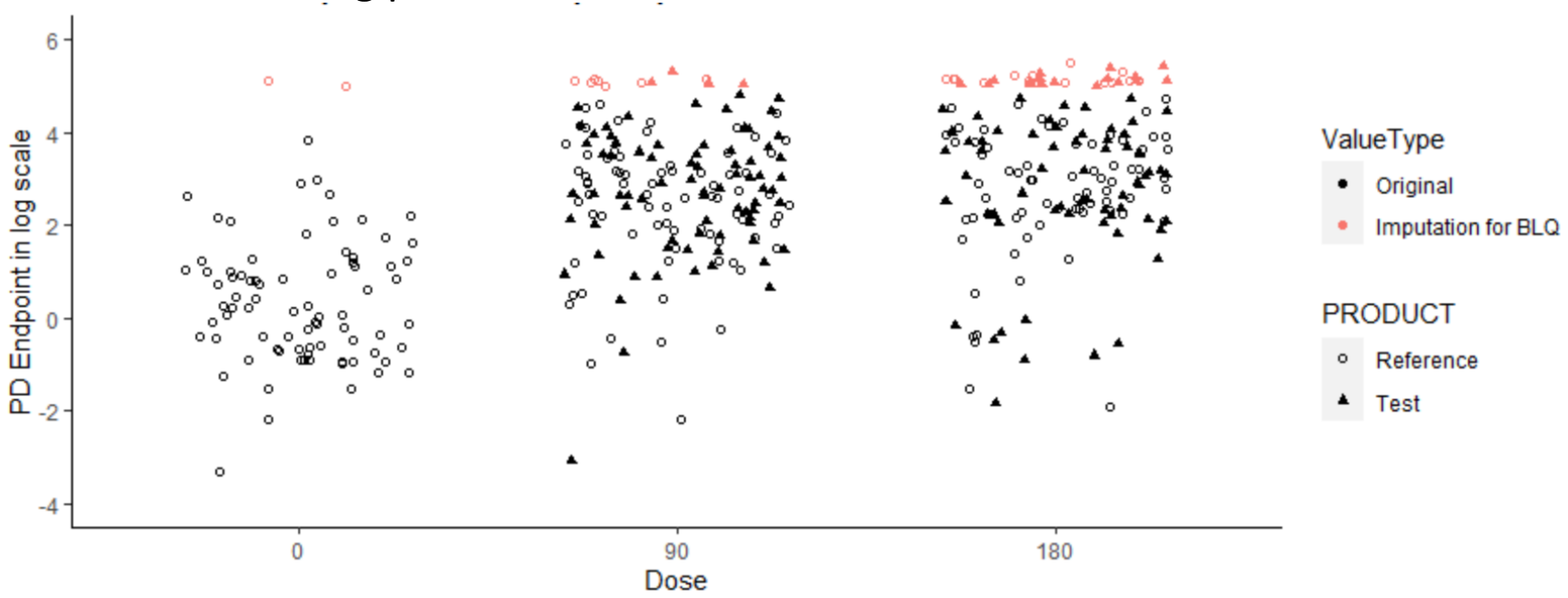
- A pharmacodynamics (PD) BE study from an approved ANDA
  - Among 84 subjects in the submitted data, 22 subjects had 44 missing values in "PD endpoint" due to detection limit (i.e., right censored data), missing proportion is about 0.11
  - Without salient deficiency in study design and implementation, given the high percentage of censored values in the study data, FDA's internal analysis adopted a modern likelihood-based modeling approach (M3 model) [5, 6] to perform data imputation for censored values
- As a hypothetic application, the Improved GSimp was applied to impute for right-censored values to support the BE assessment.

[5] Beal SL. (2001). Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 28:481–504.
[6] Ahn, J. E., Karlsson, M. O., Dunne, A., & Ludden, T. M. (2008). Likelihood based approaches to handling data below the quantification limit using NONMEM VI. Journal of pharmacokinetics and pharmacodynamics, 35(4), 401-421.

PD study case example

With the imputed values by Improved GSimp, the recommended dose-scale analysis shows that the calculated 90% confidence interval falls in the acceptance region of BE.

This assessment can enhance the credibility of data and analysis, thus supporting the decision-making process of BE assessments.



Conclusions

- Improved GSimp outperforms the original GSimp in imputation accuracy for MNAR data.

- Improved GSimp outperforms the original GSimp and other imputation methods for missing data with mixtures of MNAR and MCAR.

- The superior imputation accuracy and reliable performance of the Improved GSimp showed a potential to facilitate the decision-making process of generic drug development and regulatory assessment.

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