Model-integrated bioequivalence method for highly variable drugs with long half-life:

A simulation study comparing complete washout and incomplete washout designs

Zhe Huang[1], Xiaomei Chen[1], Mark Donnelly[2], Lanyan Fang[2], Liang Zhao[2], Mats O. Karlsson[1] and Andrew C. Hooker[1]

[1]Department of Pharmacy, Uppsala University, Uppsala, Sweden

[2]Division of Quantitative Methods and Modelling (DQMM), Office of Research and Standards (ORS), Office of Generic Drugs (OGD), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA), Silver Spring, MD, USA.

Introduction

Background

- The reference-scaled average bioequivalence approach (RSABE)[1,2] may be used to evaluate highly variable drugs (HVDs)[3], which recommends a replicate crossover design for comparison in absorption rate and extent by measuring C_{max} and AUC, respectively, with non-compartmental analysis (NCA).
- Bioequivalence (BE) studies using a replicate crossover design can be challenging for HVD with long half-lives, since a sufficient washout period (≥ 5 half-lives) between treatment periods is recommended for NCA analysis[3]. One possible solution is to use an incomplete washout design to achieve shorter study duration, and to analyze the results with a model-integrated BE approach.
- Our group previously developed a model-integrated BE method[4,5] that shows controlled type I error and higher power compared to NCA-based BE analysis.

Aims

- Develop a model-integrated RSABE method to analyze BE data for HVD with a long half-life.
- Perform a simulation study to evaluate the method's performance to compare the complete washout and incomplete washout designs.

Methods

RSABE method

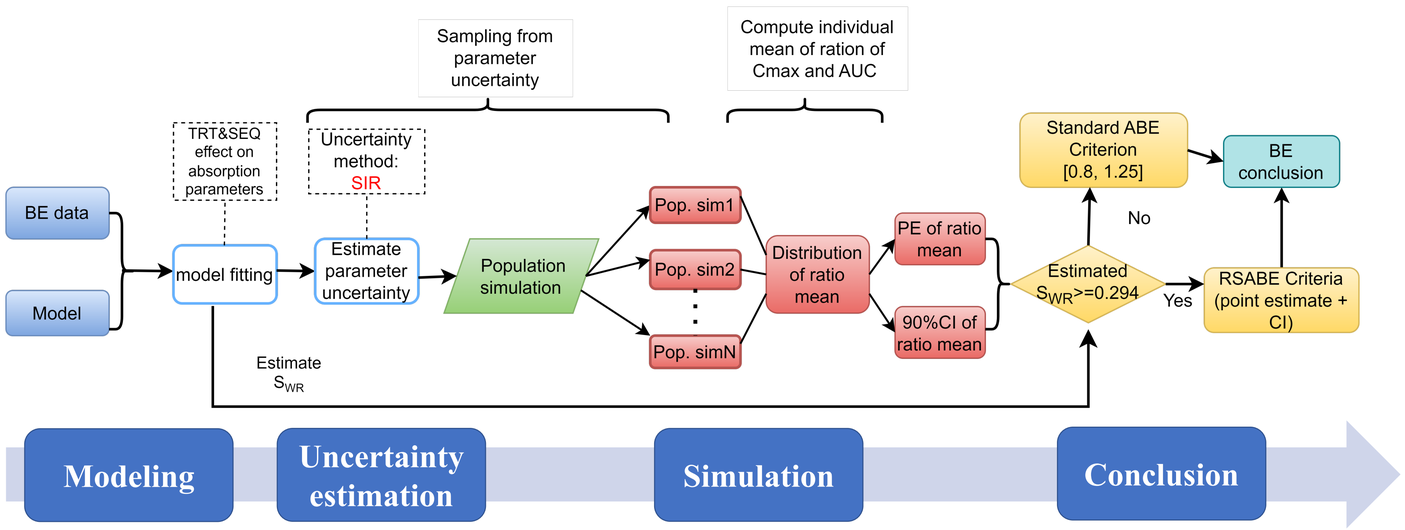
When within-subject variability of the reference standard (S_{WR}) ≥0.294, both of the following BE criteria should be satisfied for each PK parameter:

a. The 95% upper confidence bound for $(\overline{Y}_T - \overline{Y}_R)^2 - (\frac{\ln(1.25)}{0.25} * S_{WR})^2 \leq 0$.

b. The point estimate of the test/reference geometric mean ratio is within [0.8, 1.25].

Where $\overline{Y}_T$ and $\overline{Y}_R$ are the means of ln-transformed PK parameter for the test product and reference standard, respectively.

Model-integrated RSABE method workflow

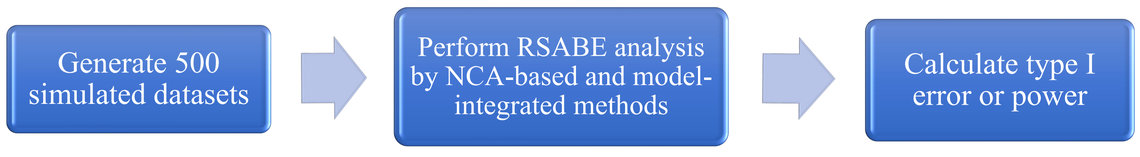


Simulation settings

- Study design:
  - 4-way, fully-replicate crossover study with rich sampling points: 18 points per each period
  - Complete washout or incomplete washout (dosing interval of 72hrs)
- Model for generating simulated datasets:
  - One compartment model with first-order absorption and first-order elimination
  - Typical half-life: 55.5 hr (≈2.3 days)
  - Two levels of within-subject variability: coefficient of variation of 30% (CV30) & 50% (CV50)
- Treatment effect (test/reference ratio) on F (FTRT) settings:
  - FTRT is set to the expanded limit $\exp(\frac{\ln(1.25)}{0.25} * S_{WR})$ for type I error evaluation

    In current study, FTRT = 1.3 for CV30 and FTRT=1.53 for CV50
  - FTRT = 0.9 for power evaluation

Simulation study procedure



Results

- Both methods control type I error with a complete washout design. The model-integrated BE method trends towards higher power at higher variability and in the overall assessment.

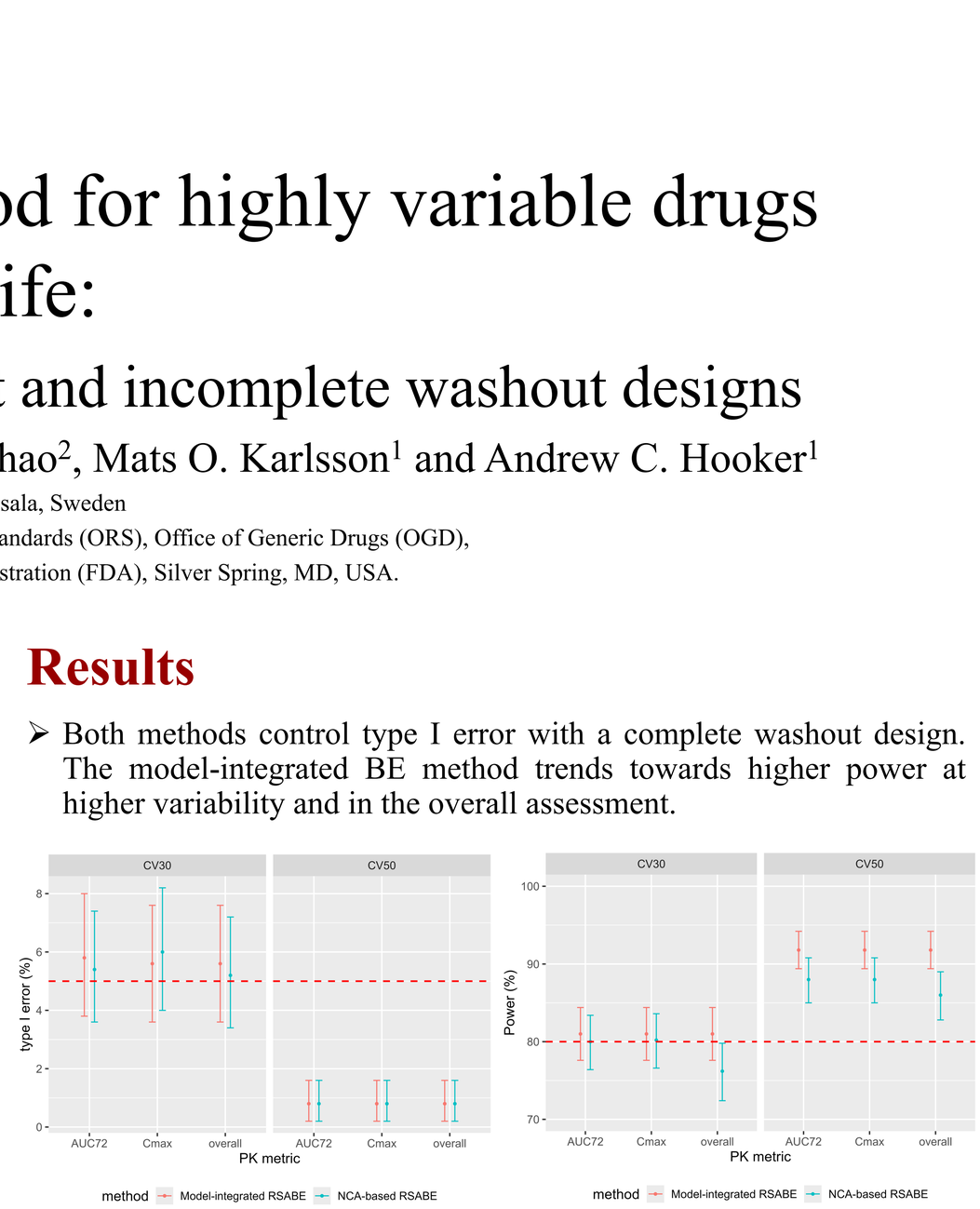


Figure 1 : Type I error and power results with 95% CIs for the complete washout design

- The model-integrated BE method with an incomplete washout design can control type I error and obtain sufficient power. The conventional NCA-based BE method should not be used to analyze this study design.

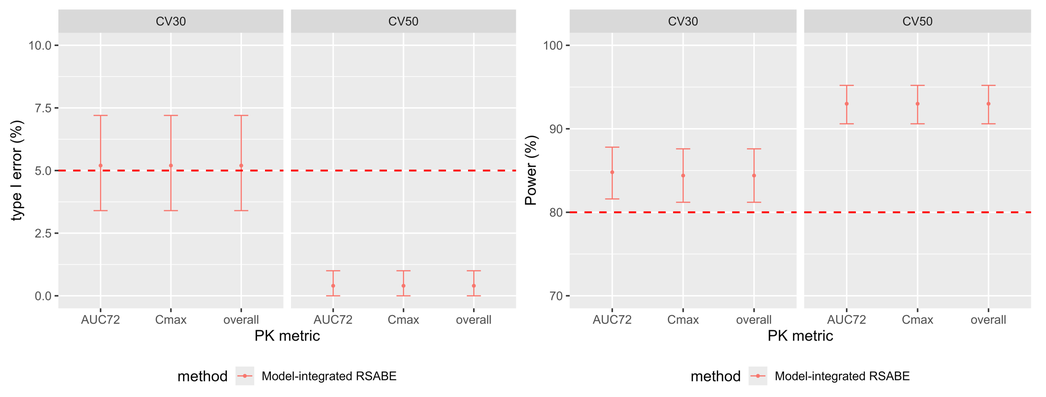


Figure 2 : Type I error and power results with 95% CIs for the incomplete washout design

- Incomplete washout design can reduce the overall study duration by 68% : 37.5 days versus 12 days.

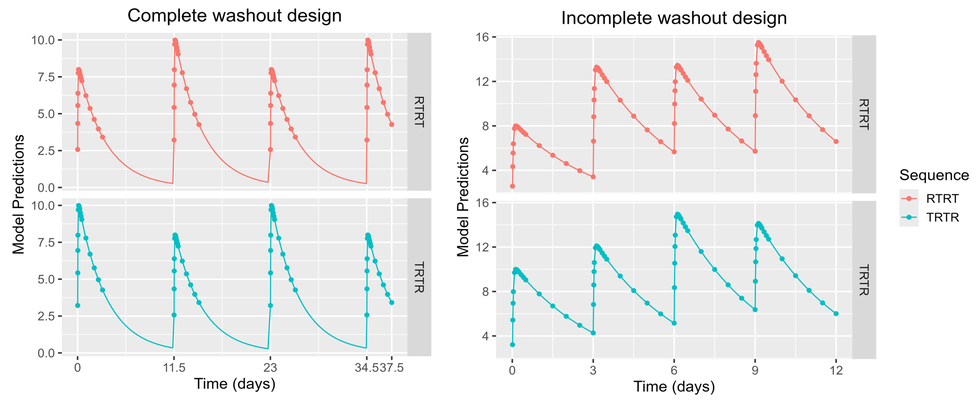


Figure 3 : Study durations for two different washout designs with the 4-way, fully-replicate crossover study

Conclusions

The model-integrated RSABE method serves as a promising tool for HVDs with a long half-life:

- ✓ is flexible enough to analyze data from both conventional BE designs with a complete washout and novel BE designs with an incomplete washout
- ✓ demonstrates comparable power and controlled type I error
- ✓ reduces the overall study duration substantially

References

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