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Improved bioequivalence assessment through model-informed and model-based strategies

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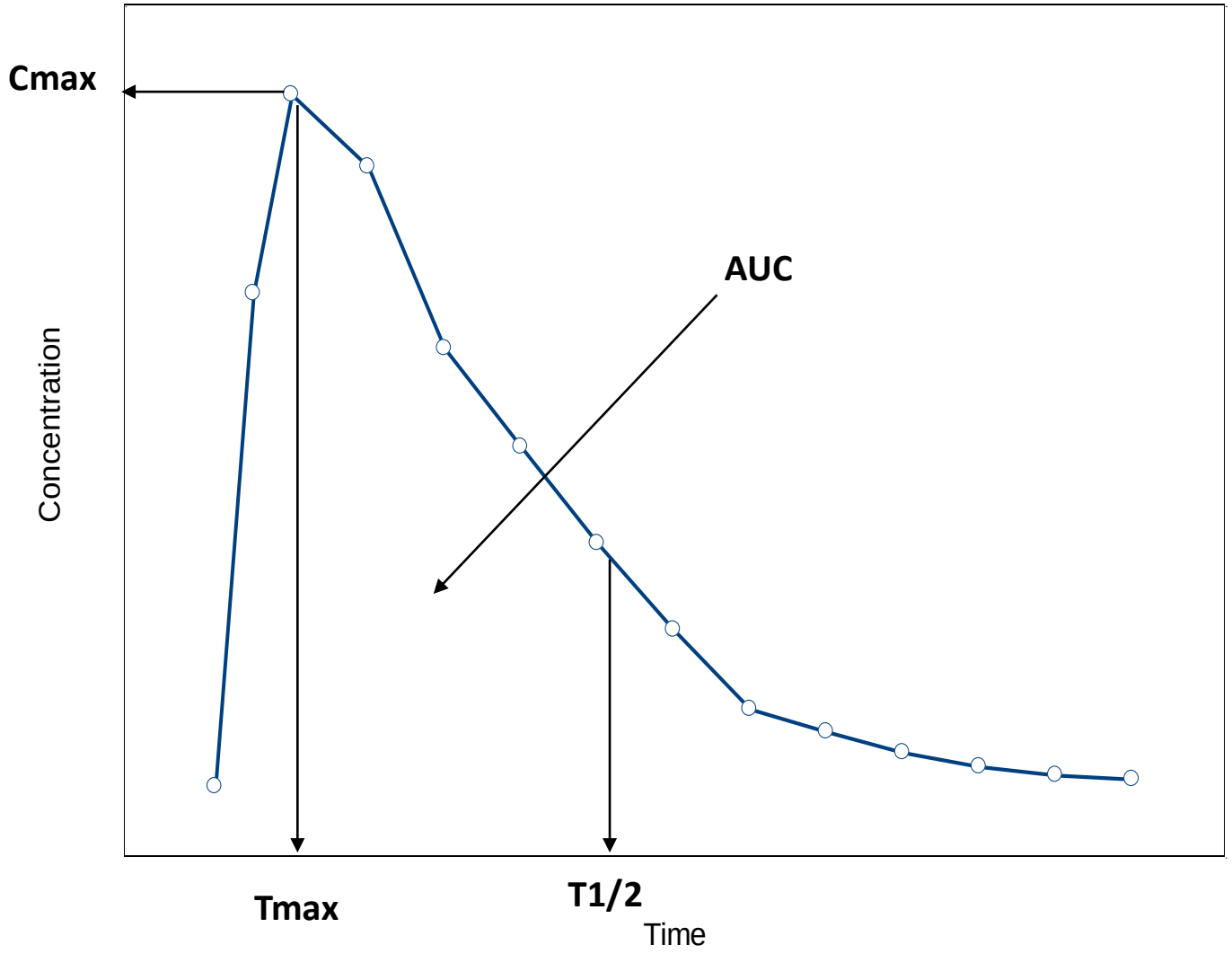
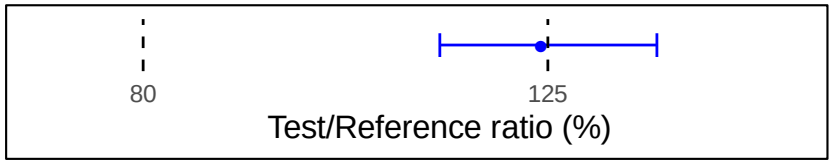
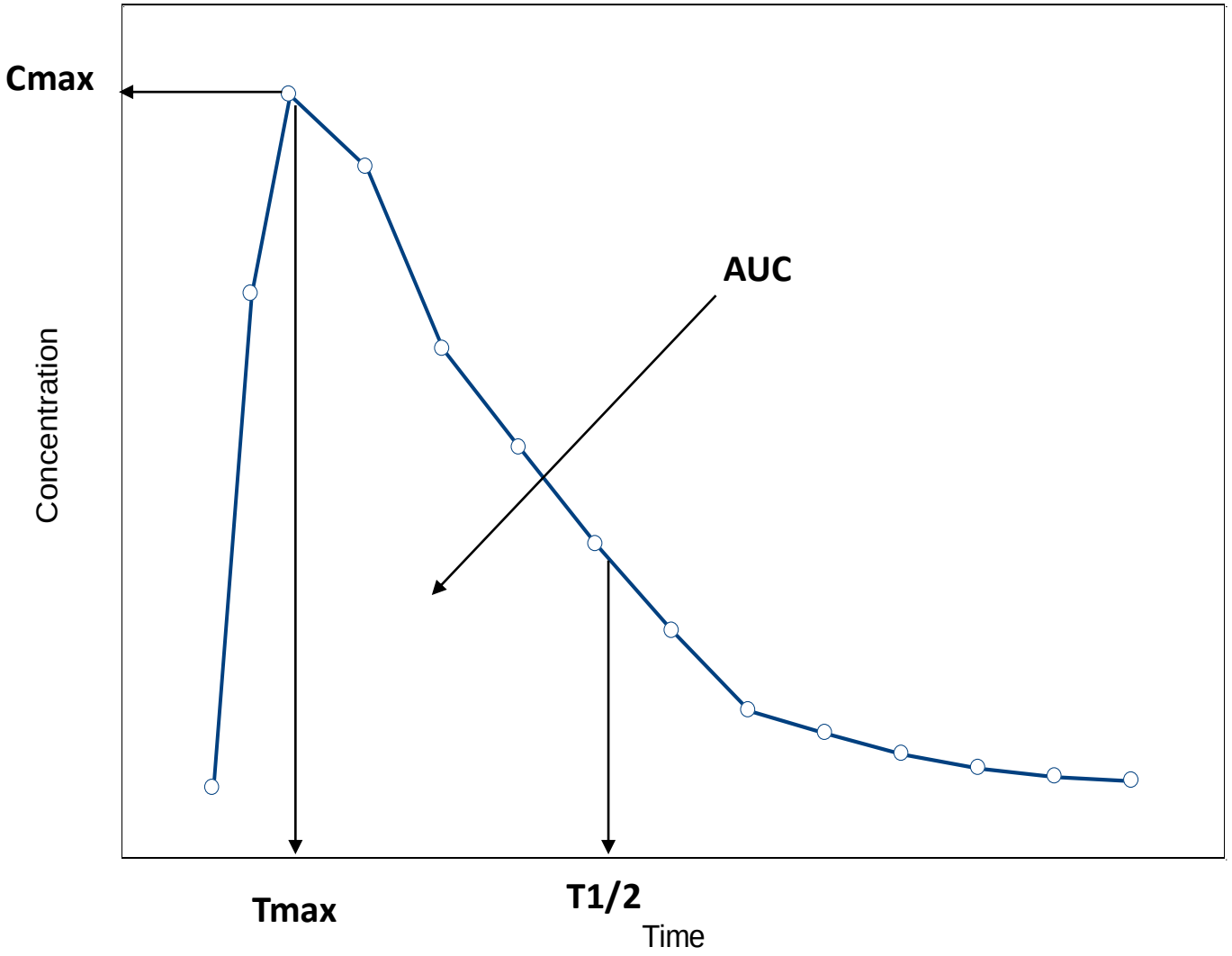
Standard bioequivalence (BE) studies



- BE determined by comparing the 90% confidence interval of the ratio (comparator vs. reference) of geometric means of secondary (summary) PK parameters with predetermined limits.



Potential problems with standard BE approaches: Problems with NCA calculations

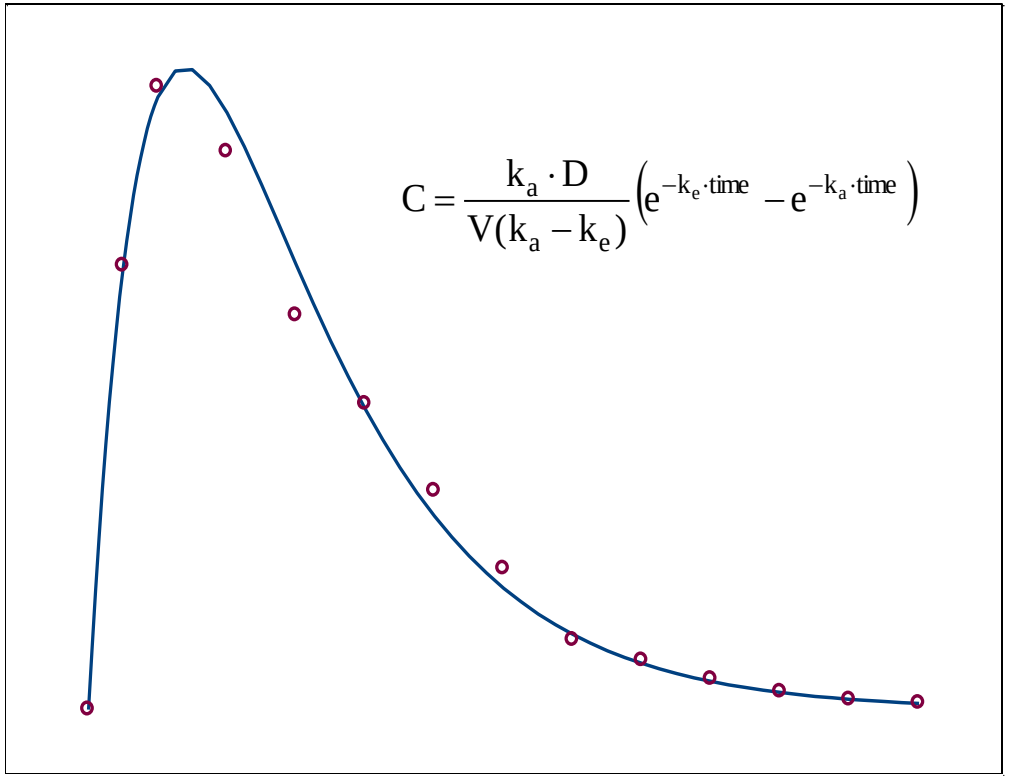


- Sparse data problems
- Assume equal weight for all observations
- Sensitivity to missing data
- Sensitivity to data below the limit of quantification
- Interpolation problems from the last observation to ∞
- Hard to separate variability sources (BSV/WSV/RUV)
- Ad hoc design of sampling times

Problems of standard bioequivalence evaluation

- Drugs with long half-life (e.g. LAI)
  - Long-term BE trial
  - Parallel study leading to low power
- Steady-state BE studies
  - Methods for establishing steady state can be inaccurate
- Highly variable drugs (HVD)
  - BE design needs 3- or 4-way crossover study
  - Estimation of between occasion variability can be biased/imprecise
- Others
  - Designs can be inefficient
  - Special formulations, e.g. local drug product needs clinical endpoint BE study
  - …

Population (NLME) model based approaches in general can handle these problems

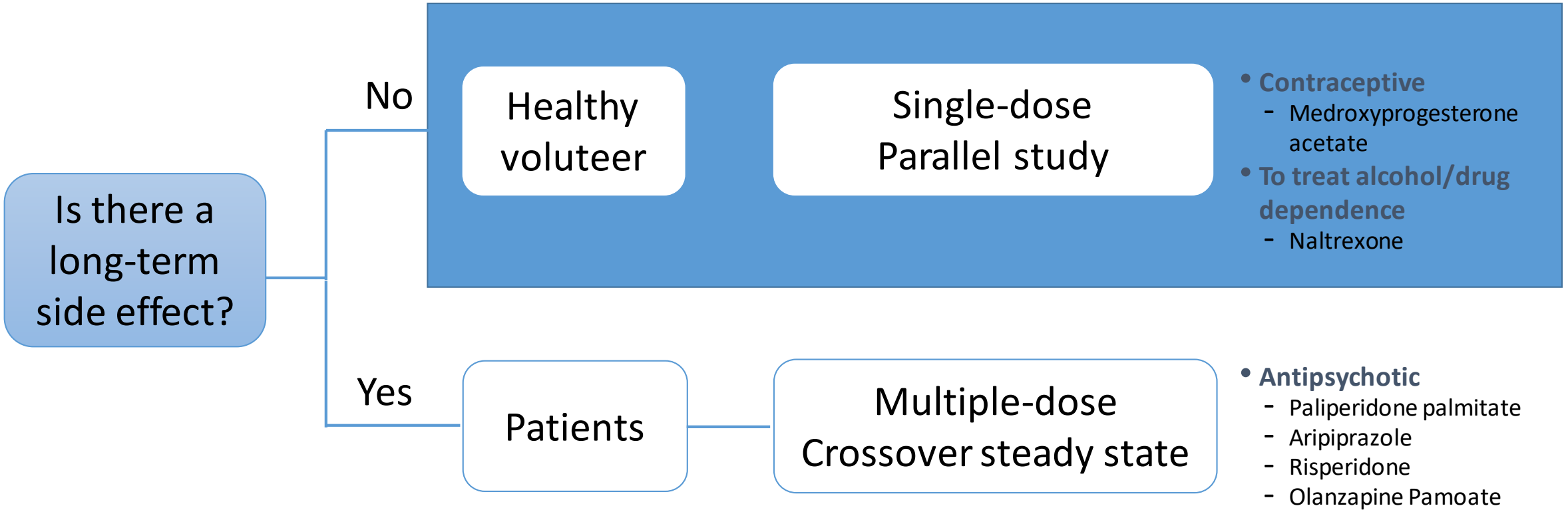


- Built to handle sparse data and works well with parallel-group studies
- NCA Problems solved:
  - assumption about equal weight of all observations
  - sensitivity to missing data
  - sensitivity to data below the limit of quantification
  - interpolation problems from the last observation to ∞
  - Sparse data problems
- Can separate variation of different levels
  - Between subject variation (BSV) on PK parameters
  - Within subject variation (WSV, occasion variation) on PK parameters
  - Residual error on concentration
- **Higher power**
- **Can optimize design (for even higher power)**

How modeling can help with BE problems and method improvements

- Model-informed BE approach
  - Use pharmacometric models to understand and optimize the operating characteristics of standard BE methods and designs
- Model-based BE analysis
- Optimal design approaches for better BE study design

Two types of BE study designs for long-acting injectables (LAI)

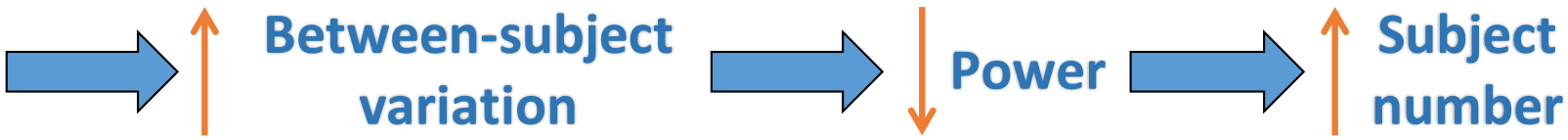


Multiple covariates affects LAI absorption, increasing variation

Single-dose parallel BE study

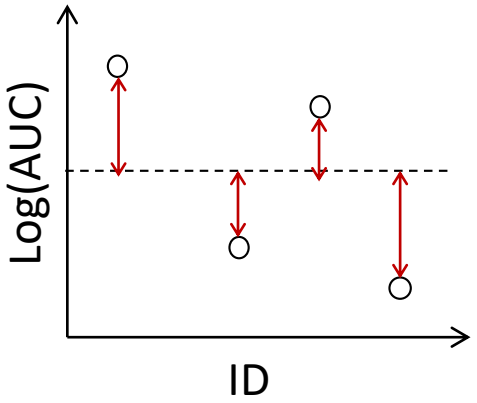
Affecting Factors

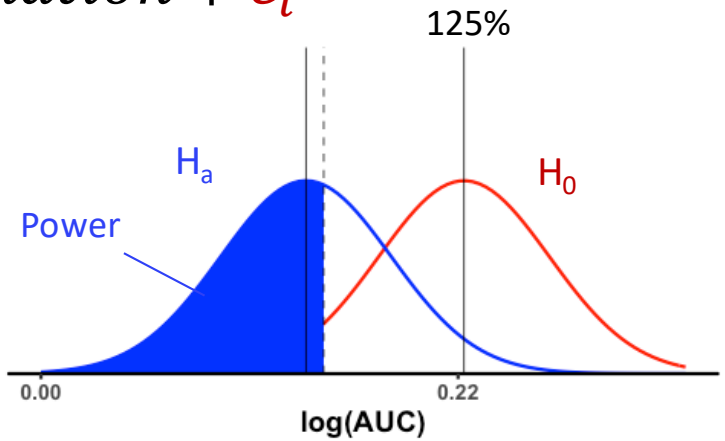
- BMI
- Sex
- Age
- Injection site
- …



Potential solution to increase power: Adding fixed covariate effects in the analysis

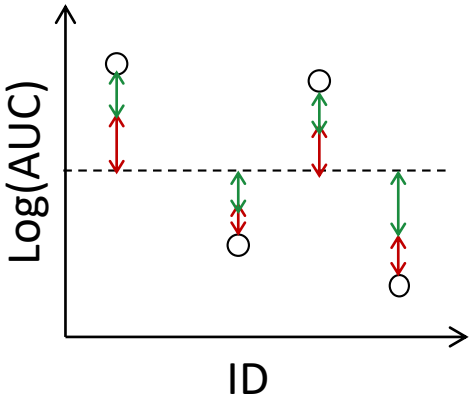
$$\log(AUC)_i = \mu + formulation + \varepsilon_i$$

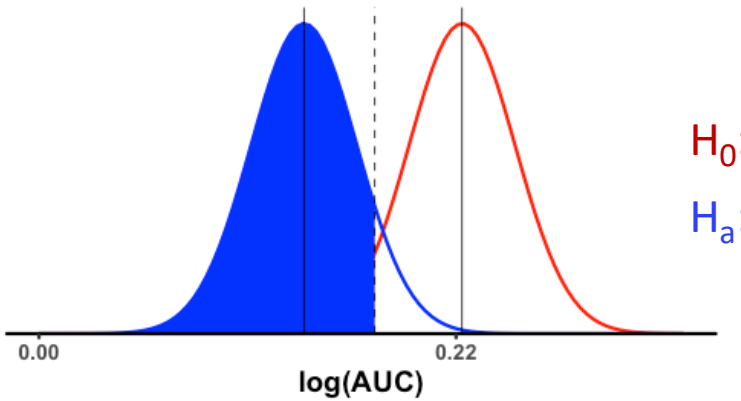




$$\log(AUC)_i = \mu + formulation + other\ covariates + \varepsilon_i$$

M&S



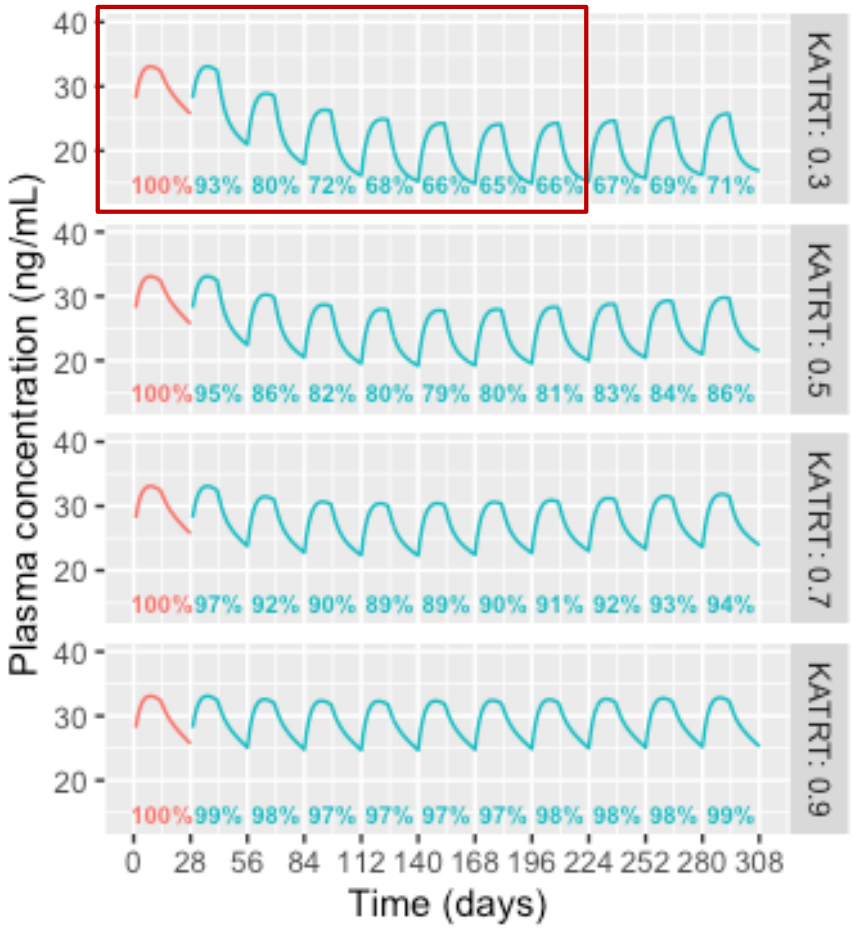


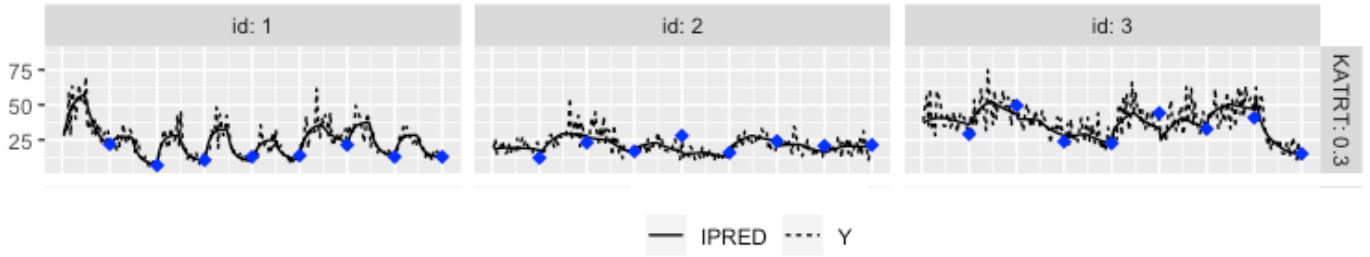
H_0: $\mu_{test} - \mu_0 \geq 0.22$

H_a: $\mu_{test} - \mu_0 < 0.22$

Assesment of steady state?

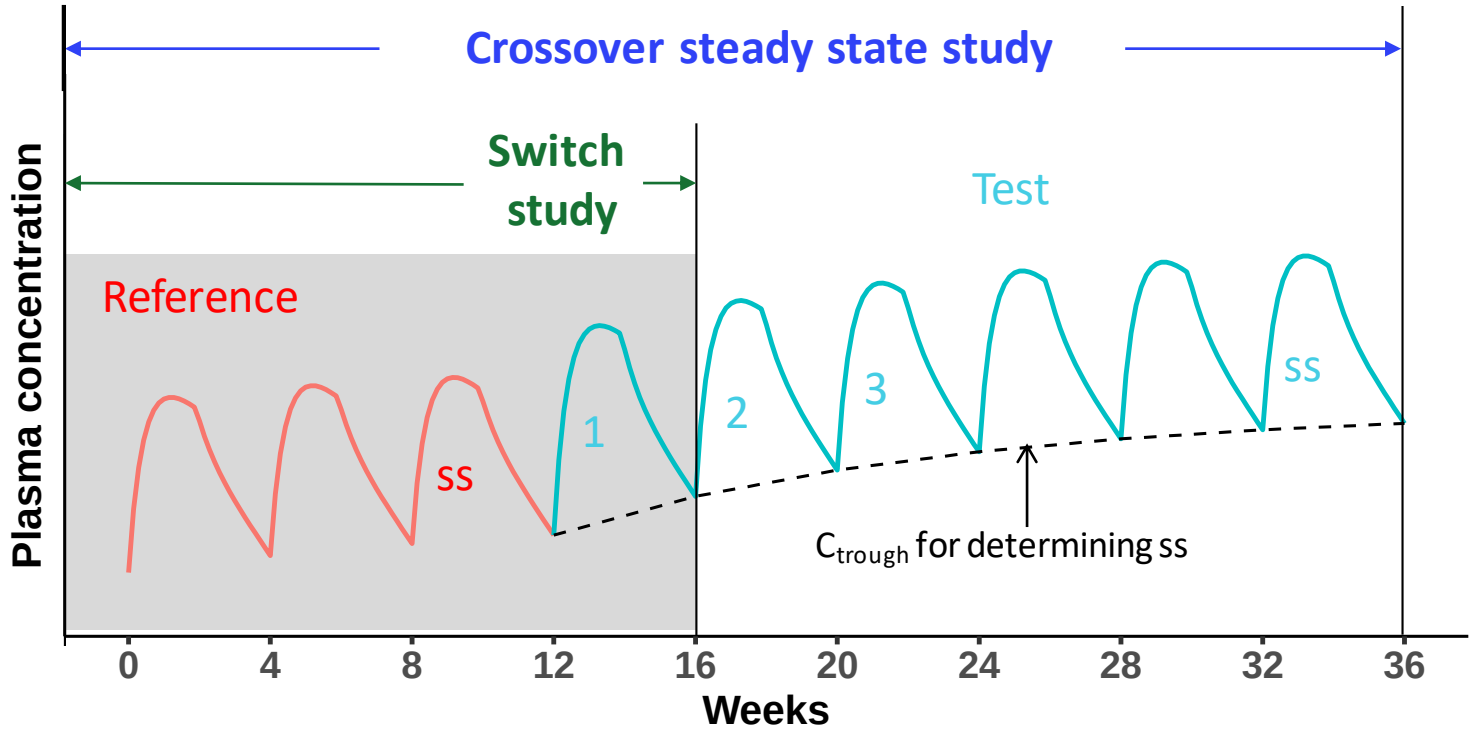
Switch study, different KA in test compound





- Standard Assessment of SS uses linear regression of last 3 trough concentrations.
- Systems with high within occasion (WSV) or residual variability (RUV) will have highly uncertain linear regression, and thus more likely be (wrongly) assessed as at SS
- Model based methods can asses SS ignoring WSV and RUV

Possible solution to reduce BE study duration: use switch study instead of requiring steady state



- **BE evaluation for switch study:**
  - What PK metrics to use?
  - What BE limit to use?

Surrogate Criteria

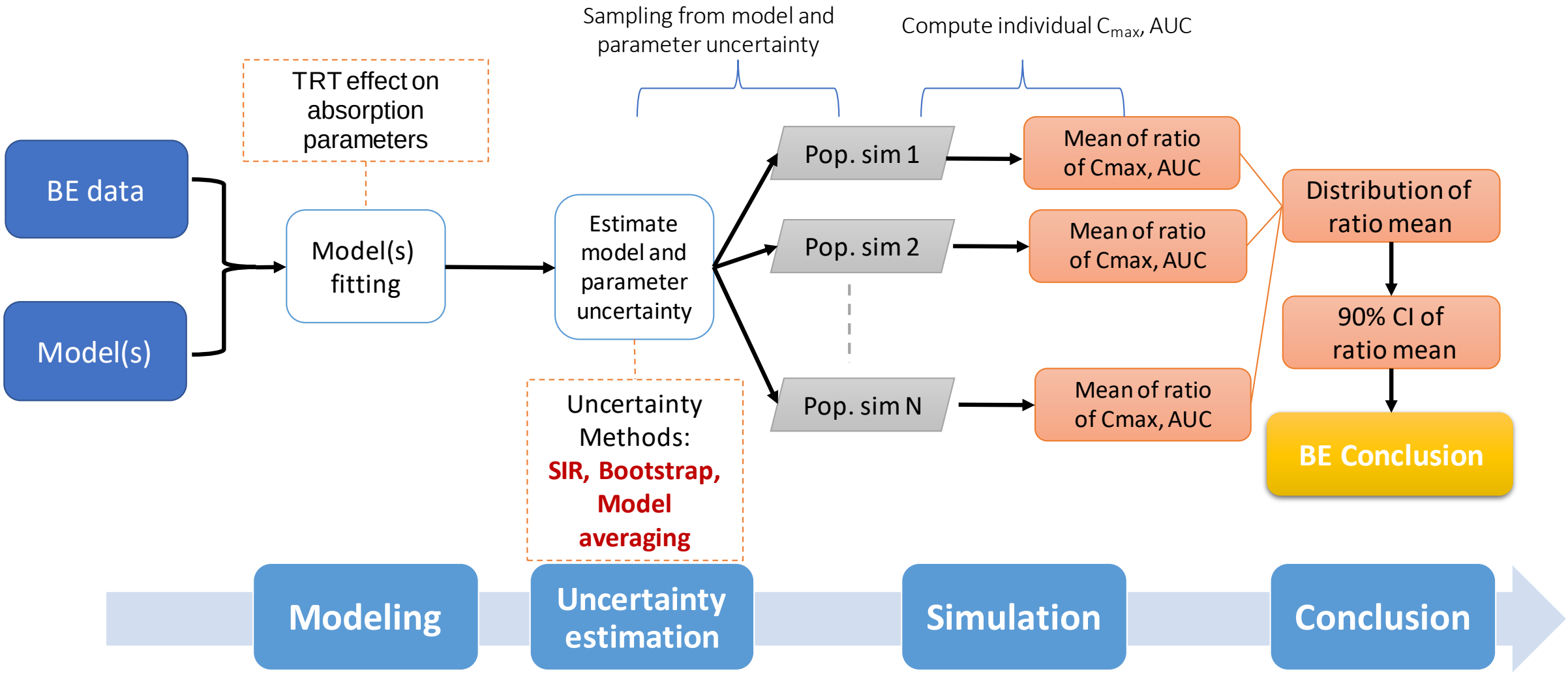
Surrogate PK metrics

E.g.: $AUC_1, C_{max,1}, pAUC, \ldots$

Surrogate limit

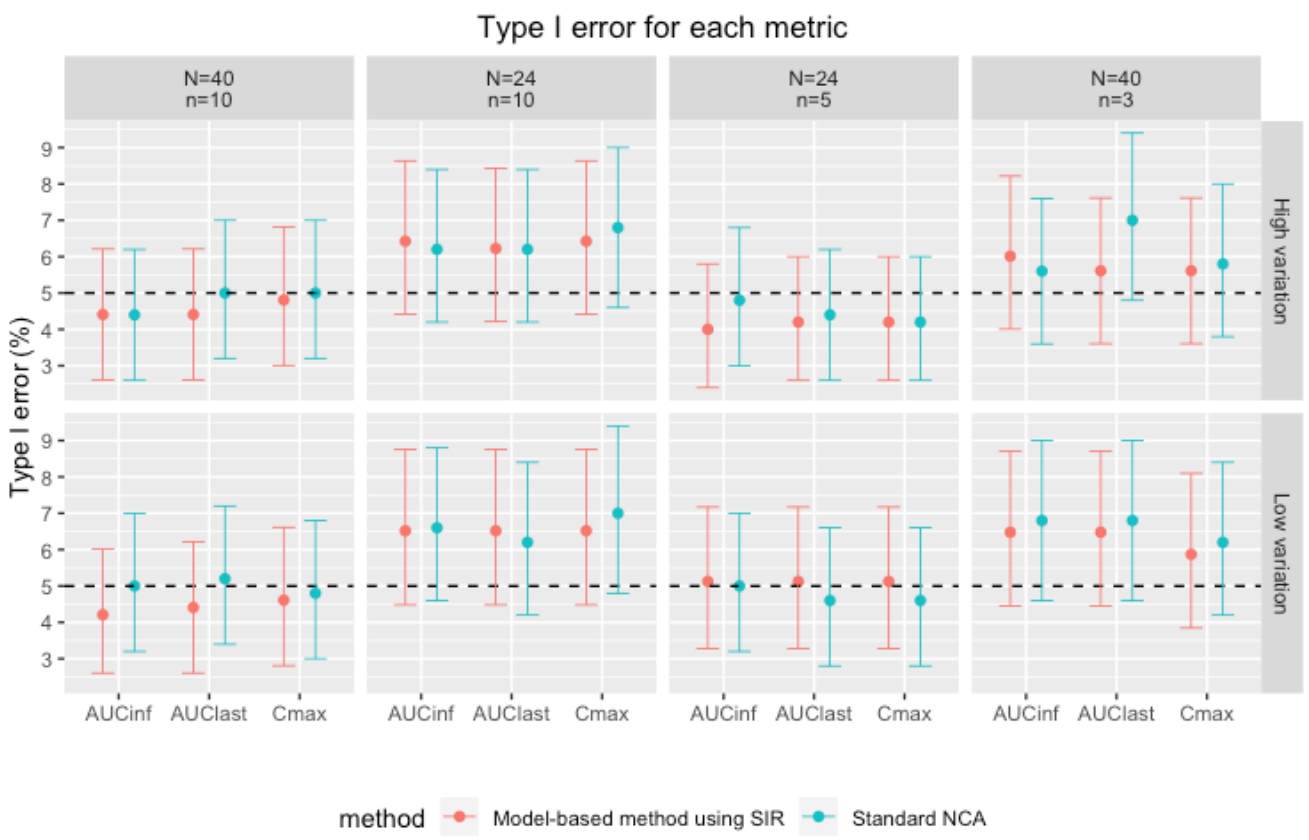
M&S

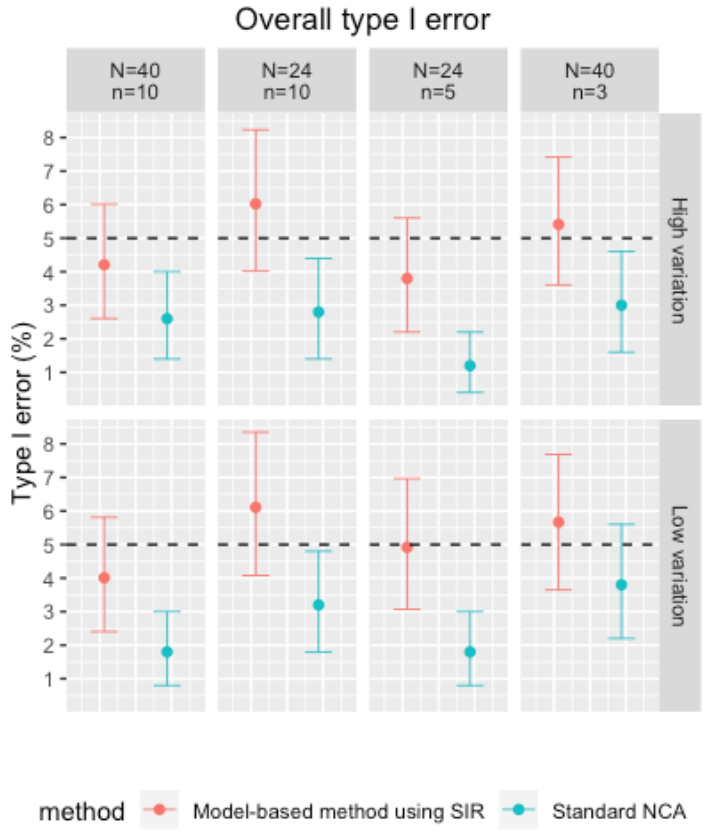
Our developed model-based BE method



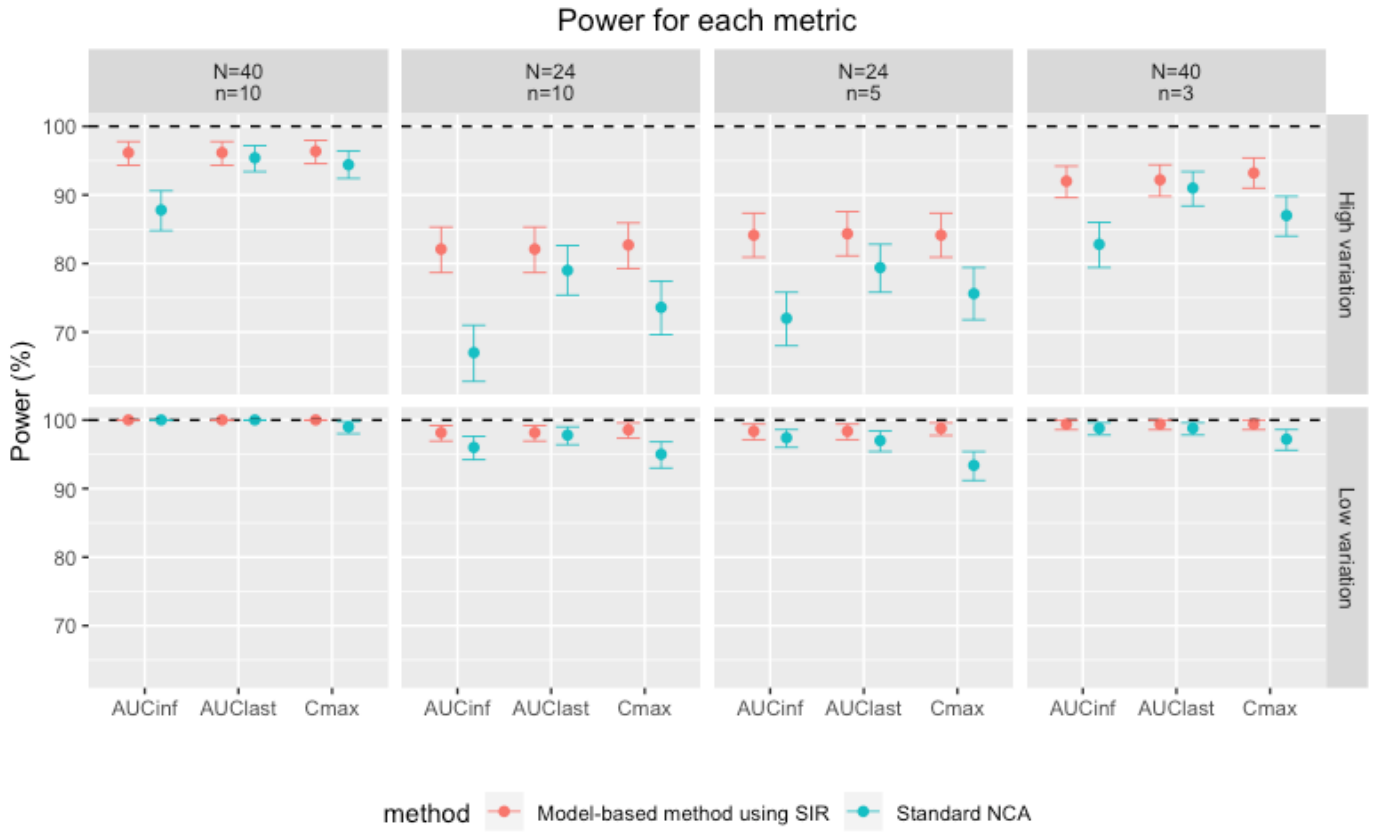
- ACOP 2019, Andrew Hooker, Development and comparison of model-based bioequivalence analysis methods on sparse data.
- ACOP 2019, Xiaomei Chen, Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches.

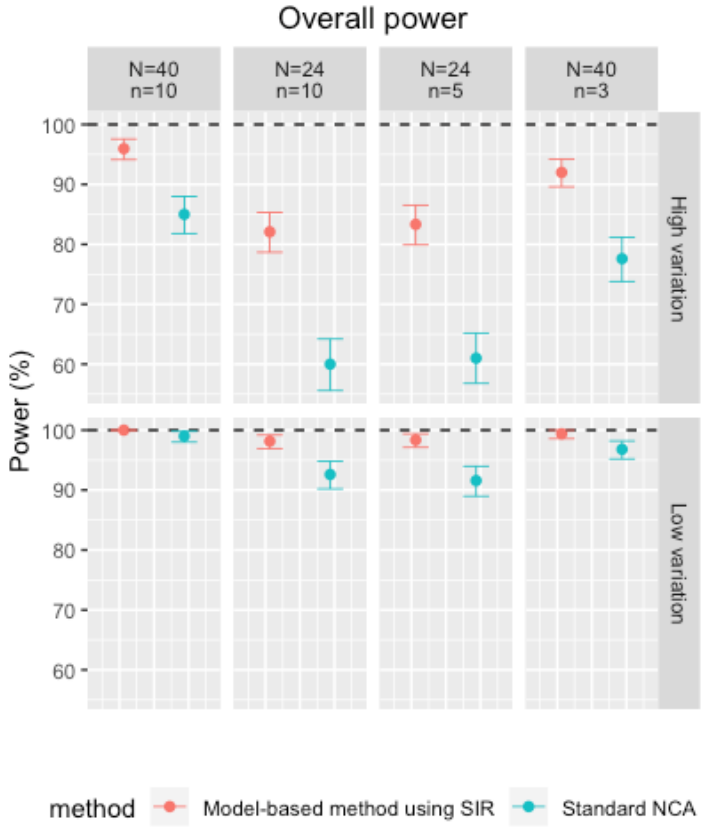
Type I error is controlled for this model-based BE method





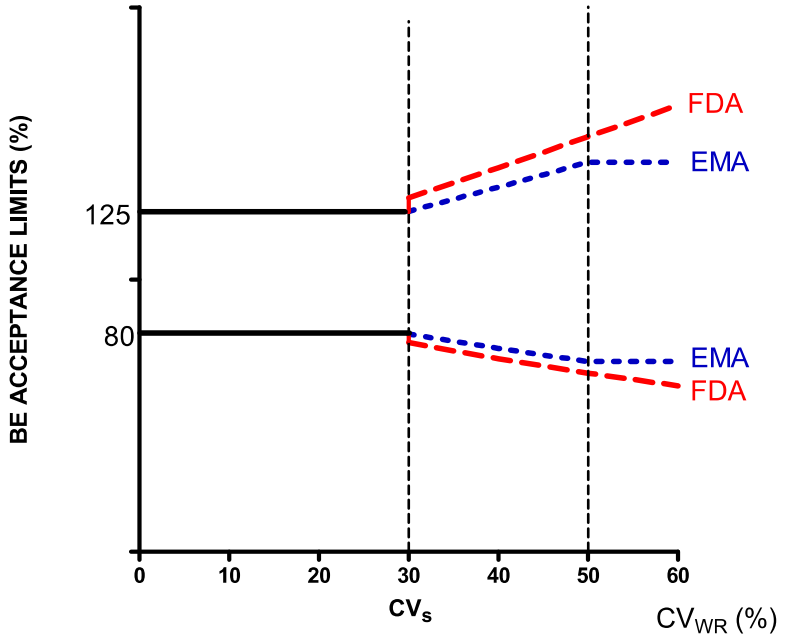
Model-based method showed higher power than NCA-based method





BE for highly variable drugs (HVD) using reference-scaled average bioequivalence (RSABE)

- RSABE: when within-subject variability (WSV) of the reference product is > 30% CV



- FDA draft guidance on Progesterone, 2011
- Verbeeck, Musuamba, 2012
- AAPS J. 2012 Dec; 14(4): 915–924, BM Davit, et.al Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration

Standard RSABE studies

- Study design
  - 4-way study with sequences of (TRTR, RTRT)
  - 3-way study with sequences of (TRR, RTR, RRT)
- Sample size: at least 24 subjects
- Using NCA:
  - Requires rich sampling
  - Extrapolation for AUCt-inf

Model based RSABE

- Shorter studies?
- Smaller studies?
- Better evaluation of WSV?

Potential problems with a model based analysis

- Uncertainty in which model best describes the system
- Model building may produce bias
- Parameters in a model may be biased/misspecified

Situations where no single PK model may be appropriate for BE analysis

- No prior model
- Can not assume true model
- Identifiability issues
- Avoid estimation bias and overestimation of precision

Model Averaging

Note: An NCA “model” could be one of the averaged models

J Pharmacokinet Pharmacodyn (2017) 44:581–597
DOI 10.1007/s10928-017-9550-0

ORIGINAL PAPER

Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection

Yasunori Aoki[1,2] · Daniel Röshammar[3,4] · Bengt Hamrén[3] · Andrew C. Hooker[1]

Received: 30 June 2016 | Revised: 22 May 2017 | Accepted: 11 June 2017
DOI: 10.1002/sim.7395

RESEARCH ARTICLE

WILEY Statistics in Medicine

Model averaging for robust assessment of QT prolongation by concentration-response analysis

A.G. Dosne[1] | M. Bergstrand[1] | M.O. Karlsson[1] | D. Renard[2] | G. Heimann[2]

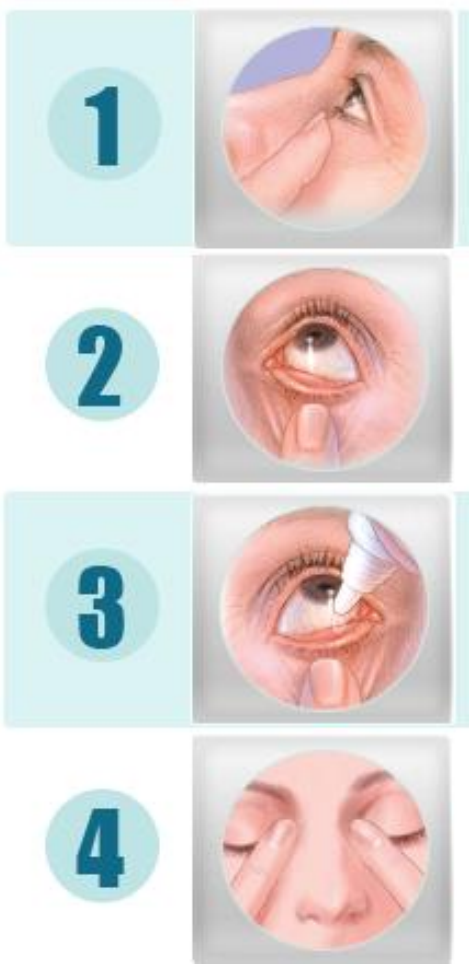
The AAPS Journal (2018) 20: 56
DOI: 10.1208/s12248-018-0205-x

Research Article

Comparison of Model Averaging and Model Selection in Dose Finding Trials Analyzed by Nonlinear Mixed Effect Models

Simon Buatois,[1,2,3,5] Sebastian Ueckert,[4] Nicolas Frey,[1] Sylvie Retout,[1,2] and France Mentré[3]

Ophthalmic drug products



Affecting factors

- Solution drainage (naso-lacrimal)
- Lacrimation
- Tear turnover
- Tear dilution
- Conjunctival absorption
- Blinking
- …

→ Low Bioavailability
High variation

- http://www.lumigan.com/Resources/How-to-Apply
- Agrahari, Drug Deliv. And Transl. Res. 2016

- **ACOP 2019, Xiaomei Chen, Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches.**

Conclusion

Model-informed approach

Modify NCA-based BE methods

Model-based approach

Use M&S in BE analysis procedure

Reduce sample size
and/or
Reduce study duration

Make BE studies more feasible
(especially in currently challenging situations)

Optimal Design approaches

Better BE study design

Backup Slides

Pharmacometric approaches will typically have **higher power** than standard methods

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e23; doi:10.1038/psp.2012.24

www.nature.com/psp

ORIGINAL ARTICLE

Comparisons of Analysis Methods for Proof-of-Concept Trials

KE Karlsson[1], C Vong[1], M Bergstrand[1], EN Jonsson[1,2] and MO I

Drug development struggles with high costs and time co
accentuated by many stakeholders in drug development. Thi
drug development. Two simulated examples, within the the
compare a pharmacometric model–based analysis to a *t*-test
investigated examples and scenarios, the conventional stati
80% power. For a scenario with a parallel design of one pla
conventional and pharmacometric approach was 4.3- and 8.
the model-based power depend on the model assumptions
was demonstrated to permit drastic streamlining of POC tria
CPT: Pharmacometrics & Systems Pharmacology (2013) **2,** e23;

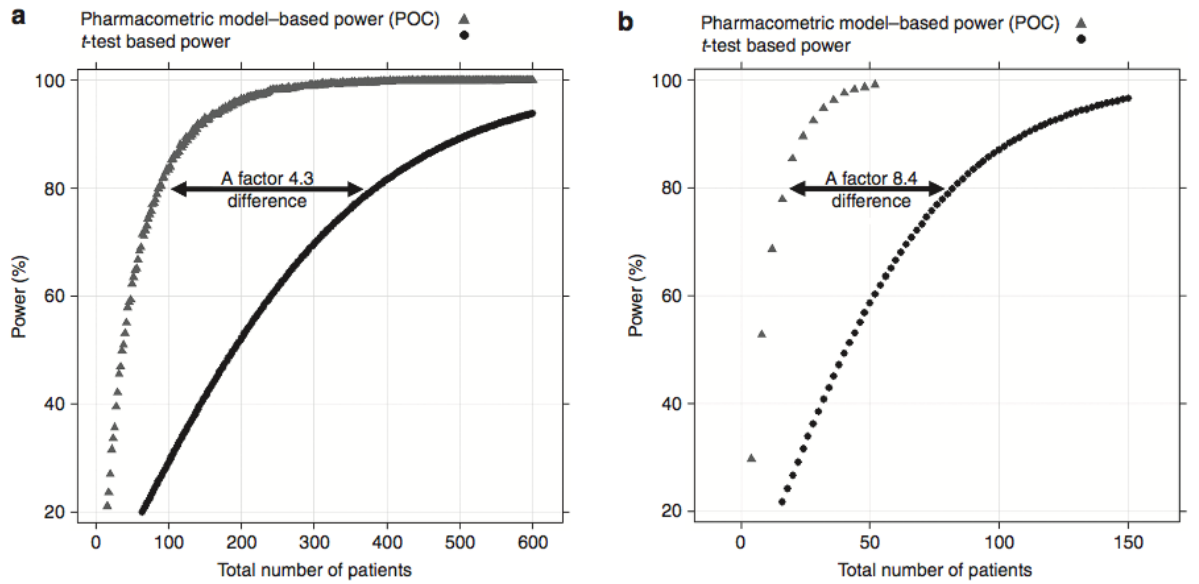
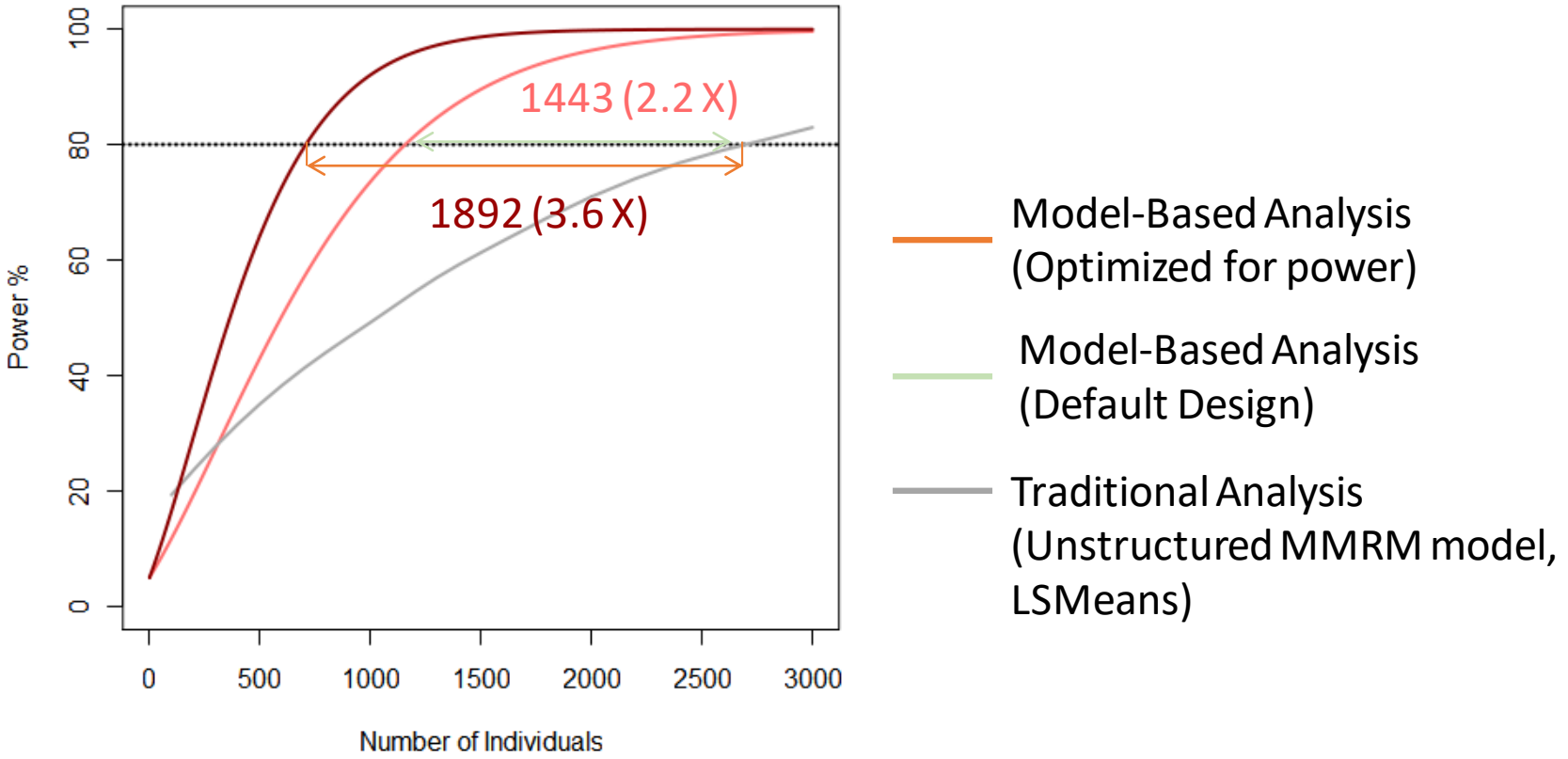


Figure 3 Power curve comparison between the pharmacometric model–based power (gray triangles) and the *t*-test based power (black diamonds), for the proof-of-concept scenario. (**a**) The power curves for the stroke example in which the difference in study size is a factor of 4.3 (90 vs. 388 total number of patients) is displayed. (**b**) In the diabetes example, the difference in study size was 8.4-fold (10 vs. 84 total number of patients) in favor of the pharmacometric approach.

With pharmacometric models one can **optimize the design of experiments for even higher power**

(Optimized) Model Based vs.
Traditional Data Analysis in Alzheimer's



Hooker et al., Model-based Trial Optimization for Phase II and III designs in Alzheimer's Disease, ACOP, 2011

Application of optimal design methodology (OD) for BE studies

Model-based OD

When using model-based BE method

→ Different ways to maximize FIM →

To reduce uncertainty of

- Model parameters (D-optimum)
- Parameters of product difference (Ds-opt)
- Secondary model based PK metric (C-optimum)

OD for NCA

When using NCA for BE data

→ To minimize MSE of PK metrics →

Improve the accuracy and precision of NCA calculations (based on model expectations)

- FIM: Fisher information matrix
- MSE: Mean squared error

Nyberg, Hooker et.al. PopED: An extended, parallelized, nonlinear mixed effects models optimal design tool. Computer Methods and Programs in Biomedicine. 2012
Jawien, W. Searching for an optimal AUC estimation method: a never-ending task? Journal of Pharmacokinetics and Pharmacodynamics 2014