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A Population PK Based Model-Integrated BE Platform

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Research projects on utilizing models for bioequivalence assesment at UU in collaboration with FDA

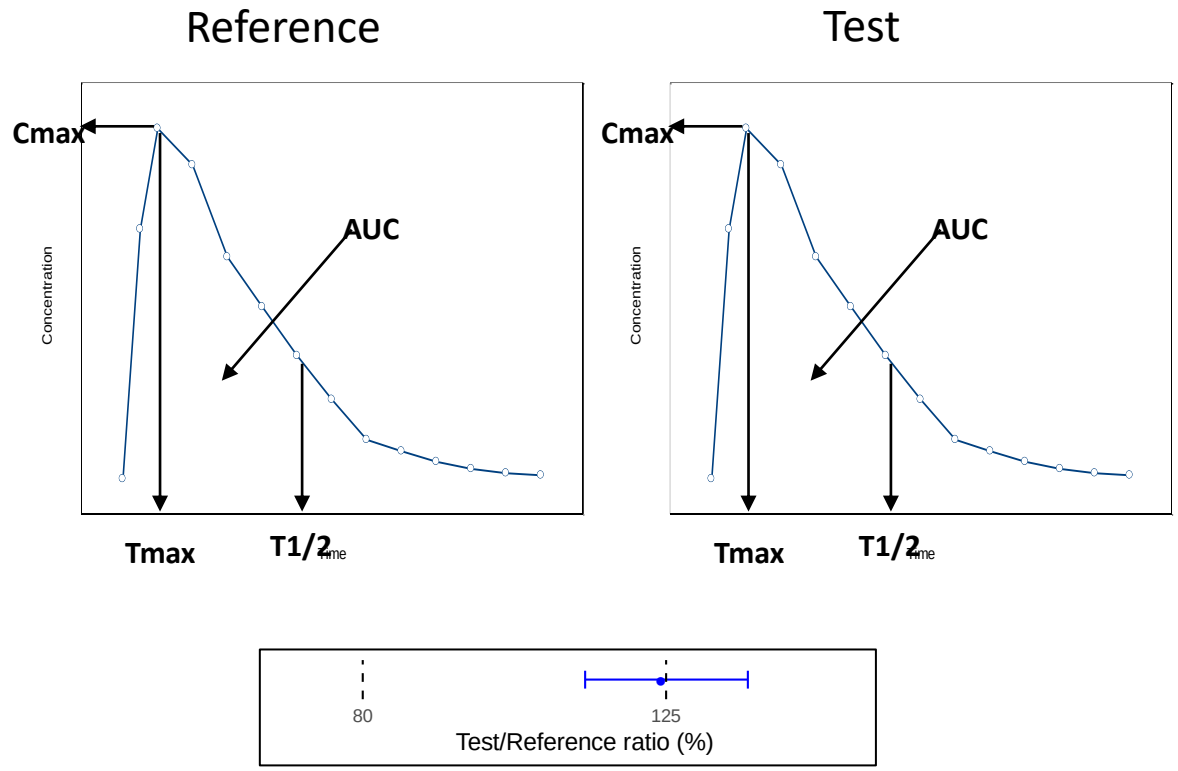
Funding from Office of Generic Drugs, FDA

- "Development and comparison of model-based bioequivalence analysis methods on sparse data"
- "Model-informed and model-integrated bioequivalence analyses for long-acting injectable products"
- "Model-integrated strategies for bioequivalence evaluation of drugs with high variability and/or long half-life."

Standard bioequivalence (BE) studies

- 2x2 crossover designs
- NCA based summary PK metrics (e.g., AUC, Cmax)

2x2 crossover designs



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Problems for standard BE studies

- NCA analysis not appropriate
- Sparse data
- Drugs with long half-life (e.g. LAI)
  - Long-term BE trial
  - Crossover steady-state studies may be needed in patients
- Highly variable drugs (HVD)
  - BE design needs 3- or 4-way crossover study
  - Estimation of between occasion variability can be biased/imprecise
- Steady-state BE studies
  - Methods for establishing steady state can be inaccurate
- Other
  - Designs can be inefficient
  - Special formulations, e.g. local drug product needs clinical endpoint BE study
  - …

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

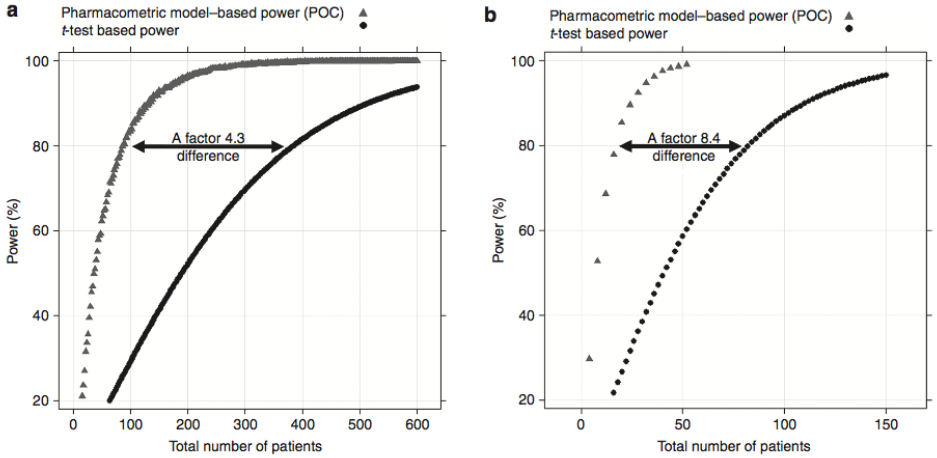
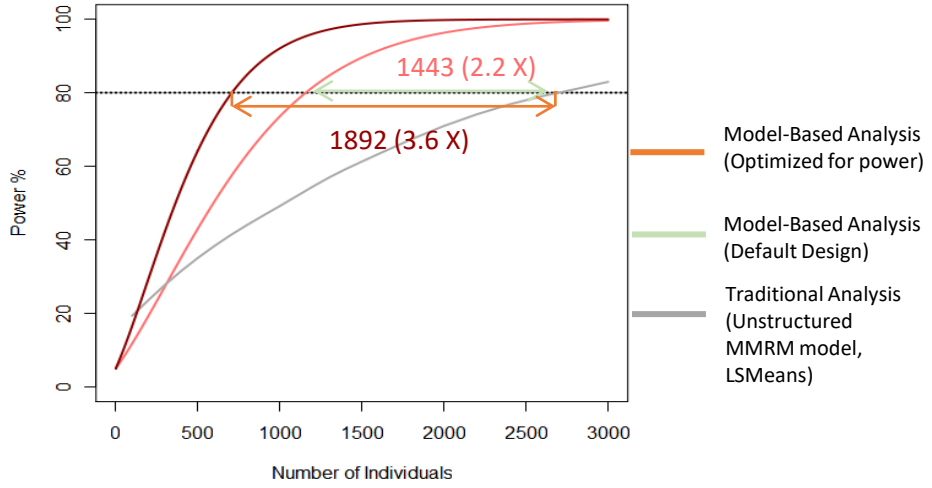


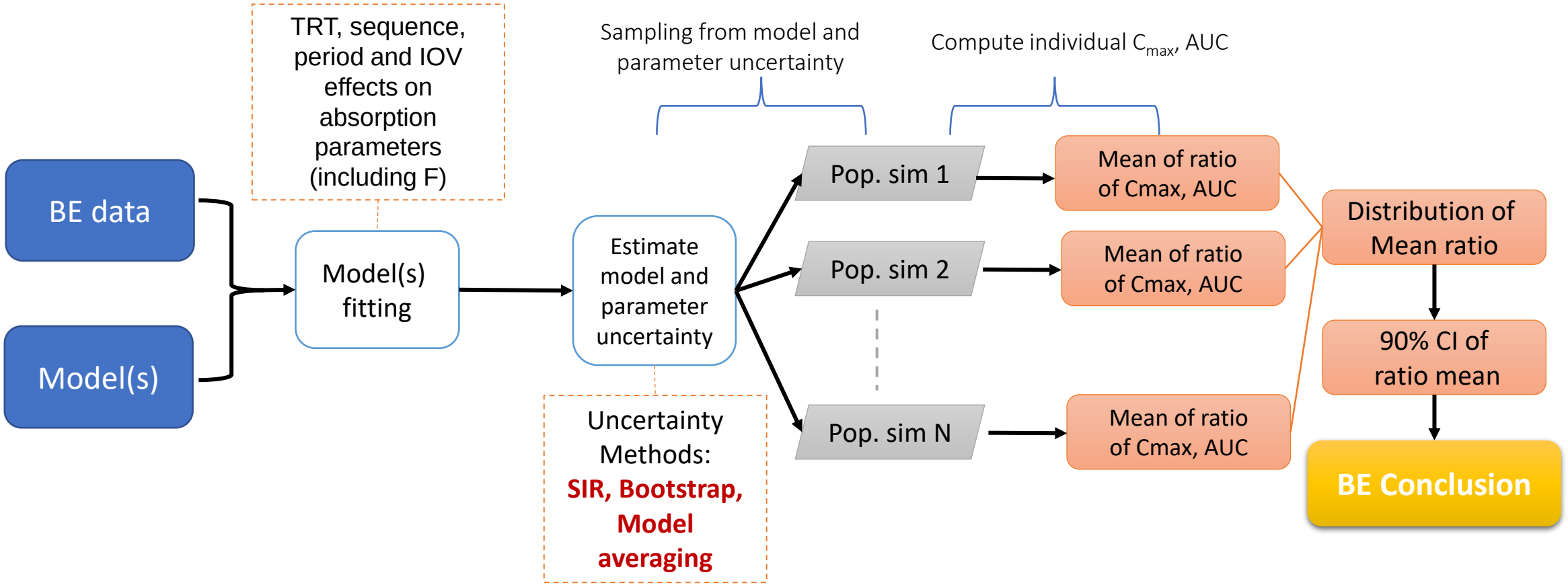
Figure 3 Power curve comparison between the pharmacometric model–based power (gray triangles) and the *t*-test based power (black diamonds), for the proof-of-concept scenario. (**a**) The power curves for the stroke example in which the difference in study size is a factor of 4.3 (90 vs. 388 total number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

Karlsson *et al.*, CPT:PSP, 2013



- Hooker *et al.*, ACOP, 2011
- Ueckert et al., JPKPD, 2013

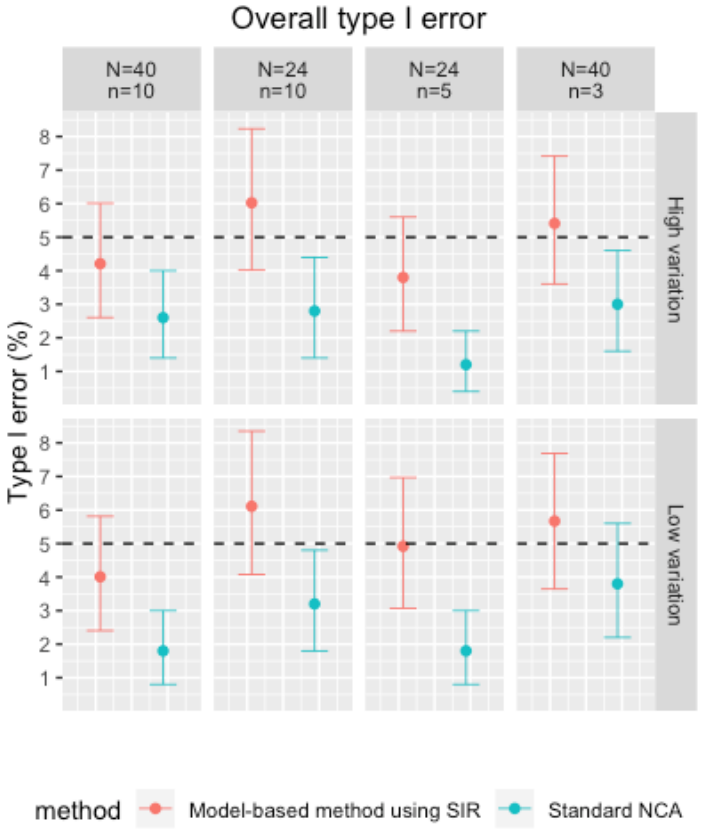
Our developed model-integrated BE method

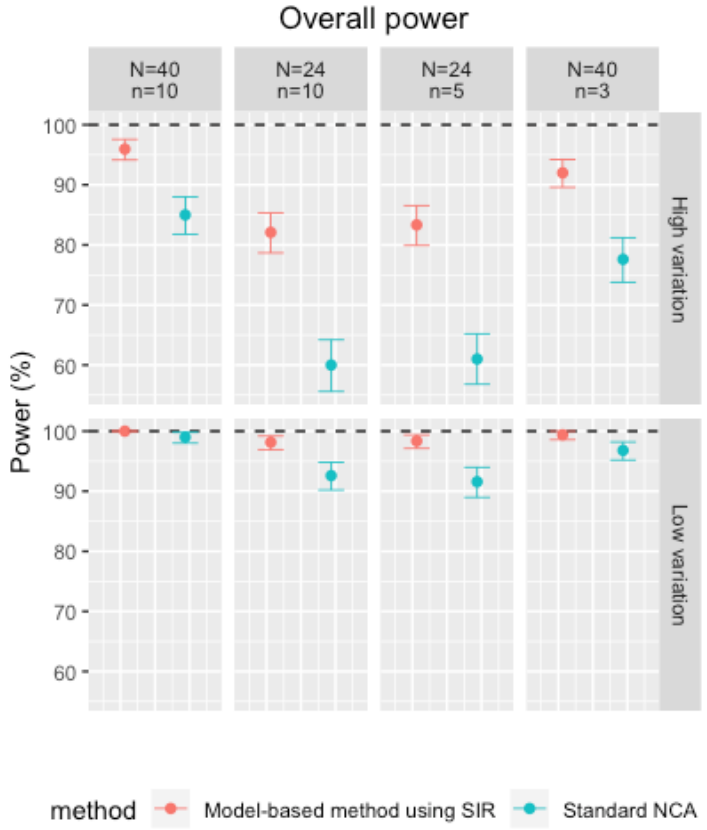


Modeling → **Uncertainty estimation** → **Simulation** → **Conclusion**

- 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.
- ACCP 2019, Mats Karlsson, Development of model-informed bioequivalence evaluation strategies for long-acting injectable products (LAI).

Type I error is controlled for this model-integrated BE method and power is higher (especially with high variation and sparser data)





N = # of individuals, n = # of observations

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

- Identifiability issues
- No prior model

Model Averaging

Avoid estimation bias and overestimation of precision

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

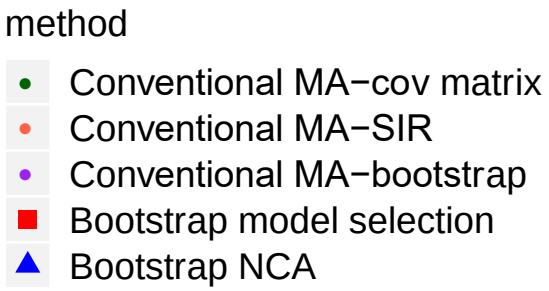
Comparison of Model Averaging and Model Selection in Dose Finding Trials Analyzed by Nonlinear Mixed Effect Models

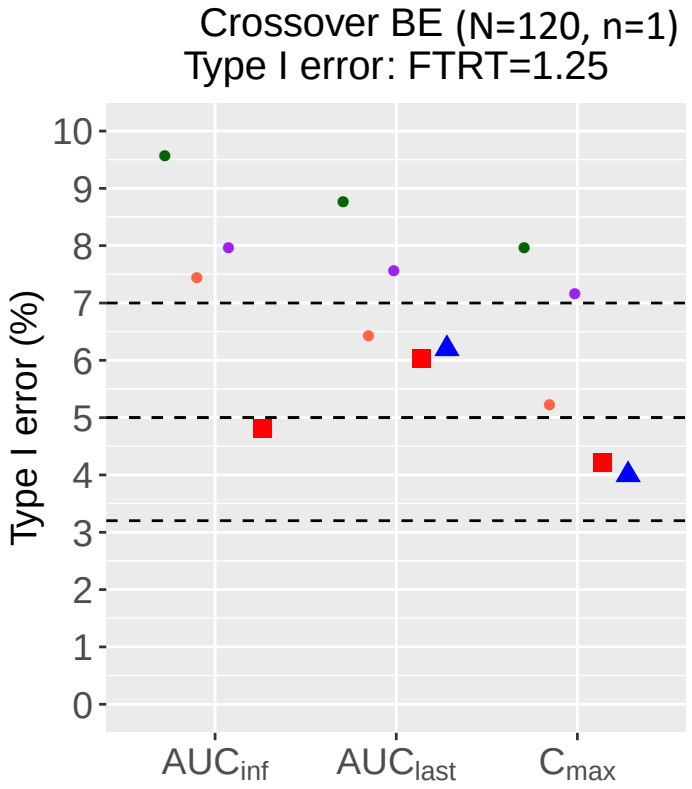
Simon Buatois,[1,2,3,5] Sebastian Ueckert,[4] Nicolas Frey,[1] Sylvie Retout,[1,2] and France Mentré[3]

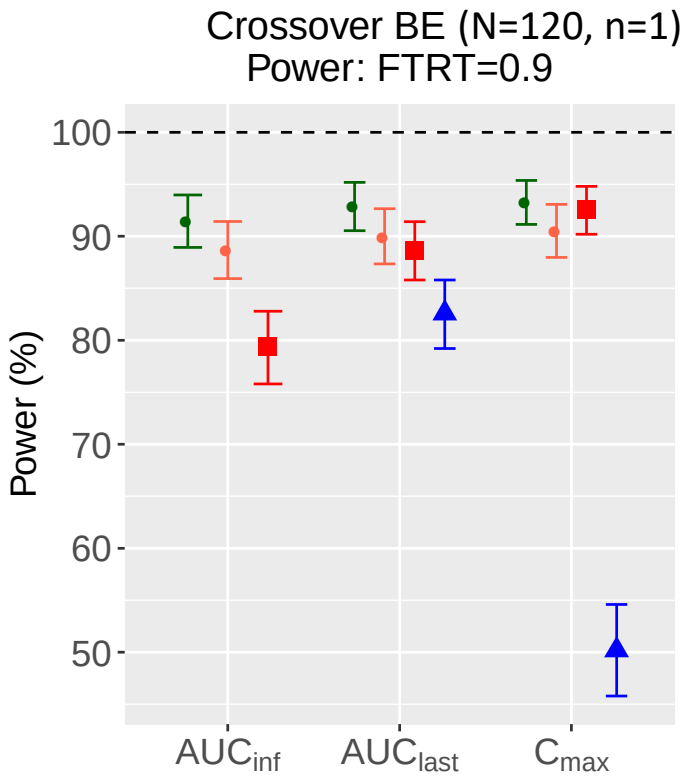
Model averaging used for ***cross-over*** BE study of ophthalmic drugs

Bootstrap model selection

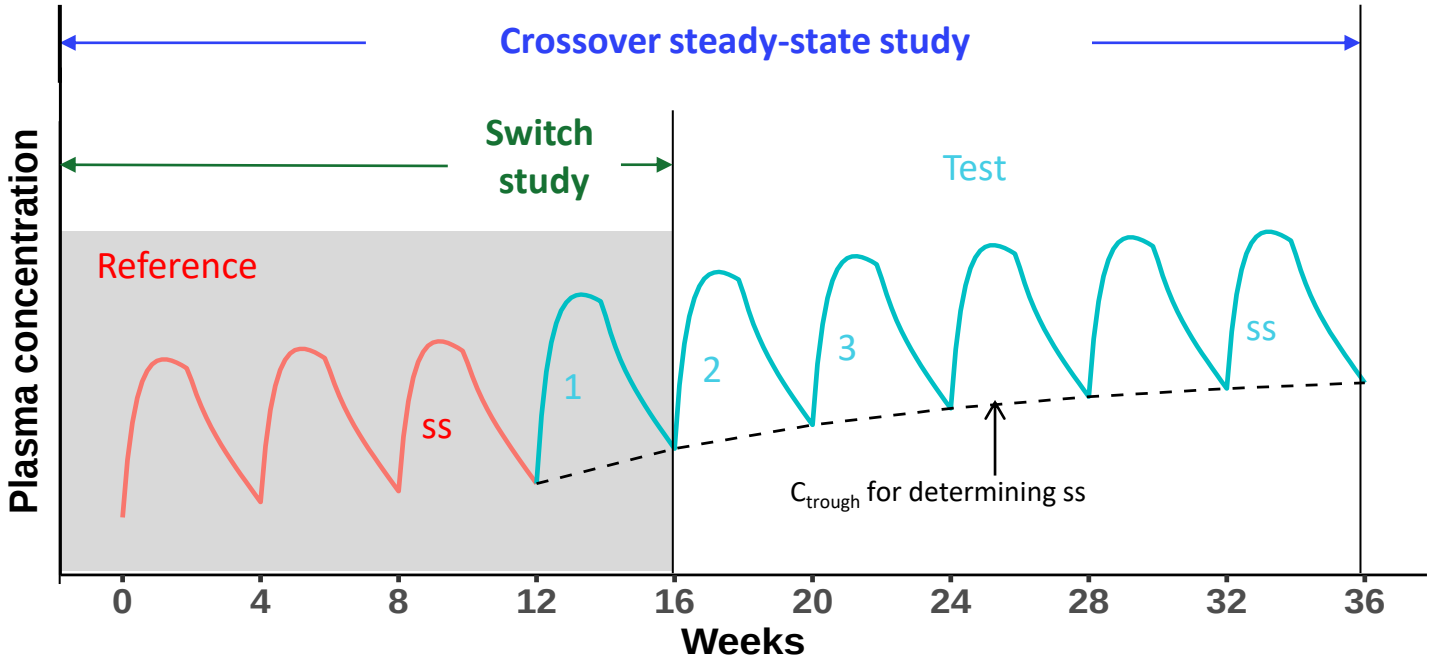
- controls type 1 error for all tests
- Allows for AUC_{inf} calculations
- Much higher power







One potential solution to reduce BE study duration for LAI: use a switch study instead of crossover steady-state



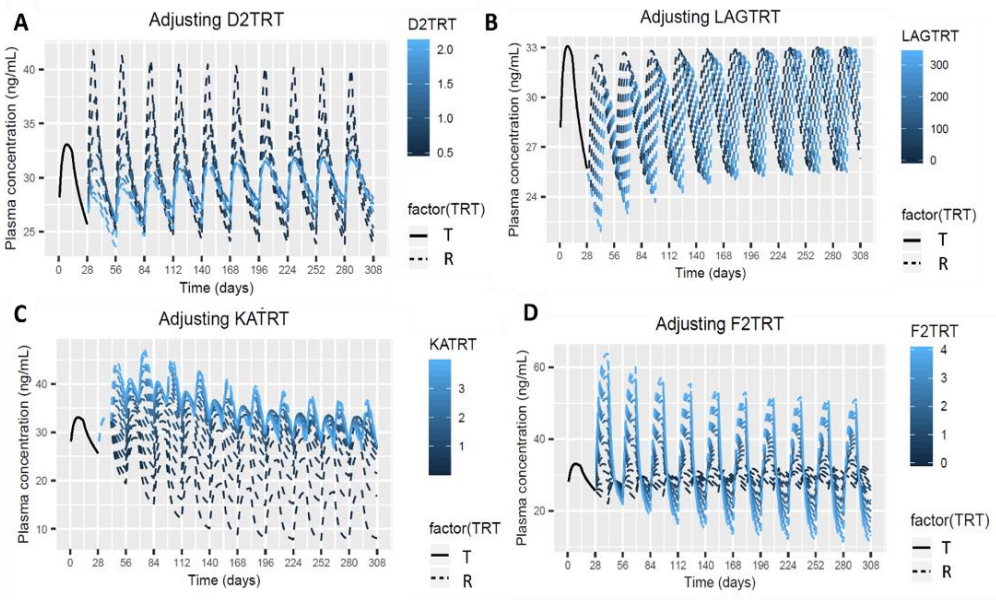
Model-based approach: allows you to separate the superposition of test from reference in first period after switch.

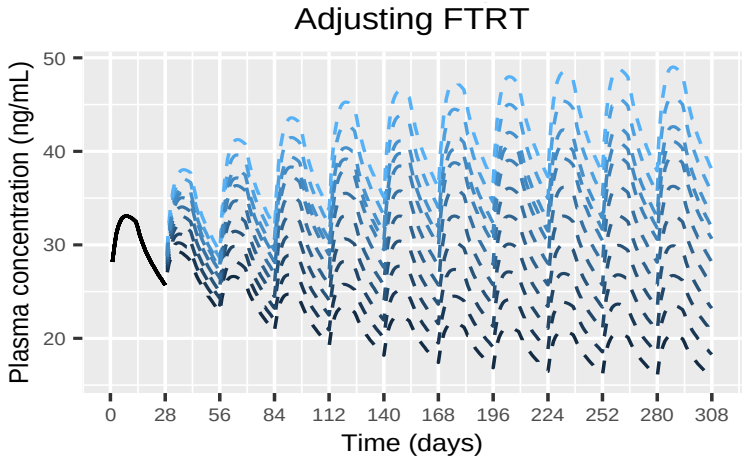
Model-assisted approach: Use models to simulate studies to determine new BE limits.

Optimal design approaches for better BE study design

For more information: https://complexgenerics.org/LAI2021/

Simulation of a typical individual

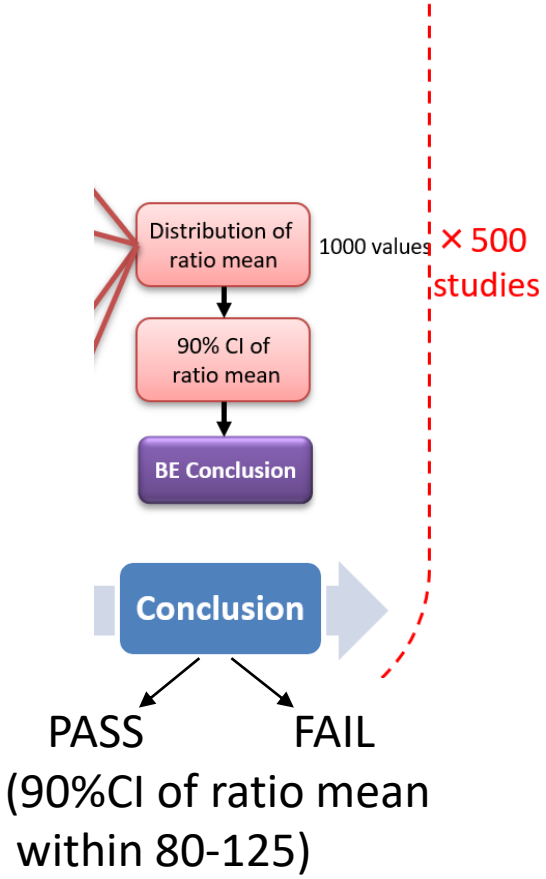




Switch study more sensitive to changes in absorption rate differences

Switch study LESS sensitive to changes in absorption extent differences

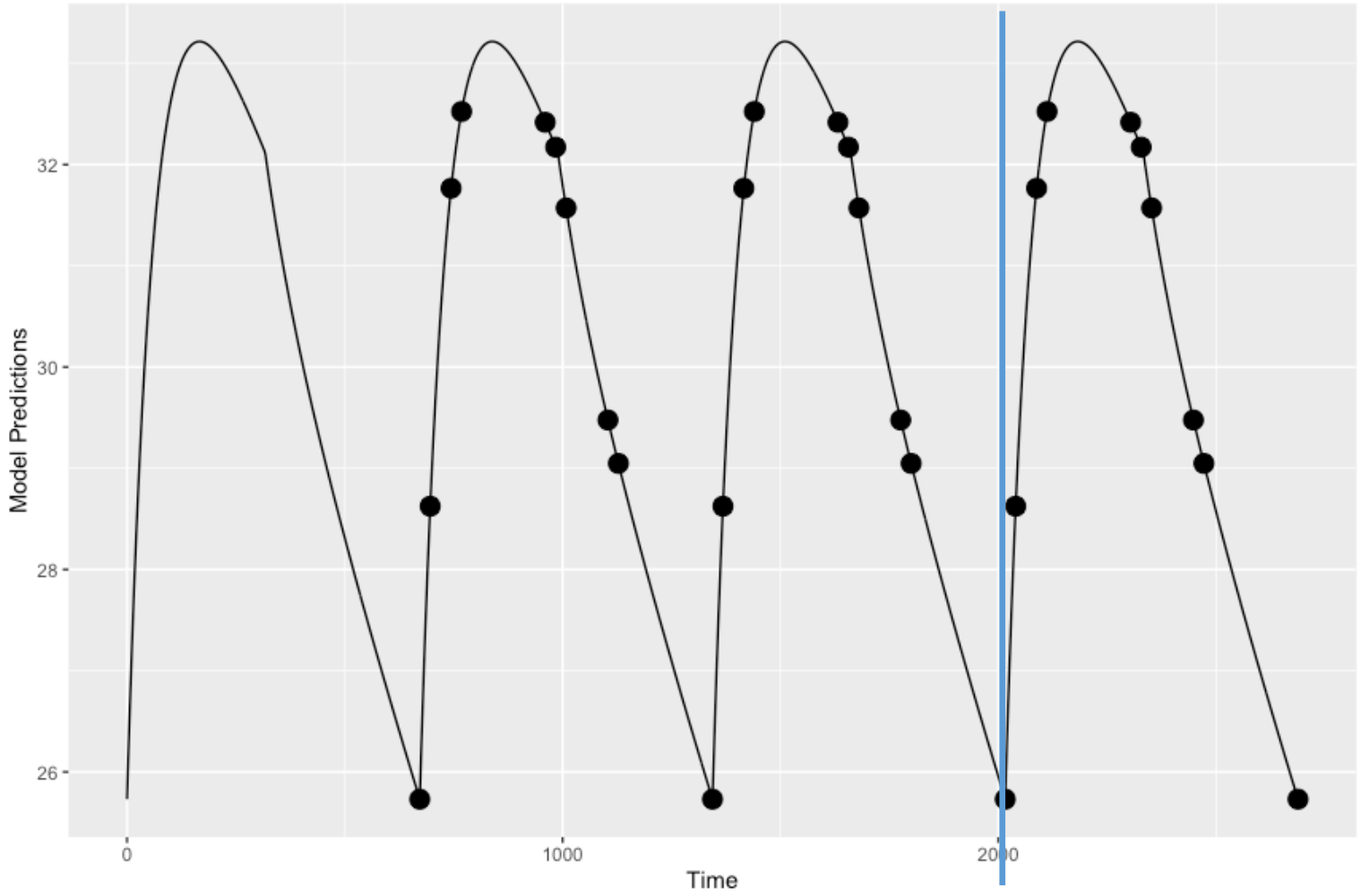
Power and type I error for model integrated-approach (worst case scenario)



		FTRT=1.1,0.9	FTRT=1.25
Study design	**PK metric**	**N for 80% Power**	**%Type I error (*95%CI)**
Switch	AUC	600	4.66 (3.10-6.38)
	Cmax		4.83 (3.10-6.72)
Crossover SS	AUC	100	2.59 (1.38-3.97)
	Cmax		2.93 (1.72-4.31)

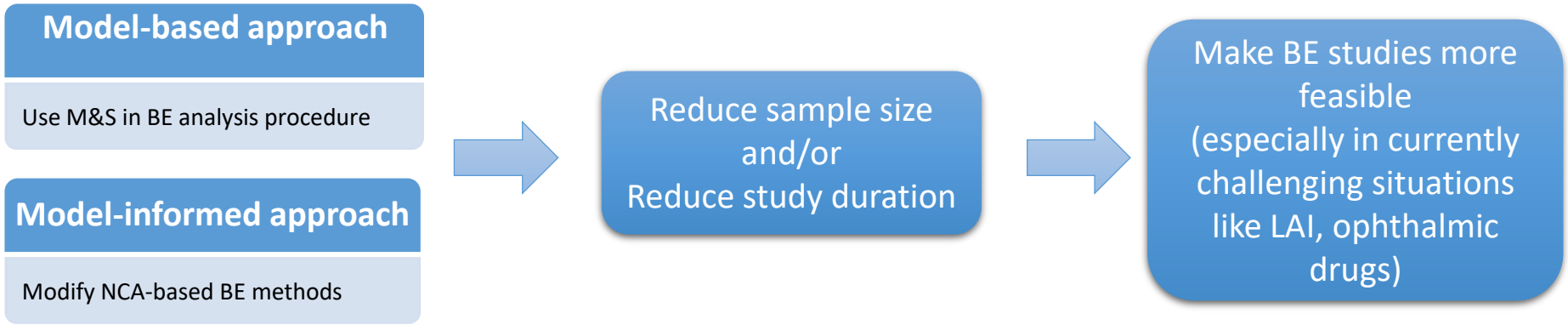
*95%CI is the 2.5% and 97.5% quantile of the binomial distribution

Model-integrated design optimization



- Model-integrated BE switch study
- Optimal design (OD) for placement of sample times
- OD based Power evaluation: 10% reduction in number of individuals
- Differences confirmed with SSE based power calculations

Summary of methods



Practical implementation – predefining models?

- A model (or a set of models)
  - Previous model based on reference product
  - Potentially build a model in a pre-defined way (current work on automated PK model building ongoing), based on prior/preliminary studies or BE study data (with caution).
- Model must then be adjusted
  - TRT, sequence, period and IOV effects on absorption parameters (including F_{rel})

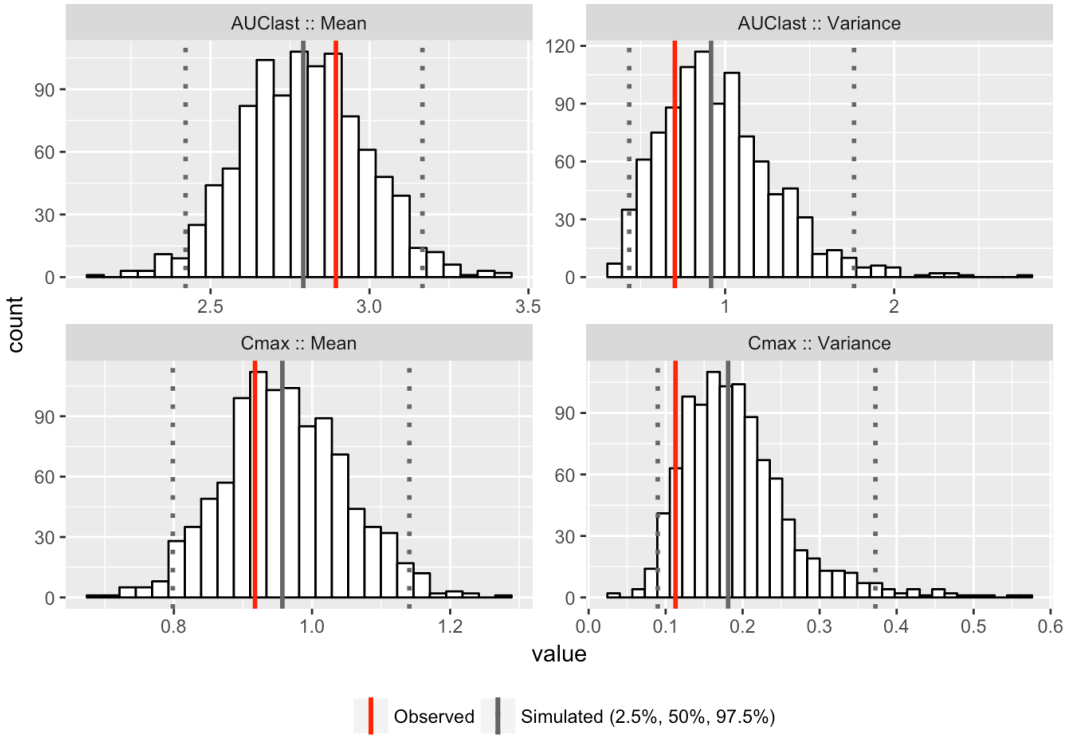
Availability of models in LAI

- 33 LAI products approved by FDA
- 27 published models for 17 of those products

- Many based on multiple studies from drug development (many subjects with multiple study designs)
  - May not be practically identifiable for a model-integrated BE study analysis

Model qualification

- Should be identifiable given the study design
  - test using optimal design software, like PopED, https://andrewhooker.github.io/PopED/.
- Non-compartmental analysis posterior predictive check of reference data.
  - NCAPPC: https://cran.r-project.org/package=ncappc



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Benefits of model sharing

- Model qualification can be done one time and shared for specific types of designs and analayses
- Improved reproducibility and validation of scientific results
- Knowledge propagation: faster development of new science
- Explicit evaluation and verification of models
- Model standardization

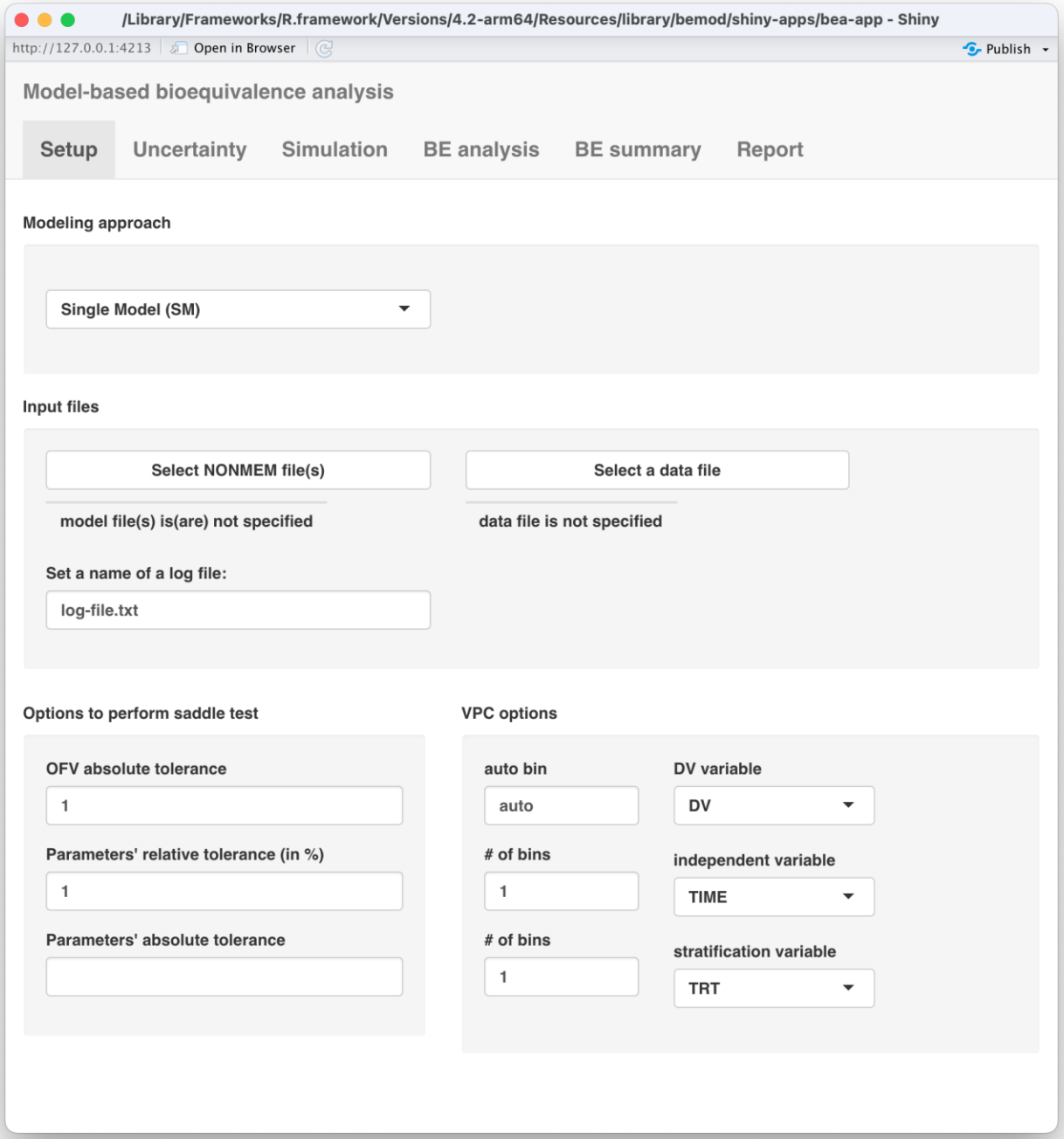
Where would we need a model master file (MMF) and how would it work?

- Acts as a model repository
  - Qualification for specific purposes
    - What was presented in a paper or submission
    - Other purposes (BE)
  - Different levels of qualification
    - Scientific panel approval
    - FDA approval
- Private MMF
  - Not published or available from submission documents
  - Analyses are performed with the model hidden from the user
- Issues
  - Will private MMFs limit scientific discourse / innovation?
  - Investment needed (development/maintenance)
  - IP issues
  - Different modeling languages, file formats, … How to actually use the information

- Example of an APP for model-integrated BE analysis of a specific LAI (PP1M) on next slides

R package *bemod*

- Included methods
  - Model-integrated methods
    - single model-based BE method
    - model averaging
    - bootstrap model selection
  - Standard NCA methods
    - Standard linear regression appraoch
    - Bootstrap NCA
- Ways to run bemod
  - using R scripts
  - using web-based platform created by R shiny
- R package ***bemodlai***
  - Depends on ***bemod*** to perform model-integrated BE methods for LAI
  - PPIM (Paliperidone 1 month) models for model-integrated BE analysis implemented in package
- Available on CRAN shortly



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Summary

- Model sharing can increase the quality of scientific work

- For model-integrated BE analysis, a way to share and qualify models for specific products and situations would aid in the practical implementation of the approach

Acknowledgements

Funding from FDA

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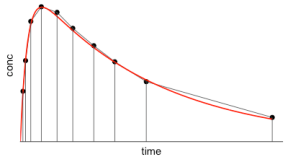
Liang Zhao
Lanyan (Lucy) Fang
Satish Sharan
Mark Donnelly
… Many more!

PM group, Uppsala University

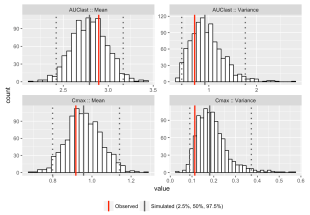
Software

bemod
bemodlai



- Model based BE testing
- To be released on CRAN

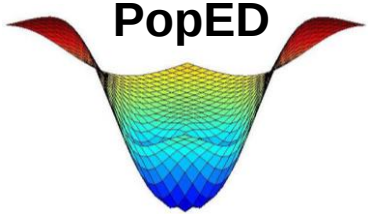
ncappc



- NCA Calculation and Population PK Model Diagnosis
- https://github.com/UUPharmacometrics/ncappc

PsN 4
Perl speaks NONMEM

- SIR
- Bootstrap
- https://uupharmacometrics.github.io/PsN/



- Optimal experimental design software
- https://andrewhooker.github.io/PopED/