Development of model-informed bioequivalence evaluation strategies for long-acting injectable products (LAI)

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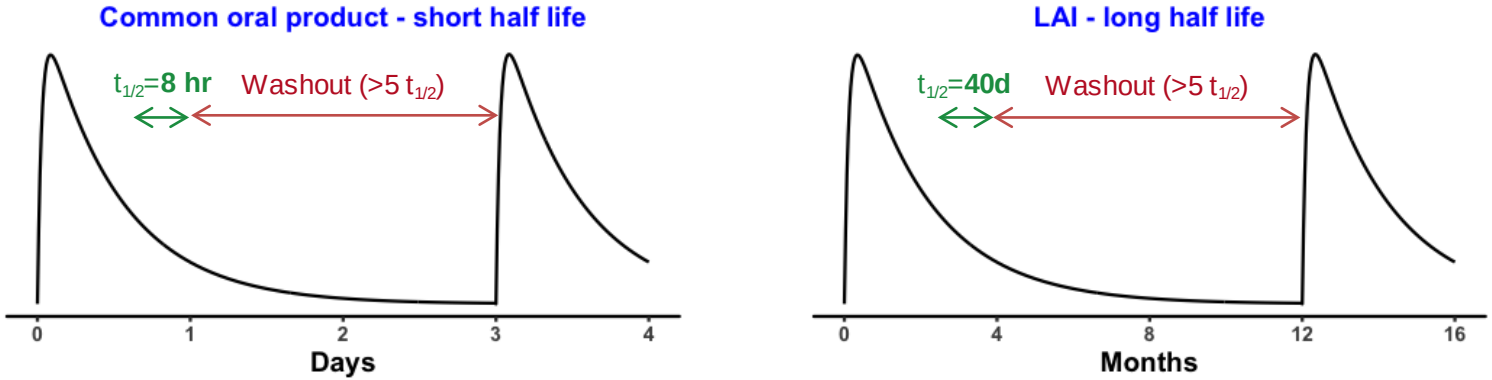
Challenges of performing BE study of LAI - Long half-life ($t_{1/2}$)

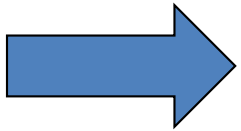
Single dose crossover BE study



It is not practical to perform a single-dose crossover BE study on LAI.

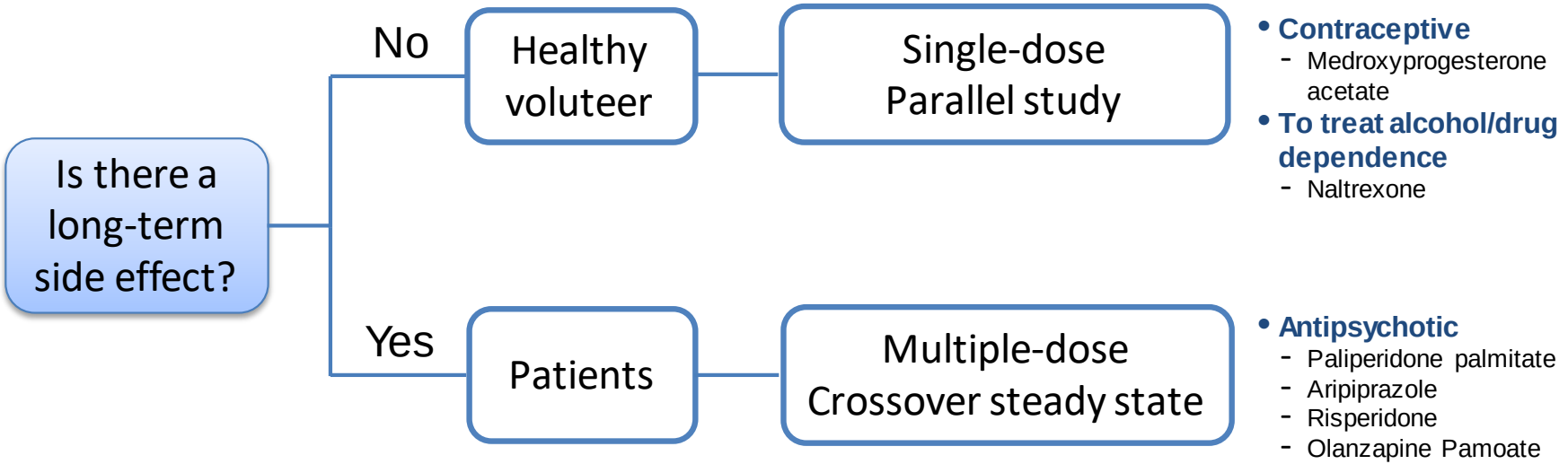
Challenges of performing BE study of LAI

Long $t_{1/2}$



- Long-term side effect
- Dropout
- Increased variation

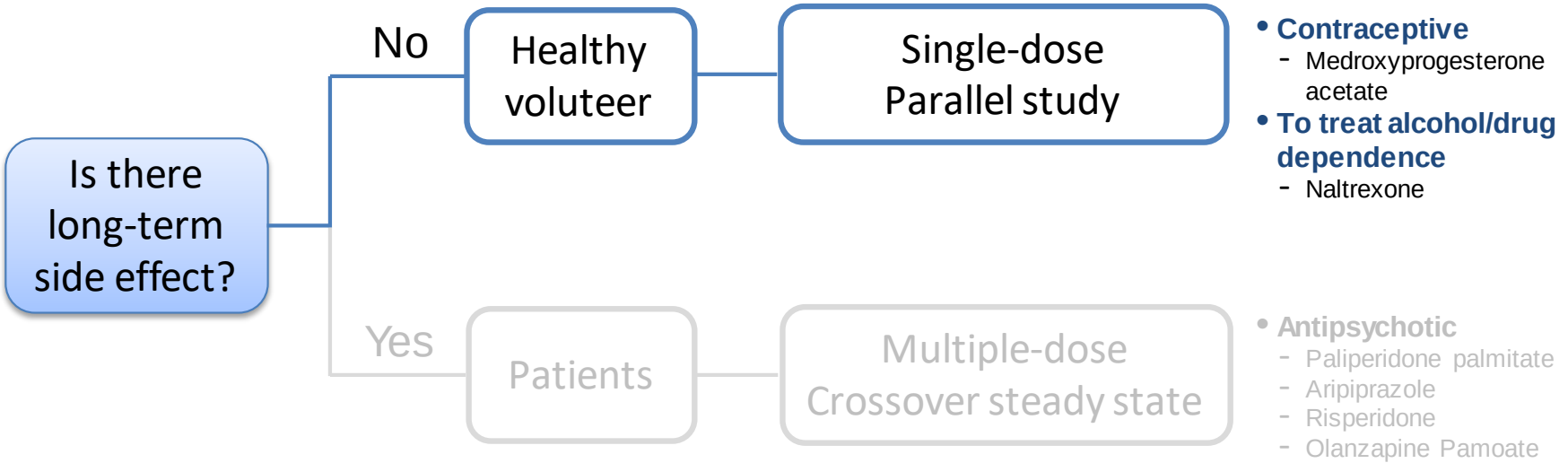
2 types of BE study designs for LAI



- **Contraceptive**
  - Medroxyprogesterone acetate
- **To treat alcohol/drug dependence**
  - Naltrexone

- **Antipsychotic**
  - Paliperidone palmitate
  - Aripiprazole
  - Risperidone
  - Olanzapine Pamoate

2 types of BE study designs for LAI



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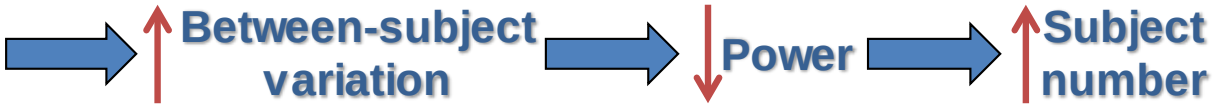
Multiple covariates affects LAI absorption, increasing variation

Single-dose parallel BE study

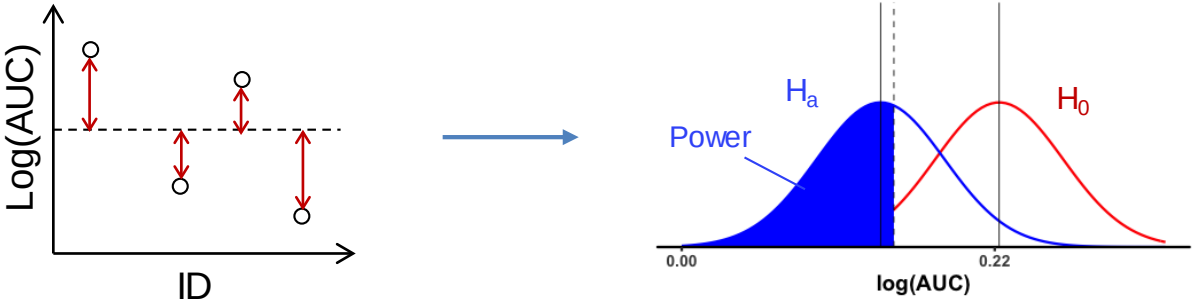
Affecting Factors

- BMI
- Sex
- Age
- Injection site
- …

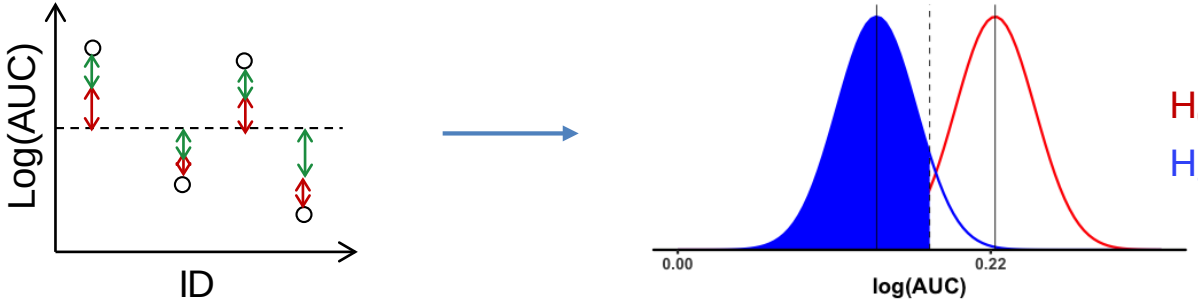


Potential solution to increase power: Adding covariate effect in the analysis

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



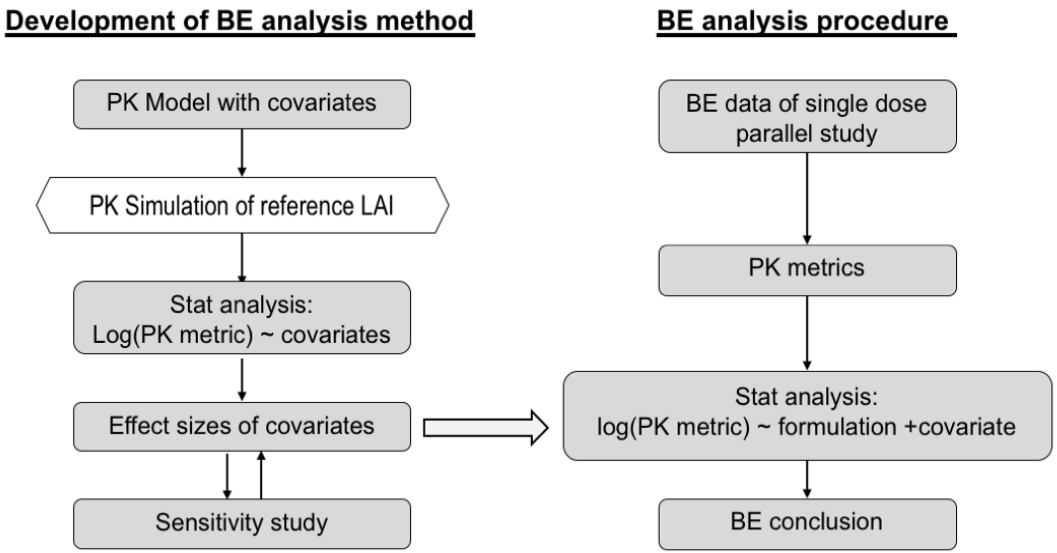
$$\log(AUC)_i = \mu + formulation + other\ covariates + \varepsilon_i$$



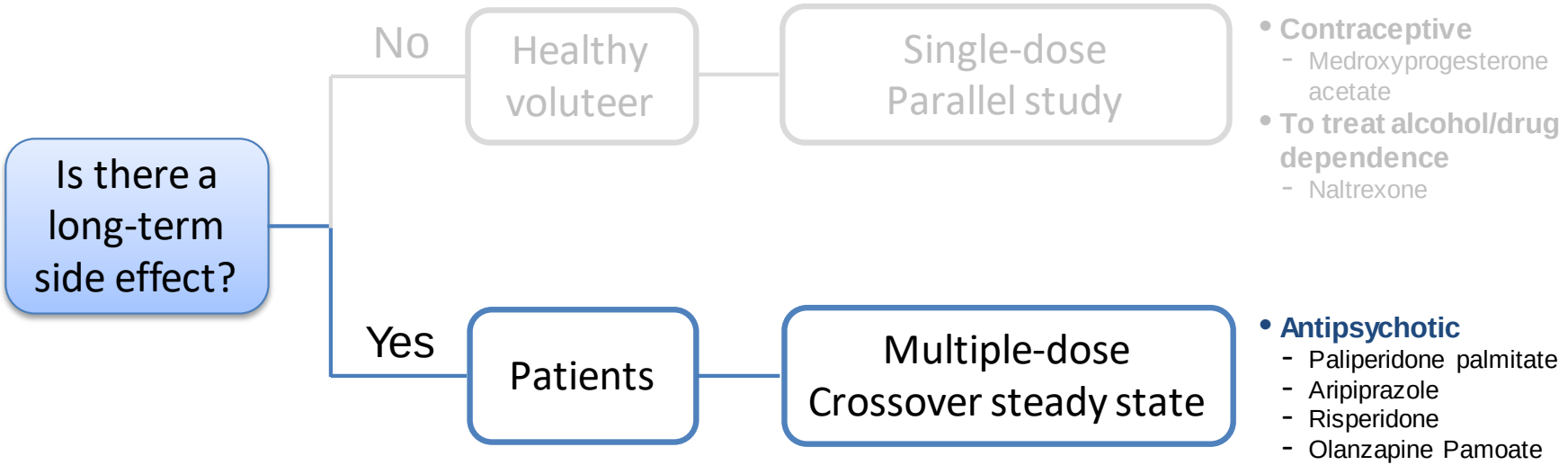
H_0: $\mu_{test} - \mu_0 \geq 0.22$

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

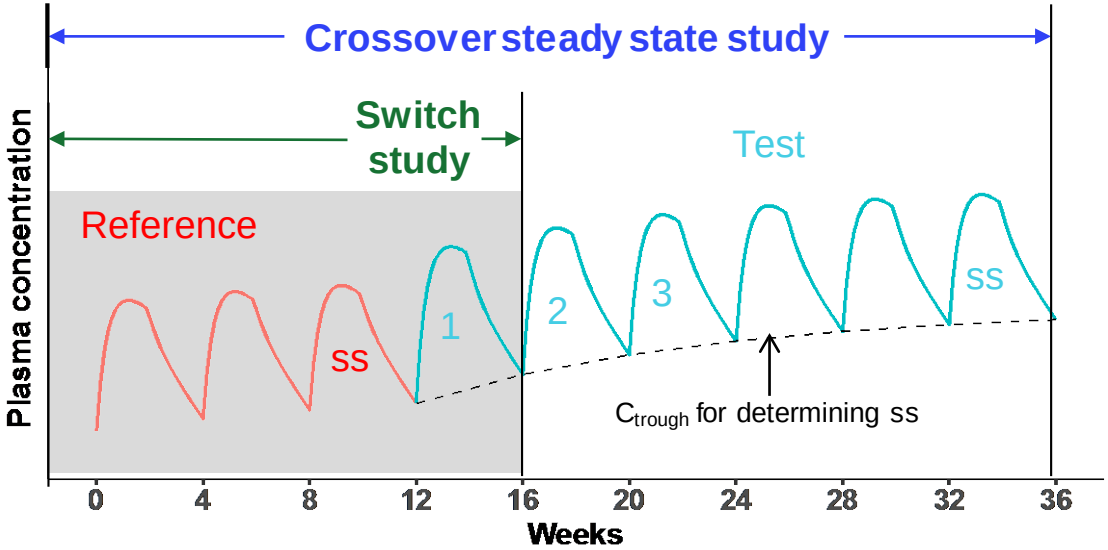
Use M&S to describe the covariate effect



2 types of BE study designs for LAI



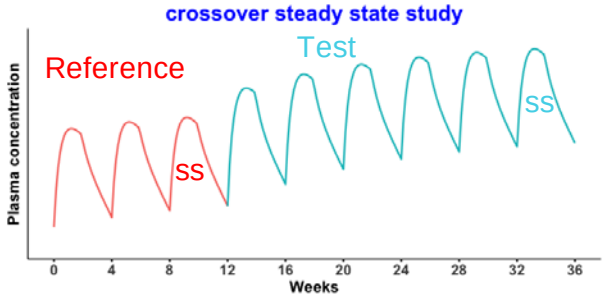
Possible solution to reduce BE study duration: use switch study instead of requiring achieving ss

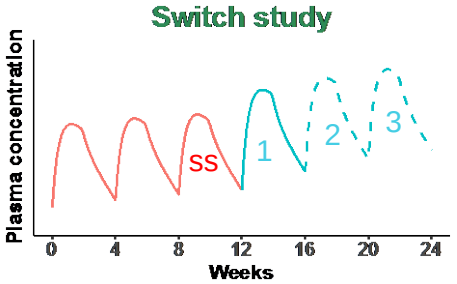


Questions about BE evaluation criteria for switch study:

- What PK metrics to use?
- What BE limit to use?

Modeling & Simulation can be used to bridge between 2 study designs in BE criteria





Regulatory Criteria

Surrogate Criteria

PK metrics

$AUC_{0-T,ss}, C_{max,ss}$

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

BE Limit

80 – 125%

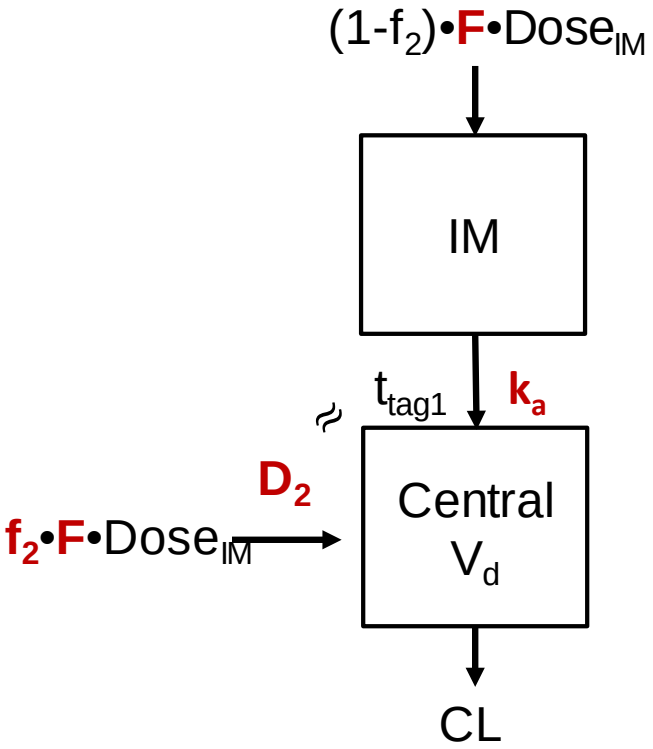
Surrogate limit

M&S

An example of a population PK model for LAI

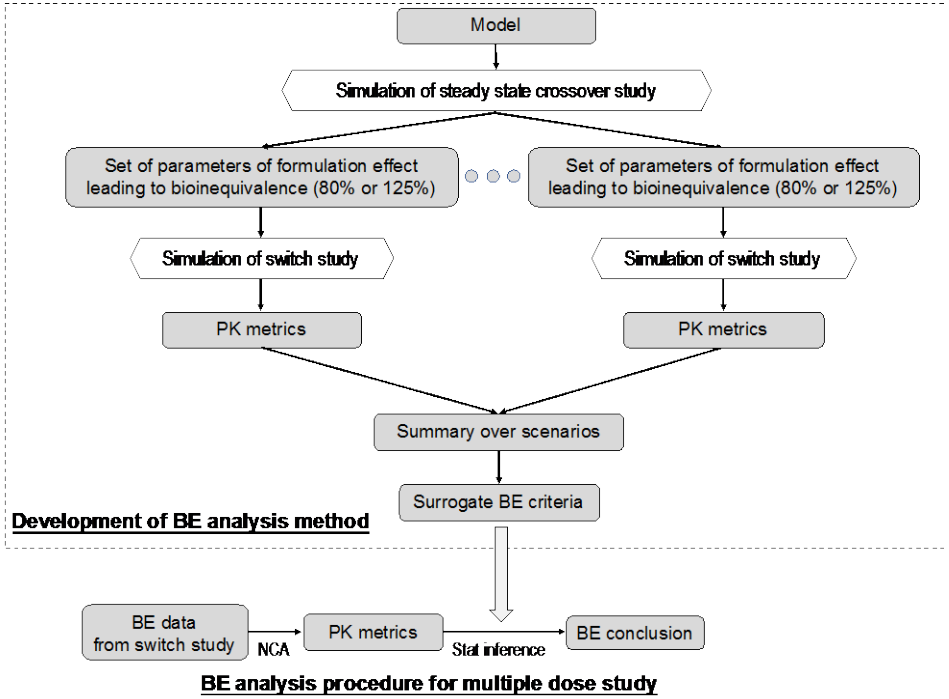
1-month Paliperidone Palmitate (PP1M)

- Intramuscular injection every month
- Well-developed pop PK model
- Absorption includes
  - Fast zero-order absorption
  - Slow first-order absorption
- Absorption parameters:
  - Total bioavailability F
  - Proportion of fast absorption f_2
  - Duration of fast absorption
  - Rate of slow absorption



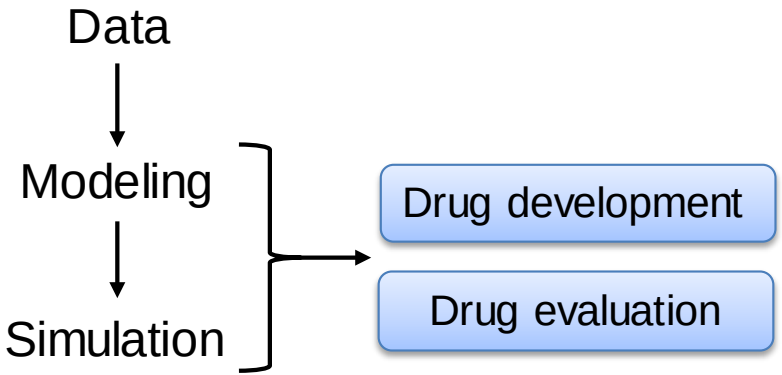
Samtani, et.al , Clin Pharmacokinet 2009

Use M&S to find surrogate criteria for switch study

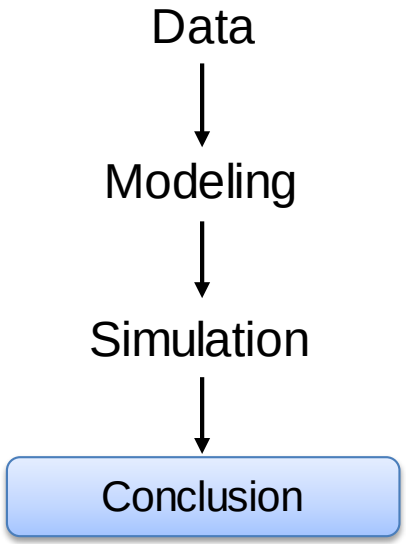


2 approaches of applying pharmacometrics

Model-informed approach



Model-integrated approach



2 approaches of applying M&S for BE studies

Model-informed approach

- M&S is used to identify suitable designs, metrics and decision criteria for BE studies
- BE study data are **not** subjected to M&S for decision-making

Model-integrated approach

- M&S may be used to identify suitable designs, metrics and decision criteria for BE studies
- BE study data are subjected to M&S for decision-making

Potential 2 approaches of applying M&S for LAI BE methods

Model-informed approach

The analysis is based on NCA, not including PK modeling

Single-dose parallel study

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

M&S

Multiple-dose crossover study

Crossover ss study Required BE criteria → Switch study Surrogate BE criteria

M&S

Model-integrated approach

The analysis include PK modeling

Data

↓

Modeling

↓

Simulation

Single-dose crossover BE study

↓

Conclusion

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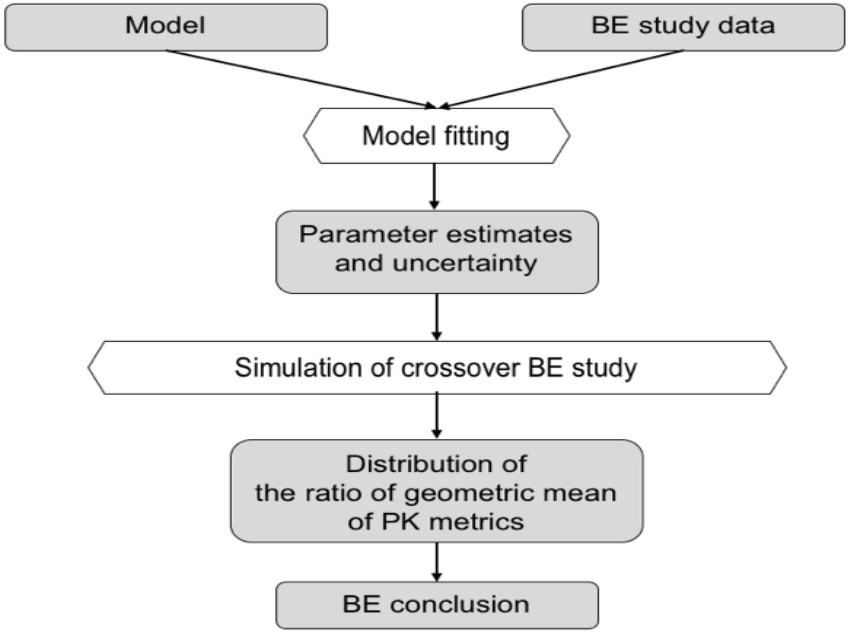
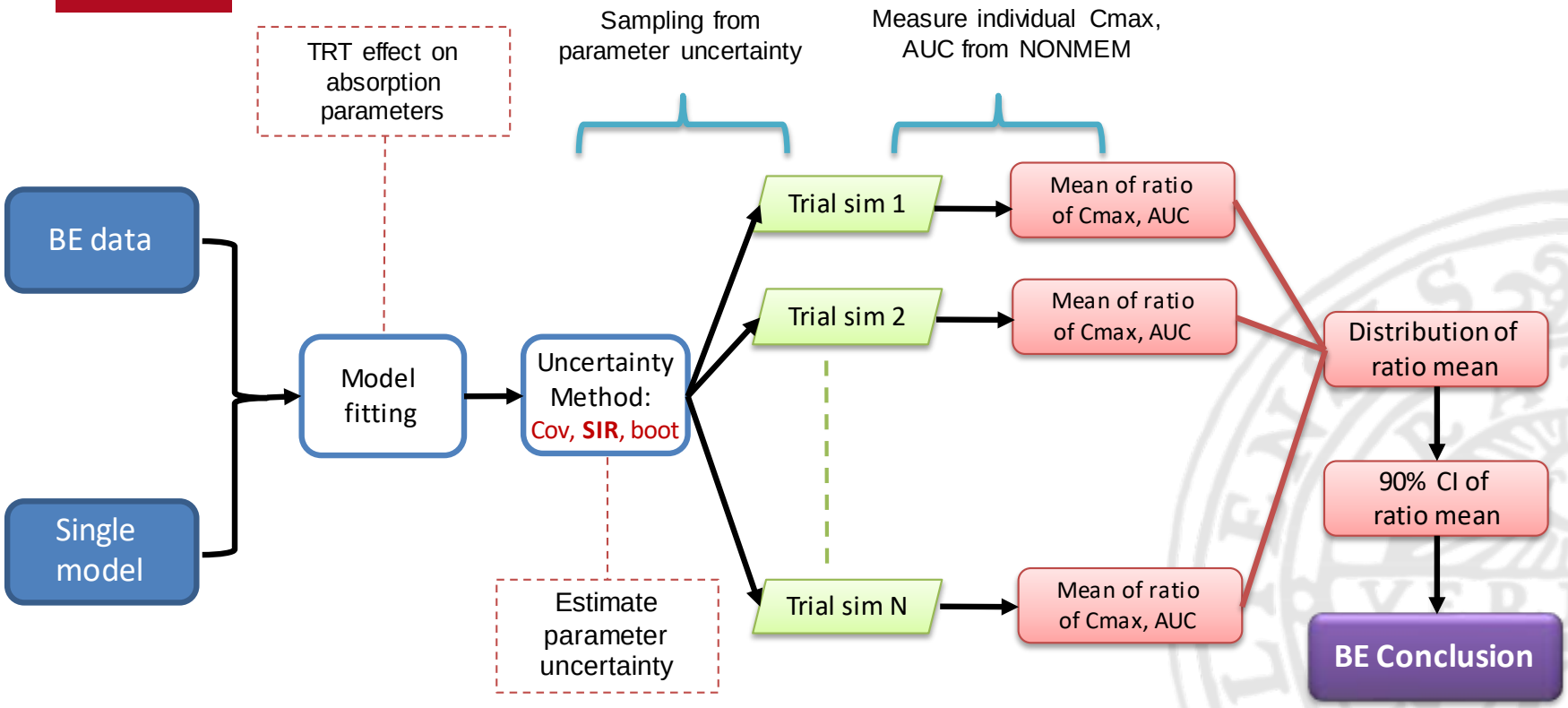
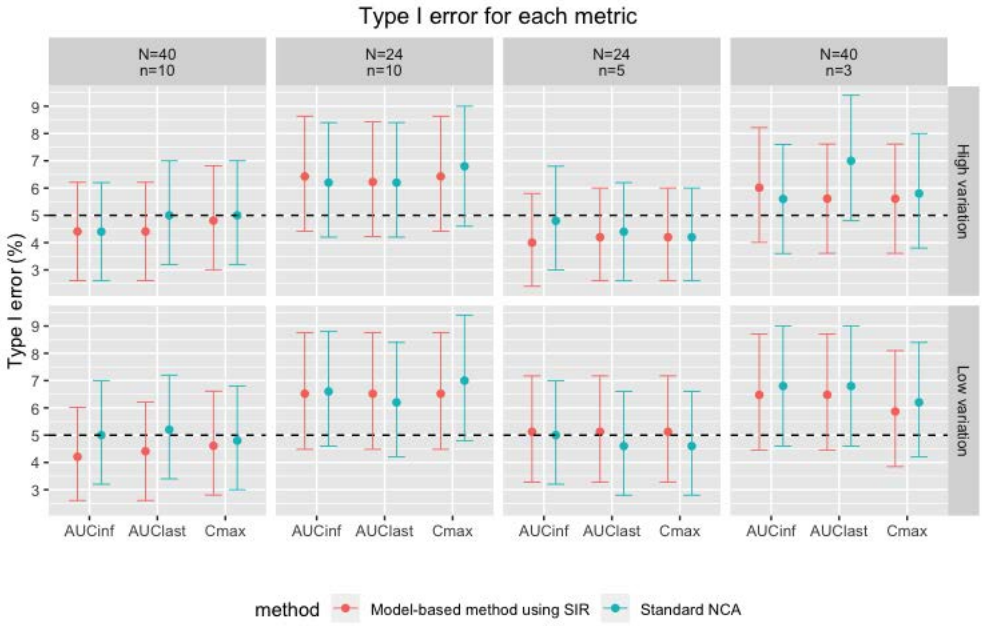
The analysis for a LAI BE dataset includes modeling and simulation

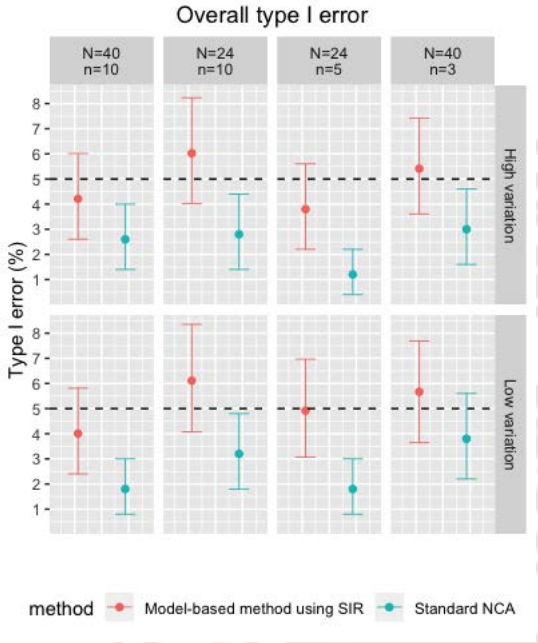


Our developed model-integrated BE method

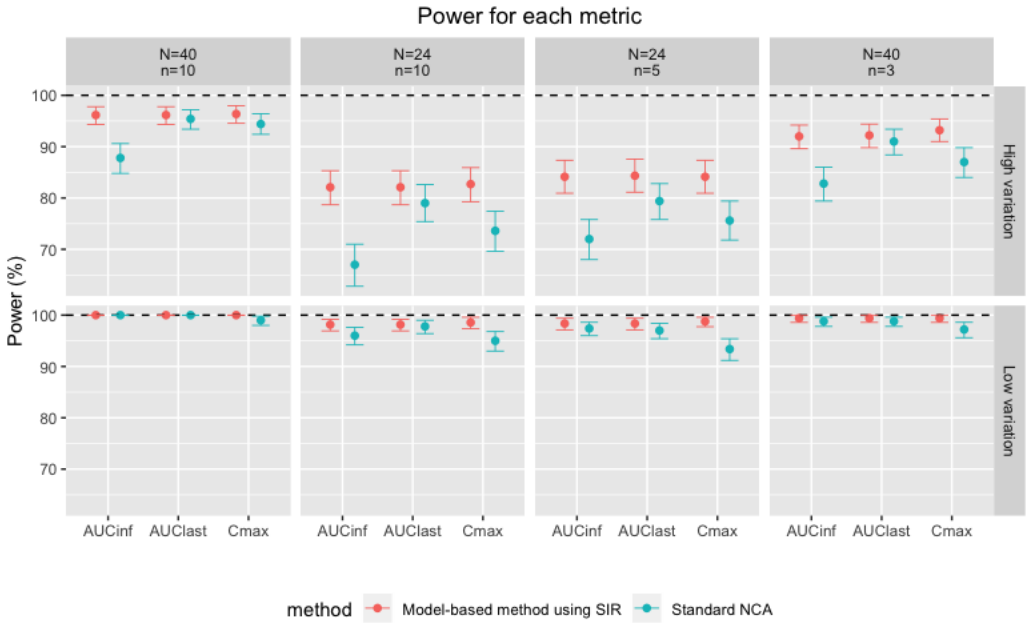


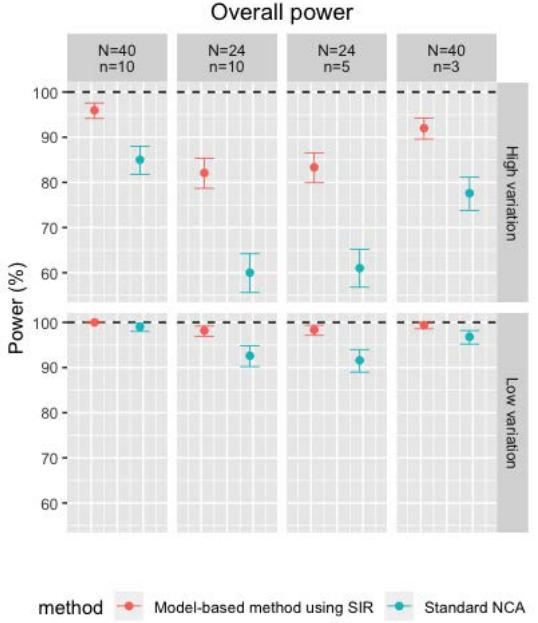
Accepted Type I error of model-integrated method for sparse BE data





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





Conclusion

Model-informed approach

To modify NCA-based BE methods for LAI

Model-integrated approach

To include M&S in LAI BE analysis procedure