The Impact of Model Selection for Personalised Dosing

David McDougall

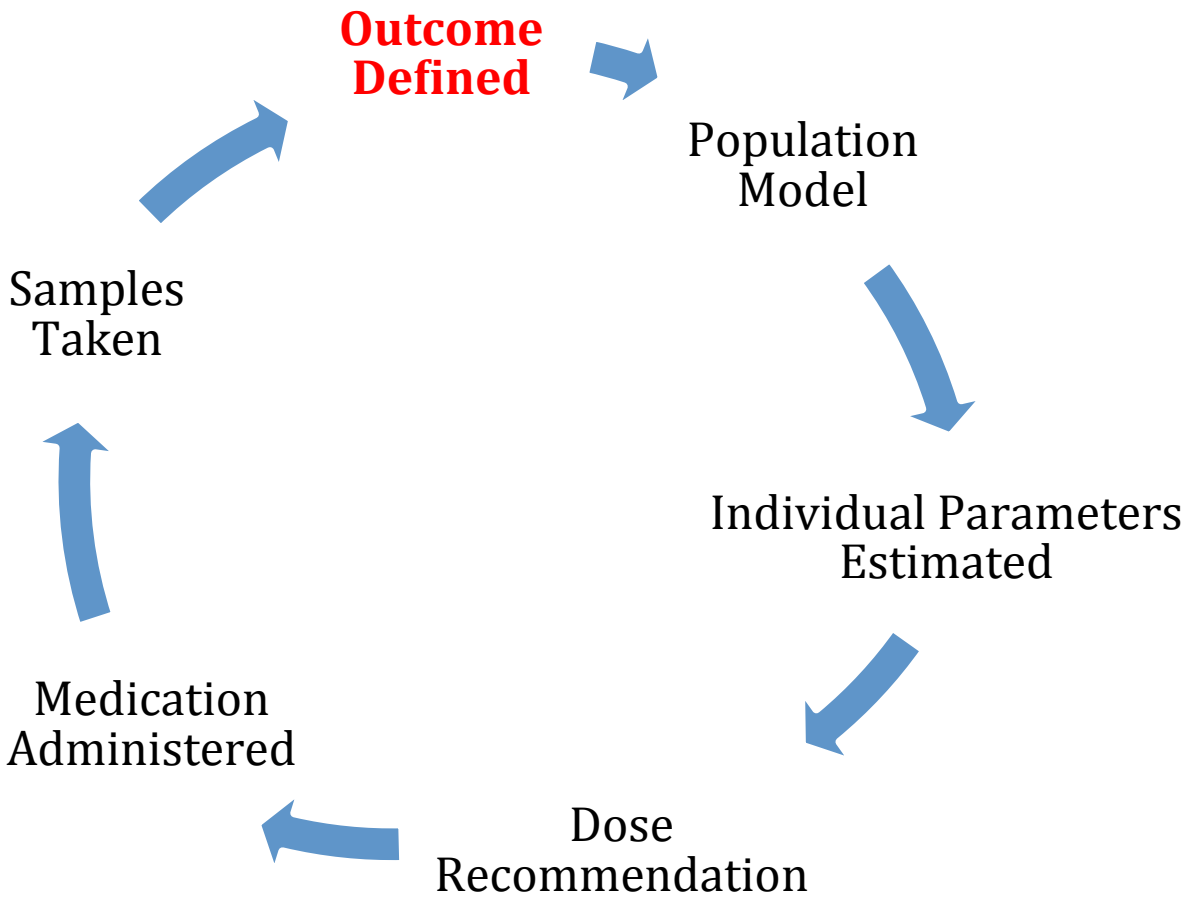
Bruce Green
Jenny Martin
Geoffrey Playford

MODEL ANSWERS

University of Queensland

david.mcdougall1@uqconnect.edu.au

Model Based Personalised Dosing (MBPD)



Barriers to MBPD in the Clinical Setting

1. **Limited evidence of improved clinical outcomes**
2. Limited intuitive integrated software packages
3. Limited understanding from clinicians

Barriers to MBPD in the Clinical Setting

1. Limited evidence of improved clinical outcomes
2. **Limited intuitive integrated software packages**
3. Limited understanding from clinicians

Barriers to MBPD in the Clinical Setting

1. Limited evidence of improved clinical outcomes
2. Limited intuitive integrated software packages
3. **Limited understanding from clinicians**

Model Selection

How close is good enough?

"Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful"

Voriconazole

- Broad-spectrum triazole antifungal
  - Non-linear elimination
  - Large BSV
  - TDM is advocated
- **Nine** published POP PK models
- The models differs significantly
  - Clearance mechanisms
  - Covariates included

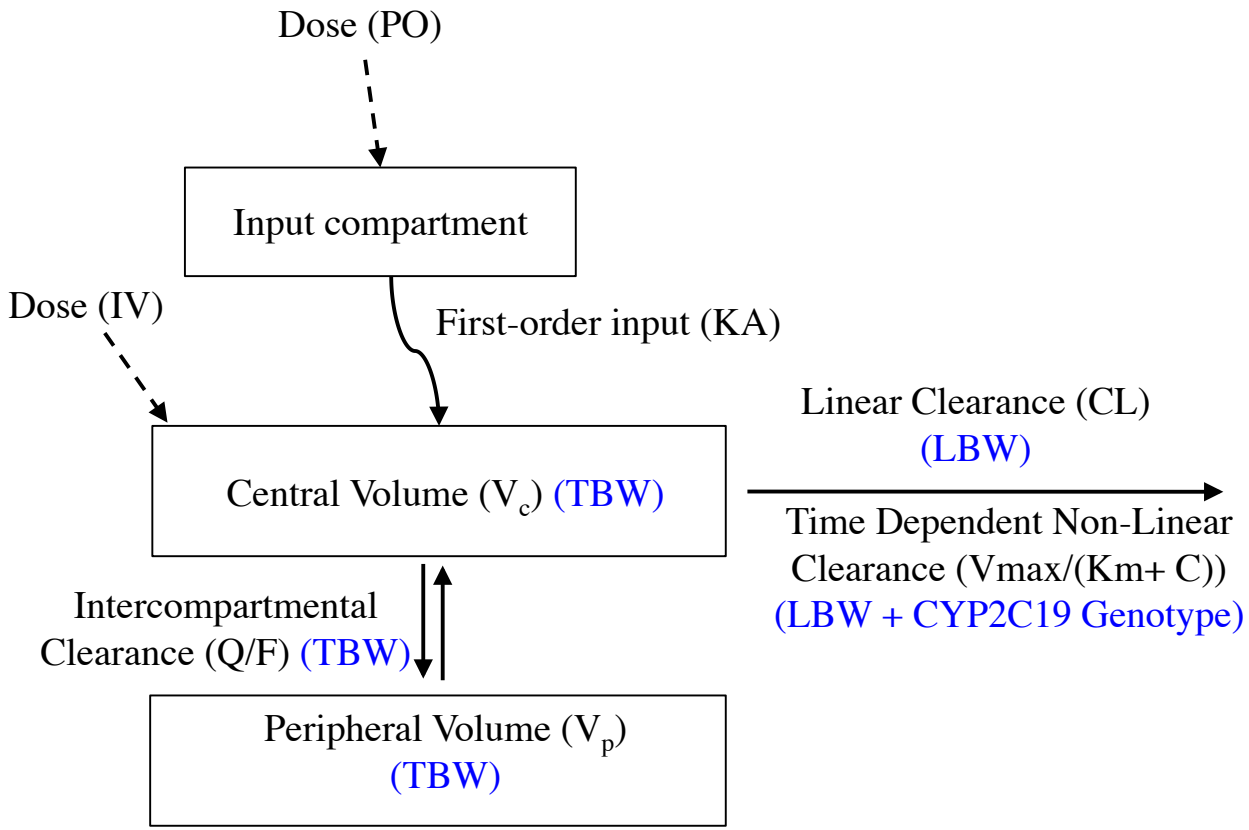
Methods

Methods: Overview

1. Develop misspecified population PK models
2. Calculate dose recommendations from the misspecified models
3. Predict the likely exposure under these dose recommendations
4. Extrapolate the probability of clinical outcomes (success / toxicity)

Methods: Misspecified Models Definition

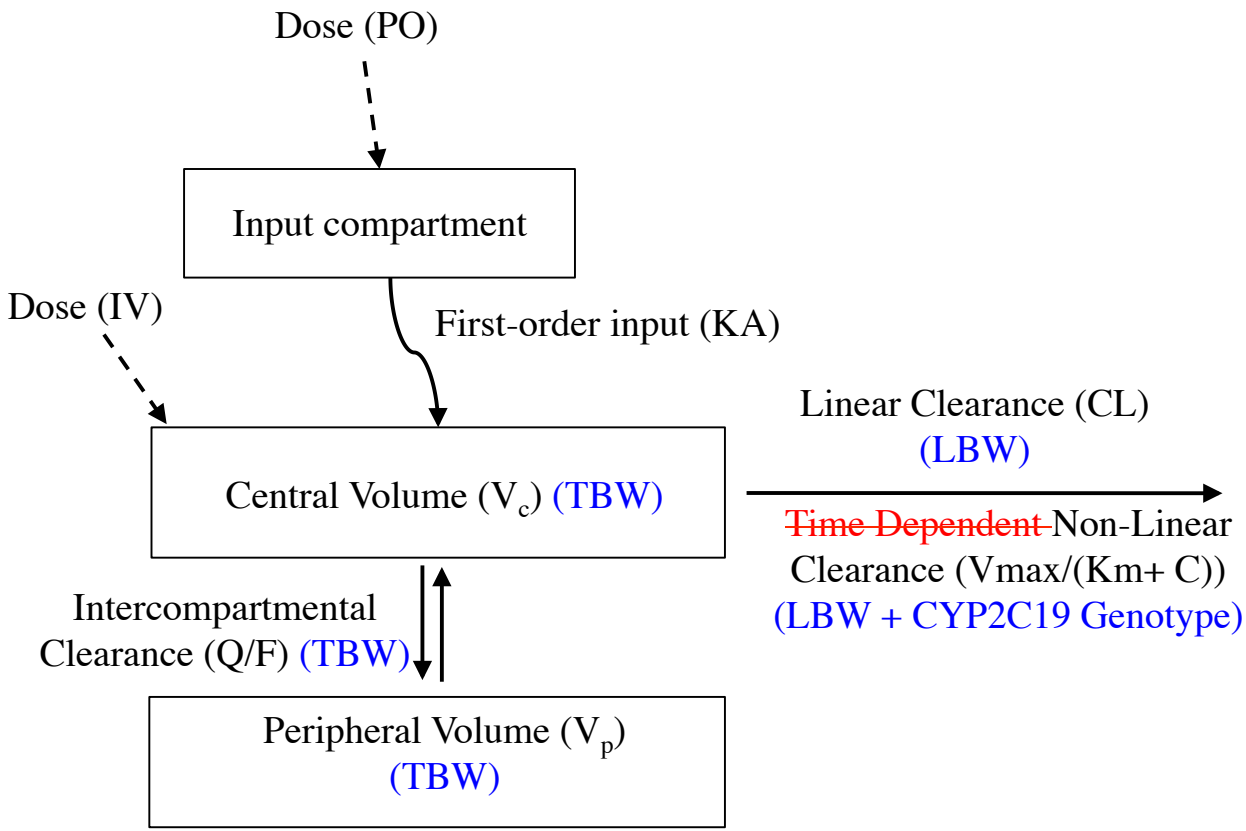
Reference Model Published Model *(Hybrid) - JPKPD 2016:43(2)*



TBW = total body weight, LBW = lean body weight, Blue = covariate effect

Methods: Misspecified Models Definition

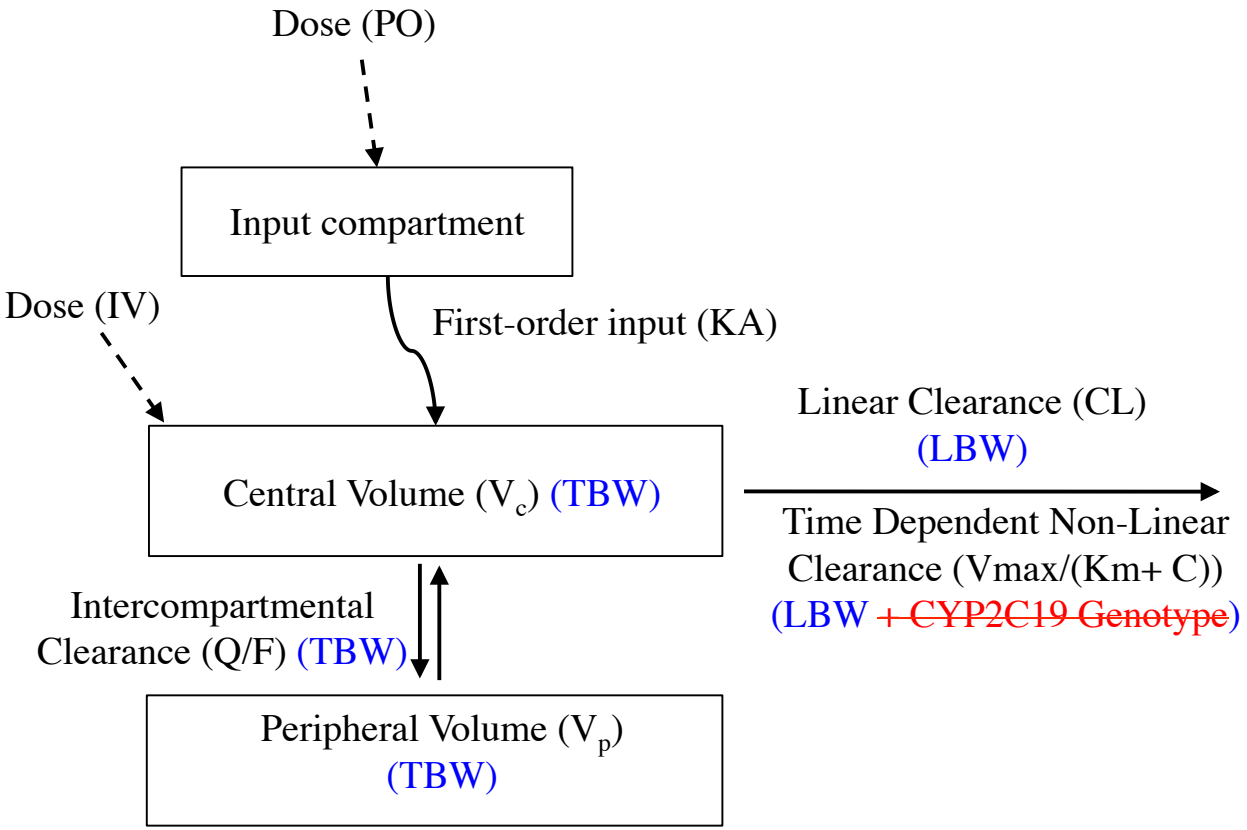
Misspecified 1 No Time Dependent Elminiation



TBW = total body weight, LBW = lean body weight, Blue = covariate effect

Methods: Misspecified Models Definition

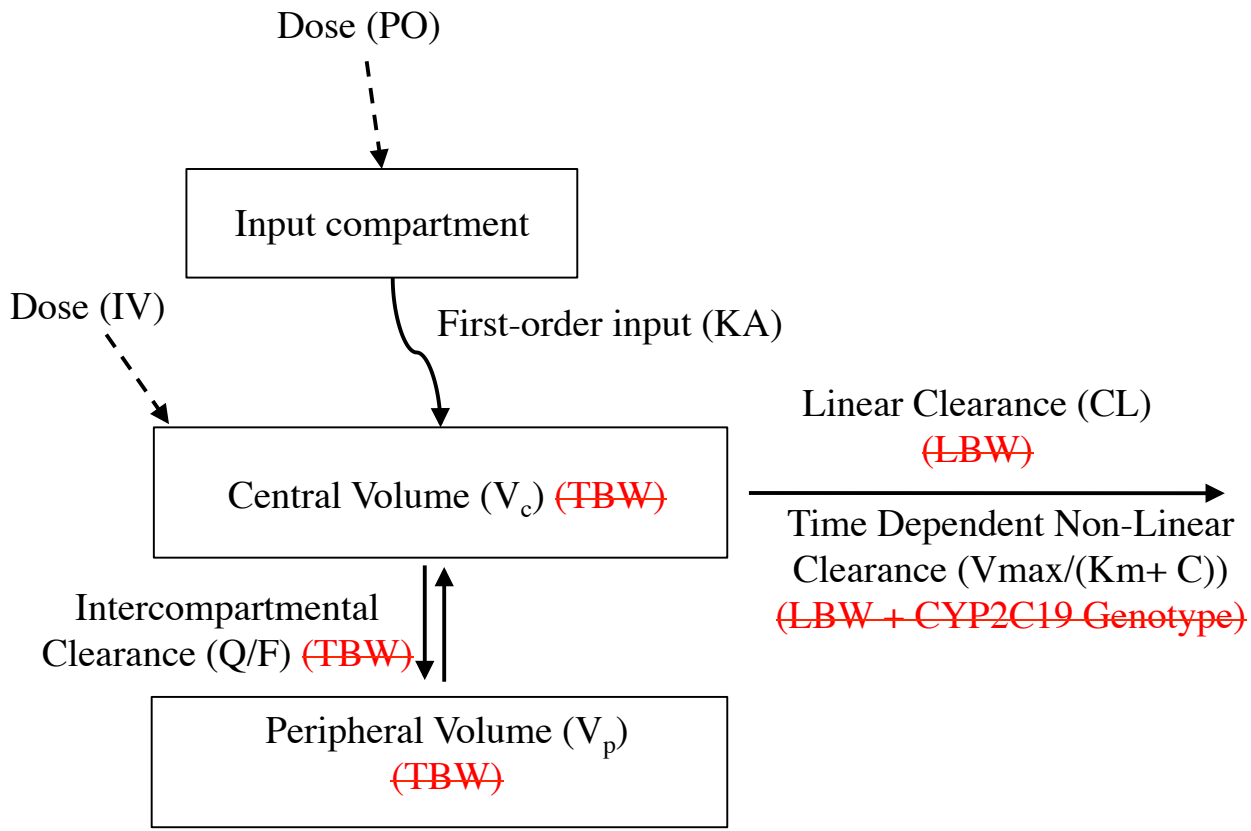
Misspecified 2 No CYP2C19 genotype as a covariate



TBW = total body weight, LBW = lean body weight, Blue = covariate effect

Methods: Misspecified Models Definition

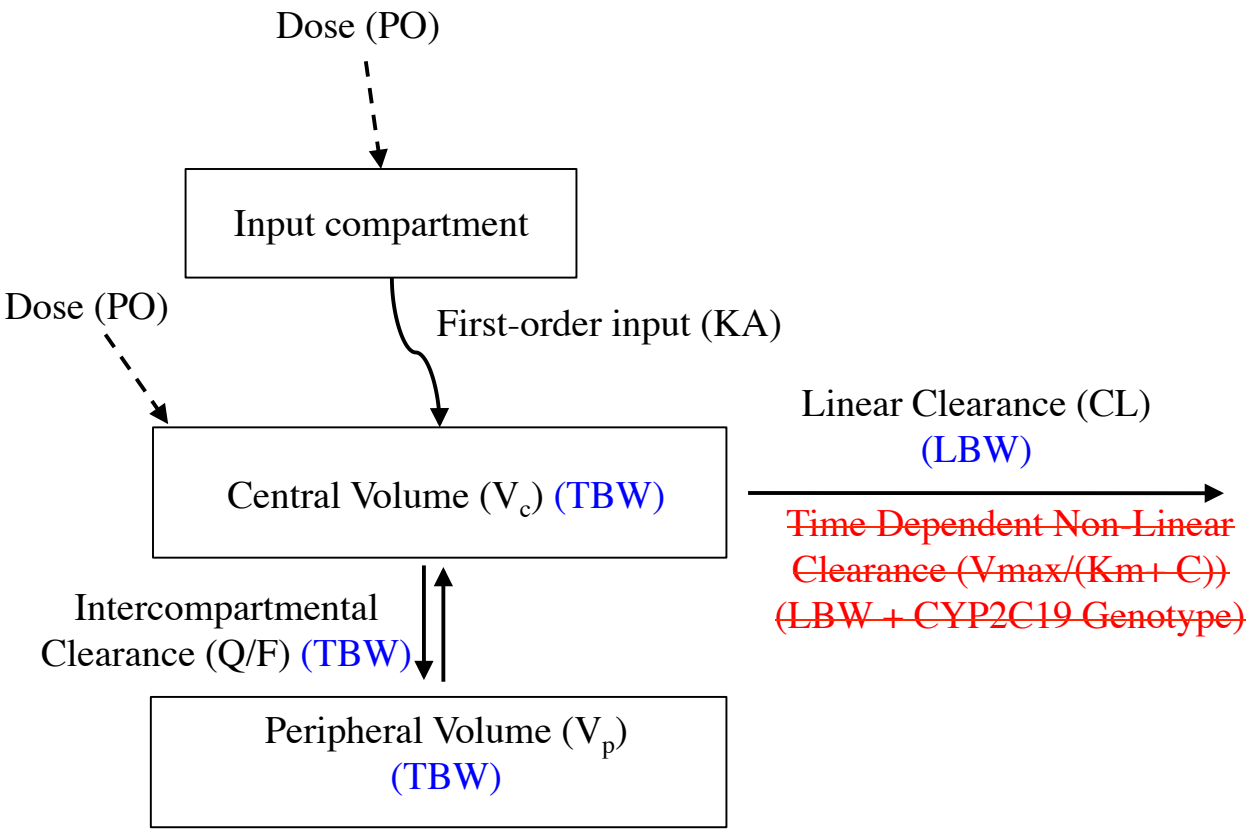
Misspecified 3 No covariates



TBW = total body weight, LBW = lean body weight, Blue = covariate effect

Methods: Misspecified Models Definition

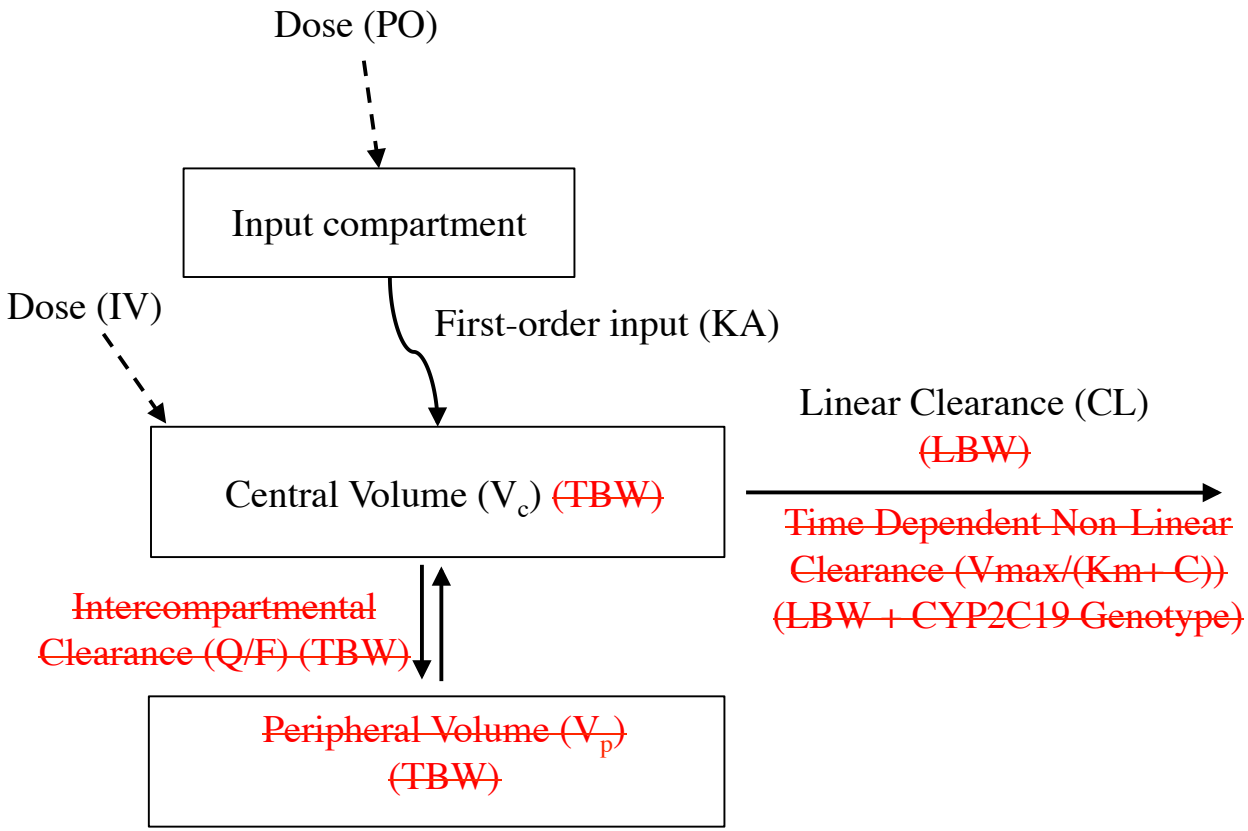
Misspecified 4 Linear Elimination Only



TBW = total body weight, LBW = lean body weight, Blue = covariate effect

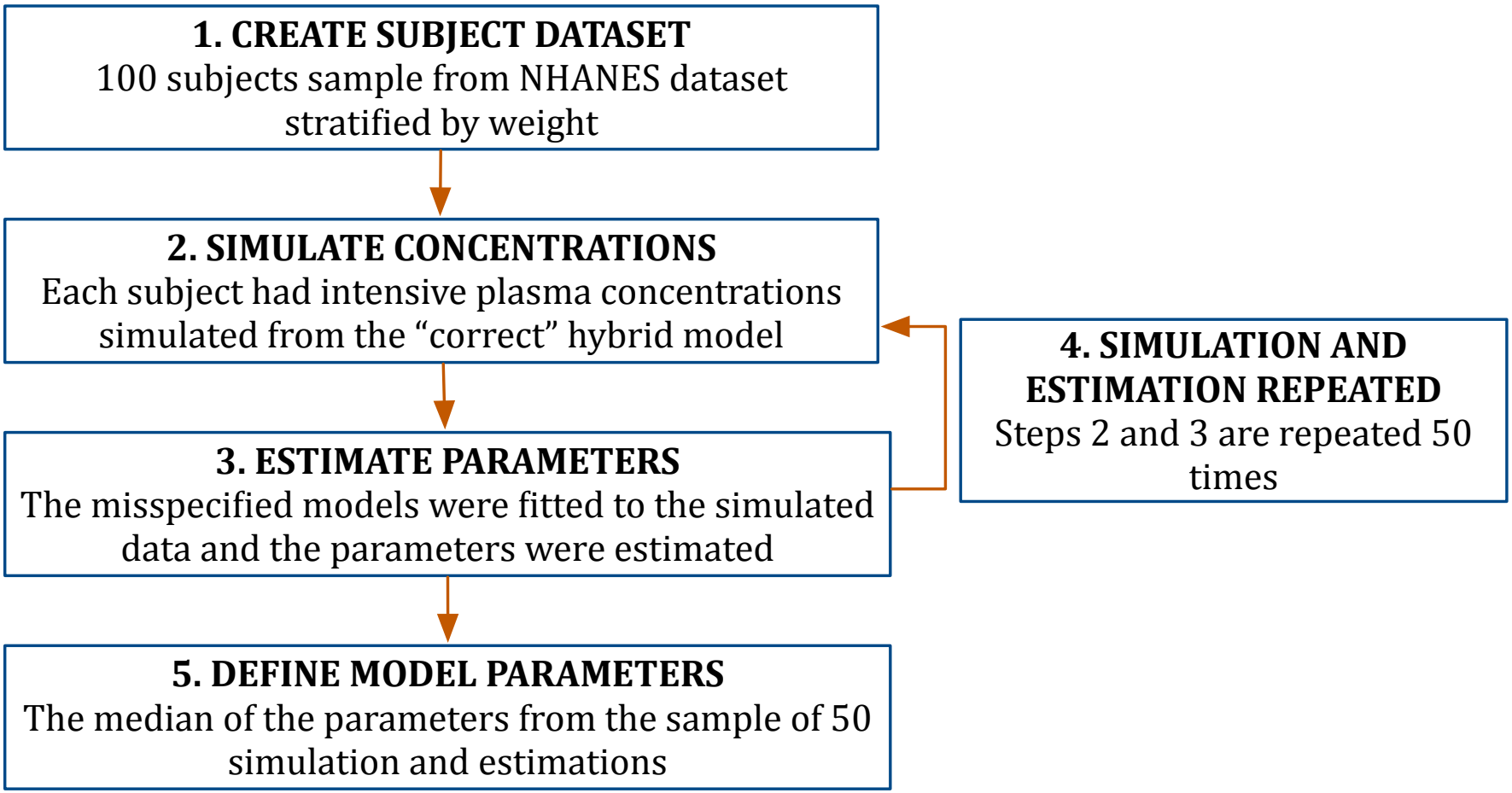
Methods: Misspecified Models Definition

Misspecified 5 Linear Elimination, 1 CMT, No Covariates

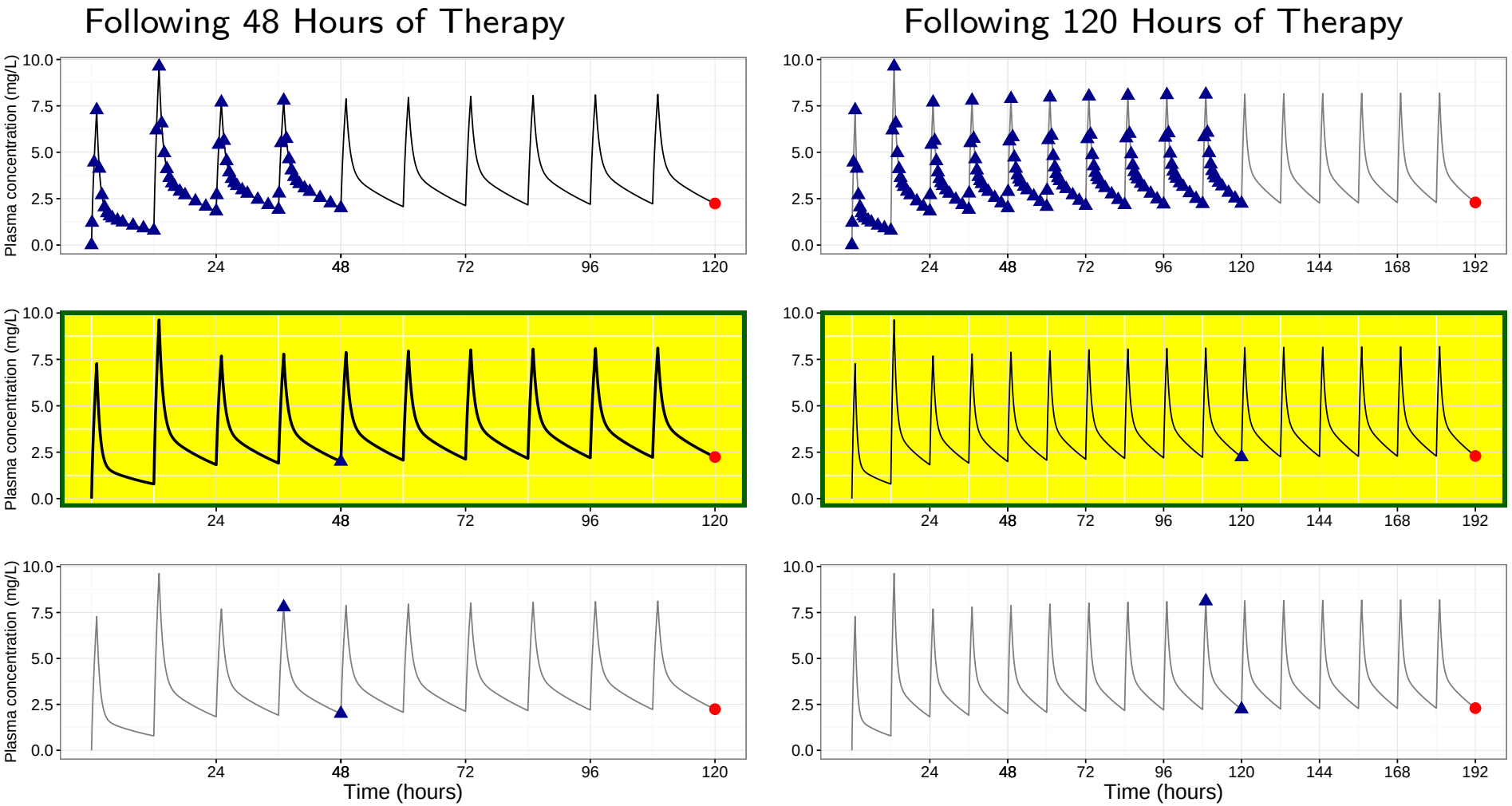


TBW = total body weight, LBW = lean body weight, Blue = covariate effect

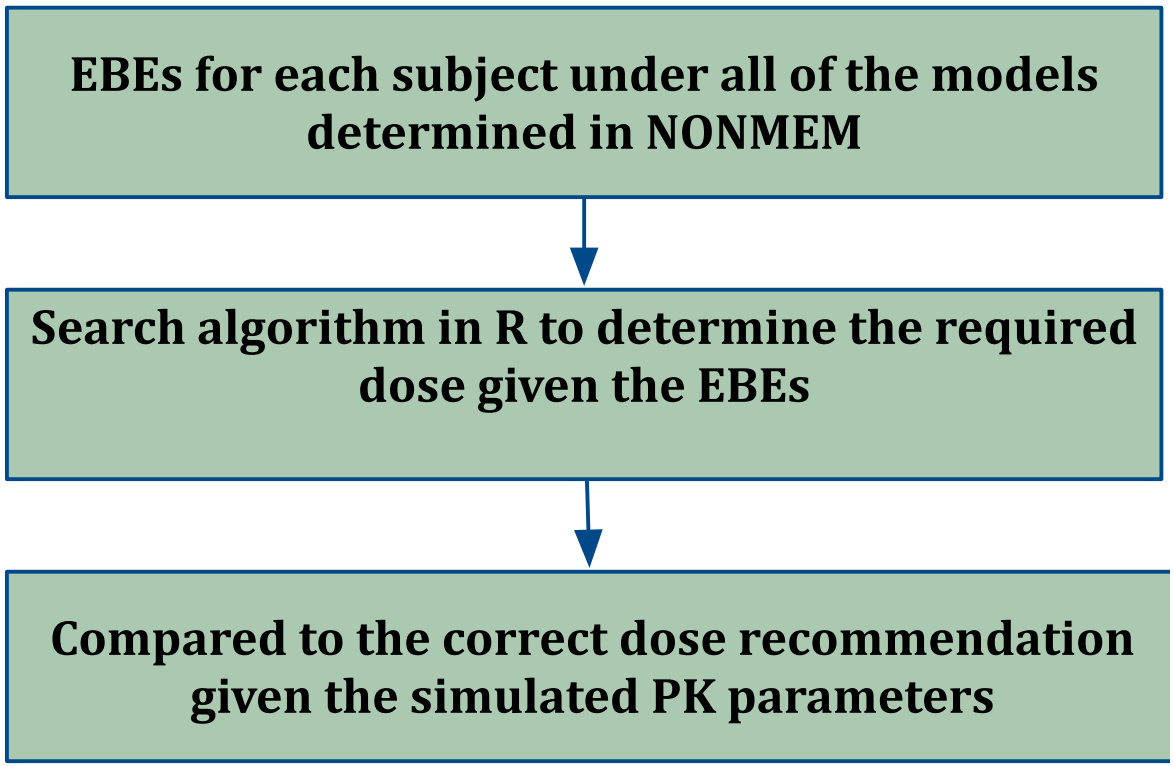
Methods: Misspecified Model Parameters Estimates



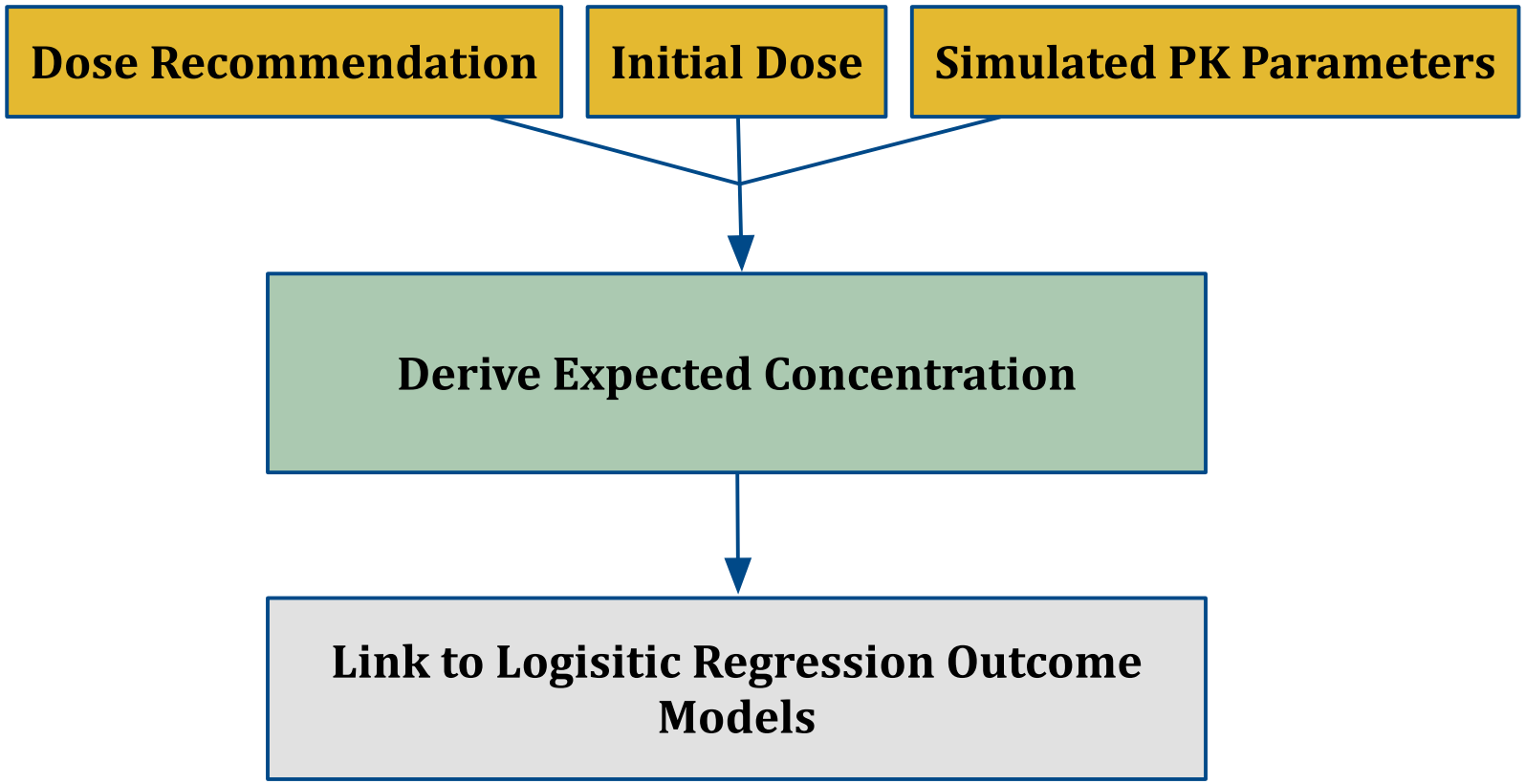
Methods: Scenarios Considered



Methods: Dose Adjustment Required

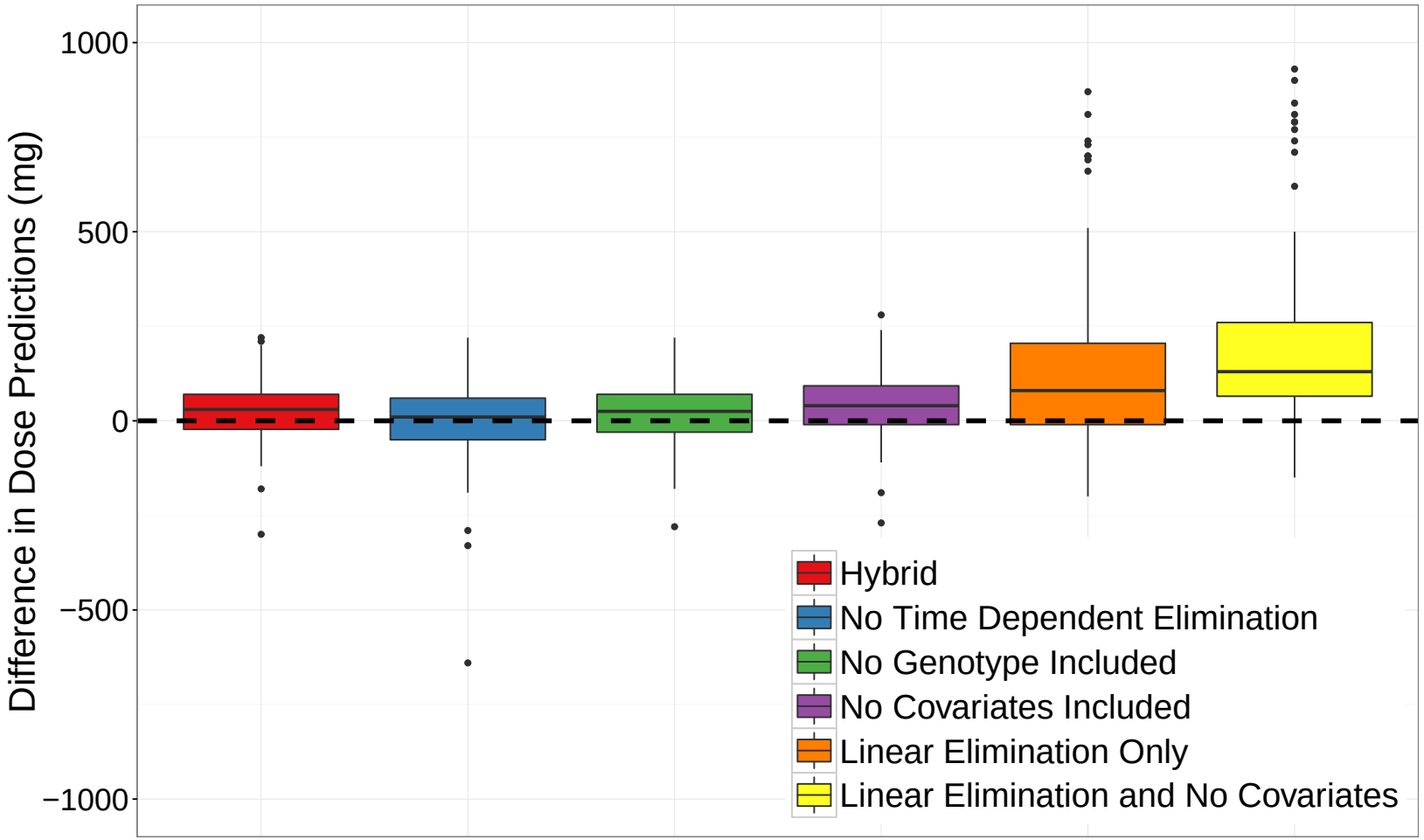


Methods: Plasma Concentrations Achieved & Clinical Outcomes

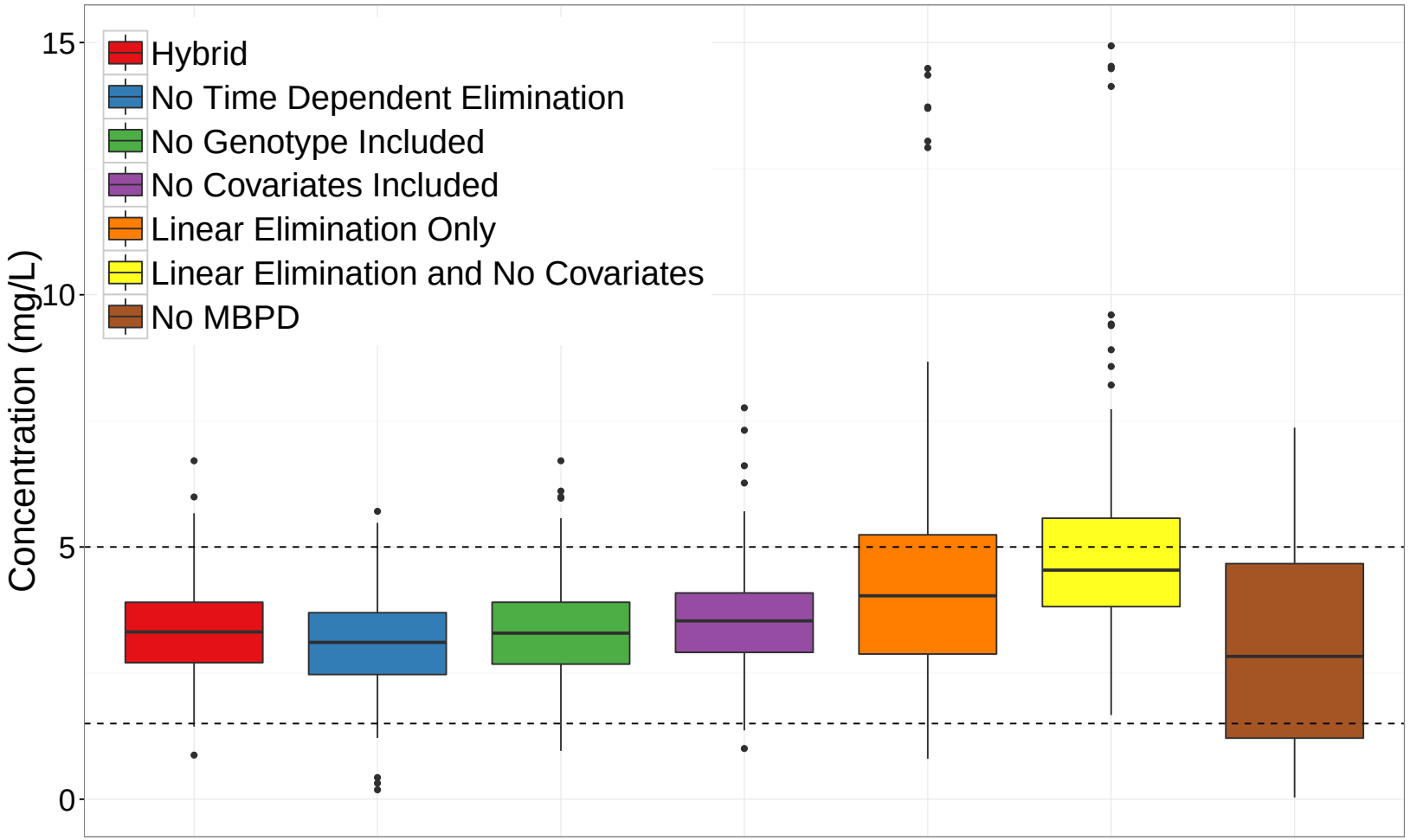


Results

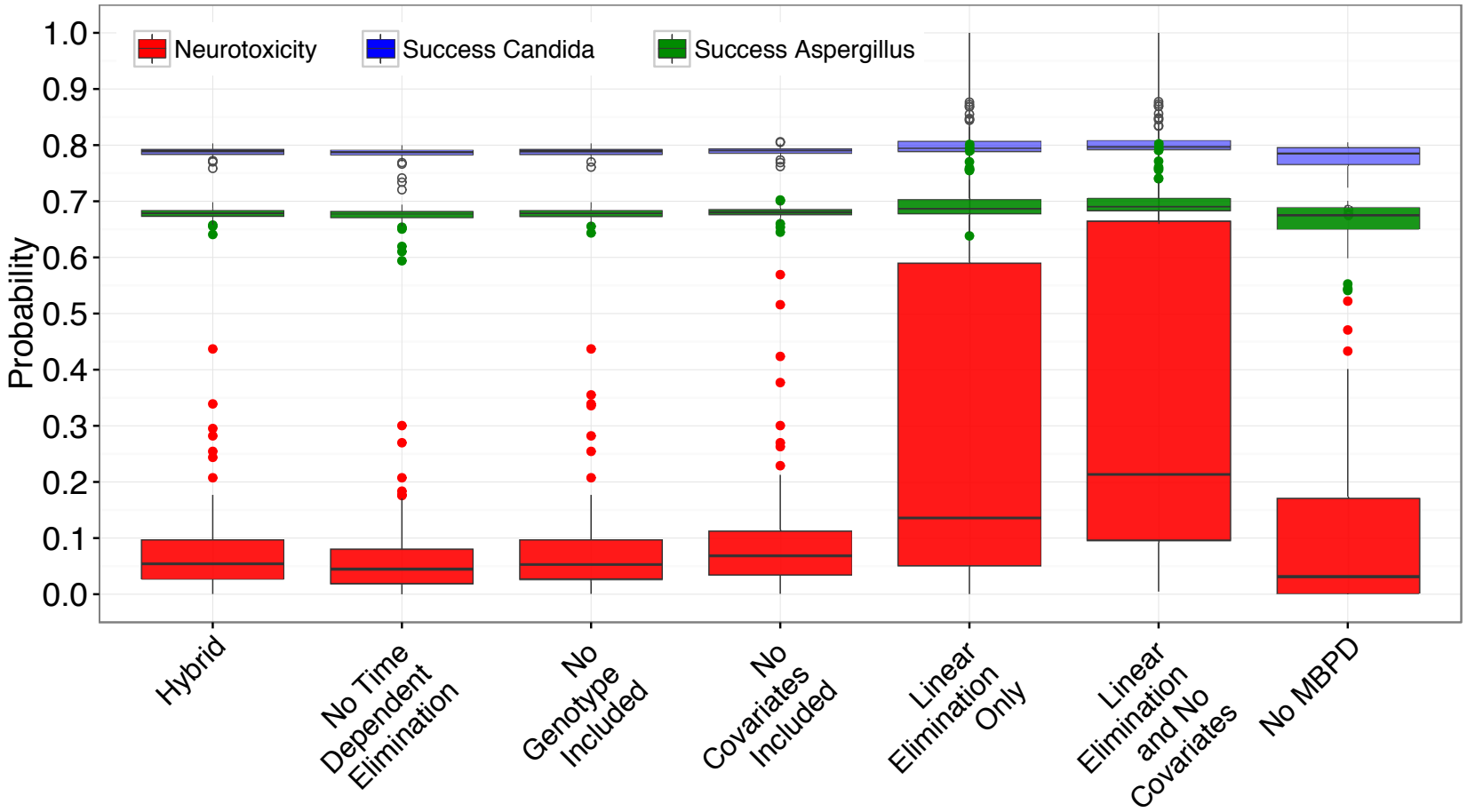
Dose Recommendations: Following 120 Hours of Therapy



Plasma Concentrations: Following 120 Hours of Therapy



Clinical Outcomes: Following 120 Hours of Therapy



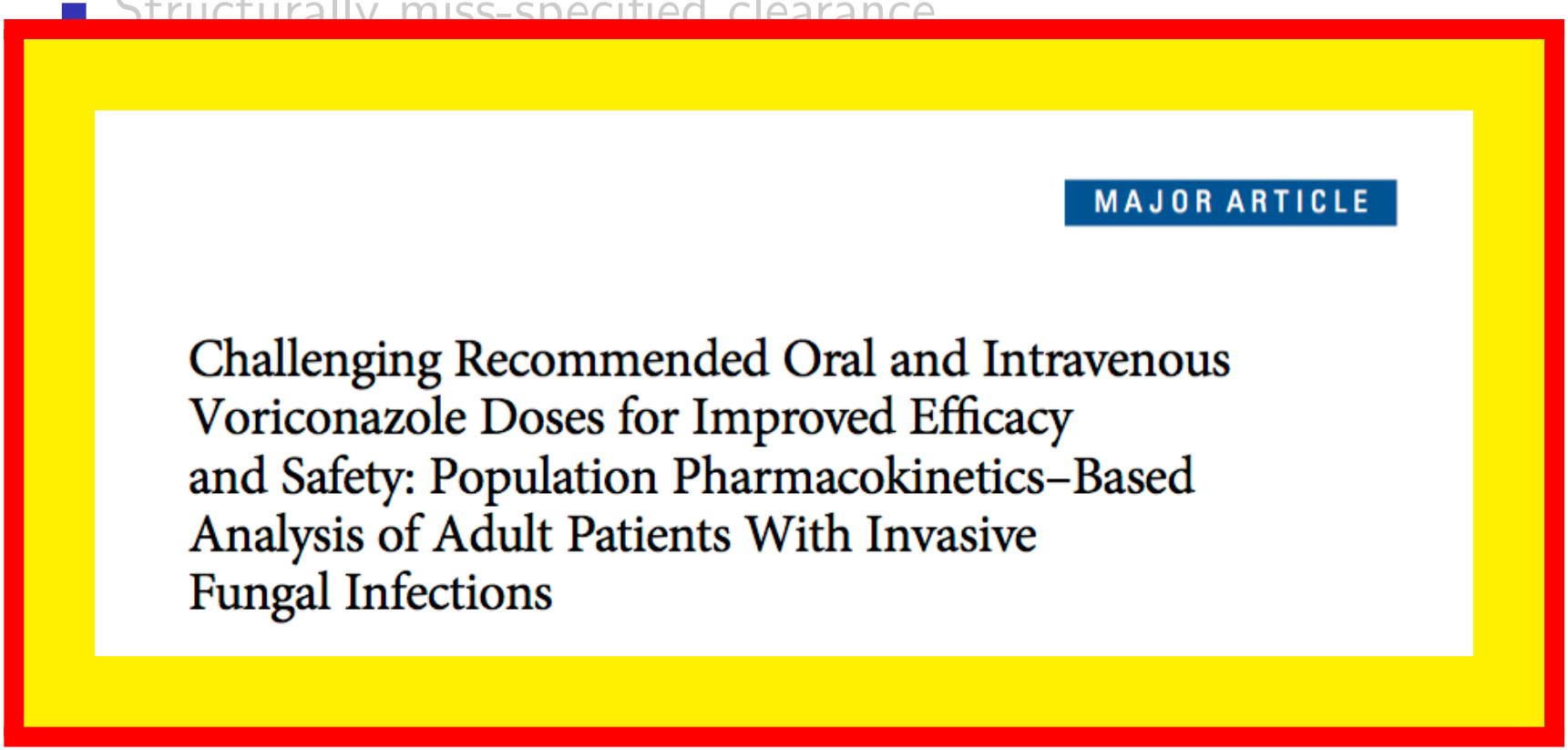
Conclusions

Conclusions: What is Important

- Structurally miss-specified clearance
  - Large, clinically relevant impact on dosage decisions and plasma concentrations achieved
  - Removing non-linear clearance from the models resulted in poor performance

Conclusions: What is Important

- Structurally miss-specified clearance



Conclusions: What is Not Important

- CYP2C19 Genotype and Other Covariates
  - An individuals genotype is often not known prior to dosing
  - The utility of knowing their genotype once plasma concentrations become available is unclear
  - Removing genotype from the model was of little clinical importance

Summary

- This research has several limitations
  - Simulation study
  - Assume the correct model
  - IV therapy only
- Accepted in AAPS Journal

Acknowledgments

MODEL ANSWERS

THE UNIVERSITY OF QUEENSLAND

AUSTRALIA