PK-SIM AND R FOR PBBM AND VBE

INTRODUCTION TO VIRTUAL BIOEQUIVALENCE WORKFLOWS

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COMPUTATIONAL TOOLS FOR VIRTUAL BIOEQUIVALENCE IN OSP

CPT: Pharmacometrics & Systems Pharmacology

TUTORIAL OPEN ACCESS

An Open-Source Framework for Virtual Bioequivalence Modeling and Clinical Trial Design

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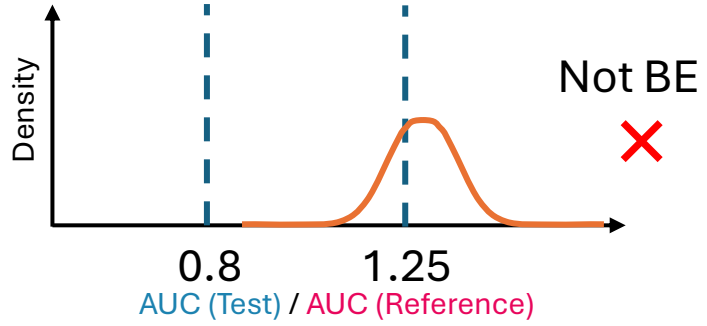
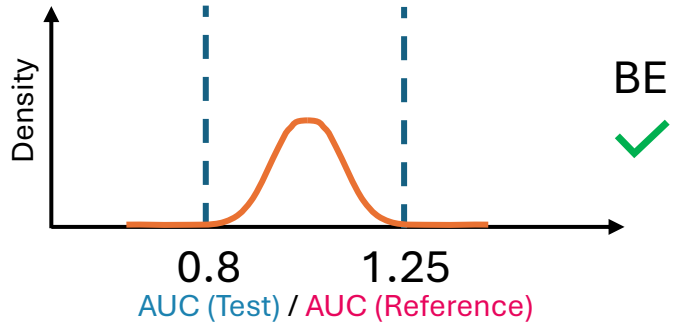
VIRTUAL BIOEQUIVALENCE AS A PATHWAY TO MARKET ENTRY FOR GENERICS

- **Drug patents & generics**
  - U.S. drug patent length ~ 20 years from filing date, much spent in development.
  - Global generics market: **> $400 billion annually** and growing.
- **Demonstration of bioequivalence can expedite approval of generics**
  - Bioequivalence (BE): test product 'similar to' previously approved reference product.
  - Standard: 90% confidence interval for AUC and Cmax ratios within 0.80–1.25.

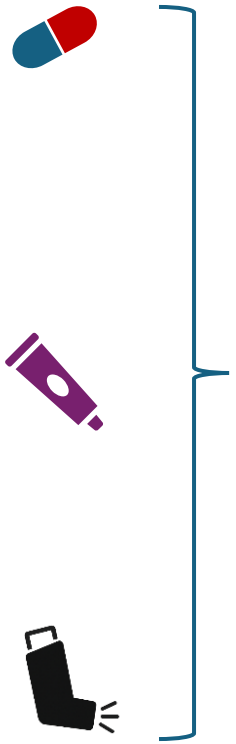




- **VBE: What and why?**
  - *Use PK models to predict probability of bioequivalence.*
  - Reduces reliance on large, costly trials.
- **Challenge: How to predict in vivo PK of the untested generic candidate to assess BE in silico**

FORMULATION ATTRIBUTES THAT IMPACT EXPOSURE

- **Oral**
  - Dissolution
- **Dermal**
  - Skin hydration effects, evaporation, release, rheology
- **Inhalation**
  - Inhaler design



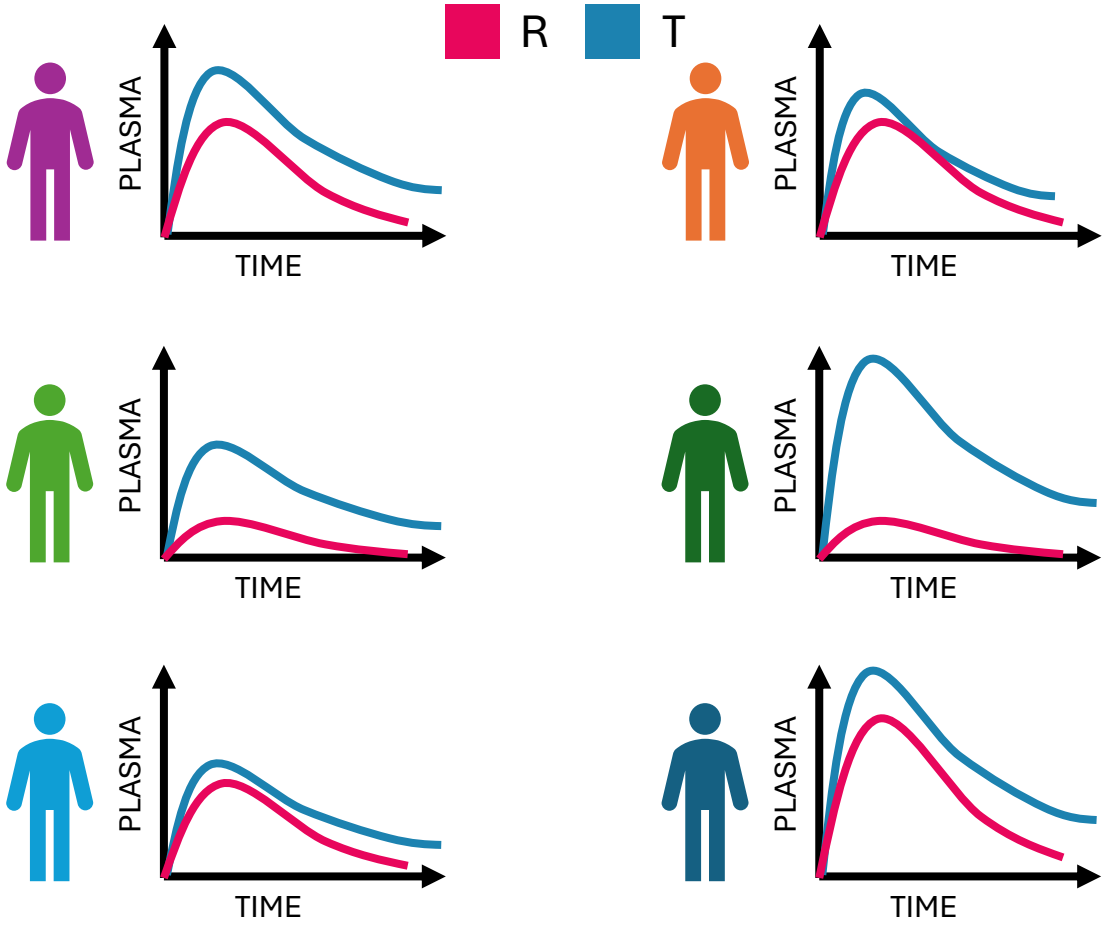
The Bioequivalence Question

Different formulations

?

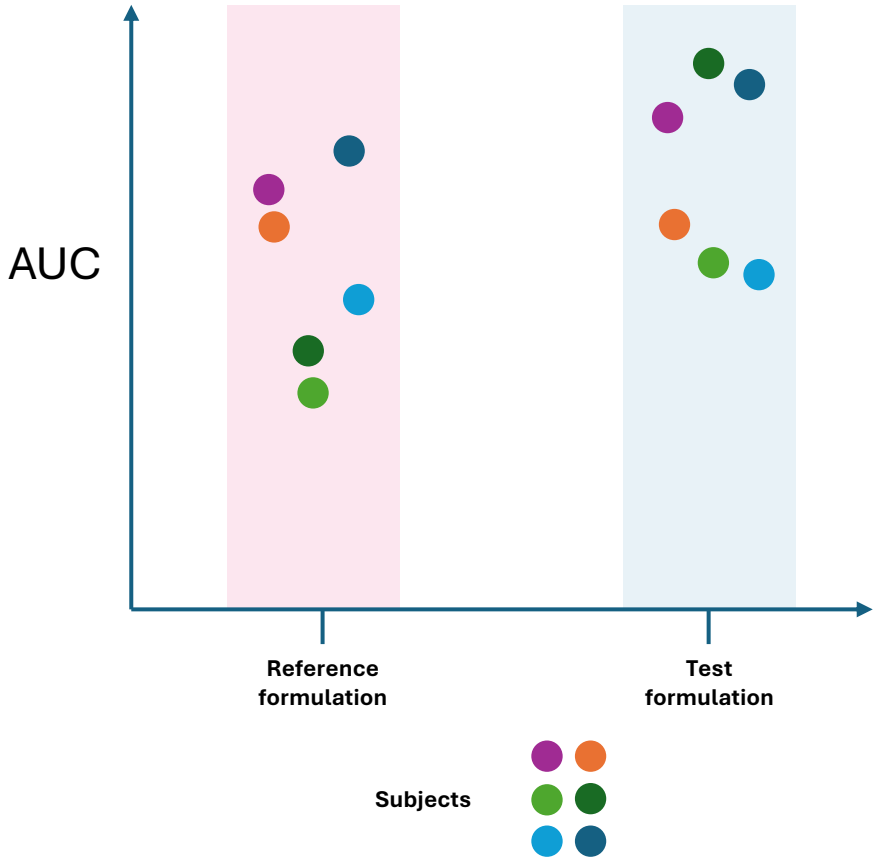
Differences in exposure?

FORMULATION EFFECTS vs BETWEEN-SUBJECT & WITHIN-SUBJECT EFFECTS



Between-subject variability (BSV)

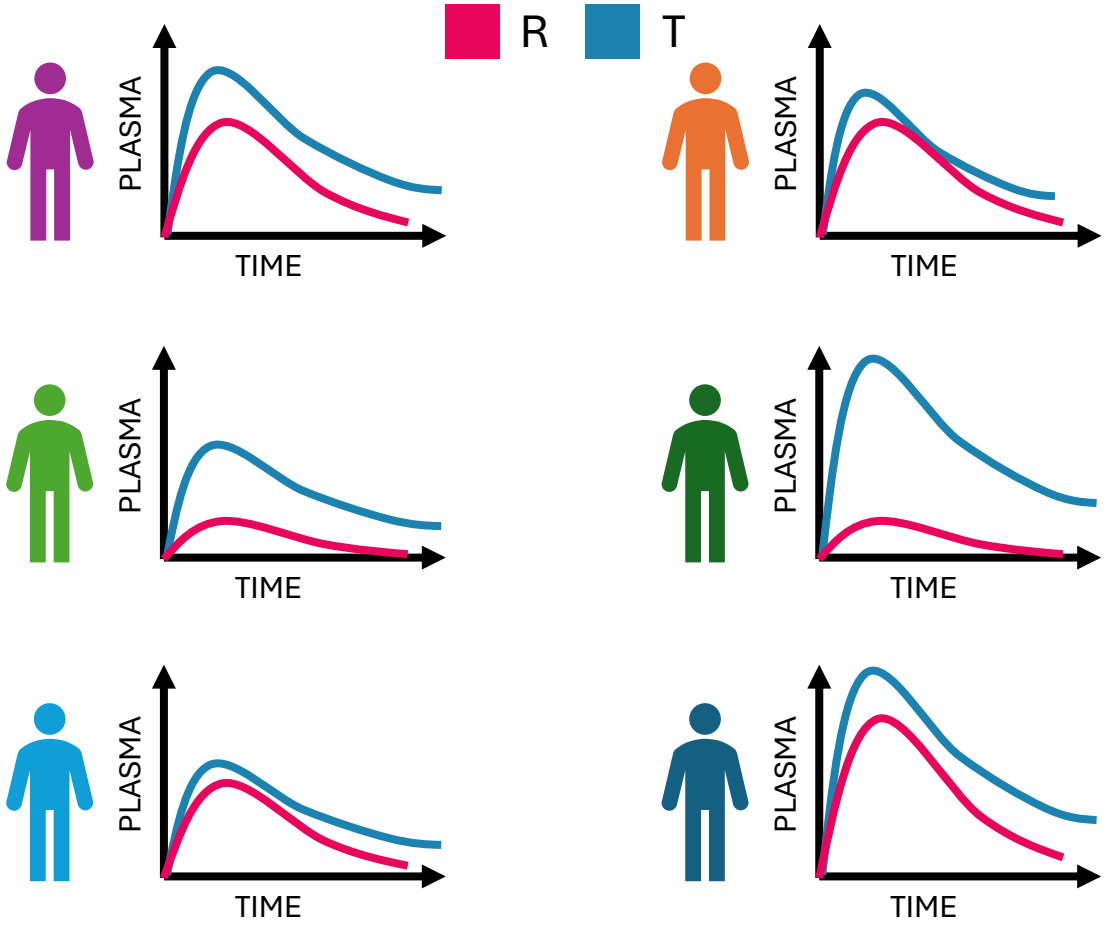
- Differences between subjects in clearance, body volume…

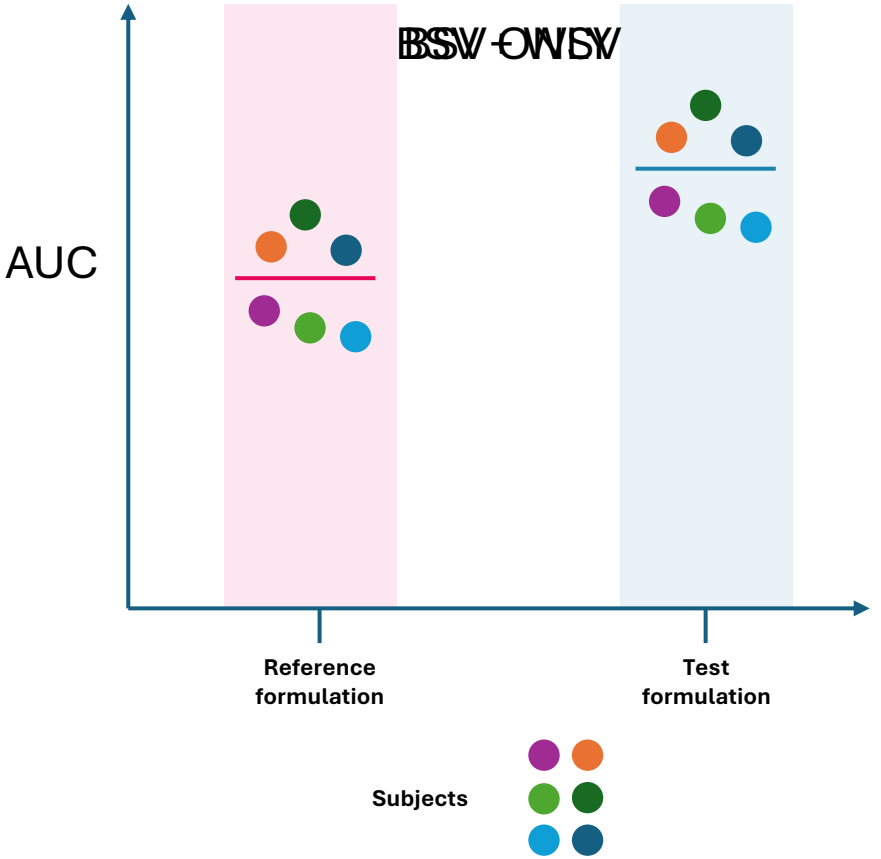


Within-subject variability (WSV)

- Changes in clearance over time, administration variability…

FORMULATION EFFECTS vs BETWEEN-SUBJECT & WITHIN-SUBJECT EFFECTS





$$AUC_{R_{ij}} = \rho e^{u_i} \rho e^{u_i} \rho \qquad AUC_{T_i} = \rho e^{\beta} \rho e^{\beta u_i} \rho$$

with $u_i \approx \mathcal{N}(0, \sigma^2_{BSV})$

and $\epsilon_{ij}, \epsilon_{ik} \sim \mathcal{N}(0, \sigma^2_{WSV})$

VIRTUAL BIOEQUIVALENCE KEY STEPS

- Use PK models to **simulate realistic clinical trial AUC, Cmax data**, including **formulation**, **BSV**, **WSV** effects – *otherwise the VBE is not valid*

- **Linear Mixed-Effect Model:** Estimate the **formulation** effect (e.g. $\frac{AUC_T}{AUC_R}$) from the simulated AUC, Cmax.

- Assess if the **formulation** effect (mean and 90% CI) lies within BE bounds:

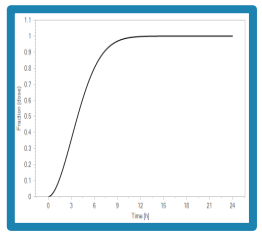
$$0.8 < \frac{AUC_T}{AUC_R} < 1.25 \qquad 0.8 < \frac{C_{max_T}}{C_{max_R}} < 1.25$$

REQUIREMENTS FOR SIMULATING CLINICAL TRIAL DATA

Models for Reference and Test

- Build mean **Reference** formulation model from subject-level clinical study data:
  - In vivo PK
  - Clinical study demographics
- Introduce subject-specific IVIVE model parameters θ to scale in vitro quantities to in vivo
- Build **Test** model using in vitro data and IVIVE.

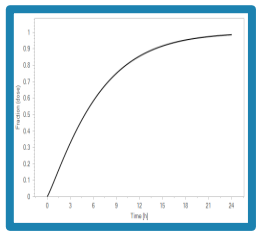
Test in vitro dissolution



IVIVE

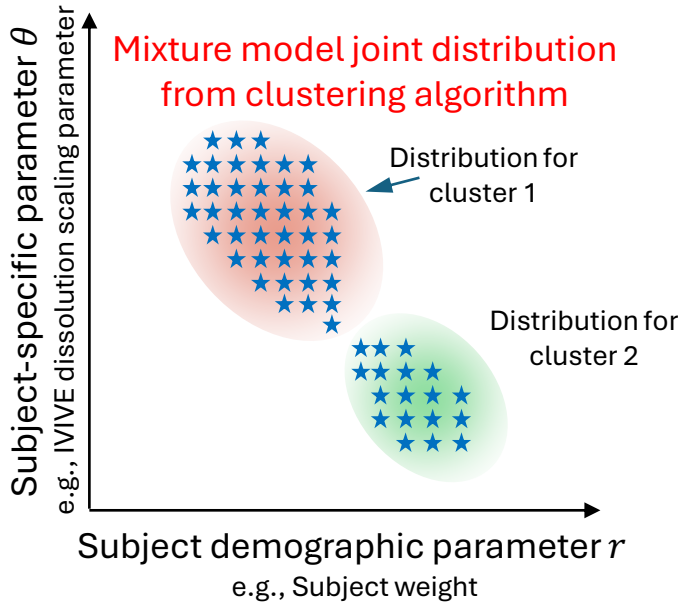
θ

Test in vivo dissolution



Between-Subject Variability

- Learn parameters with BSV and IVIVE scaling parameters θ from **Reference** formulation model clinical study data
- Nonparametric methods capture correlations between BSV parameters and demographic data



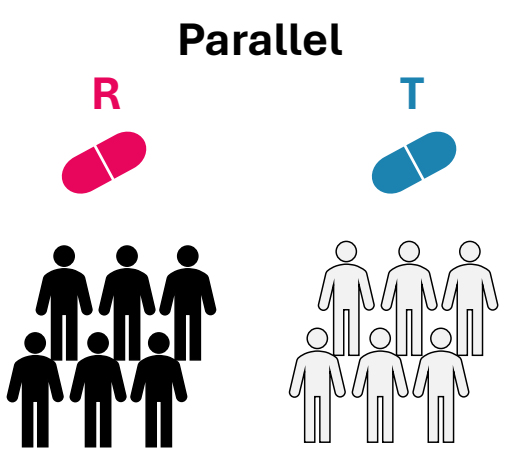
Within-Subject Variability

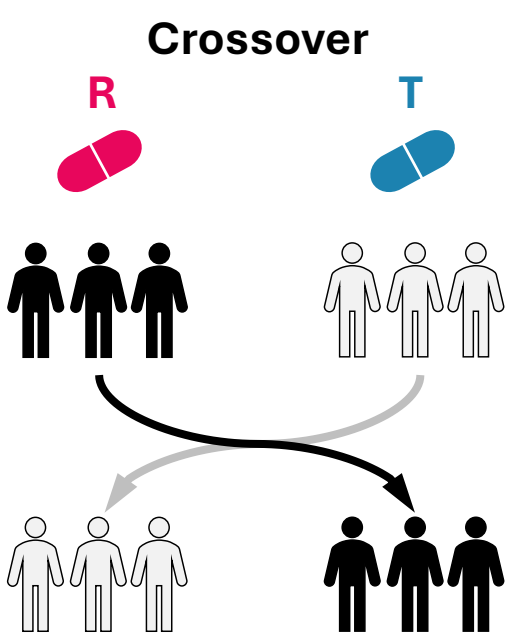
- Supply SD or CV in parameters liable to vary between administrations

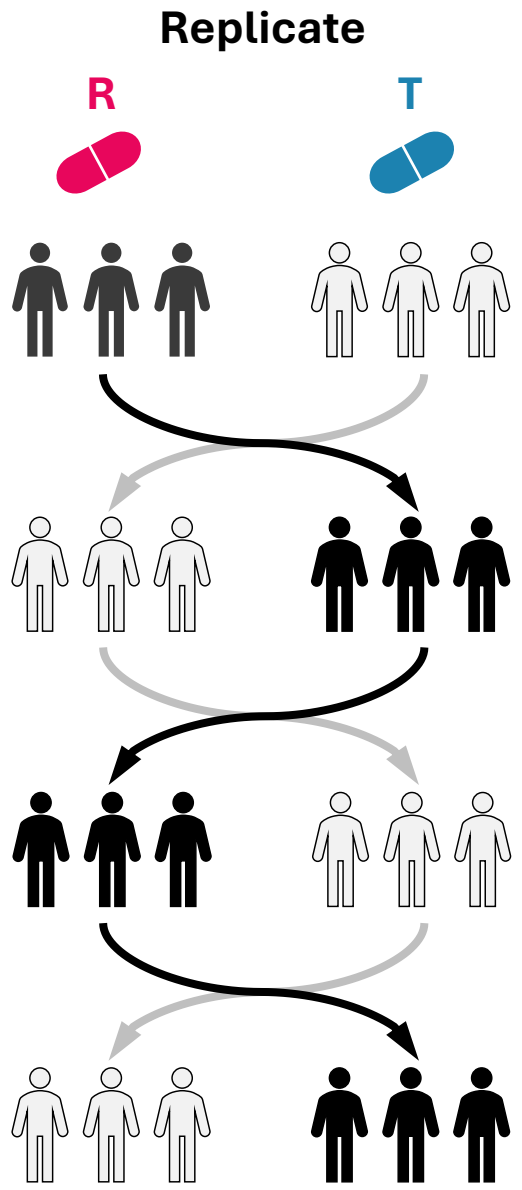
OR:

- Apply post-hoc perturbation to AUC and Cmax after simulation, based on experimental data or literature.
- Suggested CV (meta-analysis in Chung et al., 2018)
  - AUC ICV: 14.2%
  - Cmax ICV: 21.7%

FINAL STEP: CLINICAL TRIAL SIMULATION AND VBE ASSESSMENT





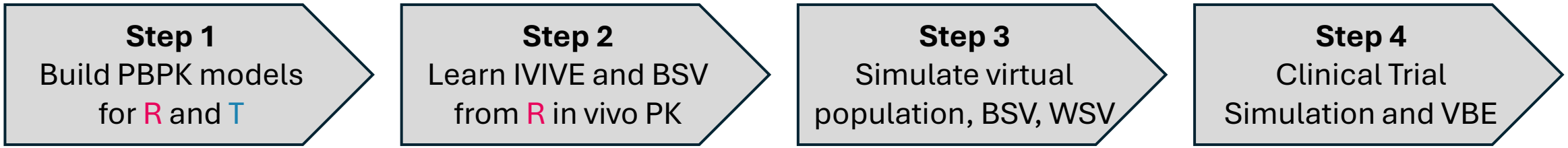


- **Simulate virtual population for Reference and Test including BSV, WSV**
- **AUC and Cmax values per virtual subject, per formulation, per replicate**
- **User input parameters:**
  - Minimum sample size (e.g. n=6, shown here)
  - Maximum sample size (e.g. n=36)
  - Sample size increment (e.g. 10)
  - **Number of trials per sample size**
  - **Number of crossover trial replicates**

Trials run for n=6,16,26,36

- Estimate formulation effect and check BE (eg. $0.8 < \frac{AUC_T}{AUC_R} < 1.25$?) for each trial size

OVERALL VBE WORKFLOW



VBE OF BUPROPION ORAL TABLETS: SUSTAINED VS. EXTENDED RELEASE

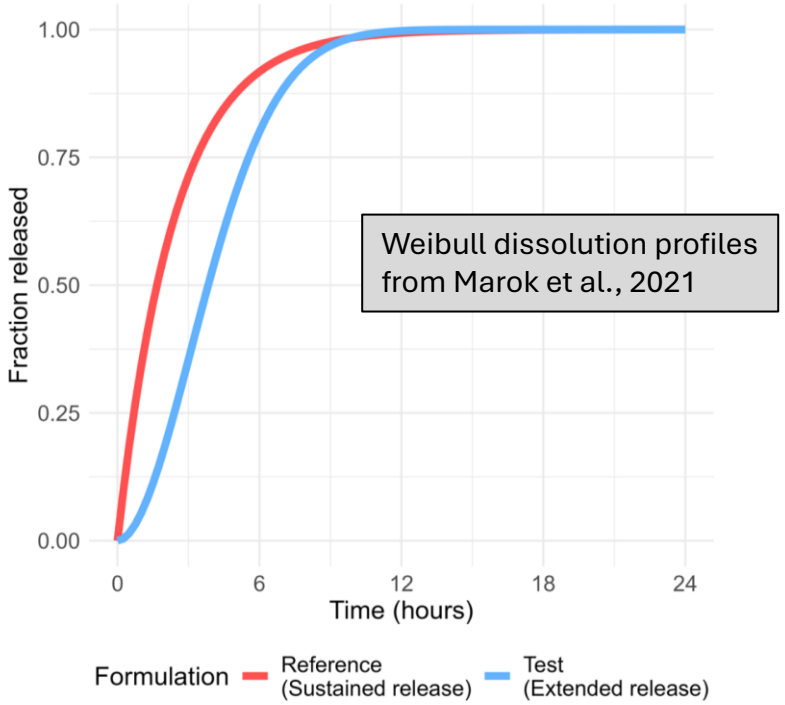
- **Bupropion**
- Antidepressant indicated for treatment of major depressive disorder
- BCS Class I, high solubility, high permeability, rapidly absorbed in gut

- **VBE assessment of two 150 mg bupropion tablet products:**
  - Reference: Sustained Release (SR)
  - Test: Extended Release (ER)

- **Are they bioequivalent in AUC and Cmax?**
  - Under what clinical trial design?
  - How many subjects per trial arm?

- **AUC:** a function of dose, bioavailability, and clearance, **only**!
- **Cmax:** depends on rate of release

R and T dissolution profiles



TUTORIAL OPEN ACCESS

An Open-Source Framework for Virtual Bioequivalence Modeling and Clinical Trial Design

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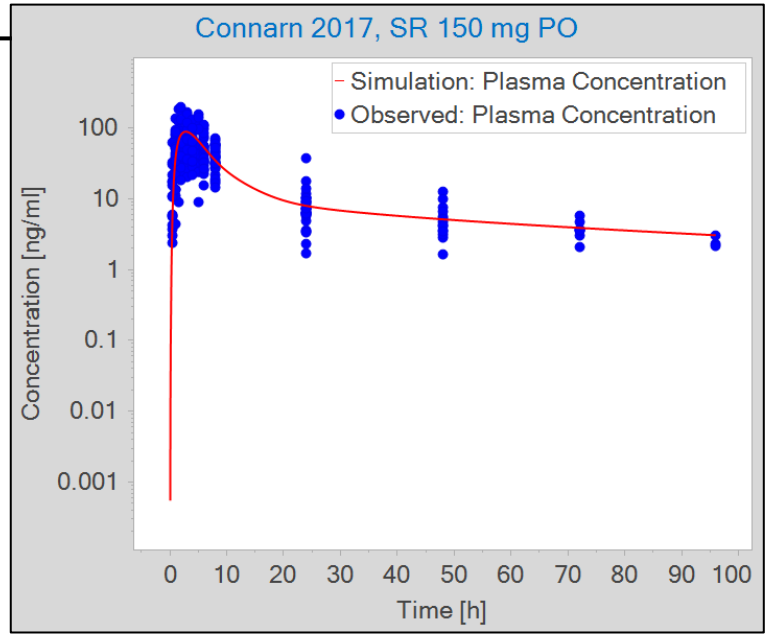
BUPROPION PBPK MODEL DEVELOPMENT STEPS

- In vivo data used to develop model for Sustained Release (reference) tablet.
- ***In a VBE study, there is typically no PK data for the test product.***
- ***Model development was blinded to Extended Release in vivo PK data.***
- The Extended Release model is built by:
  1. Updating the dissolution profile from Sustained Release to Extended Release
  2. Introduce IVIVE scalings θ_1, θ_2 of Weibull dissolution parameters

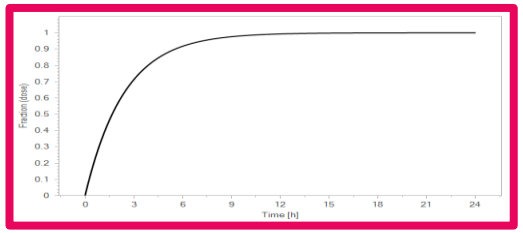
$$F(t, \theta_1, \theta_2) = 1 - \exp\left(-\alpha \cdot t^{\theta_2 \cdot \beta}\right), \qquad \alpha = \frac{\ln 2}{(\theta_1 \cdot t_{50})^{\theta_2 \cdot \beta}}$$

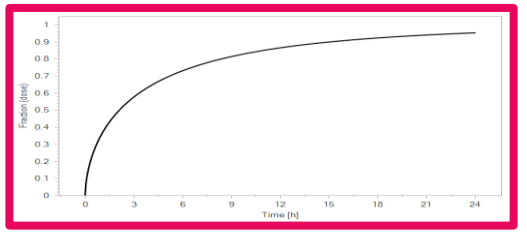


In vitro dissolution

In vivo dissolution

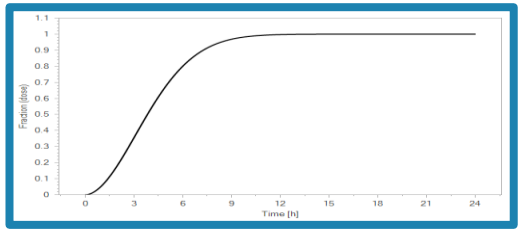
Reference: Sustained Release

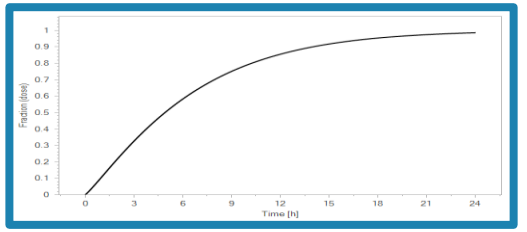




$$\theta_1 \times t_{50}$$
$$\theta_2 \times \beta$$

Test: Extended Release

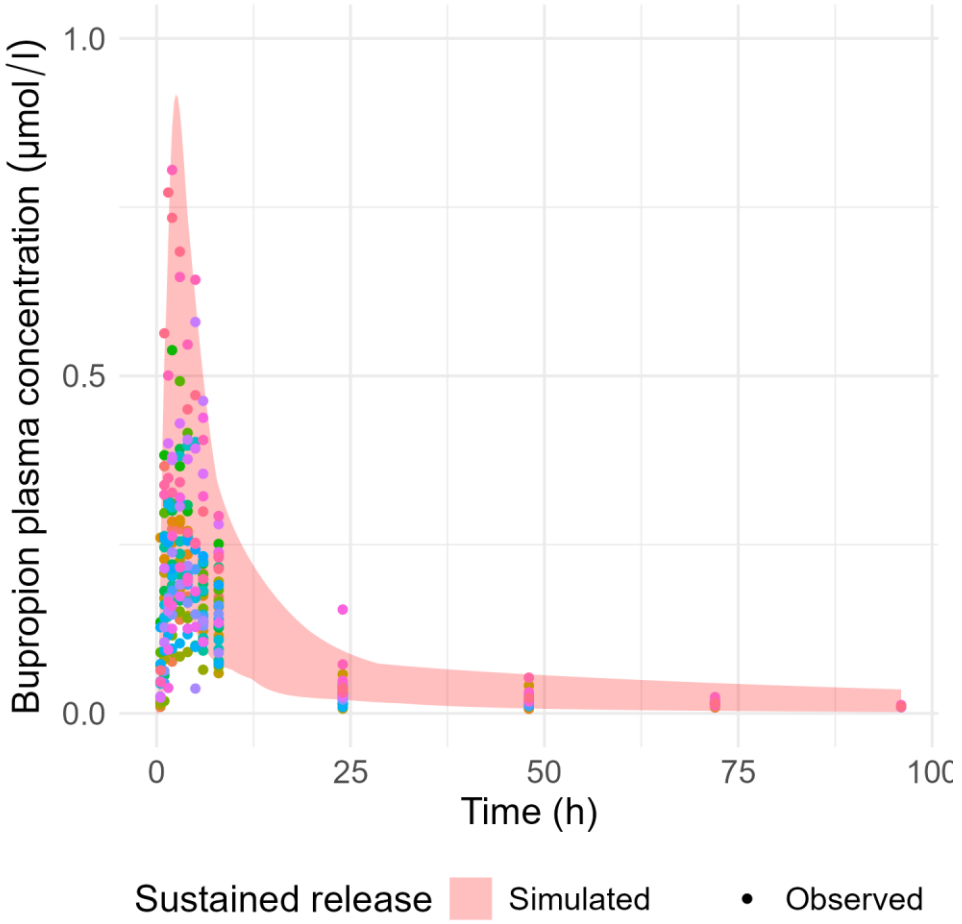




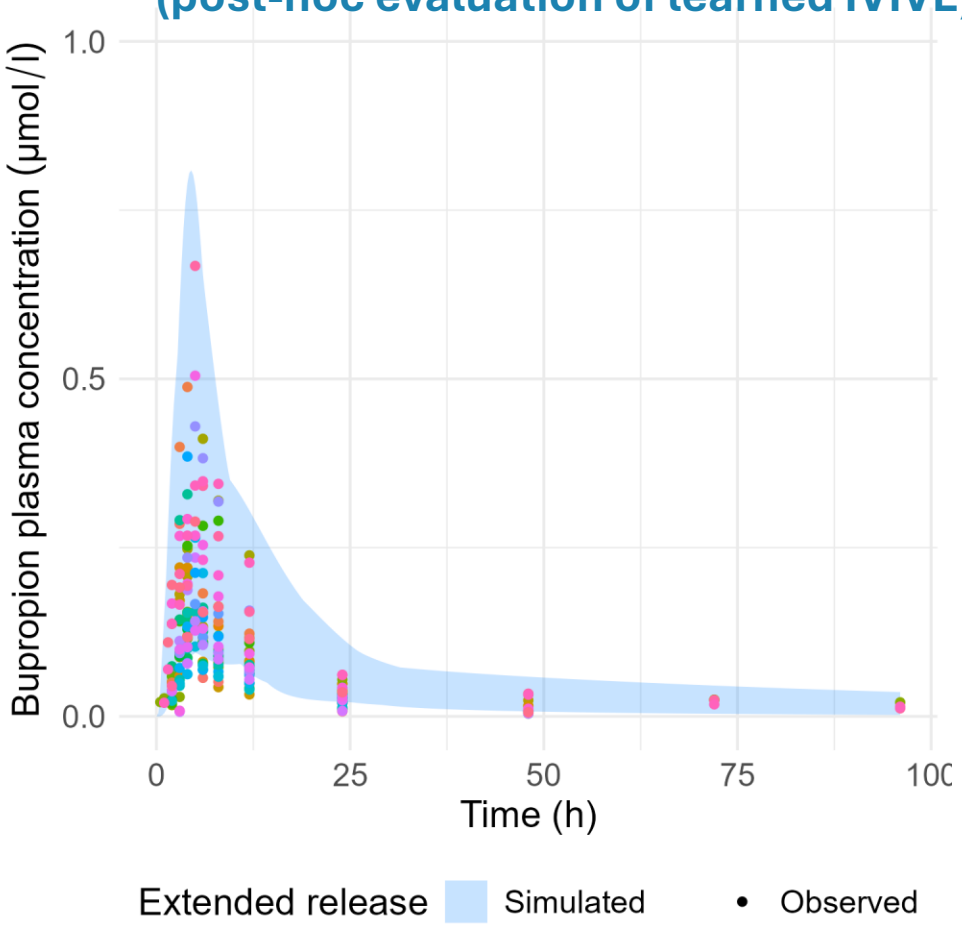
BUPROPION PBPK MODEL VALIDATION

- Nonparametric learning algorithm used to learn parameters with BSV: θ_1, θ_2, and liver clearance scaling
- Virtual population generated from learned distribution and simulated

Sustained Release



Extended Release
(post-hoc evaluation of learned IVIVE)



VBE ASSESSMENT RESULTS

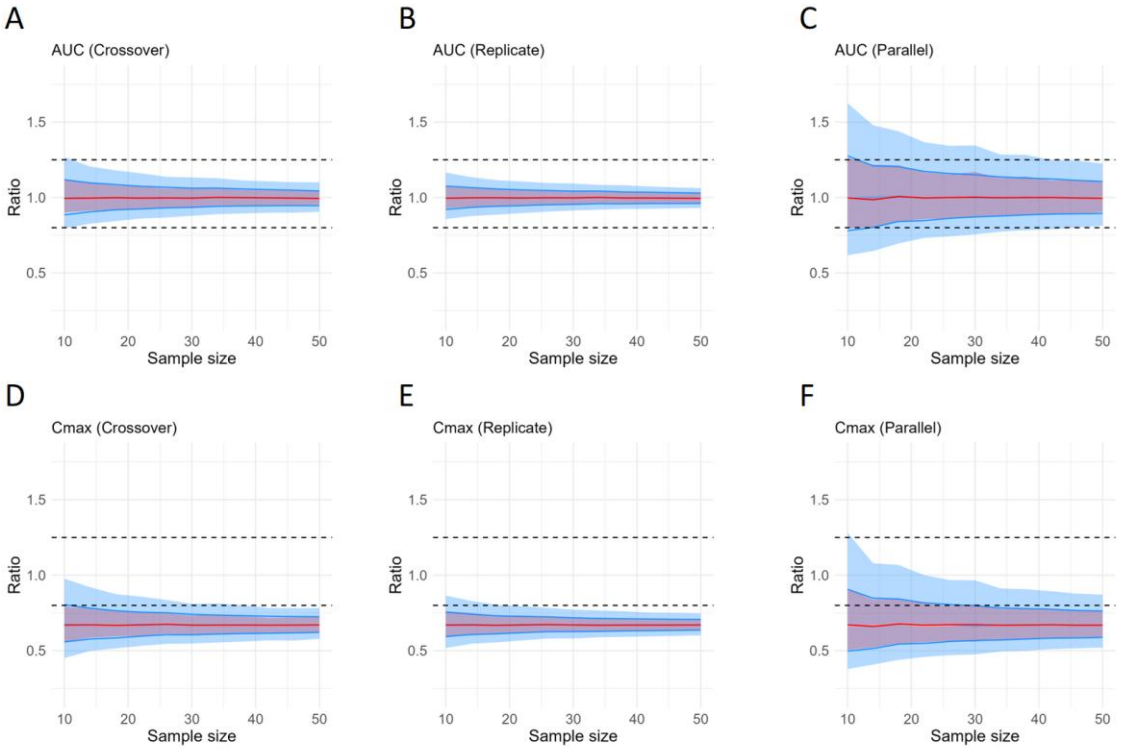
Results

- **BE in AUC under cross-over or replicate studies**
  - Almost complete absorption (F = 1) for SR and ER
  - Each subject has their own clearance *CL*
  - AUC = F × Dose / CL
  - i.e. AUC identical for SR and ER in each subject
  - $0.8 < \frac{AUC_T}{AUC_R} \approx 1 < 1.25$

- **No BE in Cmax!**
  - Cmax dependent on rate of absorption
  - SR → faster absorption → higher Cmax for SR
  - $\frac{Cmax_T}{Cmax_R} < 0.8$

- **Note:** Replicate trial design yields lower uncertainty in AUC and Cmax ratios (better quantification of WSV through repeated administration of each product to the subject)

Confidence intervals of e^{β} vs. trial size

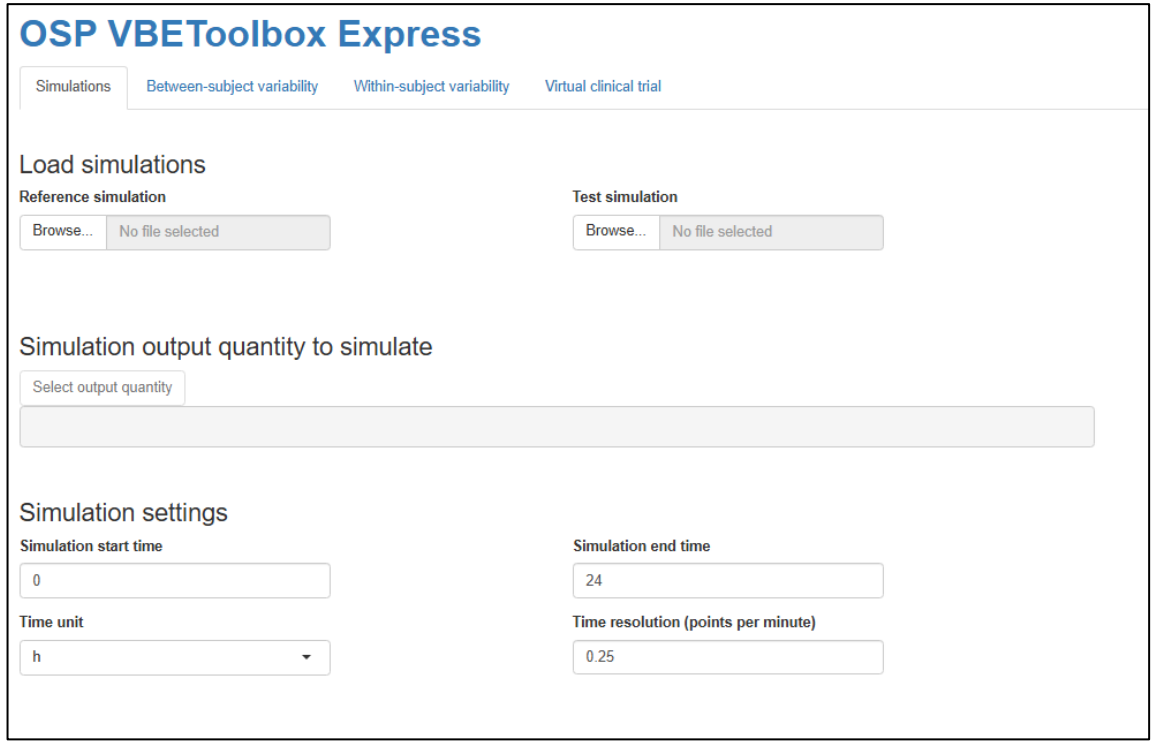


OSP VBEToolbox

https://github.com/Open-Systems-Pharmacology/OSPSuite.VBE-Toolbox

- An OSP Suite R package for conducting VBE analyses

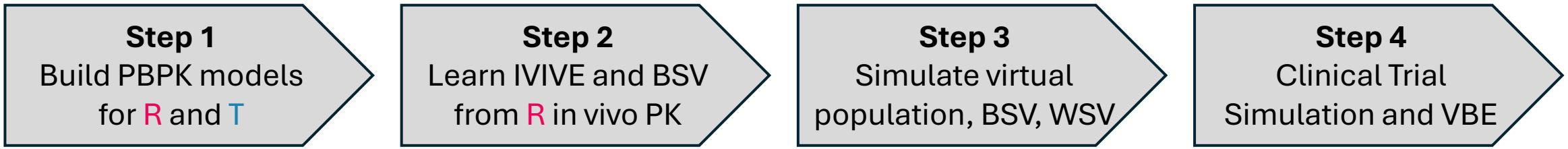
- Includes Shiny app (GUI) that automates:
  - Loading reference/test simulations
  - Adding variability (BSV and WSV)
  - Running virtual clinical trials
  - Producing plots + data summaries



Command for installing VBEToolbox:
pak::pak("Open-Systems-Pharmacology/OSPSuite.VBE-Toolbox")

# Command for launching the shiny app:
library(ospsuite.VBEToolbox)
runQuickVBE()

CONCLUSIONS



Tutorial paper presents computational tools for running a complete VBE workflow

Key VBE challenges:

1. Predicting exposure for the test formulation in absence of in vivo PK for model validation
2. Capturing BSV and WSV to simulate realistic clinical trials and assess formulation effect reliably for VBE

Workflow addresses these challenges through:

- Tools for learning IVIVE and BSV
- Tools for simulating WSV based on literature or knowledge of WSV in specific model parameters
- Tools for simulating clinical trials and evaluating VBE statistics

- Case studies presented for bupropion oral formulations and testosterone dermal formulations in paper.

VIRTUAL BIOEQUIVALENCE WORKFLOW

- Build, train, and validate PBPK models for R and T formulations.

- Build a virtual population, including BSV, representative of the target population.

1. Simulate a clinical trial:
   - Models for R and T formulations are simulated for N subjects sampled from the virtual population (**includes BSV!**).
   - Add within-subject variability (WSV)

2. Estimate formulation effect β from the simulated AUC and Cmax:

$x = 0$ for R
$x = 1$ for T

$$\log AUC_{ik} = \log \rho + \beta \cdot x + u_i + \epsilon_{ik}$$

3. This is a linear model of $\log AUC_{ik}$ vs x, and we estimate the 'slope' β from simulations of AUC for N subjects receiving R and/or T

4. If the estimate of e^{β} has 90% CI within 0.8 – 1.25, conclude BE, otherwise not BE

- Steps 1 - 4 repeated for M for trials, sampling N subjects each time.

- Probability of BE for a trial size N: Number of successful BE trials / M