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Pharmacometric Approach To Define Narrow Therapeutic Index (NTI) Drugs & Evaluate Bioequivalence (BE) Criteria for NTI Drugs

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With input from US FDA

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Recommendations

1. Therapeutic index ≤ 3 is a reasonable cutoff to define NTI drugs.

2. Therapeutic index and small increments of dose adjustment are adequate for NTI classification.

3. To achieve a passing rate of 80% in a BE trial, the maximum observed $WSV_{test}/WSV_{reference}$ is 1.4

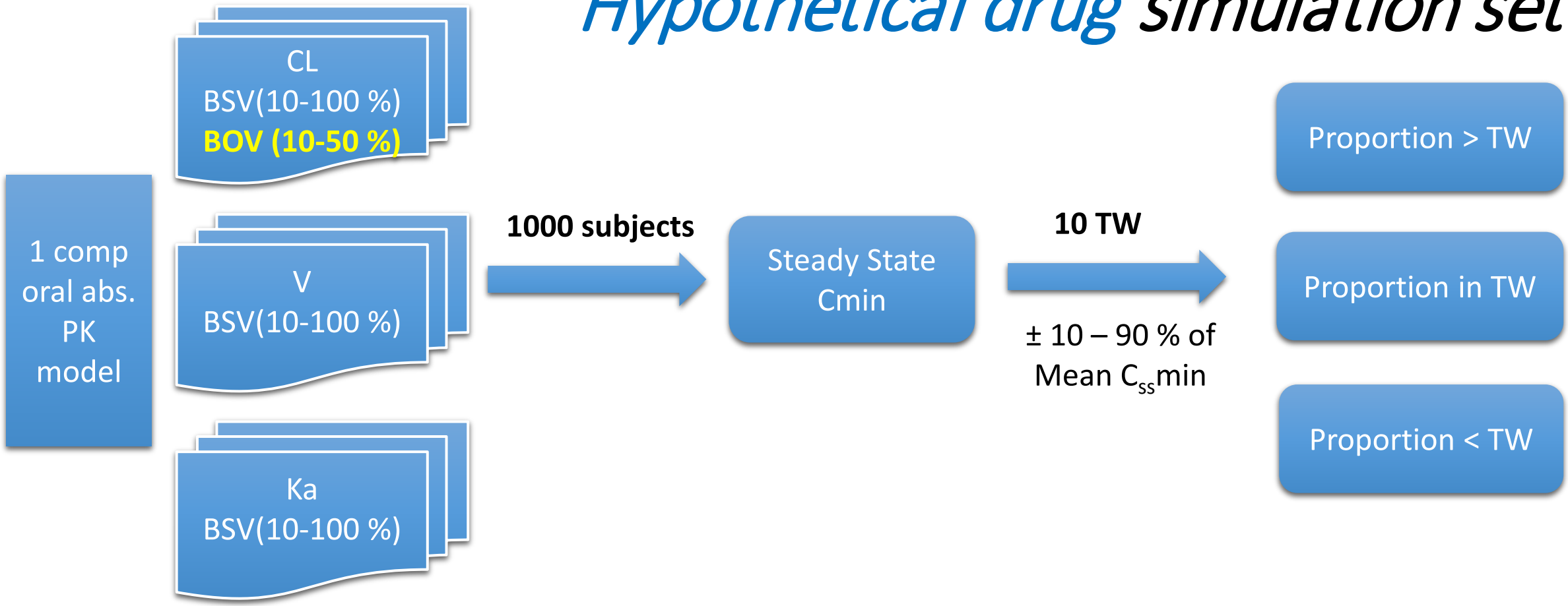
Recommendation 1:

Therapeutic index ≤ 3

10 out 13 NTI drugs have a TI ≤ 3 and 3 have a TI between 3-5

Simulation setup

Hypothetical drug simulation setup



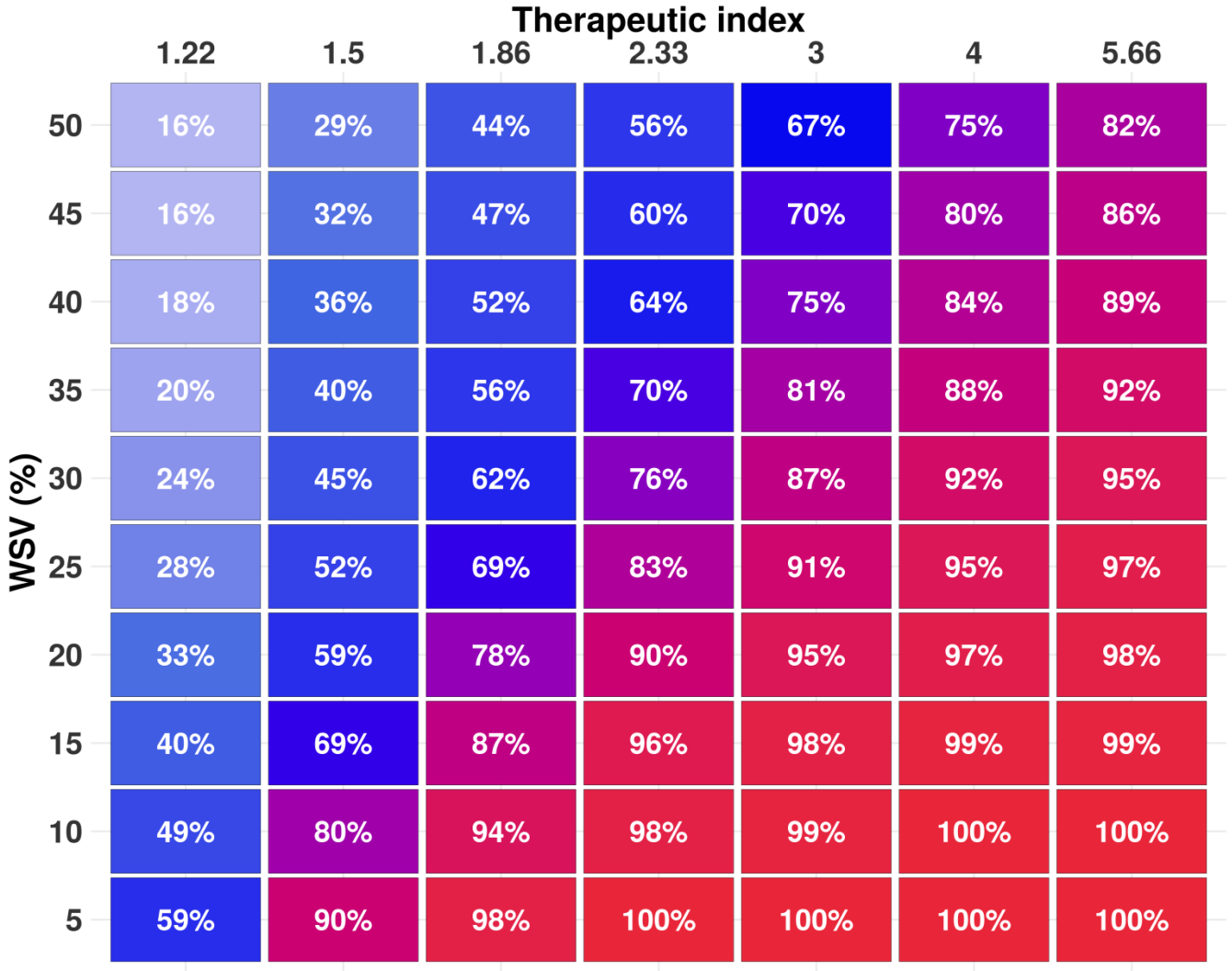
Ka – Absorption rate constant
Cl – Clearance
V – Volume of distribution
BSV – Between Subject Variability
BOV – Between Occasion Variability
WSV – Within Subject Variability
TW – Therapeutic Window

*10 BSV * 10 BOV * 10 TW = 1000 unique scenario*

1000 subjects per scenario

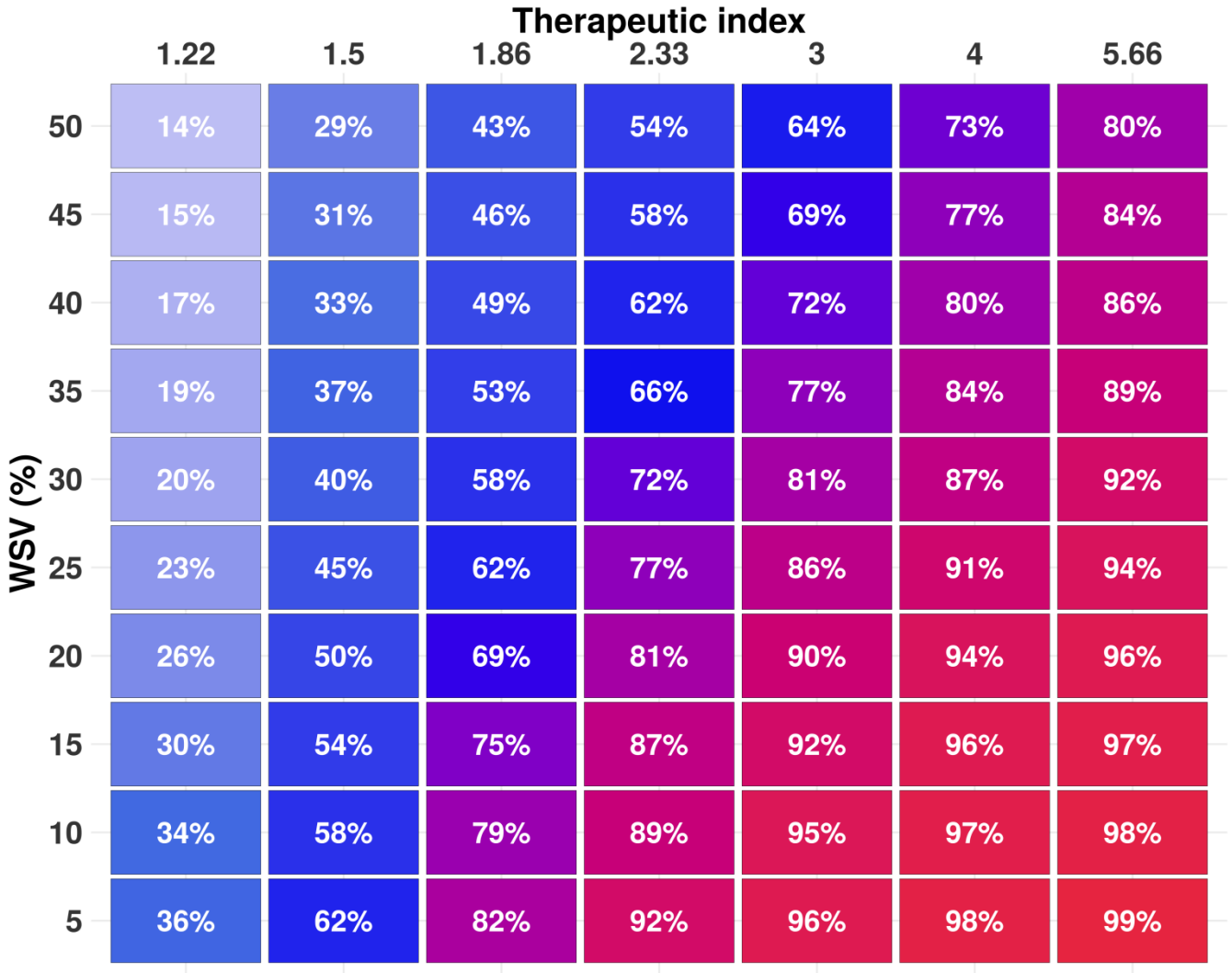
Total number of simulations – 1,000,000

Proportion of subjects within target is a function of Therapeutic index and WSV



- For a *BSV of 10%*
- E.g. At
  - *TI ≤ 3*
  - *WSV ≤ 35%*
  - *80 % responders within target*

Proportion of subjects within target is a function of Therapeutic index and WSV



- **For a *BSV of 20%***
- **E.g. At**
  - ***TI ≤ 3***
  - ***WSV ≤ 30%***
  - ***80 % responders within target***

Recommendation 2:

Therapeutic index and small increments of dose adjustment are adequate for NTI classification.

Current NTI classification criteria

- The 5 following criteria were evaluated for drugs from 4 therapeutic areas:

1. maximum of 2 fold difference between minimum effective and minimum toxic dose or maximum recommended therapeutic dose.
2. maximum of 2 fold difference between the lowest and the highest drug concentration from the recommended or observed therapeutic index.
3. Routine therapeutic monitoring.
4. Low-to-moderate within subject variability (≤ 30%).
5. doses often adjusted in small increments (<20%).

Green : drugs known as non NTIs
Red : known NTI drugs,
Blue : drugs thought to be NTI but not listed by most agencies as NTIs

ANTICOAGULANTS

- **Argatroban**
- Apixaban
- Dabigatran
- Edoxaban
- Rivaroxaban
- **Warfarin**

ANTIARRHYTHMICS

- *Amiodarone*
- **Digoxin**
- *Flecainide*
- **Quinidine**
- *Sotalol*

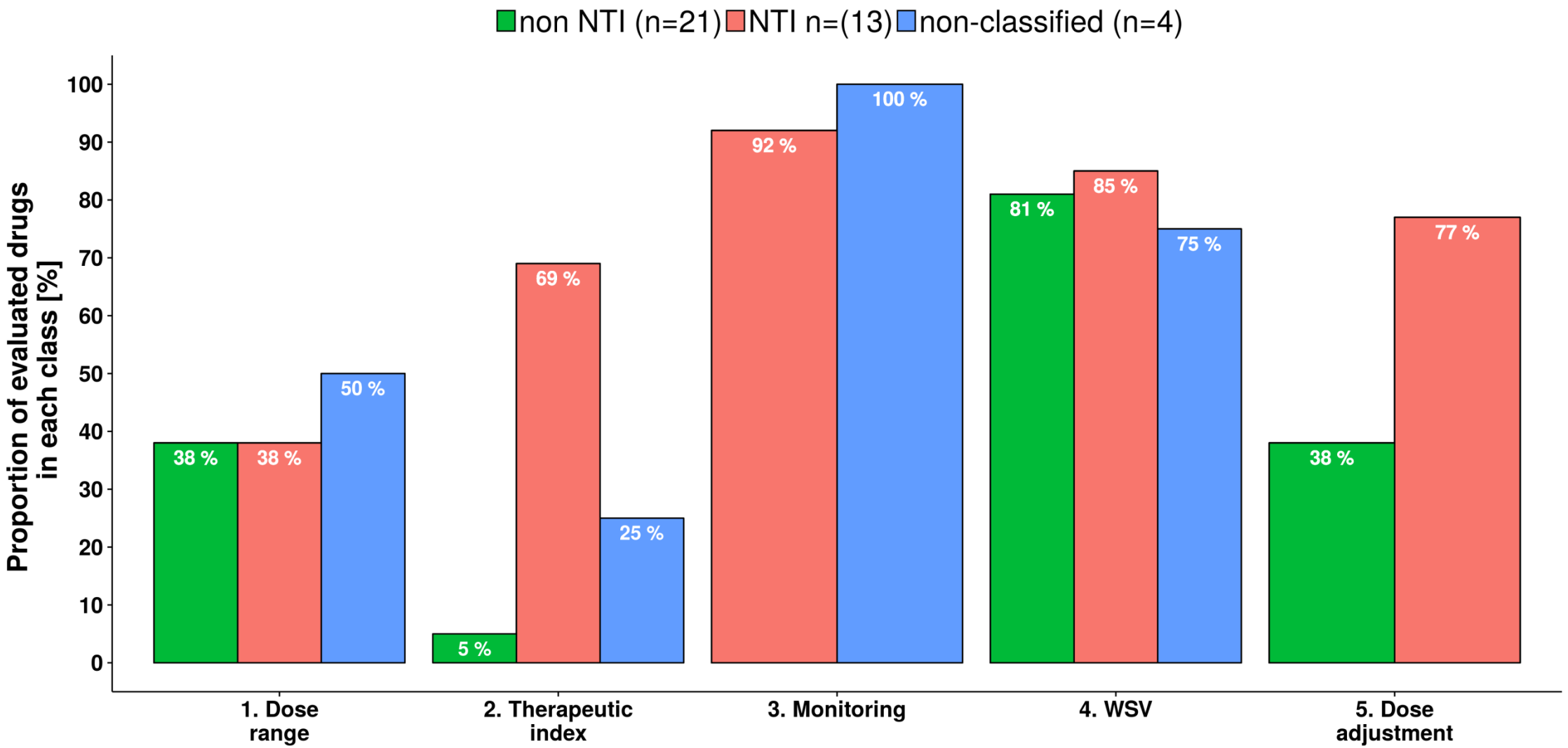
ANTIEPILEPTICS

- **Carbamazepine**
- Clonazepam
- Clobazam
- Ethosuximide
- Ezogabine
- Felbamate
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Perampanel
- Pregabalin
- **Phenobarbital**
- **Phenytoin**
- Rufinamide
- Tiagabine
- Topiramate
- **Valproate**
- Vigabatrin
- Zonisamide

IMMUNOSUPPRESSANTS

- **Cyclosporine**
- **Everolimus**
- *Mycophenolate*
- **Sirolimus**
- **Tacrolimus**

NTI Criteria 2, 5 are adequate differentiators univariately
54 % of NTI's meet both criteria 2 and 5



Recommendation 3:

Limits for WSV_{Test} / $WSV_{Reference}$ for NTI BE evaluation

Simulation of a bioequivalence trial for a *hypothetical test and reference drug*

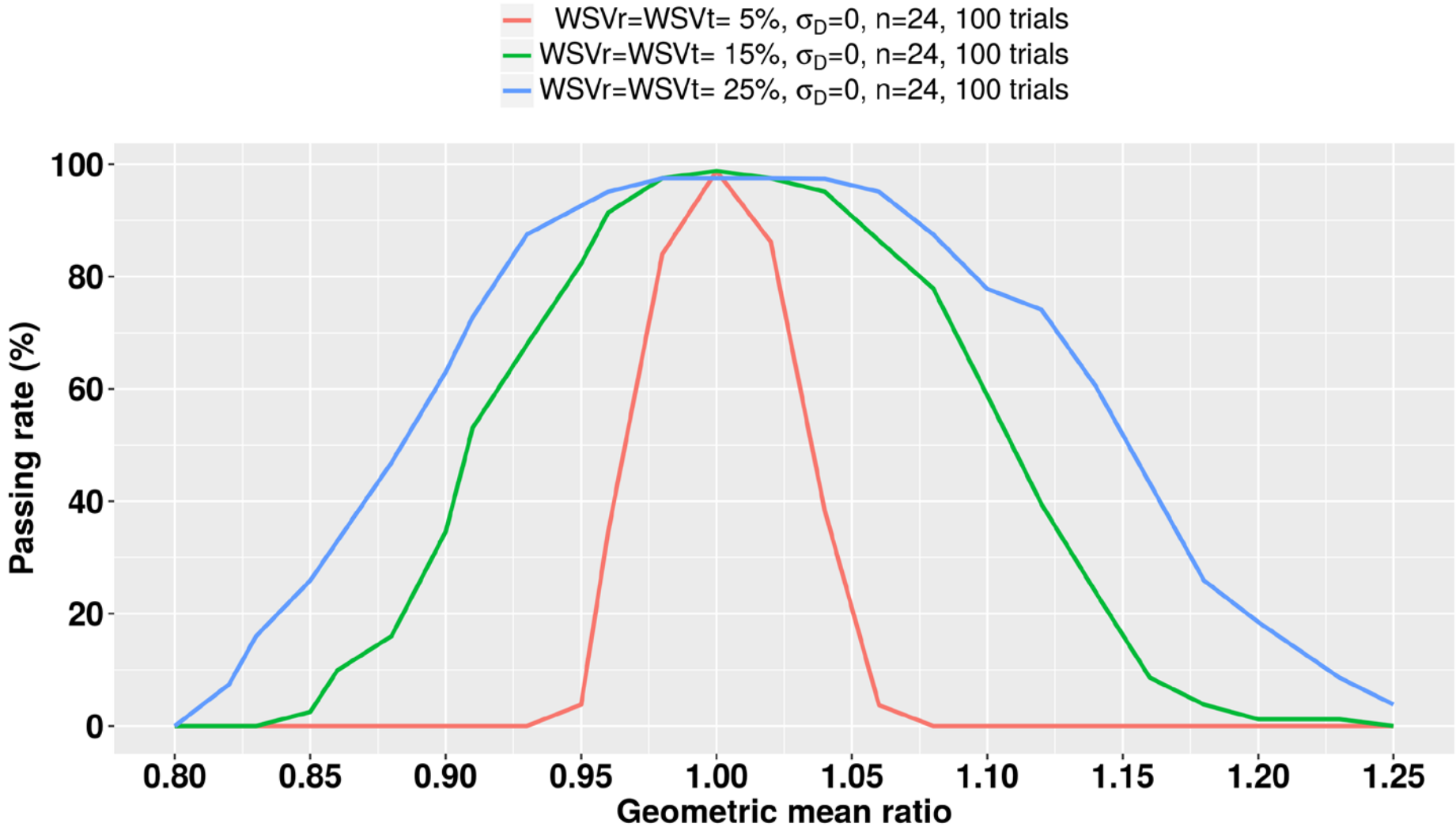
- Hypothetical drug pharmacokinetic parameters:
  - *CL = 10 L/h, V = 500 L, ka = 1 h^{-1} , F = 100 %.*
  - *Half-life = 34 h , Tmax = 4 h.*
- Difference in F between Reference and test drug:
  - *Ftr ratio = **F test / F drug = GMR** = ranges from 80 % to 125 %.*
- WSVr (reference drug) and WSVt (test drug) ranges each form:
  - ***5 to 40 (% CV).***
- Rich PK simulation (0 to 120h) for:
  - *24 subjects per unique scenario* of WSVr, WSVt and GMR permutation.*

**** 57,000 scenarios evaluated***

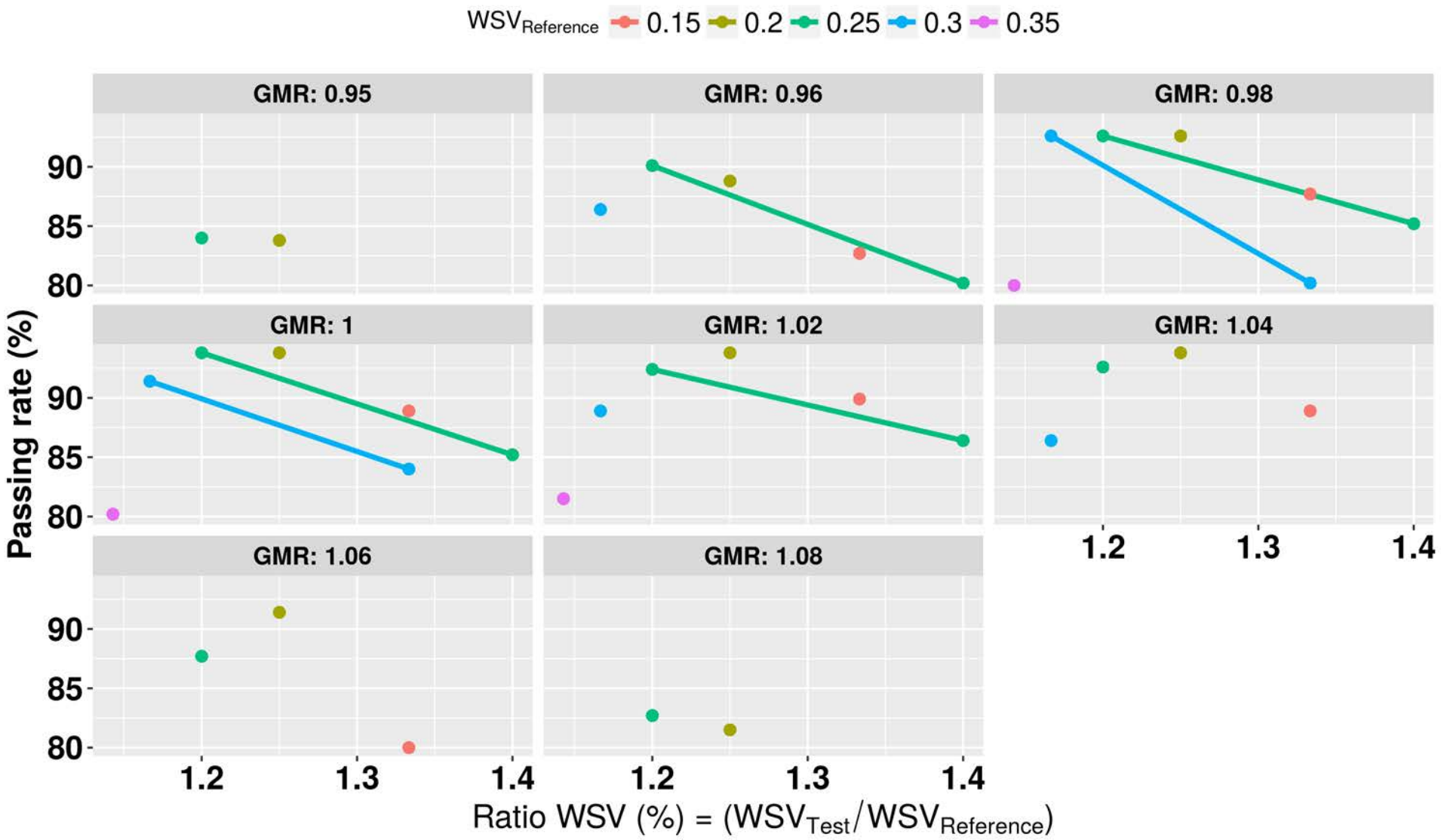
Simulate a *bioequivalence trial* for a hypothetical test and reference drug

- *4* periods*, 2* sequence bioequivalence trial: *TRTR and RTRT.*
- 100 trials per WSVr, WSVt and GMR permutation scenario.
- $AUC_{0\text{-inf}}$, $AUC_{0\text{-tlast}}$ and C_{max} were calculated.
- Bioequivalence test: Test and reference drugs are equivalent if the following three conditions passed:
  - ***RSABE***
  - ***Upper limit of the 90% CI*** *of* ***WSVt / WSVr*** *ratio* ***≤ 2.5***
  - ***ABE***
- **Validate the BE trials simulations:** BE passing rate (%) versus GMR.

Simulation validation – our setup replicates the FDA results



Scenarios where $WSV_{Test} > WSV_{Reference}$: Maximum difference for 80% BE passing rate (*RSABE + ABE + WSV comparison*):



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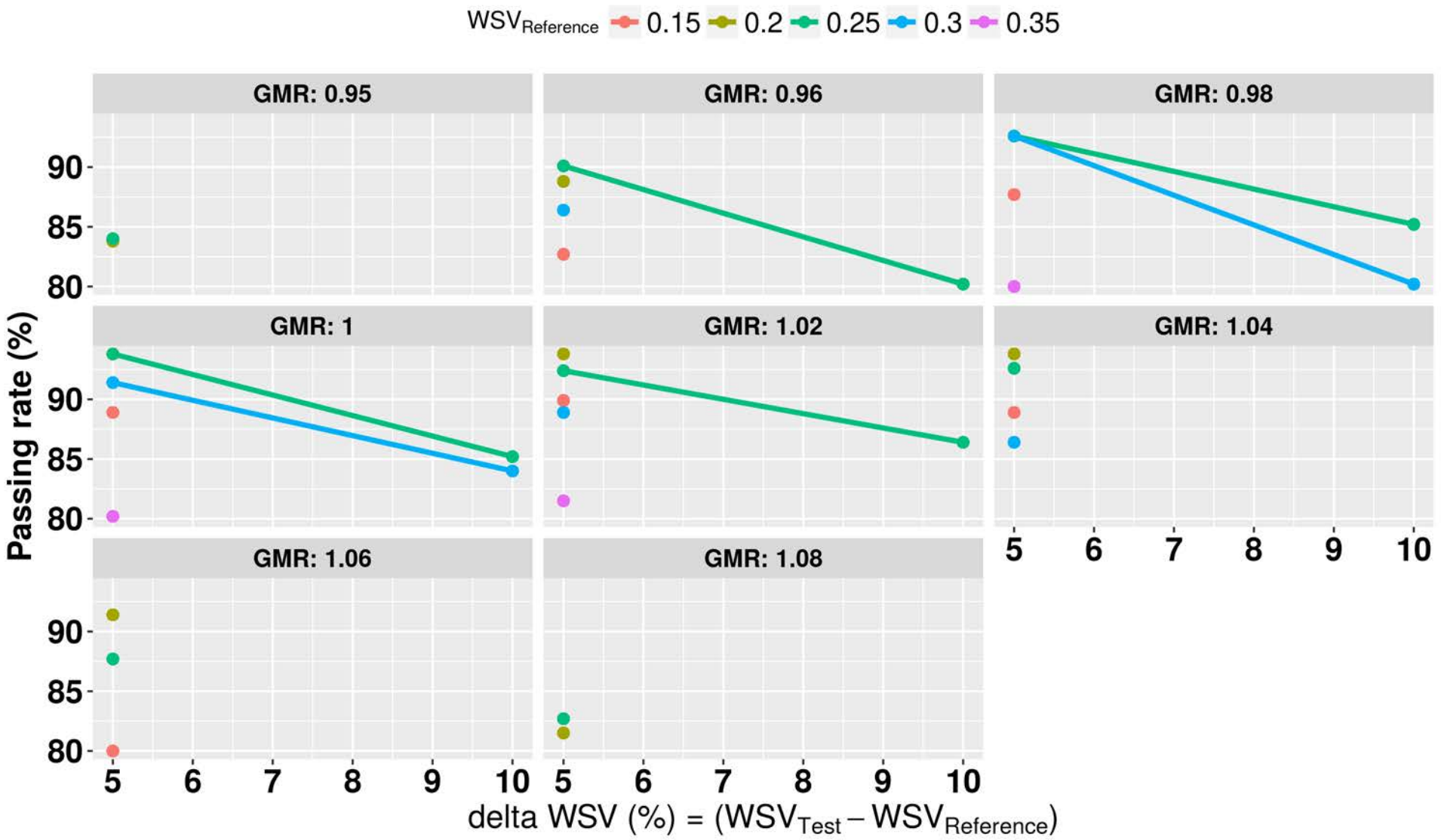
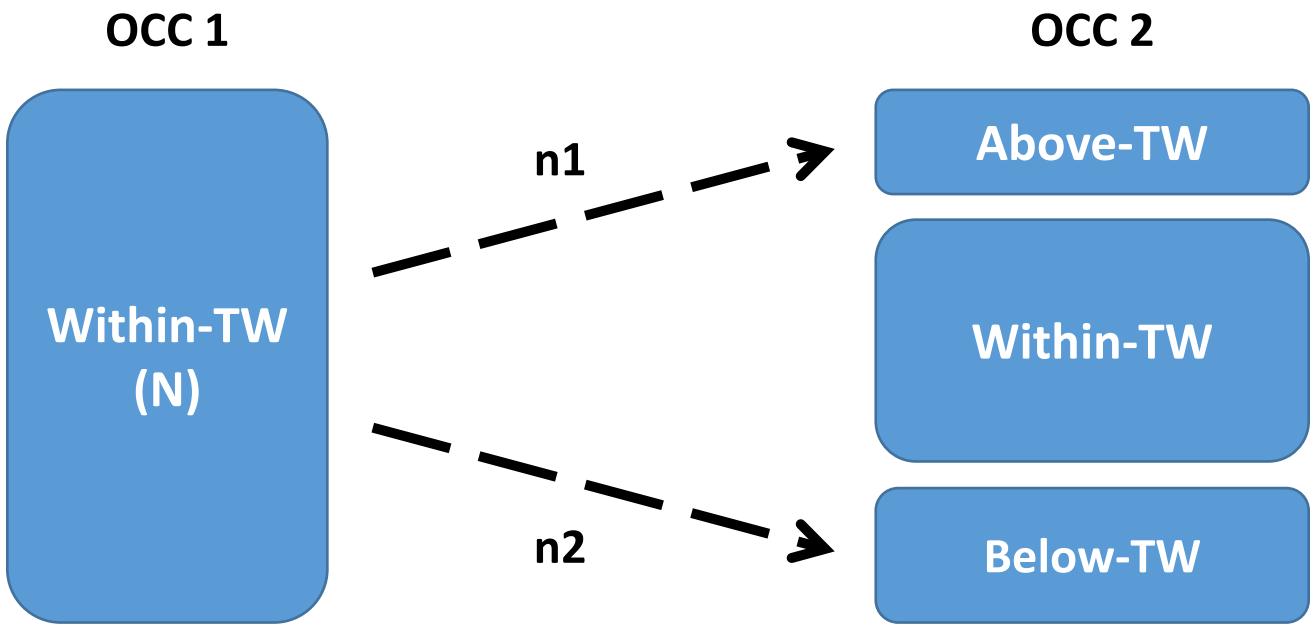
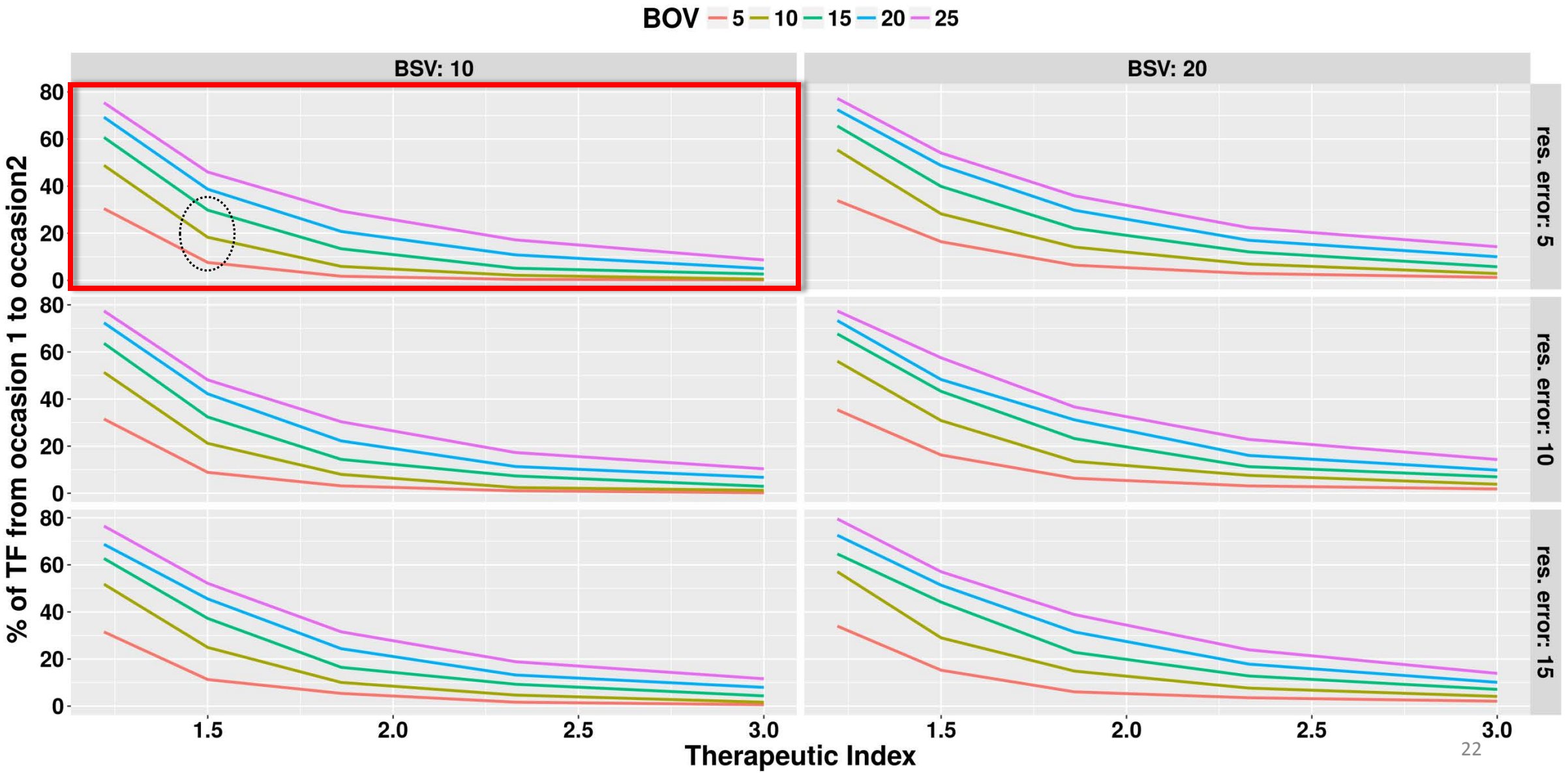


Impact of BOV on *Individual Response* after switch from OCC1 to OCC2 for a Reference drug

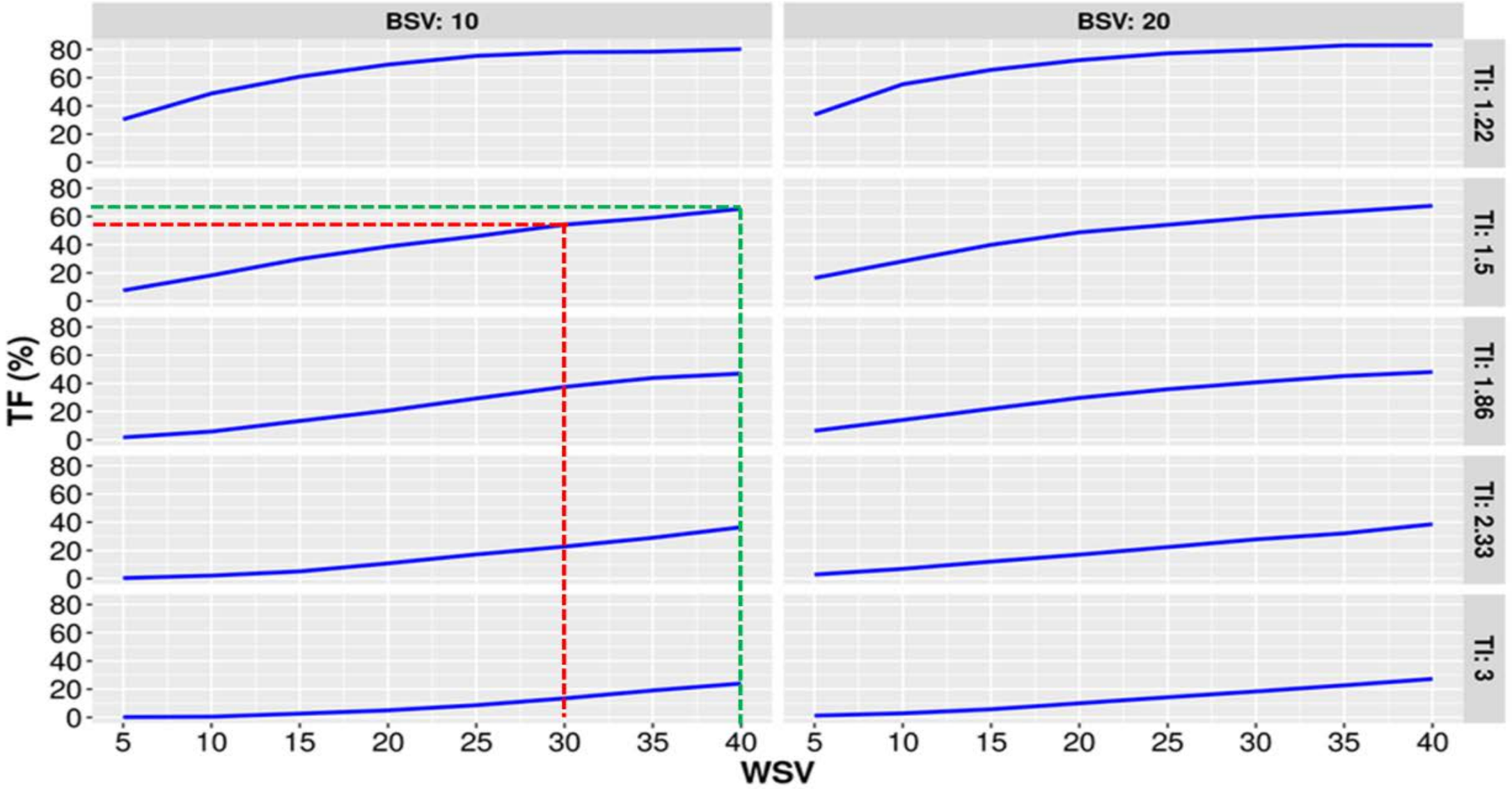
$$\textit{Proportion of Therapeutic Failure (\% TF)} = \frac{\textit{Sum of subjects moved from within−TW => out of TW between occasions}}{\textit{initial nb of subjects within−TW (at first occasion)}}$$



Individual Response – Reference vs. Reference – at TI ≤ 2:BOV ↑ → %TF ↑



Up to 10 % TF at a dWSV of 10 %



Evaluation of Bioequivalence approach and impact of therapeutic success

- For bioequivalent *Test* and *Reference* drug according to the recommended ***RABE + WSV comparison*** **approach**:
  - A maximum to 10% difference between WSV_{Test} and $WSV_{Reference}$ can be observed between bioequivalent (80% passing rate) *Test* and *Reference* drugs.
  - For such difference in WSV, where $WSV_{Test} > WSV_{Reference}$, the proportion of therapeutic failure (%TF= number of subject moving from within to outside a TW) cannot be higher than 10% for a drug with a TI of 1.5.

Recommendations

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