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Statistical challenges and opportunities in ICH M13C

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Scaled Average Bioequivalence (SABE) for HVD(P)s

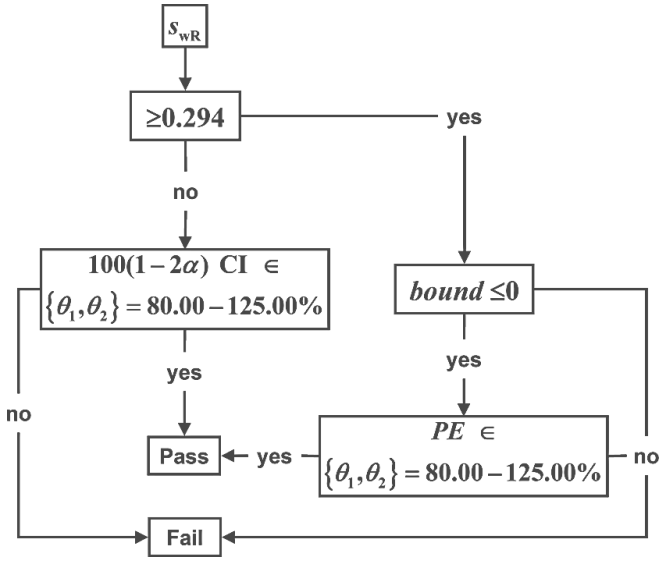
- HVD(P)s show large within-subject variability
  - Safe and efficacious *despite* their high variability
  - Large sample sizes required for Average BE based on the clinical relevant difference Δ = 20% (80 – 125%)
- Δ > 20% discussed at BioInternational conferences (1989 – 2005) and meetings of the FDA Advisory Committee for Pharmaceutical Science (1997 – 2006) if $CV_{wR} \geq 30\%$
  - *Fixed* limits based on Δ = 25% (75 – 133%) or Δ = 30% (70 – 143%)
  - *Scaled* limits based on the observed CV_{wR} in a (at least reference-) replicated design study

Implemented methods

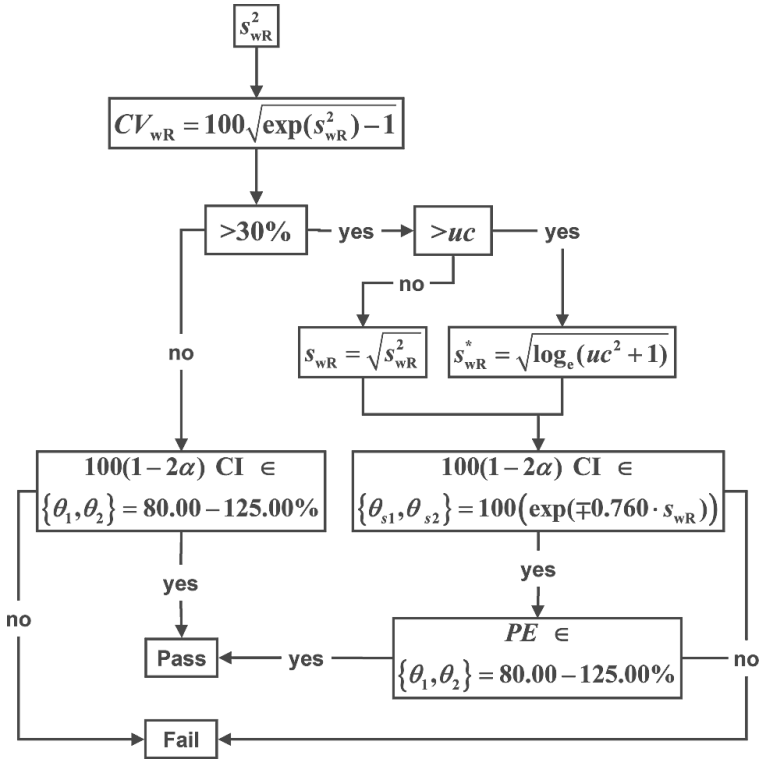
- Reference-Scaled Average Bioequivalence (RSABE)
  - US FDA and China CDE
  - If $s_{wR} \geq 0.294$ ($CV_{wR} \geq 30.05\%$); otherwise, by ABE
- Average Bioequivalence with Expanding Limits (ABEL)
  - Recommended in all [*sic*] other jurisdictions accepting SABE
  - If $CV_{wR} > 30\%$; otherwise, by ABE
  - Upper cap of expansion
    - 50% → max. 69.84 – 143.19%
    - ≈57.4% → max. 66.7 – 150.0% (Health Canada)
- In both: Point estimate constraint (80.00 – 125.00%)

The Type I Error can be inflated (increased patient's risk)

- Implemented methods of SABE are frameworks
  - BE limits are random variables dependent on the reference's variance
  - Δ unknown beforehand
  - Drugs *will* be misclassified if <u>observed</u> $s^2_{wR} \neq$ <u>true</u> σ^2_{wR}

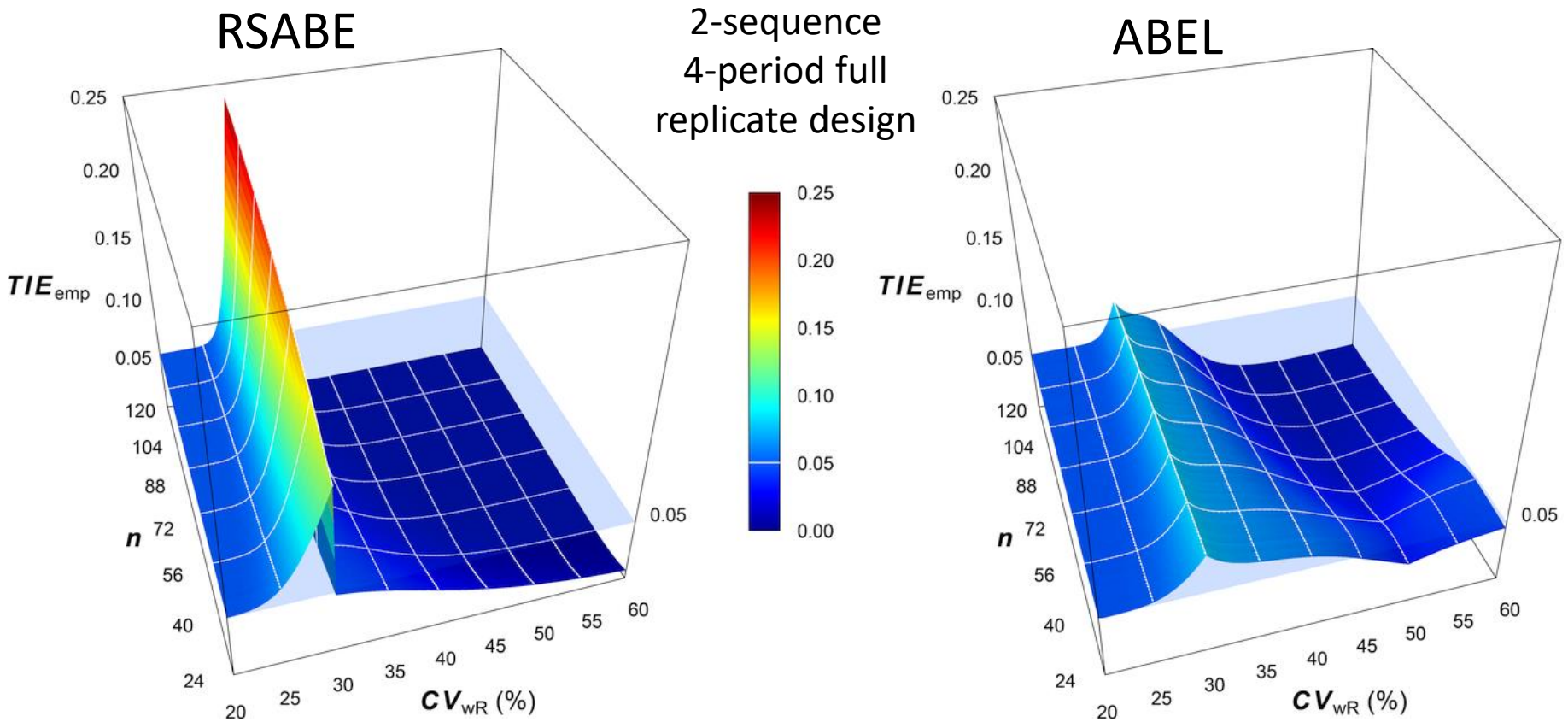


RSABE



ABEL

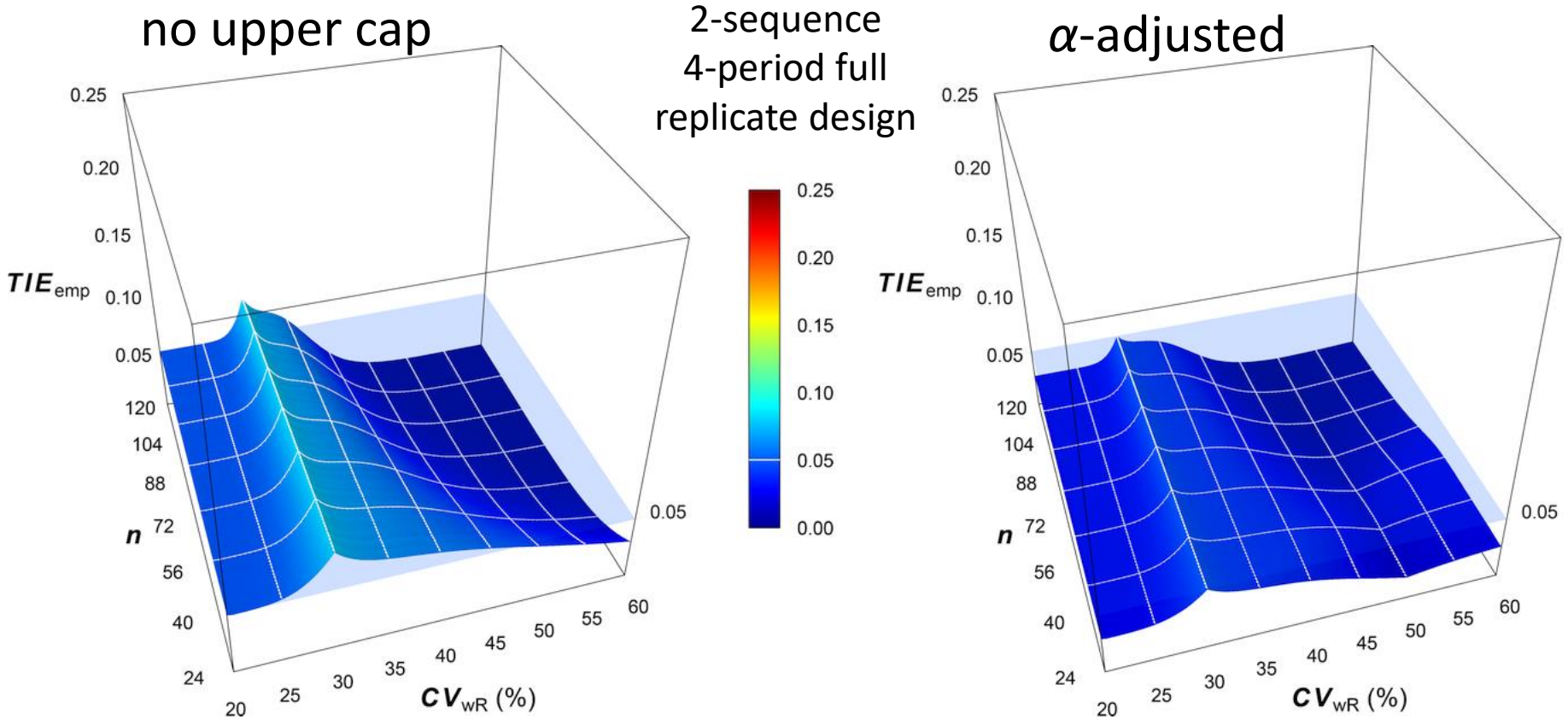
Empiric Type I Error in the implemented methods



TIE_{emp} at CV_{wR} 30%; *n* 24: 0.1335, *n* 120: 0.2418

TIE_{emp} at CV_{wR} 30%; *n* 24: 0.0804, *n* 120: 0.0838

Empiric Type I Error (ABEL, modifications)



TIE_{emp} at CV_{wR} 30%; n 24: 0.0804, n 120: 0.0838

TIE_{emp} at CV_{wR} 30%; n 24 to 120: 0.05

Conclusions (RSABE)

- The implemented method is beyond repair
  - Its maximum Type I Error is much larger than by ABEL
  - Assessing the TIE via the ‘desired consumer risk model’ (Davit *et al*. 2012) is a mere magician’s trick; I do not agree that it »maintains an acceptable Type I Error rate« (6.63% with 24 subjects in a full replicate design)
  - The decision of equivalence (*i.e.*, whether the upper bound of the linearized criterion is non-negative) is incomprehensible for physicians
  - If $s_{wR} < 0.294$ in a partial replicate design, the model is over-specified and may not converge

Conclusions (ABEL)

- The upper cap of expansion lacks a scientific rationale
  - 50% introduced in most jurisdictions due to reservations of <u>one</u> European member state
  - HC's ≈57.4% likely to give a 'nice' max. expansion of 67.7 – 150.0%
  - No issues with the Type I Error due to the inherent conservatism of the TOST procedure and the PE-constraint;
    lower sample sizes for large CV_{wR}
- α-adjusted methods
  - Control the Type I Error
  - Compromise power → large sample sizes required if true CV_{wR} > 50%

Suggestions for ICH M13C

- ABEL with modifications should be considered
  - Should be acceptable for all PK metrics
  - The upper cap should be removed
  - Biased-corrected Howe-LO and iteratively adjusted α are promising – control the Type I Error with less loss in power than other methods
- Heretical utopia (utopian heresy?)
  - Full replicate studies mandatory for the originator; alternatively agencies could collect and exchange CV_{wR} of studies → PSGs
  - *Fixed* limits ($\Delta > 20\%$): replicate designs no more needed and the Type I Error is *always* controlled

Group-Sequential (GS), Adaptive Two-Stage (TS) Designs

- In the conventional approach of pilot / pivotal studies
  - Only part of the information (T/R ratio, *CV*) of the former is used to design the latter
  - The individual data of the pilot – or a failed pivotal – are not used (they are only supportive information in the application)
- Since the T/R-ratio and the *CV* are estimates or assumptions, even a properly powered pivotal study of a bioequivalent product may fail in a fixed-sample design (probability = 1 – power)
- GSDs and TSDs allow decisions in an ‘interim analysis’

Group-Sequential Designs

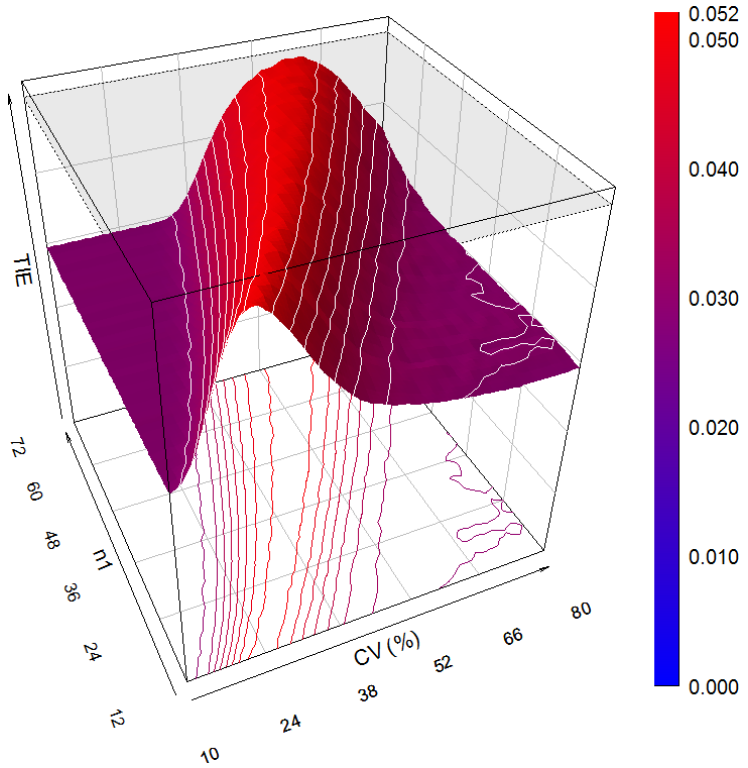
- The total sample size *n* is estimated as in a fixed-sample design
  - Analyses (interim and final) are performed with adjusted alphas (< 0.05), which must not be the same
- An interim analysis is performed at *n*/2
  - If the study passes BE already → stop for success, otherwise 2nd group is administered
  - (If the result looks promising → 2nd group is administered, otherwise stop for futility)
- Even if the study fails in the interim only by a slight margin, still *n*/2 have to be administered

Adaptive Two-Stage Designs

- If a pivotal study of a bioequivalent product fails in a fixed-sample design (probability = 1 – power) and is repeated in a larger sample size, the data of the first is not used
- In the interim analysis
  - Whether or not an adjusted α has to be used depends on the method
  - If the study passes BE already → stop for success, otherwise the total sample size is re-estimated and the 2nd group dosed
  - (If the result looks promising → 2nd group is dosed, otherwise stop for futility)

Operating Characteristics (simulation-based TSD)

Type I Error



Maximum TIE at *CV* 24% and n_1 12: 0.04895

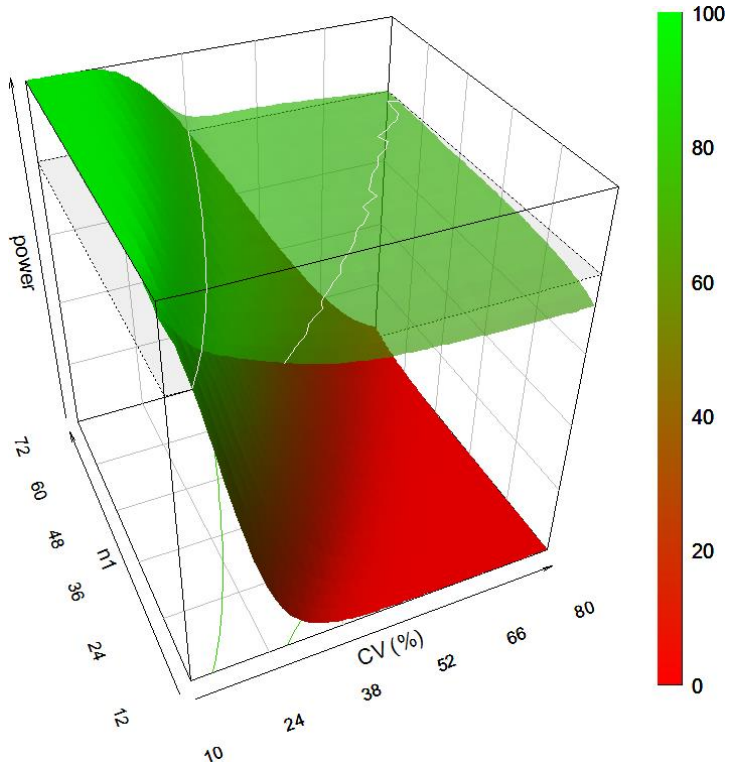
'Type 1' TSD
(Potvin *et al.* B)

Conditions:

α_{adj}	0.0294
GMR	0.95
power	80%
CV	10 – 80% (step 2%)
n_1	12 – 72 (step 2)

1 mio simulations in all combinations; significance limit for the Type I Error (TIE) 0.05036

Power



Minimum final power at *CV* 80% and n_1 12: 72.24%

Remarks

- GSDs
  - If interim is not at $n/2$ and/or final not at n → further adjustment of α
- TSDs
  - Exact methods only for 2×2×2 crossover design
  - Futility rules
    - Reduce the Type I Error
    - Negative impact on power → simulations recommended
  - Small first stage not recommended → large sample size penalty
  - 0.0294 is not a ‘natural constant’ (different conditions → different α_{adj})

Suggestions for ICH M13C

- Inverse Normal Method for 2×2×2 crossover should be recommended (based on a mathematical proof)
  - Maximum combination test or
  - Standard combination test
- Simulation-based methods should be acceptable if maximum empiric Type I Error for the entire grid of *CV* / n_1-combinations with 1 mio simulations ≤ 0.05036
  - Published methods
  - Alternatively simulations of the applicant with exhaustive documentation

Statistical challenges and opportunities in ICH M13C

Thank You!

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