Incorporating historical information in biosimilar trials

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Acknowledgement & disclaimer

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Historical data and biosimilars

- In biosimilar development:
  - the originator product has already been on the market for several years when the biosimilar development begins
  - the originator was already studied very often, both prior to market authorization and in post-marketing studies
- Idea: incorporate this historical information into the Phase III studies that are used for the approval of the biosimilar with a Bayesian approach
  - Summarize historical data in a prior distribution
  - Combine historical data with data in new study using Bayes' theorem to obtain posterior distribution
- Challenge: Type I error rate inflation is expected

Considered setting

- Parallel groups design
- Binary endpoint (responder, non-responder)
- Goal is to confirm equivalence in response rates of the test (T) and reference (R) product:

$$H_0 : |p_R - p_T| \geq \Delta \text{ vs. } H_1 : |p_R - p_T| < \Delta$$

- For Bayesian approach:
  - Informative prior for the reference product
  - Non-informative prior for the test product since no information is available prior to the study
  - Combine prior with the observed data with Bayes' theorem
- Benchmark: two-one-sided-test (TOST) frequentist approach that is the standard approach which considers the response rates in the new study only

Test decision & settings

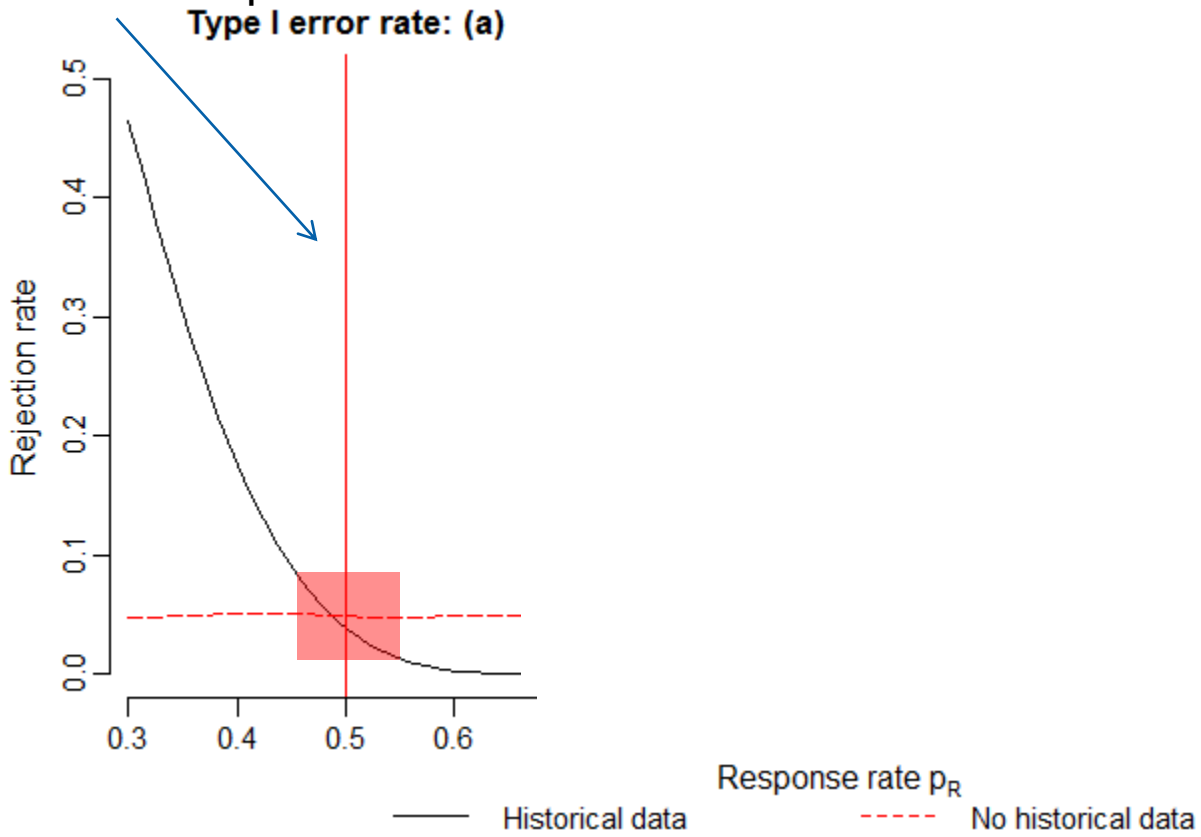
- Bayesian success criterion: Let X_R, X_T be random variables that follow the posterior distribution of T and R. Then, claim equivalence if:

$$B = P(|X_R - X_T| < \Delta) > c$$

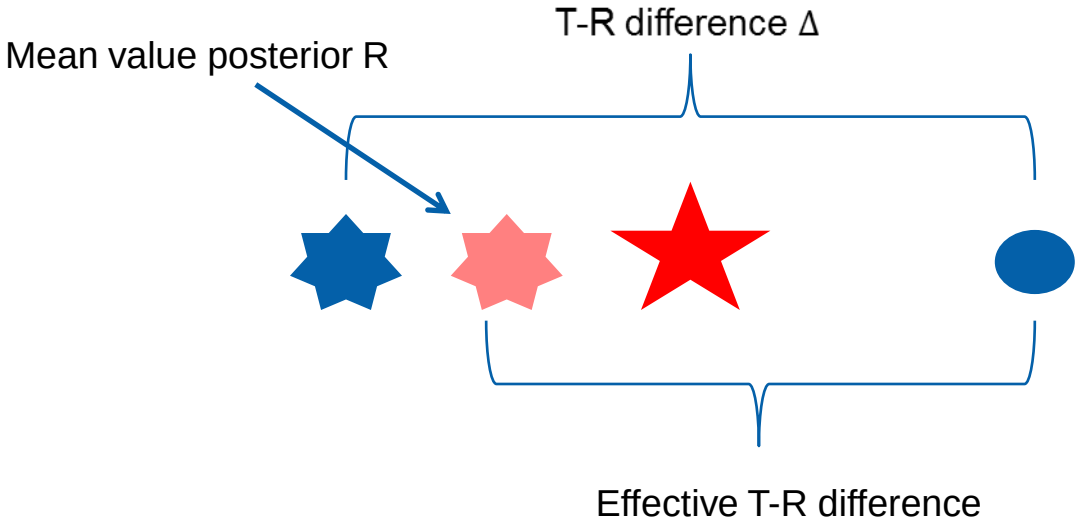
- We evaluate the operating characteristics for several true response rates for R and consider three different constellations of response rates for T (dependent on R):
  - $p_T = p_R + \Delta$ (Type I error rate: Situation (a))
  - $p_T = p_R - \Delta$ (Type I error rate: Situation (b))
  - $p_R = p_T$ (power)

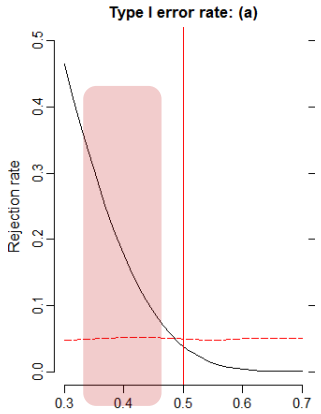
Operating characteristics

Mean value of the prior



Why do we observe this profile?





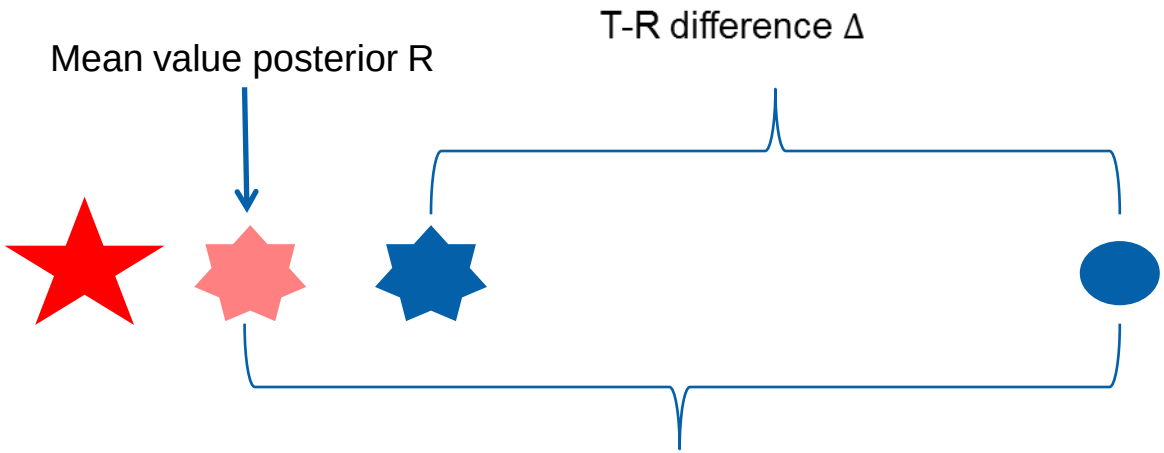
Response rate

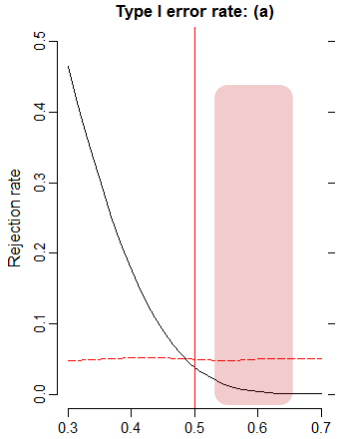
Mean value prior

Response rate T

Response rate R

Why do we observe this profile?





Response rate

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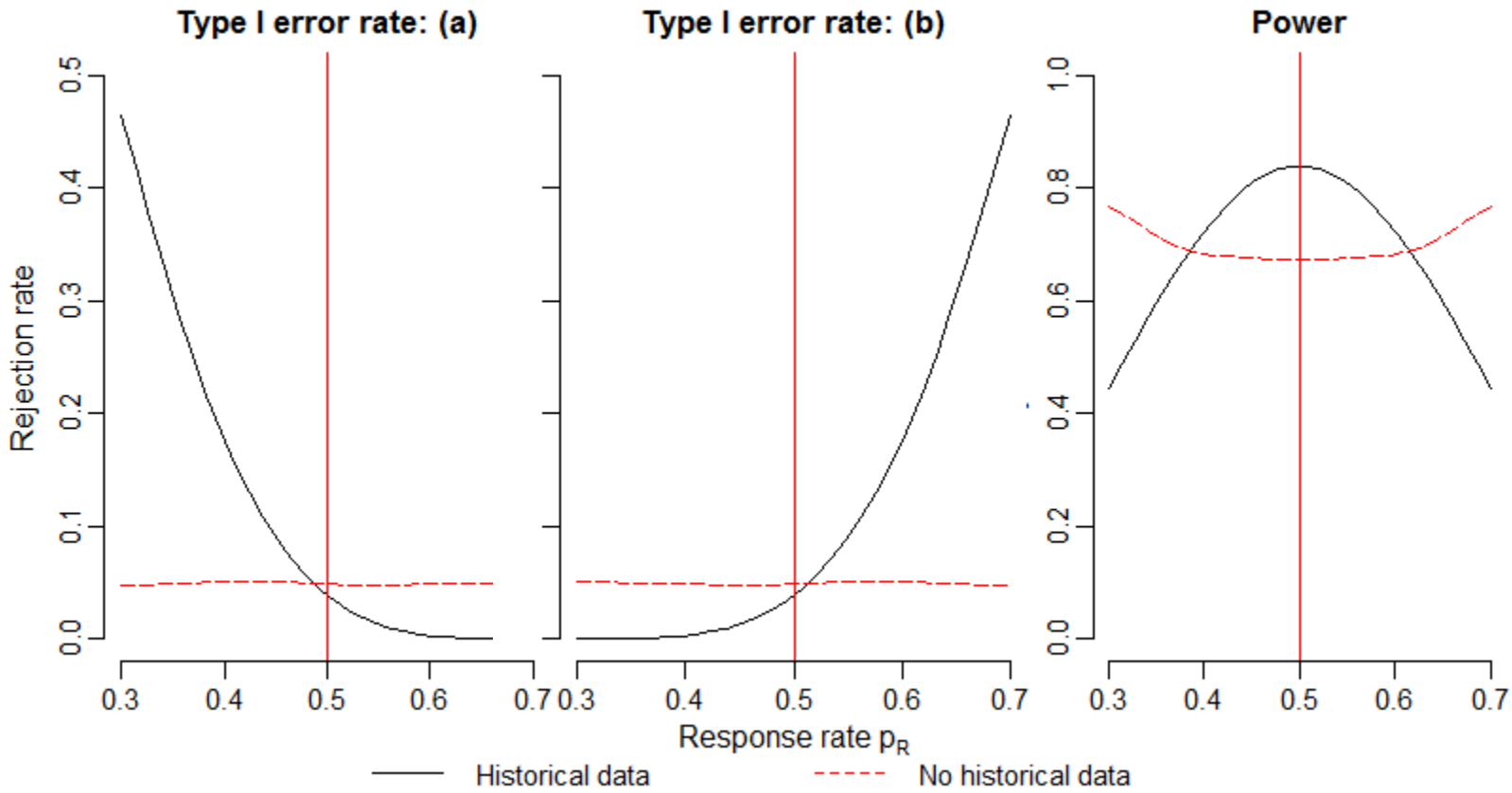
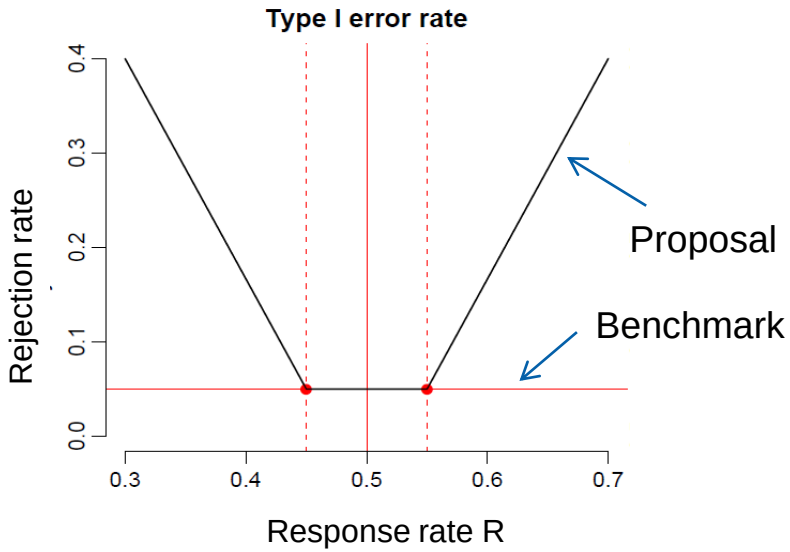
Operating characteristics

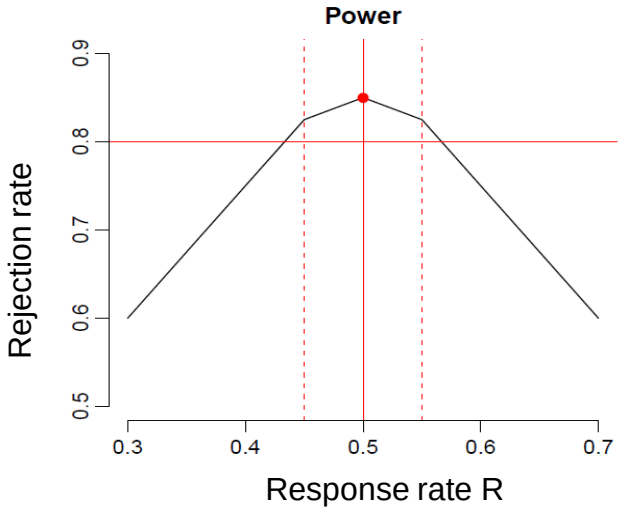


No gain in power is possible if Type I error rate is strictly controlled!

Partial Type I error rate control

- We accept that strict Type I error rate control is incompatible with a gain in power
- For biosimilars, we expect that it is possible to conduct a “similar” study
- We define an interval C in which we aim to control the Type I error rate
- Note: standard approaches do not give a relevant gain in power even if only partial Type I error rate control is required





The hybrid frequentist-Bayesian approach

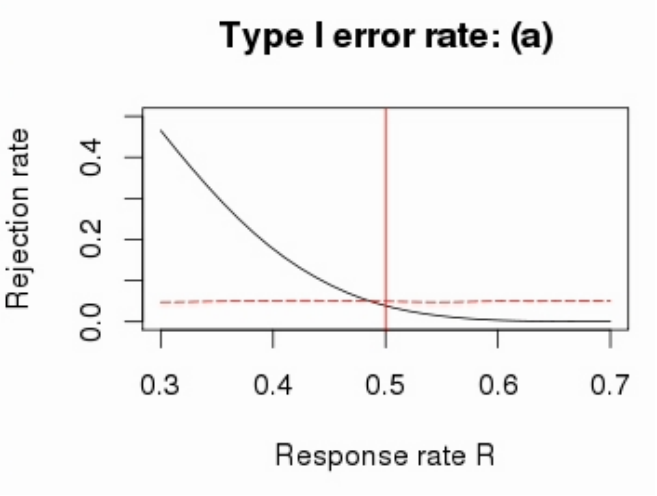
Overview of proposed method

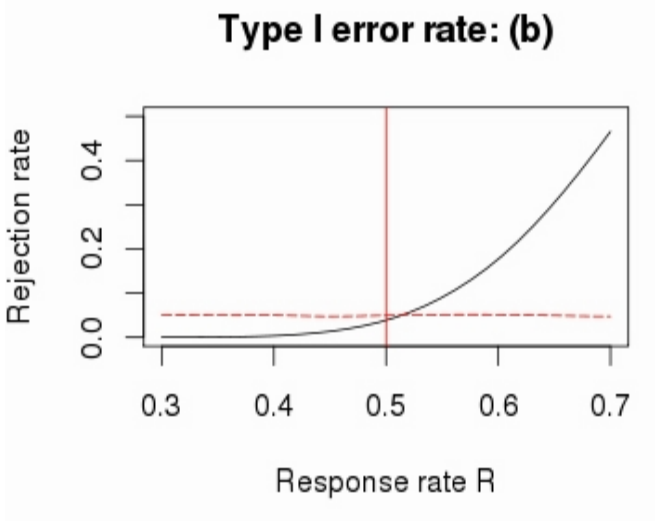
- Main goal: gain in power while controlling the Type I error rate in interval C
- Main concepts:
  - Switching rule I: if response rate of R in the new study and in the historical data are *very** different, do not use historical data
  - Switching rule II: if the response rates for T and R are *very** similar, use *lower** critical value
  - *Response rate-dependent critical values**

**: tuning parameters, can be chosen either automatically or be specified by the user*

Response rate-dependent critical values

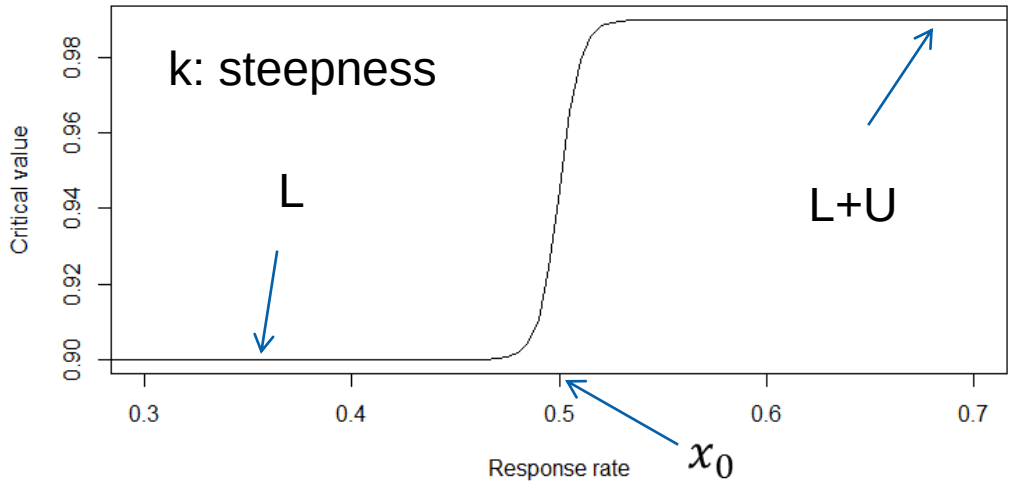
- The Type I error rate highly depends on the response rate in the new study
  ➔ Set the critical value high in regions in which the test is too liberal, and low in regions in which the test is too conservative
- The location of these regions depends on the ordering of the response rate of T and R in the new study (Situation (a) vs. Situation (b))
  ➔ Use different critical values for Situations (a) and (b)
- True response rate is not known
  ➔ Use estimated response rate





Response rate-dependent critical values

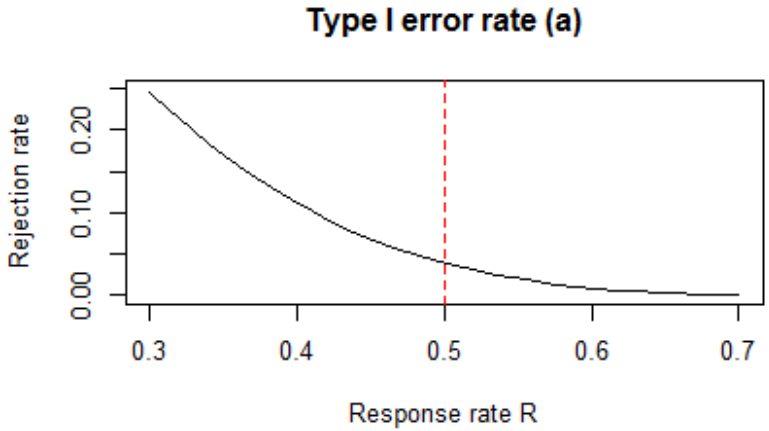
- Response rate-dependent critical values are chosen such that the Type I error rate is controlled in the interval C while the power is maximised under equality of response rates of T, R and the historical data
- Maximising a function without any assumptions on the functional form is difficult, we assume a logistic function

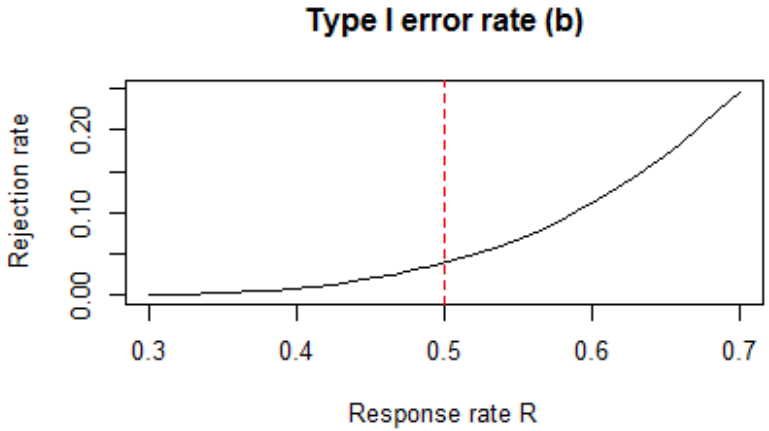


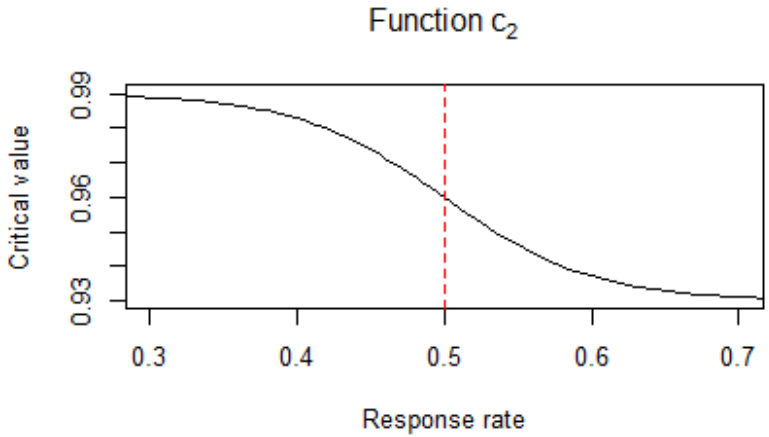
$$c_1(x) = L + \frac{U}{1 + \exp(-k(x - x_0))}$$

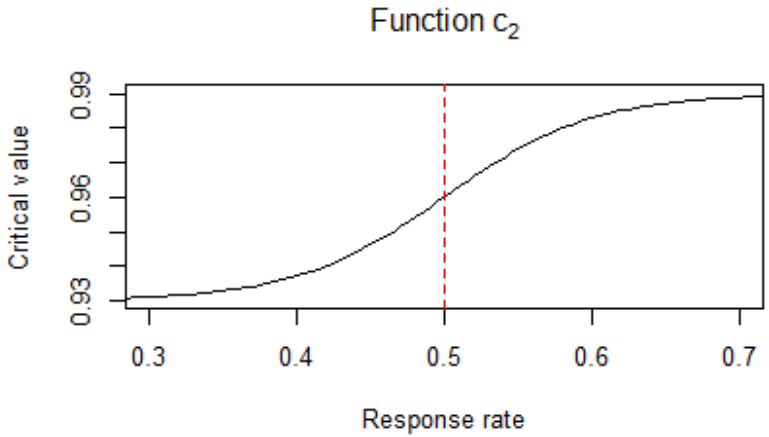
$$c_2(x) = L + \frac{U}{1 + \exp(k(x - x_0))}$$

Example: Response rate-dependent critical values

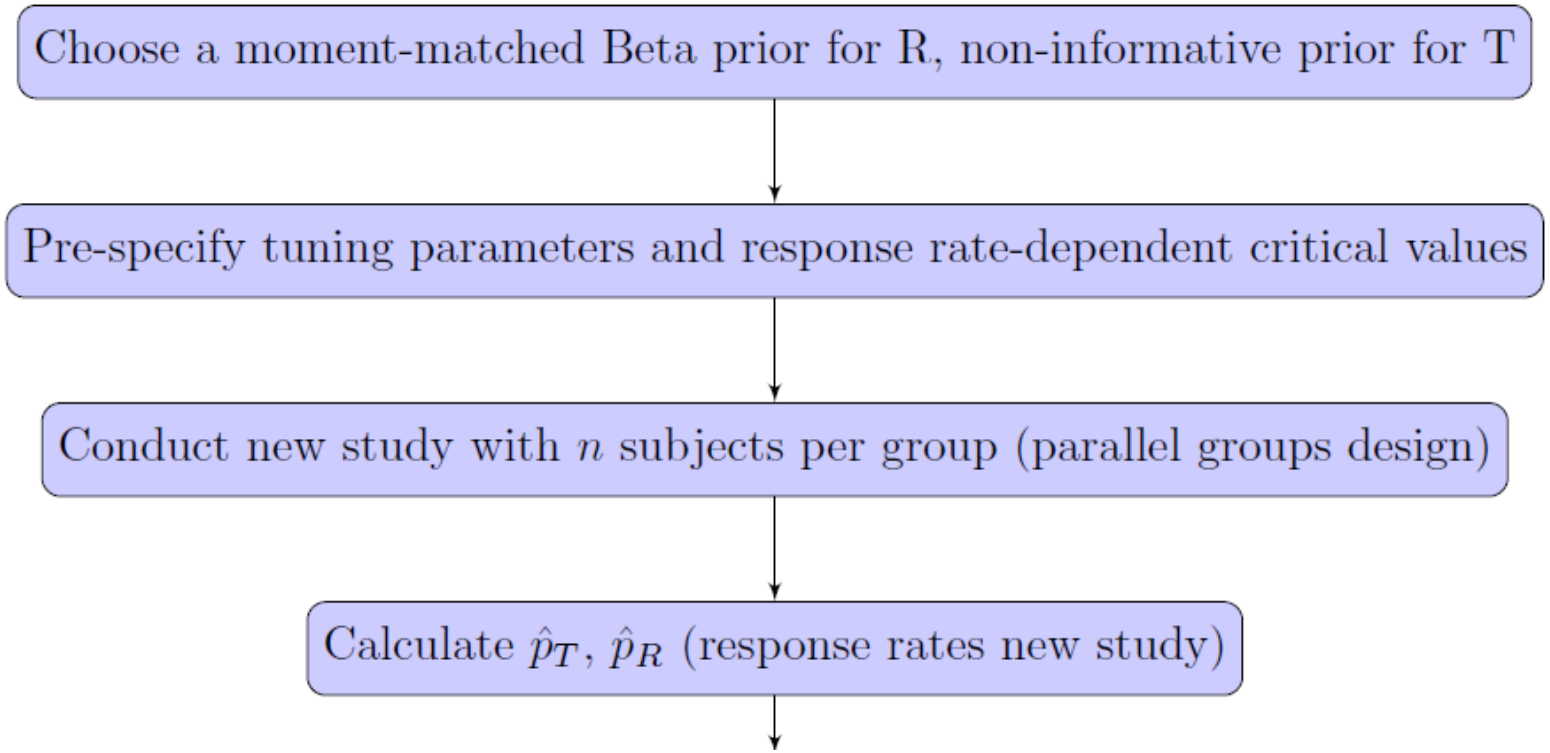




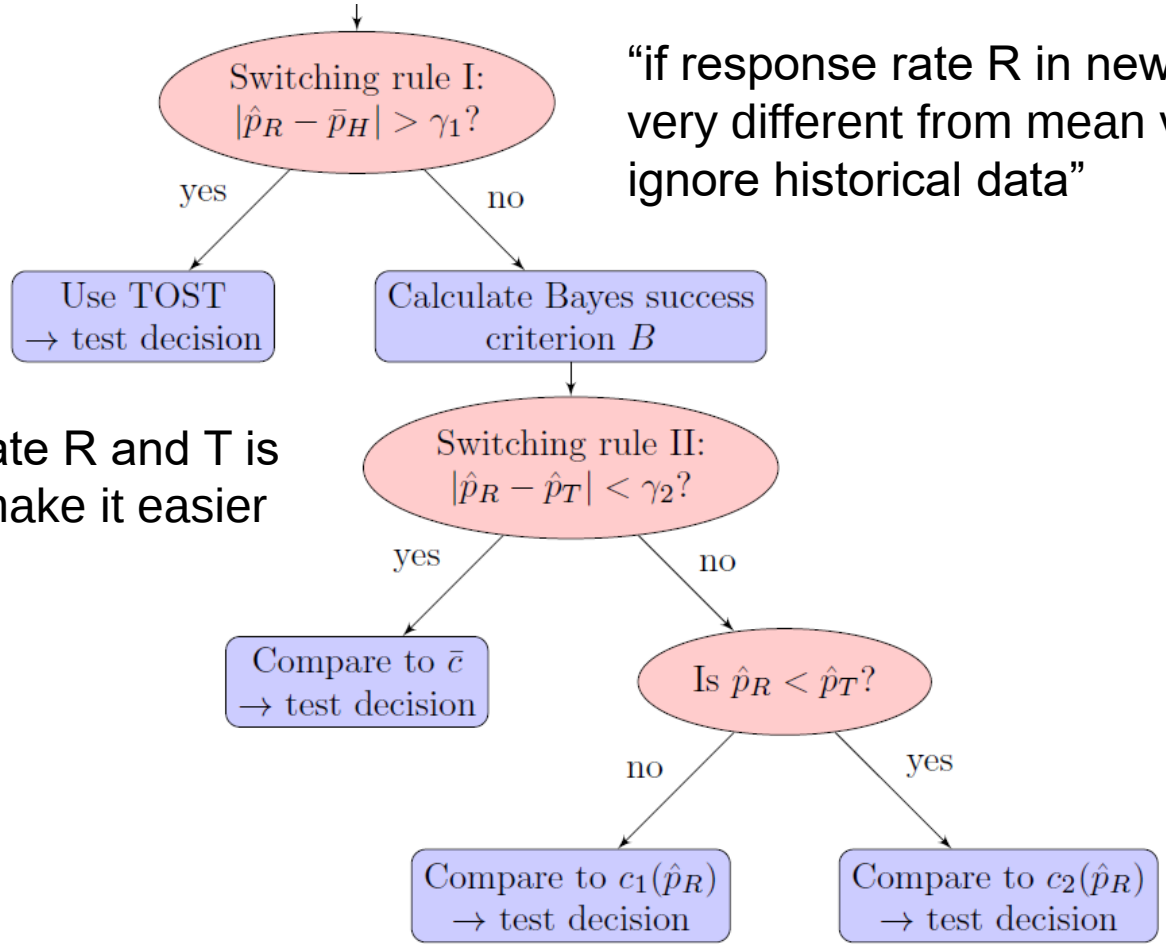




Proposed approach



Proposed approach



"if response rate R in new study is very different from mean value prior, ignore historical data"

"if response rate R and T is very similar, make it easier to reject"

Technical challenge: choice of tuning parameters

- In total 7 parameters have to be chosen:
  - 4 parameters of the response rate-dependent critical values
  - 3 tuning parameters
- In the binary case, it is possible to calculate exact rejection rates for a specific setting

$$r = \sum_{r_R=0}^{n} \sum_{r_T=0}^{n} P(X = r_T) P(Y = r_R) d_{r_T, r_R}$$

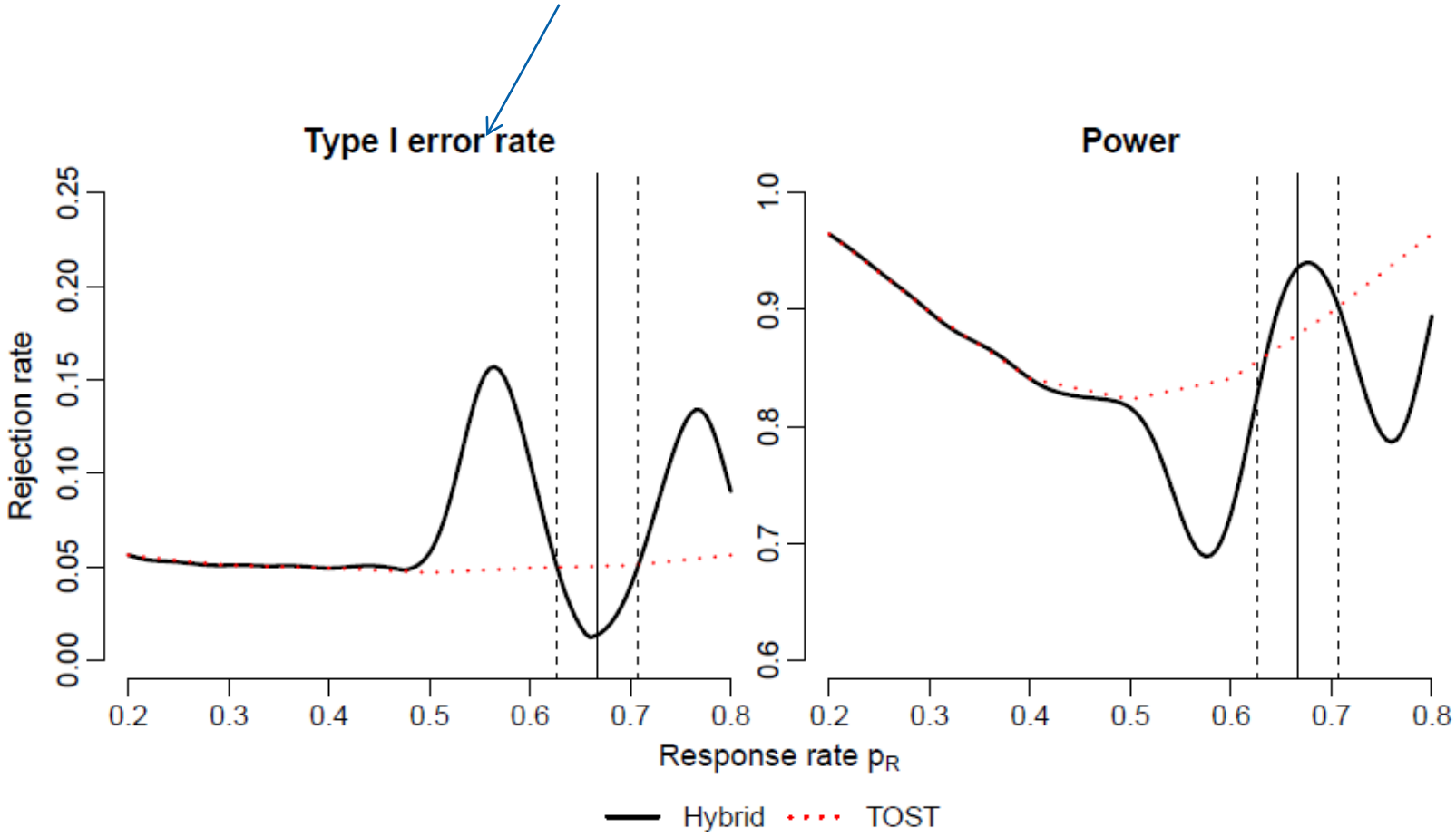
Test decision for the observed pair of responders

Probabilities to observe a specific number of responders

- Problems:
  - computational very expensive (n=150: 22801 settings)
  - local optima, flat curve
- We propose an algorithm, but recommend manual fine tuning

Example

Maximum of Situation (a) and (b)!



Case study

Planning of a hypothetical study

- Phase III study for a proposed biosimilar with the active substance adalimumab (Humira)
- Indication: Psoriasis
- Endpoint: PASI 90 (Psoriasis Area and Severity Index) responder rate at week 16
- Equivalence margin: $\Delta = 0.15$
- Sample size new study: $n = 175$

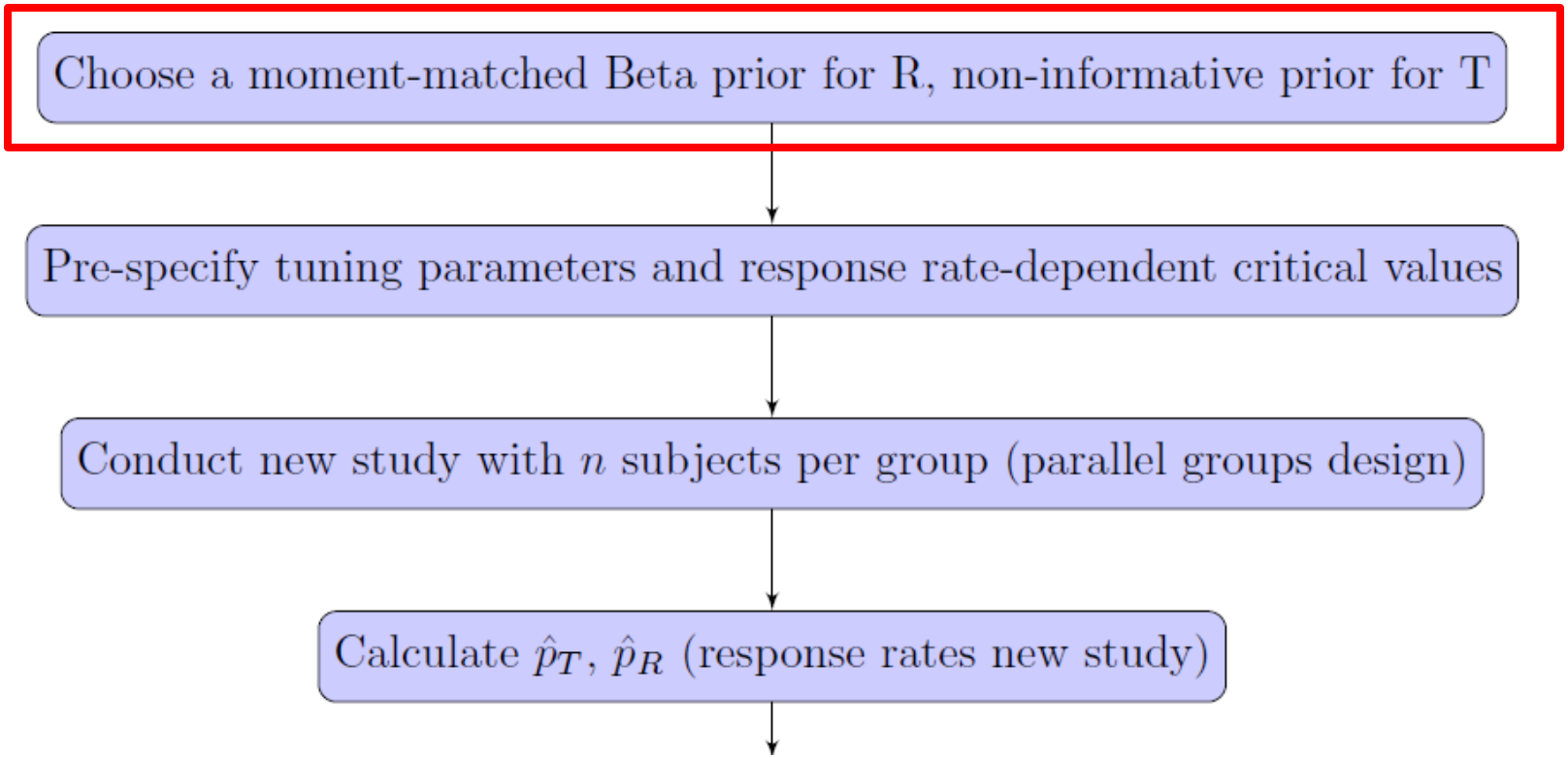
Historical information

Study	Publication	Indication	Responders/Sample size (%)
1	Menter *et al.* (2008)	moderate to severe psoriasis	366/814 (45.0)*
2	Saurat *et al.* (2008)	moderate to severe plaque psoriasis	55/108 (51.3)*
3	Thaçi *et al.* (2010)	moderate to severe psoriasis	183/364 (50.0)
4	Blauvelt *et al.* (2017)	moderate to severe psoriasis	166/334 (49.7)
5	Reich *et al.* (2017)	moderate to severe psoriasis	116/248 (46.8)
Total		886/1858 (47.7)	

- Choice of interval C:

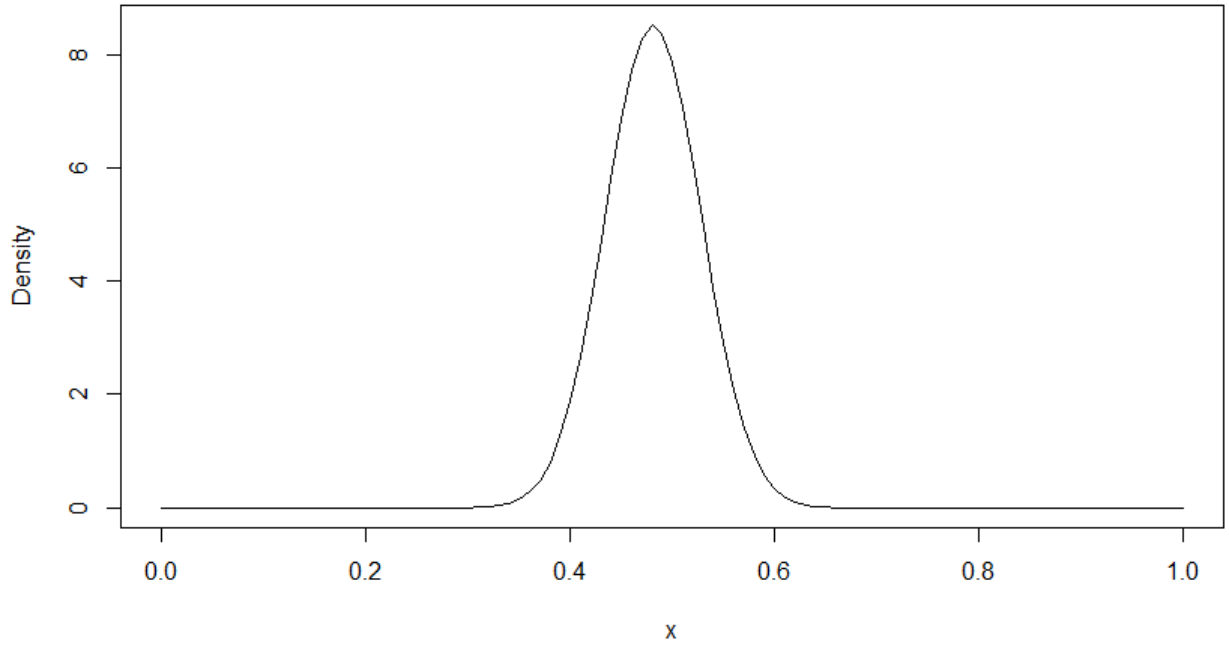
$$C = [\bar{p}_H - 0.05, \bar{p}_H + 0.05] = [0.4313, 0.5313]$$

Application of the proposed method

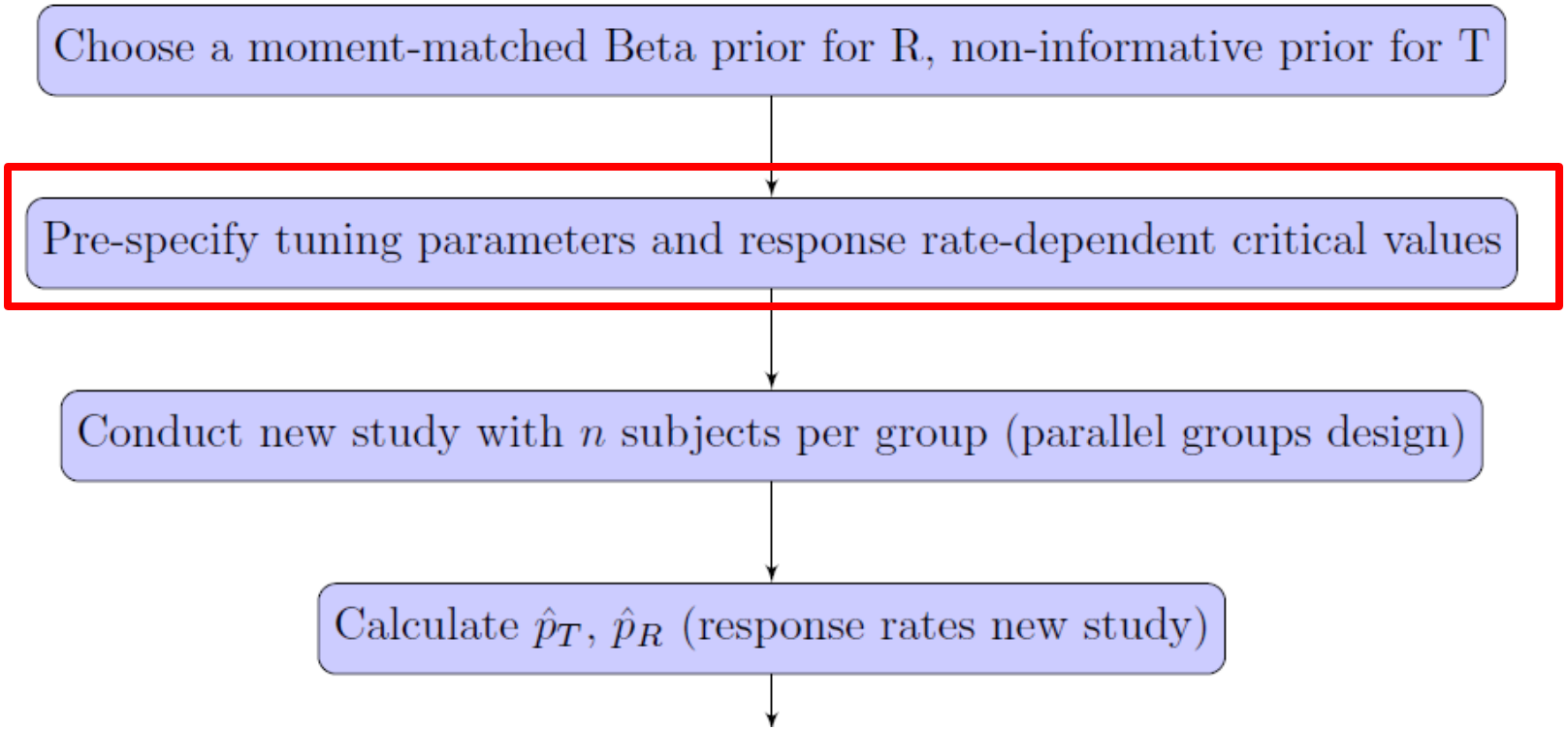


Step 1: Derivation of MAP prior

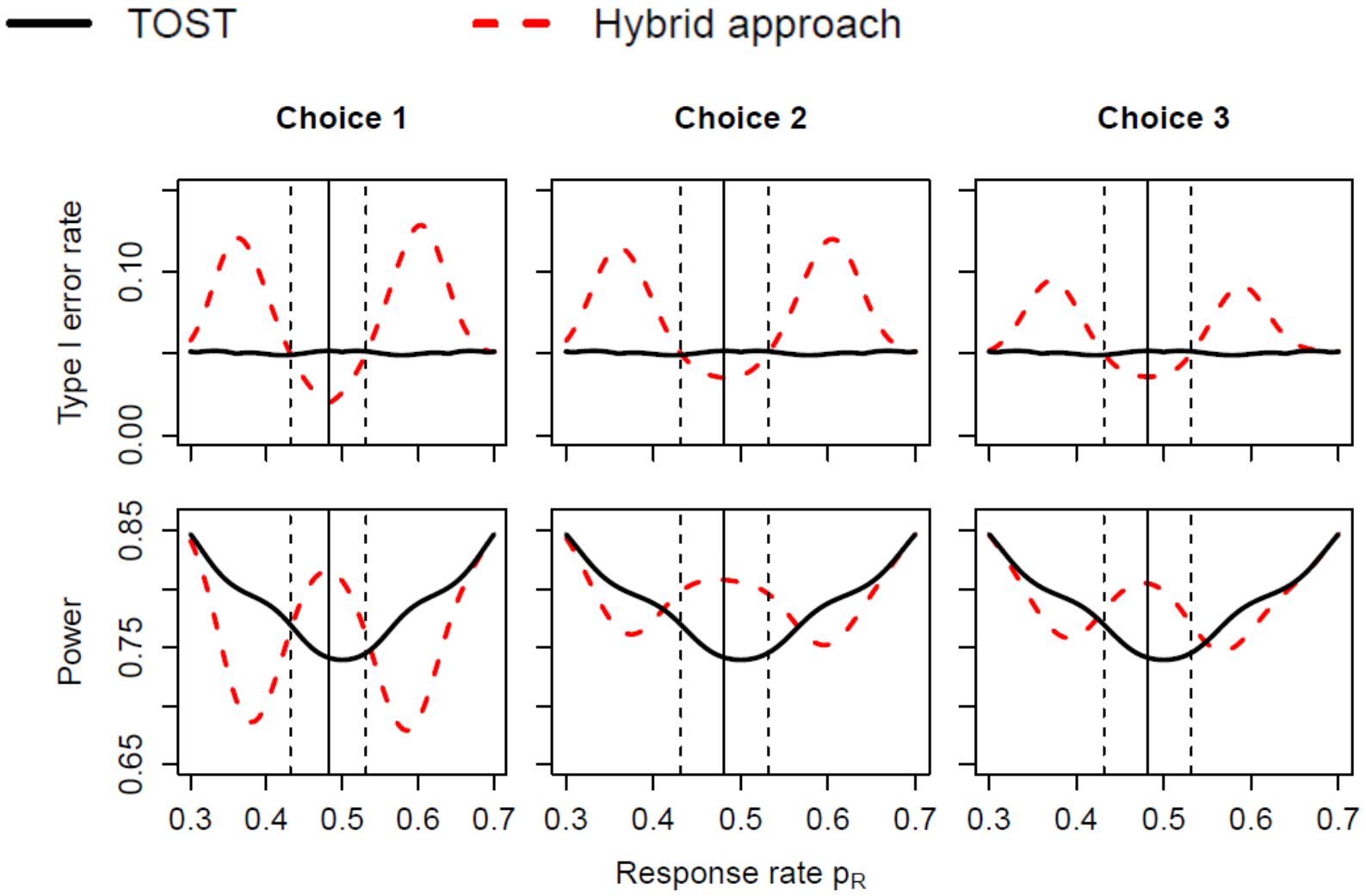
- R-package RBesT (Weber, 2017)
- Use of default assumption for hyper-parameters
- Best fit: Beta distribution with $a = 55.0844, b = 59.3647$



Application of the proposed method



Step 2: Choice of tuning parameters

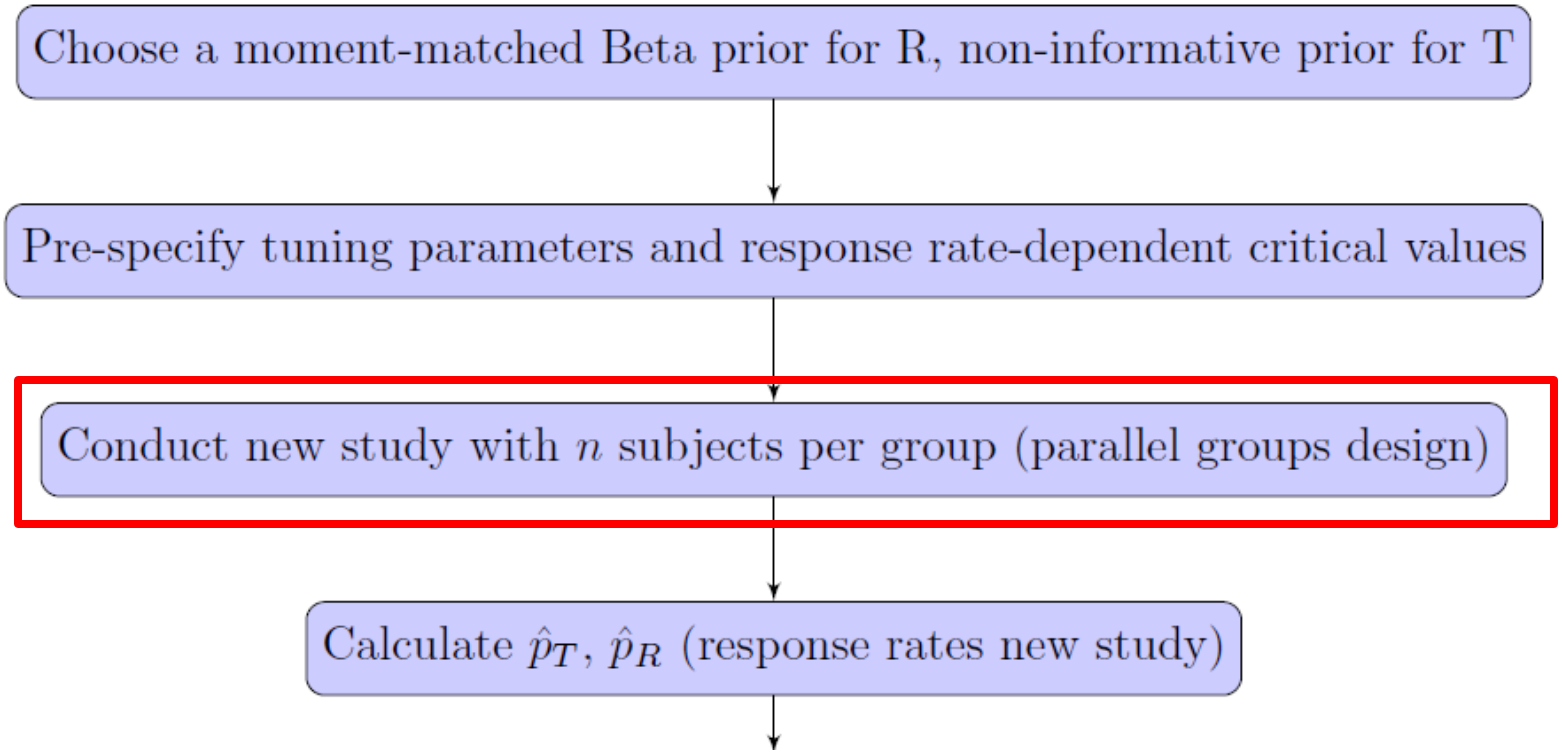


$\gamma_1 = 0.1133$
$\gamma_2 = 0.0378$
$c = 0.9$

$\gamma_1 = 0.1133$
$\gamma_2 = 0.0567$
$c = 0.9$

$\gamma_1 = 0.0944$
$\gamma_2 = 0.0567$
$c = 0.9$

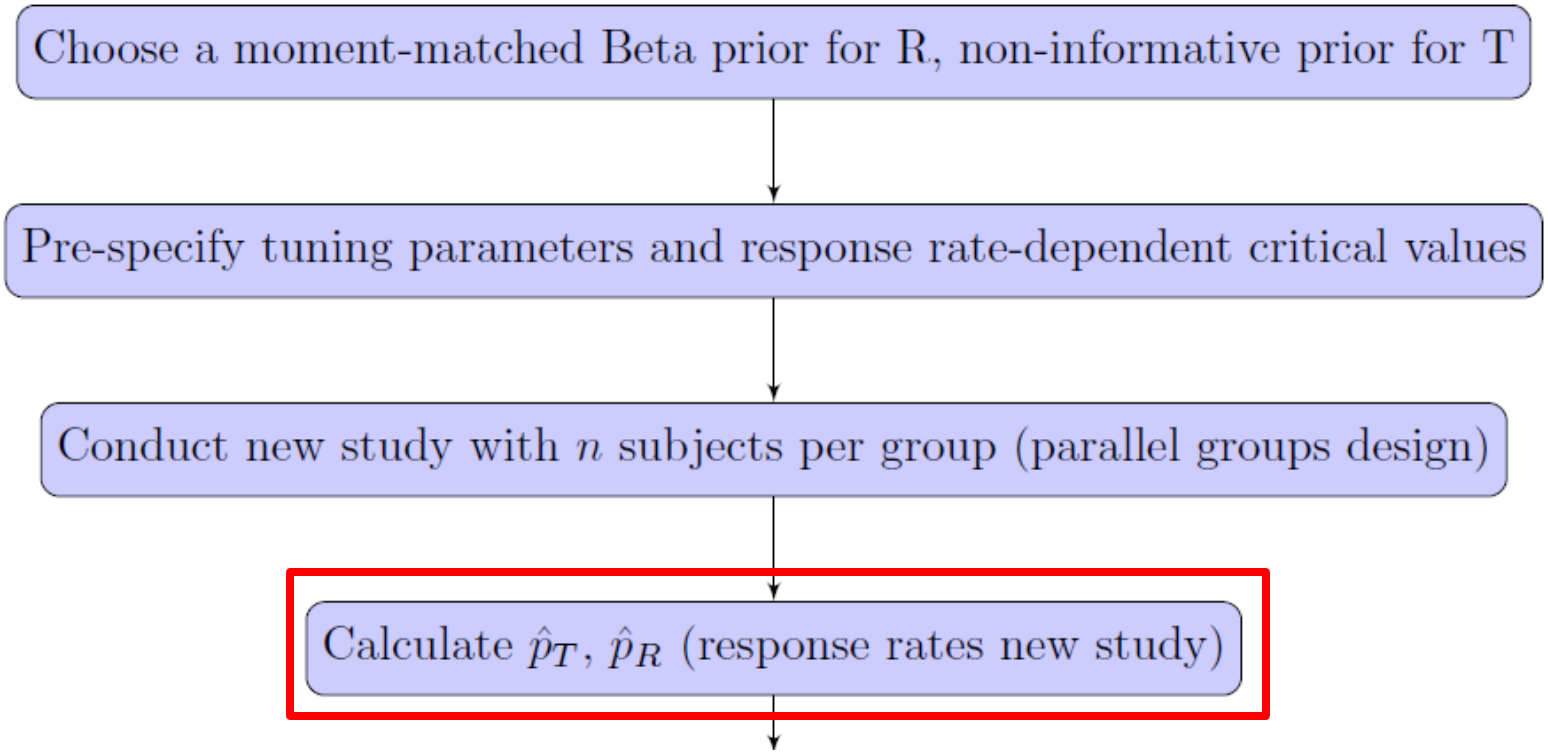
Application of the proposed method



Step 3: Conduct new study

- We consider the Phase III in psoriasis which was undertaken for the approval of Amgevita (Amgen)
  - Indication: stable moderate to severe plaque psoriasis
  - One of the endpoints: PASI 90 at week 16
  - 172 evaluated subjects in the test (biosimilar) group
  - 173 evaluated subjects in the reference (originator) group

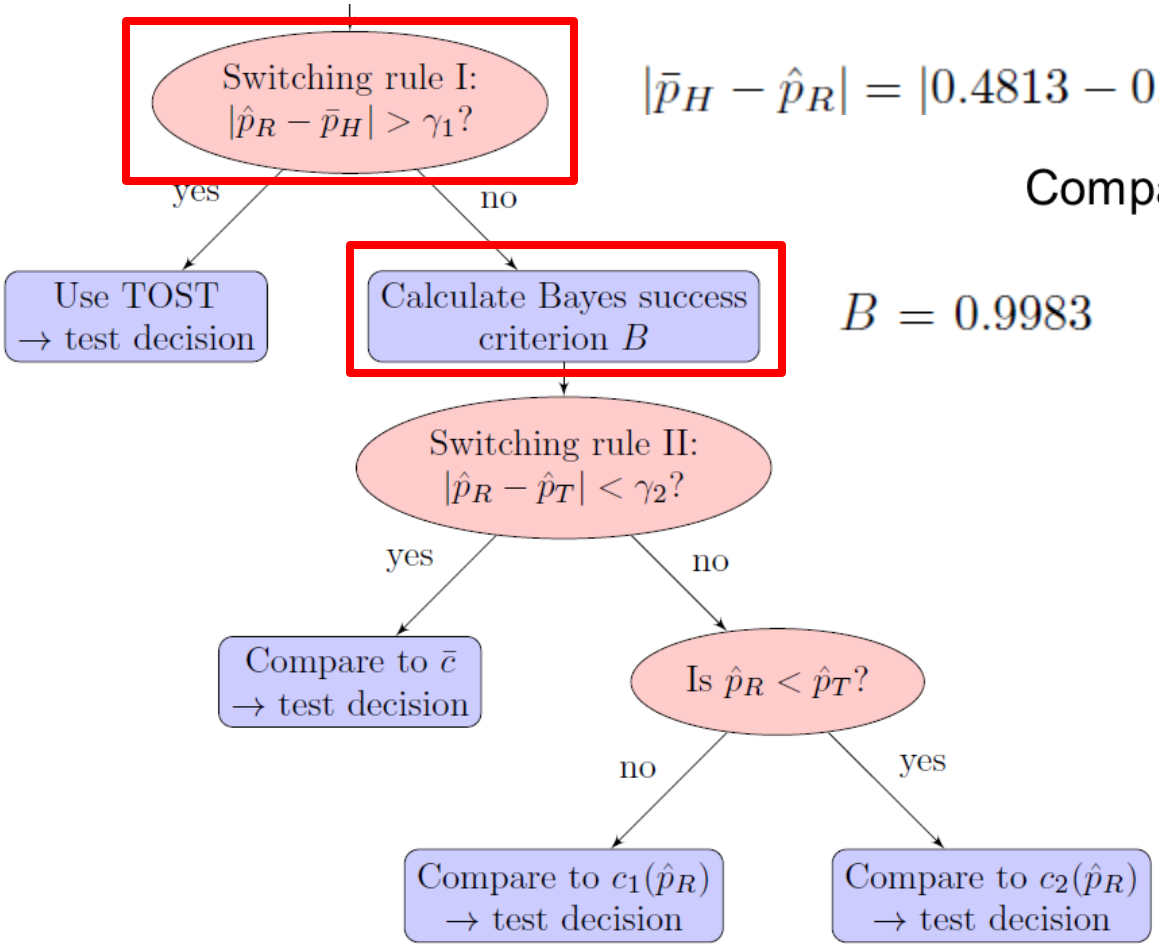
Application of the proposed method



Step 4: Study results

- 81 of 172 subjects responded on test (0.471)
- 82 of 173 subjects responded on reference (0.474)

Application of proposed method

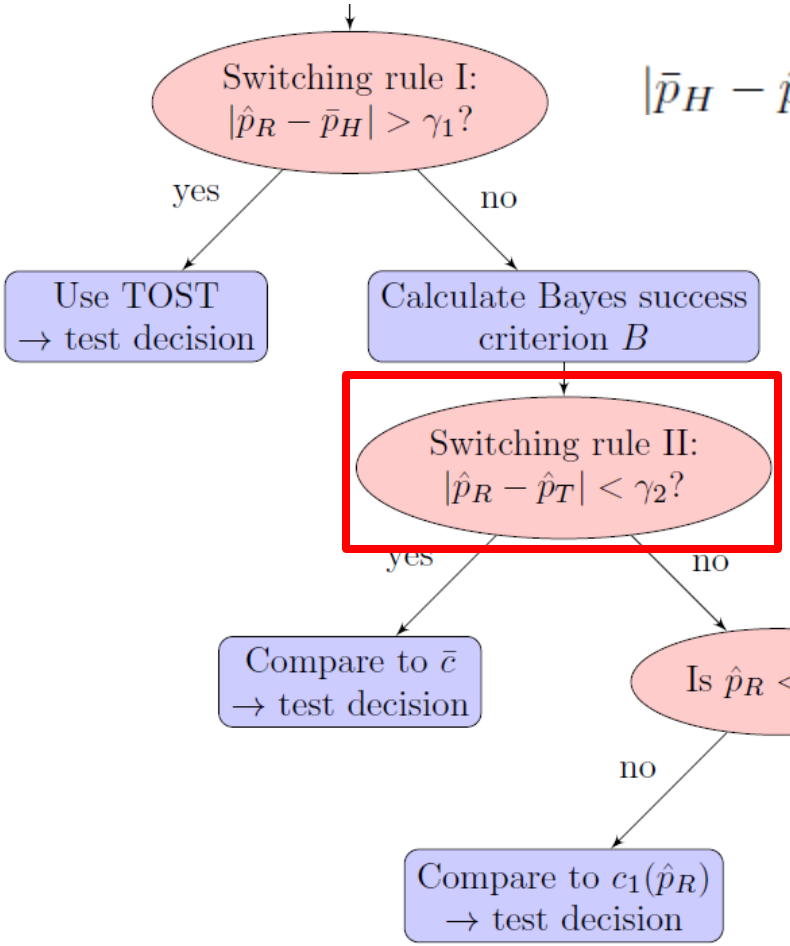


$$|\bar{p}_H - \hat{p}_R| = |0.4813 - 0.474| = 0.0073$$

Compare to: $\gamma_1 = 0.1133$

$$B = 0.9983$$

Application of proposed method



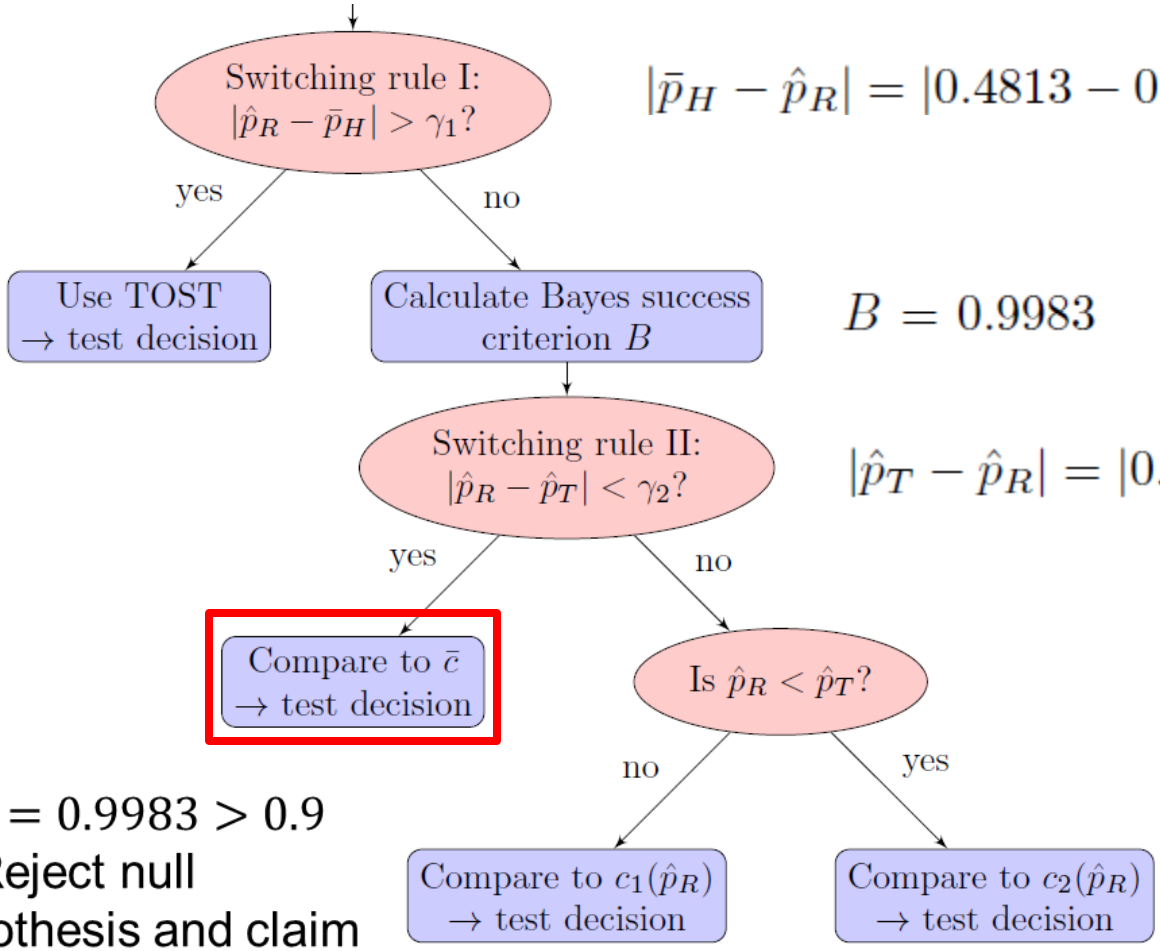
$$|\bar{p}_H - \hat{p}_R| = |0.4813 - 0.474| = 0.0073$$

$$B = 0.9983$$

$$|\hat{p}_T - \hat{p}_R| = |0.471 - 0.474| = 0.003$$

Compare to: $\gamma_2 = 0.0567$

Application of proposed method



$$|\bar{p}_H - \hat{p}_R| = |0.4813 - 0.474| = 0.0073$$

$$B = 0.9983$$

$$|\hat{p}_T - \hat{p}_R| = |0.471 - 0.474| = 0.003$$

$B = 0.9983 > 0.9$

➔ Reject null hypothesis and claim equivalence

Discussion

Discussion

- Proposed approach provides a gain in power in comparison to not using historical data while controlling the Type I error rate in the interval C
- Choice of the interval C dependent on knowledge and confidence in conducting a new study which is similar to the historical studies
- The choice of the response rate-dependent critical values and tuning parameters for the switching rules is computationally very expensive, but not difficult for the user to perform

Mielke, J., Schmidli, H. and Jones, B. (2018c): Incorporating historical information in biosimilar trials: challenges and a hybrid Bayesian-frequentist approach. *Biometrical Journal*, 60 (3), 564-582.

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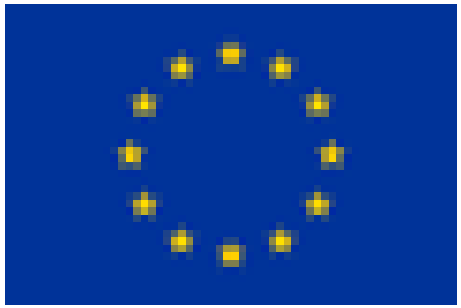
Thank you



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