Incorporating historical information in biosimilar trials

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- Biosimilars are developed as copies of already approved, large molecule drugs (biologics, the reference product).
- When biosimilar development starts, information on the efficacy of the reference product is available that could be incorporated in the biosimilar trial.
- If the historical information is included, but the historical data do not match the data in the new trial (prior-data conflict), an inflation of the Type I error rate is expected. This will, most likely, not be acceptable in biosimilar development if it occurs in scenarios which are realistic in practice.
- **We propose a hybrid Bayesian-frequentist approach for the incorporation of historical information from the reference product into the efficacy biosimilarity assessment in such a way that a gain in power is achieved, while the Type I error rate is controlled in all scenarios which are realistic in practice.**

Gain in power vs. complete Type I error rate control

Notation and hypotheses:

- Binary endpoint (responder vs. non-responder), parallel groups design
- Aim: confirm equivalent response rates of biosimilar (T) vs. reference (R)

$$H_0: |p_R - p_T| \geq \Delta \; vs. \; H_1: |p_R - p_T| < \Delta$$

- Bayesian success criterion (X_R, X_T: r.v., follow posterior distributions of R,T):

$$\mathrm{B} = P(|X_R - X_T| < \Delta) > c \qquad (1)$$

- Posteriors derived with Bayes' theorem using a non-informative prior (biosimilar) or an informative prior (reference)

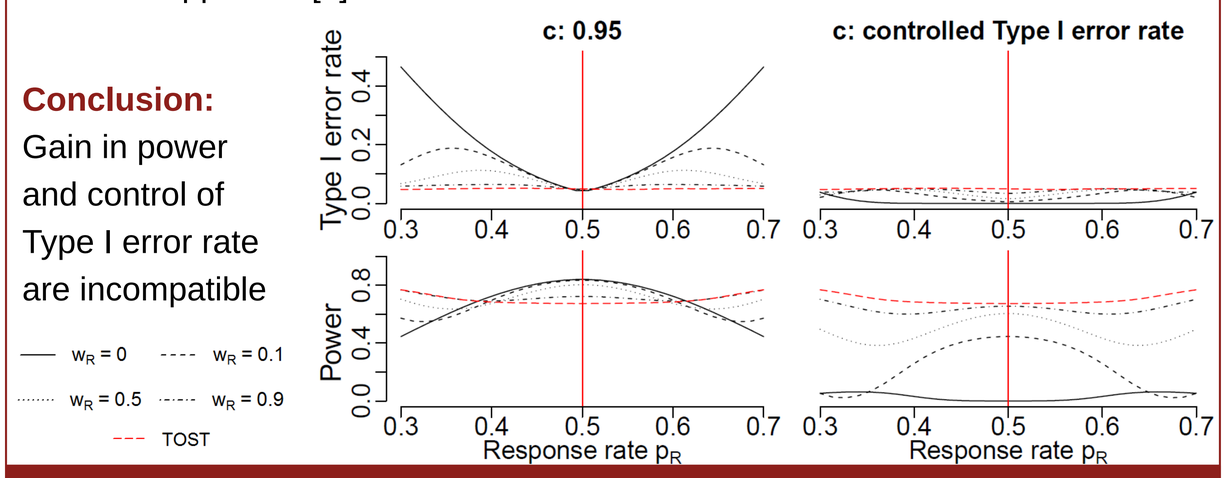
Example methodologies:

- Robustified meta-analytic-predictive (MAP) approach [1]: prior is a weighted sum of a vague prior f_v and an informative prior f_H:

$$f_{HR} = (1 - w_R) f_H + w_R f_v$$

- TOST-approach [2]

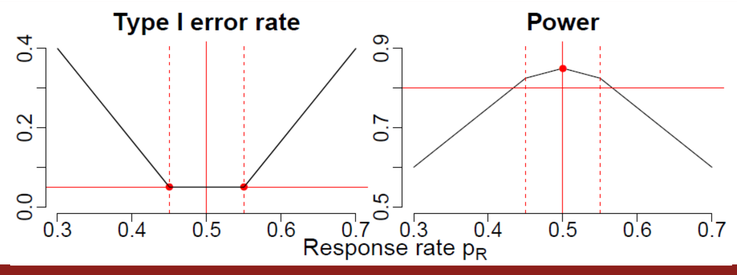
Conclusion:
Gain in power and control of Type I error rate are incompatible



Partial Type I error rate control

Control of the Type I error rate in neighboorhood of the mean value of the prior distribution $\bar{p}_H$:

$$C = [\bar{p}_H - \delta, \bar{p}_H + \delta]$$



Main concepts of the proposed hybrid approach

- Switching rule I: if response rate of R in the new study and in the historical data are *very** different, use the standard TOST approach
- Switching rule II: if the response rates of T and R in the new study are *very** similar, use *lower** critical value
- *Response rate-dependent critical values**

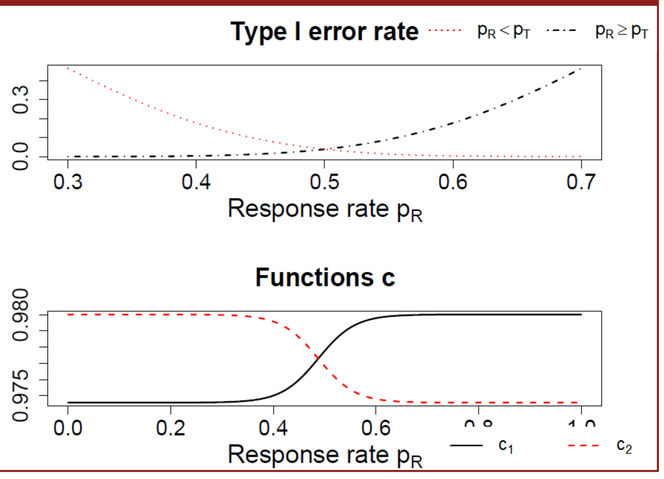
**: tuning parameters: can be chosen either automatically or be specified by the user*

Response rate-dependent critical values

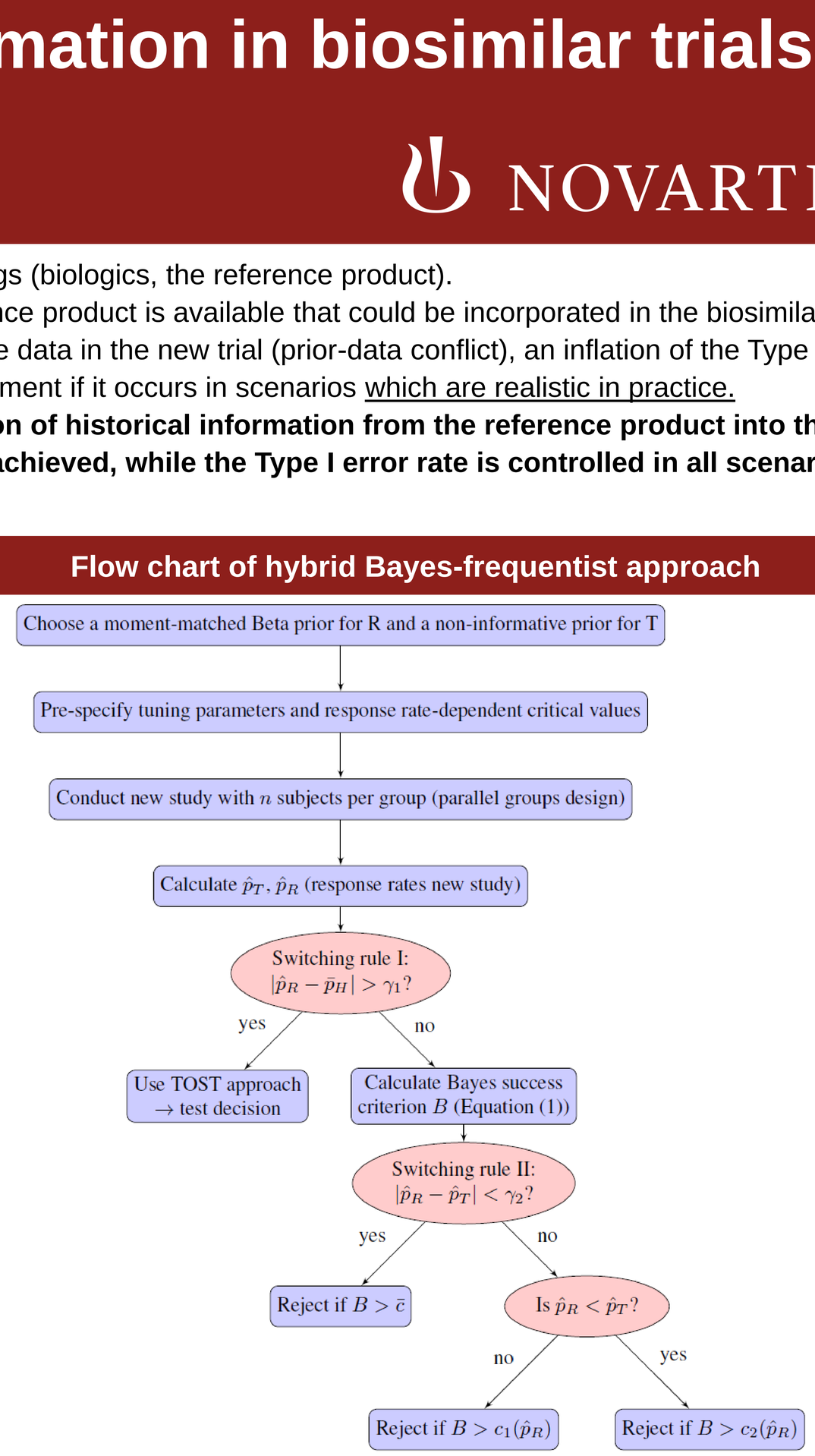
- Use of historical information leads to non-constant Type I error rate
- Aim: flatten the profile using response rate-dependent critical values

$$c_1(\hat{p}_R) = \frac{U}{1 + \exp(-k(\hat{p}_R - x_0))}$$

$$c_2(\hat{p}_R) = \frac{U}{1 + \exp(k(\hat{p}_R - x_0))}$$



Flow chart of hybrid Bayes-frequentist approach

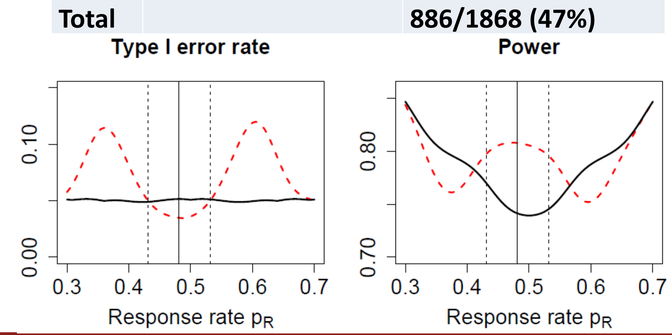


$\hat{p}_R, \hat{p}_T$: estimated response rates R, T; $\gamma_1, \gamma_2, \bar{c}$: tuning parameters; c_1, c_2: response rate-dependent critical values

Case study

- Active substance: adalimumab (Humira)
- Indication: psoriasis
- Endpoint: PASI90
- Chosen equivalence margin: $\Delta = 0.15$
- Chosen neighbourhood: $C = [\bar{p}_H - 0.05, \bar{p}_H + 0.05]$
- Informative prior derived [3] based on historical data
- Sample size: $n = 175$

Study	Publication	Responder/Total
1	Menter et al. (2008)	366/814 (45%)
2	Saurat et al. (2008)	55/108 (51%)
3	Thaci et al. (2010)	183/364 (50%)
4	Blauvelt et al. (2017)	166/334 (50%)
5	Reich et al. (2017)	116/248 (47%)
Total		**886/1868 (47%)**



Conclusions

- Approach can achieve a clear gain in terms of power (compared to TOST approach) while maintaining the desired Type I error rate profile
- Tuning computationally expensive, but not difficult for the user to perform
- All tuning parameters can be pre-specified for inclusion in a study protocol
- Choice of width of the neighbourhood is crucial and context-specific

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

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References:
[1] Schmidli, et al. (2014). *Biometrics* , **70**(4), 1023-1032.
[2] Schuirmann (1987). *Journal of Pharmacokinetics and Biopharmaceuticals*, **15**(6), 657-680.
[3] Weber (2017). RBesT: R-package.