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Adaptive Treatment Arm Selection in Multivariate Bioequivalence Trials

June 25th 2015

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Acknowledgments / References

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Presented theory based on methodological work regarding…

- **Intersection-union-tests**
  - Berger, R.L. (1982). Multiparameter hypothesis testing and acceptance sampling. *Technometrics* **24**: 295-300

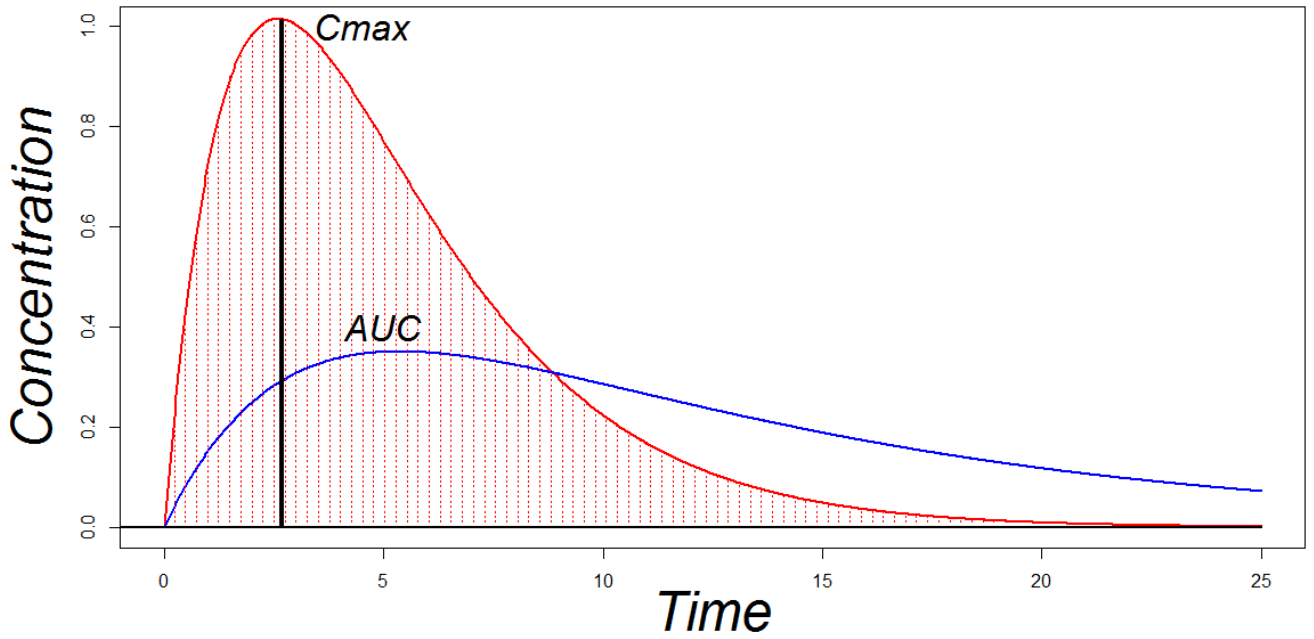
- **Inverse normal p-value combination**
  - ADDPLAN, Inc., an Aptiv Solutions Company (2014). ADDPLAN Base version 6.1 User Manual. Aptiv Solutions, Cologne Germany.

- **Adaptive treatment selection**
  - Bretz, F., König, F., Brannath, W., Glimm, E., Posch, M. (2009). Tutorial in Biostatistics: Adaptive designs for confirmatory clinical trials. *Statistics in Medicine* **28**: 1181-1217

… and discussions with/within

- **Gernot Wassmer**
- **Silke Jörgens**
- **Vladimir Dragalin**
- **BMBF project MÄQNU (03MS642G).**

Motivation



"Two pharmaceutical products are bioequivalent, if they are pharmaceutically equivalent and their bio-availabilities are similar to such a degree that their effects can be expected to be essentially the same"

- **Measures of bio-availability:**
  - **Area under the time concentration curve**
  - **Maximum drug concentration C_{max}**

Motivation

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Establishing Bio-equivalence:

- 90% confidence intervals on ratios:
  - **A and B are called bioequivalent, if 90% CI for**
    - AUC_A/AUC_B **and**
    - $C_{max;A}/C_{max;B}$

    are located within the equivalence range [0.8, 1.25]

... alternatively we consider 90% confidence intervals on the logarithms:

  - **A and B are called bioequivalent, if 90% CI for**
    - $\theta_1 := \log(AUC_A) - \log(AUC_B)$ **and**
    - $\theta_2 := \log(C_{max;A}) - \log(C_{max;B})$

    are located within the equivalence range [log(0.8) , log(1.25)]

Motivation

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Considered problem:

- Unknown optimal formulation / dose level.

Solution:

- Inclusion of several test arms.

New problem:

- Multiplicty issues: Increase in sample size required?

Proposed solution:

- Interim Analysis with selection of a test arm.

How to implement this?

Transform the problem to well-known settings.

1. Proof of bioequivalence

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What is the "Proof of bioequivalence"?

- A and B are called bioequivalent, if both 90% CIs for
  - $\theta_1 := \log(AUC_A) - \log(AUC_B)$ and
  - $\theta_2 := \log(C_{max;A}) - \log(C_{max;B})$

  are located within the equivalence range [log(0.8) , log(1.25)]

With : $\widehat{\theta}_i \sim \mathcal{N}\left(\theta_i, \frac{1}{n}\sigma_i^2\right)$ confidence intervals are given as:

$$CI_{0.9} = \left[\widehat{\theta}_i - z_{0.95}\frac{\sigma_i}{\sqrt{n}}, \widehat{\theta}_i + z_{0.95}\frac{\sigma_i}{\sqrt{n}}\right]$$

Bioequivalence is established, if for both endpoints *i* holds:

$$\log(0.8) \leq \widehat{\theta}_i - z_{0.95}\frac{\sigma_i}{\sqrt{n}} \quad \cap \quad \widehat{\theta}_i + z_{0.95}\frac{\sigma_i}{\sqrt{n}} \leq \log(1.25)$$

1. Proof of bioequivalence

What is the "Proof of bioequivalence"? (one endpoint)

Bioequivalence is established, if:

$$\log(0.8) \leq \widehat{\theta}_i - z_{0.95}\frac{\sigma_i}{\sqrt{n}} \qquad \cap \qquad \widehat{\theta}_i + z_{0.95}\frac{\sigma_i}{\sqrt{n}} \leq \log(1.25)$$

The proof of bioequivalence coincides with the rejection of:

$$H_{01} : \theta_i \leq \log(0.8) \quad \text{and} \quad H_{02} : \theta_i \geq \log(1.25)$$

at level $\alpha = 0.05$.

The proof of bioequivalence is a test at $\alpha = 0.05$ for $H_0 : \ H_{01} \cup H_{02}$.

1. Group-sequential proof of bioequivalence

Group-sequential test for bioequivalence (one endpoint)

Early rejection of “no-bioequivalence”, if all tests can be rejected early

e.g. Using Inverse-normal p-value combination

- **Stage-wise p-values $p_{i;1}$ and $p_{i;2}$ and information fraction $\omega_{i;j}$:**

$$\min\left(\sum_{i=1}^{j}\omega_{i;j}\Phi^{-1}(1-p_{i;1}),\sum_{i=1}^{j}\omega_{i;j}\Phi^{-1}(1-p_{i;2})\right)>c_j$$

- **Alternative combination:**

$$\sum_{i=1}^{j}\omega_{i;j}\Phi^{-1}(1-\max(p_{i;1},p_{i;2}))>c_j$$

... controls α, but is conservative.

2. Bioequivalence testing on multiple arms

Usual multiplicity issues hold:

- Increased probability of having at least one false positive
  - Increased critical values -> Increased required sample size.

- Null hypothesis:
  - *p* – equivalence endpoints (*2p* one-sided tests)
  - *k* – treatment arms

Alternative: At least one equivalent arm

$$H_0 : \cap_{g=1}^{k} \text{No equivalence for treatment } k = \cap_{g=1}^{k} \left(\cup_{j=1}^{2p} H_{0;j}^{g} \right)$$

Alternative: All one sided tests

  - Simplest adjustment: Bonferroni
    - Rejection of “no equivalence” for arm g, if

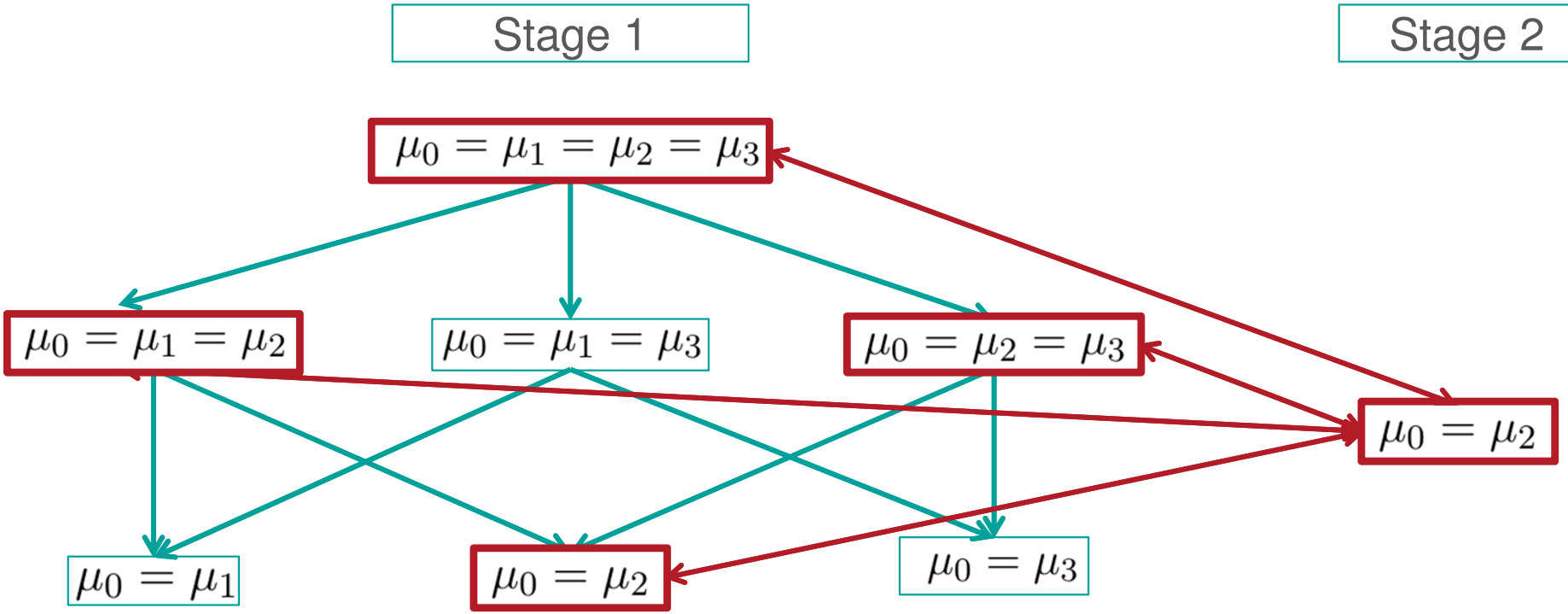
$$\max_{j=1,\ldots,2p} \; p_{1;j}^{g} \leq \frac{\alpha}{k} \Leftrightarrow \max_{j=1,\ldots,2p} \; k p_{1;j}^{g} \leq \alpha$$

2. Adaptive Treatment Arm Selection

Decrease multiplicity penalty by dropping treatment arms:

- First stage still requires multiplicity penalty
- Second stage not adjusted for multiplicity.

Adaptive treatment selection (here not with focus on Bioequivalence):

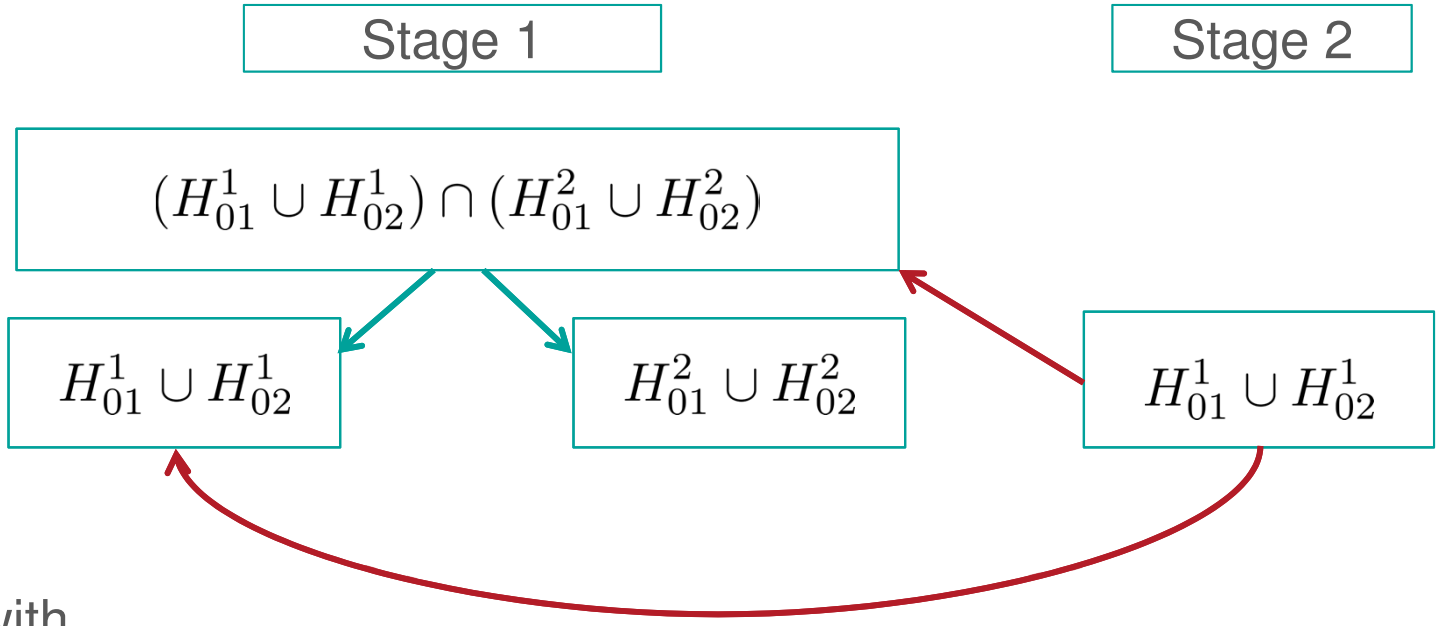


Rejection, if: $Z_2 := \max_{\mathcal{J}, s \in \mathcal{J}} \left\{ \omega_1 \Phi^{-1}(1 - p_{1;\mathcal{J}}) + \omega_2 \Phi^{-1}(1 - p_{2;s}) \right\} > c_{2;\alpha}$

2. Adaptive Treatment Arm Selection

Similar strategy for equivalence hypothesis (one endpoint)

- Rejection of “no-equivalence”, if every test for every one-sided hypotheses may be rejected:



... with

$$(H_{01}^1 \cup H_{02}^1) \cap (H_{01}^2 \cup H_{02}^2) = \left(H_{01}^1 \cap (\cup_{j=1}^2 H_{0;j}^2)\right) \cup \left(H_{02}^1 \cap (\cup_{j=1}^2 H_{0;j}^2)\right)$$

2. Adaptive Treatment Arm Selection

Decision rule:

- General number of endpoints *p*
- Rejection of $\cup_{i=1}^{2p} H_{0i}^{s}$, if:

$$\min_{i=1,\ldots,2p} \left\{\omega_1 \Phi^{-1}(1-p_{1;i}^{\mathcal{J}}) + \omega_2 \Phi^{-1}(1-p_{2;i}^{s})\right\} > c_{2;\alpha}$$

where $p_{1;i}^{\mathcal{J}} = \max\left\{p_{1;i}^{s}, 2\min\{p_{1;i}^{s}, \max_{j=1,\ldots,2p}\{p_{1;j}^{\bar{s}}\}\}\right\}$

$H_{0i}^{s} \cap (\cup_{j=1}^{2p} H_{0;j}^{\bar{s}})$

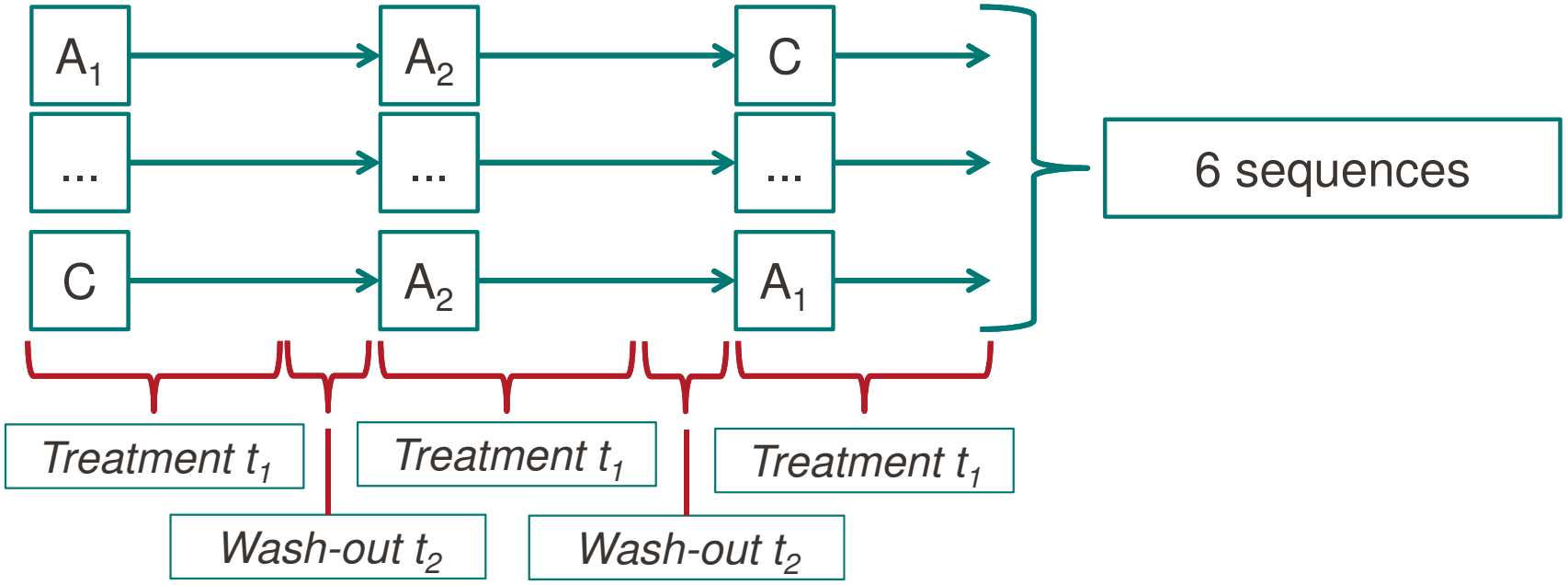
- Specially for "select the best*": $p_{1;i}^{\mathcal{J}} = 2p_{1;i}^{s},\ i = 1, \ldots, 2p$

**Best defined as arm with minimum maximum p value*

3. Cross-over design for the proof of bioequivalence

Target:

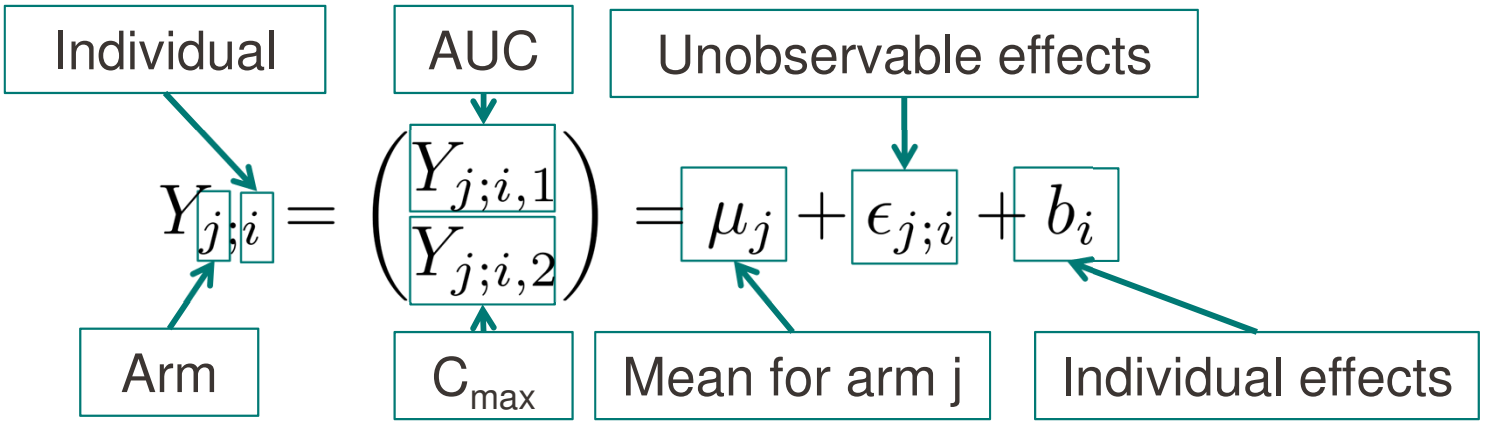
- Evaluate A_1 and A_2 for Bioequivalence against reference C
- First stage: each individual receives all arms
- Each individual randomized to one sequence of study arms:



- After treatment period t_1 estimation of AUC and Cmax for the studied arm
- Assumption: No carry-over and sequence effects

3. Cross-over design for the proof of bioequivalence

Model of observations for one treatment arm on one individual:



- Assumption on unobservable effects:

$$\epsilon_{j;i} \sim \mathcal{N}(0, \Sigma) \qquad \Sigma = \sigma_1^2 \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$$

- Assumption on individual effects:

$$b_i \sim \mathcal{N}(0, D) \qquad D = \begin{pmatrix} d_1 & 0 \\ 0 & d_2 \end{pmatrix}$$

3. Cross-over design for the proof of bioequivalence

Model of observations for all treatment arms on one individual:

AUC and C_{max} arm C

AUC and C_{max} arm A_2

$$Y_i = \begin{pmatrix} Y_{C;i} \\ Y_{A_1;i} \\ Y_{A_2;i} \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} \mu_C \\ \mu_{A_1} \\ \mu_{A_2} \end{pmatrix}, S \right)$$

- Variance structure:
  - Between treatments: $Cov(Y_{j;i}, Y_{j',i}) = D$
  - Within treatments: $Var(Y_{j;i}) = \Sigma + D$
- Maximum-Likelihood estimator for the mean parameters:

$$\widehat{\mu} = \frac{1}{n}\sum_{i=1}^{n} Y_i, \; Cov(\widehat{\mu}) = \frac{1}{n}S$$

3. Cross-over design for the proof of bioequivalence

To be studied: Bioequivalence with reference C:

Difference in AUC and C_{max} arm 1 to reference

Difference in AUC and C_{max} arm 2 to reference

$$\widehat{\theta} \sim \mathcal{N}\left(\begin{pmatrix} \mu_{A_1} - \mu_C \\ \mu_{A_2} - \mu_C \end{pmatrix}, \frac{1}{n} V\right)$$

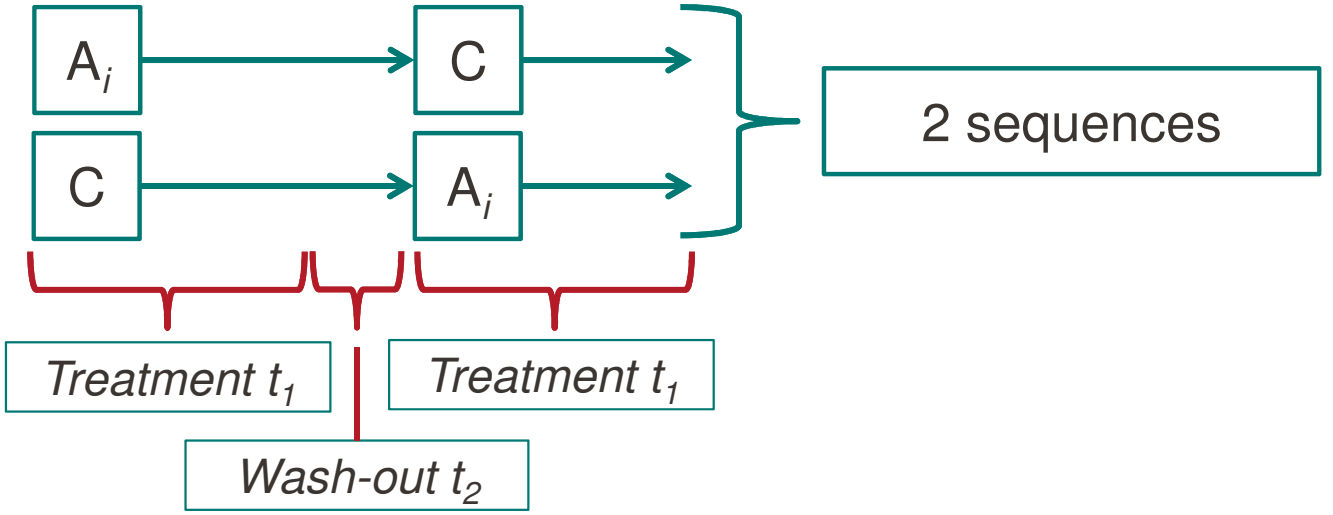
- Variance structure:
  - Between treatments: $Cov(\widehat{\theta}_j, \widehat{\theta}_{j'}) = \frac{1}{n}\Sigma$
  - Within treatments: $Var(\widehat{\theta}_j) = \frac{2}{n}\Sigma$
- Variance of estimator in dependence on treatment arms and sequence size:

$$Cov(\widehat{\theta}_1) = \frac{1}{n_1 \times 3!} V$$

3. Cross-over design for the proof of bioequivalence

Treatment arm selection:

- After interim analysis, only one arm vs. reference



- Possible advantages:
  - Time savings: Second stage savings: t_1+t_2
  - Observation savings due to reduced number of treatment arms
  - Patient savings due to reduced multiplicity
- Variance of estimator in dependence on treatment arms and sequence size:

$$Cov(\widehat{\theta}_2) = \frac{1}{2n_2} 2\Sigma$$

3. Cross-over design for the proof of bioequivalence

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Considered situations:

1. **Fixed max. number of subjects:**
    1. Dependence of power on stopping rule?
    2. Dependence of power on standard deviation?
    3. Dependence of power on interim timing?
2. Required patients for target power:
    1. Dependence of patient number on standard deviation?
    2. Dependence of patient number on interim timing?

3. Cross-over design for the proof of bioequivalence

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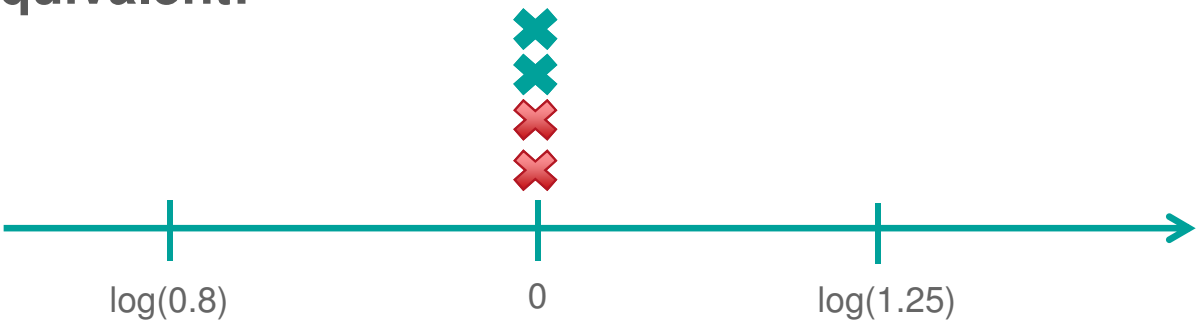
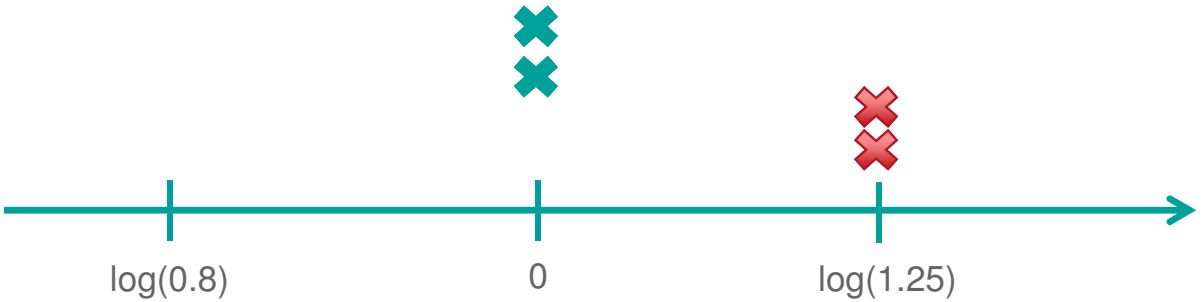
Considered scenarios:

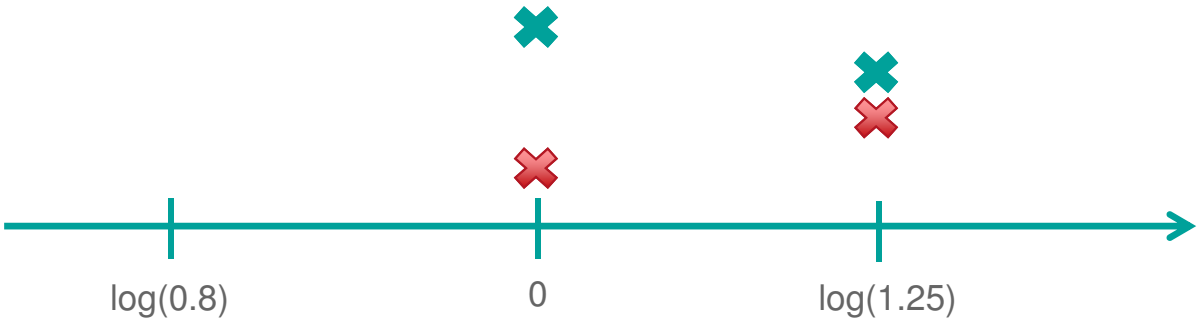
1. **Both equivalent:**



2. **Only one arm equivalent:**



3. **No arm equivalent**

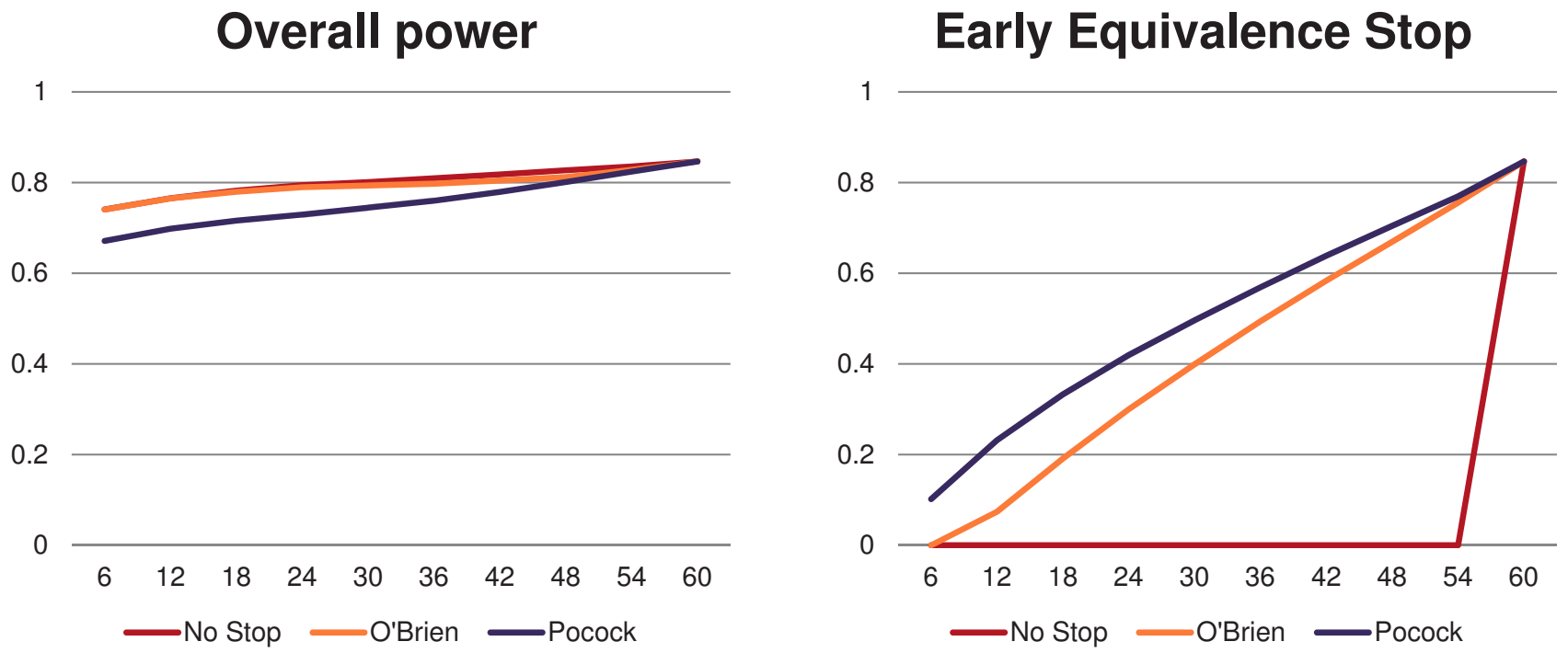


3. Cross-over design for the proof of bioequivalence

Considered situations:

1. Fixed max. number of subjects: N=60

Dependence of power on the stopping rule:



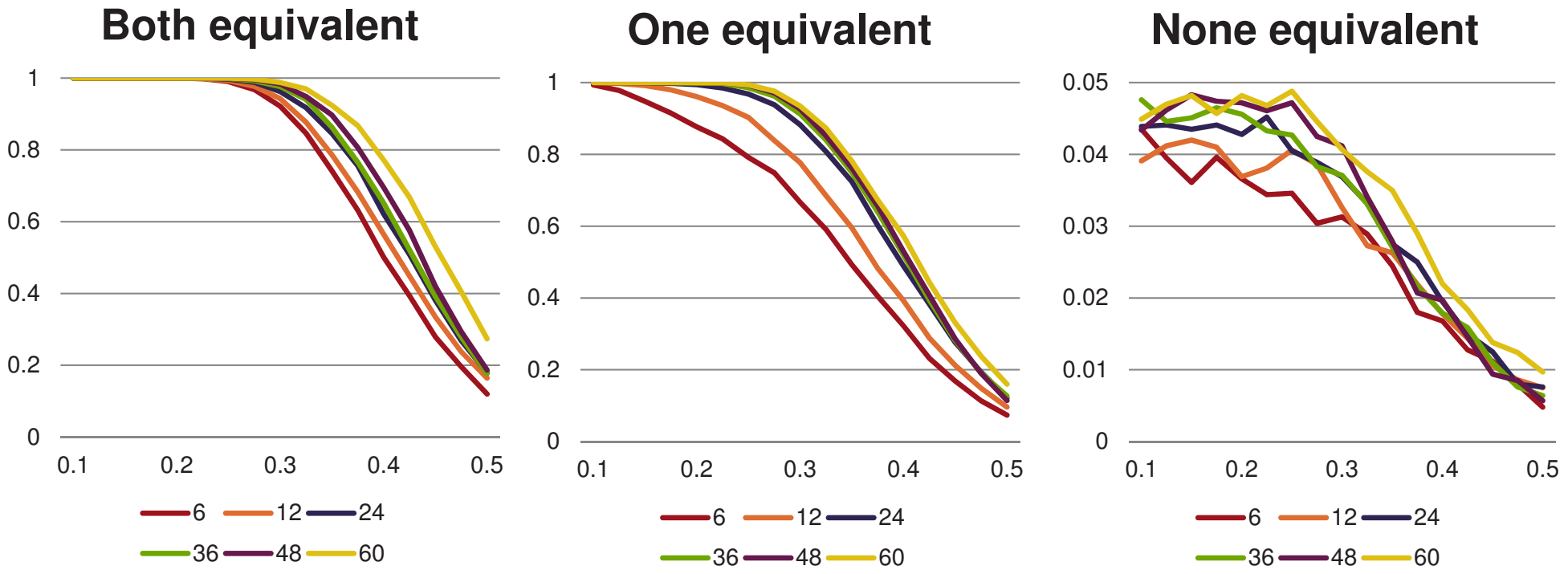
- Average across all standard deviation scenarios (0.1 – 0.5)
- O'Brien&Fleming: Power here similar to "No Stop"

3. Cross-over design for the proof of bioequivalence

Considered situations:

1. Fixed max. number of subjects: N=60

Dependence of power on the standard deviation



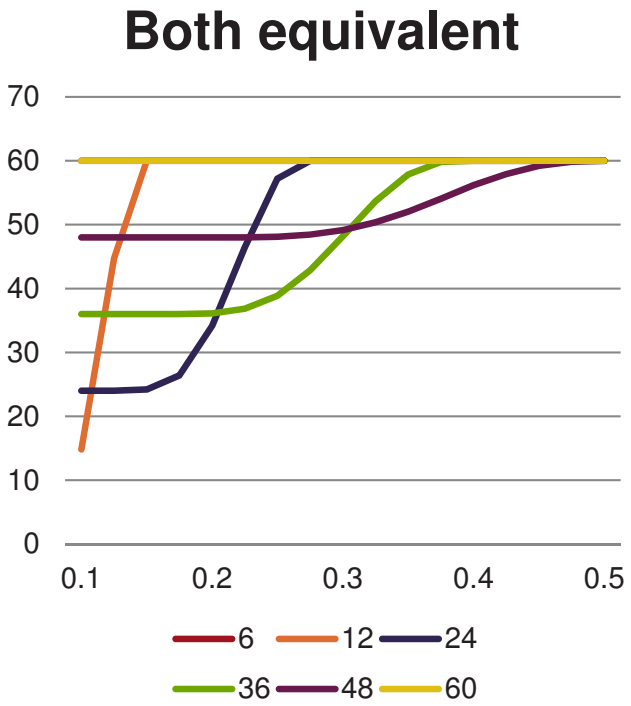
- The later the interim, the higher the power (simple...)
- Type-1 error controlled

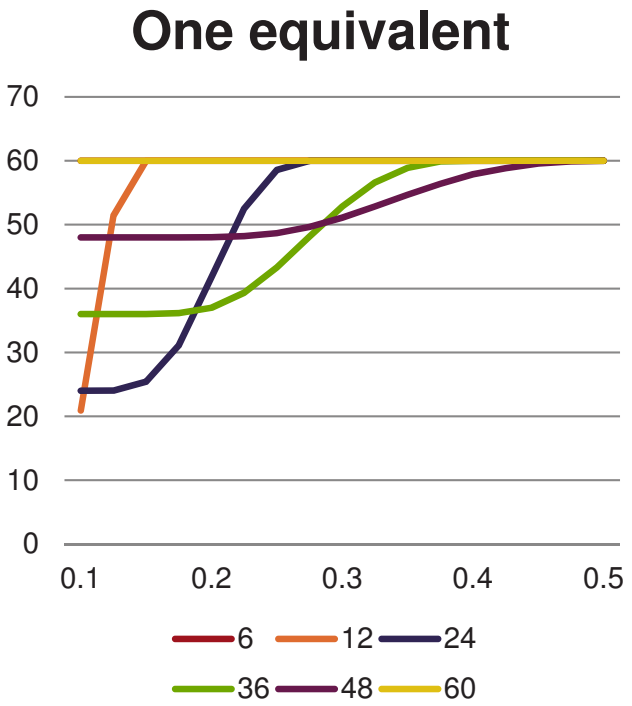
3. Cross-over design for the proof of bioequivalence

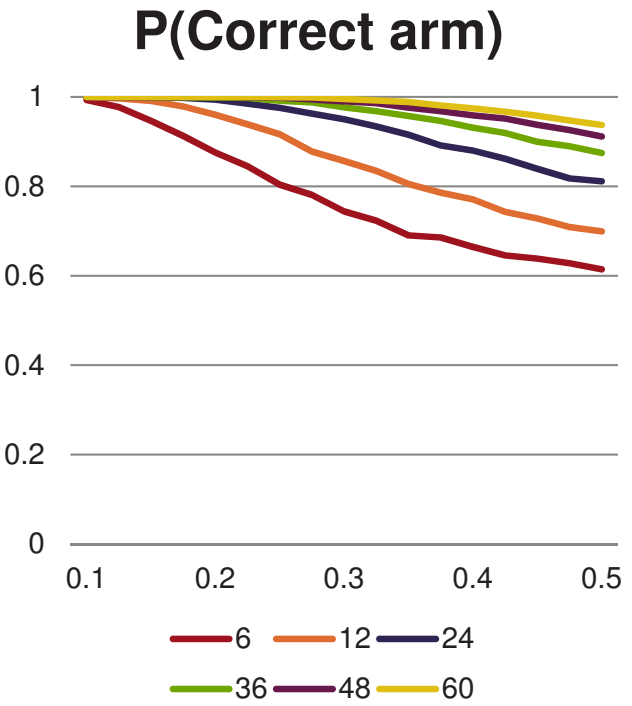
Considered situations:

1. Fixed max. number of subjects: N=60

Average number of patients / Probability to select correct arm







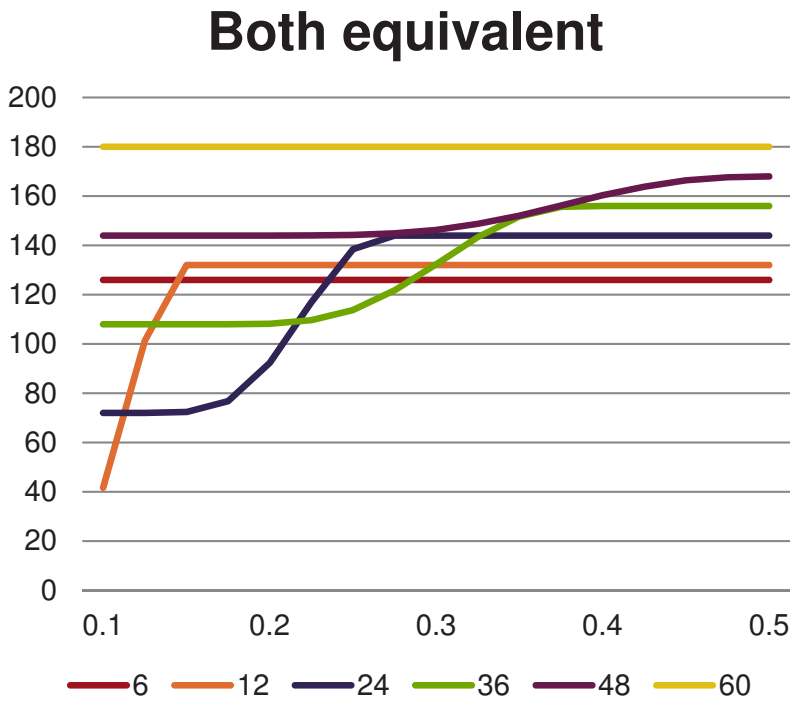
- Given similar power: treatment selection after 24 / 36 promising
- Early selection: High probability to select wrong treatment.

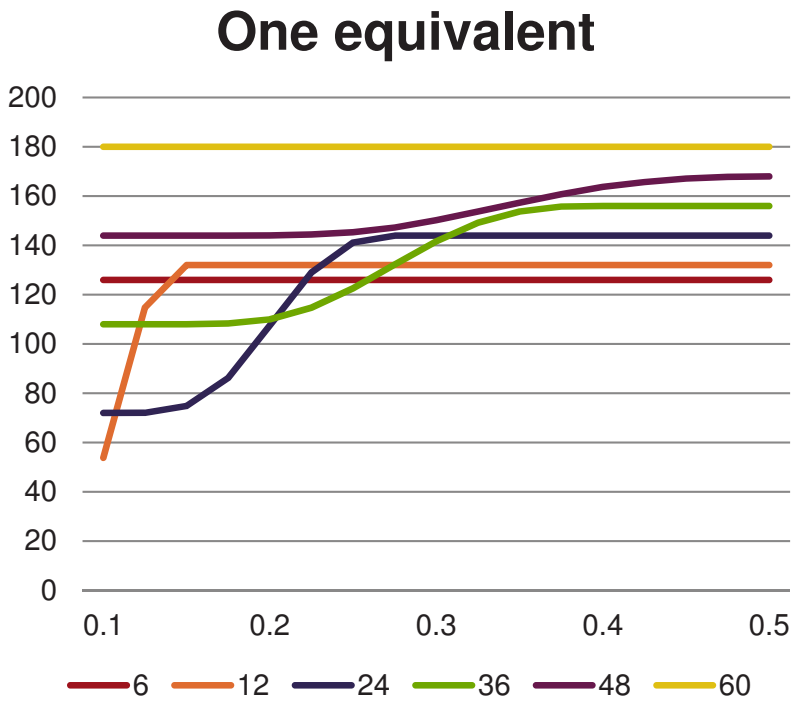
3. Cross-over design for the proof of bioequivalence

Considered situations:

1. Fixed max. number of subjects: N=60

Average number of observations





➢ Fixed designs needs much more observations

3. Cross-over design for the proof of bioequivalence

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Considered situations:

1. Fixed max. number of subjects:
    1. Dependence of power on stopping rule?
    2. Dependence of power on standard deviation?
    3. Dependence of power on interim timing?

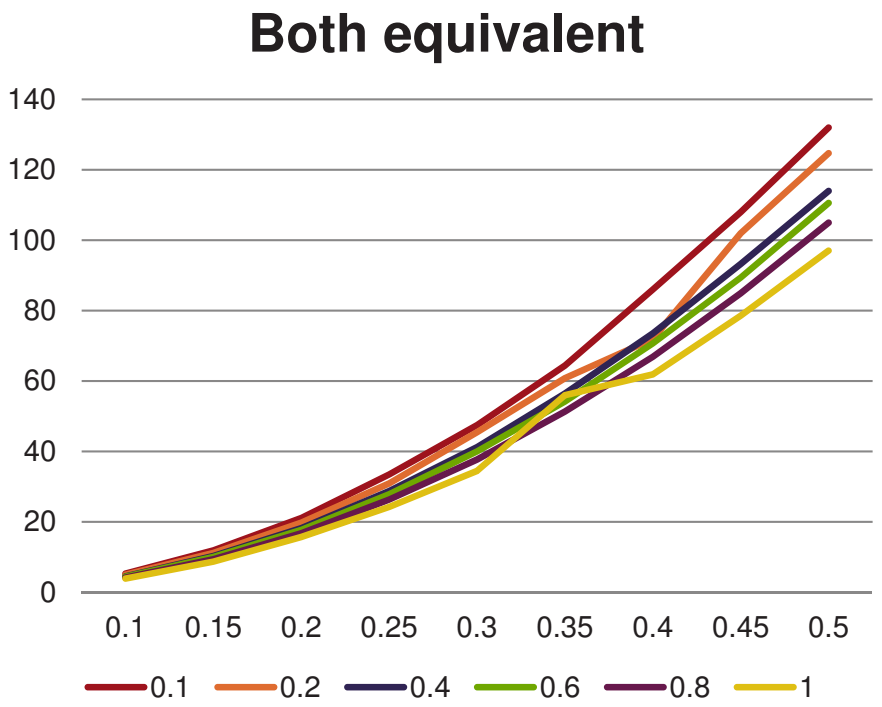
2. **Required patients for target power:**
    1. Dependence of patient number on standard deviation?
    2. Dependence of patient number on interim timing?

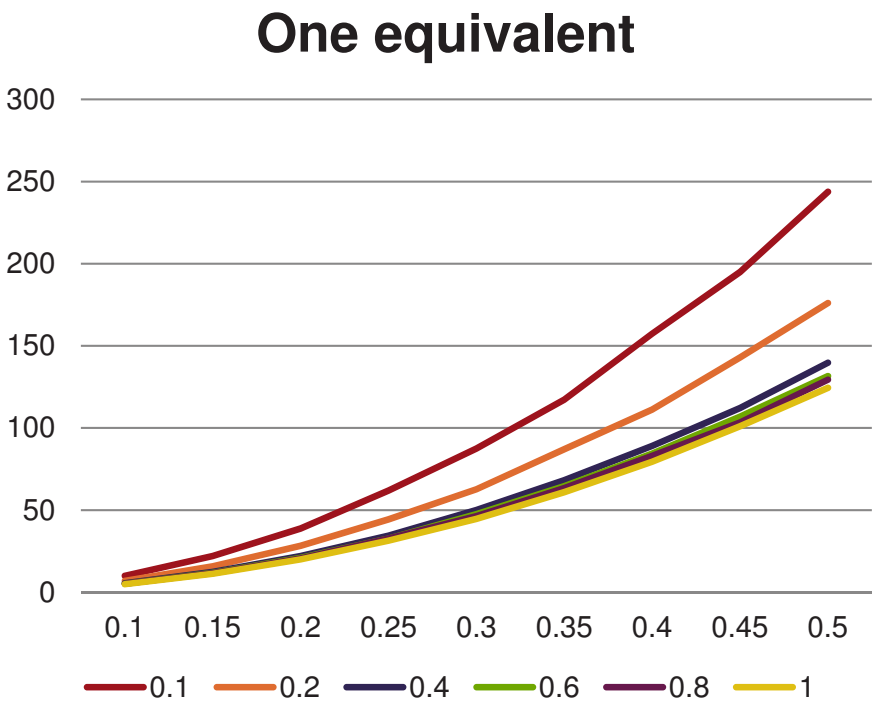
3. Cross-over design for the proof of bioequivalence

Considered situations:

1. Target power: 80%

Required Number of Patients





- Number of patients at minimum with no selection

4. Summary

Adaptive treatment arm selection in bioequivalence trials promising...

- Reduction of the required number of observations
- Reduction of study duration

... but not always the best option:

- Number of required patients may be larger than in a fixed trial
- Complex trial design (Switch from 3-way to 2-way crossover)

Need to take constraints into account, e.g.:

- High costs per patient, low costs per observation → fixed design
- High cost per observation, low costs per patient → adaptive design

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Thank you for your attention!