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Optimizing the design of a dose-finding trial: theoretical methods and practical aspects

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Dose-finding case study

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- Analgesia drug: dose-effect relationship to be estimated in clinical trial

- Doses possible: 0 (placebo), 20, 40, 60, 80, 100 mg
- ~300 patients to be randomized to one of these doses
- Treatment effect measured after 6 weeks (pain rating)

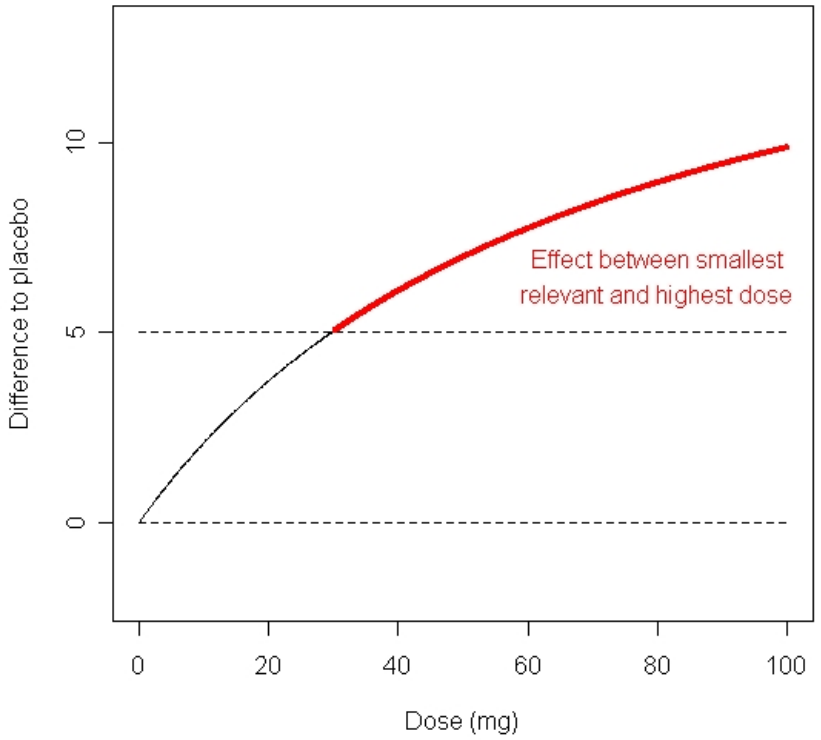
- Design question: How many patients to allocate to each of the doses?

Content

- Objective of the study
- Prior knowledge for the study
- Optimization approaches
- Determination of good dose-finding designs

Dose-finding case study: Objective

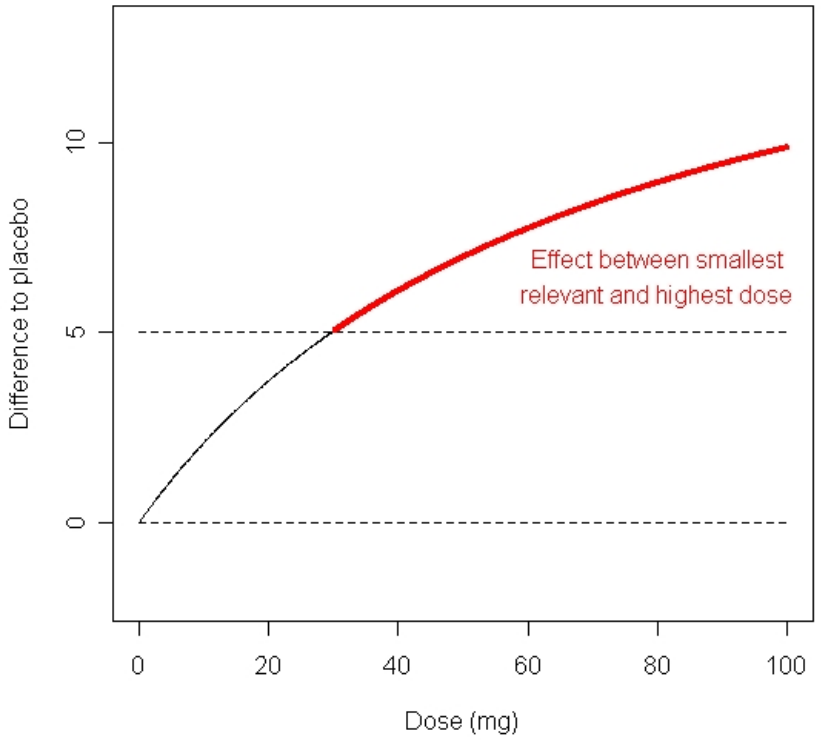
- Effects of <5 (compared to placebo-effect) are of no medical interest
- Smallest relevant dose = dose x_δ with effect 5
- We want to estimate effect between smallest relevant and highest dose (x_{max}=100mg)
- This is for us the "interesting part"



Dose-finding case study: Objective

- Further objectives:
- Test if the drug has effect
- Estimate dose with smallest relevant effect
- Estimate largest possible effect

- Aim: Frequentist analysis based on data from current study



Dose-finding case study: Objective

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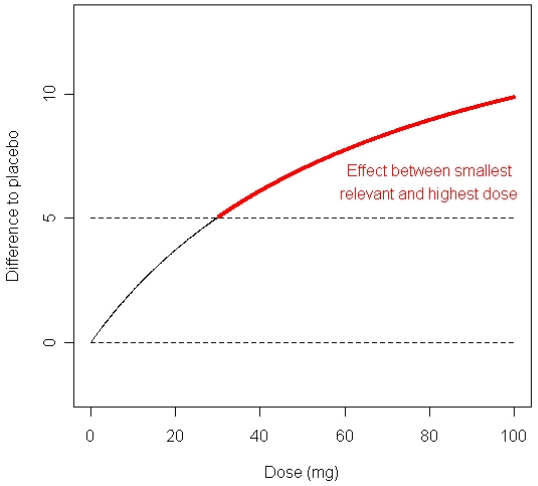
- Model

$$f(x) = f(x,\vartheta) = E_0 + \frac{E_{\max} \cdot x^{\alpha}}{ED_{50}^{\alpha} + x^{\alpha}},\ x = dose,\ \vartheta = (E_0, E_{\max}, ED_{50}, \alpha)$$

- Asymptotic **variance for LS-estimate of f(x)-f(0):** $d(x,\vartheta)$
- Take average variance for x between smallest relevant and highest dose
- Minimize it by choice of design ξ (allocation to doses)



Dose-finding case study: Objective

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- $f(x) = f(x,\vartheta) = E_0 + \dfrac{E_{\max} \cdot x^{\alpha}}{ED_{50}^{\alpha} + x^{\alpha}}, \; x = dose, \; \vartheta = (E_0, E_{\max}, ED_{50}, \alpha)$

- Asymptotic **variance of LS-estimate for f(x)-f(0):**

$$d(x,\xi,\vartheta) = (g(x,\vartheta) - g(0,\vartheta))^T \cdot M^{-1}(\xi,\vartheta) \cdot (g(x,\vartheta) - g(0,\vartheta))$$

where $$g(x,\vartheta) = \left(\frac{\partial f(x,\vartheta)}{\partial E_0}, \frac{\partial f(x,\vartheta)}{\partial E_{\max}}, \frac{\partial f(x,\vartheta)}{\partial ED_{50}}, \frac{\partial f(x,\vartheta)}{\partial \alpha} \right)^T$$

and $$M(\xi,\vartheta) = \int g(x,\vartheta) \cdot g(x,\vartheta)^T \; \xi(dx)$$

- Average variance of all LS-estimates for f(x) - f(0) with $x_\delta < x < x_{max}$ to be minimized, i.e.

$$\Phi(\xi,\vartheta) = \left(\frac{1}{x_{\max} - x_\delta} \int_{x_\delta}^{x_{\max}} d(x,\xi,\vartheta) dx \right)^{-1}$$

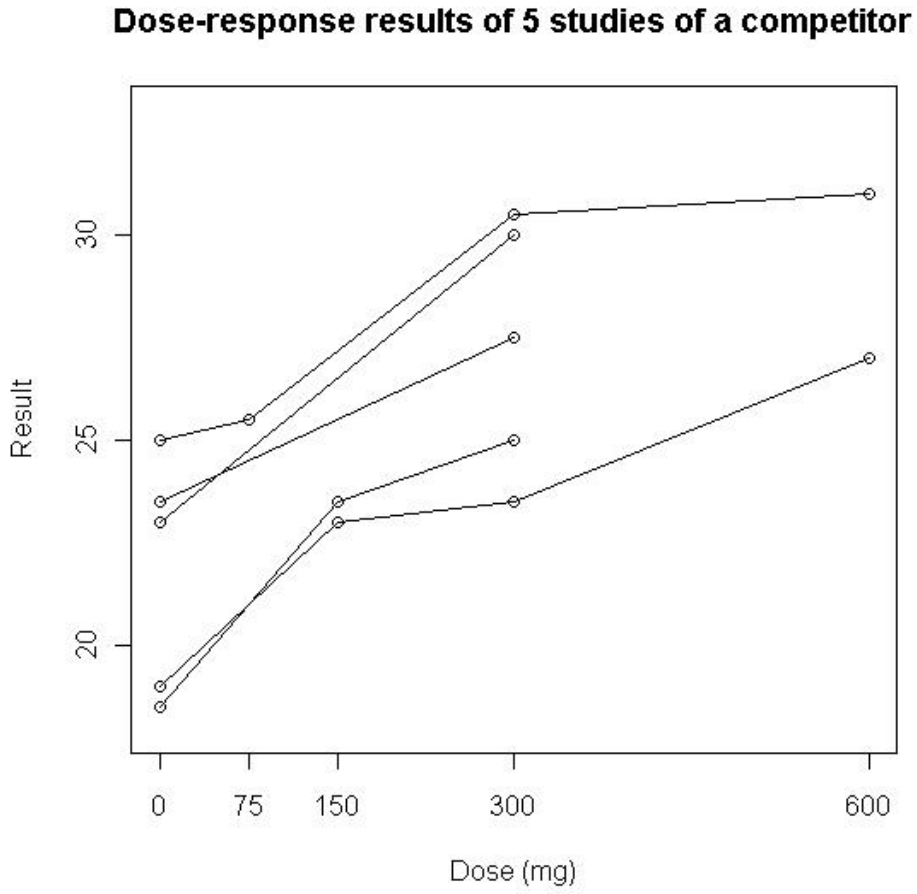
to be maximised

Dose-finding case study: Prior knowledge

- Literature data on competing drug with similar mechanism
- ➢ E_{max}-sigmoid model seems appropriate

$$f(x) = E_0 + \frac{E_{\max} \cdot x^{\alpha}}{ED_{50}^{\alpha} + x^{\alpha}}$$

- ➢ E_0 varies between studies (but is of minor interest)



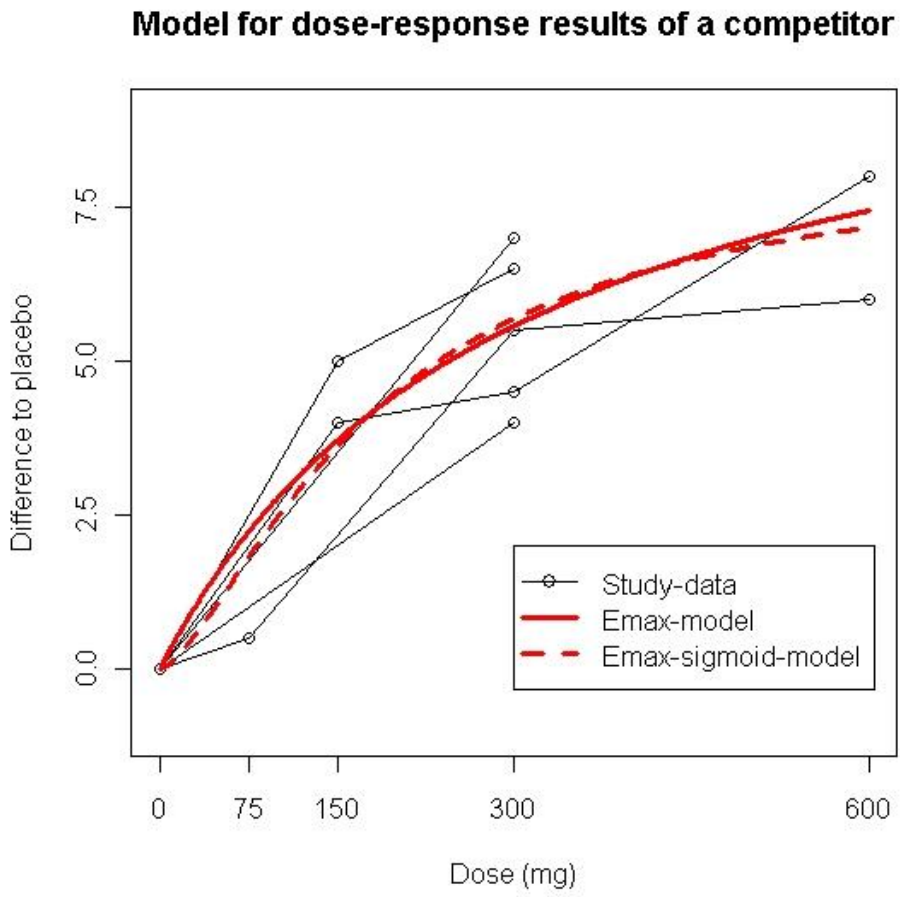
Dose-finding case study: Prior knowledge

- Model-fit

$$f(x) = E_0 + \frac{8.4 \cdot x^{1.47}}{182^{1.47} + x^{1.47}}$$

$$f(x) = E_0 + \frac{11.2 \cdot x}{304 + x}$$

➢ Parameters for prior guess scenario:
E_{max}=11.2, α=1

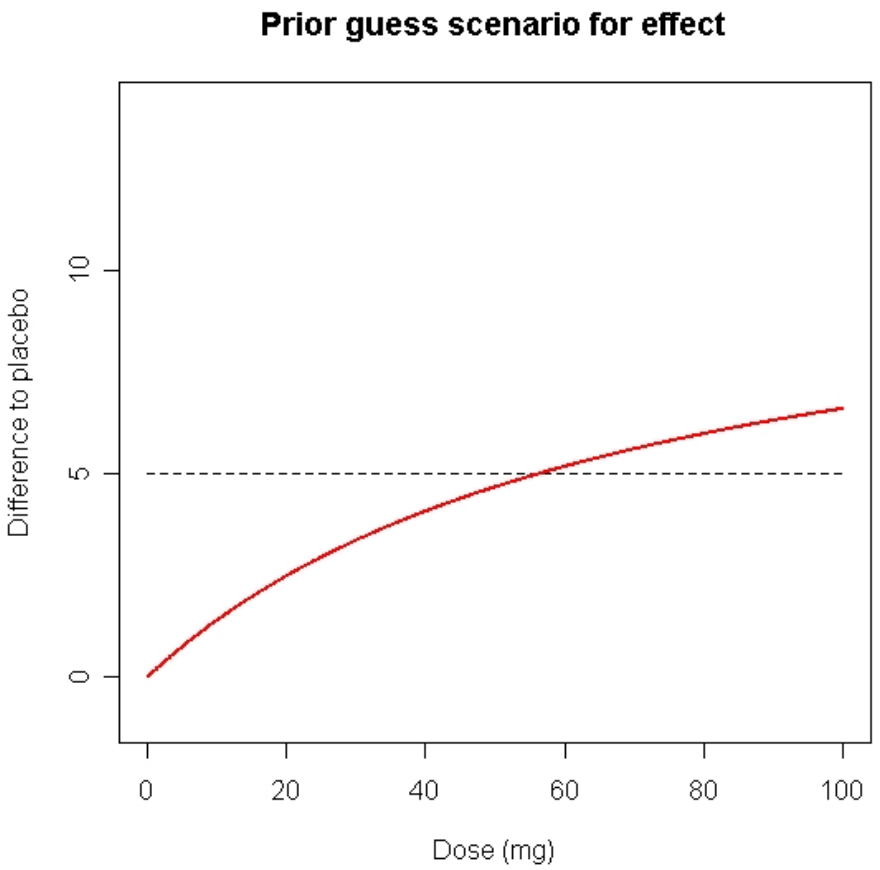


Dose-finding case study: Prior knowledge

- Preclinical studies with new drug and data on human receptor occupancy lead to prior guess $ED_{50}=70mg$

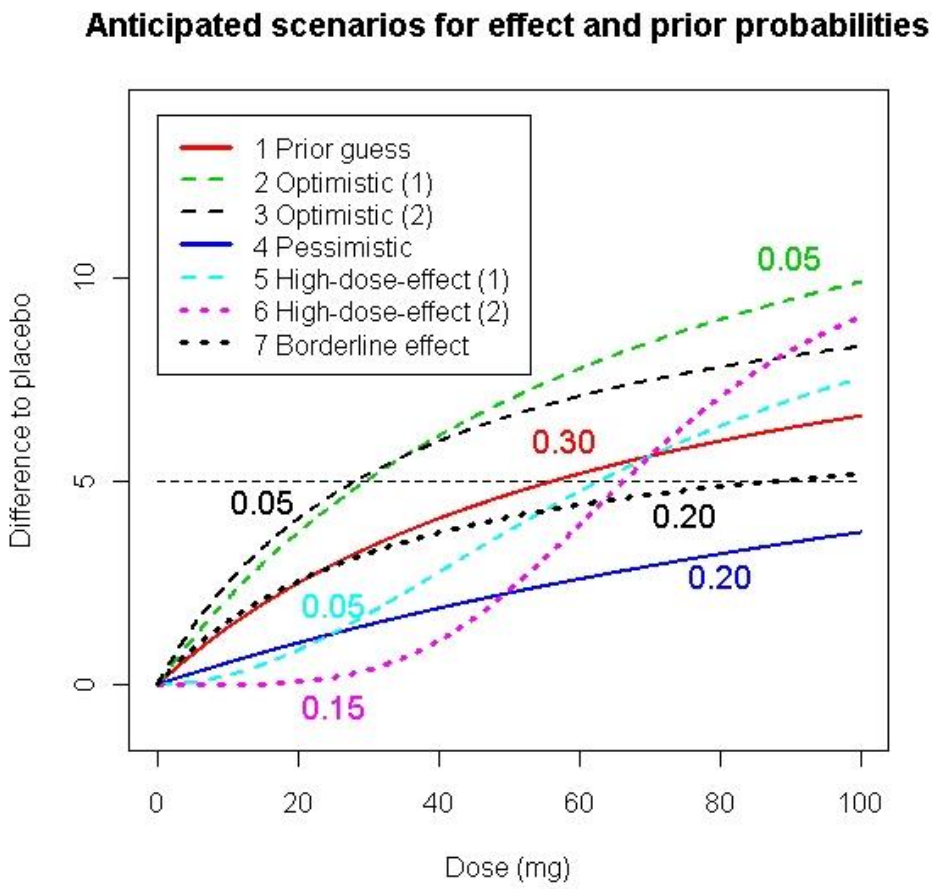
➢ Prior guess scenario

$$f(x) = E_0 + \frac{11.2 \cdot x}{70 + x}$$



Dose-finding case study: Prior knowledge

- Alternative scenarios developed (uncertainty in prior information)
- Seven scenarios
- Prior probabilities associated with scenarios (these are quite rough guesses)



Approach for optimization

- $f(x) = f(x, \vartheta) = E_0 + \dfrac{E_{\max} \cdot x^{\alpha}}{ED_{50}^{\alpha} + x^{\alpha}}, \; x = dose, \; \vartheta = (E_0, E_{\max}, ED_{50}, \alpha)$
- We want to maximize $\Phi(\xi, \vartheta) = \left(\dfrac{1}{x_{\max} - x_{\delta}} \int_{x_{\delta}}^{x_{\max}} d(x, \xi, \vartheta) dx \right)^{-1}$
- We have 7 scenarios $\vartheta_i, i = 1,...,7$ and can calculate an optimal design for each scenario (called ”locally optimal design”)
- But we need to choose the design before knowing the true scenario

Approach for optimization

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- **Prior guess** approach: Locally optimal design for prior guess scenario $\max_\xi \Phi(\xi, \vartheta_1)$

- **Bayesian optimal** design:
  Maximize $\max_\xi \sum_{i=1}^{7} \pi_i \Phi(\xi, \vartheta_i)$
  $(\pi_i = \text{prior prob. for } \vartheta_i)$

- **Maximin optimal** design: $\max_\xi \min_{i=1,\ldots,7} \Phi(\xi, \vartheta_i)$

- Possible to apply these approaches sequentially

Approach for optimization – relative to a reference design

- **Prior guess** approach: Locally optimal design for prior guess scenario

$$\max_{\xi} \Phi(\xi, \vartheta_1) / \Phi(\lambda, \vartheta_1)$$

(we use here λ = balanced design as reference design)

- **Bayesian optimal** design:

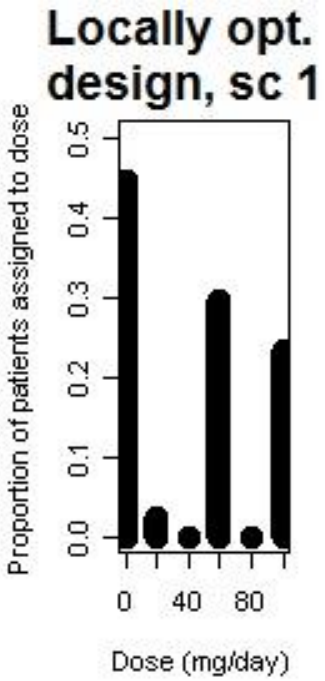
  Maximize $\max_{\xi} \sum_{i=1}^{7} \pi_i \Phi(\xi, \vartheta_i) / \Phi(\lambda, \vartheta_i)$

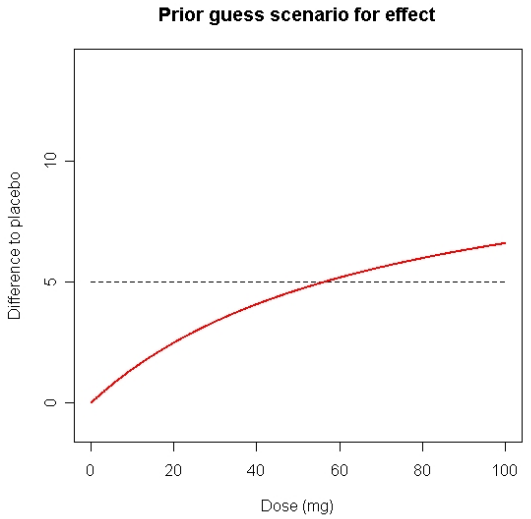
  (π_i = prior prob. for ϑ_i)

- **Maximin optimal** design: $\max_{\xi} \min_{i=1,\ldots,7} \Phi(\xi, \vartheta_i) / \Phi(\lambda, \vartheta_i)$

- Possible to apply these approaches sequentially

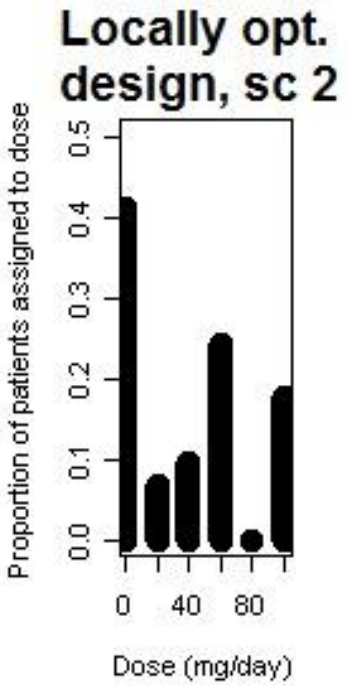
Locally optimal design for prior guess approach

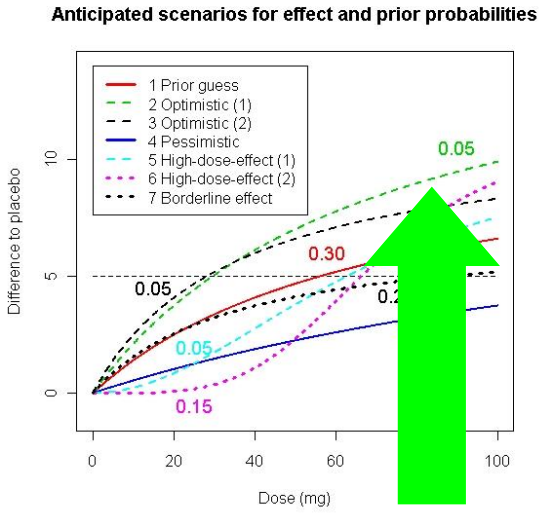




- Locally optimal design allocates
  45% to placebo, 3% to 20mg, 0% to 40mg,
  30% to 60mg, 0% to 80mg, 23% to 100mg

Locally optimal design for scenario 2 (optimistic)





- Locally optimal design allocates
  41% to placebo, 7% to 20mg, 10% to 40mg,
  24% to 60mg, 0% to 80mg, 17% to 100mg

Bayesian optimal design
(Miller, Guilbaud, Dette, 2007)

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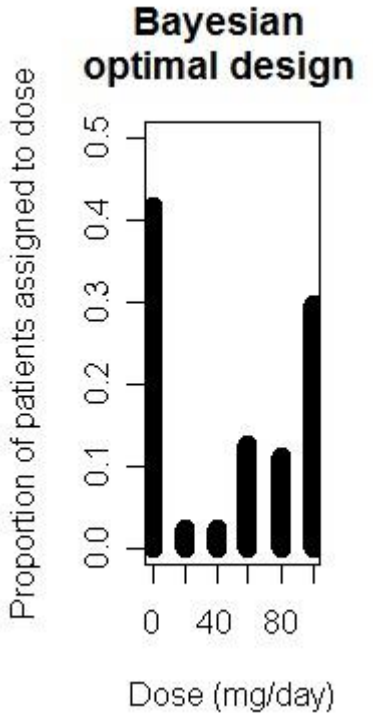
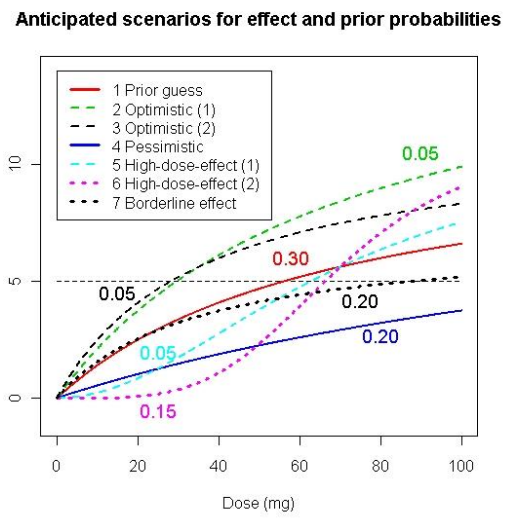
- Efficiency: **1.55**
- This means:
  the **balanced design needs 55% more patients than this optimal design** to obtain estimates with same precision



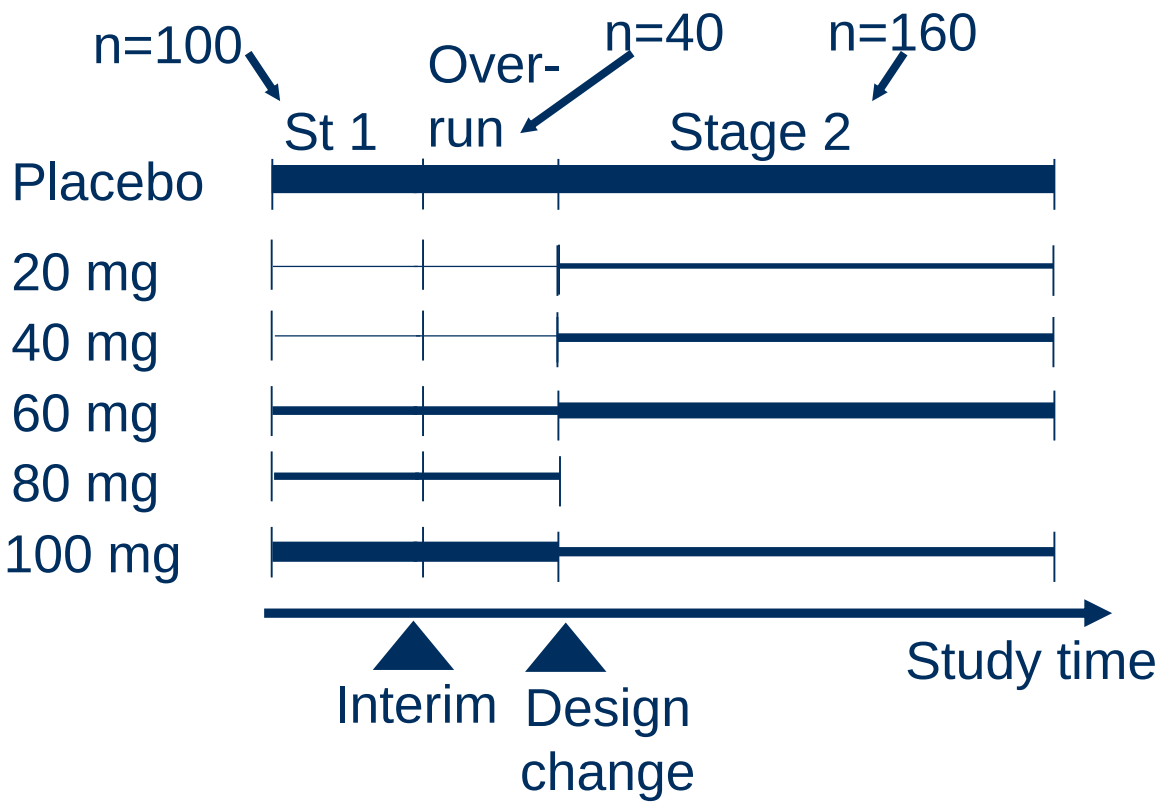


- Bayesian optimal design allocates
  42% to placebo, 2% to 20mg, 2% to 40mg,
  13% to 60mg, 11% to 80mg, 30% to 100mg

Adaptive design

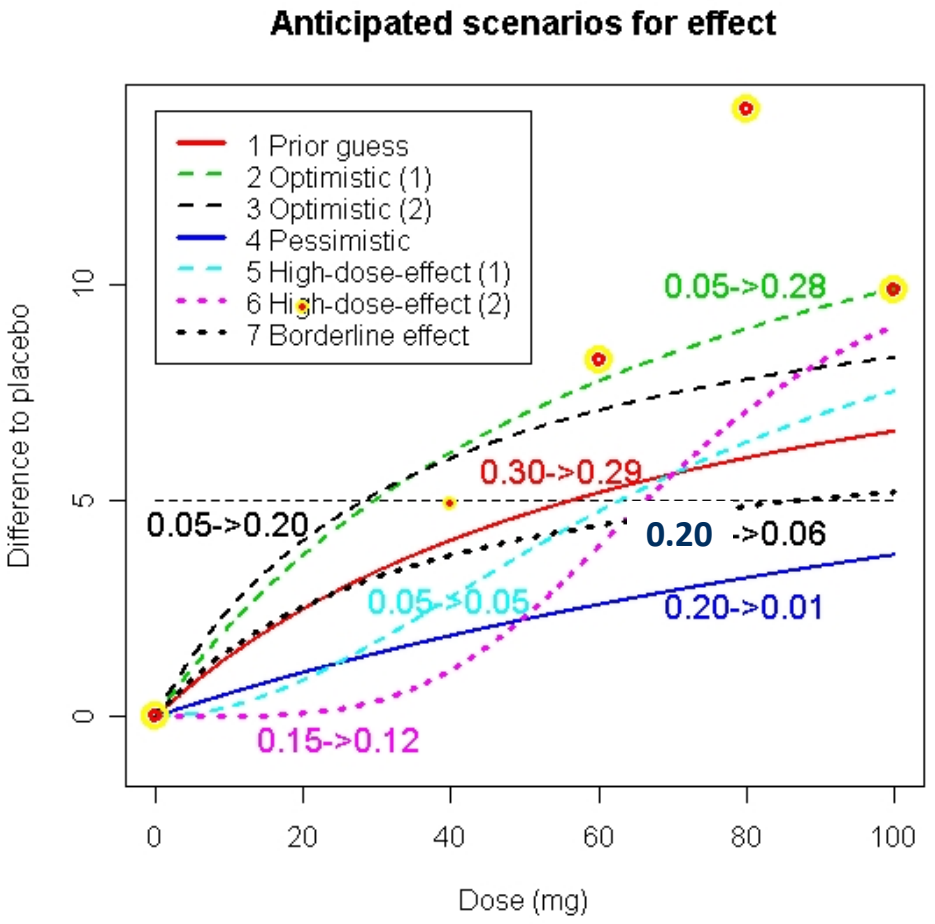
- Calculate in an interim analysis the Bayesian optimal design based on **posterior probabilities**
- Change design to the new optimal design
- The following slides show a simulated example to illustrate the adaptive design

Adaptive design



Adaptive design – simulated example

- Observed in Stage 1: red-yellow circles
- Posteriori probabilities for scenarios calculated (Bayes formula)



Adaptive design – simulated example

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- 140 patients included according to starting design

Dose	**0 mg**	**20mg**	**40mg**	**60mg**	**80mg**	**100mg**	**all**
Stage 1	41	3	2	13	11	30	100
Overrun	17	1	1	4	5	12	40
Stage 2							160
Total							**300**

Adaptive design – simulated example

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- 140 patients included according to starting design

Dose	**0 mg**	**20mg**	**40mg**	**60mg**	**80mg**	**100mg**	**all**
Stage 1	41	3	2	13	11	30	100
Overrun	17	1	1	4	5	12	40
Stage 2							160
Total	**120**	**16**	**25**	**57**	**26**	**56**	**300**

- Based on data from 100 patients: new optimal design (see total row)

Adaptive design – simulated example

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- 140 patients included according to starting design

Dose	0 mg	20mg	40mg	60mg	80mg	100mg	all
Stage 1	41	3	2	13	11	30	100
Overrun	17	1	1	4	5	12	40
Stage 2	62	12	22	40	10	14	160
Total	**120**	**16**	**25**	**57**	**26**	**56**	**300**

- Based on data from 100 patients: new optimal design (see total row)
- Remaining 160 patients allocated ("Stage 2 = Total – Stage 1 – Overrun")

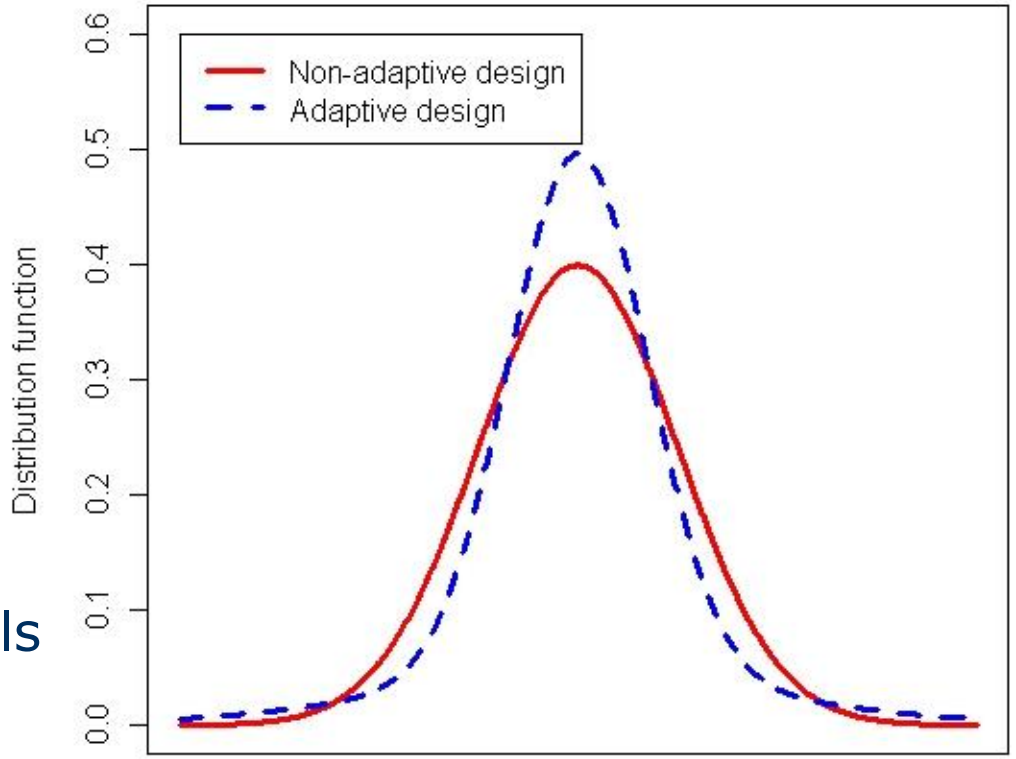
Adaptive design

- The adaptive design has **for our case study the same efficiency** than the Bayesian optimal design
- No gain of adaptation!

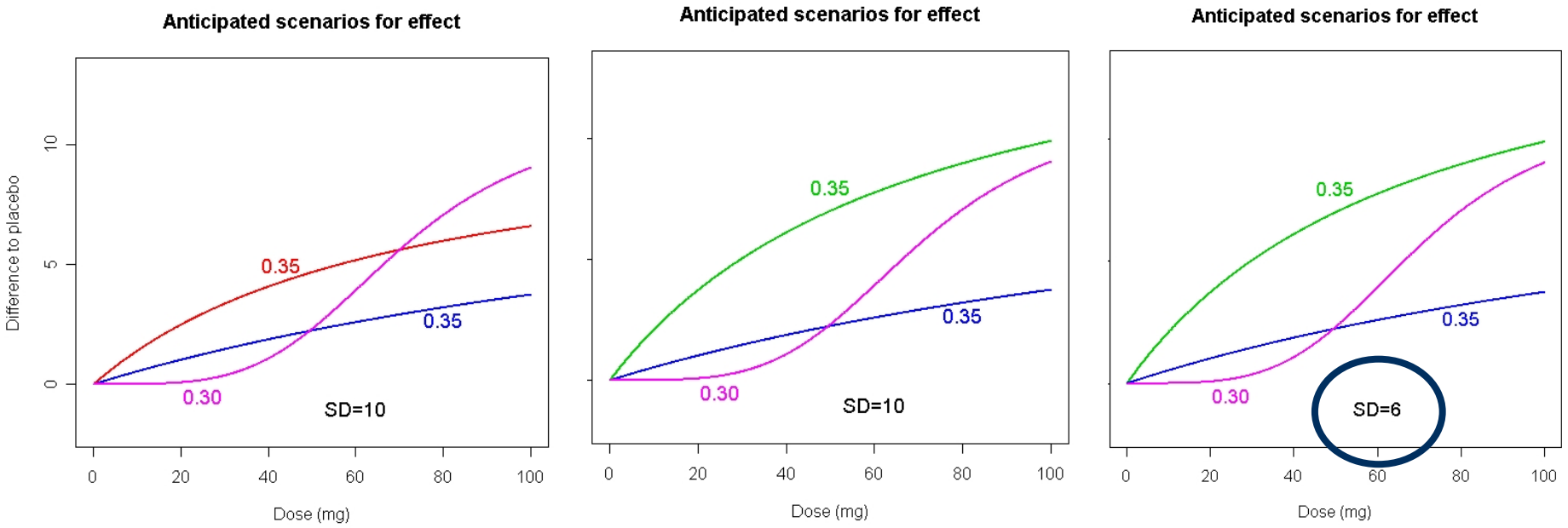
- With some low probability, interim results are far away from true values and then an inefficient design is chosen for Stage 2

Adaptive design: distribution of estimators

- For adaptive designs typically:
- distribution of estimators closer to true parameter with large probability,…
- …but has heavier tails



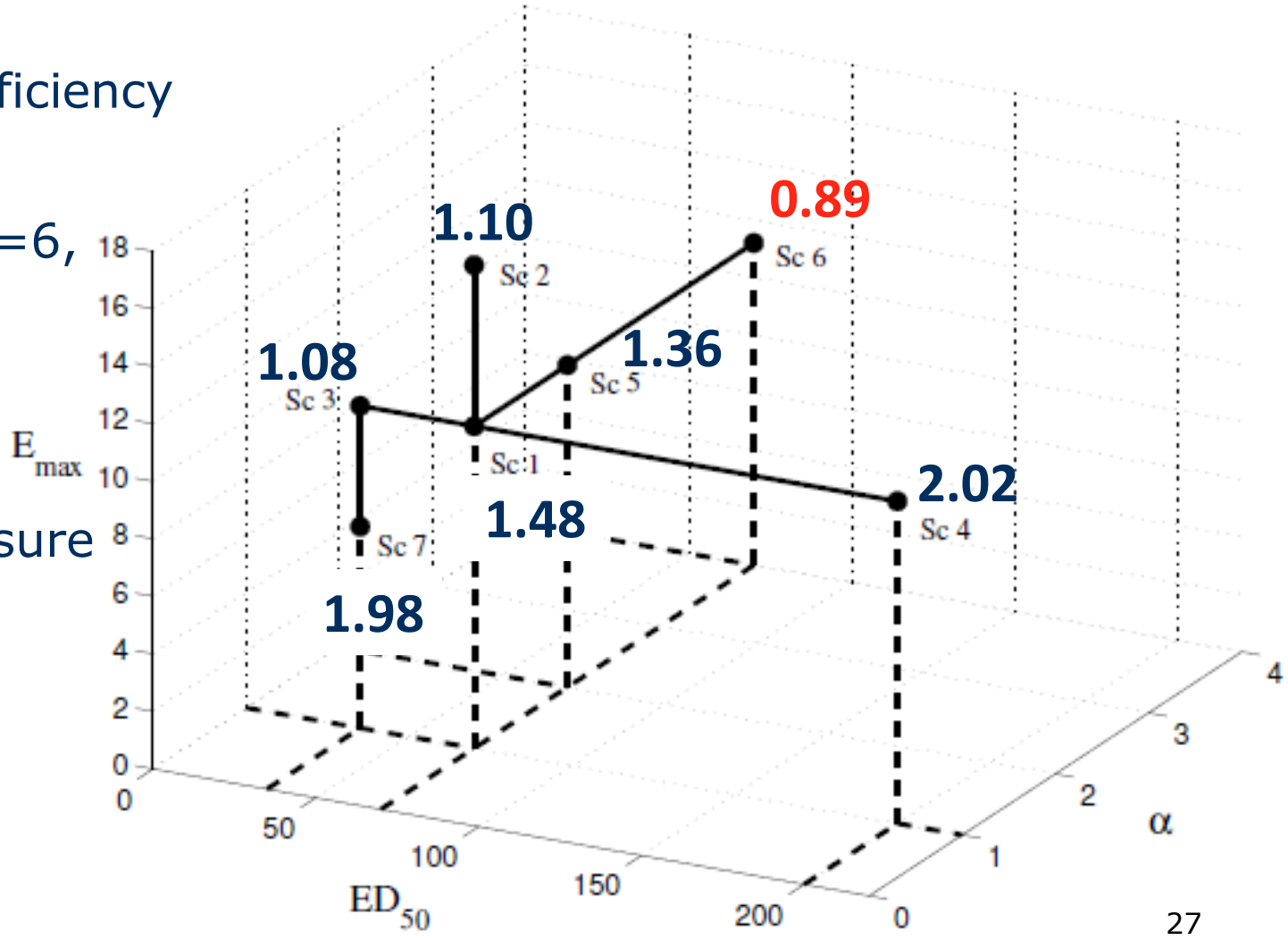
When is an adaptive design useful?
(Miller, 2015)



- No gain of adaptive design in left situation,
- A little gain in the middle situation,
- Some gain in the right picture (interim data is more informative)

Bayesian design

- Average efficiency =**1.55**
- If scenario=6, efficiency =**0.89**
- Can we ensure a minimal efficiency for all 7 scenarios?



Maximin design
(Fackle-Fornius, Miller, Nyquist, 2015)

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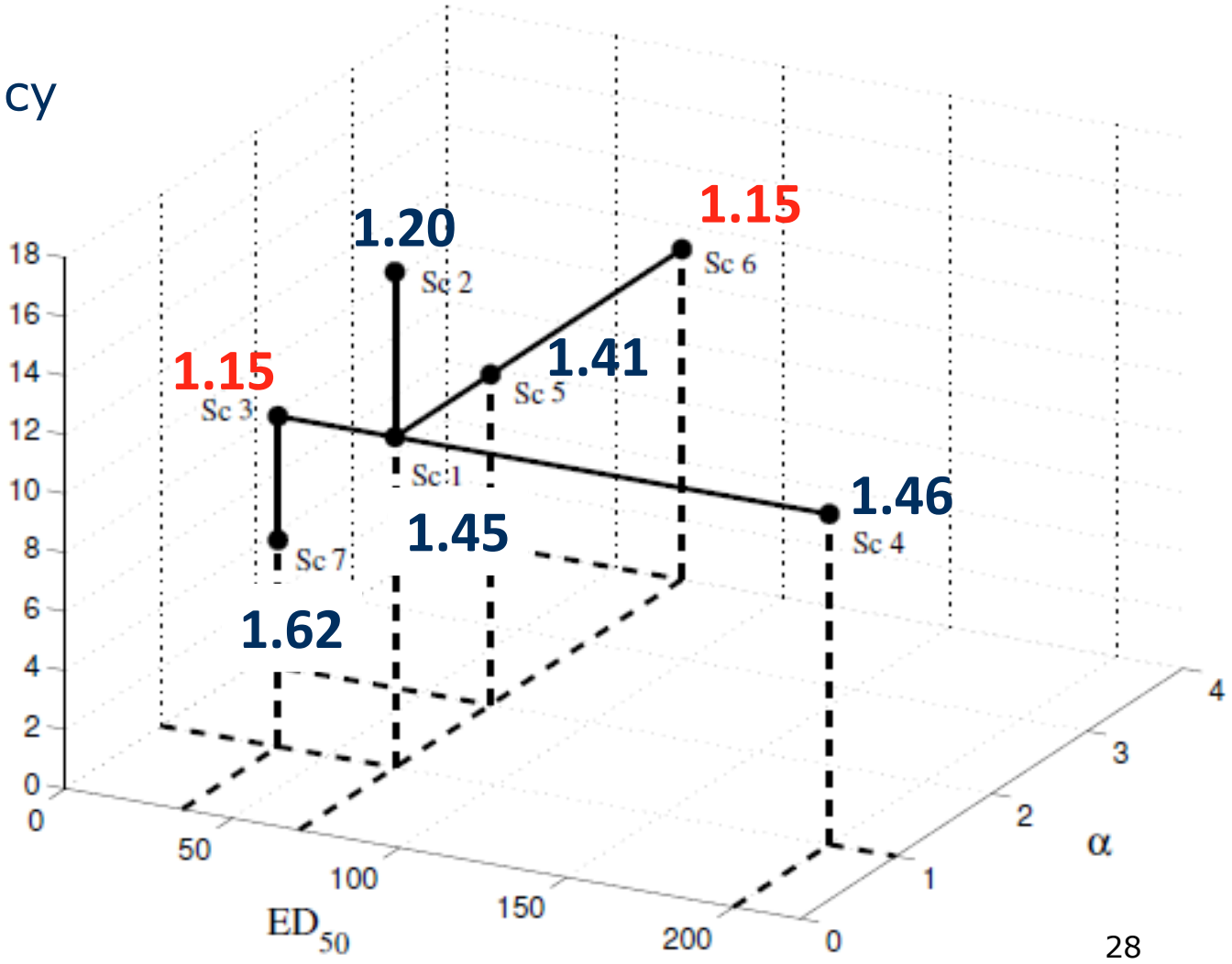
- Minimum efficiency =**1.15**

- Maximin optimal design allocates 36% to plac., 6% to 20mg, 3% to 40mg, 10% to 60mg, 27% to 80mg, 18% to 100mg



Maximin design

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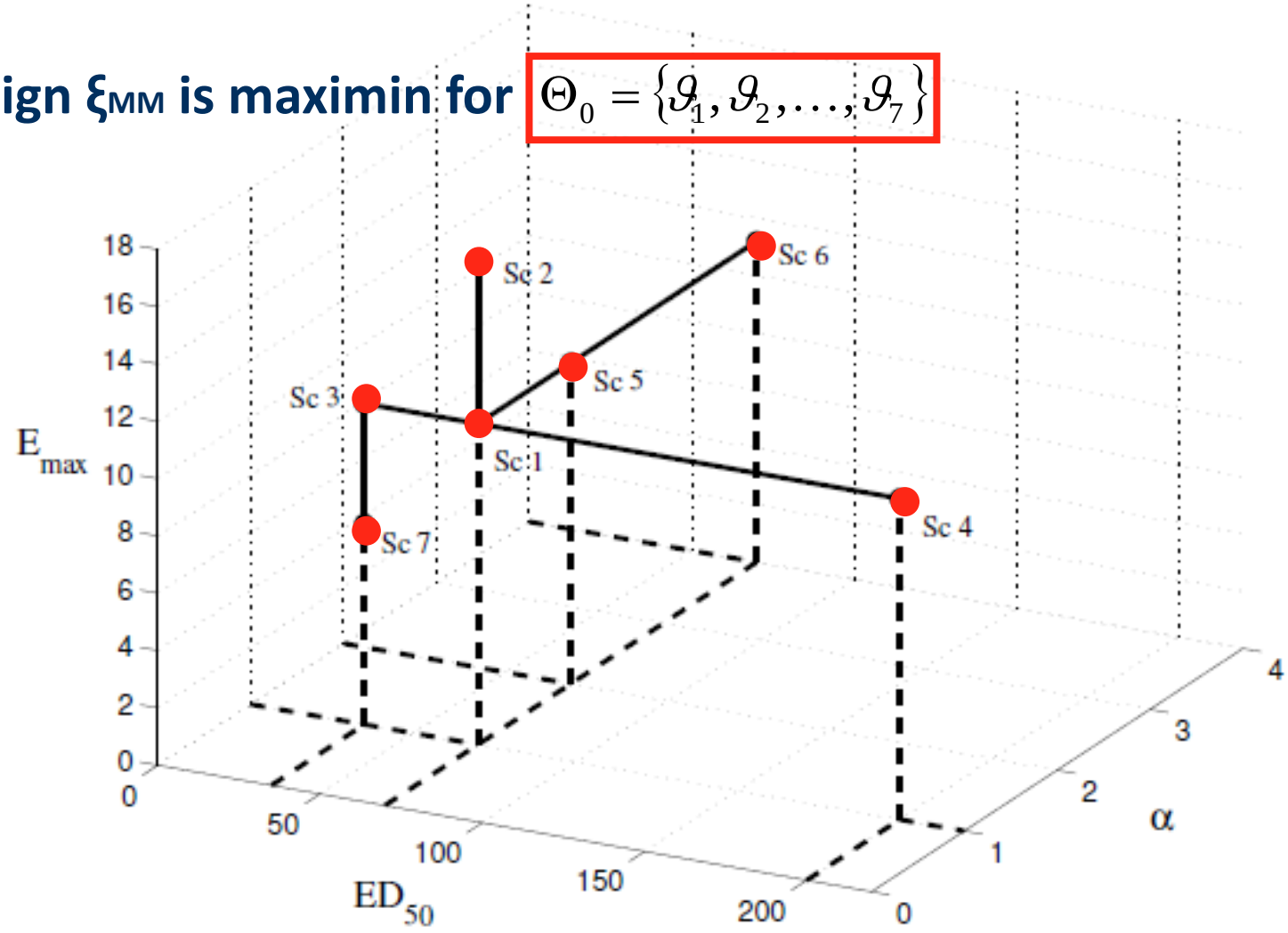
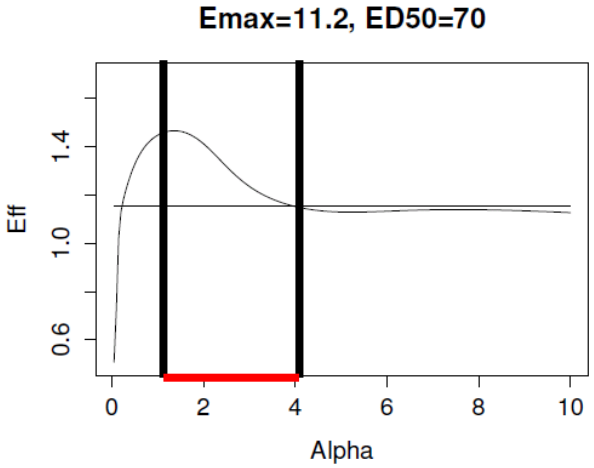
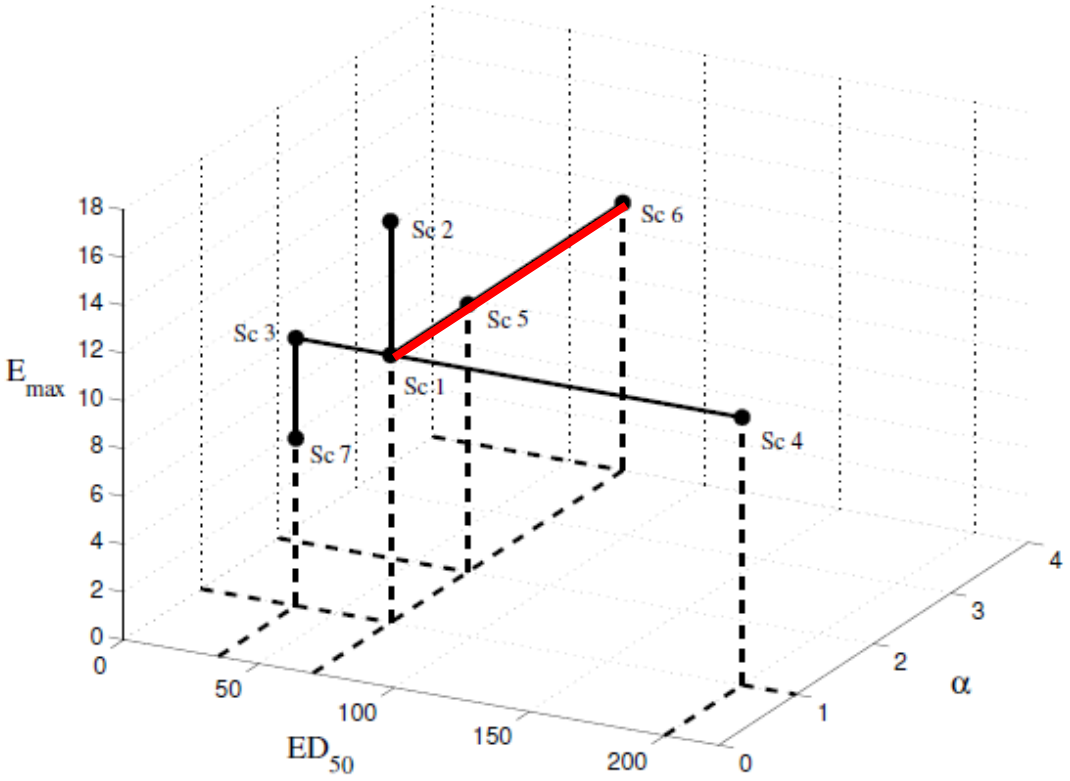
Design ξ_{MM} is maximin for $\Theta_0 = \{\vartheta_1, \vartheta_2, \ldots, \vartheta_7\}$

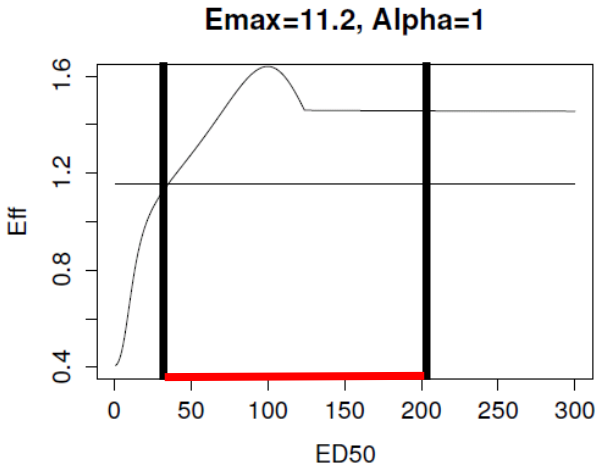


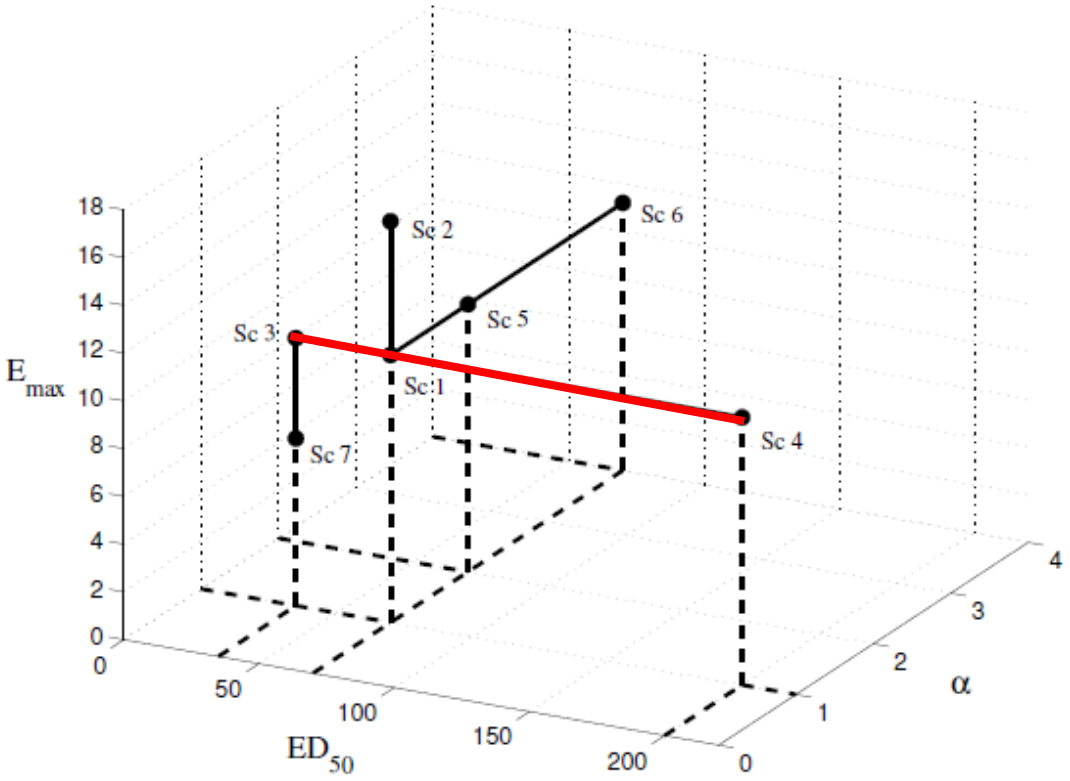
Maximin design





Maximin design





Maximin design

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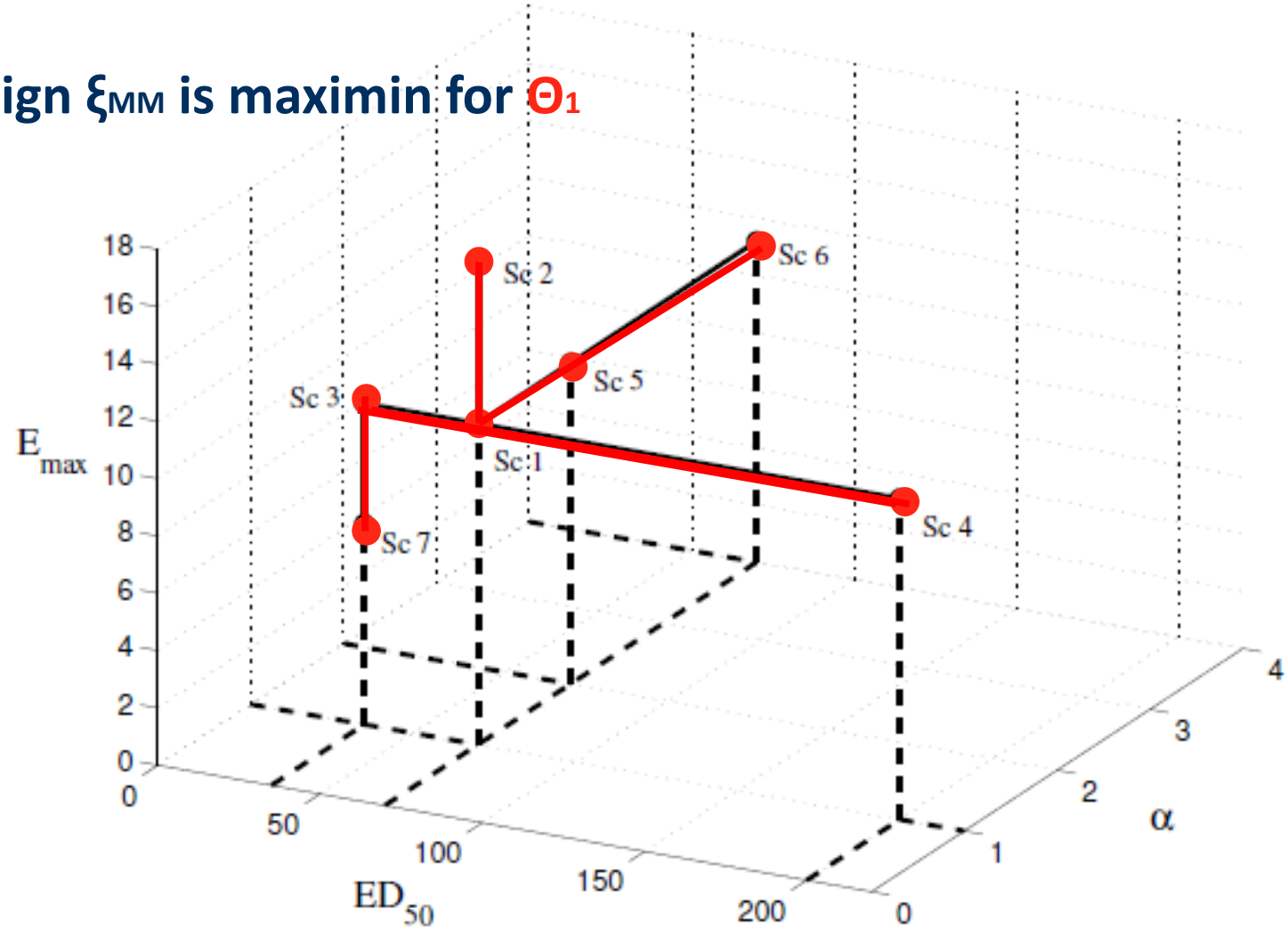
Design ξ_{MM} is maximin for Θ_1



Maximin and Bayesian design

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- Theoretical connection between Bayesian optimal and maximin optimal design:

  A maximin optimal design is a Bayesian optimal design for the “least favorable” prior distribution

- Algorithms to compute minimax design can make use of this (e.g. H-algorithm: Nyquist, 2013).

Summary

- Important to discuss **quantification of objectives** and **prior knowledge** in detail

- Different methods to optimize design can be applied
  - Bayesian optimal design can improve efficiency
  - Adaptive design not always better,…
    … but it is if there is especially large uncertainty
  - Maximin design does not require prior probabilities

- Good even to **implement just ideas** from optimal design if not possible to go through calculations formally

  (see Miller, Björnsson, Svensson, Karlsten, 2014)

References

- Fackle-Fornius E, Miller F, Nyquist H (2015). Implementation of maximin efficient designs in dose-finding studies. *Pharmaceutical Statistics*, 14, 63-73.
- Miller F, Guilbaud O, Dette H (2007). Optimal designs for estimating the interesting part of a dose-effect curve. *Journal of Biopharmaceutical Statistics,* 17, 1097-1115
- Miller F, Björnsson M, Svensson O, Karlsten R (2014). Experiences with an adaptive design for a dose-finding study in patients with osteoarthritis. *Contemporary Clinical Trials*, 37, 189-199.
- Miller F (2015). When is an adaptive design useful in clinical dose-finding trials? Manuscript in press. (see www.frank-miller.eu)
- Nyquist H (2013). Convergence of an algorithm for constructing minimax designs. In *MoDa 10 – Advances in Model-Oriented Design and Analysis*, D. Ucinski, A. Atkinson, and M. Patan (Eds.) Springer Verlag.