Adaptive Dose-Finding for Time-to-Event Outcomes with Adaptive Choice of Patient Number Based on Response Rate

Yevgen Ryeznik[1,2], Oleksandr Sverdlov[3], Andrew C. Hooker[2]

[1]Department of Mathematics, Uppsala University

[2]Department of Pharmaceutical Biosciences, Uppsala University

[3]EMD Serono

PODE 2016

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Outline

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Objectives

1. To construct a design for a time-to-event (TTE) clinical trial with censored observations in order to estimate dose-response relationship between expected TTE and dose.

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2. To determine the requisite sample size based on some predefined stopping criterion.
3. To determine doses needed for dose-response estimation and allocation proportions at these doses by adapting to available data.

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1. An adaptive design which may improve efficiency of a dose-finding clinical trial with TTE outcomes has been obtained.
2. A stopping criterion which provides an adaptive choice of a sample size has been proposed:
    - the required sample size is smaller when more events are observed in the trial; the sample size increases when the amount of censored data increases.

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Accelerated Failure Time (AFT) Model

Let $T > 0$ be a time-to-event variable:

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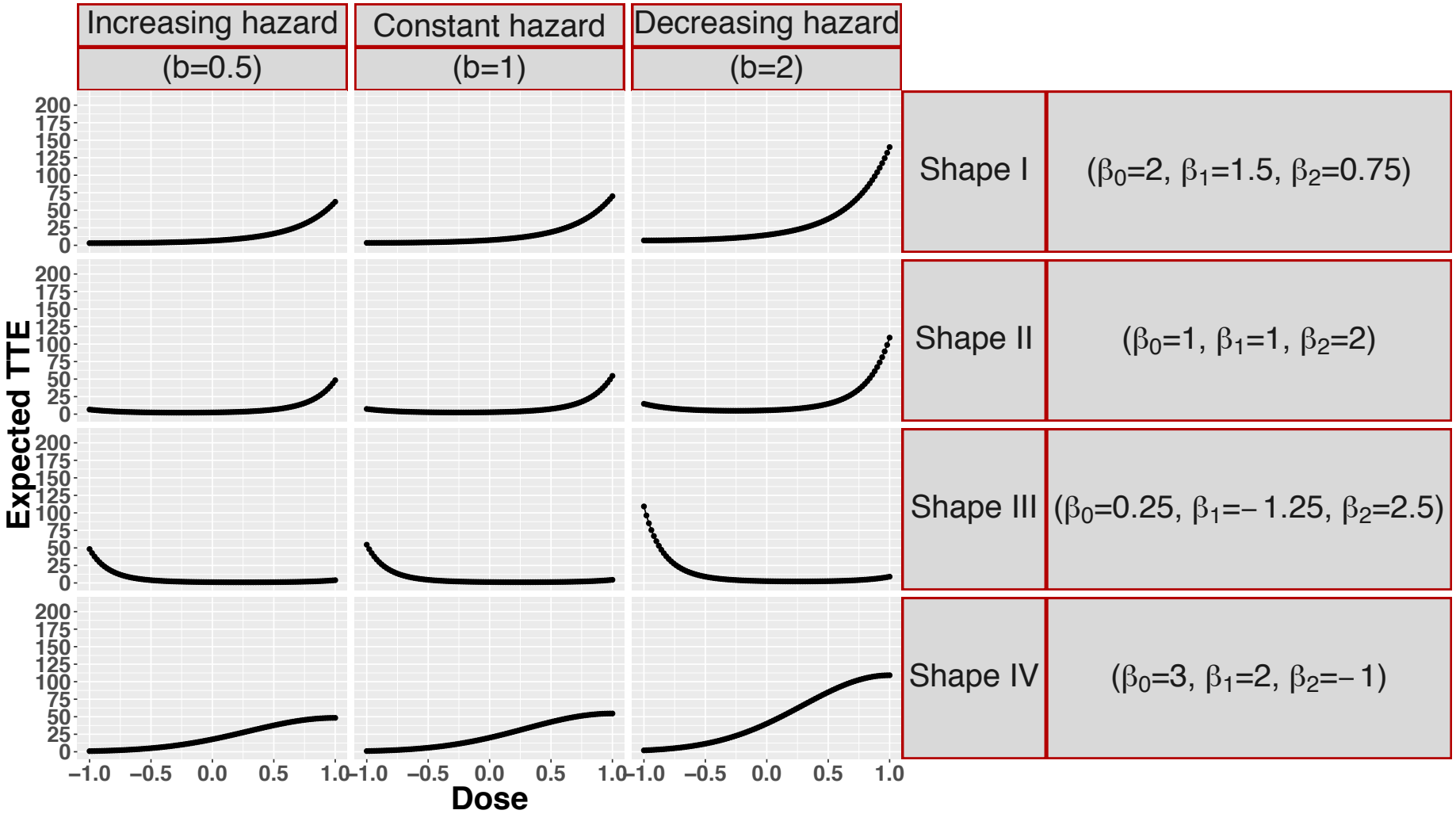
where

- x corresponds to a dose (treatment arm),
- shape parameter: $\lambda = \exp(\beta_0 + \beta_1 x + \beta_2 x^2)$,
- scale parameter: $p = b^{-1}$,
- and $\varepsilon \sim f_\varepsilon(w) = exp(w - exp(w))$ – *extreme value distribution.*

Accelerated Failure Time (AFT) Model

Dose-response relationship: $E(T|x) = \exp(\beta_0 + \beta_1 x + \beta_2 x^2)\Gamma(1+b)$.



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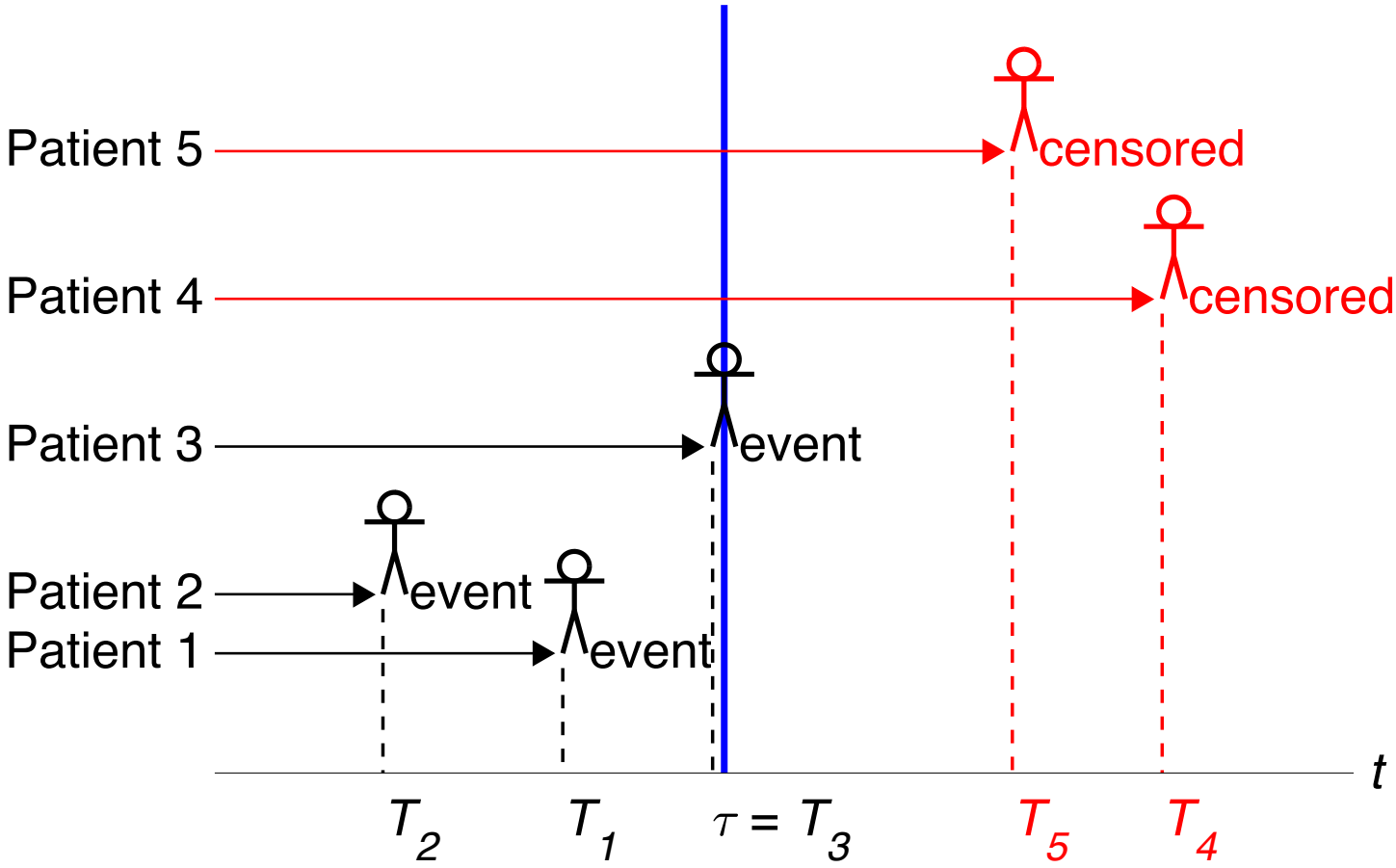
Censoring



Observed outcome is (t, δ):

$$t = \min(T, \tau)$$

$$\delta = \mathbf{1}_{\{T \leq \tau\}}$$

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Likelihood and Fisher Information

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- Then, *MLE*s of unknown model parameters $(\widehat{\boldsymbol{\theta}}_{MLE})$ are the solutions of score equations

$$\frac{\partial \log \mathcal{L}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}} = \begin{pmatrix} \frac{\partial \log \mathcal{L}(\boldsymbol{\theta})}{\partial \boldsymbol{\beta}} \\ \frac{\partial \log \mathcal{L}(\boldsymbol{\theta})}{\partial b} \end{pmatrix} = \mathbf{0}$$

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- The corresponding *Fisher Information Matrix* is

$$I(\boldsymbol{\theta}) = -\mathbf{E}\left(\frac{\partial^2 \log \mathcal{L}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^{\mathrm{T}}}\right)$$

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Experimantal Design

- A K-points design is determined by a discrete probability measure

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$$x_k \in \mathcal{X} = [-1; 1], \qquad \sum_{k=1}^{K} w_k = 1.$$

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D-optimal Design

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- Then, a *D-optimal design* is determined as a solution of the following optimization problem

$$\xi_D^* = \arg\max_{\xi} |FIM(\xi, \boldsymbol{\theta})|.$$

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D-optimal Design

- Without censoring, *D-optimal design* is a *3-points balanced (uniform) design*[a]

$$\begin{pmatrix} -1 & 0 & 1 \\ 1/3 & 1/3 & 1/3 \end{pmatrix},$$

$$\text{where} \begin{bmatrix} -1 & - & \text{minimum dose} \\ 0 & - & \text{average dose} \\ 1 & - & \text{maximum dose} \end{bmatrix}$$

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- In the presence of censoring *D-optimal design* still has 3 points but *it is shifted from the uniform design*[a].

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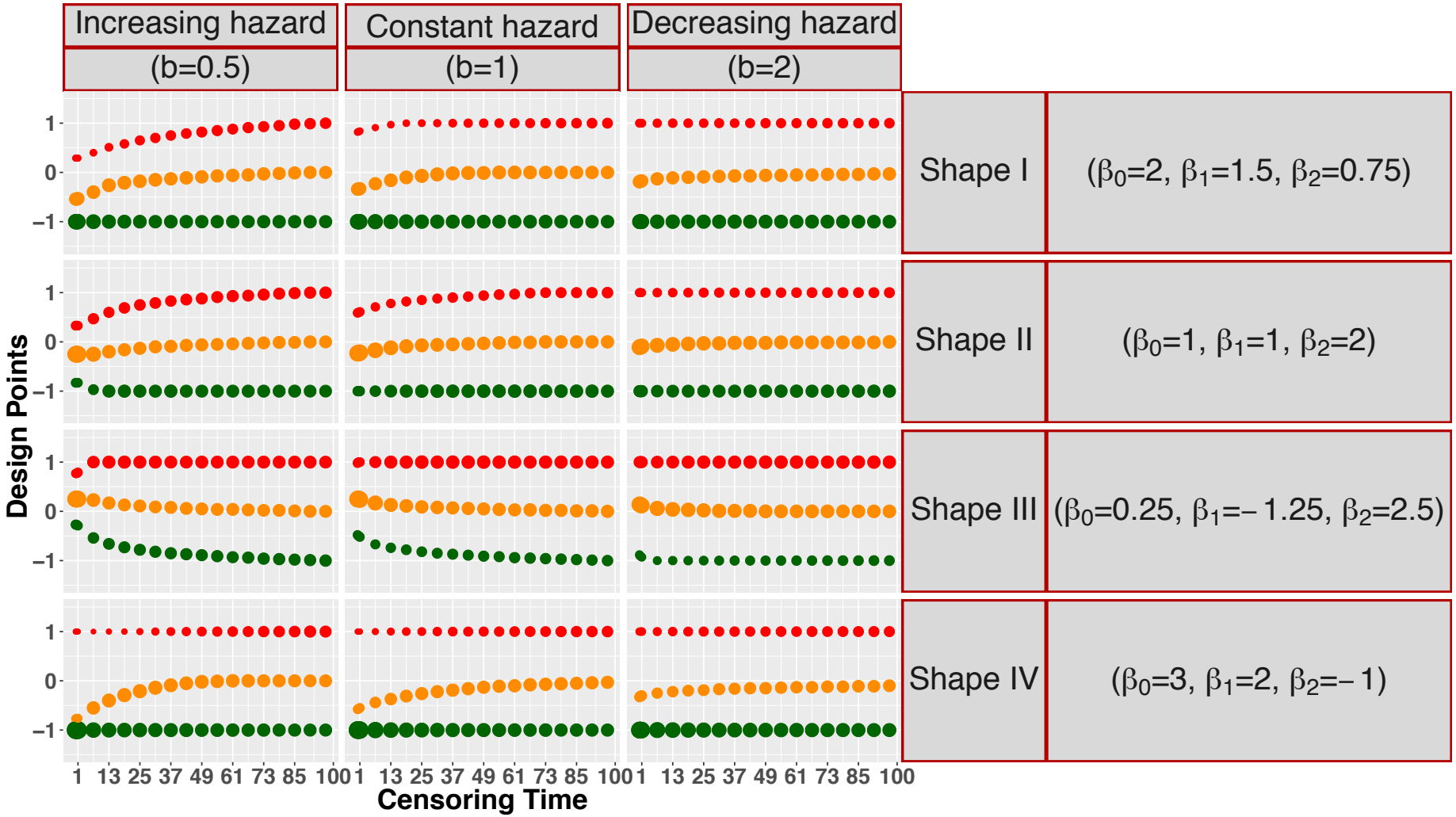

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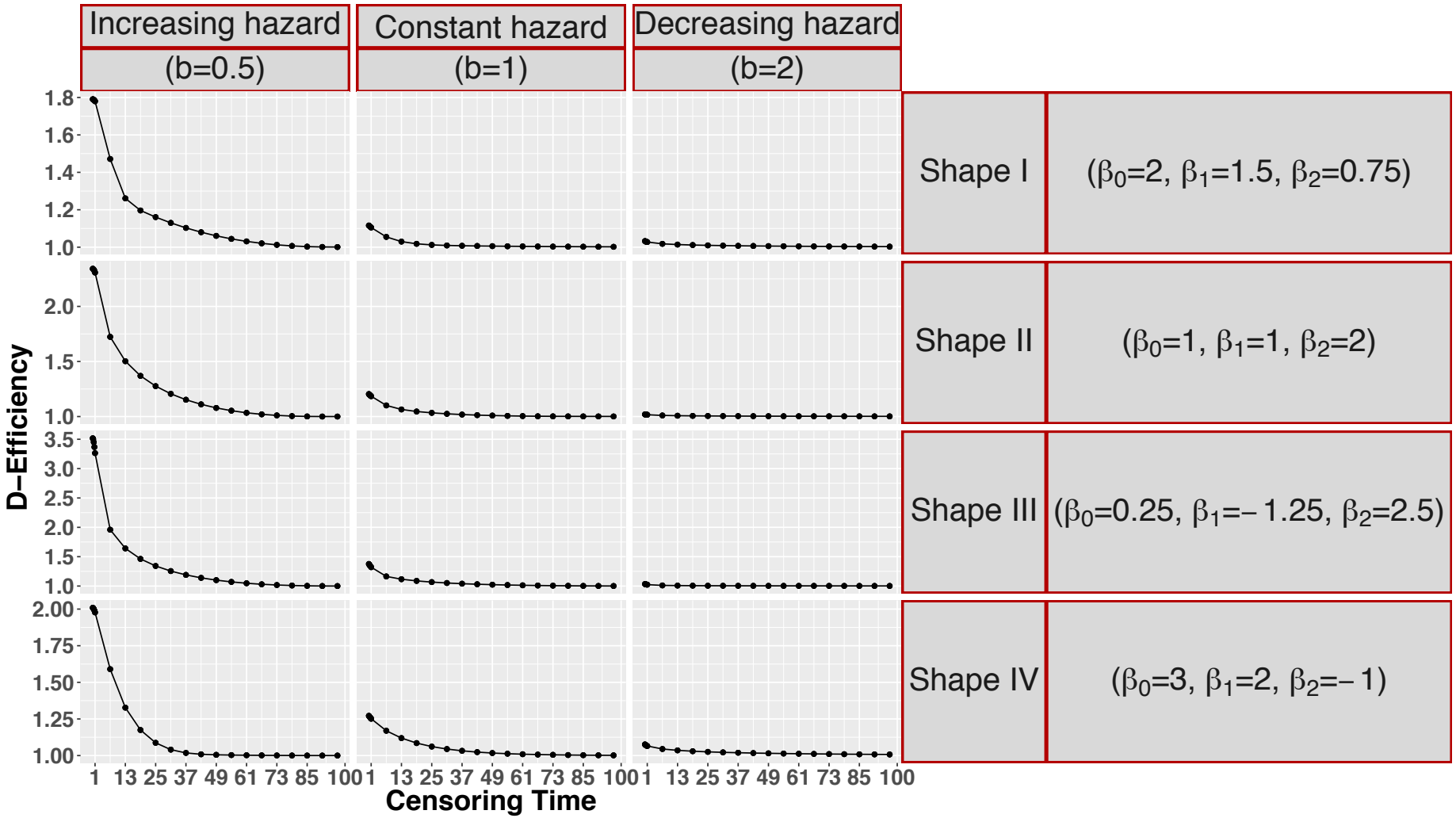
D-efficiency: $D_{eff} = \left(\frac{|FIM(\xi_D^*, \boldsymbol{\theta})|}{|FIM(\xi_U^*, \boldsymbol{\theta})|} \right)^{\frac{1}{4}}$



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Adaptive Designs

- D-optimal design ξ depends on a model parameters $\boldsymbol{\theta}$ which are *unknown* at the beginning of a study.
- In order to address this issue *adaptive design* is prposed.

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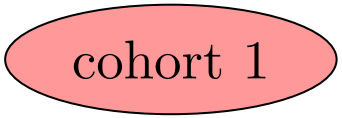
Adaptive Designs



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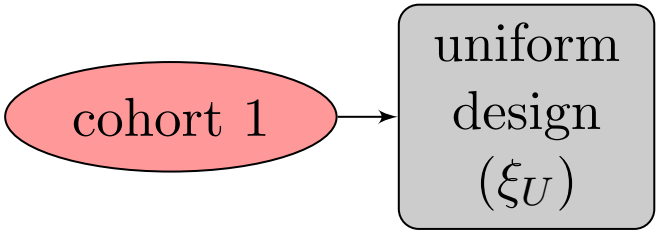

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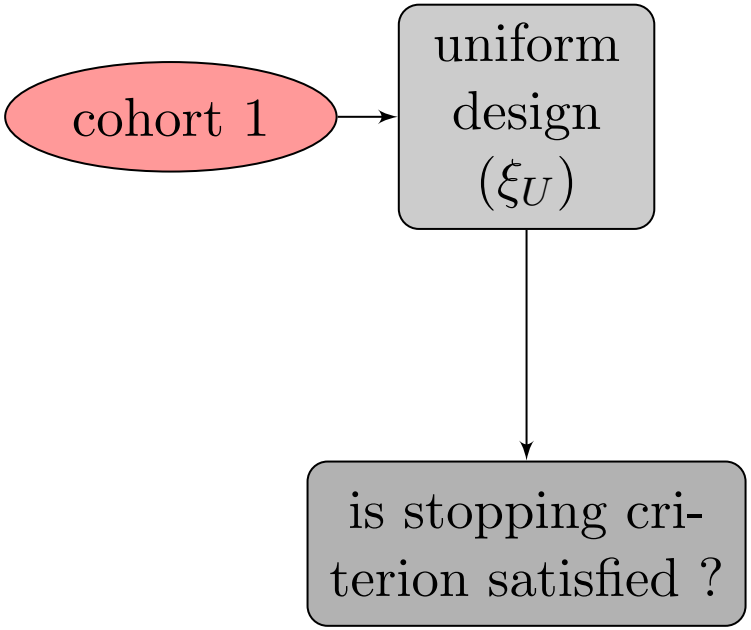

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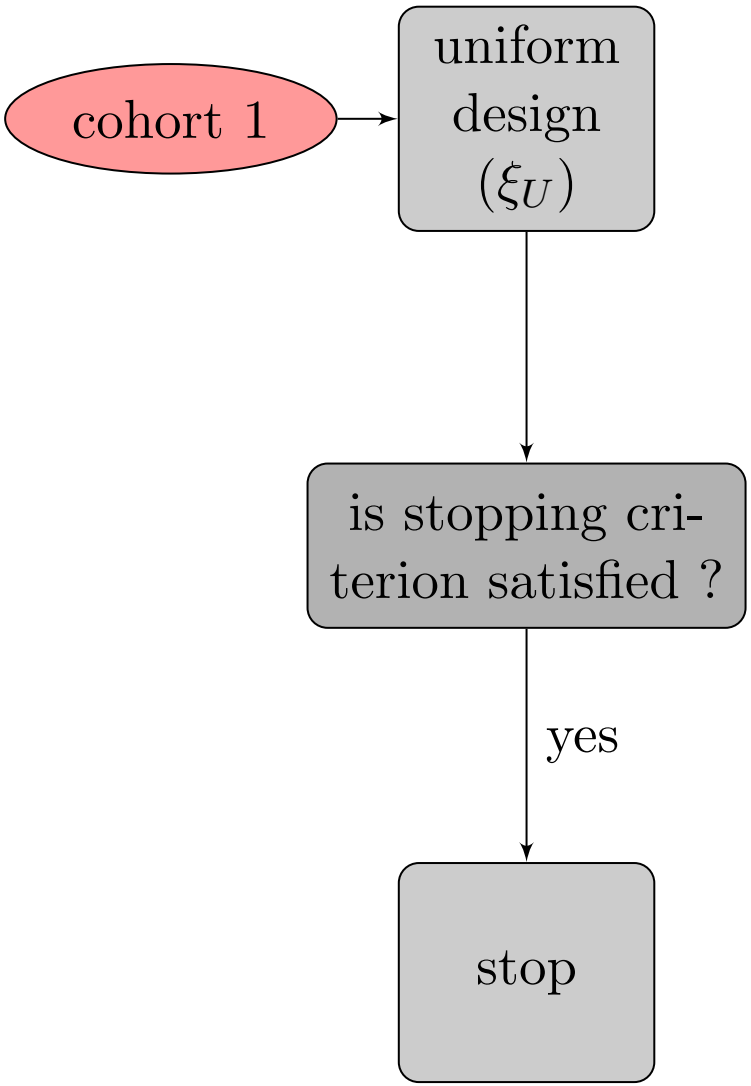

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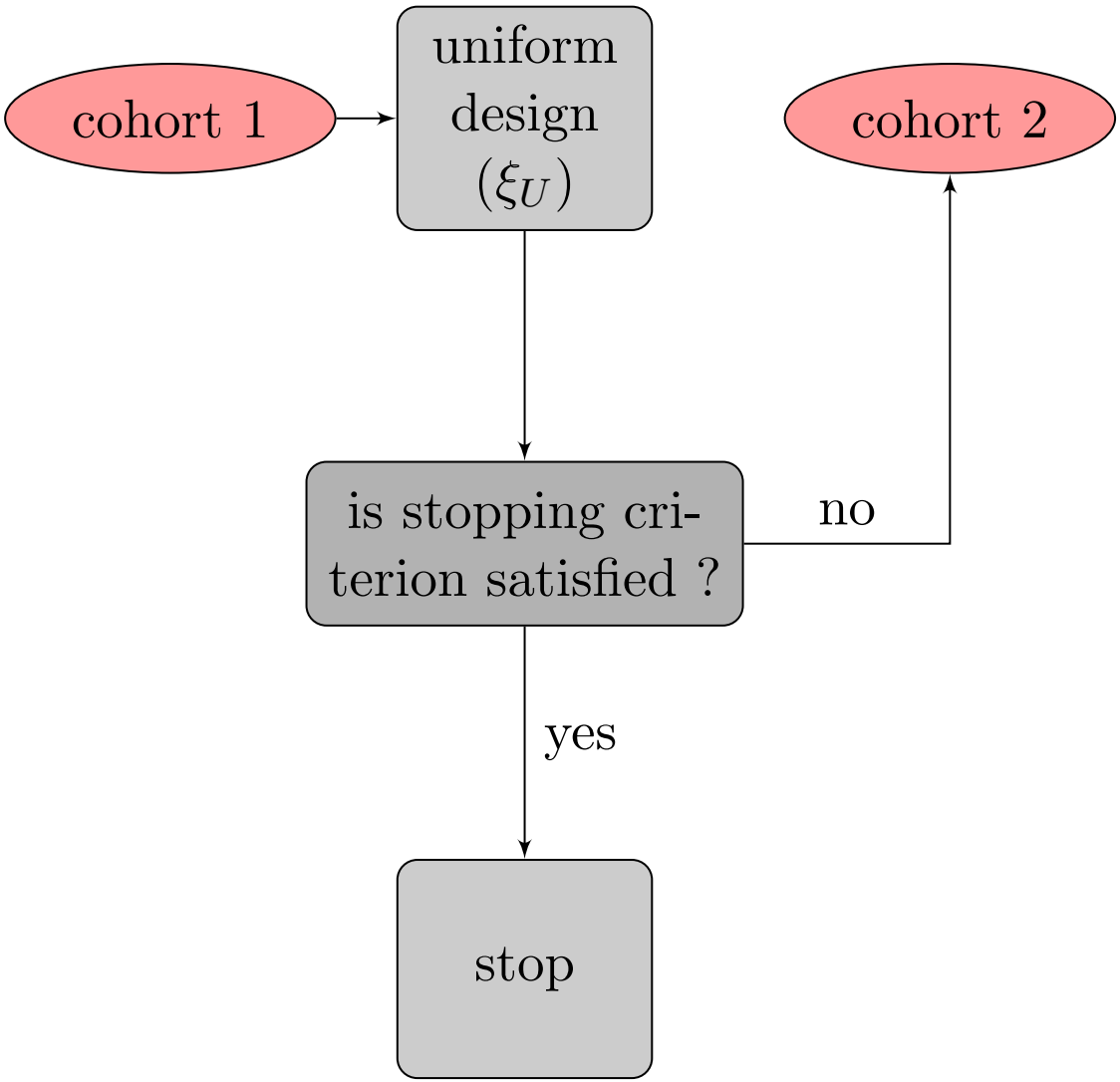

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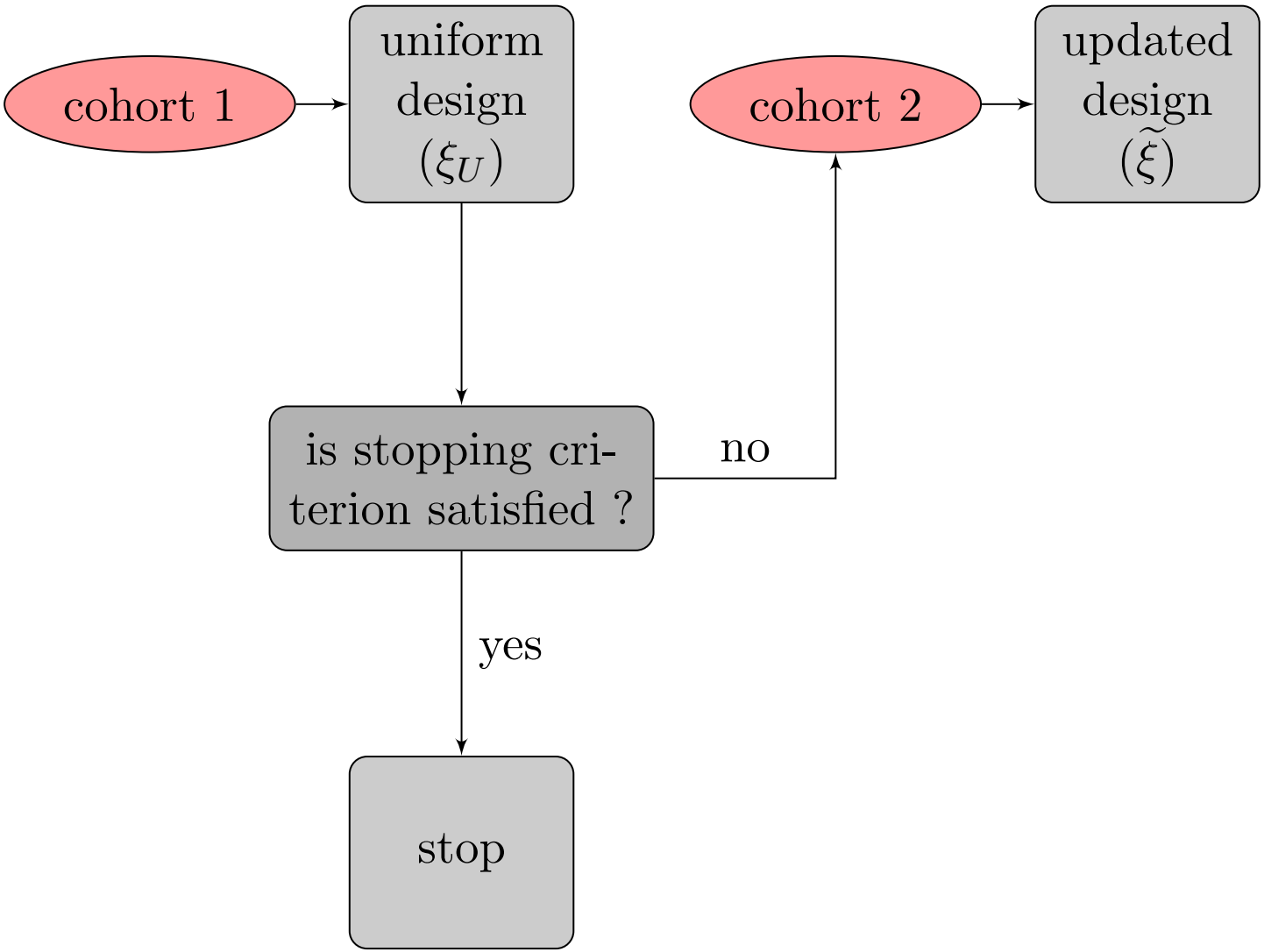

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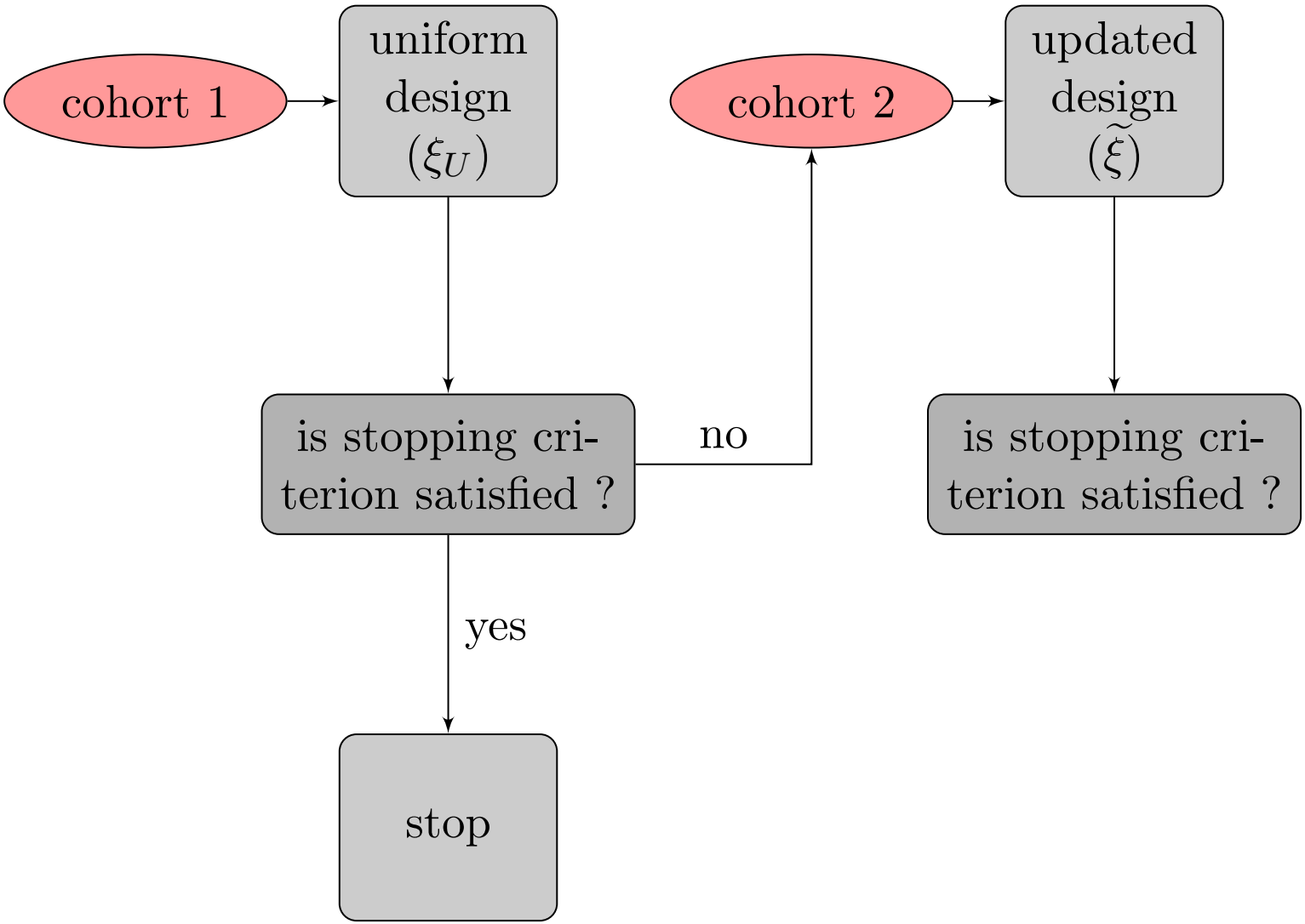

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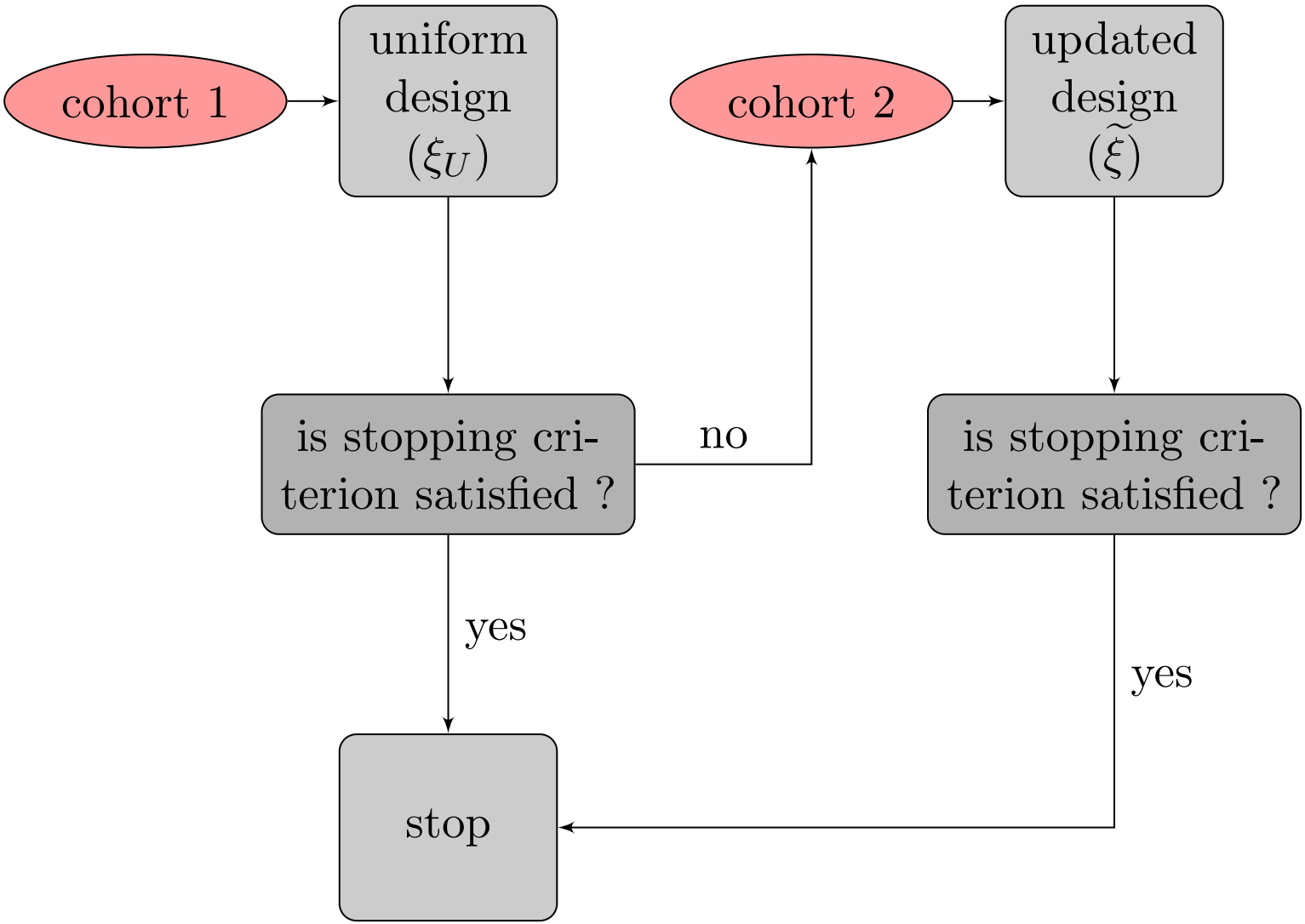

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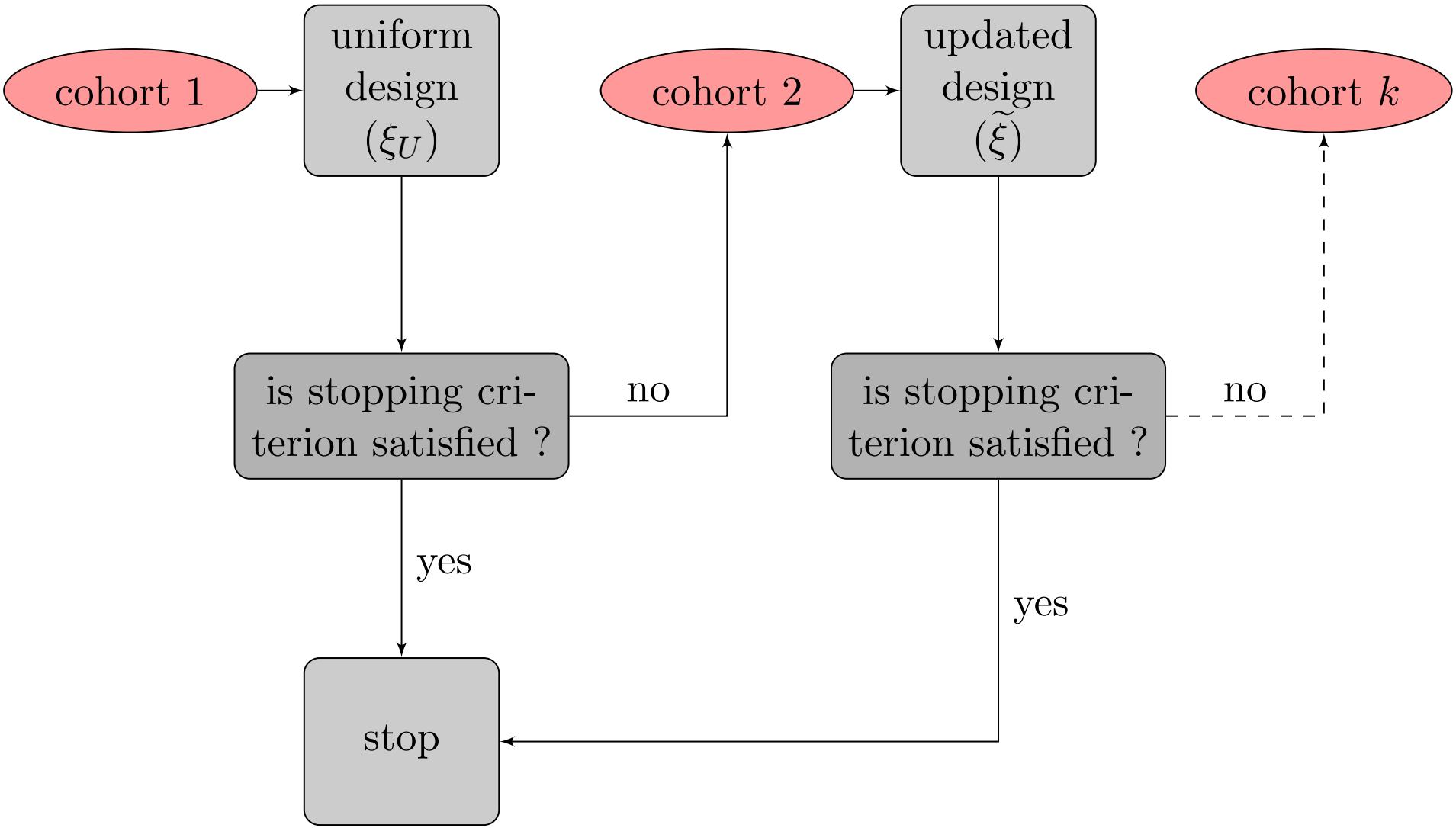

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Updated Design

Two types of design updating are possible:

$$\text{either} \quad \widetilde{\xi}_D = \arg\max_{\xi} \left\{ \log |FIM(\xi, \widehat{\boldsymbol{\theta}}_{MLE})| \right\}$$

$$\text{or} \quad \widetilde{\xi}_{ED} = \arg\max_{\xi} \int_{\Theta} \log |FIM(\xi, \boldsymbol{\theta})| \widehat{\pi}(\boldsymbol{\theta}) d\boldsymbol{\theta},$$

where

$\widehat{\boldsymbol{\theta}}_{MLE}$ are maximum likelihood estimators of $\boldsymbol{\theta}$,

$\widehat{\pi}(\boldsymbol{\theta})$ is a posterior distribution of $\boldsymbol{\theta}$

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Stopping Criterion

The following rule is proposed as a stopping criterion:

$$\max\left\{\frac{SD_{\widehat{\beta}_0}}{|\widehat{\beta}_0|}, \quad \frac{SD_{\widehat{\beta}_1}}{|\widehat{\beta}_1|}, \quad \frac{SD_{\widehat{\beta}_2}}{|\widehat{\beta}_2|}, \quad \frac{SD_{\widehat{b}}}{|\widehat{b}|}\right\} \leq \alpha, \qquad \alpha > 0,$$

where

$$\left(\widehat{\beta}_0, \widehat{\beta}_1, \widehat{\beta}_2, \widehat{b}\right) = \widehat{\boldsymbol{\theta}}_{MLE}$$

$$\left(SD_{\widehat{\beta}_0}, SD_{\widehat{\beta}_1}, SD_{\widehat{\beta}_2}, SD_{\widehat{b}}\right) = \operatorname{diag}\left\{FIM_{obs}^{-1}(\widehat{\boldsymbol{\theta}}_{MLE})\right\}$$

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Outline

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Simulations Setup

- For 3 different scales and 4 different shapes we simulate 12 models.
- We consider 3 possible values of a response rate[1]
- For each of 12 scenarios number of simulation $n_{sim} = 1000$.
- The number of subject in cohort is 30.
- Parameter α for the stoping criterion is 0.25.
- We stop simulations if number of randomized patients achives 2100 but stopping criterion is not satisfied.

[1] By response rate we assume proportion of uncensored observations.

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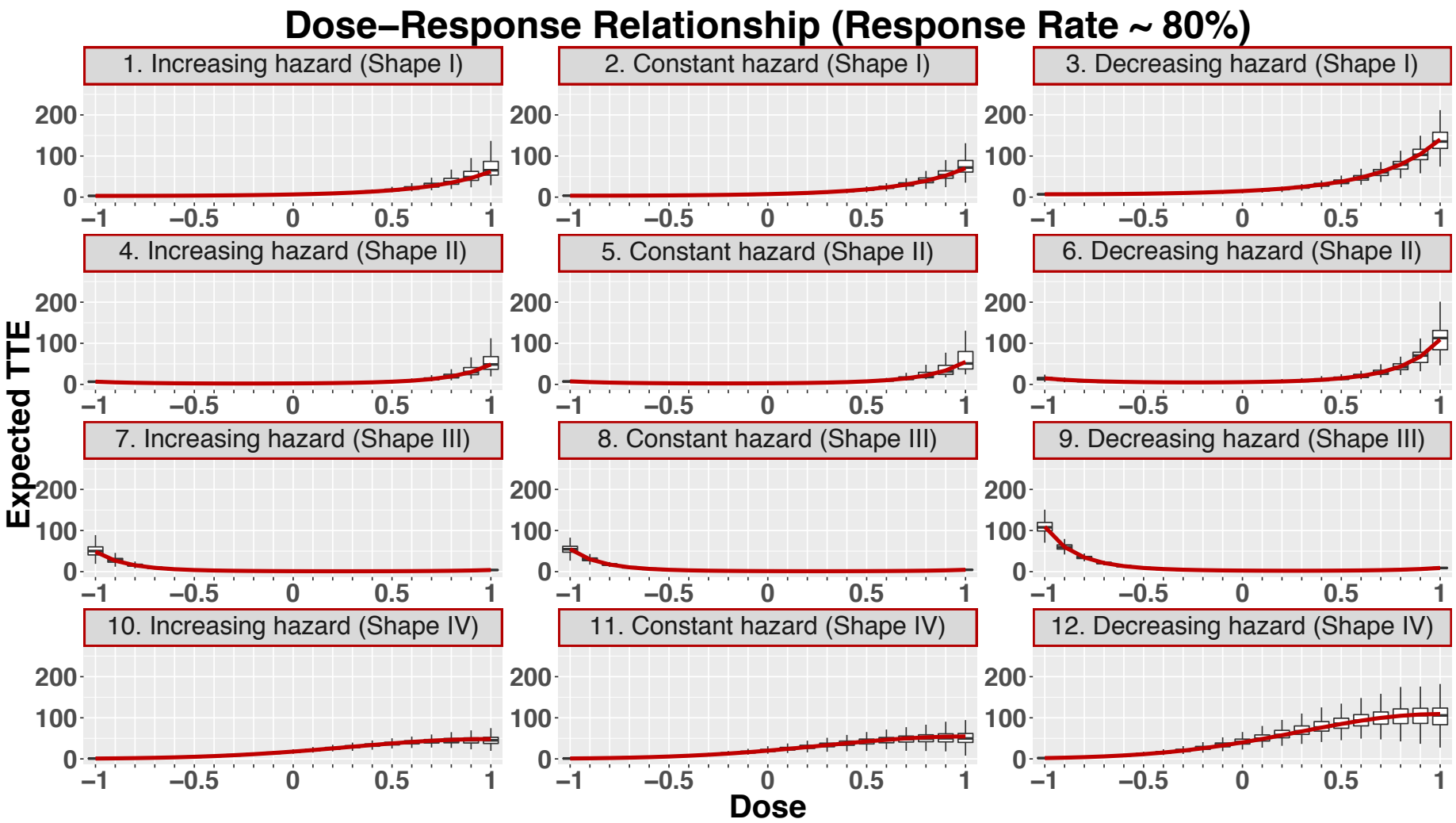
Simulations Results



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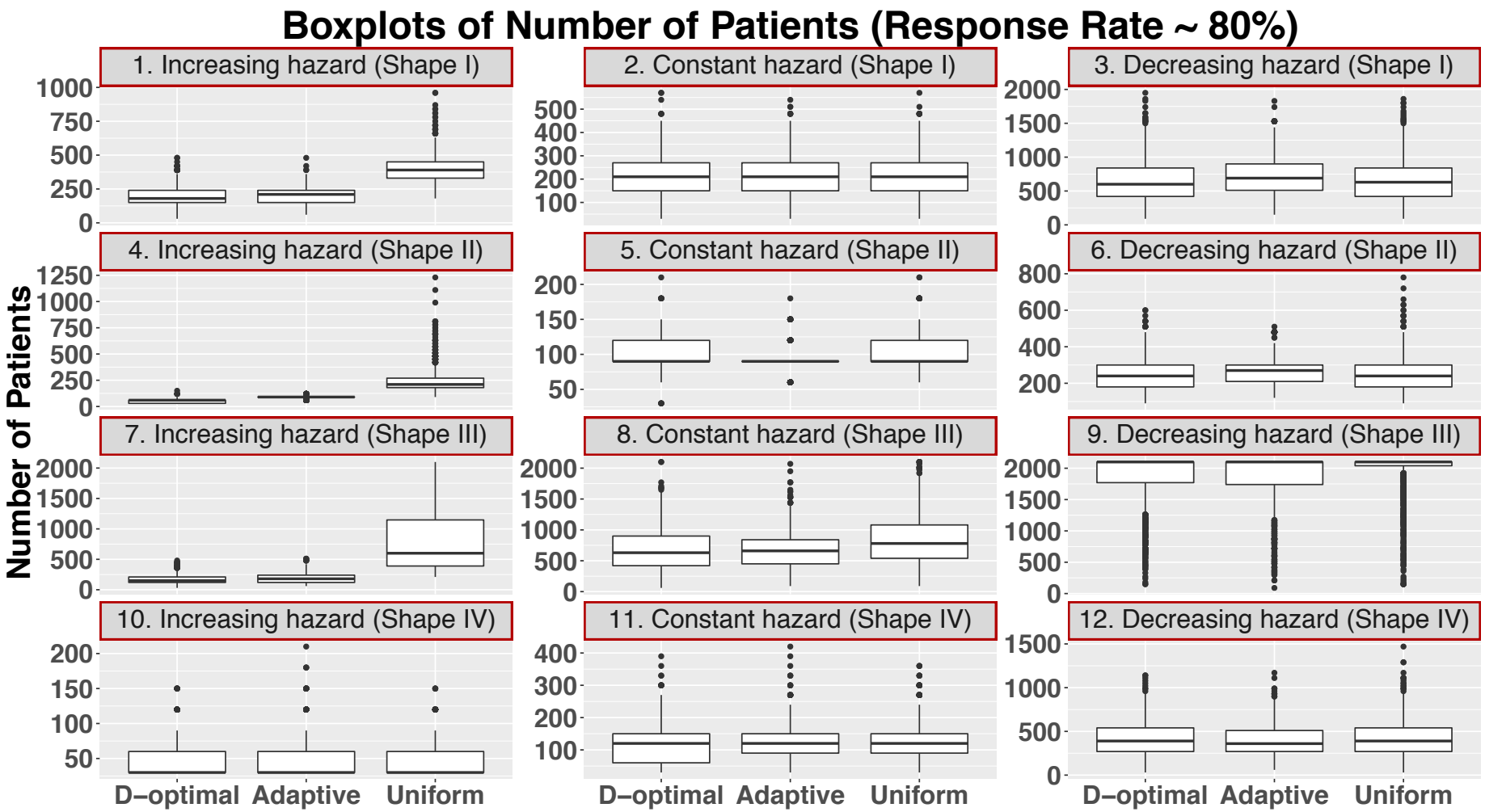

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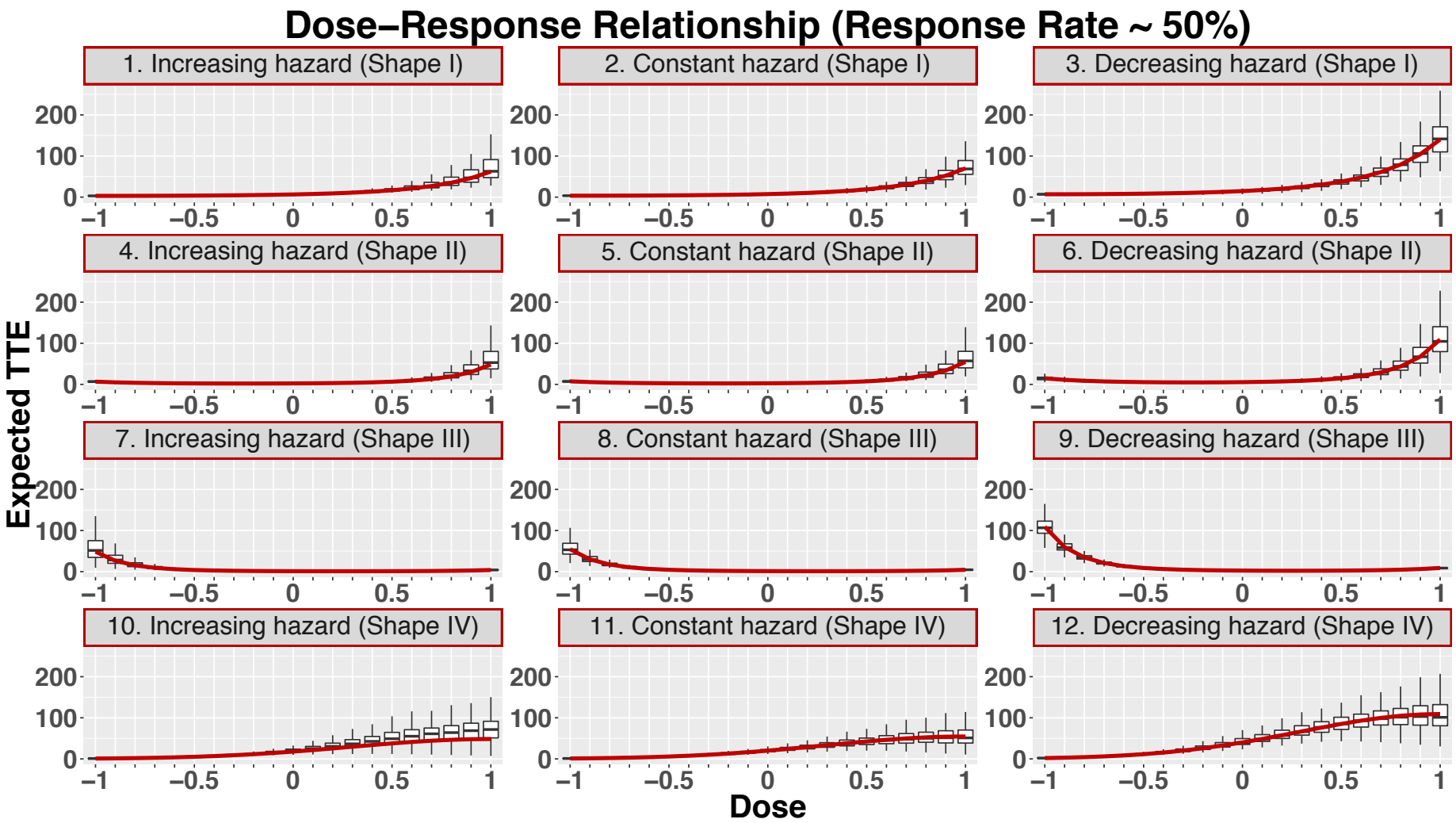

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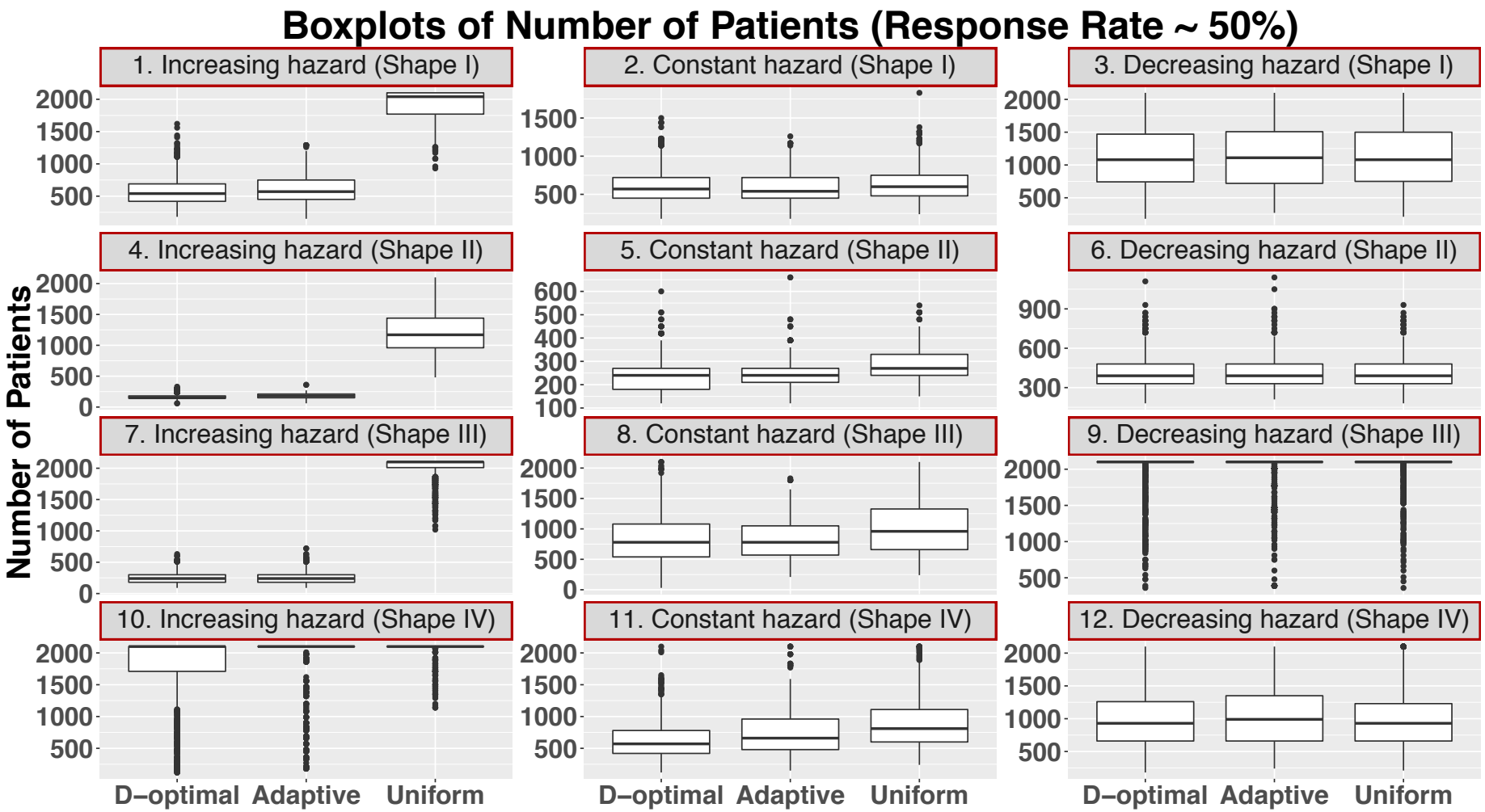

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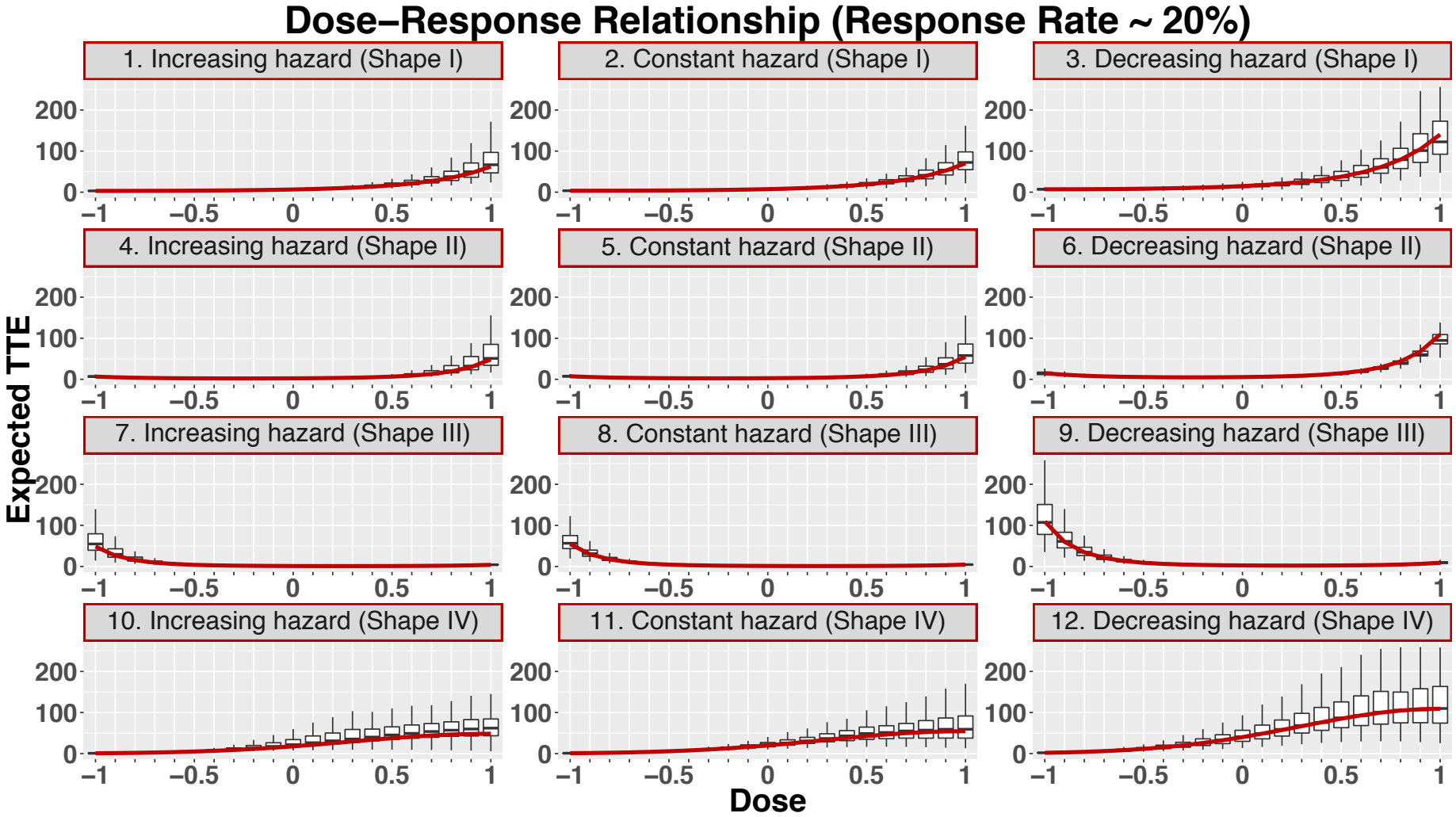

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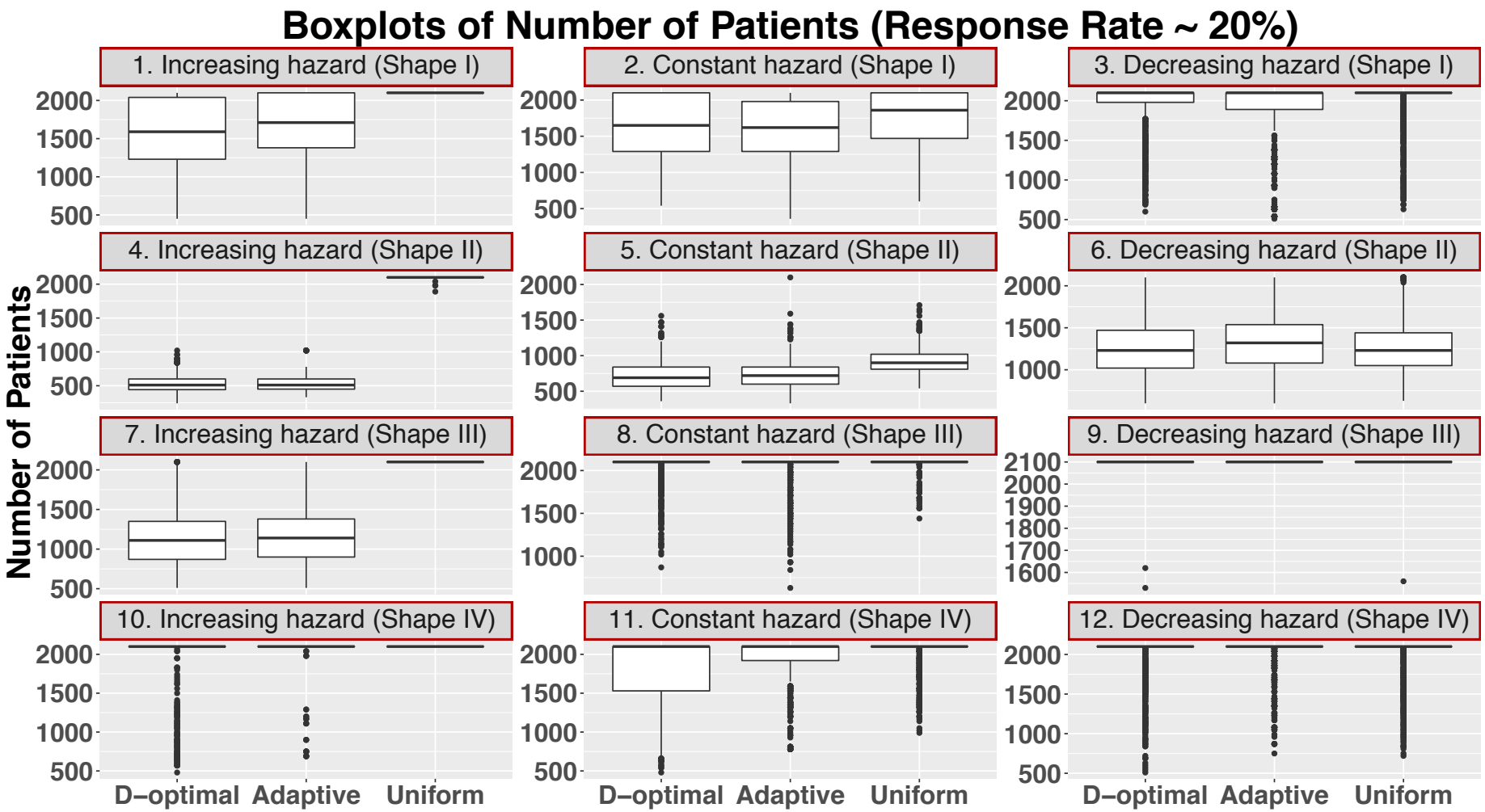

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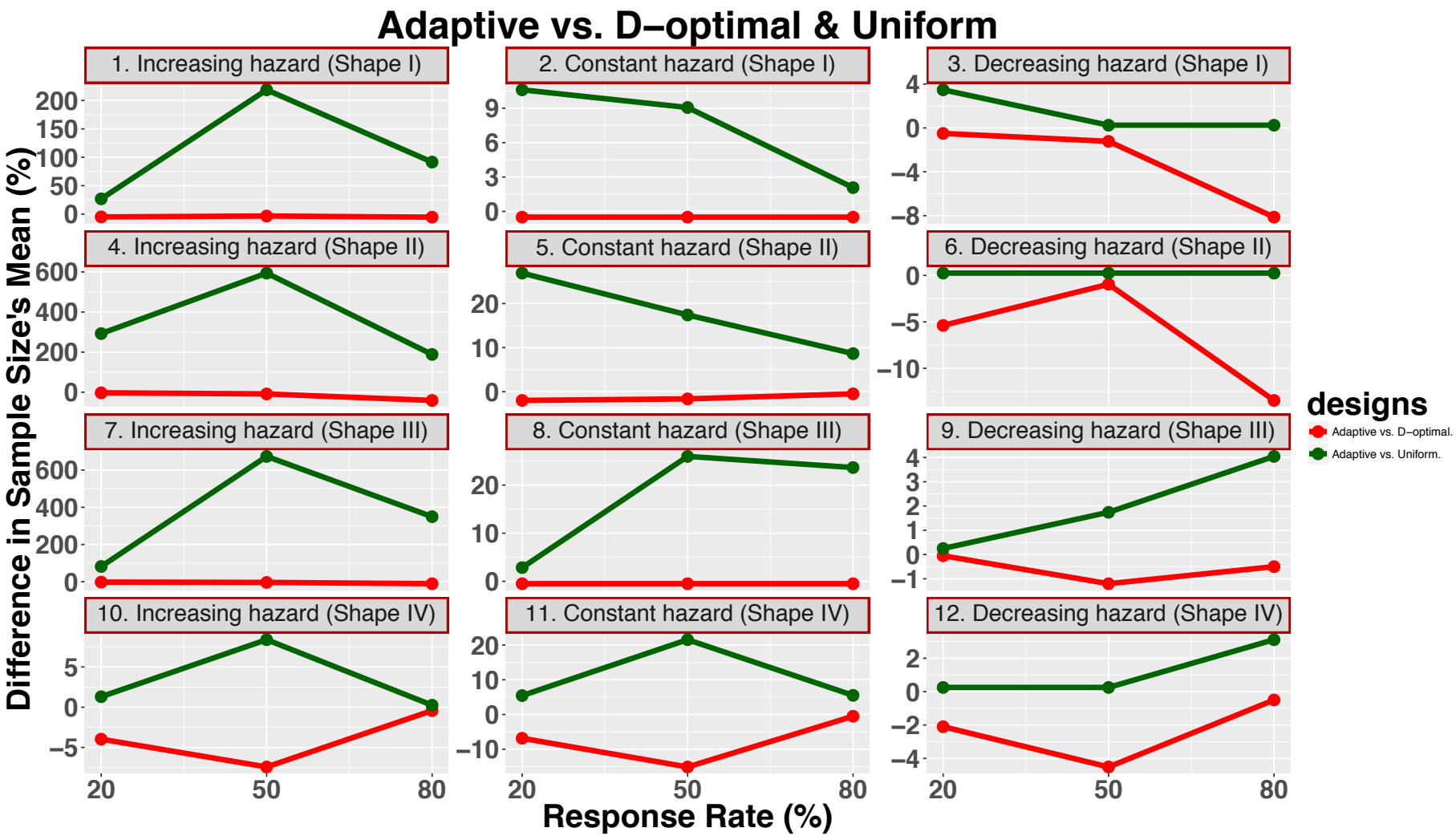

2-Stage AD (Bayesian update vs. MLEs)

When first cohort is randomized we do just one design update:

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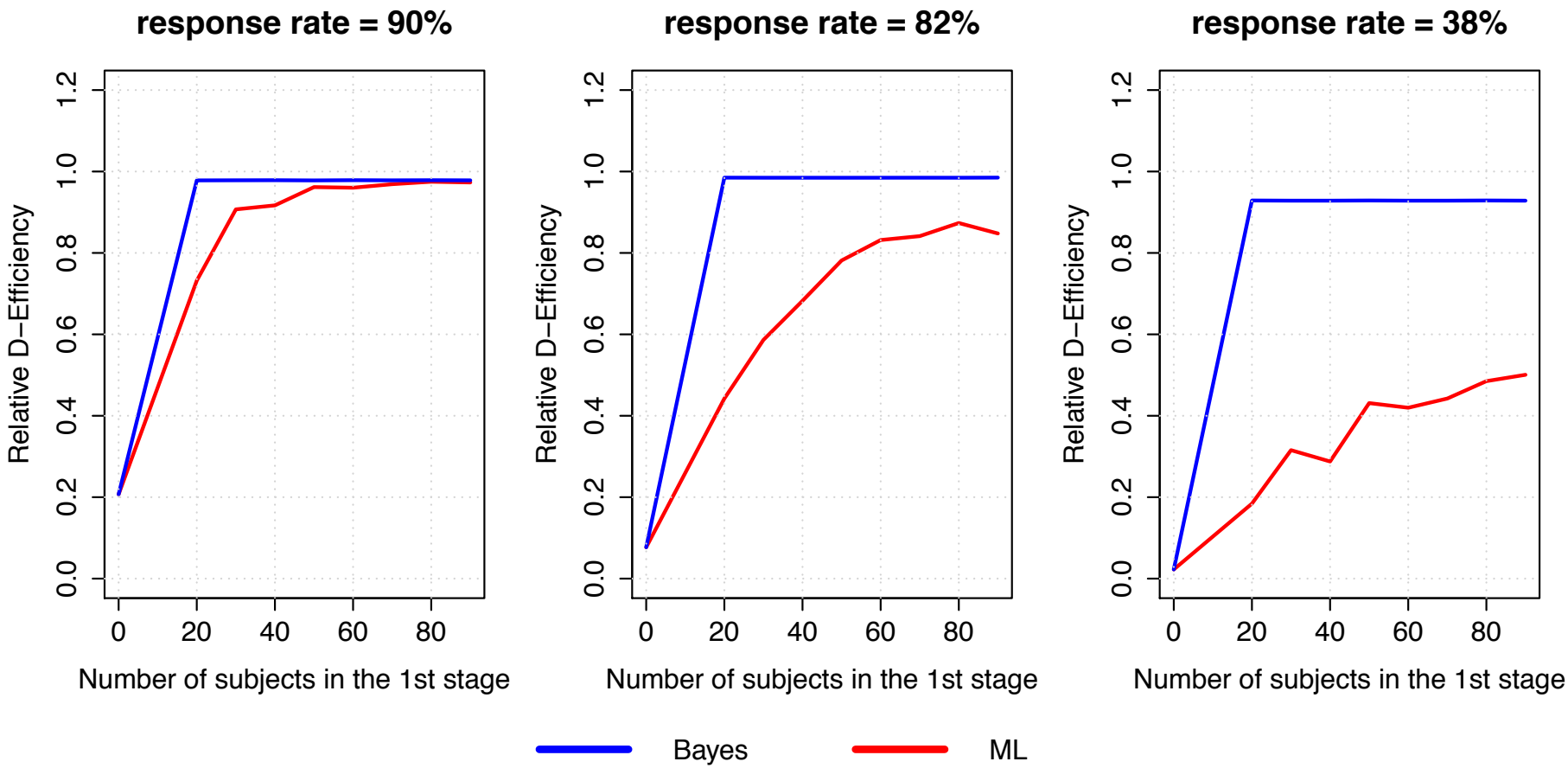
$$RelD_{eff} = \left(|FIM(\widetilde{\xi}, \boldsymbol{\theta})| / |FIM(\xi_D^*, \boldsymbol{\theta})| \right)^{\frac{1}{4}}, \quad \boldsymbol{\theta} \text{ is TRUE}$$



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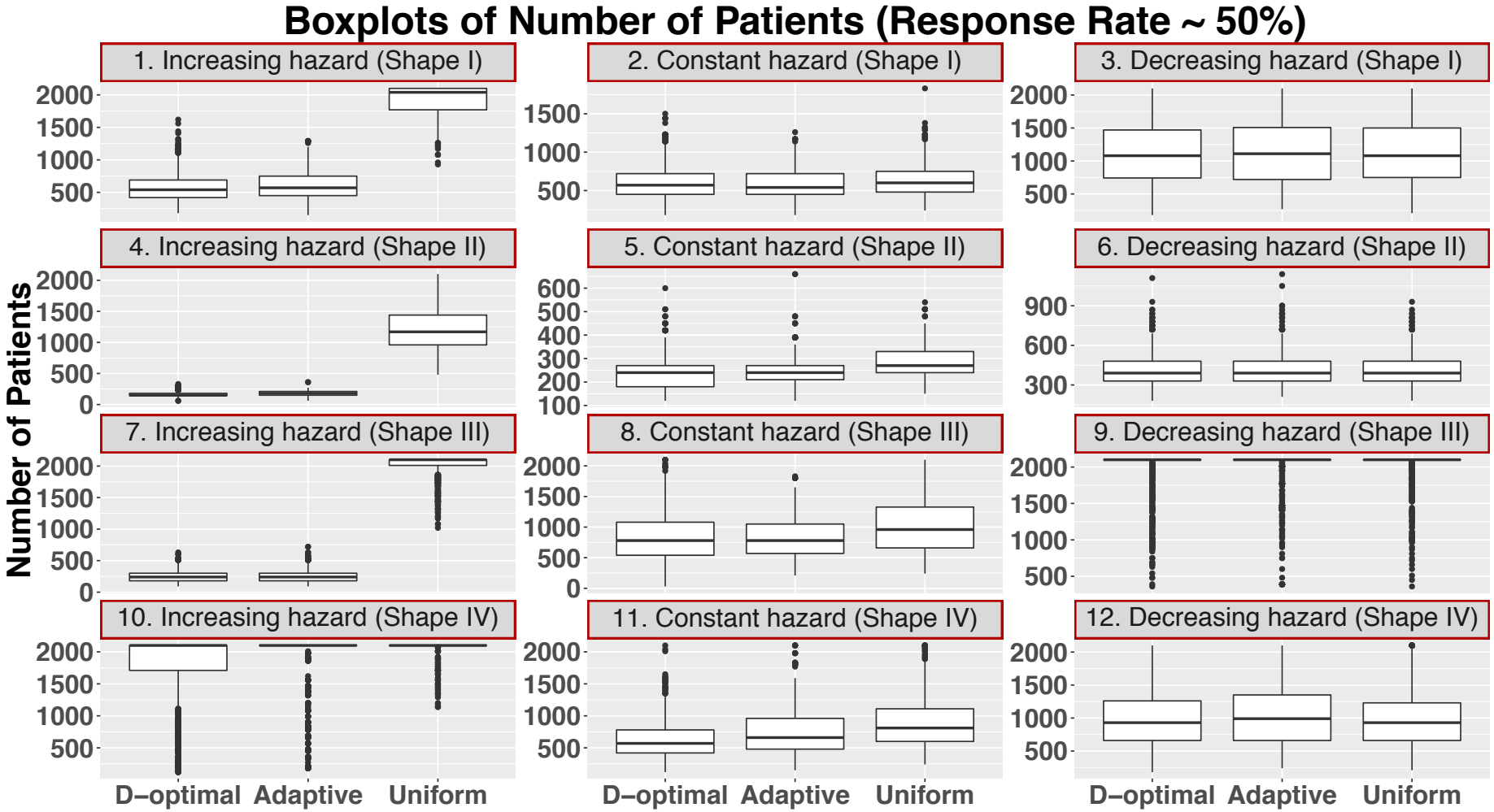

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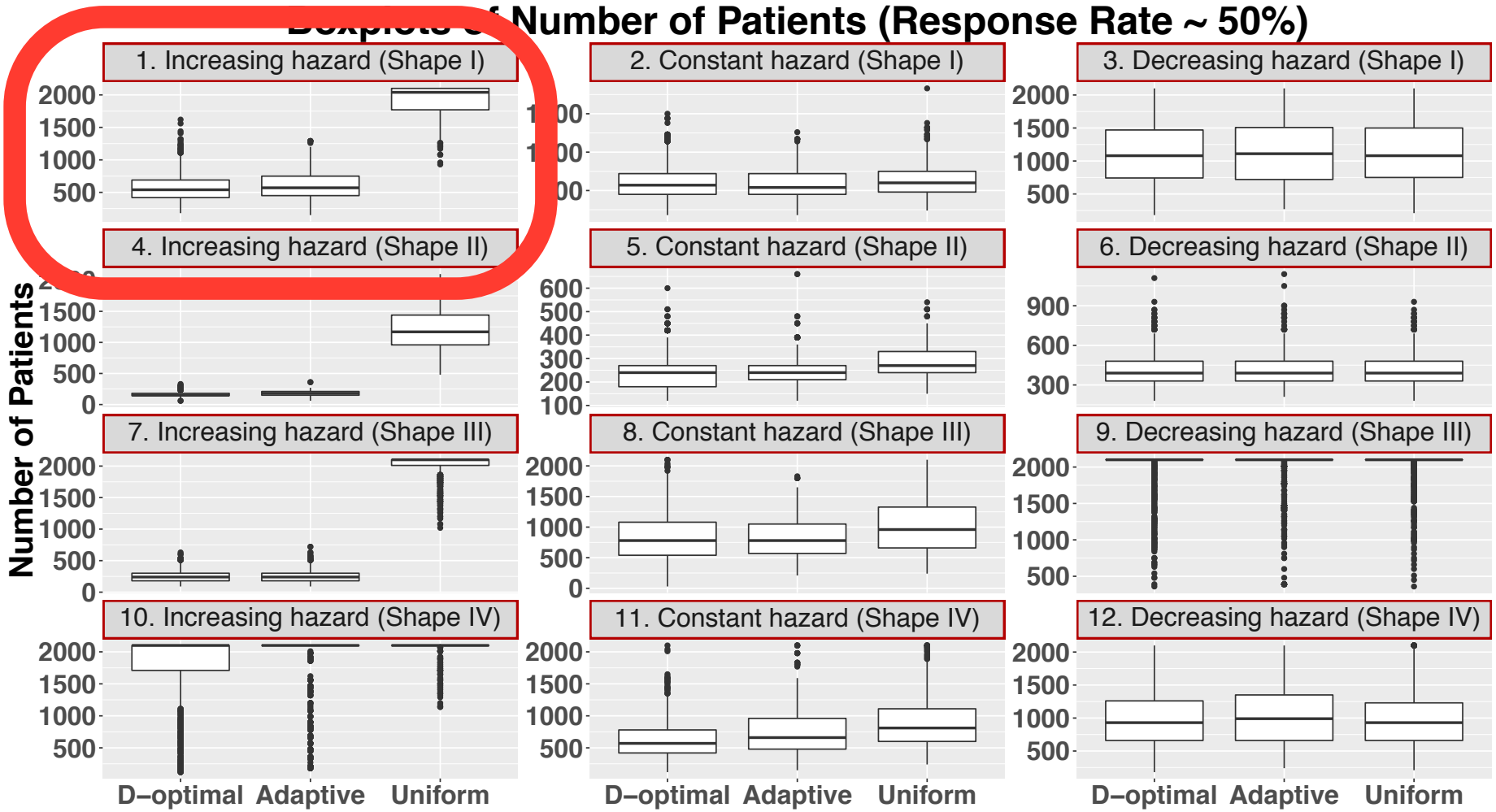

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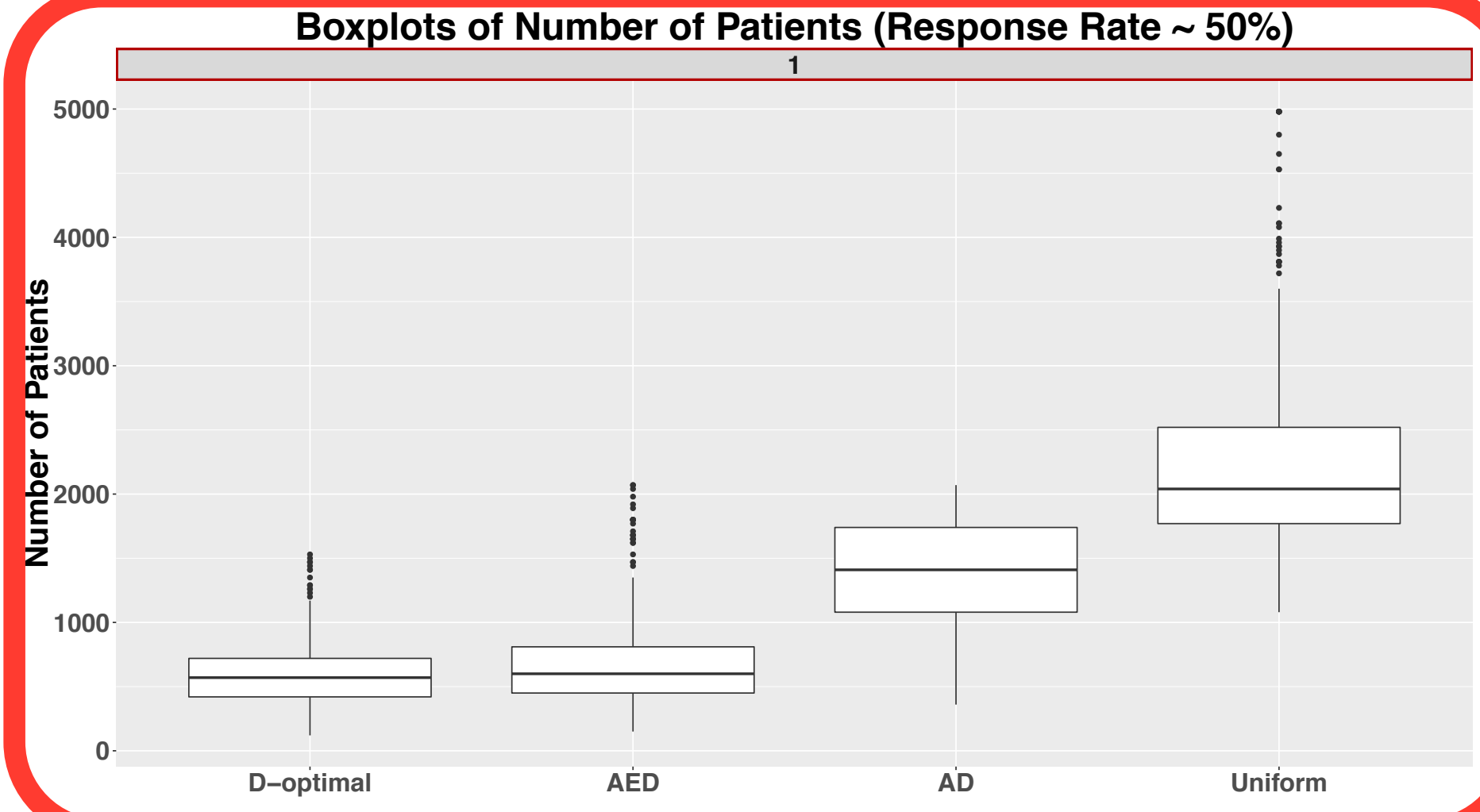

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Summary

1. The proposed adaptive design may improve efficiency of a dose-finding clinical trial with censored TTE outcomes. It allows amendation the dose levels and allocation proportions at these doses for the next cohorts of patients after interim analysis based on available data.

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Summary

1. The proposed adaptive design may improve efficiency of a dose-finding clinical trial with censored TTE outcomes. It allows amendation the dose levels and allocation proportions at these doses for the next cohorts of patients after interim analysis based on available data.

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2. The proposed stoping criterion allows adaptive choice of a requisite sample size. For high response rate we need fewer patients, while the number increases for a low response rate.

3. It seems that adaptive designs with Bayesian updating outperform adaptive designs based on MLE updating.

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Thank You!

Acknowledgments

Andrew C. Hooker
(Supervisor)

Oleksandr Sverdlov

Pharmacometrics
Research Group

This work was
supported by the
DDMoRe project.
(www.ddmore.eu)

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