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

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- 1 Objectives and Main Results
- 2 Accelerated Failure Time (AFT) Model
- 3 Optimal Design (OD) Problem
- 4 Adaptive Designs (AD)
- 5 Simulations



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Objectives

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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.



Main Results

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- 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

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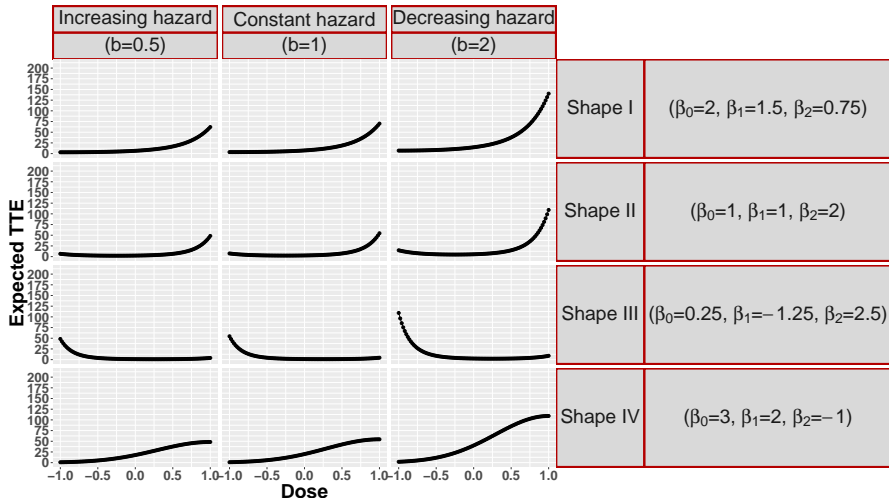
where

- 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*.



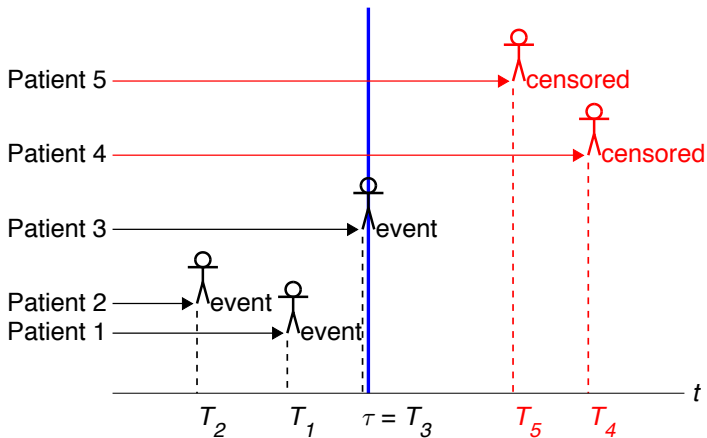
Accelerated Failure Time (AFT) Model

Dose-response relationship: $E(T|x) = \exp(\beta_0 + \beta_1x + \beta_2x^2)\Gamma(1 + b)$.





Censoring



Observed outcome is (t, δ) :

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

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



Likelihood and Fisher Information

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



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- The corresponding *Fisher Information Matrix* is

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



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

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



D-optimal Design

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

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

D-optimal Design

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

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

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

^aRyeznic Y, Hooker AC, Sverdlov O Adaptive designs for dose finding clinical trials with time-to-event outcomes. PAGE 24 (2015) Abstr 3608 [www.page-meeting.org/?abstract=3608]

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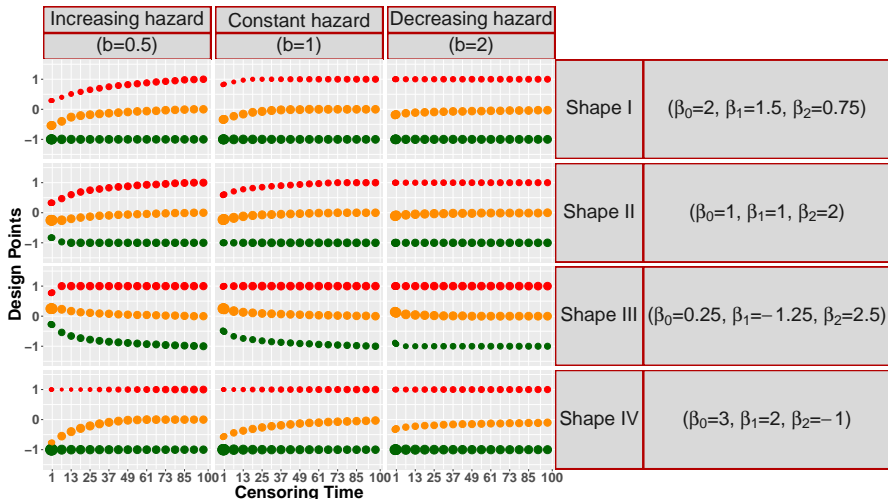
where $\begin{cases} -1 & - & \text{minimum dose} \\ 0 & - & \text{average dose} \\ 1 & - & \text{maximum dose} \end{cases}$

- 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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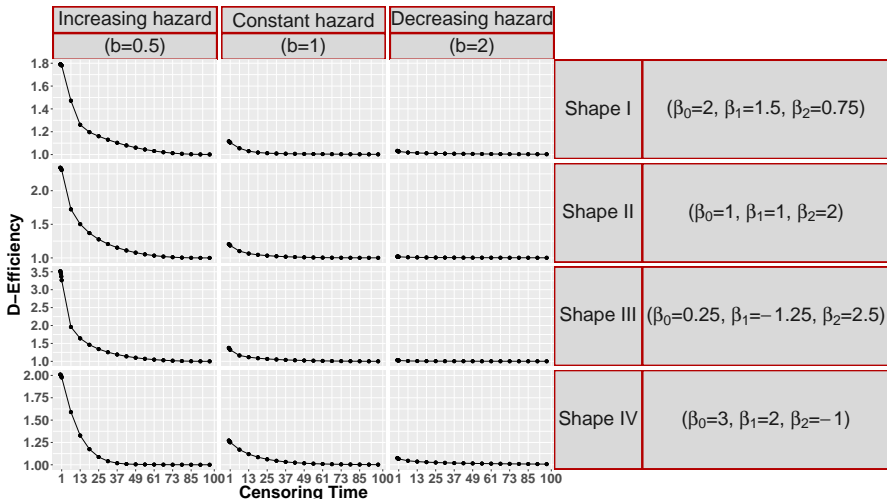


D-optimal Design





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





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Adaptive Designs

- D-optimal design ξ depends on a model parameters θ which are *unknown* at the beginning of a study.
- In order to address this issue *adaptive design* is proposed.



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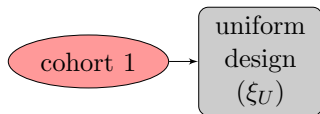
cohort 1

Adaptive Designs



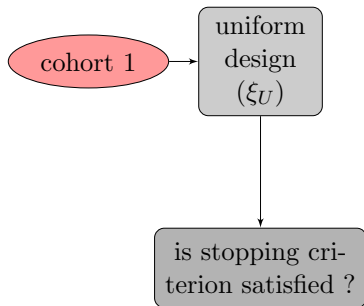
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Adaptive Designs



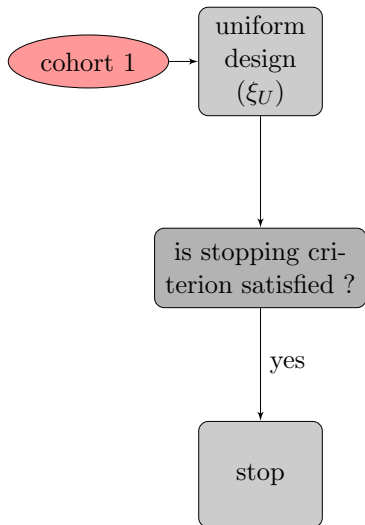


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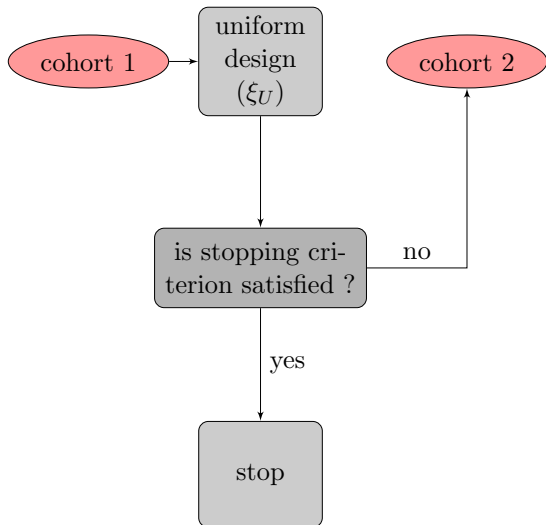


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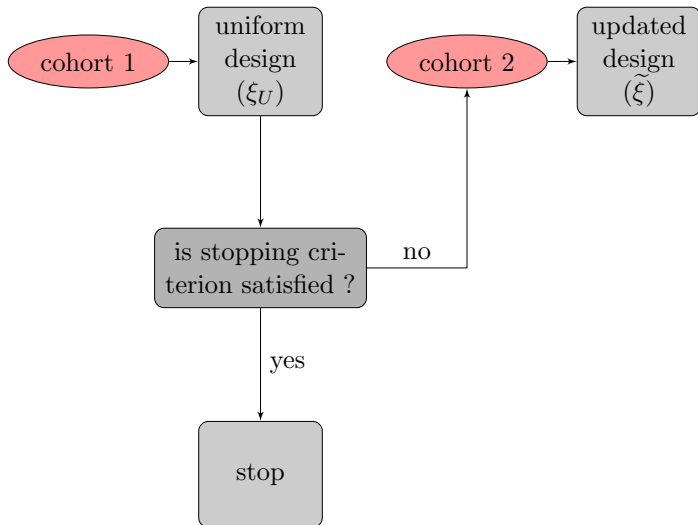


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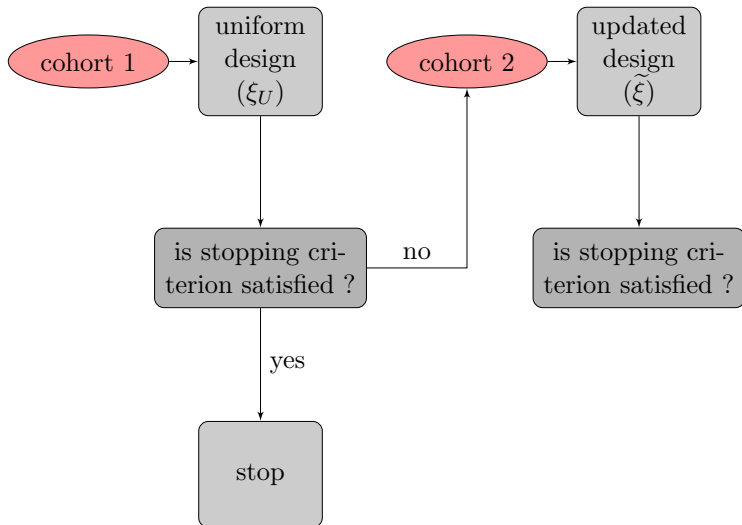


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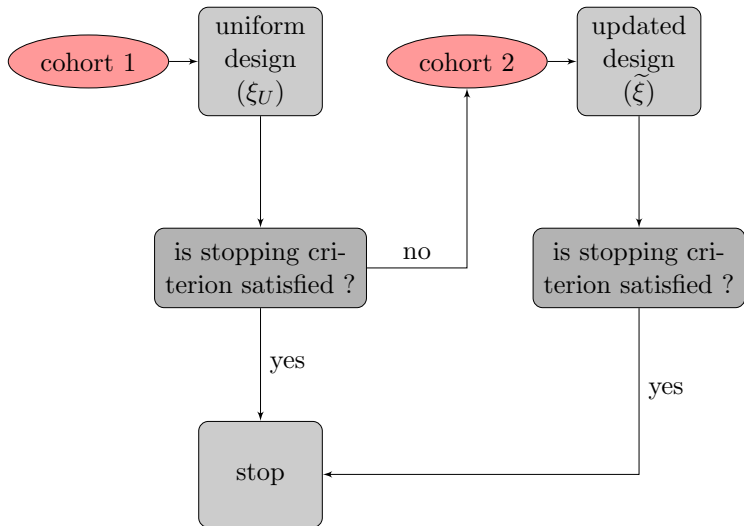


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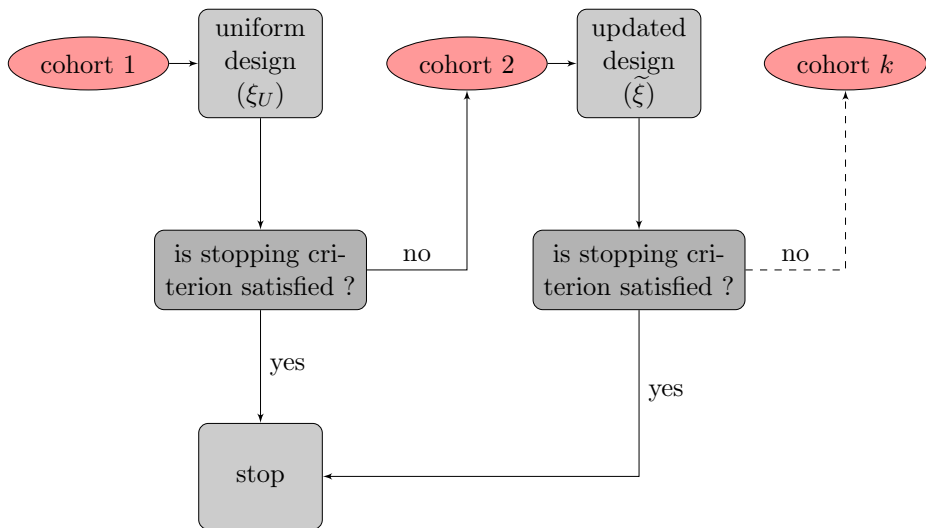


Adaptive Designs





Adaptive Designs



Updated Design

Two types of design updating are possible:

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

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

where

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

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

given data.



Stopping Criterion

The following rule is proposed as a stopping criterion:

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

where

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

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

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Simulations Setup

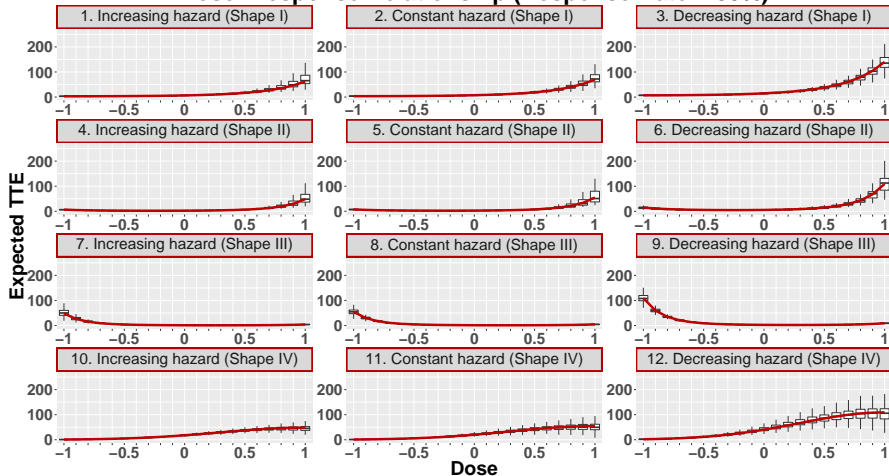
- For 3 different scales and 4 different shapes we simulate 12 models.
- We consider 3 possible values of a response rate¹
- For each of 12 scenarios number of simulation $n_{sim} = 1000$.
- The number of subject in cohort is 30.
- Parameter α for the stopping criterion is 0.25.
- We stop simulations if number of randomized patients achieves 2100 but stopping criterion is not satisfied.

¹By response rate we assume proportion of uncensored observations.



Simulations Results

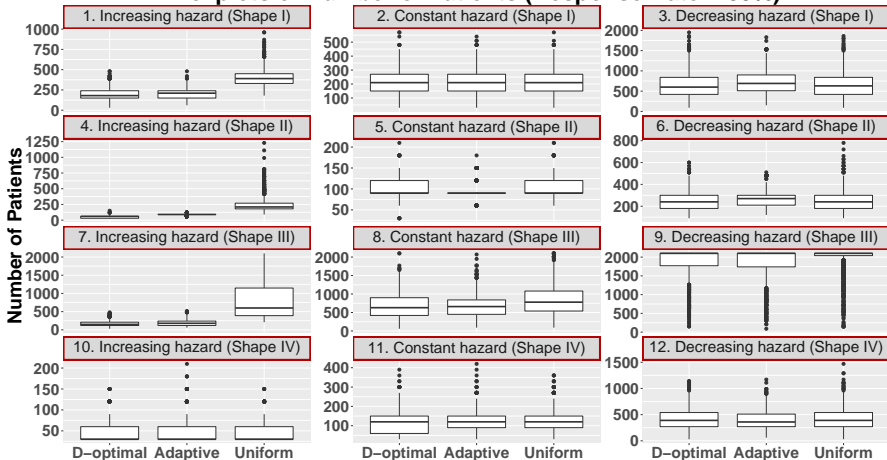
Dose-Response Relationship (Response Rate ~ 80%)





Simulations Results

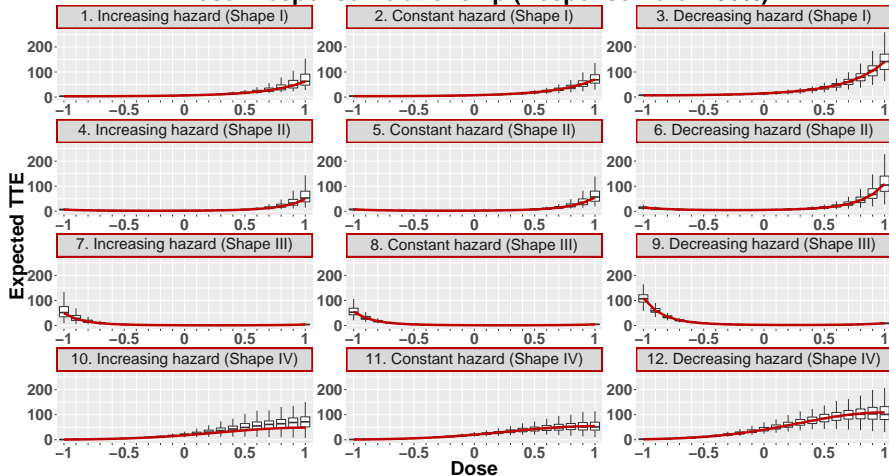
Boxplots of Number of Patients (Response Rate ~ 80%)





Simulations Results

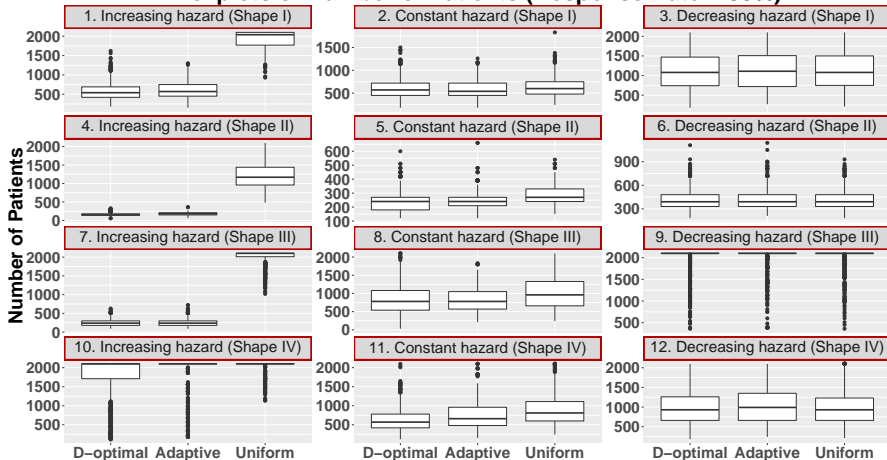
Dose-Response Relationship (Response Rate ~ 50%)





Simulations Results

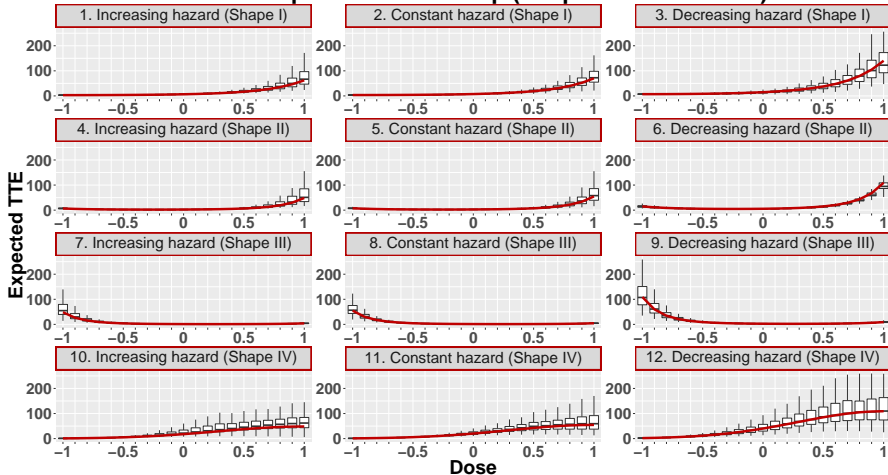
Boxplots of Number of Patients (Response Rate ~ 50%)





Simulations Results

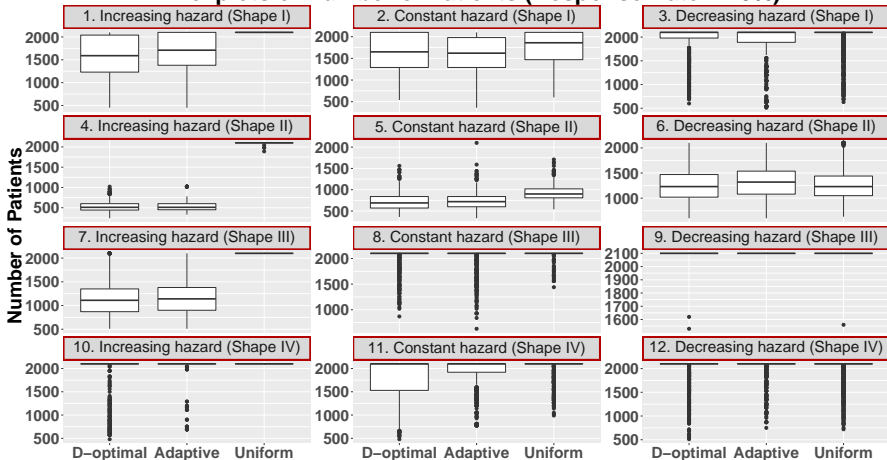
Dose-Response Relationship (Response Rate ~ 20%)





Simulations Results

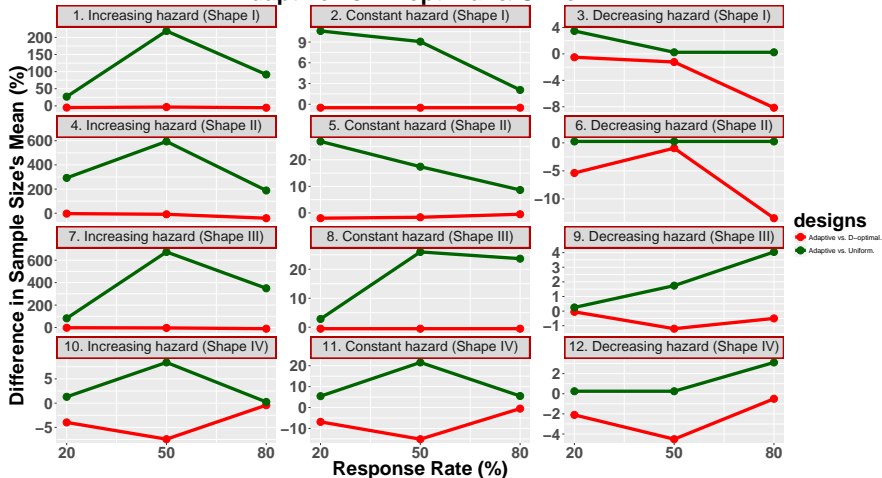
Boxplots of Number of Patients (Response Rate ~ 20%)





Simulations Results

Adaptive vs. D-optimal & Uniform





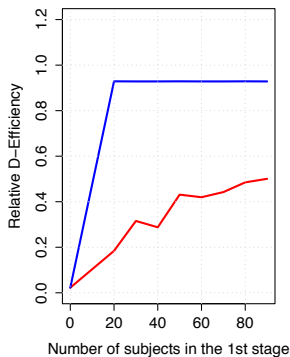
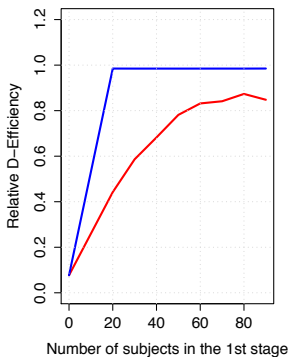
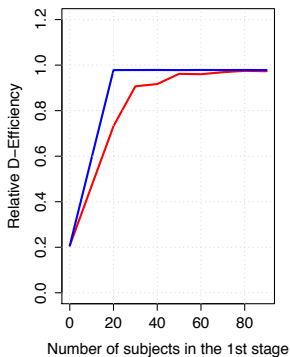
Bayesian update vs. MLEs

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

response rate = 90%

response rate = 82%

response rate = 38%



— Bayes — ML



Summary

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

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