Determining a Maximal Period of Administration for an Experimental Agent

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Motivating Example

- Agent under investigation:

  $\Rightarrow$ Recombinant human keratinocyte growth factor (KGF)

- Patient group:

  $\Rightarrow$ Allogeneic bone marrow transplant (BMT) recipients

  - Experience acute graft-versus-host disease (aGVHD)
  - Occurs within 100 days of BMT
  - Includes severe GI distress, $i.e.$ vomiting, diarrhea, bleeding

Motivating Example

- Potential treatment:

  $\Rightarrow$ Reduction of chemotherapy- and radiation-induced injury to the mucosal lining of the lower gastro-intestinal (GI) tract

- Potential toxicities:

  $\Rightarrow$ mild to moderate skin-related events such as rash, reddening, and edema

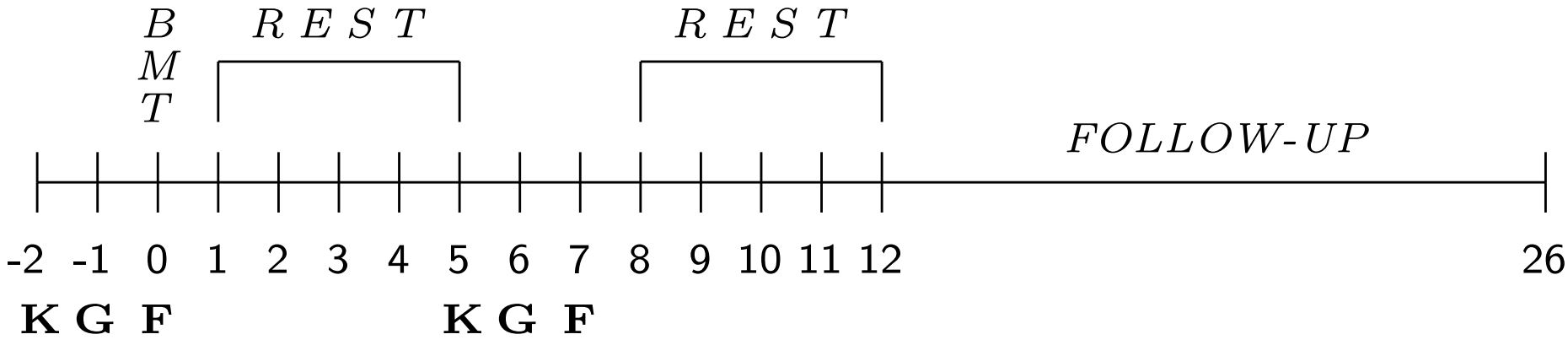
  $\Rightarrow$ reversible increases in amylase and lipase indicative of pancreas dysfunction

Motivating Example

- Prior Phase I trials
  - $\Rightarrow$ 60 mg/kg/day of IV KGF associated with mimimal toxicity in BMT recipients
  - $\Rightarrow$ administered on days -2, -1, 0, 5, 6, 7 post-BMT
    - $*$ 3-days-on/4-days-off schedule for two weeks

- Subjects followed additional two weeks after last administration of KGF.
  - $\Rightarrow$ Implicitly assumes toxicity risk for single administration ends after 18 days.

Motivating Example



Question:

$\Rightarrow$ How often can we repeat this two-week course and keep cumulative probability of toxicity close to a pre-determined threshold?

Study Design Considerations

- Sequentially enroll subjects as they are eligible
- Each two weeks of administrations = one course
- Number of courses (schedule) assigned to subject i determined from information collected on subjects $1, 2, \ldots, i-1$
- Comparing schedules:
  - Use data from enrolled subjects to compute posterior probabilities of toxicity
  - Schedule best satisfying pre-defined criteria is MTS

Study Design Considerations

- Naive approach - use standard Phase I trial design:
  - Treat each two-week course as a "dose"

    Braun, Ferrara, Levine (2003) CCT
  - Use TiTE-CRM (Cheung & Chappell, 2000, *Biometrics*) to weight information of subjects who have not completed their "dose"

- Better approach
  - Directly model hazard of toxicity for every single administration

Preliminary Notation

- Global study values:

  t^* = any given time from start of the trial when evaluation is made

  n^* = number of patients enrolled up to t^*

  τ = duration of observation for each subject

  p_τ = acceptable level of cumulative toxicity by τ

- Subject-specific values ($i = 1, \cdots, n^*$):

  e_i = *study* time when subject i enters the trial

  $\boldsymbol{s}_i = \{s_{i,1}, \ldots\ldots, s_{i,m_i}\}$ denotes successive *patient* times at which the i^{th} subject receives the agent, where $s_{i,1}$ coincides with study entry.

Preliminary Notation

Reconciling study time and subject time:

- Subject i receives the agent at $study$ times

$$0 < e_i + s_{i,1} < e_i + s_{i,2} < \cdots < e_i + s_{i,m_i}$$

Notation is very general:

- Agent may be administered whenever and as frequently as desired to each patient
- Allows for an arbitrary number of different treatment sequences to be studied in the trial
- A subject's actual administration times can deviate from scheduled times

Preliminary Notation

We restrict focus to k treatment sequences $\boldsymbol{s}^{(1)}, \cdots, \boldsymbol{s}^{(k)}$:

- $\boldsymbol{s}^{(j)} = (s_1, s_2, \ldots, s_{m(j)})$
- j^{th} sequence has a total of $m(j)$ administrations at i^{th} *patient* times $s_{i,1}, \ldots, s_{i,m(j)}$
- $\boldsymbol{s}^{(j)} \subset \boldsymbol{s}^{(j+1)}$ for each $j = 1, \ldots, k-1$
- $m(1) < m(2) \cdots < m(k)$

In the KGF trial:

- $\boldsymbol{s}^{(1)} = (0,\ 1,\ 2,\ 7,\ 8,\ 9)$
- $\boldsymbol{s}^{(2)} = (0,\ 1,\ 2,\ 7,\ 8,\ 9,\ 14,\ 15,\ 16,\ 21,\ 22,\ 23)$

Preliminary Notation

- $Y_i =$ actual, possibly yet unobserved, amount of time after study entry at which patient i experiences toxicity

- At interim study time t^* :

$$(Y_i^o, \delta_i) = \begin{cases} (Y_i, 1) & \text{if} \quad e_i + Y_i \leq t^* \\ (t^* - e_i, 0) & \text{if} \quad e_i + Y_i > t^*, \end{cases}$$

- $m_i =$ index of the last administration received by patient i at t^*

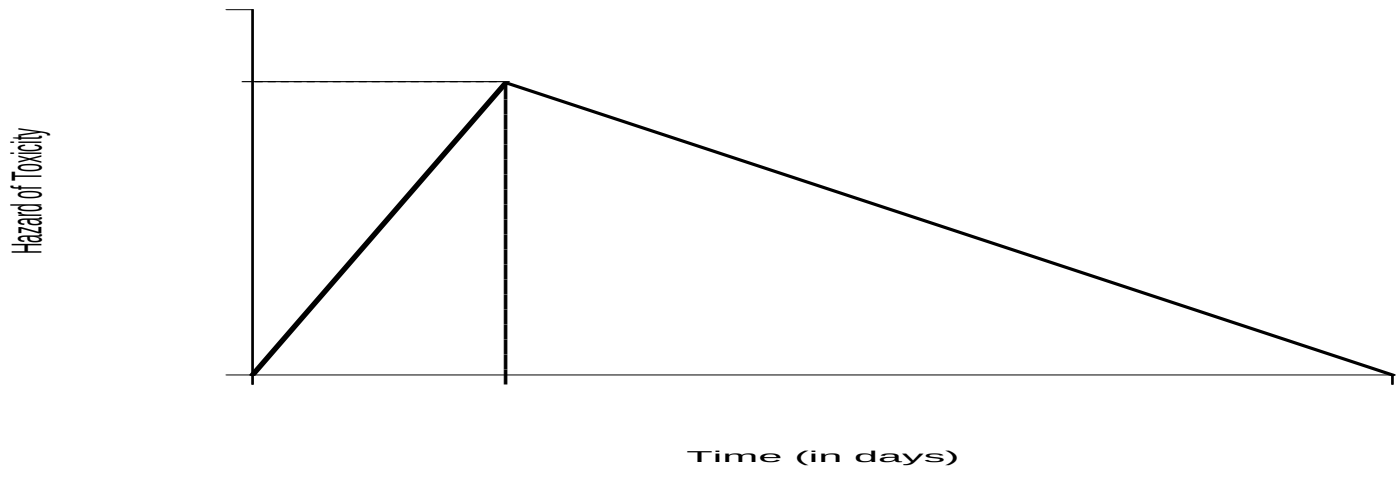
  $m_i \leq m(j)$ either due to

  (a) administrative censoring

  (b) patient i had toxicity at study time $e_i + s_{i,m_i}$ (further administration is stopped)

Modelling Single Administration Hazard

- Assume risk of toxicity increases after administration of KGF, reaches a peak, then decays to zero
- Model as a piecewise linear function:



- Hazard is identical for each administration

Modelling Single Administration Hazard

- Mathematically:

$$h(u;\boldsymbol{\theta}) = \begin{cases} \frac{\theta_2}{\theta_1} u & ; \quad 0 \leq u \leq \theta_1 \\ \\ \frac{\theta_2}{\theta_3 - \theta_1}(\theta_3 - u) & ; \quad \theta_1 < u \leq \theta_3 \end{cases}$$

θ_1 represents the point in time when $h(u;\boldsymbol{\theta})$ reaches maximum

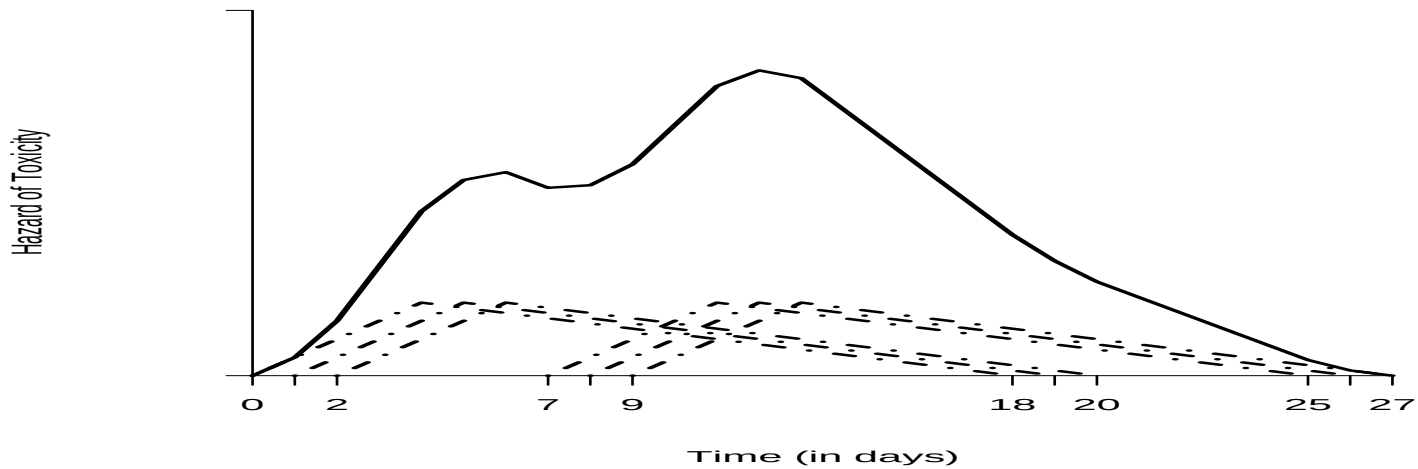
θ_2 is the hazard at $s = \theta_1$

θ_3 represents the point at which hazard vanishes

Total Hazard Function

- Using the single administration hazard function $h(u; \boldsymbol{\theta})$, we define the total hazard function for each subject:

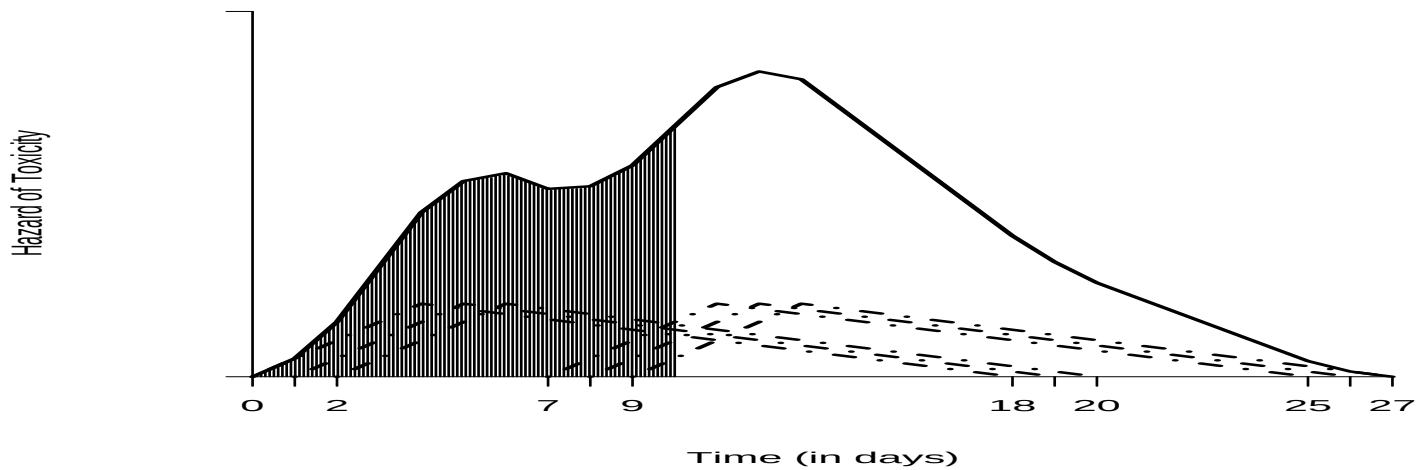
$$\lambda(t^* \mid \boldsymbol{\theta}, \boldsymbol{s}, Y^o) = \sum_{\ell=1}^{m} h(Y^o - s_\ell \mid \boldsymbol{\theta})$$



Cumulative Hazard Function

- Subject's cumulative hazard function is

$$\Lambda(t^* \mid \boldsymbol{\theta}, \boldsymbol{s}, Y^o) \quad = \quad \int_0^{Y^o} \sum_{\ell=1}^{m} h(u - s_\ell \mid \boldsymbol{\theta}) \, du$$



Functions of CHF

- Cumulative distribution function (CDF) of Y is

$$\begin{aligned} \Pr(Y \leq t^* \mid \boldsymbol{\theta}, \boldsymbol{s}, Y^o) &= F(t^* \mid \boldsymbol{\theta}, \boldsymbol{s}, Y^o) \\ &= 1 - \exp\{-\Lambda(t^* \mid \boldsymbol{\theta}, \boldsymbol{s}, Y^o)\} \end{aligned}$$

- Probability density function (PDF) is

$$f(t^* \mid \boldsymbol{\theta}, \boldsymbol{s}, Y^o) = \lambda(t^* \mid \boldsymbol{\theta}, \boldsymbol{s}, Y^o) \exp\{-\Lambda(t^* \mid \boldsymbol{\theta}, \boldsymbol{s}, Y^o)\}$$

Likelihood for θ

- At interim time t^*, we have enrolled n^* subjects
- For subject $i = 1, 2, \ldots, n^*$, we have information

$$\mathcal{D}_i = (\boldsymbol{s}_i, Y_i^0, \delta_i)$$

- Total information is $\mathcal{D}^* = (t^*, \mathcal{D}_1, \mathcal{D}_2, \ldots, \mathcal{D}_{n^*})$
- Likelihood for $\boldsymbol{\theta}$ at t^* is

$$\begin{aligned} \mathcal{L}(\mathcal{D}^* \mid \boldsymbol{\theta}) &= \prod_{i=1}^{n^*} \{f(t^* \mid \boldsymbol{\theta}, \boldsymbol{s}_i, Y_i^o)\}^{\delta_i} \\ &x \quad \prod_{i=1}^{n^*} \{1 - F(t^* \mid \boldsymbol{\theta}, \boldsymbol{s}_i, Y_i^o)\}^{1-\delta_i} \end{aligned}$$

Posterior Distribution for θ

- Denoting the prior by $p(\boldsymbol{\theta})$, the posterior of $\boldsymbol{\theta}$ is

$$g(\boldsymbol{\theta} \mid \mathcal{D}^*) \quad = \quad \frac{\mathcal{L}(\mathcal{D}^* \mid \boldsymbol{\theta}) p(\boldsymbol{\theta})}{\int \mathcal{L}(\mathcal{D}^* \mid \boldsymbol{\theta}) p(\boldsymbol{\theta}) d\boldsymbol{\theta}}.$$

- Above integral cannot be obtained analytically under our assumed model
  - Compute posterior quantities via Markov chain Monte Carlo (MCMC) methods

Eliciting Prior Distribution for θ

- We denote the prior distribution of $\boldsymbol{\theta}$ as

$$p(\boldsymbol{\theta}) = p_3(\theta_3)\ p_1(\theta_1|\theta_3)\ p_2(\theta_2)$$

- For $p_3(\theta_3)$, the investigator must identify:
  - (a) $[T_\ell, T_u]$, plausible range for θ_3
  - (b) μ_{θ_3}, the expected value of θ_3

- For $p_1(\theta_1|\theta_3)$, the investigator must identify a 95% credible interval for θ_1, denoted $m \pm d$

- For $p_2(\theta_2)$, the investigator must identify the $a\ priori$ optimal schedule, denoted $\mathbf{s}^*$

Eliciting Prior Distribution for θ_3

- We assume θ_3 has a generalized beta distribution

$$p_3(u) = \frac{(u - T_\ell)^{a_3 - 1}(T_u - u)^{b_3 - 1}}{B(a_3, b_3)(T_u - T_\ell)^{a_3 + b_3 - 1}}, \qquad T_\ell \leq u \leq T_u,$$

  where

$$\begin{aligned} B(a_3, b_3) &= \int_0^1 x^{a_3 - 1}(1 - x)^{b_3 - 1} dx \\ a_3 &= k_3(\mu_{\theta_3} - T_\ell) \\ b_3 &= k_3(T_u - \mu_{\theta_3}) \end{aligned}$$

- Tuning constant k_3 modulates variance of $p_3(u)$, which decreases as k_3 increases

Eliciting Prior Distribution for θ_1

- We also assume θ_1, conditional upon θ_3, follows a generalized beta distribution

$$p_1(u|\theta_3) = \frac{u^{a_1-1}(\theta_3 - u)^{b_1-1}}{\theta_3^{a_1+b_1-1}B(a_1, b_1)}, \qquad 0 \leq u \leq \theta_3$$

- From the 95% credible interval, $m \pm d$, we have:

$$\begin{aligned} a_1 &= \frac{m}{\theta_3}\left[\frac{4m(\theta_3 - m)}{d^2} - 1\right] \\ b_1 &= \frac{\theta_3 - m}{\theta_3}\left[\frac{4m(\theta_3 - m)}{d^2} - 1\right], \end{aligned}$$

assuming approximate symmetry of $p_1(\theta_1|\theta_3)$ about m

Eliciting Prior Distribution for θ_2

- Investigator believes schedule $\mathbf{s}^*$ is MTS

  $\Rightarrow$ Schedule $\mathbf{s}^*$ has cumulative probability of toxicity by τ closest to p_τ

- Determine θ_2^* so that

$$E\{F(\tau \mid \theta_2^*, \theta_1, \theta_3^*, \boldsymbol{s}^*, 1)\} = p_\tau,$$

  where θ_3^* is an assumed value for θ_3.

- Example:

  $\Rightarrow$ In the KGF trial, investigators believed that schedule 2 (4 weeks) was optimal assuming $\theta_3^* = 18$

  $\Rightarrow$ Each administration has a cumulative hazard of $9\theta_2^*$

  $\Rightarrow$ Entire schedule has a cumulative hazard of $108\theta_2^*$

  $\Rightarrow$ $\theta_2^* = -log(1 - p_\tau)/108 \quad -- > \ \mu_{\theta_2}$

Eliciting Prior Distribution for θ_2

- θ_2 describes the height of the single-administration hazard

  $\Rightarrow$ θ_2 is quantitatively different than θ_1 and θ_3

  $\Rightarrow$ Generalized beta distribution inappropriate choice for $p_2(u)$

- We assume θ_2 has a prior Gamma distribution

$$p_2(u) = b_2^{a_2} u^{a_2 - 1} exp\{-b_2 u\}/\Gamma(a_2), \qquad u \geq 0,$$

  where $a_2 = k_2$, $b_2 = k_2/\mu_{\theta_2}$, and $\Gamma(z) = \int_0^\infty x^{z-1} e^{-x} dx$

- Tuning constant k_2 modulates the variance of $p_2(u)$, which decreases as k_2 increases

Fine-Tuning Prior Distribution for θ

- Variances of $p_3(\theta_3)$, $p_1(\theta_1|\theta_3)$, and $p_2(\theta_2)$ heavily influence the ability of the data to influence $p(\boldsymbol{\theta})$

- Exhaustive sensitivity analysis of (d, k_2, k_3) is necessary before implementing the design
  - Simulate toxicity times for a 3-5 subjects
  - Apply design using various values of d, k_2, k_3
  - Compare the prior means for $\boldsymbol{\theta}$ to their respective posterior values

Visualizing Prior for $F(\tau \mid \boldsymbol{\theta}, \boldsymbol{s}^{(j)}, 1)$

- From $p(\boldsymbol{\theta})$, we have implied a specific prior distribution for the cumulative probability of toxicity for each schedule

- To visualize the prior distribution for $F(\tau \mid \boldsymbol{\theta}, \boldsymbol{s}^{(j)}, 1)$ for each schedule j:
  - Draw B samples from the prior distribution of $\boldsymbol{\theta}$
  - Compute B prior estimates of $F(\tau \mid \boldsymbol{\theta}, \boldsymbol{s}^{(j)}, 1)$ for each schedule j
  - Plot histograms to determine if there is any undue prior influence on those estimates, i.e, placing too much mass at 0 or 1

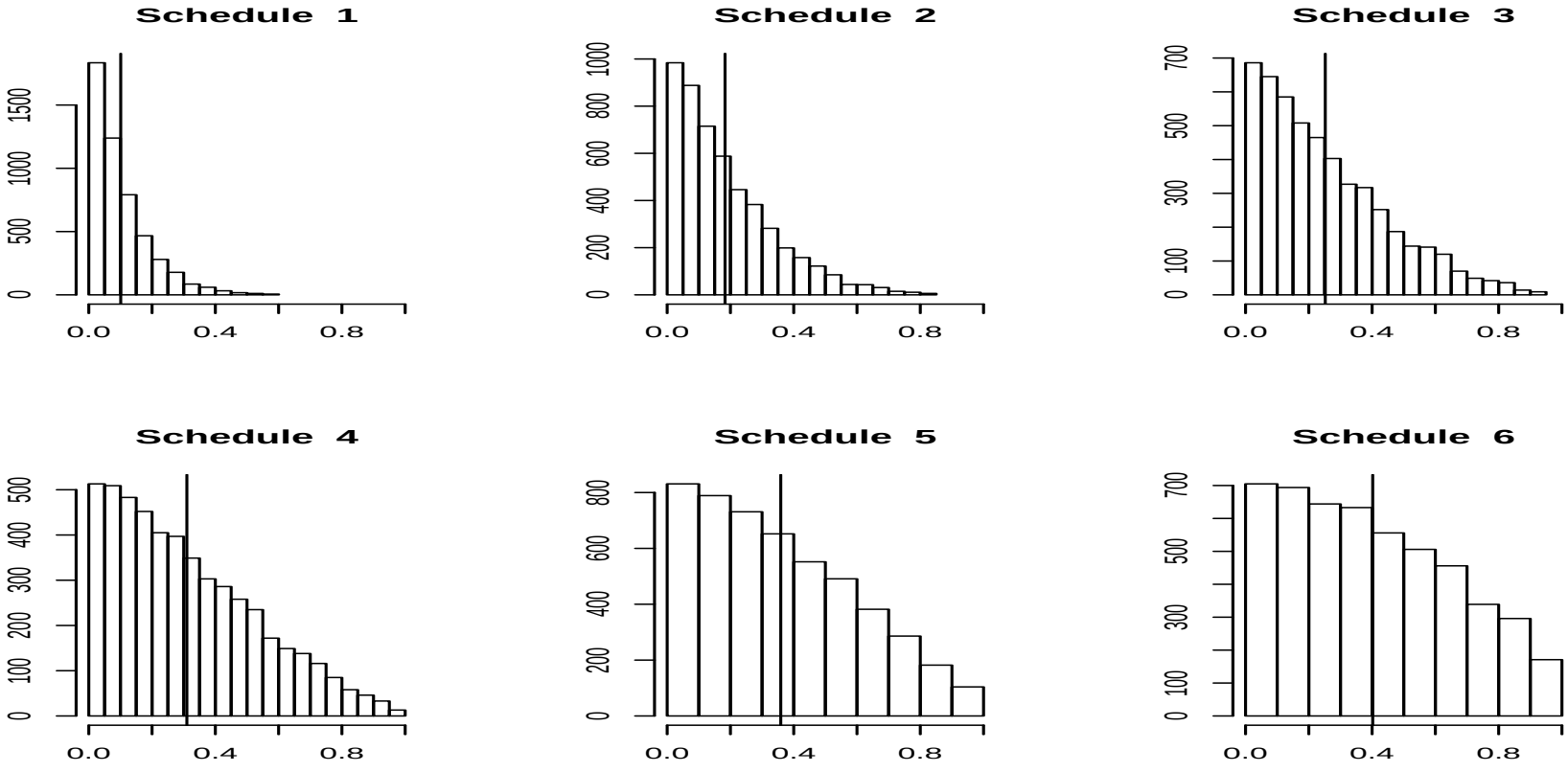
Visualizing Prior for $F(\tau \mid \boldsymbol{\theta}, \boldsymbol{s}^{(j)}, 1)$

- Example:
  - θ_3 ranges over $[4, 50]$ days, with a mean of 18 days
  - θ_1 occurs 2 ± 2 days after administration
  - θ_2 has mean 0.0021 if $p_\tau = 0.20$, Schedule 2 is the MTS and $\theta_3 = 18$
  - $k_2 = k_3 = 1$

- Mean cumulative probability of toxicity for Schedule 2 is closest to 0.20

- Variation of $F(\tau \mid \boldsymbol{\theta}, \boldsymbol{s}^{(j)}, 1)$ increases with j due the cumulative nature of the schedules

Visualizing Prior for $F(\tau \mid \boldsymbol{\theta}, \boldsymbol{s}^{(j)}, 1)$



Trial Conduct Issues

- $N =$ maximum number of patients to be enrolled in the trial
- First patient is assigned the shortest sequence, $\boldsymbol{s}^{(1)}$
- Only incremental schedule escalation is permitted
- At least M subjects must have received schedules $\mathbf{s}^{(1)}, ..., \mathbf{s}^{(j-1)}$ before schedule $\mathbf{s}^{(j)}$ is assigned
- Schedule de-escalation is permitted without any constraint

Determining Schedule Assignments

- Given p_τ, we will consider two alternative criteria for choosing each subject's sequence

- Criterion 1: At time t^*, for each $j = 1, ..., k$, compute

$$F_j^*(\tau) = E\{F(\tau \mid \boldsymbol{\theta}, \boldsymbol{s}^{(j)}, 1) \mid \mathcal{D}^*\}$$

- The best sequence is defined as that having $F_j^*(\tau)$ closest to p_τ, that is, minimizing $|F_j^*(\tau) - p_\tau|$

Determining Schedule Assignments

- Criterion 2: At time t^*, for each $j = 1, ..., k$, compute

$$\phi_j(\tau) = \Pr\{F(\tau \mid \boldsymbol{\theta}, \boldsymbol{s}^{(j)}, 1) > p_\tau \mid \mathcal{D}^*\}$$

- Given a fixed upper limit, $\bar{p}$, the best sequence is defined as the longest sequence for which $\phi_j(\tau) < \bar{p}$, that is, for which the risk of toxicity is acceptable

- Under either Criterion 1 or 2:

  Best sequence is assigned to next patient

  MTS is defined as the best sequence using information from all N subjects at the end of the trial

Assessing Performance via Simulation

- $k = 6$ schedules of KGF are investigated: 2, 4, 6, 8, 10 or 12 weeks

- Six scenarios studied: Schedule $\mathbf{s}^{(j)}$ optimal under the jth scenario
  - $\theta_1 = 2$ days; $\theta_3 = 18$ days
  - $1000\theta_2 \in [4.13, 2.07, 1.38, 1.03, 0.83, 0.69]$

- $N = 30$

- $\tau = 100$ days

- $p_\tau = 0.20$

Assessing Performance via Simulation

- Prior distributions:

  $\Rightarrow$ θ_3 has mean of 18 days; range of [4, 100] days

  $\Rightarrow$ θ_1 between 0-4 days (2 ± 2 days)

  $\Rightarrow$ Schedule 6 is MTS

  θ_2 has a prior mean 0.00069

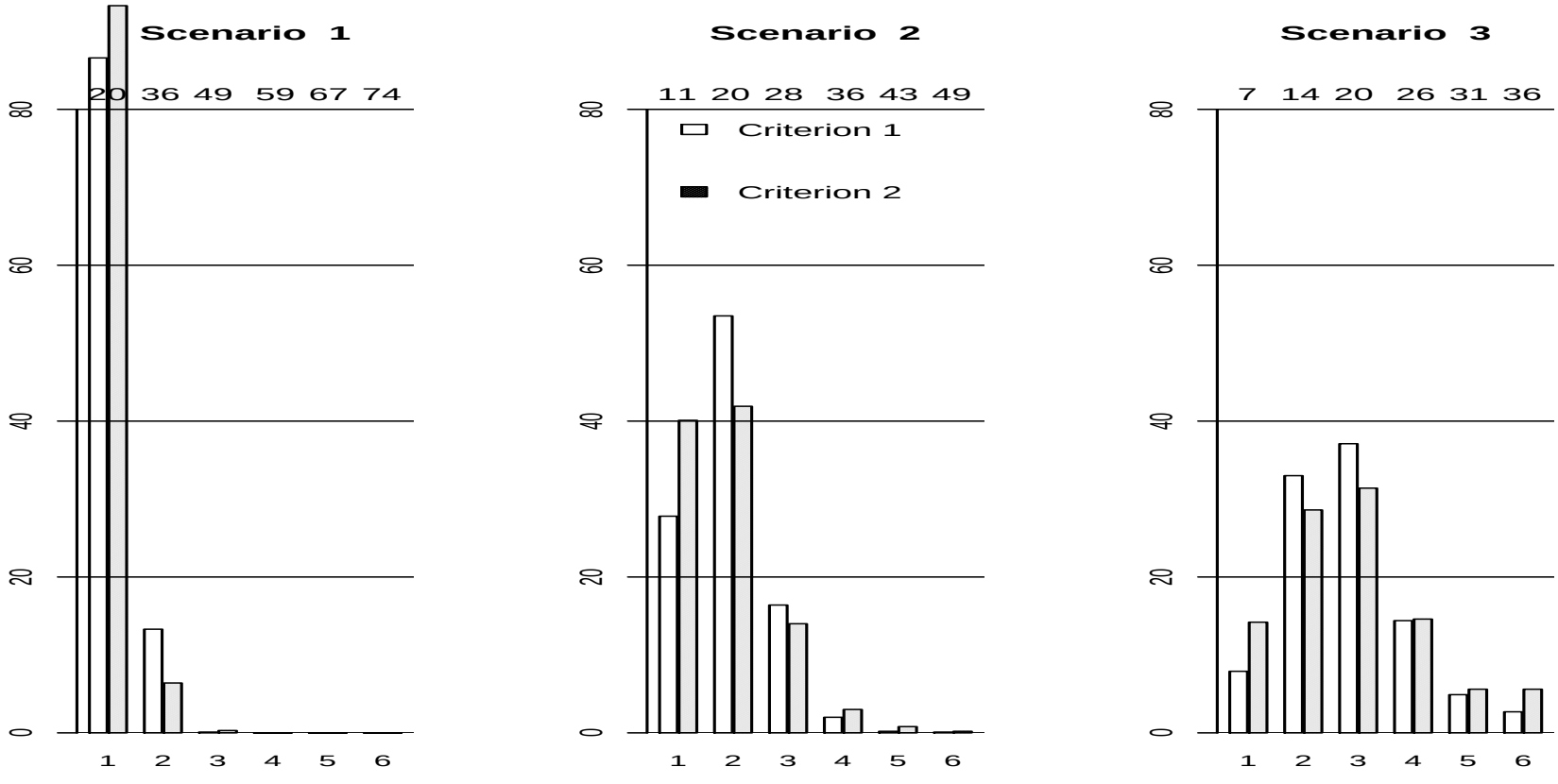
  $\Rightarrow$ $k_3 = 0.1$; $k_2 = 0.2$

- Subject inter-arrival times $\sim U[12, 16]$ days

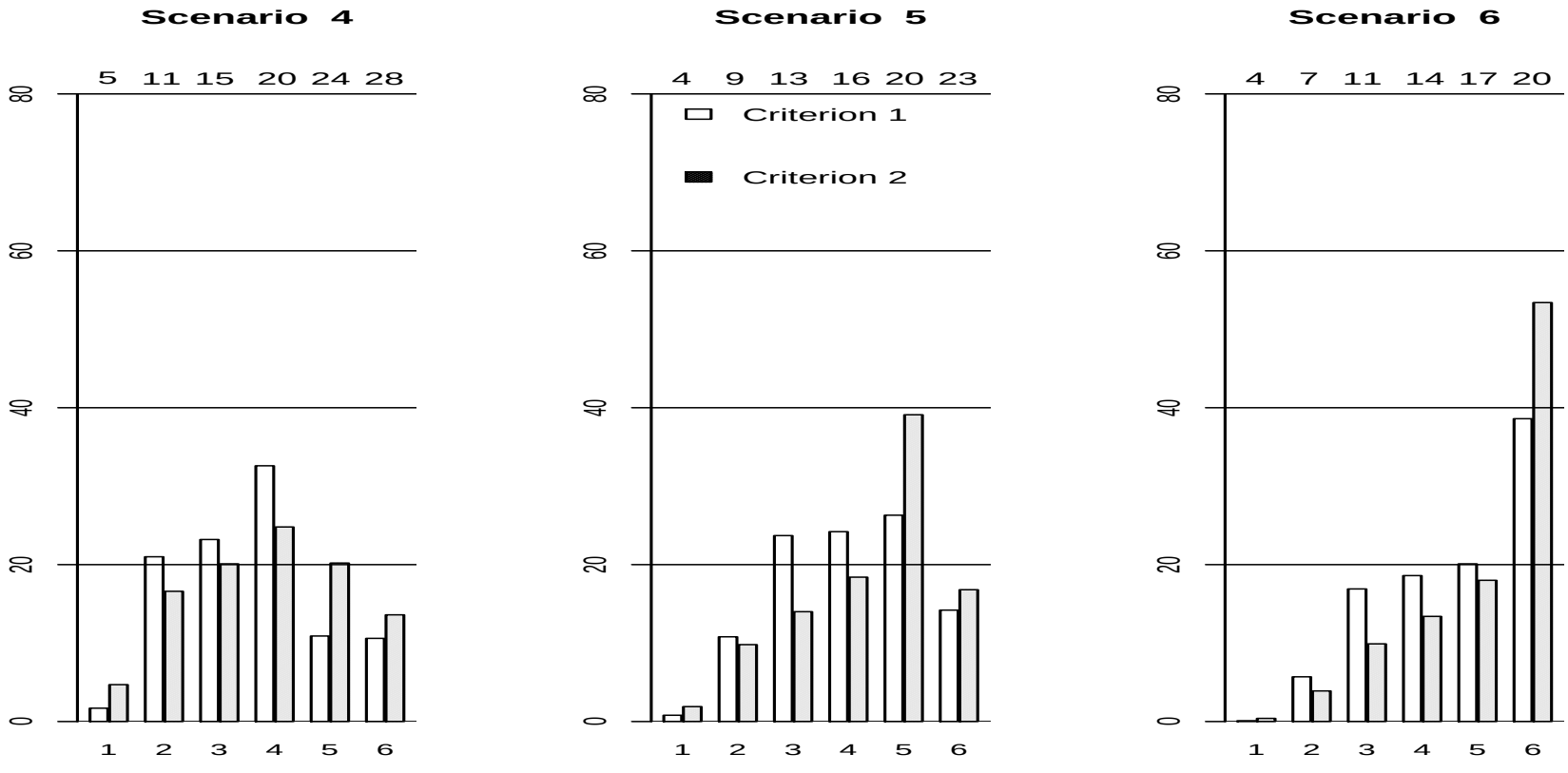
- Posteriors based upon 2000 samples; burn-in of 500 samples

- $M = 1000$ simulations

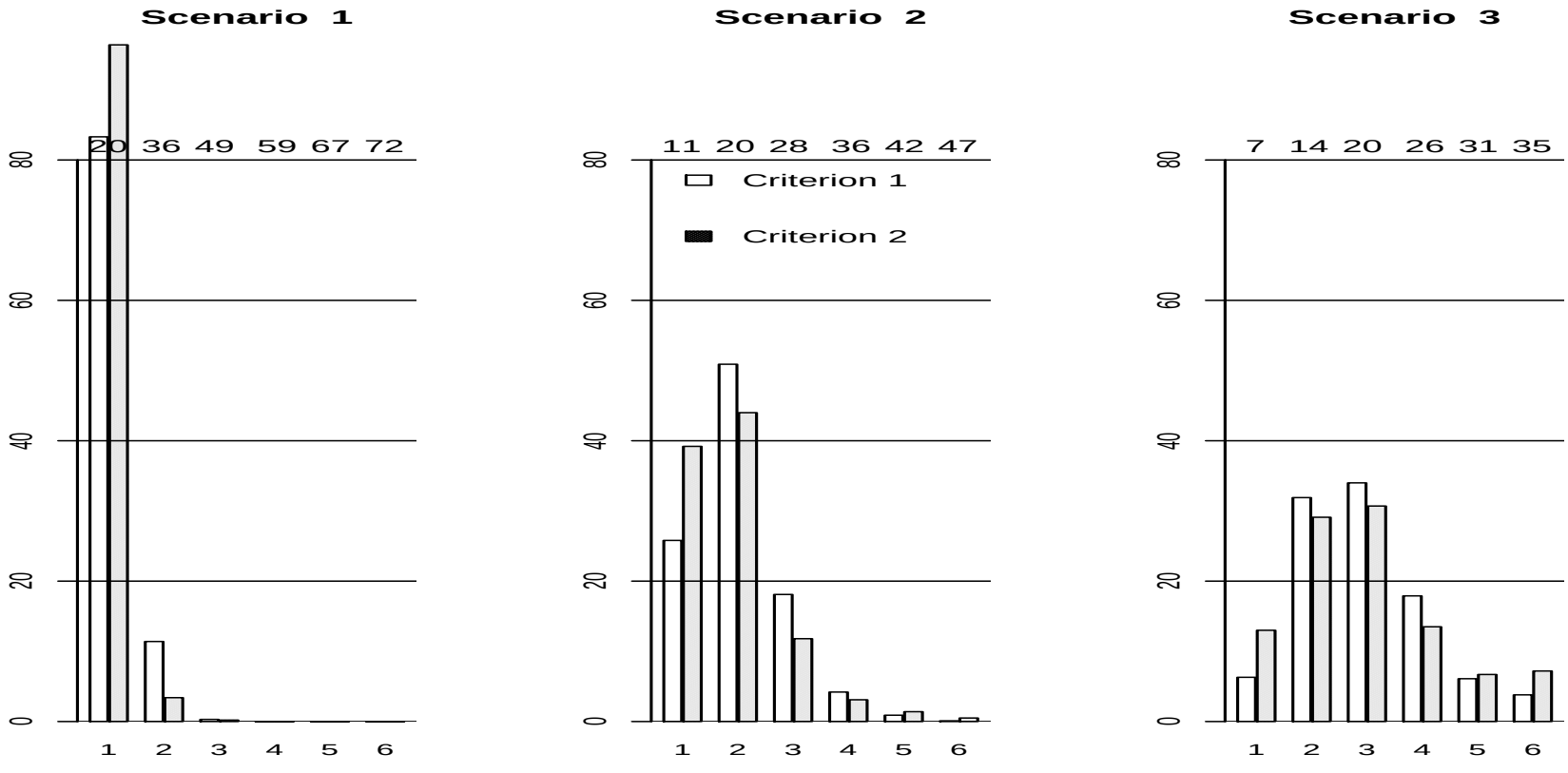
Identifying the MTS: $\theta_3 = 18$



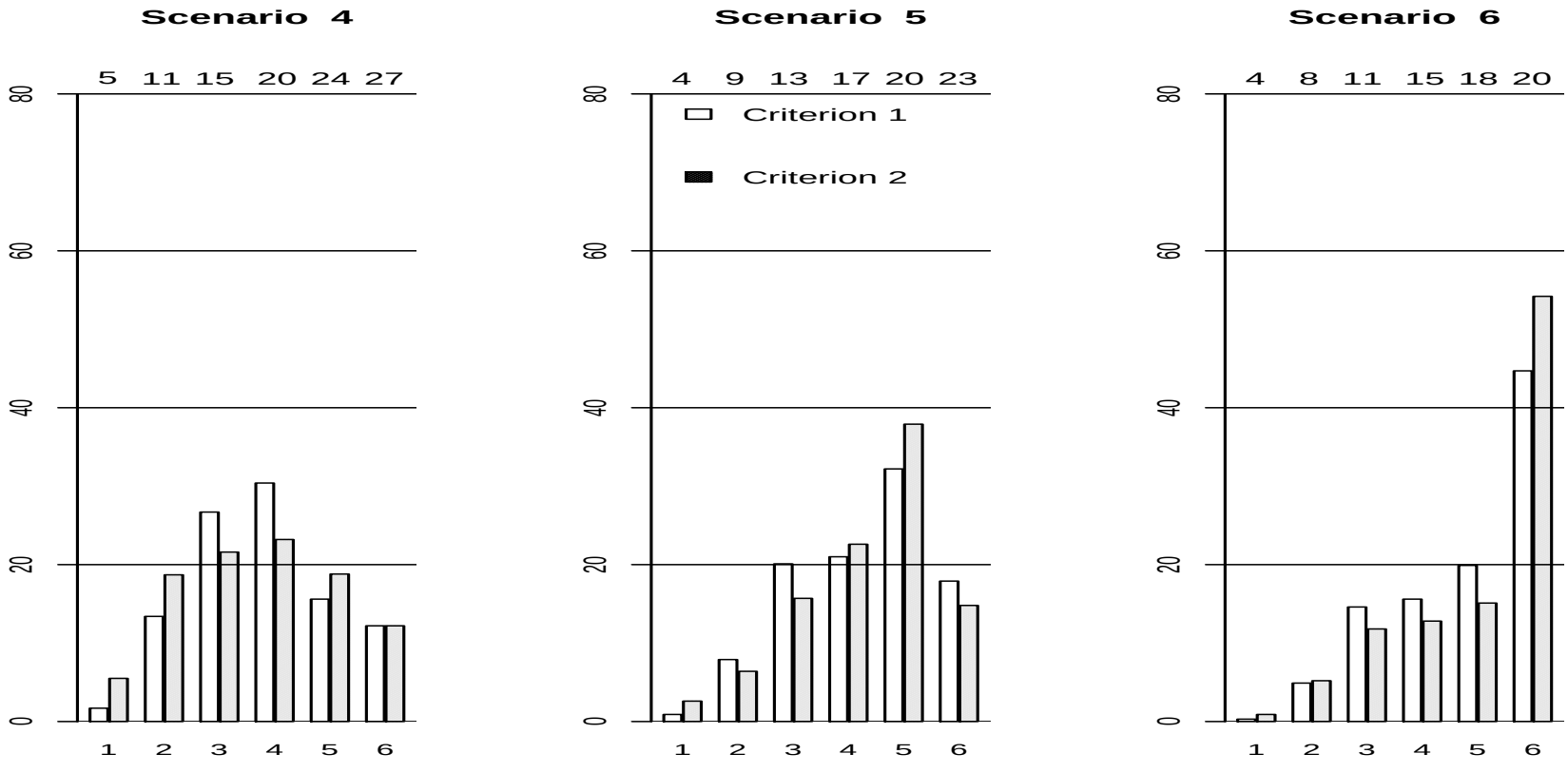
Identifying the MTS: $\theta_3 = 18$



Identifying the MTS: $\theta_3 = 50$



Identifying the MTS: $\theta_3 = 50$



Concluding Remarks

- Overall determination of MTS relatively insensitive to $p_1(\theta_1)$:
  - θ_1 influences the time at which each patient experiences toxicity
  - Has more influence on schedule assignments during the study
- Strong homogeneity assumption:
  - Patients who receive the shortest sequence $\boldsymbol{s}^{(1)}$ provide information about the toxicity of schedules $\boldsymbol{s}^{(j)}, j \geq 1$
- Extensions to Phase II & III studies of cumulative dosing
  - Adjusting for between-patient variability