

Introduction to the Design and Evaluation of Group Sequential Clinical Trials

Session 4 - Monitoring Group Sequential Trials

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Impact of Changing
the Number and
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Operating characteristics to consider at the design stage

1. Standard for evidence and efficiency of designs
 - ▶ Type I error
 - ▶ Power at various alternatives
 - ▶ Average sample number (ASN) / stopping probabilities
2. Point estimates of treatment effect corresponding to boundary decisions in favor of
 - ▶ Efficacy – Futility – Harm
3. Frequentist/Bayesian/Likelihood inference on the boundaries
4. Conditional futility/reversal of decision corresponding to boundary decisions

All dependent on the sampling density of the test statistic...

RECALL: Group sequential sampling density

- ▶ Consider independent observations X_1, \dots, X_{n_J} with $E[X_i] = \theta, i = 1, \dots, n_J$
- ▶ Interested in testing $H_0 : \theta = \theta_0$ based upon a maximum of J analyses
- ▶ Let S_j denote the test statistic computed at interim analysis j using observations $1, \dots, n_j$, and suppose that $S_j \sim N(\theta V_j, V_j), j = 1, \dots, J$
- ▶ At each analysis we partition the outcome space for statistic S_j into *stopping set* \mathcal{S}_j and *continuation set* \mathcal{C}_j
 - ▶ If $S_j \in \mathcal{S}_j$, the trial is stopped.
 - ▶ Otherwise, $S_j \in \mathcal{C}_j$ and the study continues to gather additional observations.

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RECALL: Group sequential sampling density

- Under an independent increments covariance structure, the sampling density of the bivariate group sequential statistic (M, S_M) , where $M = \min\{j : S_j \notin C_j\}$ is given by

$$p(m, s; \theta) = \begin{cases} f(m, s; \theta) & s \notin C_m \\ 0 & \text{otherwise} \end{cases},$$

where the function $f(j, s; \theta)$ is given recursively by,

$$f(1, s; \theta) = \frac{1}{\sqrt{V_1}} \phi\left(\frac{s - \theta V_1}{\sqrt{V_1}}\right)$$

$$f(j, s; \theta) = \int_{C_{j-1}} \sqrt{v_j} \phi\left(\frac{s - u - v_j}{\sqrt{v_j}}\right) f(j-1, u; \theta) du, j = 2, \dots, m$$

with $v_j = V_j - V_{j-1}$ and $\phi(x) = \frac{\exp(-x^2/2)}{\sqrt{2\pi}}$.

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Operating characteristics condition upon exact timing

- ▶ When S_j represents the score statistic resulting from a parametric probability model, $\text{Var}[S_j] = V_j = \mathcal{I}_j$ is Fisher Information
- ▶ The group sequential density (and hence all of the previously mentioned operating characteristics) will depend upon the timing of analyses as measured by the information accrued
- ▶ Most commonly, we carry out *maximal information trials*
 - ▶ Specify the maximum information that will be entertained
 - ▶ Usually in order to guarantee a specified power at a clinically relevant alternative
 - ▶ Interim analyses are then planned according to the proportion of the maximal sample size that has been accrued to the trial ($\Pi_j \equiv V_j / V_J$)

Operating characteristics condition upon exact timing

- ▶ During the conduct of a study the timing of analyses may change because:
 - ▶ Monitoring scheduled by calendar time
 - ▶ Slow (or fast) accrual
 - ▶ External causes (should not be influenced by study results)
 - ▶ Statistical information from a sampling unit may be different than originally estimated
 - ▶ Variance of measurements
 - ▶ Baseline event rates (binary outcomes)
 - ▶ Censoring and survival distributions (weighted survival statistics)
- ▶ Consequences of these changes can include
 - ▶ Change in nominal type I error rate from originally planned design
 - ▶ Change in power from originally planned design

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Example: Stopping rule chosen at design

- ▶ Test of normal mean:
 - ▶ $H_0 : \theta \leq 0.0$
 - ▶ $H_1 : \theta \geq 0.5$
- ▶ One-sided symmetric test
 - ▶ Size .025, Power .975
 - ▶ Four equally spaced analyses
 - ▶ Pocock (1977) boundary relationships

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Example: Stopping rule chosen at design

```
> dsn <- seqDesign( prob.model="normal", arms=1, null.hypothesis=0,  
+                   alt.hypothesis=0.5, test.type="greater", variance=4,  
+                   power=0.975, P=0.5, nbr.analyses=4, early.stopping="both" )
```

```
> dsn
```

PROBABILITY MODEL and HYPOTHESES:

Theta is mean response

One-sided hypothesis test of a greater alternative:

Null hypothesis : $\Theta \leq 0.0$ (size = 0.025)

Alternative hypothesis : $\Theta \geq 0.5$ (power = 0.975)

(Emerson & Fleming (1989) symmetric test)

STOPPING BOUNDARIES: Sample Mean scale

		Futility	Efficacy
Time 1	(N= 86.31)	0.0000	0.5000
Time 2	(N= 172.62)	0.1464	0.3536
Time 3	(N= 258.92)	0.2113	0.2887
Time 4	(N= 345.23)	0.2500	0.2500

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Analyses after 40%, 60%, 80%, 100% (maintain power)

```
> dsn.late.power <- update(dsn, sample.size=c(.4,.6,.8,1) )
```

```
> dsn.late.power
```

PROBABILITY MODEL and HYPOTHESES:

Theta is mean response

One-sided hypothesis test of a greater alternative:

Null hypothesis : $\Theta \leq 0.0$ (size = 0.025)

Alternative hypothesis : $\Theta \geq 0.5$ (power = 0.975)

(Emerson & Fleming (1989) symmetric test)

STOPPING BOUNDARIES: Sample Mean scale

		Futility	Efficacy
Time 1	(N= 131.97)	0.1047	0.3953
Time 2	(N= 197.95)	0.1773	0.3227
Time 3	(N= 263.93)	0.2205	0.2795
Time 4	(N= 329.91)	0.2500	0.2500

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Analyses after 40%, 60%, 80%, 100% (maintain max sample size)

```
> dsn.late.n <- update(dsn,  
  sample.size=c(.4,.6,.8,1)*max(dsn$parameters$sample.size),  
  alt.hypothesis="calculate" )
```

```
> dsn.late.n
```

PROBABILITY MODEL and HYPOTHESES:

Theta is mean response

One-sided hypothesis test of a greater alternative:

Null hypothesis : $\Theta \leq 0.0000$ (size = 0.025)

Alternative hypothesis : $\Theta \geq 0.4888$ (power = 0.975)

(Emerson & Fleming (1989) symmetric test)

STOPPING BOUNDARIES: Sample Mean scale

		Futility	Efficacy
Time 1	(N= 138.09)	0.1024	0.3864
Time 2	(N= 207.14)	0.1733	0.3155
Time 3	(N= 276.19)	0.2155	0.2732
Time 4	(N= 345.23)	0.2444	0.2444

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Changes in the number of analyses

- ▶ During the conduct of a study, the number of analyses may also be different from design stage
 - ▶ Monitoring scheduled by calendar time
 - ▶ Slow (or fast) accrual
 - ▶ External causes (should not be influenced by study results)
- ▶ This will also result in changes to design operating characteristics

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Example: Stopping rule chosen at design (cont'd)

```
> dsn <- seqDesign( prob.model="normal", arms=1, null.hypothesis=0,  
+                   alt.hypothesis=0.5, test.type="greater", variance=4,  
+                   power=0.975, P=0.5, nbr.analyses=4, early.stopping="both" )
```

```
> dsn
```

PROBABILITY MODEL and HYPOTHESES:

Theta is mean response

One-sided hypothesis test of a greater alternative:

Null hypothesis : $\Theta \leq 0.0$ (size = 0.025)

Alternative hypothesis : $\Theta \geq 0.5$ (power = 0.975)

(Emerson & Fleming (1989) symmetric test)

STOPPING BOUNDARIES: Sample Mean scale

		Futility	Efficacy
Time 1	(N= 86.31)	0.0000	0.5000
Time 2	(N= 172.62)	0.1464	0.3536
Time 3	(N= 258.92)	0.2113	0.2887
Time 4	(N= 345.23)	0.2500	0.2500

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Analyses after 20%, 40%, 60%, 80%, 100% (maintain power)

```
> dsn.5.power <- update(dsn, sample.size=c(.2,.4,.6,.8,1) )
```

```
> dsn.5.power
```

PROBABILITY MODEL and HYPOTHESES:

Theta is mean response

One-sided hypothesis test of a greater alternative:

Null hypothesis : $\Theta \leq 0.0$ (size = 0.025)

Alternative hypothesis : $\Theta \geq 0.5$ (power = 0.975)

(Emerson & Fleming (1989) symmetric test)

STOPPING BOUNDARIES: Sample Mean scale

		Futility	Efficacy
Time 1	(N= 72.10)	-0.0590	0.5590
Time 2	(N= 144.20)	0.1047	0.3953
Time 3	(N= 216.31)	0.1773	0.3227
Time 4	(N= 288.41)	0.2205	0.2795
Time 5	(N= 360.51)	0.2500	0.2500

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```
> dsn.5.n <- update(dsn,  
  sample.size=c(.2,.4,.6,.8,1)*max(dsn$parameters$sample.size),  
  alt.hypothesis="calculate" )
```

```
> dsn.5.n
```

PROBABILITY MODEL and HYPOTHESES:

Theta is mean response

One-sided hypothesis test of a greater alternative:

Null hypothesis : $\Theta \leq 0.0000$ (size = 0.025)

Alternative hypothesis : $\Theta \geq 0.5109$ (power = 0.975)

(Emerson & Fleming (1989) symmetric test)

STOPPING BOUNDARIES: Sample Mean scale

		Futility	Efficacy
Time 1	(N= 69.05)	-0.0603	0.5713
Time 2	(N= 138.09)	0.1070	0.4039
Time 3	(N= 207.14)	0.1811	0.3298
Time 4	(N= 276.19)	0.2253	0.2856
Time 5	(N= 345.23)	0.2555	0.2555

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Result of changing schedule of analyses

► Summary for Pocock boundary relationships

Analysis Times	Alt	Max N	Bound
=====	=====	=====	=====
.25, .50, .75, 1.00	.500	345.23	.2500
.40, .60, .80, 1.00	.500	329.91	.2500
.40, .60, .80, 1.00	.489	345.23	.2444
.20, .40, .60, .80, 1.00	.500	360.51	.2500
.20, .40, .60, .80, 1.00	.511	345.23	.2555

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Result of changing schedule of analyses

► Summary for O'Brien-Fleming boundary relationships

Analysis Times	Alt	Max N	Bound
=====	=====	=====	=====
.25, .50, .75, 1.00	.500	256.83	.2500
.40, .60, .80, 1.00	.500	259.44	.2500
.40, .60, .80, 1.00	.503	256.83	.2513
.20, .40, .60, .80, 1.00	.500	259.45	.2500
.20, .40, .60, .80, 1.00	.503	256.83	.2513

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Constrained O'Brien-Fleming Design

- ▶ It is often desirable to modify a stopping rule at the design stage to maintain a particular set of boundary constraints
- ▶ For example, an O'Brien-Fleming stopping rule is known for extreme conservatism at early analysis
 - ▶ One-sided level .025 test of a normal mean with four equally spaced analyses
 - ▶ Stopping at first analysis for efficacy requires a fixed sample P-value of less than .0001

```
> obf <- seqDesign( prob.model="normal", arms=1, null.hypothesis=0,  
+                   alt.hypothesis=0.5, test.type="greater", variance=4,  
+                   power=0.975, P=1, nbr.analyses=4, early.stopping="both" )
```

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Constrained O'Brien-Fleming Design

```
> obf
```

PROBABILITY MODEL and HYPOTHESES:

Theta is mean response

One-sided hypothesis test of a greater alternative:

Null hypothesis : $\Theta \leq 0.0$ (size = 0.025)

Alternative hypothesis : $\Theta \geq 0.5$ (power = 0.975)

(Emerson & Fleming (1989) symmetric test)

STOPPING BOUNDARIES: Sample Mean scale

		Futility	Efficacy
Time 1	(N= 64.21)	-0.5000	1.0000
Time 2	(N= 128.41)	0.0000	0.5000
Time 3	(N= 192.62)	0.1667	0.3333
Time 4	(N= 256.83)	0.2500	0.2500

```
> seqBoundary(obf, scale="P")
```

STOPPING BOUNDARIES: Fixed Sample P-value scale

		Futility	Efficacy
Time 1	(N= 64.21)	0.9774	0.0000
Time 2	(N= 128.41)	0.5000	0.0023
Time 3	(N= 192.62)	0.1237	0.0104
Time 4	(N= 256.83)	0.0226	0.0226

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Constrained Boundaries Example

Constrained O'Brien-Fleming Design

- ▶ Some sponsor's wish for the operating characteristics of an O'Brien-Fleming design but desire a slightly less conservative first boundary
- ▶ One possibility is to constrain the O'Brien-Fleming design at the first analysis so that the efficacy bound corresponds to a P-value of 0.0005
- ▶ In order to maintain the overall type I error rate, the value of G must be re-computed using this constraint
- ▶ This can be done using an `exact.constraint`:

```
> bnd.const <- as.seqBoundary( cbind(matrix(NA,nrow=4,ncol=3),  
                                   c(.0005,rep(NA,3))), scale="P" )
```

```
> bnd.const
```

```
STOPPING BOUNDARIES: Fixed Sample P-value scale
```

	a	b	c	d
Time 1	NA	NA	NA	5e-04
Time 2	NA	NA	NA	NA
Time 3	NA	NA	NA	NA
Time 4	NA	NA	NA	NA

Constrained Boundaries Example

Constrained O'Brien-Fleming Design

```
> obf.const <- update( obf, exact.constraint=bnd.const )  
> obf.const
```

PROBABILITY MODEL and HYPOTHESES:

Theta is mean response

One-sided hypothesis test of a greater alternative:

Null hypothesis : $\Theta \leq 0.0$ (size = 0.025)

Alternative hypothesis : $\Theta \geq 0.5$ (power = 0.975)

STOPPING BOUNDARIES: Sample Mean scale

		Futility	Efficacy
Time 1	(N= 64.31)	-0.4990	0.8207
Time 2	(N= 128.61)	0.0005	0.5005
Time 3	(N= 192.92)	0.1670	0.3337
Time 4	(N= 257.23)	0.2502	0.2502

```
> seqBoundary(obf.const, scale="P")
```

STOPPING BOUNDARIES: Fixed Sample P-value scale

		Futility	Efficacy
Time 1	(N= 64.31)	0.9773	0.0005
Time 2	(N= 128.61)	0.4989	0.0023
Time 3	(N= 192.92)	0.1231	0.0102
Time 4	(N= 257.23)	0.0224	0.0224

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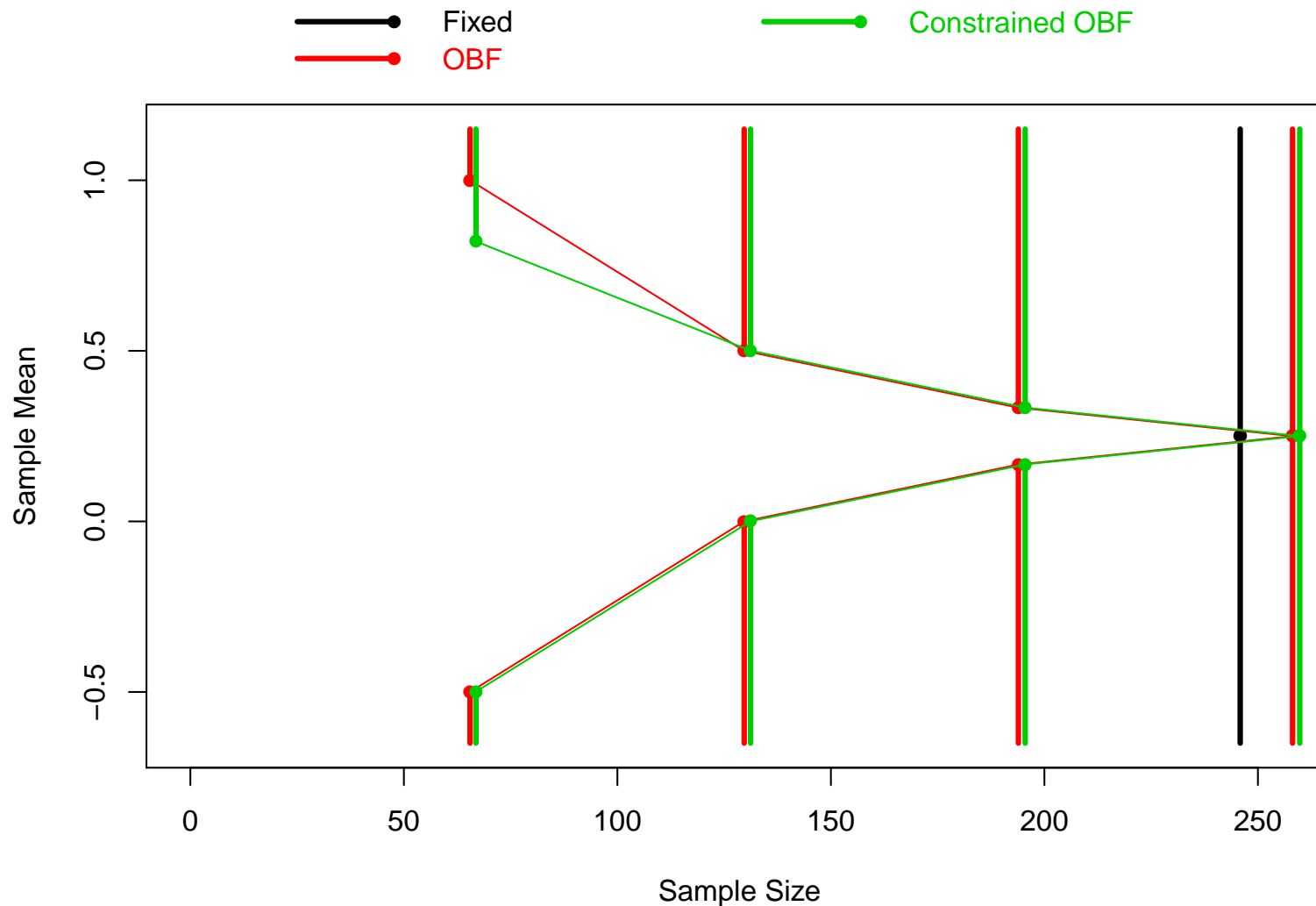
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Constrained Boundaries Example

Constrained O'Brien-Fleming Design

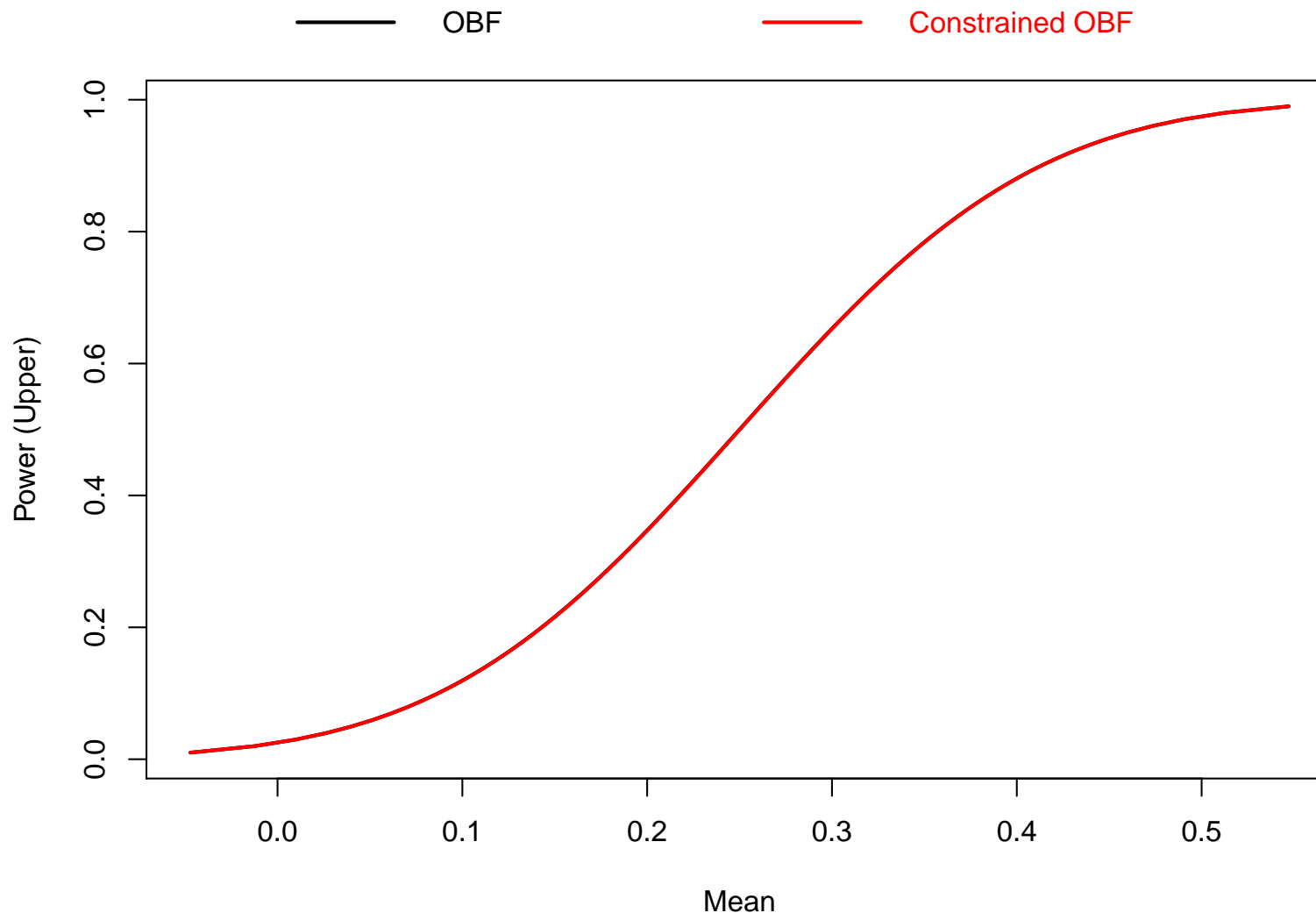
- Comparison of stopping boundaries (sample mean scale)



Constrained Boundaries Example

Constrained O'Brien-Fleming Design

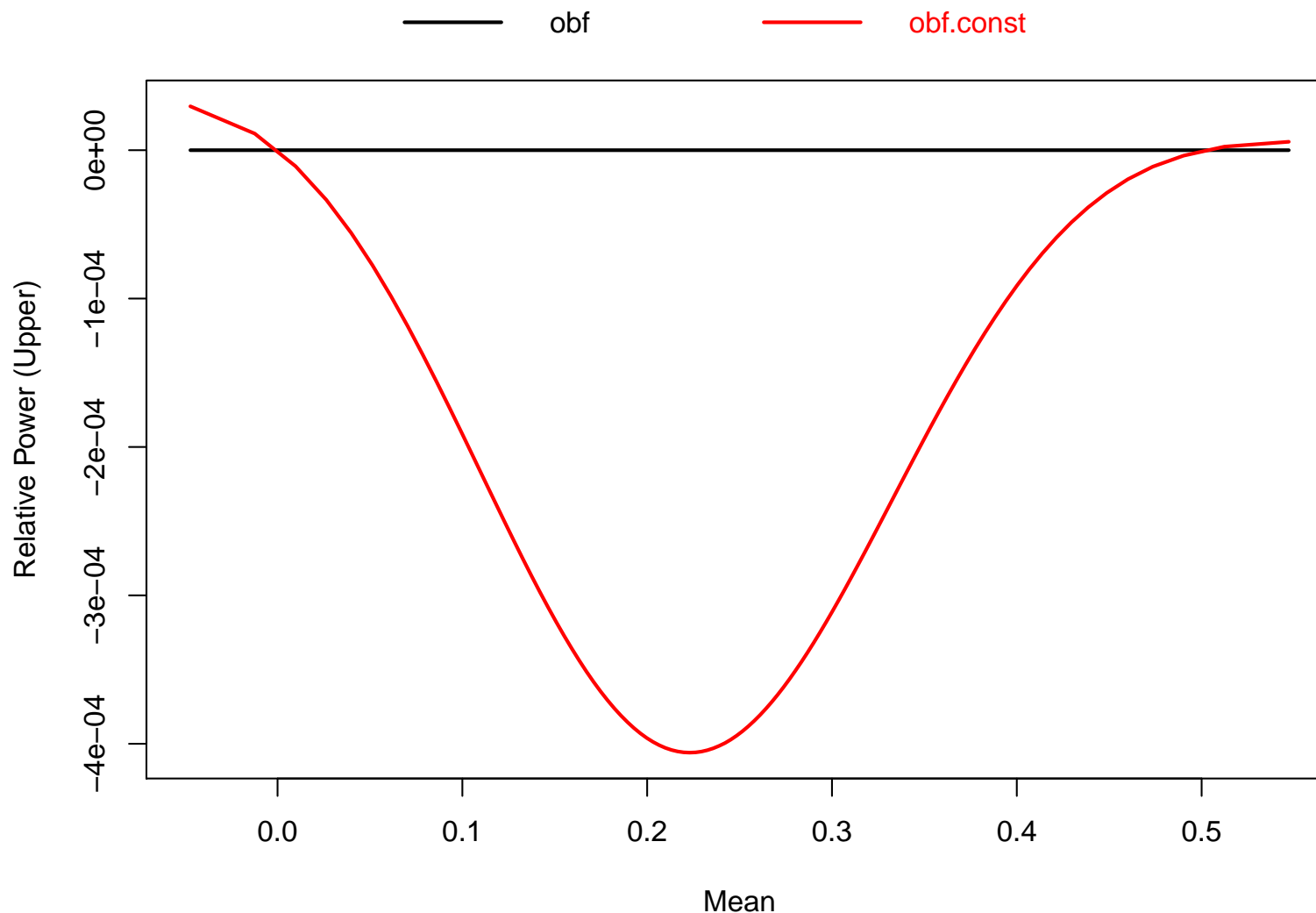
- Comparison of statistical power



Constrained Boundaries Example

Constrained O'Brien-Fleming Design

- Comparison of statistical power

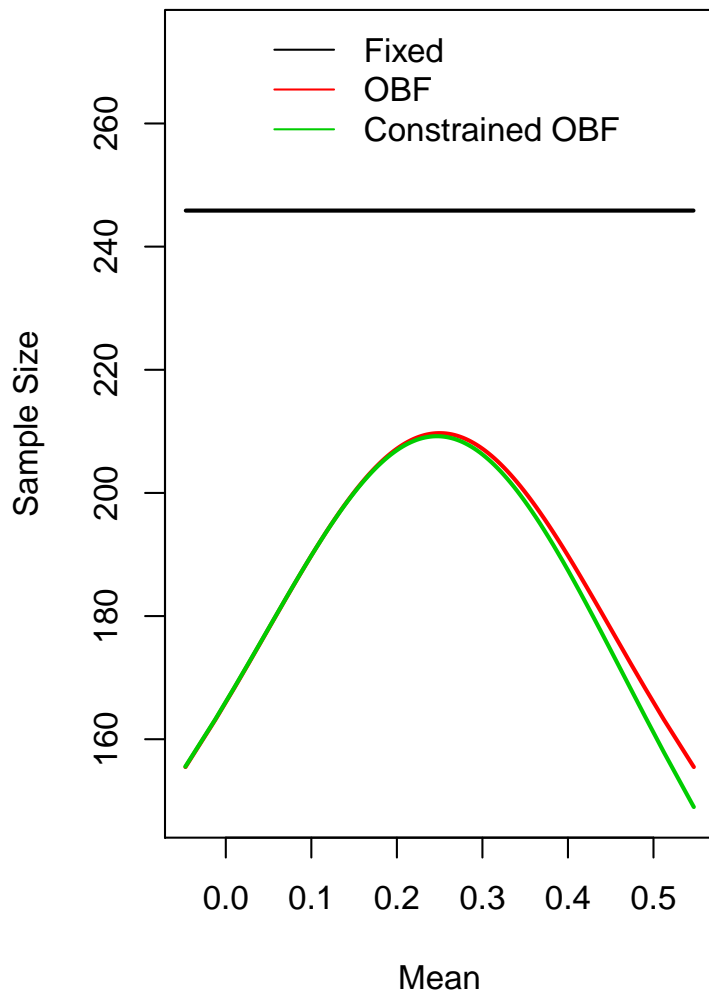


Constrained Boundaries Example

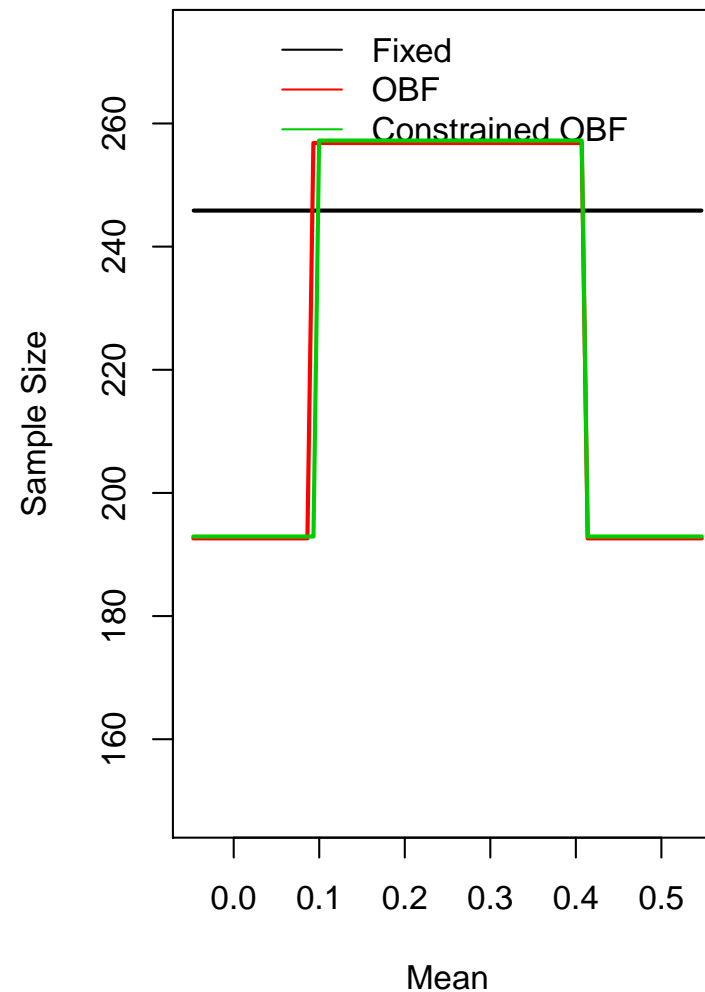
Constrained O'Brien-Fleming Design

- Comparison of sample size distribution

Average Sample Size



75th percentile



Result of changing schedule of analyses

- ▶ As previously noted, during the conduct of a study the timing of analyses may change because:
 - ▶ Monitoring scheduled by calendar time
 - ▶ Slow (or fast) accrual
 - ▶ External causes (should not be influenced by study results)
 - ▶ Statistical information from a sampling unit may be different than originally estimated
 - ▶ Variance of measurements
 - ▶ Baseline event rates (binary outcomes)
 - ▶ Censoring and survival distributions (weighted survival statistics)

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Result of changing schedule of analyses

- ▶ Need methods that allow flexibility in determining number and timing of analyses
- ▶ Should maintain some (but not, in general, all) desired operating characteristics, e.g.:
 - ▶ Type I error
 - ▶ Type II error
 - ▶ Maximal sample size
 - ▶ Futility properties
 - ▶ Bayesian properties

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Popular methods for flexible implementation of group sequential boundaries

1. Christmas tree approximation for triangular tests: Whitehead and Stratton (1983)
2. Error spending functions: Lan and DeMets (1983); Pampallona, Tsiatis, and Kim (1995)
3. Constrained boundaries in unified design family: Emerson (2000); Burrington & Emerson (2003)

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Common features

- ▶ Stopping rule specified at design stage parameterizes the boundary for some statistic (boundary scale)
 - ▶ Error spending family (Lan & Demets, 1983) → proportion of type I error spent
 - ▶ Unified family (Emerson & Kittelson, 1999) → point estimate (MLE)
- ▶ At the first interim analysis, parametric form is used to compute the boundary for actual time on study
- ▶ At successive analyses, the boundaries are recomputed accounting for the exact boundaries used at previously conducted analyses
- ▶ Maximal sample size estimates may be updated to maintain power
 - ▶ For binary outcomes, generally use pooled estimate of event rates to withhold treatment effect from study sponsor

Implementing error spending functions

- ▶ *Error spending* (also known as α -spending) allow flexible implementation by pre-specifying a rate at which the type I error will be “spent” at each interim analysis; specifically:
 - ▶ Let α denote the type I error probability for the trial.
 - ▶ Use the group sequential sampling density to calculate the stopping probabilities (α_j) over the prior interim analyses.
 - ▶ Let α_j denote the probability of rejecting the null hypothesis at the j th interim analysis (then $\alpha = \sum_j \alpha_j$).
 - ▶ *Error spending function*: Let $\alpha(\Pi)$ denote a function that constrains the probability of rejecting the null hypothesis at or before $100 \times \Pi\%$ of the total information; that is:

$$\alpha(\Pi) = \frac{1}{\alpha} \sum_{j: \Pi_j < \Pi} \alpha_j \quad (1)$$

Thus, $\alpha(\Pi)$ is the proportion of the total type I error that has been “spent” when there is Π information in the trial.

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Implementing error spending functions

► Examples of error spending functions:

Constant spending: $\alpha(\Pi) = \Pi$

Power family: $\alpha(\Pi) = \Pi^P, P > 1$

Approximate O'Brien-Fleming: $\alpha(\Pi) = \Phi\left(\frac{Z_{\alpha/2}}{\sqrt{\Pi}}\right)$

Approximate Pocock: $\alpha(\Pi) = \ln[1 + (e - 1)\Pi]$

Hwang, Shih, Decani, 1990: $\alpha(\Pi) = \frac{1 - e^{-\gamma\Pi}}{1 - e^{-\gamma}}, \gamma \neq 0$

where $\Phi()$ is the standard normal cdf.

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- ▶ Consider the sepsis trial introduced in Session 2 and suppose we wish to conduct a trial with four equally spaced analyses utilizing an O'Brien-Fleming stopping rule
 - ▶ One-sided type I error .025
 - ▶ N=1700 maximal patients

```
> sepsis.fix <- seqDesign(prob.model="proportions", arms=2,
                           size=.025, power="calculate",
                           null.hypothesis= c(.30, .30),
                           alt.hypothesis=c(0.25,0.30),
                           sample.size=1700, test.type="less")

> #***** pre-trial monitoring plan
> sepsis.obf <- update(sepsis.fix,nbr.analyses=4,P=1)
> sepsis.obf
```

```
STOPPING BOUNDARIES: Sample Mean scale
                      Efficacy Futility
Time 1 (N= 425)    -0.1733    0.0866
Time 2 (N= 850)    -0.0866    0.0000
Time 3 (N= 1275)   -0.0578   -0.0289
Time 4 (N= 1700)   -0.0433   -0.0433
```

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► Pre-trial analysis timing in terms of information:

- Recall $V = 0.25 \times 0.75 + 0.3 \times 0.7$
- Pre-trial planned information:

$$I = \frac{N_J/2}{V} = \frac{850}{0.3975} = 2138.4$$

► Pre-trial plan for analysis timing:

Π_j	N_j	Information: $\frac{N_j}{2V}$
0.25	425	534.6
0.50	850	1069.2
0.75	1275	1603.8
1.00	1700	2138.4

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Error spending functions

Implementing error spending functions - Sepsis trial

- ▶ Suppose the first interim analysis was conducted after data on 520 subjects (263 on the antibody arm, 257 on the placebo arm)
- ▶ Further suppose that 52 deaths were observed on the antibody arm and 65 deaths were observed on the placebo arm

$$\hat{\theta}_1 = \frac{52}{263} \quad \hat{\theta}_0 = \frac{65}{257}$$

- ▶ Observed information at first interim analysis:

$$\hat{S}_1 = \frac{\hat{\theta}_1(1 - \hat{\theta}_1)}{263} + \frac{\hat{\theta}_0(1 - \hat{\theta}_0)}{257} = 0.0013384$$

$$\frac{1}{\hat{S}_1} = 747.2$$

$$\Pi = 747.2/2138.4 = 0.34942$$

Thus, we estimate that the first interim analysis has occurred at 34.9% of the planned total information.

Implementing error spending functions - Sepsis trial

- ▶ Pre-trial error-spending function:
 - ▶ Use `seqOC(sepsis.obf, theta=0)` to get the lower stopping probabilities at the interim analyses. These are the values of α_j . The pretrial error-spending function, $\alpha(\Pi)$ has values at Π_j defined by equation (1).

Π_j	a_j	Stopping Prob (α_j)	Cumulative type I error	Error spending function $\alpha(\Pi_j)$
0.25	-0.1733	0.00003	0.00003	0.00123
0.50	-0.0866	0.00229	0.00232	0.09274
0.75	-0.0578	0.00886	0.01176	0.44703
1.00	-0.0433	0.01382	0.02500	1.00000

- ▶ To get values of $\alpha(\Pi)$ for $\Pi \neq \Pi_j$ we can either:
 - ▶ Use an error-spending function that approximates the pre-trial plan
 - ▶ Use linear interpolation

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Implementing error spending functions - Sepsis trial

- ▶ Using linear interpolation to find the critical value at 34.9% of total information:

$$\begin{aligned}\alpha(0.349) &= \alpha(0.25) + [\alpha(0.50) - \alpha(0.25)] \frac{0.349 - 0.25}{0.50 - 0.25} \\ &= 0.00003 + 0.00229 \times \frac{0.099}{0.25} \\ &= 0.00091872\end{aligned}$$

- ▶ Because this is the first interim analysis, we can calculate the revised value for a_1 directly from the normal density:

$$\begin{aligned}\frac{a_1}{\sqrt{\hat{S}_1}} &= \Phi^{-1}(0.00091872) \\ &= -3.1153\end{aligned}$$

Thus, $a_1 = -3.1938\sqrt{0.0013384} = -0.11397$, and so we would continue because $\hat{\theta}^{(1)} = -0.0552 > -0.11397$.

Implementing error spending functions

► Notes:

- At subsequent interim analyses we would repeat this process, but would need to account for the decision criteria used at earlier interim analyses to determine how much error should be spent and what the critical value should be.
- We can develop analogous stopping criteria for the futility (d_j) boundary using a β -spending function.
- I am not illustrating the above points because:
 - Error-spending scales do not directly elucidate the scientific/clinical aspects of the stopping criteria.
 - Error-spending scales do not do directly address changes in the estimated standard deviation at subsequent interim analyses.
- (Note: any scale can be expressed on the sample mean scale, so you can (and should) consider the inference on the boundary when evaluating error-spending decision criteria.)

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Implementing error spending functions

- ▶ Error spending families have been implemented in RCTdesign
 - ▶ To get the error spending function from an existing design:
 - > `update(sepsis.obf, display.scale="E")`
 - ▶ To design a monitoring plan in the error spending scale:
 - > `update(sepsis.obf, design.scale="E", P=-1, display.scale="E")`
 - > `update(sepsis.obf, design.scale="E", P=-1, display.scale="X")`
 - ▶ This implements the power family of error spending functions described above: $\alpha(\Pi) = \Pi^P \times \alpha$

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Constrained boundaries

- ▶ Constrained boundaries allow the same flexibility as error spending functions, but are constructed in the scale of the estimated treatment effects (or any scale desired).
- ▶ Overview:
 - ▶ Calculate the estimated information at the interim analysis as a proportion of the total information.
 - ▶ Calculate a revised group sequential design:
 - ▶ Use the values of a_ℓ and d_ℓ that were actually used at earlier interim analyses ($\ell < j$).
 - ▶ Calculate the new future values for a_ℓ and d_ℓ for $\ell \geq j$ using the original boundary shape function.
 - ▶ Find the value of G that maintains the desired operating characteristics.
 - ▶ (Implemented in the function `seqMonitor`).

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Constrained boundaries - Sepsis example

- ▶ Recall the pre-trial interim analysis stopping rules:
 - ▶ With a “less than” alternative hypothesis:

$$a_j = -G\Pi_j^{-1}\sqrt{\frac{V}{850}}$$

$$d_j = (-2G + G\Pi_j^{-1})\sqrt{\frac{V}{850}}$$

- ▶ Pre-trial design ($\Pi_j = (0.25, 0.50, 0.75, 1.0)$, $G = 2.0032$):

Π_j	a_j	d_j
0.25	-0.1733	0.0866
0.50	-0.0866	0.0000
0.75	-0.0578	-0.0289
1.00	-0.0433	-0.0433

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Constrained boundaries - Sepsis example

- ▶ Suppose we observe $\hat{\theta}^{(1)} = -0.0552$ at 34.9% of total information.
- ▶ Calculate the revised design:
 - ▶ Use the same boundary shape function, but update as follows:

```
sepsis.IA1 <- update(sepsis.obf,  
  sample.size=c(520,850,1275,1700),  
  null.hypothesis=c(65/257,65/257),  
  alt.hypothesis=c(52/263,65/257))
```

- ▶ Now $G = 2.0036$ and the new stopping boundaries are:

Π_j	a_j	d_j
520	-0.1325	0.0514
850	-0.0810	0.0000
1275	-0.0541	-0.0270
1700	-0.0405	-0.0405

- ▶ Decision: continue the trial because $a_1 < \hat{\theta}^{(1)} < d_1$.

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Constrained boundaries - Sepsis example

- ▶ This approach can be automated using the (`seqMonitor()` function):
 - ▶ Create a vector of the results at the first interim analysis:

```
Y.1 <- c(rep(1, 52), rep(0, 263-52), rep(1, 65), rep(0, 257-65))  
tx.1 <- c(rep(1, 263), rep(0, 257))
```

- ▶ Determine revised boundaries and a stopping decision:

```
IA1 <- seqMonitor(sepsis.obf, response=Y.1,  
                  treatment=tx.1, future.analyses=c(850, 1275, 1700))
```

- ▶ Results include:
 - ▶ Recommendation (continue)
 - ▶ Estimate ($\hat{\theta}_1 = -0.055$)
 - ▶ Revised stopping boundaries:

Π_j	a_j	d_j
520	-0.1325	0.0514
850	-0.0810	0.0000
1275	-0.0541	-0.0270
1700	-0.0405	-0.0405

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Challenges in monitoring the Hodgkin's trial

- ▶ For a more complete example, let's consider monitoring the Hodgkin's trial from Sessions 2 and 3
- ▶ Recall that the primary endpoint was time to death with possible right-censoring
- ▶ Testing for group differences was based upon the logrank statistic (score test for the proportional hazards model)
- ▶ Under the proportional hazards model, statistical information is directly proportional to the number of observed events
- ▶ One complication in monitoring such a trial is to translate the from events to calendar time so that analyses/meetings can be scheduled

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Chosen design

- `Eff11.Fut8` : $P=1.1$ efficacy bound with $P=0.8$ futility bound (Unified Family)

PROBABILITY MODEL and HYPOTHESES:

Theta is hazard ratio (Treatment : Comparison)

One-sided hypothesis test of a lesser alternative:

Null hypothesis : $\text{Theta} \geq 1.00$ (size = 0.0250)

Alternative hypothesis : $\text{Theta} \leq 0.67$ (power = 0.7804)

STOPPING BOUNDARIES: Sample Mean scale

		a	d
Time 1	(N= 49)	0.2748	1.3782
Time 2	(N= 98)	0.5474	0.9403
Time 3	(N= 147)	0.6799	0.8151
Time 4	(N= 196)	0.7549	0.7549

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Chosen design

- `Eff11.Fut8` : $P=1.1$ efficacy bound with $P=0.8$ futility bound (Unified Family)

	Efficacy Bound			Futility Bound		
	lo.hr	lo.ztat	lo.pval	up.hr	up.zstat	up.pval
Time 1	0.275	-4.521	0.000	1.378	1.123	0.869
Time 2	0.547	-2.983	0.001	0.940	-0.305	0.380
Time 3	0.680	-2.339	0.010	0.815	-1.239	0.108
Time 4	0.755	-1.968	0.025	0.755	-1.968	0.025

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Timing of analyses

- ▶ Assumed
 - ▶ Uniform accrual over 3 years
 - ▶ One additional year of followup
 - ▶ Median survival in control arm of 9 months

```
> seqPHSubjects( Eff11.Fut8, controlMedian=0.75,
                  accrualTime=3, followupTime=1 )
  accrualTime followupTime    rate hazardRatio controlMedian nSubjects
1           3             1 75.459          1.00           0.75     226.38
2           3             1 80.598          0.67           0.75     241.79

  analysisTimes.1 analysisTimes.2 analysisTimes.3 analysisTimes.4
1           1.4474           2.2448           2.9599           4.0000
2           1.5033           2.3067           3.0142           4.0000
```

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Timing of analyses

- ▶ Hypothetical data
 - ▶ Uniform accrual (80 subjects per year)
 - ▶ Median survival in the control arm of 1 year
 - ▶ True hazard ratio of 0.70
- ▶ Result
 - ▶ Longer median survival in control arm will result in longer time to accrue specified events
- ▶ Based upon initial estimates data is analyzed at 1.5 years of followup for DSMB meeting

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1st interim analysis

► Monitoring at first interim analysis

- Data stored in data frame `hodgData`
 - `grp` : Indicator of treatment group
(0=control, 1=treatment)
 - `obsSurv` : Observed survival times
 - `event` : Indicator of mortality

► Define response as a survival object

```
resp <- Surv( hodgData$obsSurv, hodgData$event )
```

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1st interim analysis

- ▶ Monitoring at first interim analysis
 - ▶ Specify remaining analysis at intended schedule to (roughly) maintain power (98, 147, 196)
 - ▶ Use function `seqMonitor()` to analyze current data and produce constrained boundaries

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1st interim analysis

► Result of `seqMonitor()` at 1st analysis

RECOMMENDATION:

Continue

OBSERVED STATISTICS:

Sample Size	Crude Estimate	Z Statistic
39	1.139	0.4062

PROBABILITY MODEL and HYPOTHESES:

Theta is hazard ratio (Treatment : Comparison)

One-sided hypothesis test of a lesser alternative:

Null hypothesis : $\text{Theta} \geq 1.0000$ (size = 0.0250)

Alternative hypothesis : $\text{Theta} \leq 0.6696$ (power = 0.7804)

STOPPING BOUNDARIES: Sample Mean scale

	a	d
Time 1 (N= 39)	0.1895	1.6495
Time 2 (N= 98)	0.5468	0.9399
Time 3 (N= 147)	0.6795	0.8147
Time 4 (N= 196)	0.7546	0.7546

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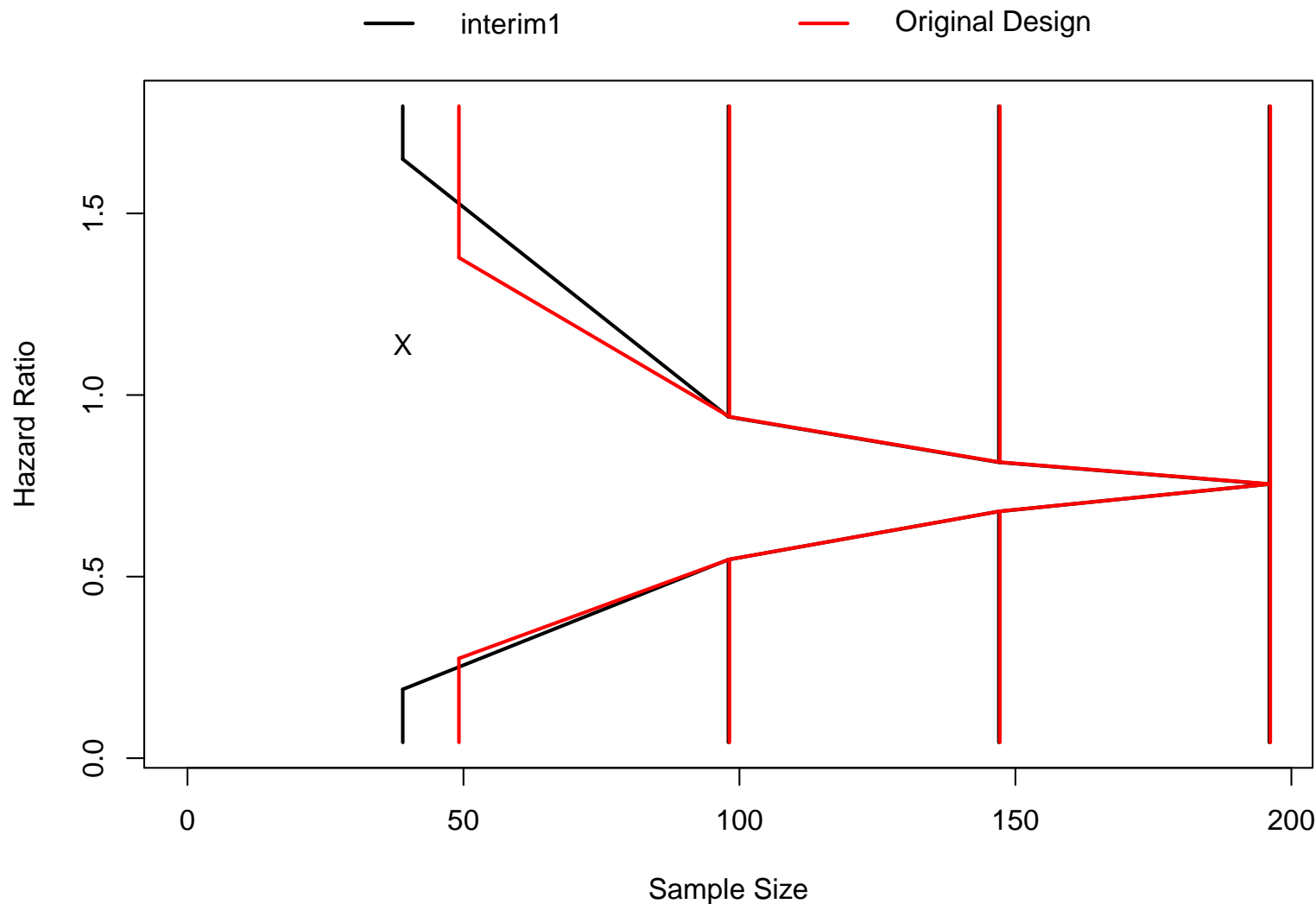
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Timing of 1st analysis

- Plot or monitoring result at 1st analysis



1st interim analysis

- ▶ Monitoring at first interim analysis
 - ▶ Notice that because of the longer median survival, the number of events at the first analysis are lower than expected (39 vs 49)
 - ▶ Would like to stick to original analysis schedule and accrual rate
 - ▶ Need to estimate event rates using POOLED data and estimate new analysis times

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Estimate pooled survival at 1st analysis

- ▶ Estimate hazard from pooled data based upon exponential fit

```
> expFit <- survReg(Surv(obsSurv, event) ~ 1,  
                    dist = "exponential", data = hodgData)  
> estHaz <- exp( - expFit$coef )
```

Estimate event rates

- ▶ Estimate timing of future analyses based upon new pooled survival estimate

```
> seqPHSubjects( Eff11.Fut8, controlMedian=log(2)/estHaz,  
                 accrualTime=3, followupTime=1 )  
accrualTime followupTime    rate hazardRatio cntrlMedian nSubjects  
1           3           1 87.999         1.00      1.1665   263.9991  
2           3           1 96.757         0.67      1.1665   290.2737  
analysisTimes.1 analysisTimes.2 analysisTimes.3 analysisTimes.4  
1           1.582587       2.389780       3.086729       4.000000  
2           1.626356       2.436201       3.127887       4.000000
```

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Estimate pooled survival at 1st analysis

- Determine the amount of additional followup needed in order to obtain desired events while maintaining accrual of 80 patients per year for 3 years

	accrualTime	followupTime	rate	hazardRatio	controlMedian	nSubjects
1	3	1.572187	80	1.00	1.166507	240
2	3	2.215662	80	0.67	1.166507	240

	analysisTimes.1	analysisTimes.2	analysisTimes.3	analysisTimes.4
1	1.672433	2.534704	3.312677	4.572187
2	1.813171	2.733575	3.630260	5.215662

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Timing of 2nd interim analysis

- ▶ Monitoring at second interim analysis
 - ▶ Based upon previous estimates of pooled survival, next analysis conducted at 2.75 years
 - ▶ Specify remaining analysis at intended schedule to (roughly) maintain power (147, 196)
 - ▶ Use function `seqMonitor()` to analyze current data and produce constrained boundaries

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2nd interim analysis

► Result of `seqMonitor()` at 2nd analysis

RECOMMENDATION:

Continue

OBSERVED STATISTICS:

Sample Size	Crude Estimate	Z Statistic
39	1.1395	0.4062
107	0.7571	-1.4233

PROBABILITY MODEL and HYPOTHESES:

Theta is hazard ratio (Treatment : Comparison)

One-sided hypothesis test of a lesser alternative:

Null hypothesis : $\text{Theta} \geq 1.0000$ (size = 0.0250)

Alternative hypothesis : $\text{Theta} \leq 0.6698$ (power = 0.7804)

STOPPING BOUNDARIES: Sample Mean scale

	a	d
Time 1 (N= 39)	0.1895	1.6495
Time 2 (N= 107)	0.5784	0.9077
Time 3 (N= 147)	0.6797	0.8149
Time 4 (N= 196)	0.7548	0.7548

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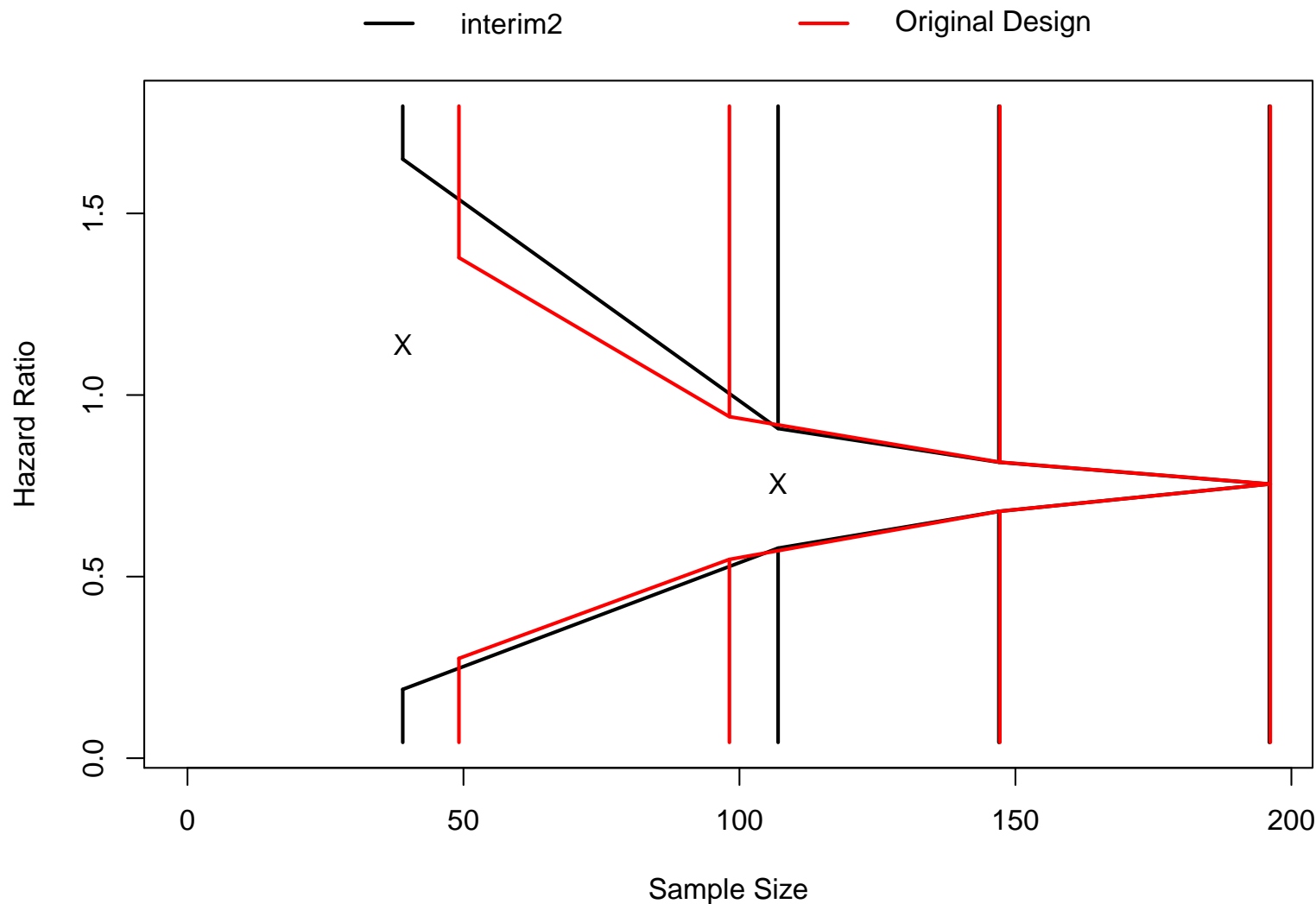
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Timing of 2nd analysis

- Plot or monitoring result at 2nd analysis



Estimate timing for future analyses

- Based upon new pooled event rates, determine the amount of additional followup needed in order to obtain desired events while maintaining accrual of 80 patients per year for 3 years

	accrualTime	followupTime	rate	hazardRatio	controlMedian	nSubjects
1	3	1.753815	80	1.00	1.246134	240
2	3	2.446173	80	0.67	1.246134	240

	analysisTimes.1	analysisTimes.2	analysisTimes.3	analysisTimes.4
1	1.719462	2.599327	3.408330	4.753815
2	1.864917	2.805022	3.751868	5.446173

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Timing of 3rd interim analysis

- ▶ Monitoring at 3rd interim analysis
 - ▶ Based upon previous estimates of pooled survival, next analysis conducted at 3.5 years
 - ▶ Specify remaining analysis at intended schedule to (roughly) maintain power (196)
 - ▶ Use function `seqMonitor()` to analyze current data and produce constrained boundaries

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3rd interim analysis

► Result of `seqMonitor()` at 3rd analysis

RECOMMENDATION:

Continue

OBSERVED STATISTICS:

Sample Size	Crude Estimate	Z Statistic
39	1.1395	0.4062
107	0.7571	-1.4233
144	0.7648	-1.6044

PROBABILITY MODEL and HYPOTHESES:

Theta is hazard ratio (Treatment : Comparison)

One-sided hypothesis test of a lesser alternative:

Null hypothesis : $\text{Theta} \geq 1.00$ (size = 0.0250)

Alternative hypothesis : $\text{Theta} \leq 0.67$ (power = 0.7804)

STOPPING BOUNDARIES: Sample Mean scale

	a	d
Time 1 (N= 39)	0.1895	1.6495
Time 2 (N= 107)	0.5784	0.9077
Time 3 (N= 144)	0.6739	0.8201
Time 4 (N= 196)	0.7549	0.7549

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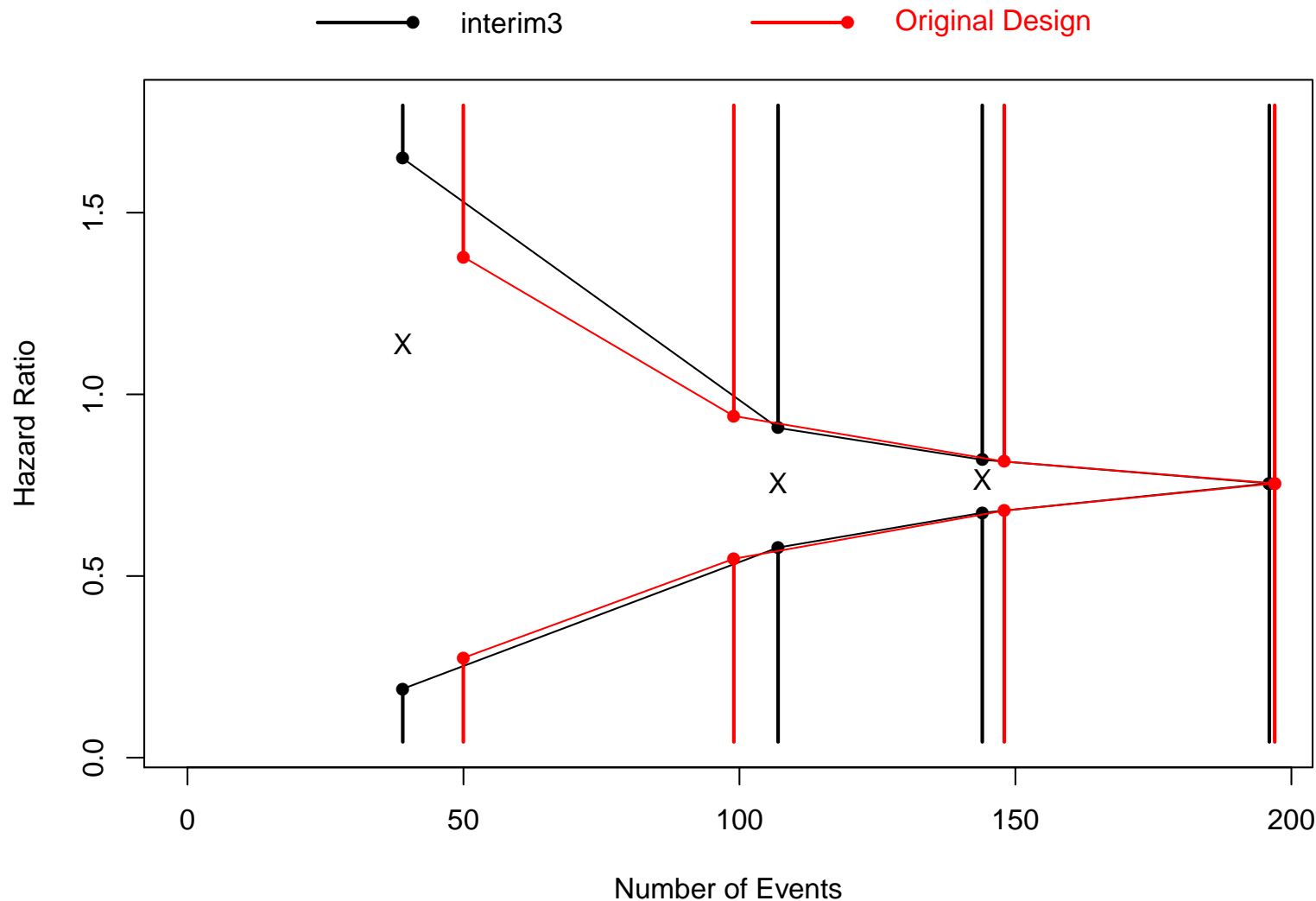
Estimation of statistical
information

Measuring study time

Case Study : Hodgkin's Trial

Timing of 3rd analysis

- Plot or monitoring result at 3rd analysis



Estimate timing for future analyses

- Based upon new pooled event rates, determine the amount of additional followup needed in order to obtain desired events while maintaining accrual of 80 patients per year for 3 years

	accrualTime	followupTime	rate	hazardRatio	controlMedian	nSubjects
1	3	1.933717	80	1.00	1.324366	240
2	3	2.673878	80	0.67	1.324366	240

	analysisTimes.1	analysisTimes.2	analysisTimes.3	analysisTimes.4
1	1.764297	2.661064	3.503763	4.933717
2	1.914171	2.873225	3.872611	5.673878

Impact of Changing
the Number and
Timing of Analyses

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Example : Constrained
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Timing of final analysis

- ▶ Monitoring at final analysis
 - ▶ Based upon previous estimates of pooled survival, next analysis conducted at 5 years
 - ▶ Omit the `future.analyses` option
 - ▶ Use function `seqMonitor()` to analyze final data

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Final analysis

► Result of `seqMonitor()` at final analysis

RECOMMENDATION:

Stop with decision for Lower Alternative Hypothesis

OBSERVED STATISTICS:

Sample Size	Crude Estimate	Z Statistic
39	1.1395	0.4062
107	0.7571	-1.4233
144	0.7648	-1.6044
199	0.7067	-2.4489

PROBABILITY MODEL and HYPOTHESES:

Theta is hazard ratio (Treatment : Comparison)

One-sided hypothesis test of a lesser alternative:

Null hypothesis : $\Theta \geq 1.0000$ (size = 0.0250)

Alternative hypothesis : $\Theta \leq 0.6714$ (power = 0.7804)

STOPPING BOUNDARIES: Sample Mean scale

	a	d
Time 1 (N= 39)	0.1895	1.6495
Time 2 (N= 107)	0.5784	0.9077
Time 3 (N= 144)	0.6739	0.8201
Time 4 (N= 199)	0.7567	0.7567

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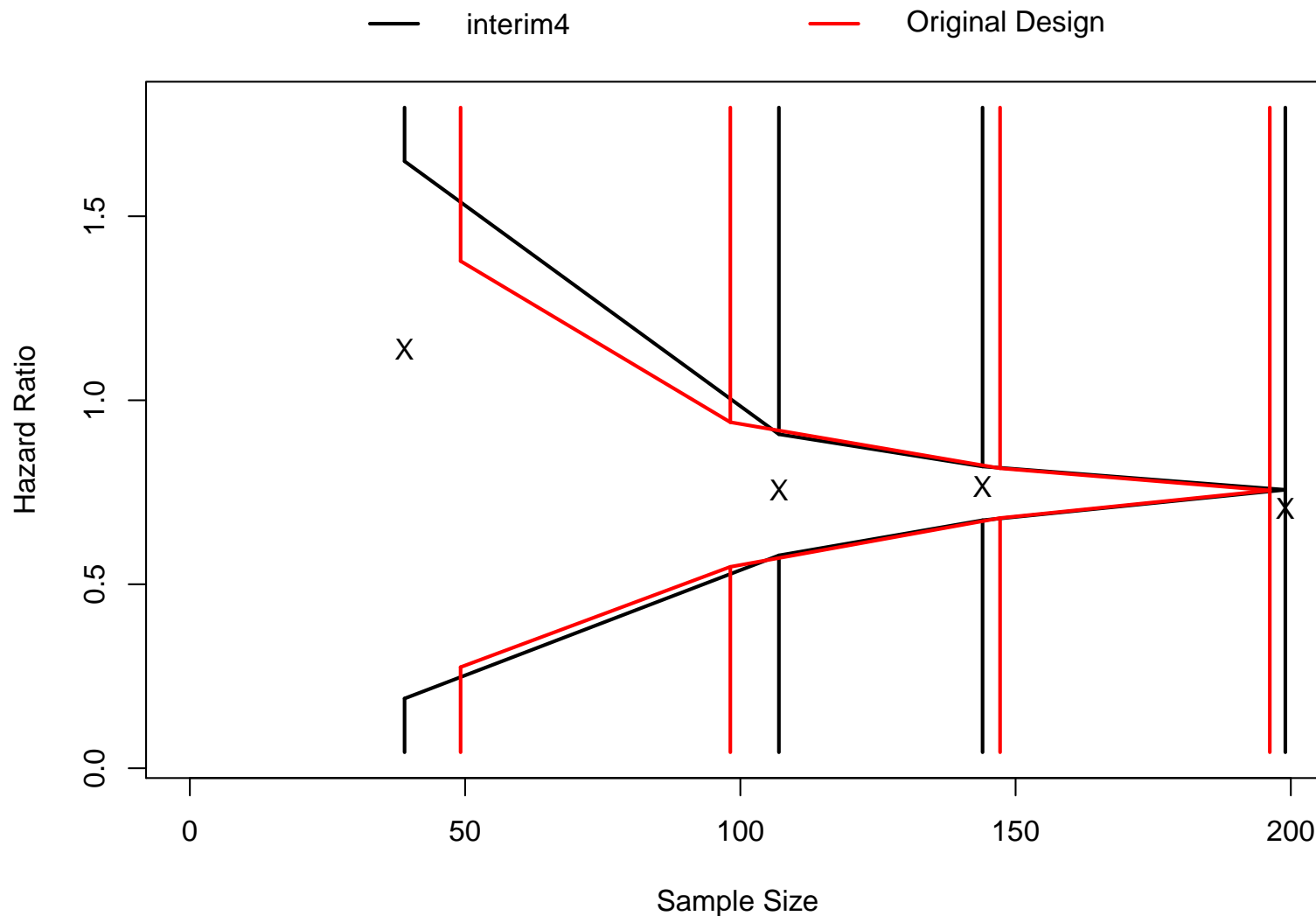
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Timing of final analysis

- Plot or monitoring result at final analysis



Final analysis

► Result of `seqMonitor()` at final analysis

INFERENCE:

Adjusted estimates based on observed data:

	analysis.index	observed	MLE	BAM	RBadj
1	4	0.7067	0.7067	0.7099	0.728

Inferences based on Analysis Time Ordering:

	MUE	P-value	****	CI	****
1	0.7166	0.01299	(0.5381,	0.9599)	

Inferences based on Mean Ordering:

	MUE	P-value	****	CI	****
1	0.7166	0.01299	(0.5381,	0.9599)	

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Design stage vs. implementation stage

- ▶ At time of study design
 - ▶ Sample size (power, alternative) calculations based on specifying statistical information available from each sampling unit
- ▶ During conduct of study
 - ▶ Statistical information from a sampling unit may be different than originally estimated
 - ▶ Variance of measurements
 - ▶ Baseline event rates
 - ▶ (Altered sampling distribution for treatment levels)

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Computation of sample size

- ▶ Sample size formulas used in group sequential test design

$$N = \frac{\delta_1^2 V}{(\Delta_1 - \Delta_0)^2}$$

- ▶ N : maximal number of sampling units
- ▶ δ_1 : alternative for which a standardized form of a level α test has power β
- ▶ $1/V$: statistical information contributed by each sampling unit

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Computation of sample size

- ▶ Sample size formulas used in group sequential test design are completely analogous to those used in fixed sample studies

$$N = \frac{\delta_1^2 V}{(\Delta_1 - \Delta_0)^2}$$

- ▶ In a fixed sample two arm test of an (approximately) normal mean we have
 - ▶ $\delta_1 = z_{1-\alpha/2} + z_\beta$
 - ▶ $V = 2\sigma^2$

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Incorrect estimates of information at design stage

- ▶ Effect of using incorrect estimates of statistical information at the design stage
 - ▶ Using the specified sample size, the design alternative will not be detected with the desired power
 - ▶ Using the specified sample size, the alternative detected with the desired power will not be the design alternative
 - ▶ In order to detect the design alternative with the desired power, a different sample size is needed

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Maintaining maximal sample size or power

- ▶ If maximal sample size is maintained, the study discriminates between null hypothesis and an alternative measured in units of statistical information

$$N = \frac{\delta_1^2 V}{(\Delta_1 - \Delta_0)^2} = \frac{\delta_1^2}{\left(\frac{(\Delta_1 - \Delta_0)^2}{V}\right)}$$

- ▶ If statistical power is maintained, the study sample size is measured in units of statistical information

$$\frac{N}{V} = \frac{\delta_1^2}{(\Delta_1 - \Delta_0)^2}$$

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Measuring study time

Measuring study time

- ▶ Flexible methods compute boundaries at an interim analysis according to study time at that analysis
- ▶ Study time can be measured by
 - ▶ Proportion of planned number of subjects accrued (maintains maximal sample size)
 - ▶ Proportion of planned statistical information accrued (maintains statistical power)
 - ▶ (Calendar time— not really advised)

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Measuring study time

- ▶ In either case, we must decide how we will deal with estimates of statistical information at each analysis when constraining boundaries
- ▶ Statistical information in clinical trials typically has two parts
 - ▶ V = variability associated with a single sampling unit
 - ▶ The distribution of sampled levels of treatment
- ▶ In many clinical trials, the dependence on the distribution of treatment levels across analyses is only on the sample size N

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Possible approaches

- ▶ At each analysis estimate the statistical information available, and use that estimate at all future analyses
 - ▶ Theoretically, this can result in estimates of negative information gained between analyses
- ▶ At each analysis use the sample size with the current best estimate of V
 - ▶ The 1:1 correspondence between boundary scales (see Session 3) is broken at previously conducted analyses

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Possible approaches

- ▶ In `RCTdesign`, all probability models have statistical information directly proportional to sample size for block randomized experiments, thus we chose to update V at all analyses using the current best estimate
- ▶ Other statistical packages (PEST, EaSt) constrain boundaries using the estimate of statistical information available at the previous analyses.
- ▶ There is no clear best approach

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Possible approaches

- ▶ Overall, I think it makes more sense to use the best estimate of the variance of an observation when estimating a sampling distribution.
- ▶ This avoids the possibility of negative information, but allows the conflicting results described above.

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