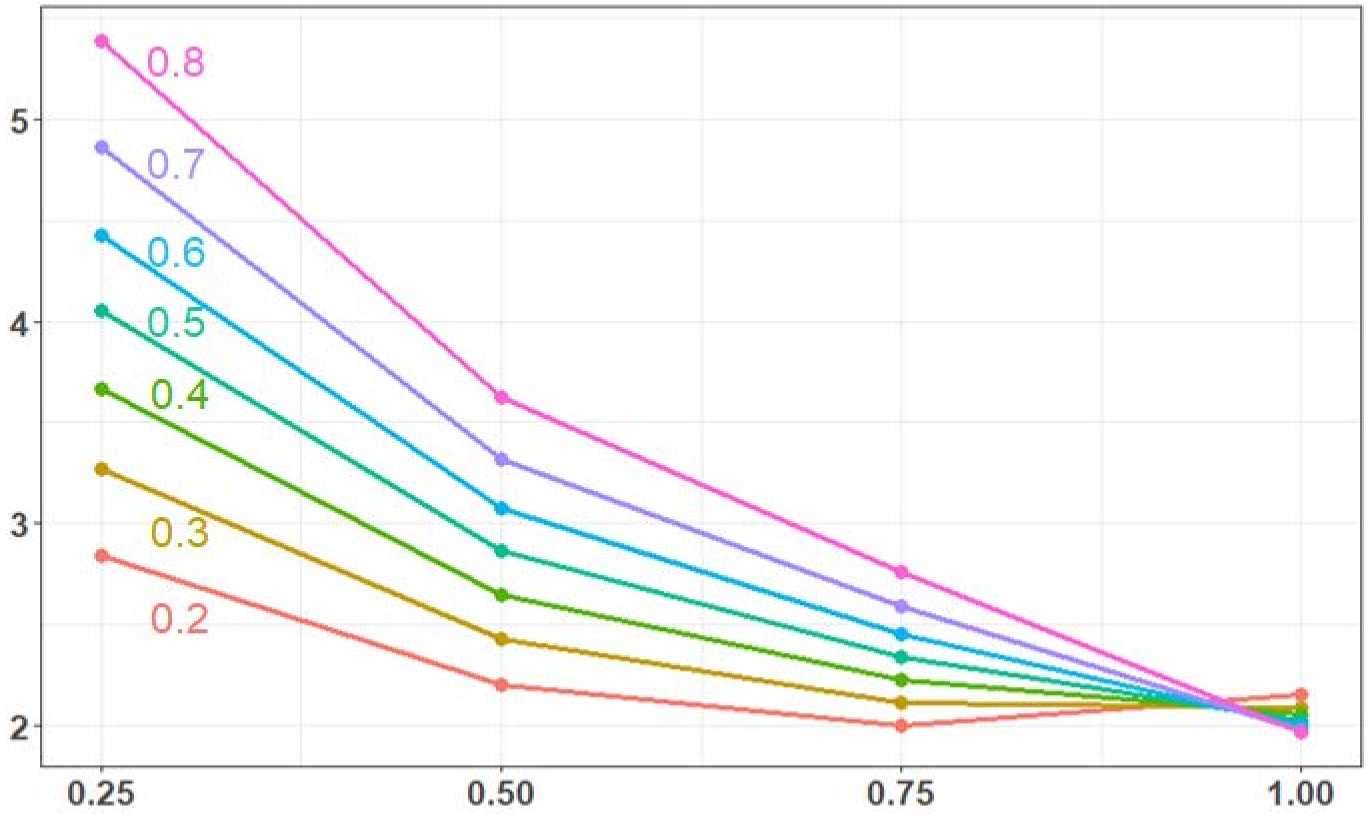

An adaptive-flavored group sequential design with connection to conditional error

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Group sequential design

- During a trial, look at cumulative data multiple times after groups of patients complete assessment
- Decisions at interim analyses
  - Stop for futility, Stop for efficacy, Continue to the next analysis
- Ethics
  - Stop unnecessary exposure to toxic or ineffective treatments
  - Timely access to new effective treatments for all patients
- Economics
  - Reduce loss (futility)
  - Market new product early (efficacy)

Interim analyses for efficacy

- Interim analyses are usually conducted by Data Monitoring Committee (DMC)
- If interim data suggest that likelihood to be significant at the final analysis is very high, DMC may recommend stopping for efficacy
  - Sponsor may unblind data and claim success
- Challenge: Multiple chances to claim success
  - Inflating Type I error
- Opportunity: Cumulative data used for analyses
  - Test statistics are correlated among interim and final analyses

Group sequential design with efficacy interim analyses

- Test H_0: $\theta \leq 0$ against H_1: $\theta > 0$ with K analyses
  - $K - 1$ interim and 1 final analysis
- Interim analyses are often planned according to sample size or number of events
- E.g., A trial with four analyses when 125, 250, 375, 500 patients complete assessment
  - $t_1 = \frac{125}{500} = 0.25, t_2 = 0.5, t_3 = 0.75, t_4 = 1$
- More formally, the timing of interim analyses is according to statistical information time (or fraction)

$$t_k = \frac{\text{information up to analysis } k}{\text{information up to the final analysis}}$$

- Information: inverse of the variance of the estimate
  - Normal endpoint: proportional to the sample size
  - Survival endpoint: proportional to the number of events

Canonical distribution

- $Z_k, k = 1, \ldots, K$ are test statistics at the interim and final analyses
  - E.g, z test at information time t_k
- Under H_0, Z_k's follow an asymptotic multivariate normal distribution (Jennison and Turnbull, 2000)
  - $\mathrm{E}(Z_k) = 0$
  - $\mathrm{Var}(Z_k) = 1$
  - $\mathrm{Corr}(Z_j, Z_k) = \sqrt{t_j/t_k}$, $1 \le j < k \le K$
- E.g., A trial with four analyses at $t_k = k/4$, $k = 1, \ldots, 4$
  - $\mathrm{Corr}(Z_1, Z_2, Z_3, Z_4) = \begin{bmatrix} 1 & \sqrt{1/2} & \sqrt{1/3} & \sqrt{1/4} \\ & 1 & \sqrt{2/3} & \sqrt{2/4} \\ & & 1 & \sqrt{3/4} \\ & & & 1 \end{bmatrix}$

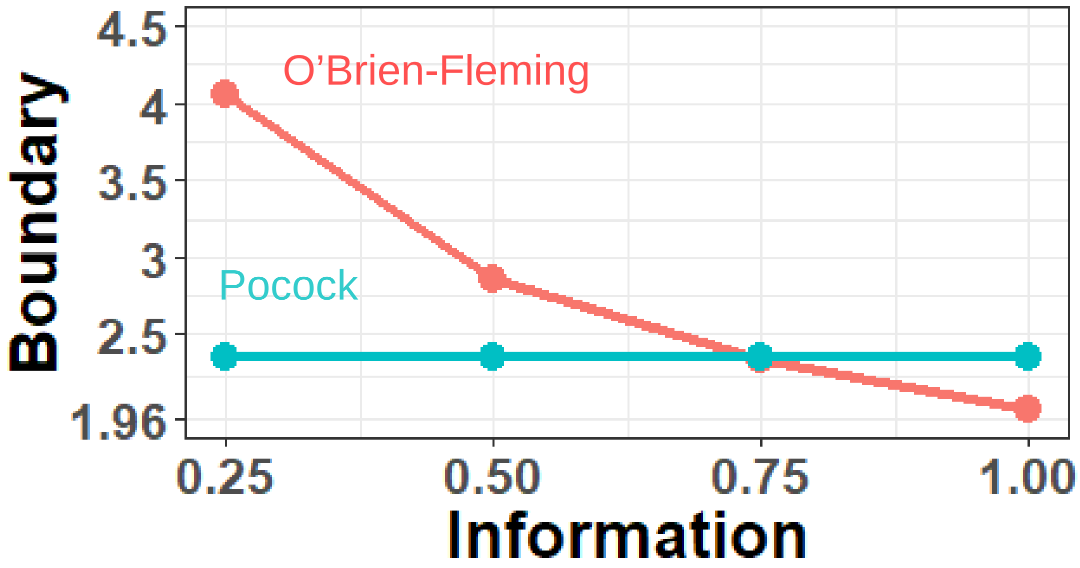
Boundary for test statistics

- Let c_k be the boundary value for analysis k
- H_0 is rejected if $Z_k \geq c_k$ for any $k = 1, \dots, K$
- Type I error—crossing the boundary at any analysis

$$P\left(\bigcup_{k=1}^{K} Z_k \geq c_k\right) = \alpha$$

- In addition, constraints on the relationship among c_k's
  - Pocock (1977): $c_k = c_K$ for $k = 1, \dots, K$
  - O'Brien-Fleming (1978): $c_k = c_K \times {t_k}^{-0.5}$
  - Wang and Tsiatis (1987): $c_k = c_K \times {t_k}^{\Delta-0.5}$
  - These were originally proposed assuming equal-spaced analyses

Properties of the boundary approach for four equally-spaced analyses



- Easy to communicate for decision making
  - Constraints on the scale of test statistics
- Less flexible that the number and timing of analyses are pre-specified
  - Boundary value for the current analysis depends on the timing of future analyses

Error spending function

- An extension is to “spend” α across the interim and final analysis
- Error spending function $\alpha(t)$ specifies how much α is spent up to time $0 \leq t \leq 1$
  - $\alpha(0) = 0$
  - $\alpha(1) = \alpha$
  - $\alpha(t)$ is increasing in t
- Boundary values (c_k) can be obtained by equating
  - Error spent to analysis k: $\alpha(t_k) - \alpha(t_{k-1})$ and
  - Probability of crossing the boundary only at analysis k: $P(Z_1 < c_1, \ldots, Z_{k-1} < c_{k-1}, Z_k \geq c_k)$

Properties of error spending function approach

- Flexible in the number and timing of analyses
  - Boundary value for the current analysis does not depend on the timing of future analyses
- Less transparent to derive boundary values
- Lan-DeMets (1983): $\alpha(t) = 2 - 2\Phi\left(\frac{z_{\alpha/2}}{\sqrt{t}}\right)$
  - Approximates O’Brien-Fleming
  - Derived using the Brownian motion
- Lan-DeMets (1983): $\alpha(t) = \alpha \log[1 + (e-1)t]$
  - Approximates Pocock
  - Derived to approximate Pocock boundary numerically

More flexible error spending functions

- Gamma family (Hwang, Shih, DeCani, 1990)

$$\alpha_\gamma(t) = \alpha \frac{1 - e^{-\gamma t}}{1 - e^{-\gamma}}$$

  – $\gamma = -4$ approximates O'Brien-Fleming and $\gamma = 1$ approximates Pocock

- Power family (Jennison and Turnbull, 2000)

$$\alpha_\rho(t) = \alpha t^\rho$$

  – $\rho = 3$ approximates O'Brien-Fleming and $\rho = 0.75$ approximates Pocock

- Less interpretable in their mathematical forms
- No statistical meaning of the parameter except the above approximation

ACCOMPLISH trial

- ACCOMPLISH trial compared the effect in hypertensive patients at high risk for CV events between
  - benazepril / amlodipine (B/A) -- treatment
  - benazepril / hydrochlorothiazide (B/H) -- control
- Large outcome trial (11506 patients and 1642 events) included a group sequential scheme using the Lan-DeMets O'Brien-Fleming spending function
- At the first two interim analyses, stopping boundaries were not approached
- Third analysis (720 events, information time 0.44), a strong observed effect favoring the B/A arm ($z_3 = 3.18$); however, slightly below the O'Brien-Fleming criterion ($c_3 = 3.2$)
- DMC suspected that the boundary might well be crossed if the outcome of cases awaiting adjudication were known
- DMC suggested the next DMC meeting much sooner than had previously been planned (without conveying unblinded information)

Conditional error in O'Brien-Fleming boundary

- How to determine the stopping boundary for the next analysis?
  - Spending function allows changing the timing but it does not allow choosing a sooner time because of a positive treatment effect
- The conditional error approach in adaptive designs (Müller and Shäfer, 2001) is valid
  - Conditional on the observed effect at the current analysis, the probability of rejecting H_0 in the future
  - It should be the same between
    - Proceeding at analyses as originally planned
    - Proceeding with the expedited analysis as an additional analysis
- The conditional error rate is 0.5 and $c = 2.92$ for the expedited analysis
- If we plugged in the timing to the spending function, $c = 2.94$

Conditional error in O'Brien-Fleming boundary

- The closeness between these two boundary values is not a coincidence
- O'Brien-Fleming boundary has a conditional error of 0.5 (Jennison and Turnbull, 2000)
- At an interim analysis, if
  - the test statistic is equal to the boundary value and
  - the future data are generated under H_0,

then the expectation of test statistics for the next analysis will be equal to the boundary again

  - 50% chance to cross the boundary → conditional error = 0.5

Questions of interest

- How does the boundary behave if it has a conditional error of say, 0.6 or 0.4?
- Is there a family of group sequential designs that is connected to adaptive designs via conditional error?
- To derive the group sequential design, is it possible to connect the boundary and spending function in a closed form?
  - E.g., Brownian motion was used for Lan-DeMets O’Brien-Fleming spending function

Proposed design

- Consider an interim analysis at time $0 < t < 1$ and the final analysis at time $t_F = 1$
- Let c_t and c_{t_F} be the respective boundary values
- Suppose that at the interim analysis, the observed test statistic is right on the boundary, i.e., $Z_t = c_t$
- Under H_0, the conditional distribution of the final statistic is

$$Z_{t_F} | Z_t = c_t \sim N\left(c_t\sqrt{t}, 1 - t\right)$$

Conditional error

- The conditional error is

$$P_{H_0}\left(Z_{t_F} \geq c_{t_F} | Z_t = c_t\right) = 1 - \Phi\left(\frac{c_{t_F} - c_t\sqrt{t}}{\sqrt{1-t}}\right)$$

- Set $P_{H_0}\left(Z_{t_F} \geq c_{t_F} | Z_t = c_t\right) = \gamma$ and we have

$$c_t\sqrt{t} = c_{t_F} - z_\gamma\sqrt{1-t}, \text{ where } z_\gamma = \Phi^{-1}(1-\gamma)$$

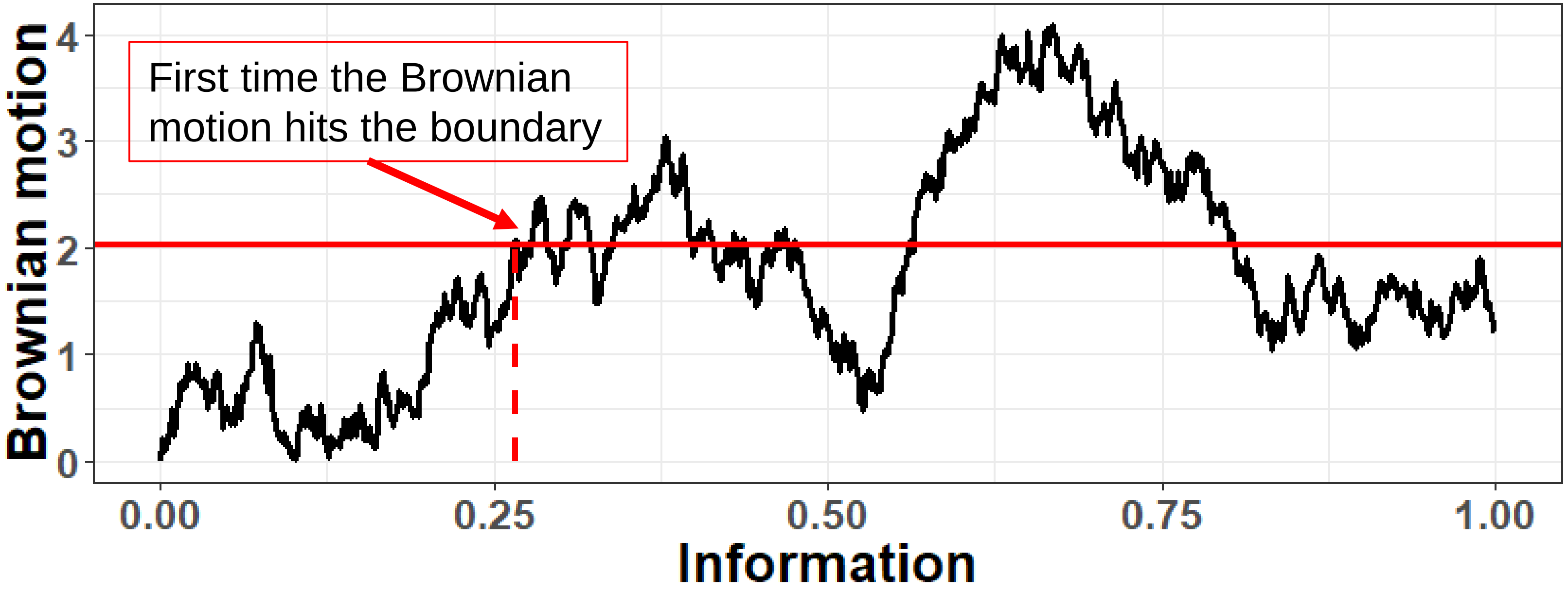
- This provides the relationship between c_t and c_{t_F} such that the conditional error is γ at the interim analysis
- Stopping rule
  - In a group sequential design with the conditional error being γ, stop at the interim analysis if the actual conditional error $\geq \gamma$

Brownian motion

- The standard Brownian motion process

$$B(t) = Z_t\sqrt{t} \sim N(0,t) \text{ under } H_0$$

- Let the boundary value be $b_t = c_t\sqrt{t}$ for $B(t)$



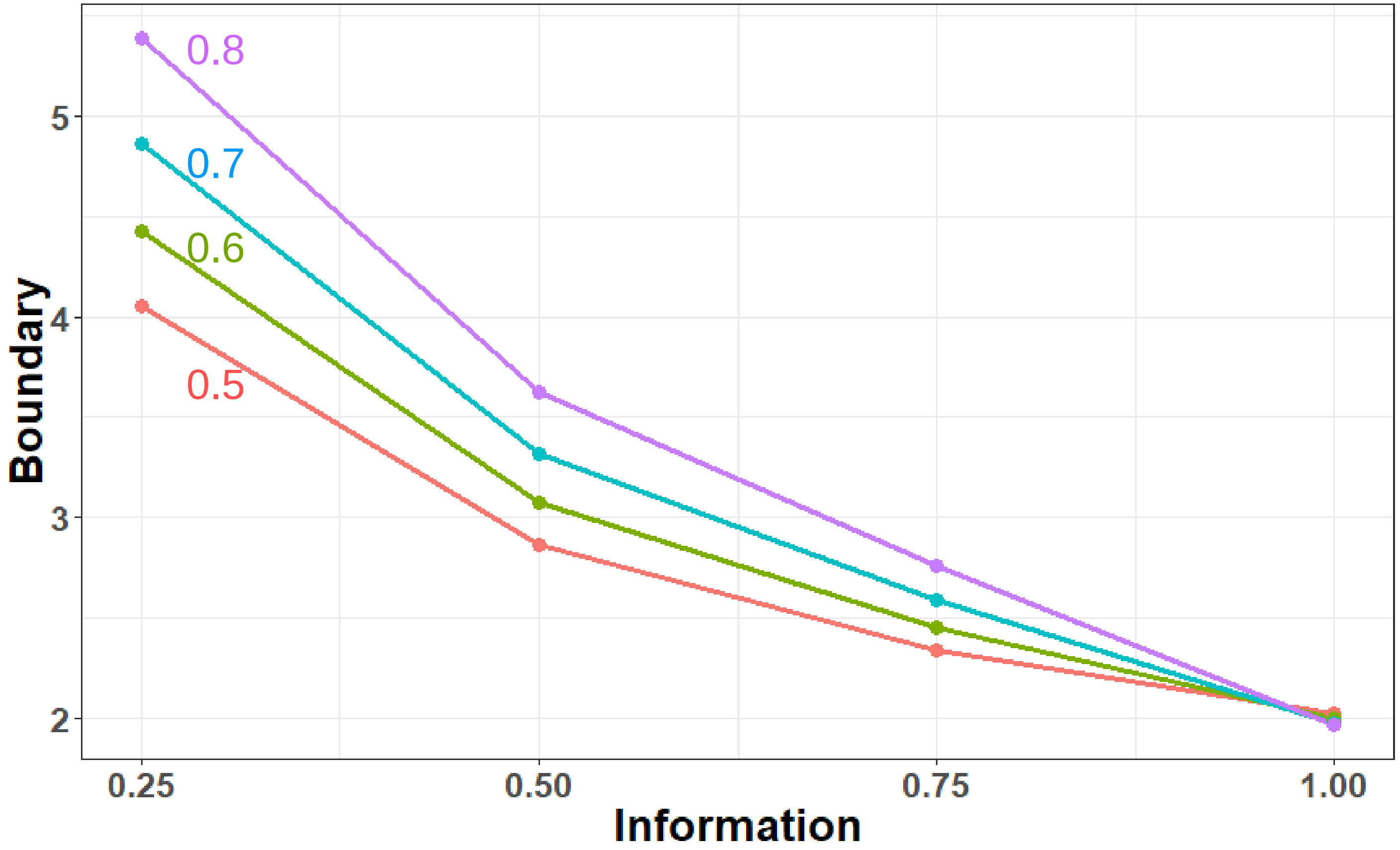
Spending function

- From $c_t\sqrt{t} = c_{t_F} - z_\gamma\sqrt{1-t}$, we have $b_t = b_{t_F} - z_\gamma\sqrt{1-t}$
- Let t be the first exit time across the boundary b_t from below
- Standard Brownian motion calculation gives spending function as the probability of exiting before time t

$$P(\tau \leq t) = 2 - 2\Phi\left(\frac{z_{\alpha/2} - z_\gamma\sqrt{1-t}}{\sqrt{t}}\right) = \alpha_\gamma(t)$$

- Lan-DeMets O'Brien-Fleming boundary is a special case
  - $\gamma = 0.5, z_\gamma = 0$
  - $c_t\sqrt{t} = c_{t_F}$
  - $\alpha(t) = 2 - 2\Phi\left(\frac{z_{\alpha/2}}{\sqrt{t}}\right)$

Properties for four-equally spaced analyses



- The larger γ (conditional error) is, the more conservative early boundaries are (the less conservative the final boundary is)
- Large γ means higher power to reject the null hypothesis, under the same sample size (e.g., O'Brien-Fleming is more powerful than Pocock)

Approximation of spending function approach

- The boundary approach provides the exact conditional error of γ
- The spending function approximates the γ well
  - Within ± 0.1 of γ for all values investigated

γ	Method	c_1	c_2	c_3	c_4
0.8	Boundary approach	5.389	3.621	2.756	1.966
	Actual conditional error	***0.8***	***0.8***	***0.8***	
0.8	Spending function	5.826	3.845	2.863	1.963
	Actual conditional error	***0.864***	***0.857***	***0.849***	

- The spending function approach provides slightly more conservative boundaries for early analyses

Sometimes a perfect ending is not always what you expect it to be.

-- from the movie *A Perfect Ending*

What about $\gamma < 0.5$?

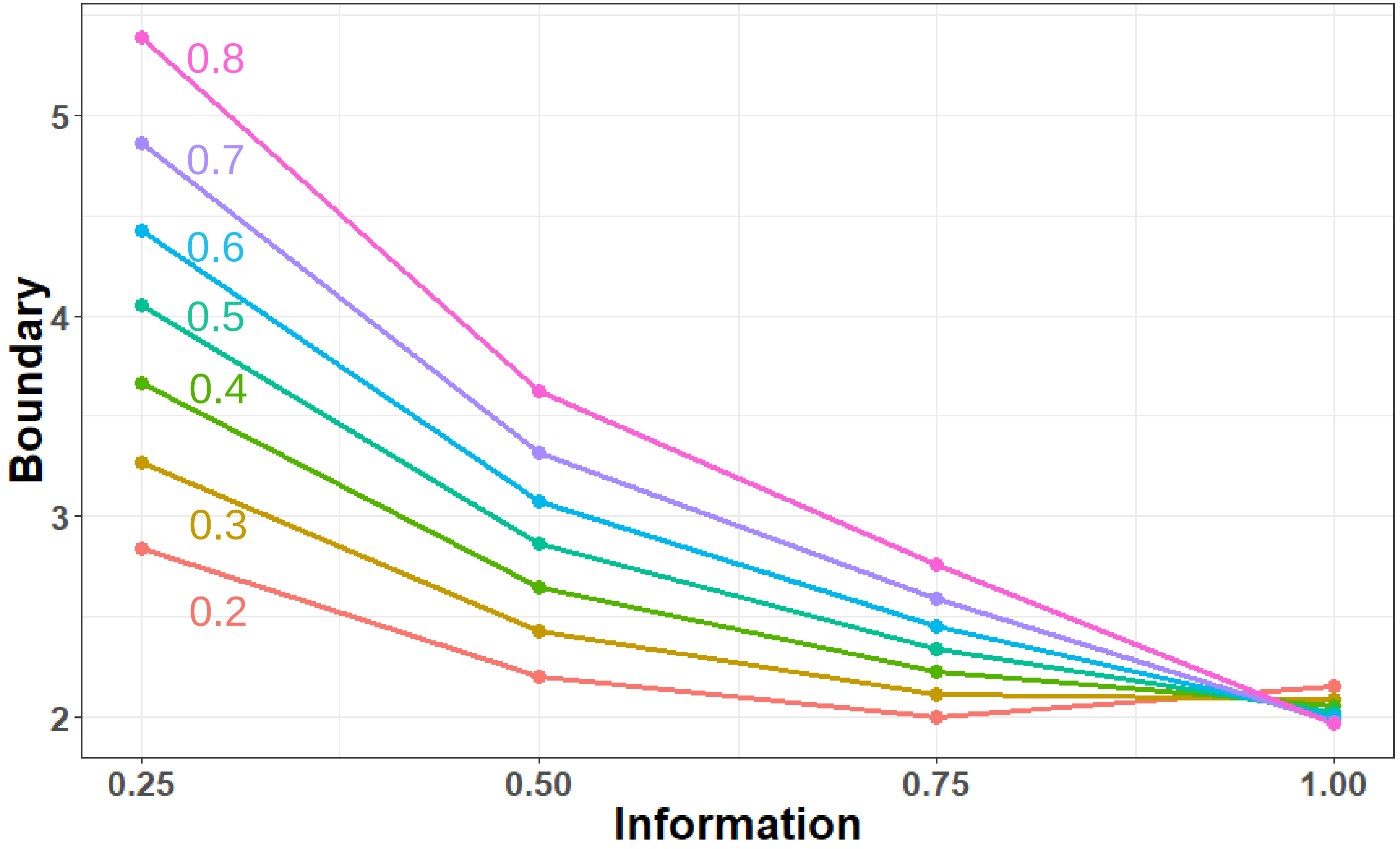
Valid range of γ

- A requirement on spending function to be increasing in t
- This means $0.5 \leq \gamma < \infty$
- This also means that the previous $\alpha_\gamma(t)$ does not allow less conservative interim boundaries than O'Brien-Fleming
- Could modify $\sqrt{1-t}$ to allow a wide range and good operating characteristics

$$\alpha_\gamma(t) = \begin{cases} 2 - 2\Phi\left(\frac{z_{\alpha/2} - z_\gamma (1-t)}{\sqrt{t}}\right), & if\ 1 - \Phi\left(\frac{z_{\alpha/2}}{2}\right) \leq \gamma < 0.5 \\ 2 - 2\Phi\left(\frac{z_{\alpha/2} - z_\gamma \sqrt{1-t}}{\sqrt{t}}\right), & if\ 0.5 \leq \gamma < 1 \end{cases}$$

  - $0.131 < \gamma < 1$ when $\alpha = 0.025$

Properties for four-equally spaced analyses



- The larger γ (conditional error) is, the more conservative early boundaries are (the less conservative the final boundary is)

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  - Within ± 0.1 of γ for all values investigated

γ	Method	c_1	c_2	c_3	c_4
0.2	Spending function	3.016	2.350	2.208	2.224
	Actual conditional error	***0.204***	***0.213***	***0.267***	
0.3	Spending function	3.516	2.574	2.239	2.097
	Actual conditional error	***0.348***	***0.348***	***0.376***	
0.4	Spending function	3.940	2.774	2.295	2.044
	Actual conditional error	***0.466***	***0.454***	***0.455***	

- The combined family has a wide range and good operating characteristics

Connection with adaptive designs

- In the conventional adaptive design framework using the conditional error
  - Start with a group sequential boundary (e.g., gamma family)
  - Then change the design at an interim analysis
  - Calculate the updated boundary so that the conditional error rate is maintained
- But the conditional error has almost no link with the gamma parameter
- Why don't use the conditional error rate as a parameter in the group sequential boundary
  - If we set a conditional error rate (e.g., specify γ)
  - We will know the boundary follows $\alpha_\gamma(t)$ approximately to give a conditional error of γ

Conclusion

- A group sequential design that
  - Has a statistically interpretable parameter (conditional error)
  - Closed-form relationship between boundary values and the spending function
- The use of the Brownian motion introduces a general framework for further extensions
- The proposed group sequential design connects with the adaptive design via conditional error
- Xi D, Gallo P. An additive boundary for group sequential designs with connection to conditional error. Statistics in Medicine. 2019. https://doi.org/10.1002/sim.8325
- R program https://github.com/xidongdxi/gsd

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Thank you