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Adaptive Designs for Group Sequential Clinical Survival Experiments

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Overview

I. Two-Sample Clinical Trial Statistics

- A. Large-sample background
- B. Loss-functions & constraints on actions

II. Asymptotic Formulation & Two Examples

III. General Two-look Optimized Plans

- A. Work with Eric Leifer, NHLBI

IV. Plans Allowing Accrual Continuation

- B. Work with A. Koutsoukos, Amgen, and L. Rubinstein, NCI

Two-Sample Clinical Trial Statistics

Data format : $(E_i\,,\ T_i^*\,,\ \Delta_i^*\,,\ Z_i\,,\quad i=1,\,\ldots,\,N_A(\tau)\,)$
for analysis at time t_*.

E_i entry-times, N_A arrival-counting, τ accrual-horizon

X_i failure time, C_i indep. right-cens., Z_i trt. gp.
(X_i, C_i cond. indep. given Z_i & strat. variable V_i)

$$T_i^* = X_i \wedge C_i \wedge (t_* - E_i)\ ,\quad \Delta_i = I_{[X_i \le C_i \wedge (t_* - E_i]})$$

PROBLEM: test $H_0:\ S_{X|Z}(t|z) \equiv S_X(t)\ ,\ z=0,1$
with multiple interim looks & experimentwise validity.

TEST STATISTIC : for look at t_*, define

$$Y_z^*(s) = \sum_j I_{[Z_j=z,\,T_j^* \ge s]}\ ,\quad Y^*(s) = Y_1^*(s) + Y_0^*(s) \quad \textit{at-risk}$$

$$W(t_*) = \sum_i \int K(s, \hat{S}_X(s))\{Z_i - \frac{Y_1^*(T_i^* \wedge s)}{Y^*(T_i^* \wedge s)}\}\,\Delta_i^*\, dI_{[T_i \le s]}$$

asympt. indep. incr., with estimated variance $\hat{V}(t_*)\ =$

$$\sum_i \int K^2(s, \hat{S}_X(s))\{\frac{Y_1^*(T_i^* \wedge s) Y_0^*(T_i^* \wedge s)}{Y^*(T_i^* \wedge s)}\}\,\Delta_i^*\, dI_{[T_i \le s]}$$

Reject based on $-W(t_*) \ge b(t_*)\sqrt{\hat{V}(t_*)}$

Clinical-Trial Actions & Losses

Decision-Theoretic Set-up:

Actions: look-times t_{k*} & boundaries $b_{k*} = b(t_*)$ for $W/\hat{V}^{1/2}$

but additional flexibility relating accrual to interim results is possible !

Prior: $\pi(d\vartheta)$ for group-difference log hazard ratio parameter ϑ (within semiparametric model).

Losses: costs of experimentation $c_1(t, \vartheta)$, wrong decision $c_2(\vartheta)$, late (correct) decision $c_3(t, \vartheta)$,

these loss elements introduced in Leifer (2000) thesis. Costs are economic within-trial, ethical within-trial, and economic after-trial.

What can the adaptive actions depend on ?

Available actions are, at any look-time: (1) stop & reject, (2) stop & accept, or (3) continue with specified additional look time and **accrual/followup rules**.

Adaptively curtailed followup not a realistic option. Look-times and accrual rate could depend on cumulative response data.

Current Approaches

(1) Look-times pre-specified, accrual as rapid as possible within pre-specified interval $[0, \tau]$.

Stopping boundary (upper & lower) for $W(t_k)/\hat{V}^{1/2}(t_k)$ specified with shape from parametric family $b_k(c), a_k(c)$ to achieve experimentwise α , e.g. $b_k =$

c : *Pocock* 1977;
$c \cdot \sqrt{V(t_k)}$: *O'Brien-Fleming* 1979;
2-param (power-law) form: *Pampallona-Tsiatis* 1994

Other authors: *Jennison et al., Chang et al.*

(2) Variant: times as level-crossing times for $V(t)$ (often referred to as *information time* because V is variance of score statistic).

Lan-DeMets 1983, *Sellke-Siegmund* 1983

(3) Variant: specifies incremental $\alpha(t_k)$ to be spent at each look-time, summing to α. Allows current estimates of accrual & variance.

Slud & Wei 1982, *Lan & DeMets* 1983

(4) Methods with interim design changes based on predictive or conditional power, *stochastic curtailment* etc.

Lan et al. 1982, *Proschan et al.* 1992, & others

General Setting for Research Tasks

All methods rely on asymptotically Gaussian time-indexed statistic-numerator $n^{-1/2}\, W(t)$ with indep. incr.'s, and variance function $V(t)$ to be estimated in real or information time.

$V(t)$ in H_0 is functional of $(\; S_X, S_{C|Z}, \Lambda_A \equiv E(N_A)\;)$

$$\int K^2(S_X(s))\, \frac{\pi(1-\pi)\Lambda_A(t-s) S_{C|Z}(s|1) S_{C|Z}(s|0)}{\Lambda_A(t)(\pi(S_{C|Z}(s|1) + (1-\pi) S_{C|Z}(s|0))}\, dF_X(s)$$

Control parameters: At each $t = t_k$, can choose t_{k+1}, a_{k+1}, b_{k+1} and factor $(r(u), \quad t_k < u \le t_{k+1})$ (fraction of potential accrual to accept).

PROBLEM 1: To optimize times and cutoffs when $r \equiv 1$.

PROBLEM 2: To maintain overall nominal significance level, while allowing $r < 1$ in some settings.

Main Computational Method of optimizing boundaries is parametric search for parametric boundary classes, or **backward induction**.

Optimal Boundary in 2-Look Problem (*w. Leifer*)

Data: $W(t) = B(t_i) + \vartheta t_i, \quad i = 1, 2 \quad t_1$ is fixed in advance, continuation-time $t_2 - t_1 \geq 0$ is chosen as function of $W(t_1)$.

Loss for stopping at τ with Rejection indicator z :

$$c_1(\tau, \vartheta) + c_3(\tau, \vartheta) + z\,(c_2(\vartheta) - c_3(\tau, \vartheta))\,(2I_{[\vartheta \leq 0]} - 1)$$

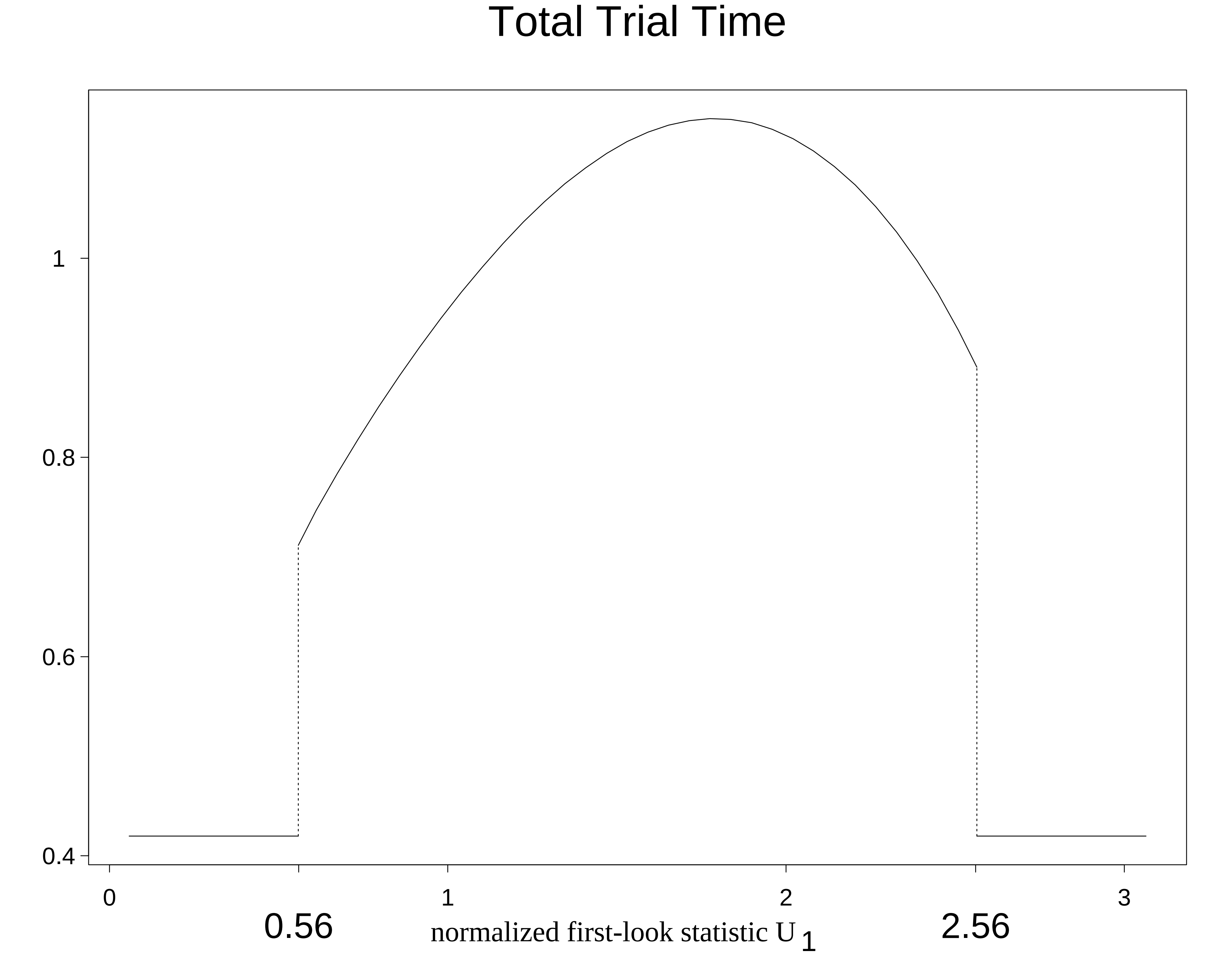
Problem to find min-risk test under prior $\pi(d\vartheta)$, with sig. level $\leq \alpha$ and type II error at $\vartheta_1 \leq \beta$.

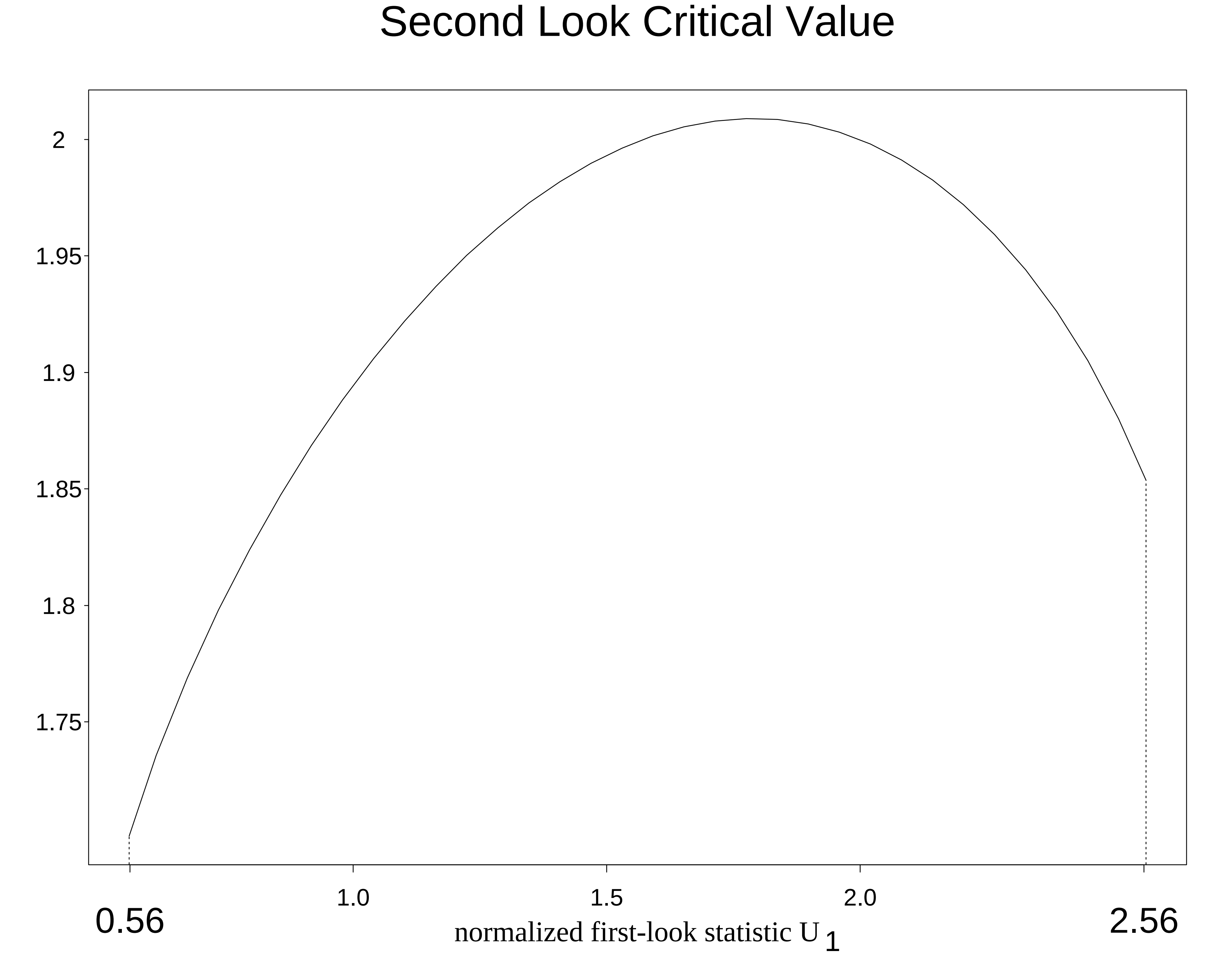
Under regularity conditions on loss elements (*piece-wise smoothness*, $c_2 \geq c_3$, $c_1 \nearrow \infty$) and prior $\pi(d\vartheta)$ assigning positive mass to neighborhoods of 0, $\vartheta_1 > 0$:

can show that optimal procedures are nonrandomized (w.p.1 after small random perturbation of c_1) and essentially unique, rejecting for $W(t_2) \geq b_2(W(t_1))$.

Example. $\alpha = .025$, $\beta = .1$, $\vartheta_1 = log(1.5)$,
time scaled so $\tau_{fix} = 1$. Optimized $t_1 = .42 \cdot \tau_{fix}$.

e^ϑ = hazard ratio	0.9	1.0	1.25	1.5	1.75
$1.51 \cdot \pi(\{\vartheta\})$	0.2	1.0	0.2	0.1	0.01
$c_1(t, \vartheta)$	t	t	t	t	t
$c_2(\vartheta)$	200	100	50	250	500


Total Trial Time
1
0.8
0.6
0.4
0
1
2
3
0.56
2.56
normalized first-look statistic U 1



Second Look Critical Value
2
1.95
1.9
1.85
1.8
1.75
1.0
1.5
2.0
0.56
2.56
normalized first-look statistic U 1

Fixed-Length Adaptively Stopped Accrual
(*with Koutsoukos & Rubinstein*)

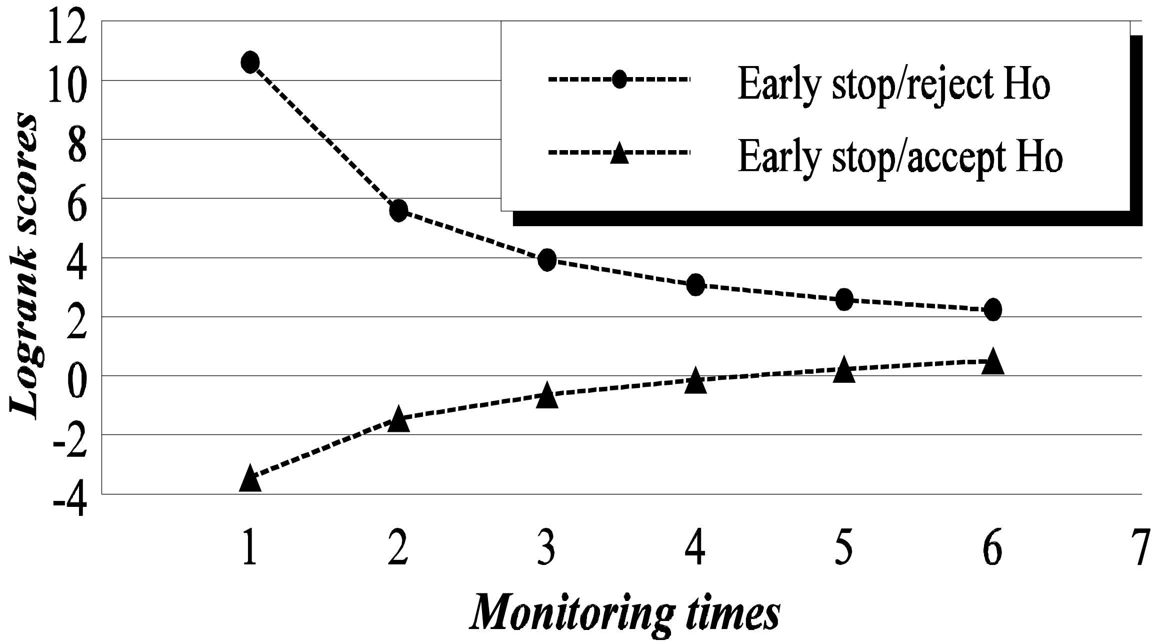
Times $t_j = j$ fixed, $j = 1, \ldots, K$. Idea is to specify immediate lower and upper stopping boundaries a_j, b_j for $W(j)$, in simple parameterized form (eg, $a_j \equiv -a/\sqrt{j}$, $b_j \equiv b$) plus in-between stopping boundary c_j to be used for decision to continue trial with modified (eg stopped) accrual. If this boundary is crossed at j, continue to fixed later time (eg $j+1$) and stop, with rejection only if $W(j+1) > R_{j+1}$.

With $\{a_j,\, b_j,\, c_j\}$ specified, can optimize alternative-averaged power over R_{j+1} subject to experimentwise sig. level α.

Example given in the following pictures – taken from Koutsoukos, Rubinstein & Slud (2000) — has $K = 7$, with maximum accrual period $[0, 6]$.

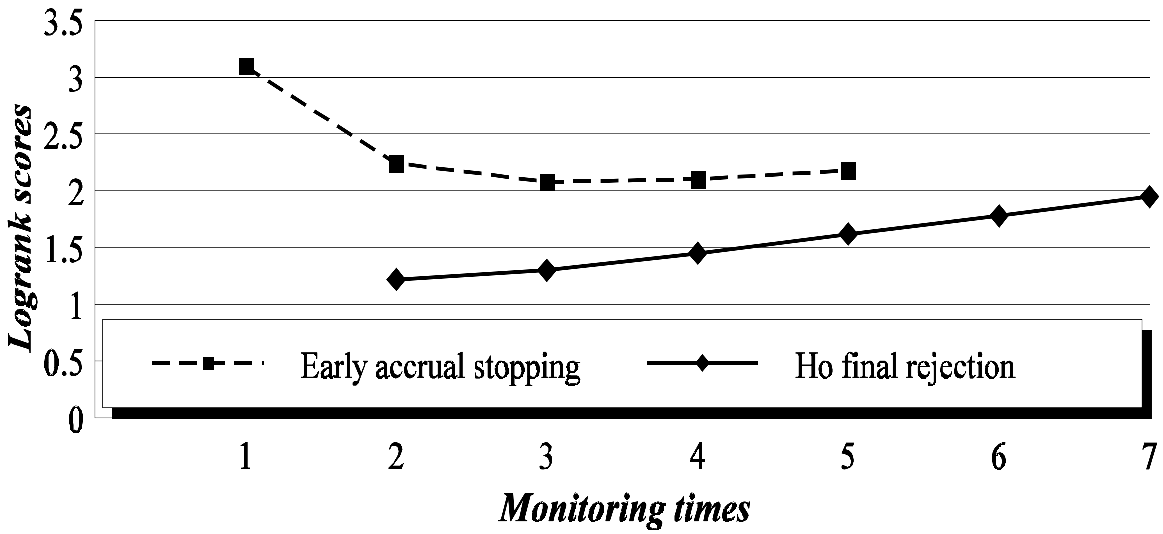
Objective here has been to sketch augmented control parameters: loss structure does not ordinarily incorporate importance (eg for ethical concerns) of flexibility of stopped accrual.

Figure 1: EAS Early Stopping Bounds



- **The upper bound is a standard O'Brien-Fleming upper bound for a 7 look design, with α=.025.**
- **The lower bound is an asymmetric lower bound taken from an O'Brien-Fleming 6 look design, yielding .05 probability of crossing for Δ=1.4 (for which the trial has power 80%).**

Figure 2: EAS Accrual Stopping and Rejection Bounds



- **The H_0 final rejection (1-sided) bound is optimized with respect to power against a defined mix of alternative hypotheses.**
- **The early accrual stopping bound and rejection bound, together, yield .05 conditional probability of failure to reject H_0 after stopping accrual at the boundary (assuming a defined mix of alternative hypotheses).**

References

For clinical-trial large sample theory:

Tsiatis (1982), Andersen & Gill (1982), Sellke & Siegmund (1983), Slud (1984)

For group-sequential boundaries:

Pocock (1977), O'Brien & Fleming (1979), Slud & Wei (1982), Lan & DeMets (1983) , Pampallona & Tsiatis (1994) plus others (Jennison, Chang, ...)

For adaptive modifications:

Proschan, Follman & Waclawiw (1992), and misc. others

For decision-theoretic formulations:

Anscombe (1963), Colton (1963), Jennison (1987), Siegmund (1985 book), Freedman & Spiegelhalter (1989), Leifer (2000, thesis)

For review and Repeated Conf Int approach:

Jennison & Turnbull (1990 Stat. Sci., 2000 book)

For the procedures in this talk:

Koutsoukos, Rubinstein & Slud (2000) adaptive-accrual; Leifer & Slud (2004) 'optimal 2-look' preprint.