Biost 524: Design of Medical Studies

Lecture 9:
Sequential Stopping Rules

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Lecture Outline

- Sequential Monitoring
  - Choice of Stopping Rules
  - Evaluation of Designs
  - Adaptive Designs

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Sequential Monitoring

Choice of Stopping Rules

Where am I going?

- A wide variety of stopping rules have been proposed for different RCT settings.
- Families of designs have been described on a variety of statistical scales.

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Statistical Planning

- Satisfy collaborators as much as possible
  - Discriminate between relevant scientific hypotheses
    - Scientific and statistical credibility
  - Protect economic interests of sponsor
    - Efficient designs
    - Economically important estimates
  - Protect interests of patients on trial
    - Stop if unsafe or unethical
    - Stop when credible decision can be made
  - Promote rapid discovery of new beneficial treatments

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Statistical Criteria

- Extreme estimates of treatment effect
- Statistical significance (Frequentist)
  - At final analysis: Curtailment
  - Based on experimentwise error
    - Group sequential rule
    - Error spending function
- Statistical credibility (Bayesian)
- Probability of achieving statistical significance / credibility at final analysis
  - Condition on current data and presumed treatment effect

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Working Example

- Fixed sample two-sided tests
  - Test of a two-sided alternative ($\theta_+ > \theta_0 > \theta_-$)
    - Upper Alternative: H_+: $\theta \geq \theta_+$ (superiority)
    - Null: H_0: $\theta = \theta_0$ (equivalence)
    - Lower Alternative: H_-: $\theta \leq \theta_-$ (inferiority)
  - Decisions:
    - Reject H_0, H_- (for H_+) $\Longleftrightarrow$ $T \geq c_U$
    - Reject H_+, H_- (for H_0) $\Longleftrightarrow$ $c_L \leq T \leq c_U$
    - Reject H_+, H_0 (for H_-) $\Longleftrightarrow$ $T \leq c_L$

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Sampling Plan: General Approach

- Perform analyses when sample sizes N1. . . NJ
  - Can be randomly determined
- At each analysis choose stopping boundaries
  - $a_j < b_j < c_j < d_j$
- Compute test statistic $T_j = T(X_1 . . . X_{Nj})$
  - Stop if $T_j < a_j$ (extremely low)
  - Stop if $b_j < T_j < c_j$ (approximate equivalence)
  - Stop if $T_j > d_j$ (extremely high)
  - Otherwise continue (maybe adaptive modification of analysis schedule, sample size, etc.)
    - Boundaries for modification of sampling plan

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Choice of Stopping Rule

- The choice of stopping rule will vary according to the exact scientific and clinical setting for a clinical trial
  - Each clinical trial poses special problems
  - Wide variety of stopping rules needed to address the different situations
  - (One size does not fit all)

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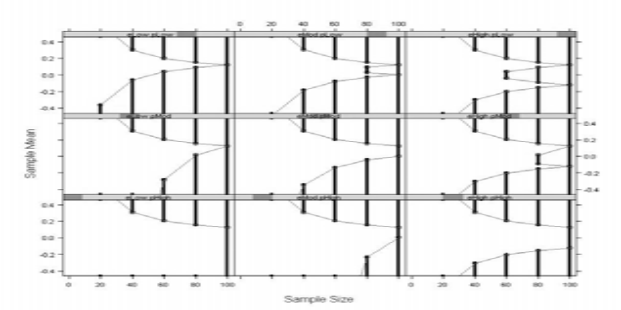
Unified Family: MLE Scale

- Down columns: Early stopping vs no early stopping
- Across rows: One-sided vs two-sided decisions



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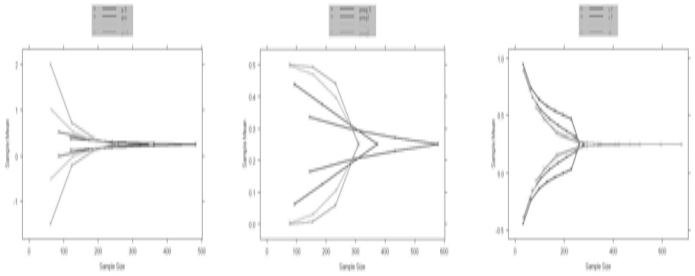
Unified Family: MLE Scale

- All of the rules depicted have the same type I error and power to detect the design alternative



Impact on Sampling Density

- When using a stopping rule, the sampling density depends on exact stopping rule
  - This is obvious from what we have already seen.
  - A fixed sample test is merely a particular stopping rule:
    - Gather all N subjects' data and then stop

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Compared to Fixed Sample

- The magnitude of the effect of the stopping rule on trial design operating characteristics and statistical inference can vary substantially
  - Rule of thumb:
    - The more conservative the stopping rule at interim analyses, the less impact on the operating characteristics and statistical inference when compared to fixed sample designs.

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Reasons for Early Stopping

- Efficacy, Futility, Harm
- Ethical
  - Individual
    - Protect patients on study
    - Protect patients who might be accrued to study
  - Group
    - Promote rapid discovery of new treatments
- Economic
  - Avoid unnecessary costs of RCT
  - Facilitate earlier marketing

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Role of Futility Boundaries

- When clinically relevant improvement has been convincingly ruled out and no further useful information to be gained
  - (Is further study of subgroups or other endpoints still in keeping with informed consent?)
- Futility boundaries usually do not indicate harm
- Because most RCT do not reject the null hypothesis, the major savings in early stopping are through a futility boundary
  - Also, not as much need for early conservatism

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Potential Issue

- Compared to a stopping rule with no futility boundary
  - The critical value at the final analysis can be lower
    - Some of the trials stopped early for futility might have otherwise been type I errors at the final analysis
    - Depends on the early conservatism of the futility boundary

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Nonbinding Futility

- Some clinical trialists believe that FDA requires that the futility rule be ignored when making inference
  - Such builds in conservatism
  - True type I error is smaller than nominal
  - True power is smaller than normal
- This is purposely using the wrong sampling density
  - Not good statistics—game theory must be motivation

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Correct Inference

- The statistically correct, efficient approach is to base inference on the real futility boundary
  - Demands correct pre-specification of the futility boundary
  - Demands a clear paper trail of analyses performed

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Boundary Scales

- Stopping rule for one test statistic is easily transformed to a rule for another statistic
  - "Group sequential stopping rules"
    - Sum of observations
    - Point estimate of treatment effect
    - Normalized (Z) statistic
    - Fixed sample P value
    - Error spending function
  - Bayesian posterior probability
  - Stochastic Curtailment
    - Conditional probability
    - Predictive probability

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Correspondence Among Scales

- Choices for test statistic T_j
  - All of those choices for test statistics can be shown to be transformations of each other
  - Hence, a stopping rule for one test statistic is easily transformed to a stopping rule for a different test statistic
  - We regard these statistics as representing different scales for expressing the boundaries

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Relative Advantages

- Which is the best scale to view a stopping rule?
  - Maximum likelihood estimate
  - Z score / fixed sample P value
  - Error spending scale
  - Stochastic curtailment
    - Conditional power
    - Predictive power

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Statistics Used In Science

- "Scientific scales"
  - Summary measures of the effect
    - Means, medians, geometric means, proportions…
  - Interval estimates for those summary measures
    - (Probabilities merely used to characterize the definition of the interval)
- "Statistical scales"
  - The precision with which you know the true effect
    - Power, P values, posterior probabilities
  - Predictions of the sample you will obtain
    - Conditional power, predictive power

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Example

- Pre-hospital emergency setting
  - Severe trauma
- Waiver of informed consent
  - Effectiveness studies
  - Impact on prisoners, minors, DOD
  - Notification of participants
- Treatment in field
  - Hospital care according to current local standards
  - Largely passive collection of hospital data

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Hypertonic Resuscitation

- Hypertonic saline +/- dextran vs normal saline
  - Osmotic pressure to restore blood volume
  - Modulation of immune response during reperfusion
- Hypovolemic shock
  - SBP $\leq$ 70 OR SBP $\leq$ 90 and HR $\geq$ 108
  - Proportion alive at 28 days
    - 4.8% absolute improvement (69.4% vs 64.6%)

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Sample Size

- Multiple comparison issue
  - HSD vs NS
  - HS vs NS
- Bonferroni adjustment
  - One-sided level 0.0125 tests
- Experimentwise power: 80%
  - Each comparison has 62.6% power
- Sample size: 3,726
  - 1 HSD : 1 HS : 1.414 NS

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Noninferiority

- Department of Defense
  - 250 cc HS weighs less than 2,000 cc NS
  - Even if no benefit from HS, may want to use if not inferior to NS
- Proving noninferior
  - Define margin of "unacceptably inferior"
    - Absolute decrease of 3%
  - CI at end of trial must exclude the margin
    - 80% confidence interval

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Okay, so far?

- 4.8% improvement in 28 day survival
  - 28 day survival clinically relevant?
  - 4.8% improvement clinically important?
  - Realistic based on prior knowledge?
- Experimentwise errors
  - HS and HSD clinically equivalent?
  - 0.025 type I error, 80% power statistically credible?

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Okay, so far?

- Noninferiority
  - 3% decrease justified? In civilians?
  - 80% confidence interval reasonable standard?
  - Are we answering the DoD's questions?
    - (Additional fluids not restricted)
- Sample size of 3,726 without consent?

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Statistical Sampling Plan

- Ethical and efficiency concerns are addressed through sequential sampling
  - During the conduct of the study, data are analyzed at periodic intervals and reviewed by the DMC
  - Using interim estimates of treatment effect
    - Decide whether to continue the trial
    - If continuing, decide on any modifications to
      - scientific / statistical hypotheses and/or
      - sampling scheme

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Protocol Stopping Rule

	N Accrue	Futility Boundary Z	Efficacy Boundary Z
First	621	-4.000	6.000
Second	1,242	-2.800	4.170
Third	1,863	-1.800	3.350
Fourth	2,484	-1.200	2.860
Fifth	3,105	-0.700	2.540
Sixth	3,726	-0.290	2.290

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Efficacy Boundary

	N Accrue	Efficacy Boundary Z	Crude Diff	Est (95% CI; One-sided P)
First	621	6.000	0.272	0.263 (0.183, 0.329); P < 0.0001
Second	1,242	4.170	0.134	0.129 (0.070, 0.181); P < 0.0001
Third	1,863	3.350	0.088	0.082 (0.035, 0.129); P = 0.0004
Fourth	2,484	2.860	0.065	0.060 (0.019, 0.102); P = 0.0025
Fifth	3,105	2.540	0.052	0.048 (0.010, 0.085); P = 0.0070
Sixth	3,726	2.290	0.042	0.040 (0.005, 0.078); P = 0.0130

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Futility Boundary

	N Accrue	Futility Boundary Z	Crude Diff	Est (95% CI; One-sided P)
First	621	-4.000	-0.181	-0.172 (-0.238, -0.092); P > 0.9999
Second	1,242	-2.800	-0.090	-0.084 (-0.137, -0.026); P = 0.9973
Third	1,863	-1.800	-0.047	-0.041 (-0.088, 0.006); P = 0.9581
Fourth	2,484	-1.200	-0.027	-0.022 (-0.064, 0.019); P = 0.8590
Fifth	3,105	-0.700	-0.014	-0.010 (-0.048, 0.028); P = 0.7090
Sixth	3,726	-0.290	-0.005	-0.003 (-0.041, 0.032); P = 0.5975

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Sequential Monitoring

Evaluation of Designs

Where am I going?

- RCT design is most often an iterative process that involves
  - Defining an initial design,
  - Evaluating its operating characteristics, and
  - Modifying the design to better address constraints.

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Evaluation of Designs

- Process of choosing a trial design
  - Define candidate design
    - Usually constrain two operating characteristics
      - Type I error, power at design alternative
      - Type I error, maximal sample size
  - Evaluate other operating characteristics
    - Different criteria of interest to different investigators
  - Modify design
  - Iterate

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Collaboration of Disciplines

Discipline	Collaborators	Issues
Scientific	Epidemiologists Basic Scientists Clinical Scientists	Hypothesis generation Mechanisms Clinical benefit
Clinical	Experts in disease / treatment Experts in complications	Efficacy of treatment Adverse experiences
Ethical	Ethicists	Individual ethics Group ethics
Economic	Health services Sponsor management Sponsor marketers	Cost effectiveness Cost of trial / Profitability Marketing appeal
Governmental	Regulators	Safety Efficacy
Statistical	Biostatisticians	Estimates of treatment effect Precision of estimates
Operational	Study coordinators Data management	Collection of data Study burden Data integrity

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Which Operating Characteristics

- The same regardless of the type of stopping rule
  - Frequentist power curve
    - Type I error (null) and power (design alternative)
  - Sample size requirements
    - Maximum, average, median, other quantiles
    - Stopping probabilities
  - Inference at study termination (at each boundary)
    - Frequentist or Bayesian (under spectrum of priors)
  - (Futility measures
    - Conditional power, predictive power)

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At Design Stage

- In particular, at design stage we can know
  - Conditions under which trial will continue at each analysis
    - Estimates
      - » (Range of estimates leading to continuation)
    - Inference
      - » (Credibility of results if trial is stopped)
    - Conditional and predictive power
  - Tradeoffs between early stopping and loss in unconditional power

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Operating Characteristics

- For any stopping rule, however, we can compute the correct sampling distribution with specialized software
  - From the computed sampling distributions we then compute
    - Bias adjusted estimates
    - Correct (adjusted) confidence intervals
    - Correct (adjusted) P values
  - Candidate designs are then compared with respect to their operating characteristics

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Case Study: Clinical Trial In Gm- Sepsis

- Randomized, placebo controlled Phase III study of antibody to endotoxin
  - Intervention: Single administration
  - Endpoint: Difference in 28 day mortality rates
    - Placebo arm: estimate 30% mortality
    - Treatment arm: hope for 23% mortality
  - Analysis: Large sample test of binomial proportions
    - Frequentist based inference
    - Type I error: one-sided 0.025
    - Power: 90% to detect $\theta < -0.07$
    - Point estimate with low bias, MSE; 95% CI

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Evaluation: Sample Size

- Number of subjects is a random variable
  - Quantify summary measures of sample size distribution as a function of treatment effect
    - maximum (feasibility of accrual) **(Sponsor)**
    - mean (Average Sample N- ASN) **(Sponsor, DMC)**
    - median, quartiles
  - Stopping probabilities **(Sponsor)**
    - Probability of stopping at each analysis as a function of treatment effect
    - Probability of each decision at each analysis

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Sample Size

- What is the maximal sample size required?
  - Planning for trial costs
  - Regulatory requirements for minimal N treated
- What is the average sample size required?
  - Hopefully low when treatment does not work or is harmful
  - Acceptable to be high when uncertainty of benefit remains
  - Hopefully low when treatment is markedly effective
    - (But must consider burden of proof)

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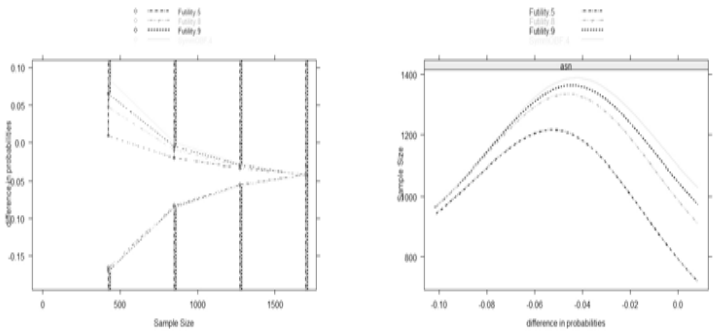
ASN Curve

- Expected sample size as function of true effect



Evaluation: Power Curve

- Probability of rejecting null for arbitrary alternatives
  - Level of significance (power under null) **(Regulatory)**
  - Power for specified alternative
  - Alternative rejected by design
    - Alternative for which study has high power
      - Interpretation of negative studies **(Scientists)**

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Evaluation: Boundaries

- Decision boundary at each analysis: Value of test statistic leading to early stopping
  - On the scale of estimated treatment effect
    - Inform DMC of precision **(DMC, Statisticians)**
    - Assess ethics **(DMC)**
      - May have prior belief of unacceptable levels
    - Assess clinical importance **(Marketing)**
  - On the Z or fixed sample P value scales **(Often asked for, but of questionable relevance)**

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Evaluation: Inference

- Inference on the boundary at each analysis
  - Frequentist
    - Adjusted point estimates
    - Adjusted confidence intervals
    - Adjusted P values

    (Scientists, Statisticians, Regulatory)
  - Bayesian
    - Posterior mean of parameter distribution
    - Credible intervals
    - Posterior probability of hypotheses
    - Sensitivity to prior distributions

    (Scientists, Statisticians, Regulatory)

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Frequentist Inference

	O'Brien-Fleming				Pocock			
N	MLE	Bias Adj Estimate	95% CI	P val	MLE	Bias Adj Estimate	95% CI	P val
Efficacy								
425	-0.171	-0.163	(-0.224, -0.087)	0.000	-0.099	-0.089	(-0.152, -0.015)	0.010
850	-0.086	-0.080	(-0.130, -0.025)	0.002	-0.070	-0.065	(-0.114, -0.004)	0.018
1275	-0.057	-0.054	(-0.096, -0.007)	0.012	-0.057	-0.055	(-0.101, -0.001)	0.023
1700	-0.043	-0.043	(-0.086, 0.000)	0.025	-0.050	-0.050	(-0.099, 0.000)	0.025
Futility								
425	0.086	0.077	(0.001, 0.139)	0.977	0.000	-0.010	(-0.084, 0.053)	0.371
850	0.000	-0.006	(-0.061, 0.044)	0.401	-0.029	-0.035	(-0.095, 0.014)	0.078
1275	-0.029	-0.031	(-0.079, 0.010)	0.067	-0.042	-0.044	(-0.098, 0.002)	0.029
1700	-0.043	-0.043	(-0.086, 0.000)	0.025	-0.050	-0.050	(-0.099, 0.000)	0.025

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At Design Stage: Example

- With O'Brien-Fleming boundaries having 90% power to detect a 7% absolute decrease in mortality
  - Maximum sample size of 1700
  - Continue past 1275 if crude difference in 28 day mortality is between -2.9% and -5.7%
  - If we just barely stop for efficacy after 425 patients we will report
    - Estimated difference in mortality: -16.3%
    - 95% confidence interval: -8.7% to -22.4%
    - One-sided lower P < 0.0001

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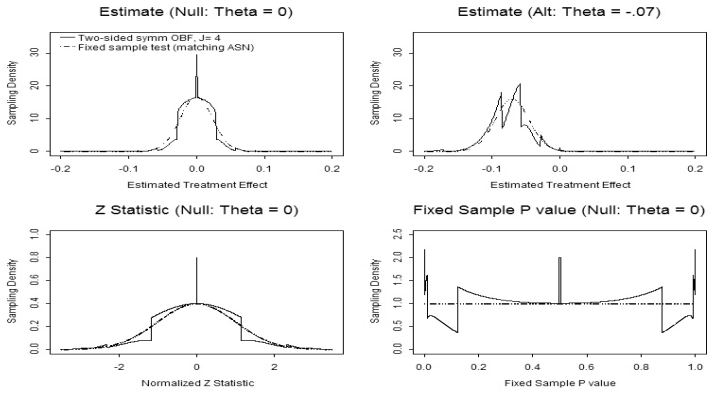
Z scale, Fixed Sample P value



Error Spending Functions

- My view: Poorly understood even by the researchers who advocate them
  - There is no such thing as THE Pocock or O'Brien-Fleming error spending function
    - Depends on type I or type II error
    - Depends on number of analyses
    - Depends on spacing of analyses

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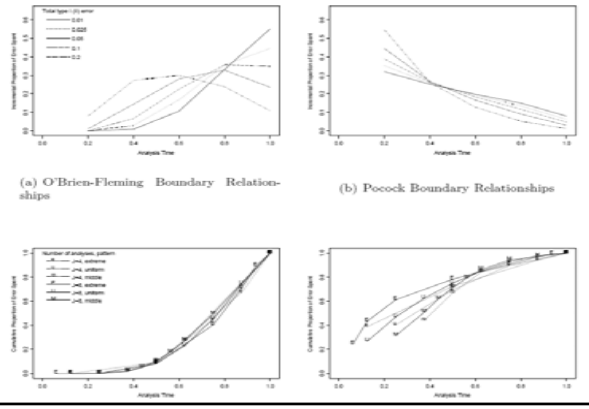
OBF, Pocock Error Spending



(a) O'Brien-Fleming Boundary Relationships

(b) Pocock Boundary Relationships

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Function of Alternative

- Error spending functions depend on the alternative used to compute them
  - The same design has many error spending functions
- JSM 2009: Session on early stopping for harm in a noninferiority trial
  - Attempts to use error spending function approach
  - How to calibrate with functions used for lack of benefit?

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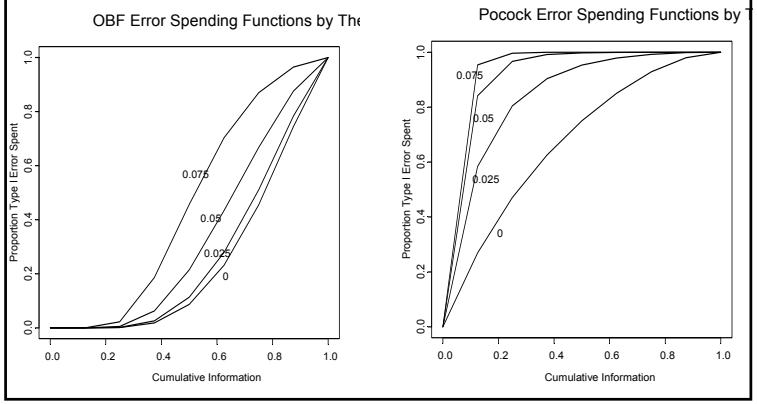
Error Spent by Alternative



Evaluation: Futility

- Consider the probability that a different decision would result if trial continued **(Scientists, Sponsor)**
  - Compare unconditional power to fixed sample test with same sample size
  - Conditional power
    - Assume specific hypotheses
    - Assume current best estimate
  - Predictive power
    - Assume Bayesian prior distribution

(Often asked for, but of questionable relevance)

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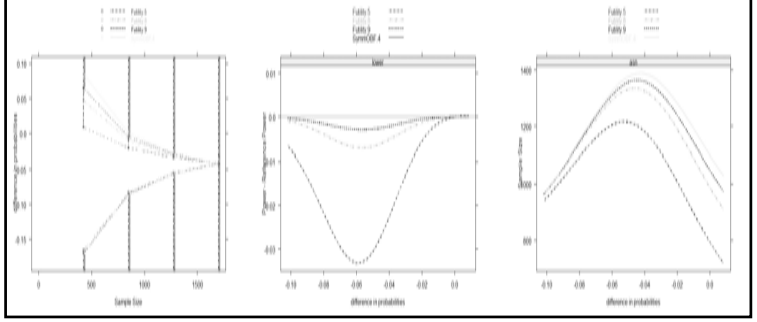
Efficiency / Unconditional Power

- Tradeoffs between early stopping and loss of power
- Boundaries Loss of Power Avg Sample Size



But What If?

- It is common for people to ask about the possibility of a reversed decision
  - But suppose we did not stop for futility. What would be the probability of getting a significant result if we continued to the maximal sample size
- This is easily computed conditional on the observed results IF we know the true treatment effect
  - Conditional power: Assume a particular effect
  - Predictive power: Use a Bayesian prior distribution

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Stochastic Curtailment

- Stopping boundaries chosen based on predicting future <u>data</u>
- Probability of crossing final boundary
  - Frequentist: Conditional Power
    - A Bayesian prior with all mass on a single hypothesis
  - Bayesian: Predictive Power

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Stochastic Curtailment

- Boundaries transformed to conditional or predictive power
  - Key issue: Computations are based on assumptions about the true treatment effect
    - Conditional power
      - "Design": based on hypotheses
      - "Estimate": based on current estimates
    - Predictive power
      - "Prior assumptions"

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So What?

- Why not use stochastic curtailment?
  - What treatment effect should we presume?
    - Hypothesis rejected; current estimate?
  - What threshold should be used for a "low" probability
    - Choice of thresholds poorly understood
      - 10%, 20%, 50%, 80%?
      - How should it depend on sample size and treatment effect
  - Inefficient designs result
    - Conditional and predictive power do not correspond directly to unconditional power

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Assumed Effect and Threshold

- Probability threshold should take into account the timing of the analysis and the presumed treatment effect
  - It is not uncommon for naïve users to condition on a treatment effect that has already been excluded

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Predictive Power: Example 1

- Sepsis trial to detect difference in 28 day survival: Null 0.00 vs Alt -0.07 (90% power)
- Futility bounday at first of 4 analyses
  - Futile if observed diff > 0.0473 (so wrong direction)
  - Inference at boundary
    - Bias adjusted: 0.038 (95% CI -0.037 to 0.101)

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Predictive Power: Example 1

- MLE: 0.0473 Bias Adj: 0.038 (CI: -0.037, 0.101)

Presumed True Effect	Predictive Power
-0.086	71.9%
-0.070	43.2%
-0.037	10.3%
Spons prior	2.8%
Flat prior	0.8%
0.047	<0.005%

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Predictive Power: Ex 2 (OBF)

- Sepsis trial to detect difference in 28 day survival: Null 0.00 vs Alt -0.07 (90% power)
- Futility bounday at first of 4 analyses
  - Futile if observed diff > 0.0855 (so wrong direction)
  - Inference at boundary
    - Bias adjusted: 0.077 (95% CI 0.000 to 0.139)

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Predictive Power: Ex 2 (OBF)

- MLE: 0.0855 Bias Adj: -0.077 (CI: 0.000, 0.139)

Presumed True Effect	Predictive Power
-0.086	50.0%
-0.070	26.5%
0.000	.03%
Spons prior	0.3%
Flat prior	0.03%
0.085	<0.005%

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Key Issues

- Very different probabilities based on assumptions about the true treatment effect
  - Extremely conservative O'Brien-Fleming boundaries correspond to conditional power of 50% (!) under alternative rejected by the boundary
  - Resolution of apparent paradox: if the alternative were true, there is less than .003 probability of stopping for futility at the first analysis

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Stopping Probs for θ = -0.07

Group Sequential test

		Efficacy	Futility	
N= 425	0.009	< - 0.170	> 0.047	0.003
N= 850	0.298	< - 0.085	> - 0.010	0.022
N= 1275	0.401	< - 0.057	> - 0.031	0.039
N= 1700	0.179	< - 0.042	> - 0.042	0.048
Total	0.888			0.112

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Apples with Apples

- Can compare a group sequential rule to a fixed sample test providing
  - Same maximal sample size (N= 1700)
  - Same (worst case) average sample size (N= 1336)
  - Same power under the alternative (N= 1598)
- Consider probability of "discordant decisions"
  - Conditional probability (conditional power)
  - Unconditional probability (power)

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Cond/Uncond Comparison

- Probability of achieving the opposite result at the final analysis
  - Conditional probability
    - Probability among all studies that would stop at that analysis
  - Unconditional probability
    - Change in power of the test due to early stopping

Group Sequential test

	Efficacy		Futility	
	Cond	Uncond	Cond	Uncond
N= 425	0.002	0.000	0.348	0.001
N= 850	0.003	0.001	0.263	0.006
N= 1275	0.009	0.004	0.172	0.007
N= 1700	0.094	0.017	0.182	0.009
Total	0.024	0.022	0.197	0.022

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Ordering of the Outcome Space

- Choosing a threshold based on conditional power can lead to nonsensical orderings based on unconditional power
  - Decisions based on 35% conditional power may be more conservative than decisions based on 18% conditional power
  - Can result in substantial inefficiency (loss of power)

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Further Comments

- Neither conditional power nor predictive power have good foundational motivation
  - Frequentists should use Neyman-Pearson paradigm and consider optimal unconditional power across alternatives
    - And conditional/predictive power is not a good indicator in loss of unconditional power
  - Bayesians should use posterior distributions for decisions

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Evaluation: Marketable Results

- Probability of obtaining estimates of treatment effect with clinical or marketing appeal
  - Modified power curve **(Marketing, Clinicians)**
    - Unconditional
    - Conditional at each analysis
  - Predictive probabilities at each analysis

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Sequential Monitoring

Adaptive Designs

Where am I going?

- There has been much recent interest in the ability to modify an RCT design in the middle of the trial
- My view: You can always sell perpetual motion machines to the public
  - Many of the "adaptive designs" are strikingly ill-advised on scientific grounds as well as being statistically inefficient

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Sequential Sampling Strategies

- Two broad categories of sequential sampling
  - Prespecified stopping guidelines
  - Adaptive procedures

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Adaptive Sampling Plans

- At each interim analysis, possibly modify
  - Scientific and statistical hypotheses of interest
  - Statistical criteria for credible evidence
  - Maximal statistical information
  - Randomization ratios
  - Schedule of analyses
  - Conditions for early stopping

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Adaptive Sampling: Examples

- Prespecified on the scale of statistical information
  - E.g., Modify sample size to account for estimated information (variance or baseline rates)
    - No effect on type I error IF
      - Estimated information independent of estimate of treatment effect
        - » Proportional hazards,
        - » Normal data, and/or
        - » Carefully phrased alternatives
      - And willing to use conditional inference
        - » Carefully phrased alternatives

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Estimate Alternative

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

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

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Estimate Sample Size

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

$$n = \frac{\delta_1^{\,2} V}{(\Delta_1 - \Delta_0)^2} \qquad \frac{n}{V} = \frac{\delta_1^{\,2}}{(\Delta_1 - \Delta_0)^2}$$

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Adaptive Sampling: Examples

- E.g., Proschan & Hunsberger (1995)
  - Modify ultimate sample size based on conditional power
    - Computed under current best estimate (if high enough)
  - Make adjustment to inference to maintain Type I error

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Incremental Statistics

- Statistic at the j-th analysis a weighted average of data accrued between analyses

$$\hat{\theta}_j = \frac{\sum_{k=1}^{j} N_k^* \hat{\theta}_k^*}{N_j} \qquad Z_j = \frac{\sum_{k=1}^{j} \sqrt{N_k^*}\, Z_k^*}{\sqrt{N_j}}.$$

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Conditional Distribution

$$\hat{\theta}_j^* \mid N_j^* \sim N\left(\theta, \frac{V}{N_j^*}\right)$$

$$Z_j^* \mid N_j^* \sim N\left(\frac{\theta - \theta_0}{\sqrt{V / N_j^*}}, 1\right)$$

$$H_0$$

$$P_j^* \mid N_j^* \sim U(0,1).$$

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Unconditional Distribution

- A mixture of normals, rather than a normal distribution

$$\Pr\left(Z_j^* \le z\right) = \sum_{n=0}^{\infty} \Pr\left(Z_j^* \le z \mid N_j^*\right) \Pr\left(N_j^* = n\right).$$

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Two Stage Design

- Proschan & Hunsberger consider worst case
  - At first stage, choose sample size of second stage
    - $N_2 = N_2(Z_1)$ to maximize type I error
  - At second stage, reject if $Z_2 > a_2$
- Worst case type I error of two stage design

$$\alpha_{worst} = 1 - \Phi\left(a_2^{(Z)}\right) + \frac{\exp\left(-\left(a_2^{(Z)}\right)^2 / 2\right)}{4},$$

  - Can be more than two times the nominal
    - $a_2 = 1.96$ gives type I error of 0.0616
    - (Compare to Bonferroni results)

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Better Approaches

- Proschan and Hunsberger describe adaptations using restricted procedures to maintain experimentwise type I error
  - Must prespecify a conditional error function which would maintain type I error
    - Then find appropriate a_2 for second stage based on N_2 which can be chosen arbitrarily
  - But still have loss of power

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Other Approaches

- Bauer and Kohne:
  - Use R.A. Fisher's method for combining independent P values
- L. Fisher:
  - Variance spending function using prespecified weights at each stage
- Muller and Schafer:
  - Maintain conditional power function from some prespecified fixed sample test

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Disadvantage Common to All

- Nonintuitive weighting of information from the different stages
  - Stages are not necessarily assigned weights proportional to the statistical information (sample size)
- Violation of the sufficiency principle
  - Inference depends on more information than is available in the minimal sufficient statistic

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Motivation for Adaptive Designs

- Scientific and statistical hypotheses of interest
  - Modify target population, intervention, measurement of outcome, alternative hypotheses of interest
  - Possible justification
    - Changing conditions in medical environment
      - Approval/withdrawal of competing/ancillary treatments
      - Diagnostic procedures
    - New knowledge from other trials about similar treatments
    - Evidence from ongoing trial
      - Toxicity profile (therapeutic index)
      - Subgroup effects

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Motivation for Adaptive Designs

- Modification of other design parameters may have great impact on the hypotheses considered
  - Statistical criteria for credible evidence
  - Maximal statistical information
  - Randomization ratios
  - Schedule of analyses
  - Conditions for early stopping

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Cost of Planning Not to Plan

- Major issues with use of adaptive designs
  - What do we truly gain?
    - Can proper evaluation of trial designs obviate need?
  - What can we lose?
    - Efficiency? (and how should it be measured?)
    - Scientific inference?
      - Science vs Statistics vs Game theory
      - Definition of scientific/statistical hypotheses
      - Quantifying precision of inference

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Prespecified Modification Rules

- Adaptive sampling plans exact a price in statistical efficiency
  - Tsiatis & Mehta (2002)
    - A classic prespecified group sequential stopping rule can be found that is more efficient than a given adaptive design
  - Shi & Emerson (2003)
    - Fisher's test statistic in the self-designing trial provides markedly less precise inference than that based on the MLE
      - To compute the sampling distribution of the latter, the sampling plan must be known

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Conditional/Predictive Power

- Additional issues with maintaining conditional or predictive power
  - Modification of sample size may allow precise knowledge of interim treatment effect
    - Interim estimates may cause change in study population
      - Time trends due to investigators gaining or losing enthusiasm
    - In extreme cases, potential for unblinding of individual patients
      - Effect of outliers on test statistics

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Final Comments

- Adaptive designs versus prespecified stopping rules
  - Adaptive designs come at a price of efficiency and (sometimes) scientific interpretation
  - With adequate tools for careful evaluation of designs, there is little need for adaptive designs

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Sequential Monitoring

Documentation of Designs

Where am I going?

- Prespecification of the RCT design, monitoring plan, and analysis plan is of utmost importance

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Specify Stopping Rule

- Null, design alternative hypotheses
- One-sided, two-sided hypotheses
- Type I error, Power to detect design alternative
- For each boundary
  - Hypothesis rejected
  - Error
  - Boundary scale
  - Boundary shape function parameters
- Constraints (minimum, maximum, exact)

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Documentation of Rule

- Specification of stopping rule
- Estimation of sample size requirements
- Example of stopping boundaries under estimated schedule of analyses
  - sample mean scale, others?
- Inference at the boundaries
- Power under specific alternatives
- Behavior under possible scenarios
  - Alternative baseline rates, variability

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Implementation

- Method for determining analysis times
- Operating characteristics to be maintained
  - Power (up to some maximum N?)
  - Maximal sample size
- Method for measuring study time
- Boundary scale for making decisions
- Boundary scale for constraining boundaries at previously conducted analyses
- (Conditions stopping rule might be modified)

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Analysis Plan

- Stopping rule for inference
  - Nonbinding futility?
- Method for determining P values
- Method for point estimation
- Method for confidence intervals
- Handling additional data that accrues after decision to stop

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