(Frequentist and Bayesian)

Evaluation of Clinical Trial Designs

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Course Structure

Topics:

- Overview
- Frequentist approach
  - Inferential methods
  - Fixed Sample Clinical Trial Design
  - Group Sequential Sampling Plans
  - Evaluation of clinical trial designs
- Bayesian approach
  - Inferential methods
  - Probability models
  - Nonparametric Bayes
  - Evaluation of clinical trial designs

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Fair Warning

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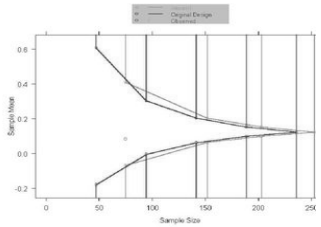
As You See It



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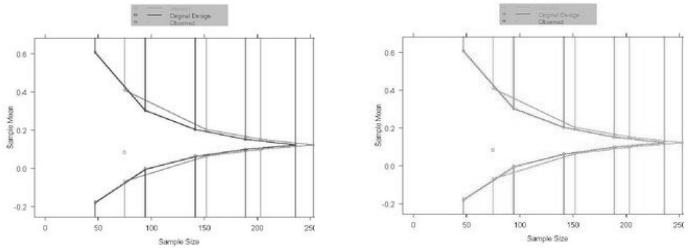
As You See It As I See It



(www.vischeck.com)

Overview

Clinical Trial Setting

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Fundamental Philosophy

Statistics is about science.

Science is about proving things to people.

- Other scientists
- Community at large

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Scientific Studies

A well designed study

- Discriminates between the most important, viable hypotheses
- Is equally informative for all possible outcomes
  - Binary search using prior probability of being true
  - Also consider simplicity of experiments, time, cost

(The Scientist Game)

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Clinical Trials

Experimentation in human volunteers

- Investigate a new treatment / preventive agent
  - Safety
    - Phase I; Phase II
  - Efficacy
    - Phase II (preliminary); Phase III
  - Effectiveness
    - Phase III (therapy); Phase IV (prevention)

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Collaboration of Multiple 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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Scientific Hypotheses

Collaboration among investigators to

- Define intervention
- Define patient population
- Define general goal
  - Clinical measurement for outcome
  - Relevant benefit to establish: Two or more of
    - Superiority, noninferiority, approximate equivalence, nonsuperiority, inferiority

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Typical Scientific Hypotheses

The intervention when administered to the target population will tend to result in outcome measurements that are

{ higher than, lower than, or about the same as } { an absolute standard, or measurements in a comparison group }

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Experimental Design

Plan collection of a sample which allows

- Administration of intervention (ethically)
- Measurement of outcomes
- Statistical analysis of results
  - Variability of subjects means that results need to be reported in probabilistic terms
    - Point estimate of summary measure of response
    - Interval estimate to quantify precision
    - Quantification of error rates for decisions
    - (Binary decision?)

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Refining Scientific Hypotheses

In order to be able to perform analysis

- Modify intervention, endpoints to increase precision (without changing relevance)
- Probability model for response
  - Choose summary measure of response distribution
- Precise statement of hypotheses to be discriminated
  - Stated in terms of summary measure

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Comparison of Summary Measures

Typical approaches to compare response across two treatment arms

- Difference / ratio of means (arithmetic, geometric, …)
- Difference / ratio of medians (or other quantiles)
- Median difference of paired observations
- Difference / ratio of proportion exceeding some threshold
- Ratio of odds of exceeding some threshold
- Ratio of instantaneous risk of some event
  - » (averaged across time?)
- Probability that a randomly chosen measurement from one population might exceed that from the other
- …

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Statistical Models

Issues when choosing statistical models

- Criteria for quantifying credibility of results
  - Frequentist
  - Bayesian
- Computational methods and formulas
- Covariate adjustment
- …

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Impact of Statistical Model

Choice of statistical model impacts the scientific question actually addressed as well as the statistical precision

- Robustness of inference depends on methods of computing the summary measures to be compared
- Interpretation of positive and negative studies depends on computation of sampling variance

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Overview

Where I Am Going:

"A revolution no one will notice"

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Ultimate Goal

Design and analysis of clinical trials to allow quantification of the strength of evidence for or against scientific hypotheses

– AND to allow concise presentation of results

Need to convince the audience, who may

– Disagree on what are most important hypotheses
  - What precision is necessary for what endpoints?
– Disagree on definition of statistical evidence
  - Frequentist vs Bayesian (with varying priors)

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My Optimality Criterion

I believe statistical methods should always take the scientific setting into account

- Science ideally progresses through a series of experiments successively addressing more refined questions
- I am against unnecessarily assuming the answer to more detailed questions than I am trying to address in the scientific study

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There are two types of people in the world:

- Those who dichotomize everything, and
- Those who don't.

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Classification of Statistical Models

Breiman (2000): The two approaches to data analysis

- Model based vs algorithmic
  - (e.g., regression vs trees, neural nets)

This talk:

- Frequentist vs Bayesian
- (Semi)Parametric vs nonparametric

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Outline

Frequentist Methods

- Frequentist inference in fixed sample designs
- Probability models
  - (Semi)parametric vs nonparametric
- Sequential sampling

Bayesian Methods

- Bayesian paradigm
- "Coarsened" nonparametric Bayes
- Concise presentation of results

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Frequentist Methods

Frequentist Inference
in
Fixed Sample Designs

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Illustrative Example

Hypothetical clinical trial

- Two groups: Treatment and Placebo
- Primary outcome variable: continuous
- Notation

Treatment :

$$X_1, \ldots, X_n \overset{iid}{\sim} F \qquad E[X_i] = \mu \qquad Var[X_i] = \sigma^2$$

Control :

$$Y_1, \ldots, Y_m \overset{iid}{\sim} G \qquad E[Y_i] = \nu \qquad Var[Y_i] = \tau^2$$

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Measure of Treatment Effect

We choose some summary measure of the difference between the distributions of response across the treatment arms

- Criteria (in order of importance)
  - Scientifically (clinically) relevant
    - Also reflects current state of knowledge
  - Intervention is likely to affect
    - Could be based on ability to detect variety of changes
  - Statistical precision

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Measure of Treatment Effect

A common choice: Difference in means

Treatment effect : $\mu - \nu$

Why?

- Occasionally most relevant (health care costs)
- Sensitive to a wide variety of changes in distribution of response
- Statistically most efficient in the presence of normally distributed data

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Statistical Design of Experiment

Design experiment by looking to the future: Consider how the results of the study will be reported

- The single "best" estimate of treatment effect
- An interval estimate to quantify precision
- A quantification of the strength of evidence for or against particular hypotheses
- Our conclusion from the study
  - A binary decision

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One-sided Statistical Hypotheses

Define hypotheses to be discriminated

One-sided hypotheses :

$$H_0 : \theta \le \theta_0 \quad vs \quad H_1 : \theta > \theta_1$$

Decisions for superiority or not sufficiently superior

(One-sided test can also be defined for one-sided lesser alternative)

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Two-sided Statistical Hypotheses

Define hypotheses to be discriminated

Two-sided hypotheses :

$$H_1 : \theta \ne \theta_1 \quad vs \quad H_{01} : \theta = \theta_0$$
$$H_{01} : \theta = \theta_0 \quad vs \quad H_1 : \theta \ne \theta_1$$

Resembles two superposed one-sided tests

- Decisions for superiority, inferiority, approximate equivalence

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Classical Hypothesis Testing

Reject hypothesis if observed data is rare when that hypothesis is true

Consider probability of falsely rejecting each hypothesis

- Usually fix type I error at some prescribed level
- Try for high power (low type II error) for some "design alternative"

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Implementation

Define "rare data" for each hypothesis

- Choose test statistic
  - Often based on an estimate of treatment effect

$$T(X,Y) = \hat{\theta}$$

  - Reject low treatment effect when estimate is so high as to only occur, say, with 5% probability

$$\text{Reject } H_0 : \theta \le \theta_0 \text{ if } \hat{\theta} > c_{\theta_0, 1-\alpha},$$
$$\text{where } \Pr(\hat{\theta} > c_{\theta_0, 1-\alpha} \mid \theta_0) = \alpha$$

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Hallmark of Frequentist Inference

Frequentist inference makes probability statements about the distribution of the data conditional on a presumed treatment effect, e.g.,

Critical value : $\Pr\left(\hat{\theta} \geq c_{\theta_0,1-\alpha} \mid \theta_0\right) = \alpha$

CI for $\hat{\theta} \pm z$: $\left(\hat{\theta} : \frac{\alpha}{2} \geq \Pr\left(\hat{\theta} \geq z \mid \theta\right) \geq 1 - \frac{\alpha}{2}\right)$

Unbiased estimates : $E\left(\hat{\theta} \mid \theta\right) = \theta$

Efficient estimates : minimize $Var\left(\hat{\theta} \mid \theta\right)$

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Sampling Distribution

Frequentist inference thus requires knowledge of the sampling distribution for the estimate of treatment effect

- Sampling distribution under the null
  - Necessary and sufficient to have the correct size test
- Sampling distribution under alternatives
  - Necessary to compute
    - power of tests
    - confidence intervals
    - optimality of estimators

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Derivation of Sampling Distribution

To compute sampling distribution

$$\Pr\left(\hat{\theta} \geq t \mid \theta\right)$$

need to know the probability model to obtain

- Formula for $\hat{\theta}$
- Definition of hypotheses
- Distribution of (X, Y) under every hypothesis

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Typical Sampling Distribution

In the probability models most often used for frequentist inference, the sampling distribution is approximately normal

- Fixed sample setting (no early stopping)
- Large samples

$$\hat{\theta} \mid \theta \sim N\left(\theta, \frac{V}{n}\right)$$

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Approximate Frequentist Inference

Standard frequentist inference is then

- Consistent point estimate $\hat{\theta}$
- 100(1-a)% confidence interval

$$\hat{\theta} \pm z_{1-\alpha/2}\sqrt{\frac{V}{n}}$$

- P value to test $H_0: \theta = \theta_0$

$$P = 2\left(1 - \Phi\left(\frac{|\hat{\theta} - \theta_0|}{\sqrt{V/n}}\right)\right)$$

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Frequentist Methods

Sample Size Determination

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Decision Theoretic Approach

Design study with sufficient precision to be able to reject at least one hypothesis with high confidence

- Equivalent criteria for rejection
  - type I error = type II error
  - interval estimate does not contain both the null and alternative hypotheses
- Asymmetric definitions of rejection
  - Arbitrary power

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Sample Size Computation

Number of "sampling units" to obtain desired precision

Level of significance α when $\theta = \theta_0$

Power β when $\theta = \theta_1$

Variability V within 1 sampling unit

$$n = \frac{(z_{1-\alpha/2} + z_{\beta})^2 V}{(\theta_1 - \theta_0)^2}$$

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When Sample Size Constrained

Often (usually?) logistical constraints impose a maximal sample size

- Compute power to detect specified alternative

$$\Phi\left(\frac{|\theta_1 - \theta_0|}{\sqrt{V/n}} - z_{1-\alpha/2}\right)$$

- Compute alternative detected with high power

$$|\theta_1 - \theta_0| \geq z_{1-\alpha/2} + z_{\beta}\sqrt{\frac{V}{n}}$$

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Threshold for Statistical Significance

Having chosen a sample size, we can compute

- Threshold for declaring statistical significance

Reject $H_0: \theta = \theta_0$ if $\hat{\theta} - \theta_0 \geq z_{1-\alpha/2}\sqrt{\frac{V}{n}}$

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Inference at Threshold

We can also anticipate the inference we will make if we observe an estimate exactly at the threshold

- P value equal to type I error
- Confidence interval

$$\hat{\theta} \pm z_{1-\alpha/2}\sqrt{\frac{V}{n}}$$

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Frequentist Methods

Evaluation of
Fixed Sample Clinical
Trial Designs

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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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Operating Characteristics

- Frequentist power curve
  - Type I error (null) and power (design alternative)
- Sample size requirements
- Threshold for statistical significance
- Frequentist inference at threshold
  - Point estimate
  - Confidence interval
  - P value

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Collaboration of Multiple Disciplines

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Ethical	Ethicists	Individual ethics Group ethics
Economic	Health services Sponsor management Sponsor marketers	Cost effectiveness Cost of trial / Profitability Marketing appeal
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Evaluating Sample Size

Consider

- Feasibility of accrual **(Sponsor)**
- Credibility of results
  - "3 over n rule": We may have missed an important subgroup with different response patterns **(Scientists, Regulatory)**
  - When combined with results from earlier trials **(Sponsor, Regulatory)**

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Evaluating Power Curve

Probability of rejecting null for arbitrary alternatives

- Type I error (power under null) (Regulatory)
- Power for specified alternative (Scientists)
- Alternative rejected by design (Scientists)
  - Alternative for which study has high power
    - Interpretation of negative studies

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Evaluating Boundaries

Threshold for declaring statistical significance

- On the scale of estimated treatment effect
  - Assess clinical importance (Clinicians, Ethics)
  - Assess economic importance (Marketing)

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Evaluating Inference

Inference on the boundary for statistical significance (Scientists, Statisticians, Regulatory)

- Frequentist
  - Point estimates
  - Confidence intervals
  - P values

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Frequentist Methods

Sequential Sampling: Stopping Rules

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Statistical Design: Sampling Plan

Ethical and efficiency concerns are addressed through sampling which might allow early stopping

- During the conduct of the study, data are analyzed and reviewed at periodic intervals
- Using interim estimates of treatment effect
  - Decide whether to continue the trial
  - If continuing, decide on any modifications to sampling scheme

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Criteria for Early Stopping

- Results convincing for specific hypotheses
  - Superiority, approximate equivalence, inferiority
- Results suggestive of inability to ultimately establish a hypothesis of interest
  - Futility
- No advantage in continuing
  - No need to collect additional data on safety, longer term follow-up, other secondary endpoints

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Basis for Early Stopping

- Extreme estimates of treatment effect
- Curtailment:
  - Boundary reached early
  - Stochastic Curtailment: High probability that a particular decision will be made at final analysis
- Group sequential test:
  - Formal decision rule in classical frequentist framework controlling experimentwise error
- Bayesian analysis:
  - Posterior probability of hypothesis is high

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General Stopping Rule

- Analyses when sample sizes $N_1, \ldots, N_J$
  - Can be randomly determined
- At jth analysis choose stopping boundaries
  - $a_j < b_j < c_j < d_j$
- Compute test statistic $T(X_1, \ldots, X_{N_j})$
  - Stop if $T < a_j$ (extremely low)
  - Stop if $b_j < T < c_j$ (approximate equivalence)
  - Stop if $T > d_j$ (extremely high)
  - Otherwise continue (with possible adaptive modification of analysis schedule, sample size, etc.)

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Categories of Sequential Sampling

Prespecified stopping guidelines

Adaptive procedures

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Prespecified Stopping Plans

Prior to first analysis of data, specify

- Rule for determining maximal statistical information
  - E.g., fix power, maximal sample size, or calendar time
- Rule for determining schedule of analyses
  - E.g., according to sample size, statistical information, or calendar time
- Rule for determining conditions for early stopping
  - E.g., boundary shape function for stopping boundaries on the scale of some test statistic

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Boundary Scales

A stopping rule for one test statistic is easily transformed to a stopping rule for another

- "Group sequential stopping rules"
  - Sum of observations
  - Point estimate of treatment effect
  - Normalized (Z) statistic
  - Fixed sample P value
  - Error spending function
- Conditional probability
- Predictive probability
- Bayesian posterior probability

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Families of Stopping Rules

Parameterization of boundary shape functions facilitates search for stopping rules

- Can be defined for any boundary scale

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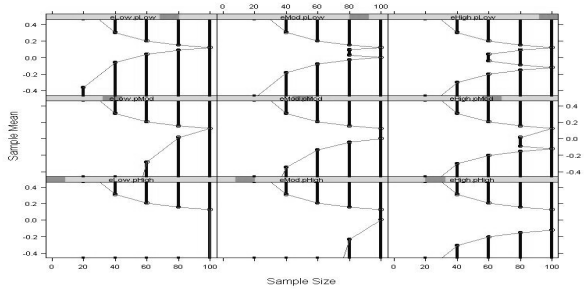
Example: Unified Family

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



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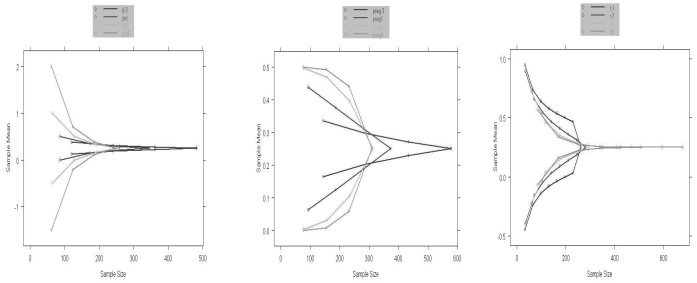
Example: Unified Family

A wide variety of boundary shapes possible

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



Adaptive Sampling Plans

At each analysis of the data, the sampling plan can be modified to account for changed perceptions of possible results

- E.g., Proschan & Hunsberger (1995)
  - Use conditional power considerations to modify ultimate sample size
- E.g., Self-designing Trial (Fisher, 1998)
  - Prespecify weighting of groups "just in time"
    - Weighting for each group only need be specified at immediately preceding analysis

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Adaptive Sampling: The Price

Adaptive sampling plans are less efficient

- 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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Prespecified Sampling: The Price

Full knowledge of the sampling plan is needed to assess the full complement of frequentist operating characteristics

- In order to obtain inference with maximal precision and minimal bias, the sampling plan must be well quantified
- (Note that adaptive designs using ancillary statistics pose no special problems if we condition on those ancillary statistics.)

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Major Issue: Frequentist Inference

Frequentist operating characteristics are based on the sampling distribution

- Stopping rules do affect the sampling distribution of the usual statistics
  - MLEs are not normally distributed
  - Z scores are not standard normal under the null
    - (1.96 is irrelevant)
  - The null distribution of fixed sample P values is not uniform
    - (They are not true P values)

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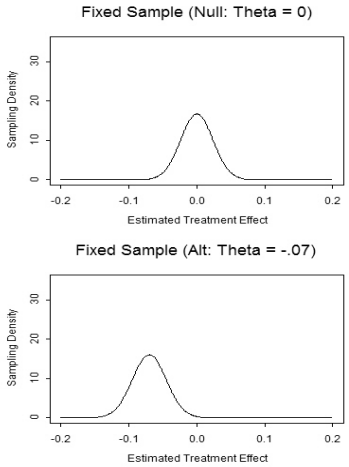
Sampling Distribution of Estimates



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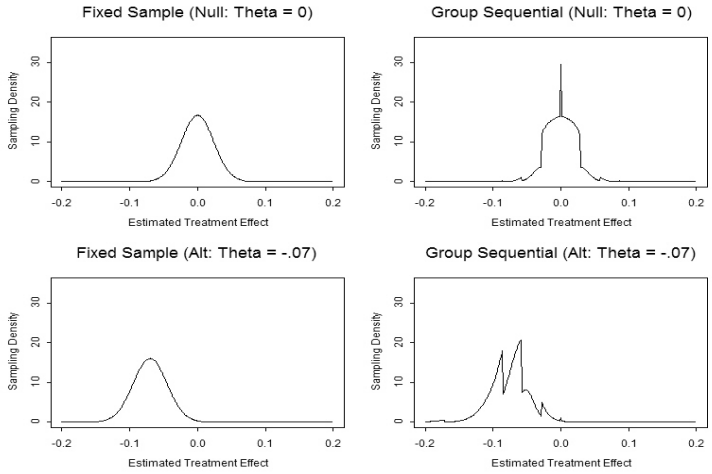
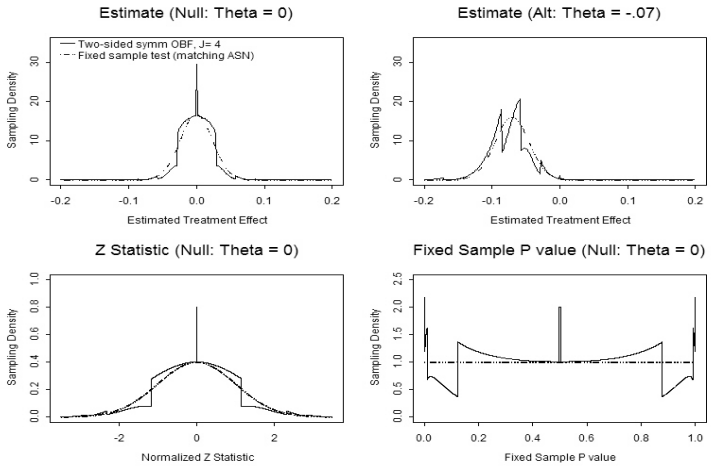
Sampling Distribution of Estimates



Sampling Distributions of Statistics



Operating Characteristics

For any stopping rule we can compute the correct sampling distribution and obtain

- Power curves
- Sample size distribution
- Bias adjusted estimates
- Correct (adjusted) confidence intervals
- Correct (adjusted) P values

- Candidate designs can then be compared with respect to their operating characteristics

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Sequential Sampling Issues

- Design stage
  - Satisfy desired operating characteristics
    - E.g., type I error, power, sample size requirements
- Monitoring stage
  - Flexible implementation of the stopping rule to account for assumptions made at design stage
    - E.g., sample size adjustment to account for observed variance
- Analysis stage
  - Providing inference based on true sampling distribution of test statistics

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Bottom Line

"You better think (think)
think about what you're
trying to do…"
- Aretha Franklin

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Frequentist Methods

Evaluation of
Group Sequential
Clinical Trial Designs

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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 ? < -0.07
  - Point estimate with low bias, MSE; 95% CI

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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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Operating Characteristics

Same general operating characteristics of interest no matter 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 each boundary
  - Frequentist point estimate, confidence interval, P value
- Futility measures
  - Conditional power, predictive power

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Evaluating Sample Size

Sample size a random variable

- Summary measures of 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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Evaluating Power Curve

Probability of rejecting null for arbitrary alternatives

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

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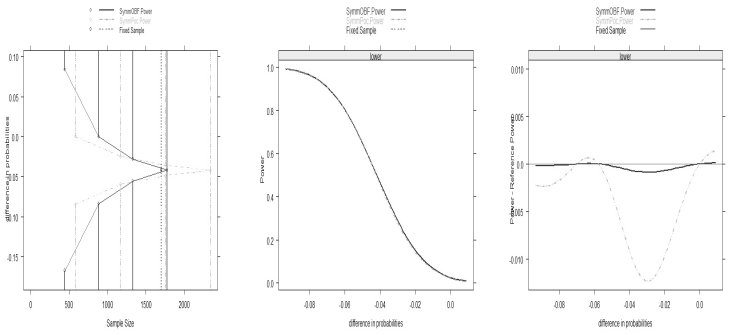
Case Study: Boundaries and Power Curves

O'Brien-Fleming, Pocock boundary shape functions when J= 4 analyses and maintain power



Case Study: Impact of Interim Analyses

Required increased maximal sample size in order to maintain power

- Maximal sample size with 4 analyses
  - O'Brien-Fleming: N= 1773 (4.3% increase)
  - Pocock : N= 2340 (37.6% increase)
- Need to consider
  - Average sample size
  - Probability of continuing past 1700 subjects
  - Conditions under which continue past 1700 subjects

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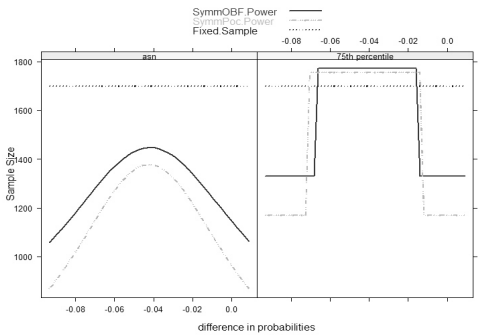
Case Study: ASN, 75th %tile of Sample Size

O'Brien-Fleming, Pocock boundary shape functions;J=4 analyses and maintain power



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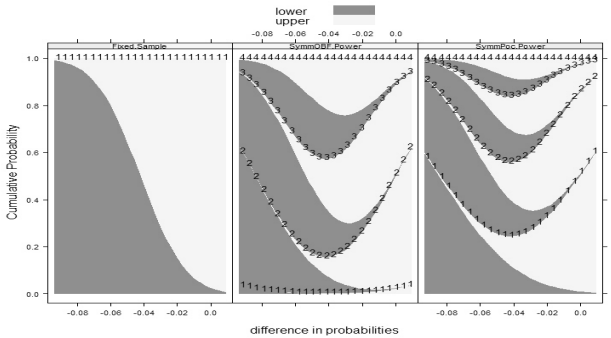
Case Study: Cumulative Stopping Probabilities

O'Brien-Fleming, Pocock boundary shape functions when J=4 analyses and maintain power



Case Study: Impact of Interim Analyses

Increased maximal sample size actually afforded better efficiency on average

- Pocock boundary shape function: lower ASN over range of alternatives examined
  - This improved behavior despite the 36.7% increase in maximal sample size
- Worst case behavior
  - O'Brien-Fleming: never more than N= 1773
  - Pocock continues past 1755 only if MLE for treatment effect is between -0.0357 and -0.0488
    - » Always less than 16.01% chance, which occurs when the difference in mortality is -0.0422

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Case Study: Sponsor's Preferences

Sponsor preferred not to increase maximal sample size beyond N= 1700

- When investigating the boundaries, the sponsor was surprised to find that a difference of -0.042 would be statistically significant
  - No one had informed the clinical and management teams of the boundary for the fixed sample test
  - Such an effect was only of borderline clinical importance

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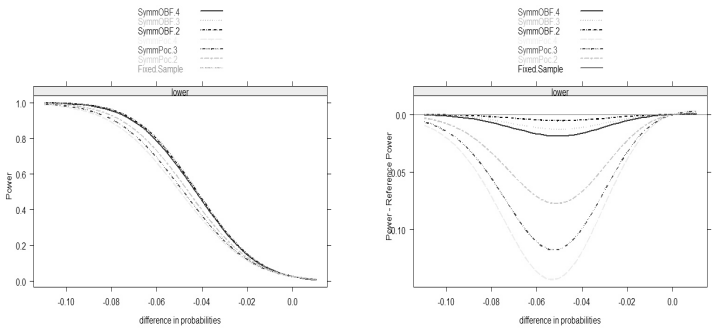
Case Study: Power Curves: Maintain N

OBF, Poc boundary shape functions when J= 2, 3, or 4 analyses and maintain N = 1700



Evaluating Boundaries

Stopping boundary at each analysis

- On the scale of estimated treatment effect **(DMC, Statisticians)**
  - Inform DMC of precision **(DMC)**
  - Assess ethics
    - » May have prior belief of unacceptable levels
  - Assess clinical, economic importance **(Clinicians, Marketing)**
- On the Z, fixed sample P value, or error spending scales **(Often asked for, but of questionable relevance)**

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Case Study: Tabled boundaries on MLE Scale

	Sample Size	Efficacy Boundary	Futility Boundary
O'Brien-Fleming			
Time 1	**425**	**-0.1710**	**0.0855**
Time 2	**850**	**-0.0855**	**0.0000**
Time 3	**1275**	**-0.0570**	**-0.0285**
Time 4	**1700**	**-0.0427**	**-0.0427**
Pocock			
Time 1	**425**	**-0.0991**	**0.0000**
Time 2	**850**	**-0.0701**	**-0.0290**
Time 3	**1275**	**-0.0572**	**-0.0419**
Time 4	**1700**	**-0.0496**	**-0.0496**
Fixed Sample			
Time 1	**1700**	**-0.0418**	**0.0418**

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Evaluating Inference

Inference on the boundary at each analysis

- Frequentist
  - Adjusted point estimates **(Scientists, Statisticians, Regulatory)**
  - Adjusted confidence intervals
  - Adjusted P values

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Case Study: Inference on the Boundaries

	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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Evaluating Futility

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 (Often asked for, but of questionable relevance)
  - Assume specific hypotheses
  - Assume current best estimate
- Predictive power
  - Assume Bayesian prior distribution

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Case Study: Futility Boundary

Sponsor desired greater efficiency when treatment effect is low

- Explored asymmetric designs with a range of boundary shape functions from unified family
  - P= 0.5 (Pocock), 0.8, 0.9, 1.0 (O'Brien-Fleming)
- Compare unconditional power and ASN curves
  - Rationale: Are we losing power by stopping early?
    - If not, then we are not making bad futility decisions on average

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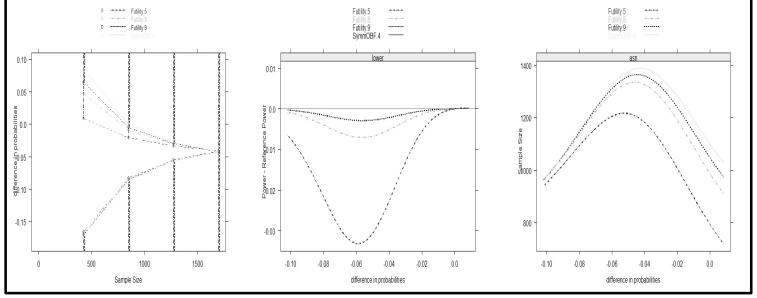
Case Study: Boundaries, Power, ASN Curves

O'Brien-Fleming efficacy, spectrum of futility boundaries; J= 4 analyses and N=1700

Boundaries Power (Relative to Symmetric OBF) ASN



Case Study: Sponsor's Futility Boundary

Sponsor opted for futility boundary based on P= 0.8

- Power – ASN tradeoff
  - Worst case loss of power .0071
    - (from 0.738 to 0.731 when difference in mortality is -0.0566)
  - 10.2% gain in average efficiency under null
    - (ASN from 1099 to 987 when difference in mortality is 0.00)

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Case Study: Stochastic Curtailment

We are sometimes asked about stochastic curtailment

- Boundaries can be expressed on conditional power and predictive power scales
  - Conditional power:
    - Probability of later reversing the potential decision at interim analysis by conditioning on interim results and presumed treatment effect
  - Predictive power:
    - Like conditional power, but use a Bayesian prior for the presumed treatment effect

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Case Study: Stochastic Curtailment

Key issue: Computations are based on assumptions about true treatment effect

- Conditional power
  - "Design": assume hypothesis being rejected
    - » (assumes observed data is relatively misleading)
  - "Estimate": assume that current data is representative
    - » (assumes observed data is exactly accurate)
- Predictive power
  - "Prior assumptions": Use Bayesian prior distribution
    - » "Sponsor": Centered at -0.07; plus/minus SD of 0.02
    - » "Noninformative"

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Case Study: Boundaries on Futility Scales

	Symmetric O'Brien-Fleming					O'Brien-Fleming Efficacy, P=0.8 Futility				
		Conditional Power		Predictive Power			Conditional Power		Predictive Power	
N	MLE	Design	Estimat	Sponsor	Noninf	MLE	Design	Estimat	Sponsor	Noninf
	Efficacy (rejects 0.00)					*Efficacy (rejects 0.00)*				
425	**-0.171**	**0.500**	**0.000**	**0.002**	**0.000**	**-0.170**	**0.500**	**0.000**	**0.002**	**0.000**
850	**-0.085**	**0.500**	**0.002**	**0.015**	**0.023**	**-0.085**	**0.500**	**0.002**	**0.015**	**0.023**
1275	**-0.057**	**0.500**	**0.091**	**0.077**	**0.124**	**-0.057**	**0.500**	**0.093**	**0.077**	**0.126**
	Futility (rejects -0.0855)					*Futility (rejects -0.0866)*				
425	**0.085**	**0.500**	**0.000**	**0.077**	**0.000**	**0.047**	**0.719**	**0.000**	**0.222**	**0.008**
850	**0.000**	**0.500**	**0.002**	**0.143**	**0.023**	**-0.010**	**0.648**	**0.015**	**0.247**	**0.063**
1275	**-0.028**	**0.500**	**0.091**	**0.241**	**0.124**	**-0.031**	**0.592**	**0.142**	**0.312**	**0.177**

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Case Study: Education of DMC, Sponsor

Very different probabilities based on assumptions about 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 .0001 probability of stopping for futility at the first analysis

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Stochastic Curtailment Comments

Neither conditional power nor predictive power have good foundational motivation

- Frequentists should use Neyman-Pearson paradigm and consider optimal unconditional power across alternatives
- Bayesians should use posterior distributions for decisions

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Stochastic Curtailment Comments

My experience

- I have consulted with many researchers on successive clinical trials
  - Often I am asked about stochastic curtailment the first time
  - Never have I been asked about it on the second trial

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Evaluating Marketable Results

Probability of obtaining estimates of treatment effect with clinical (and therefore marketing) appeal

- Modified power curve **(Marketing)**
  - Unconditional
  - Conditional at each analysis
- Predictive probabilities at each analysis

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Case Study: Marketability

Potential to have statistically significant treatment effect estimate of -0.06 or better

- O'Brien-Fleming efficacy boundary at third analysis:
  - Terminate if bias adjusted estimate -0.055 or better
  - What is the chance of obtaining -0.06 or better at the fourth analysis if study continues?
    - If true effect is -0.07, probability of 4.1% of BAM < -0.06
    - If true effect is -0.06, probability of 3.6% of BAM < -0.06

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Case Study: Modification for Marketability

Modify third analysis efficacy boundary to correspond to BAM of -0.06 or better

- Probability of BAM < -0.06 increases
  - If true effect is -0.07: from 66.6% to 68.6%
  - If true effect is -0.06: from 50.4% to 54.0%

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Final Comments

Adaptive designs versus prespecified stopping rules

- Adaptive designs come at a price of efficiency
- With careful evaluation of designs, there is little need for adaptive designs
  - Everything I showed today was known prior to collecting any data in the clinical trial
  - Prespecified stopping rules can be chosen which find best tradeoffs among the various collaborators' optimality criteria

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Limitations of Foregoing

We have not yet verified that the clinical trial design will be judged credible by a sufficiently large segment of the scientific community

- Bayesians do not regard frequentist inference as relevant
- We thus need to consider how to evaluate the Bayesian operating characteristics

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Bayesian Methods

Bayesian Paradigm

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Hallmark of Frequentist Inference

Frequentist inference considers the distribution of the data conditional on a presumed (fixed) treatment effect

Power curve : $\pi(\theta) = \Pr(\hat{\theta} > c_{\theta_0, 1-\alpha} \mid \theta)$

CI for $\hat{\theta}$: $\hat{\theta} \pm z_{1-\frac{\alpha}{2}} \cdot \widehat{SE}(\hat{\theta})$ where $\widehat{SE}(\hat{\theta}) = \frac{\hat{\theta}}{z_{1-\frac{\alpha}{2}}}$

Unbiased estimates : $E(\hat{\theta} \mid \theta) = \theta$

Efficient estimates : minimize $Var(\hat{\theta} \mid \theta)$

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Bayesian Paradigm

In the Bayesian paradigm, the parameter measuring treatment effect is regarded as a random variable

- A prior distribution for θ reflects
  - Knowledge gleaned from previous trials, or
  - Frequentist probability of investigators' behavior, or
  - Subjective probability of treatment effect

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Posterior Distribution

Bayes' rule is used to update beliefs about parameter distribution conditional on the observed data

$$p(\theta \mid X, Y) = \frac{p(X, Y \mid \theta)\, p(\theta)}{\int p(X, Y \mid \theta)\, p(\theta)\, d\theta}$$

where

$p(\theta)$ is a prior distribution for θ

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Bayesian Inference

Bayesian inference is then based on the posterior distribution

- Point estimates:
  - A summary measure of the posterior probability distribution (mean, median, mode)
- Interval estimates:
  - Set of hypotheses having the highest posterior density
- Decisions (tests):
  - Reject a hypothesis if its posterior probability is low
  - Quantify the posterior probability of the hypothesis

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Information Required for Inference

Information required for inference

- Frequentist
  - Tests: need the sampling distribution under the null
  - Estimates: need the sampling distribution under all hypotheses
- Bayesian
  - Tests and estimates: need the sampling distribution under all hypotheses and a prior distribution

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Frequentist vs Bayesian

- Frequentist
  - A precise (objective) answer to not quite the right question
  - Well developed nonparametric and moment based analyses (e.g., GEE)
  - Conciseness of presentation
- Bayesian
  - A vague (subjective) answer to the right question
  - Adherence to likelihood principle in parametric settings (and coarsened approach)

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Example: 4 Full Houses in Poker

Bayesian:

- Knows the probability that I might be a cheater based on information derived prior to observing me play
- Knows the probability that I would get 4 full houses for every level of cheating that I might engage in
- Computes the posterior probability that I was not cheating (probability after observing me play)
- If that probability is low, calls me a cheater

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Example: 4 Full Houses in Poker

Frequentist:

- –Hypothetically assumes I am not a cheater
- –Knows the probability that I would get 4 full houses if I were not a cheater
- –If that probability is sufficiently low, calls me a cheater
  - Even if the frequentist dealt the cards!

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Frequentist AND Bayesian

I take the view that both approaches need to be accomodated in every analysis

- •Goal of the experiment is to convince the scientific community, which likely includes believers in both standards for evidence
- •Bayesian priors should be chosen to reflect the population of priors in the scientific community

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Unified Approach

Joint distribution for data and parameter

$$p(X, Y, \theta)$$

Frequentist considers

$$p(X, Y \mid \theta)$$

Bayesian considers

$$p(\theta \mid X, Y)$$

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Issues to be Addressed

Choice of probability model for data

- For unified approach to make sense, the frequentist and Bayesian should use the same conditional distribution of the data
  - – "Law of the Unconscious Frequentist":
    - Gravitate toward models with good nonparametric behavior

Choice of prior distributions

- Everyone brings their own

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Bayesian Methods

Probability Models

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Probability Models

Parametric, semiparametric, and nonparametric models for two samples

- My definition of semiparametric models is a little stronger than some statisticians
  - The distinction is to isolate models with assumptions that I think too strong
- Notation for two sample probability model

$$\text{Treatment}: \quad X_1, \ldots, X_n \overset{iid}{\sim} F$$

$$\text{Control}: \quad Y_1, \ldots, Y_m \overset{iid}{\sim} G$$

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Parametric Models

F, G are known up to some finite dimensional parameter vectors

$$F(t) = F(t, \theta_X)$$

$$G(t) = G(t, \theta_Y)$$

where:

$\theta = (\theta_X, \theta_Y)$ has known form

θ is finite dimensional and unknown

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Parametric Models: Examples

Normal: $X_i \sim N(\mu_X, \sigma_X^2)$ $Y_j \sim N(\mu_Y, \sigma_Y^2)$

Bernoulli: $X_i \sim B(1, \pi_X)$ $Y_j \sim B(1, \pi_Y)$

Exponential: $X_i \sim E(\lambda_X)$ $Y_j \sim E(\lambda_Y)$

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Semiparametric Models

Forms of F, G are unknown, but related to each other by some finite dimensional parameter vector

- G can be determined from F and a finite dimensional parameter
- (Most often: Under the null hypothesis, F = G)

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Semiparametric Models: Notation

$F(t) = F(t, \theta_X)$

$G(t) = G(t, \theta_Y)$

where:

$\theta = (\theta_X, \theta_Y)$ has unknown form (in t)

θ_X is finite dimensional and known (identifiability)

θ_Y is finite dimensional and unknown

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Semiparametric Models: Examples

Shift: $G(t) = F(t - \theta)$

Shift-scale: $G(t) = F\left(\frac{t - \theta_1}{\theta_2}\right)$

Accel failure: $G(t) = F(\theta t)$

Prop hzd: $1 - G(t) = [1 - F(t)]^{\theta}$

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Nonparametric Models

Forms of F, G are completely arbitrary and unknown

- An infinite dimensional parameter is needed to derive the form of G from F
- (Sometimes we consider "nonparametric families with restrictions", e.g., stochastic ordering)

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A Logical Disconnect

"Because the light is so
much better
here under the streetlamp"

- a drunk looking for the keys
he lost half a block away

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History

In the development and (especially) teaching of statistical models, parametric models have received undue emphasis

- Examples:
  - t test is typically presented in the context of the normal probability model
  - theory of linear models stresses small sample properties
  - random effects specified parametrically
  - Bayesian (and especially hierarchical Bayes) models are replete with parametric distributions

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The Problem

Incorrect parametric assumptions can lead to incorrect statistical inference

- Precision of estimators can be over- or understated
  - Hypothesis tests do not attain the nominal size
- Hypothesis tests can be inconsistent
  - Even an infinite sample size may not detect the alternative
- Interpretation of estimators can be wrong

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Inflammatory Assertion

(Semi)parametric models are not typically in keeping with the state of knowledge as an experiment is being conducted

- The assumptions are more detailed than the hypothesis being tested, e.g.,
  - Question: How does the intervention affect the first moment of the probability distribution?
  - Assumption: We know how the intervention affects the 2nd, 3rd, …, 8 central moments of the probability distribution.

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Foundational Issues: Null

Which null hypothesis should we test?

- The intervention has no effect whatsoever

$$H_0 : F(t) ? G(t), ? t$$

- The intervention has no effect on some summary measure of the distribution

$$H_0 : ? \; ? ? _0$$

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Foundational Issues: Alternative

What should the distribution of the data under the alternative represent?

- Counterfactual
  - An imagined form for *F(t), G(t)* if something else were true
- Empirical
  - The most likely distribution of the data if the alternative hypothesis about ? were true

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My Views

The null hypothesis of greatest interest is rarely that a treatment has no effect

- Bone marrow transplantation
- Women's Health Initiative
- National Lung Screening Trial

The empirical alternative is most in keeping with inference about a summary measure

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An Aside

The above views have important ramifications regarding the computation of standard errors for statistics under the null

- Permutation tests (or any test which presumes *F=G* under the null) will generally be inconsistent

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Problem with (Semi)parametrics

Many mechanisms would seem to make it likely that the problems in which a fully parametric model or even a semiparametric model is correct constitute a set of measure zero

•Exception: independent binary data must be binomially distributed in the population from which they were sampled randomly (exchangeably?)

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Supporting Arguments

Example 1: Cell proliferation in cancer prevention

- Within subject distribution of outcome is skewed (cancer is a focal disease)
- Such skewed measurements are only observed in a subset of the subjects
- The intervention affects only hyperproliferation (our ideal)

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Supporting Arguments

Example 2: Treatment of hypertension

- Hypertension has multiple causes
- Any given intervention might treat only subgroups of subjects (and subgroup membership is a latent variable)
- The treated population has a mixture distribution
  - (and note that we might expect greater variance in the group with the lower mean)

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Supporting Arguments

Example 3: Effects on rates

- The intervention affects rates
- The outcome measures a cumulative state
- Arbitrarily complex mean-variance relationships can result

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A Non-Solution: Model Checking

Model checking is apparently used by many to allow them to believe that their models are correct.

- From a recent referee's report:
  - "I know of no sensible statistician (frequentist or Bayesian) who does not do model checking."
- Apparently the referee believes the following unproven proposition:
  - If we cannot tell the model is wrong, then statistical inference under the model will be correct

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A Non-Solution: Model Checking

Counter example: Exponential vs Lognormal medians

- Pretest with Kolmogorov-Smirnov test (n=40)
  - Power to detect wrong model
    - 20% (exp); 12% (lnorm)
  - Coverage of 95% CI under wrong model
    - 85% (exp); 88% (lnorm)

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A Non-Solution: Model Checking

Model checking particularly makes little sense in a regulatory setting

- Commonly used null hypotheses presume the model fits in the absence of a treatment effect
  - Frequentists would be testing for a treatment effect as they do model checking
- Bayesians should model any uncertainty in the distribution
  - Interestingly, if one does this, the estimate indicating parametric family will in general vary with the estimate of treatment effect

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Impact on Statistical Optimality

Impact on what we teach about optimality of statistical models

- Clearly, parametric theory may be irrelevant in an exact sense (though as guidelines it is still useful)
- Much of what we teach about the optimality of nonparametric tests is based on semiparametric models
  - e.g., Lehmann, 1975: location-shift models

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Example: Wilcoxon Rank Sum Test

Common teaching:

- A nonparametric alternative to the t test
- Not too bad against normal data
- Better than t test when data have heavy tails
- (Some texts refer to it as a test of medians)

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Example: Wilcoxon Rank Sum Test

More accurate guidelines:

- In the general case, the t test and the Wilcoxon are not testing the same summary measure
  - Wrong size as a test of *Pr(X > Y)* unless you assume a semi-parametric model on some scale
  - Inconsistent test of *F(t) = G(t)*
  - (And the Wilcoxon is not transitive)
- Efficiency results when a shift model holds for some monotonic transformation of the data
  - If propensity to outliers is different between groups, the t test may be better even with heavy tails
- (The variance can be modified to achieve consistency)

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Nonparametric Approach

The summary measure (functional) measuring treatment effect is just some difference between distributions

$$? \; ? \; d?F, G?$$

•(Almost always, the problem is ultimately reduced to a 1-dimensional statistic)

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Comparison of Summary Measures

Typical approaches to compare response across two treatment arms

- Difference / ratio of means (arithmetic, geometric, …)
- Difference / ratio of medians (or other quantiles)
- Median difference of paired observations
- Difference / ratio of proportion exceeding some threshold
- Ratio of odds of exceeding some threshold
- Ratio of instantaneous risk of some event
  - » (averaged across time?)
- Probability that a randomly chosen measurement from one population might exceed that from the other
- …

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Goal

We thus want to find nonparametric models which

- Include commonly chosen parametric models
- Can be implemented in a Bayesian setting

It is useful to consider how (semi)parametric models are actually used

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Statistical Models

How are (semi)parametric assumptions really used in statistical models?

- Choice of functional for comparisons
- Formula for computing the estimate of the functional
- Distributional family for the estimate
- Mean-variance relationship across alternatives
- Shape of distribution for data

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Choice of Functional

•Parametric: Driven by efficiency of functional for the particular parametric family

- Normal: use mean
- Lognormal: use (log) geometric mean
- Double exponential: use median
- Uniform: use maximum

•Semiparametric: Choose functional for scientific relevance, etc., then adopt a semiparametric model in which desired functional is basic to model

- Survival data: consider hazard ratio and use proportional hazards

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Choice of Functional

Better bases for choosing summary measure for decisions in order of importance (nonparametric)

- Current state of scientific knowledge
- Scientific (clinical) relevance
- Potential for intervention to affect the measure
- Statistical accuracy and precision of analysis

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Statistical Models

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Computing Estimates

- Parametric: Estimate parameters and then derive summary measures from parametric model
  - E.g., estimating the median
    - Normal: estimate mean; median=mean
    - Exponential: estimate mean; median = mean / log(2)
    - Lognormal: estimate geometric mean; median = geometric mean

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Computing Estimates

- Semiparametric:
  - Parameter is fundamental to probability model
  - Use both groups to estimate parameter using the assumption that we can transform one group by the parameter and obtain the same distribution as the other group
    - E.g., proportional hazards model
      - » Hazard ratio estimate is average of hazard ratios at each failure time

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(Semi)parametric Example

Survival cure model (Ibrahim, 1999, 2000)

- Probability model
  - Proportion p_i is cured (survival probability 1 at 8) in the i-th treatment group
  - Noncured group has survival distribution modeled parametrically (e.g., Weibull) or semiparametrically (e.g., proportional hazards)
  - Treatment effect is measured by ? = $p_1 - p_0$
- The problem as I see it: Incorrect assumptions about the nuisance parameter can bias the estimation of the treatment effect

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Computing Estimates

- Nonparametric: Estimate summary measures from nonparametric empirical distribution functions
  - E.g., use sample median for inference about population medians
  - Often the nonparametric estimate agrees with a commonly used (semi)parametric estimate
    - Interpretation may depend on sampling scheme
    - In this case, the difference will come in the computation of the standard errors

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Statistical Models

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Distribution for Estimate

- Parametric: Use probability theory to derive distribution of estimate
  - E.g., estimating the median
    - Normal: sample mean is normal
    - Exponential: sum is gamma
    - Lognormal: log geometric mean is normal
- Semiparametric:
  - Small sample properties: Conditional distributions based on permutation
  - Large sample properties: Asymptotics

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Distribution for Estimate

- Nonparametric: Asymptotic normal theory (almost always)
  - Most nonparametric estimators involve a sum somewhere
  - Central limit theorem holds (like it or not)
    - Thus gamma distributions converge to a normal…

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Statistical Models

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- Shape of distribution for data

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Mean-Variance Relationships

Asymptotically, most summary measures have a limiting normal distribution (exception is the supremum of the difference between the cdf's)

- In this setting, we need only estimate the variance of the sampling distribution under specific hypotheses
  - Formulas
  - Bootstrapping within groups (Population model)
  - Permutation distributions (Randomization model)

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Asymptotic Distributions

$$\overline{X} \sim N\left(\mu, \frac{\sigma^2}{n}\right)$$

$$X_{0.5} \sim N\left(mdn(X), \frac{1}{4 f^2 mdn(X)}\right)$$

$$U = \sum_{i,j} 1_{[X_i > Y_j]} \overset{H_0}{\sim} N\left(\frac{mn}{2}, \frac{mn(m+n+1)}{12}\right)$$

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Mean-Variance Relationships

In most cases, however, it must be recognized that we can only estimate the variance under the truth, which may not correspond to a hypothesis of interest

- If the intervention can affect the variance of the summary measures, then we must account for a mean-variance relationship when considering different hypotheses

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Mean-Variance Relationships

Example: Two sample test of binomial proportion

$$\hat{p}_X \sim \left(p_X, \frac{p_X(1-p_X)}{n}\right) \quad \hat{p}_Y \sim \left(p_Y, \frac{p_Y(1-p_Y)}{m}\right)$$

$$Var(\hat{p}_X - \hat{p}_Y) = \frac{p_X(1-p_X)}{n} + \frac{p_Y(1-p_Y)}{m}$$

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Example: Estimating Variances

Two sample test of binomial proportion

- Estimated variance is subject to
  - –Sampling variability
  - –Difference between the truth and the hypothesis

$$\widehat{Var}(\hat{p}_X - \hat{p}_Y) = \frac{\hat{p}_X(1-\hat{p}_X)}{n} + \frac{\hat{p}_Y(1-\hat{p}_Y)}{m}$$

$$\widehat{Var}_0(\hat{p}_X - \hat{p}_Y) = \frac{\bar{p}(1-\bar{p})}{n} + \frac{\bar{p}(1-\bar{p})}{m}$$

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Estimating Mean-Variance

Estimating mean variance relationships

- – May not be too important for frequentist tests of the null hypothesis, because convention often dictates the null variance we should use
  - Use randomization and/or population variances in adversarial argument
- However confidence intervals and all Bayesian inference are statements about what data would arise under a variety of hypotheses
  - We must have some idea about how the variance might change with the mean

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Mean-Variance Relationship

Possible approaches to the mean-variance relationship estimation

- Explore various mean-variance relationships
  - – Bootstrap tilting could be used here

$$Var(\hat{p}_X - \hat{p}_Y) = \ldots = r$$

- Assume no mean-variance relationship
- Sensitivity analyses intermediate to the two

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Mean-Variance Relationship

A key issue is deciding how many observations are present for estimating the mean-variance relationship

- If the control group can be used to estimate behavior under the null and the treatment group under the alternative, then possibly have two
- If an active intervention modifies the response in both groups or in population model, then may only have one

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Statistical Models

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- Distributional family for the estimate
- Mean-variance relationship across alternatives
- Shape of distribution for data

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Statistical Models

Shape of distribution for data

- Only really an issue for prediction, which is not considered here

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Bayesian Methods

Nonparametric
Bayesian Models

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Possible Approaches

Nonparametric Bayesians have focussed primarily on Dirichlet process priors

- Prior placed on all multinomial distributions
- Can be chosen to include all distributions

Interpretation of priors is extremely difficult

- How much mass is placed on bimodal distributions?

Correspondence with frequentist methods?

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"Coarsened" Data Approach

Modification for nonparametric models

- Use summary measure estimate as the data
  - Use asymptotic distributions under population model

$$p(\theta \mid \hat{\theta}) = \frac{p(\hat{\theta} \mid \theta)\,\pi(\theta)}{\int p(\hat{\theta} \mid \theta)\,\pi(\theta)\,d\theta}$$

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Impact of Coarsening Data

If

- the parameter estimate is the sufficient statistic,
- if the estimate is approximately normal, and
- the mean-variance relationship is correct

Then

- the only difference is using the approximate normal distribution instead of the parametric form

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Advantage of Coarsening Data

- Same probability model typically used by frequentists
  - Robust inference about summary measure
- Specification of prior distributions on the parameter of interest
  - Choice of conjugate normals allows conciseness of presentation using contour plots

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Concise Reporting of Results

The chief advantage of frequentist inference (to my mind) is that it presents a standard for concise presentation of results

- Estimates, standard errors, P values, CI

Bayesian analysis requires such a presentation for every prior

- Your prior does not matter to me
- A consensus prior will not capture the diversity of prior opinion

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Sensitivity Analysis Across Priors

In the context of the coarsened Bayes approach, we can adopt a standard based on conjugate normal priors

- Two dimensional space of prior distributions
  - Prior mean (pessimism)
  - Prior standard deviation (dogmatism)
    - Also can be measured as information in prior relative to that in planned sample

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Sensitivity Analysis Across Priors

- Bayesian inference as a contour plot for each inferential quantity
  - Posterior mean
  - Limits of credible intervals
  - Posterior probabilities
- Under sequential sampling, present contour plots for each analysis time

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Case Study: Posterior Mean at Second Analysis

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Case Study: Posterior Probability of Hypotheses

Nonparametric Bayesian Models

Advantages and disadvantages of such sensitivity analyses

- To the extent that people can only describe the first two moments of their prior:
  - A convenient standard for presentation
  - But, normal prior is less informative than other priors having the same mean and variance

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Mean-Variance Relationship

Mean-variance relationship

- Provide a prior distribution for summary measure that incorporates a prior on the mean-variance relationship
- Note that the concept of updating the prior is probably not valid here, because there is really no added information about mean-variance relationship
  - The mean variance relationship is observed at two points (at most)

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Nonparametric Bayesian Models

Ramifications

- The approach to using estimates as the data does mean that in some cases we cannot regard that we are continually updating our posterior
  - E.g.: The sample median of the combined sample is not necessarily a weighted mean of the sample median from two separate samples

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Secondary Endpoints

The approach proposed here requires a graph for every number that would have been reported in a frequentist analysis

- I doubt many editors will agree

It should be clear, however, that the frequentist nonparametric estimate and standard error are sufficient for a reader to perform his/her own sensitivity analysis

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Final Comments

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Final Comments

The driving force in a clinical trial should be a valid scientific experiment in an ethical manner

- The approach proposed here has placed greatest emphasis on
  - robustness, and
  - communicability (concise standards)

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Final Comments

There are many aspects which could be improved

- Behavior of estimates for mean-variance relationship
  - Empirical approaches
- Robustness to "model misspecification"
  - e.g., linear contrasts used with nonlinear trends
- Adjustment for covariates

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Final Comments

There are some important issues not really addressed at all

- Time-varying treatment effects
  - Nonproportional hazards
  - Longitudinal data

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