Clinical Trials
Definition and Motivation
Public Health Objective
Statistical foundations
Trial Monitoring: Motivation and Implications

Introduction to the Design and Evaluation of Group Sequential Clinical Trials

Session 1 - Scientific Setting

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Overview

Module 9: Introduction to the Design and Evaluation of Group Sequential Clinical Trials

Session 1: Scientific setting
Session 2: Fixed-sample design
Session 3: Evaluation of group sequential clinical trial designs
Session 4: Bayesian evaluation of group sequential clinical trial designs

Clinical Trials: Definition

A clinical trial is

- A planned experiment which involves patients that is designed to elucidate the most appropriate treatment of future patients. (Pocock, 1983)
- A planned experiment designed to assess the efficacy of a treatment in humans by comparing the outcomes in a group of patients treated with those observed in a comparable group of patients receiving a control treatment, where patients in both groups are enrolled, treated, and followed over the same time period. (Minert, 1986)

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Clinical Trials: Definition

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Types of questions that can be evaluated in clinical trials

- Therapeutic intervention studies:
  - Safety: Is risk of treatment-related toxicities suitably low?
  - Efficacy: Treatment benefits on disease processes?
  - Effectiveness: Does the treatment offer benefits when used as part of standard routine practice?
- Non-therapeutic intervention studies:
  - Mechanistic studies: Studies of drug mechanism of action.
  - Behaviorial interventions: Examples: Smoking cessation; diabetes prevention.
  - Prevention studies: Examples: Women's Health Initiative (HRT for prevention of cardiovascular disease); lung cancer screening trial.
  - Community intervention studies: Interventions on schools to promote healthy lifestyles.
- Our focus in this course is on medical intervention studies.

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Clinical Trials: Definition

Clinical trials as experiments

- As scientific experiments clinical trials must:
  - Answer a scientifically meaningful questions.
    - Must discriminate between viable hypotheses
  - Provide results that inform (convince) medical practice.
    - Use valid materials and methods
    - Use valid measurement of the experimental outcome
    - Provide a valid quantification of uncertainty in the experiment.

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Clinical Trials: Definition

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As experiments on humans clinical trials must:

- Be ethically justifiable for the individuals entering the trial:
  - As much as possible, minimize harm and maximize benefit for individuals in the trial.
  - Avoid giving individual participants harmful treatments.
  - Avoid giving individual participants inferior treatments.
- Maintain the ethical responsiveness to all likely future recipients of the therapy under evaluation:
  - Identify (and approve) new beneficial therapies.
  - Avoid approving ineffective or harmful treatments.
  - Avoid unnecessary delays in the evaluation process.

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Public Heath Objective in Clinical Trials

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Public Health Objective

- Evidence-based medicine requires:
  - Results in the sample reflect effects in standard practice.
    - Does the trial population reflect the target population?
    - Do diagnostic procedures reflect standard practice?
    - Does ancillary/rescue therapy reflect standard practice?
- (Reiterating) Our ultimate goal should be to:
  - Identify (and approve) new beneficial therapies.
  - Avoid approving ineffective or harmful treatments.

The Public Health Objective

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Our objective is to have trials with high positive predictive value

- Positive predictive value (PPV):
  - *Diagnostic testing:* prevalence of diseased individuals among those with a positive diagnostic test.
  - *Clinical trials:* prevalence of truly beneficial therapies among those which are identified by a positive clinical trial.
  - PPV is calculated using Bayes rule:

$$PPV = \frac{\beta\pi}{\beta\pi + \alpha(1-\pi)}$$

where :

$$\begin{aligned} \beta &= \textit{sensitivity} \\ 1-\alpha &= \textit{specificity} \\ \pi &= \textit{prevalence} \end{aligned}$$

The Public Health Objective

Clinical trials as diagnostic tests

- The statistical hypothesis test is a diagnostic test for beneficial treatments.
  - α-level: probability of observing a positive (statistically significant) test in absence of a true treatment effect:
    - Level of significance is 1 - specificity.
    - Choosing $\alpha = 0.05$ gives 95% specificity.
  - Statistical power (β): Probability of observing a positive (statistically significant) test when there is a true treatment effect:
    - Power is sensitivity.
    - 80% sensitivity is a common (though not ideal) choice.
  - Prevalence (π_0): the percentage of effective treatments among all tested treatments.
  - Positive predictive value: probability that a statistically significant trial indicates a truly effective treatment.

$$PPV = \frac{\beta\pi_0}{\beta\pi_0 + \alpha(1-\pi_0)}$$

The Public Health Objective: How does the design determine PPV?

PPV is increased through good experimental practice

$$PPV = \frac{\beta\pi_0}{\beta\pi_0 + \alpha(1-\pi_0)}$$

* Increase π_0:
  - Careful planning of preliminary studies
  - Avoid "novel" and "innovative" ideas
  - Careful specification of hypothesis-driven research
* Increase β:
  - Good practice (no missing data, low variation in outcome assessment, good adherence, etc.)
  - Increase sample size.
* Reduce α:
  - Pre-specify outcomes
  - Pre-specify all analyses
  - Avoid multiple comparisons
  - Avoid surrogate outcomes.
  - Avoid subgroups

The Public Health Objective: How does the design determine PPV?

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References: PPV as a function of π_0, α, and β

** *EfficiencyForTargetedTX.pdf* discusses effect of power (sensitivity) and α-level (specificity) on the PPV of phase II/III clinical trials.

Scenario	Number of trials	π_0	Phase II trials α_2	Phase II trials β_2	Phase III trials α_3	Phase III trials β_3	Pos	Pos	PPV
1	1000	0.10	*	*	0.05	0.975	98	45	0.685
2	12500	0.10	0.05	0.15	0.05	0.800	150	28	0.842
3	11765	0.20	0.05	0.15	0.05	0.800	282	24	0.923
4	13245	0.01	0.05	0.15	0.05	0.800	16	33	0.327
5	9091	0.10	0.05	0.15	0.05	0.975	133	20	0.867
6	15385	0.10	0.05	0.15	0.05	0.500	115	35	0.769
7	6780	0.10	0.20	0.15	0.05	0.800	81	61	0.571
8	6780	0.10	0.20	0.15	0.10	0.800	81	122	0.400

** *Evaluation of Strategies for the Phase II to Phase III Progression in Treatment Discovery*:
(Sanchez, 2014) http://rctdesign.org/TechReports/SanchezThesis201404.pdf

The Public Health Objective How do clinical trials determine PPV?

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Summary remarks

- A wide range of situations/therapies are studied in trials.
- Globally, clinical trials need to assure:
  - Scientific credibility
  - Ethical experiments
  - Efficient experiments:
    - Minimize time
    - Minimal number of extra subjects
    - Minimize cost
  - A high prevalence of truly beneficial therapies among all therapies used in routine care.

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Evidence-based practice

- As a scientific experiment, the results of a clinical trial are used to rule out (or rule in) hypotheses about treatment effects.
- The standards for rejecting (or accepting hypotheses) are based on statistical criteria.
- Clinical trial designs should be evaluated by the potential inference upon trial completion.

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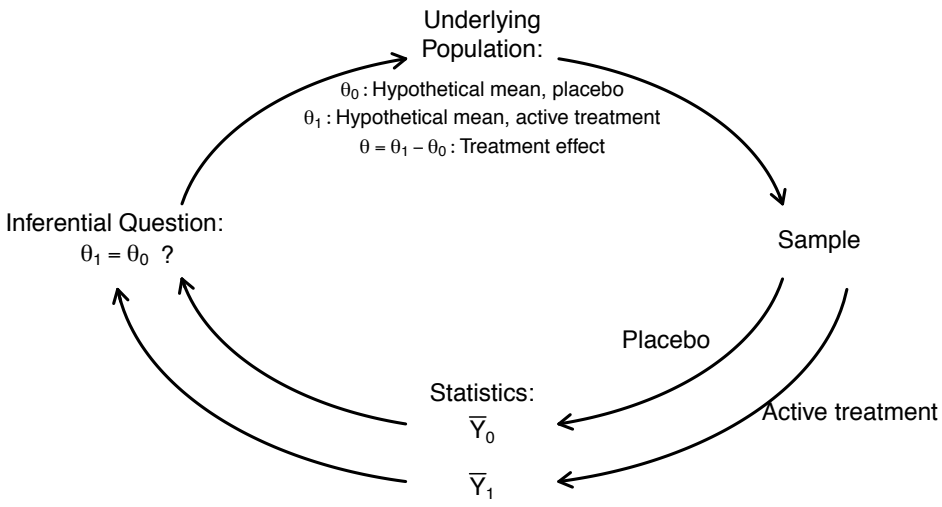
Recall Empirical Objective:

Use observed trial result ($\hat{\theta}$) to make inference about underlying population θ



Statistical foundations

Four main inferential elements

1. Point estimate: $\hat{\theta}$ is the “best" estimate of θ.
2. Interval estimate: Values of θ that are consistent with the trial results.
3. Expression of uncertainty (p-value): To what degree is a particular hypothesis (the “null" hypothesis) consistent with the observed trial results?
4. Decision: Based on the above measures, what decision should be reached about the use of a new therapy?

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Trial monitoring

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Why monitor a clinical trial?

- Monitoring for quality control; for example,
  - Patient accrual.
  - Data quality/completeness.
  - Unanticipated adverse events.
- Monitoring study endpoint(s); for example,
  - Treatment benefits.
  - Toxicity differences.
- Good quality control should be part of every study to ensure that the study achieves its goals.
- Monitoring study endpoints is not applicable in every study, and requires special statistical methods to avoid increased statistical errors.

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Elements of trial monitoring

Reasons to monitor trial endpoints

- To maintain the validity of the informed consent for:
  - Subjects currently enrolled in the study.
  - New subjects entering the study.
- To ensure the ethics of randomization.
  - Randomization is only ethical under equipoise.
  - If there is not equipoise, then the trial should stop.
- To identify the best treatment as quickly as possible:
  - For the benefit of all patients (i.e., so that the best treatment becomes standard practice).
  - For the benefit of study participants (i.e., so that participants are not given inferior therapies for any longer than necessary).

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Elements of trial monitoring

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Monitoring trial endpoints

Monitoring endpoints must be done properly to avoid bias:

- Data driven analyses cause bias:
  - Analyzing study results because they look good leads to an overestimate of treatment benefits.
- Publication/presentation of ‘preliminary results’ can affect:
  - Ability to accrue subjects.
  - Type of subjects that are referred and accrued.
  - Treatment of patients not in the study.
- Failure to design for interim analyses can lead to hasty decisions subject to:
  - Inadequate consideration of trade-offs between competing endpoints (toxicity versus benefit).
  - External pressures from study investigators or sponsors.
  - Lack of objectivity by study monitors.

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Elements of trial monitoring

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Monitoring trial endpoints

Thus:

- Monitoring of study endpoints is often required for ethical reasons.
- Monitoring of study endpoints must carefully planned as part of study design to:
  - Avoid bias
  - Assure careful decisions
  - Maintain desired statistical properties

Elements of trial monitoring

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How are trials monitored?

- “Data Safety and Monitoring Boards (DSMB)" are used to avoid biased decisions:
  - DSMB members are *independent* of the study investigators
  - The DSMB reviews unblinded data in the midst of a trial to:
    - Assure the trial is safe to continue.
    - Make decisions about early termination based on the statistical monitoring plan (“group-sequential clinical trial design").
- DSMB composition:
  - Subject-matter specialists (2-4)
  - Biostatistician (1-2).

Elements of trial monitoring

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Trial monitoring plan

Trial monitoring plan is typically pre-specified in 2 documents:

- DSMB charter:
  - Defines scope of trial monitoring
  - Defines DSMB responsibilities
  - Defines sponsor responsibilities
  - Pre-specifies monitoring plans and decisions (reasons for stopping)
- Interim Statistical Analysis Plan (ISAP):
  - Defines monitoring endpoint(s)
  - Pre-specifies analysis timing, decision criteria, and rationale
  - Pre-specifies methods for implementation (changes to analysis timing)
  - Pre-specifies adjustments to statistical inference about treatment effects

Monitoring the primary endpoint: Illustration of statistical implications

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Illustration setting (trial design):

Consider a clinical trial evaluating *superiority* of a new agent:

- Measure of treatment effect ($\theta = \theta_1 - \theta_0$) defined based on fixed-sample design:
  - Primary endpoint
  - Probability model
  - Functional
  - Contrast
  - Statistical hypotheses
  - Statistical standards for decisions (i..e., frequentist or Bayes)
- Suppose large values of θ denote superiority of the new agent.

Monitoring the primary endpoint: Illustration of statistical implications

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Illustration setting (interim analysis plan):

- Suppose that the trial is planned with interim analyses after outcomes are measured on $N_1 < N_2 < ... < N_J$ participants.
- Let $\hat{\theta}_j$ denote the estimated treatment effect at the jth analysis ($j = 1, ..., J$).
- Consider stopping criteria $a_j < d_j$ with:

$$\begin{aligned} \hat{\theta}_j \geq d_j &\Rightarrow \text{Decide new treatment is superior} \\ \hat{\theta}_j \leq a_j &\Rightarrow \text{Decide new treatment is not superior} \\ a_j < \hat{\theta}_j < d_j &\Rightarrow \text{Continue trial} \end{aligned}$$

Set $a_J = d_J$ so that the trial stops by the Jth analysis.

Illustration of statistical implications

Example: O'Brien-Fleming (OBF) 2-sided design

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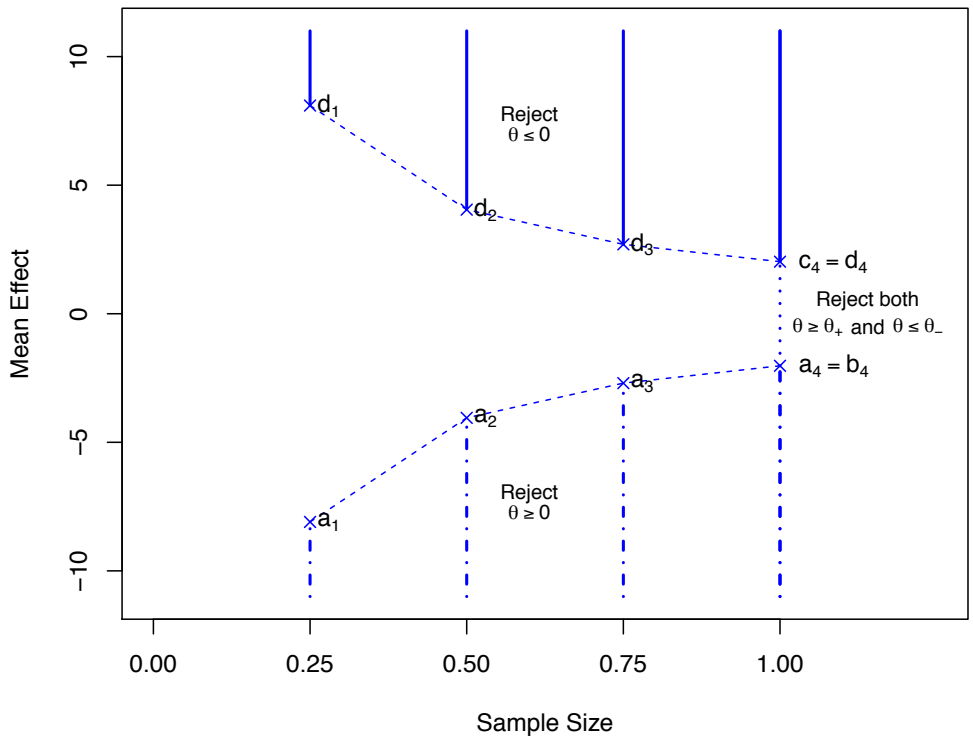
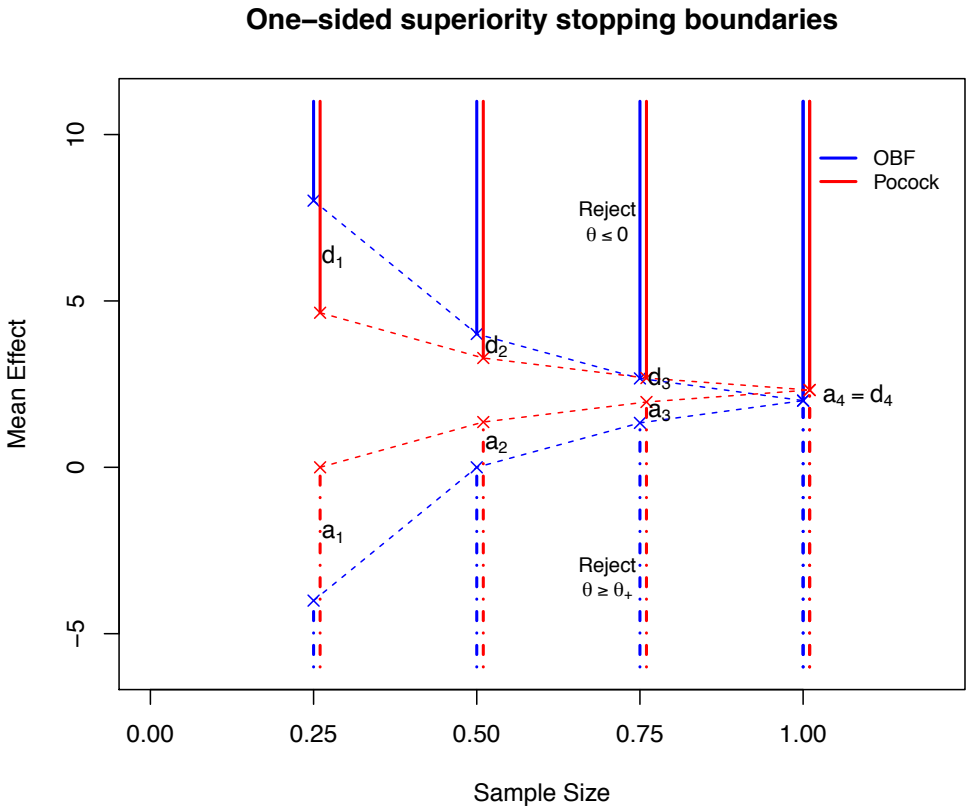


Illustration of statistical implications

Example: OBF versus Pocock 1-sided designs



Effect of stopping boundaries on the sampling density

[Simulated sample paths]

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Illustration of statistical implications

Example: O'Brien-Fleming (OBF) 2-sided design

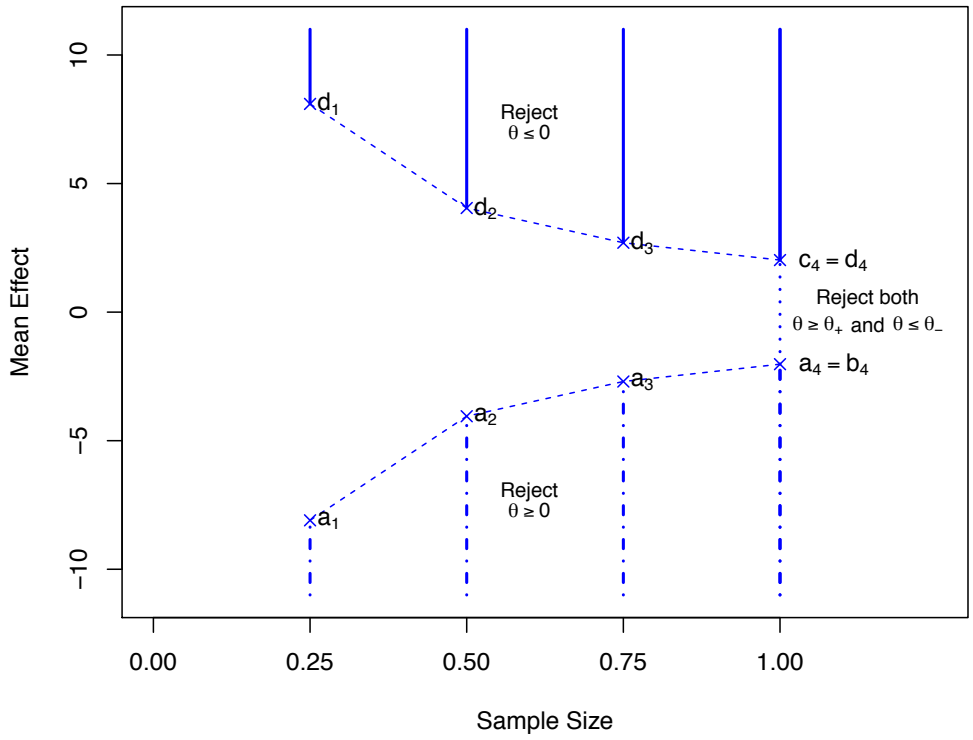

Illustration of statistical implications

Sampling density for OBF boundaries with $\theta = 0$ and $\theta = 3.92$ (corresponding Normal sampling density for comparison):

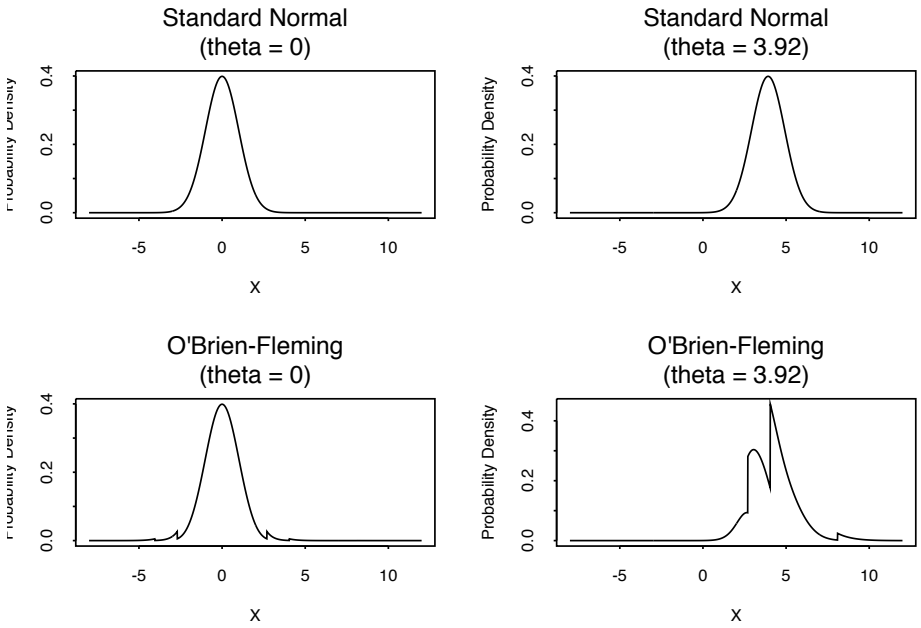

Illustration of statistical implications

Example: OBF versus Pocock 1-sided designs

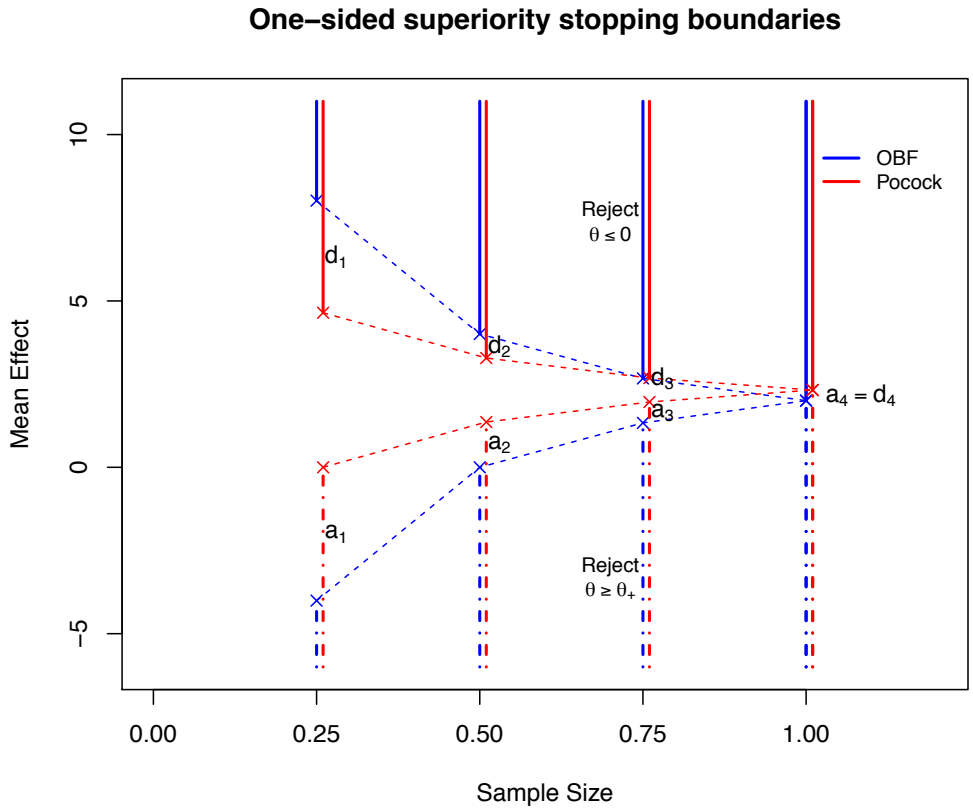

Illustration of statistical implications

Sampling density for OBF and Pocock 1-sided designs.

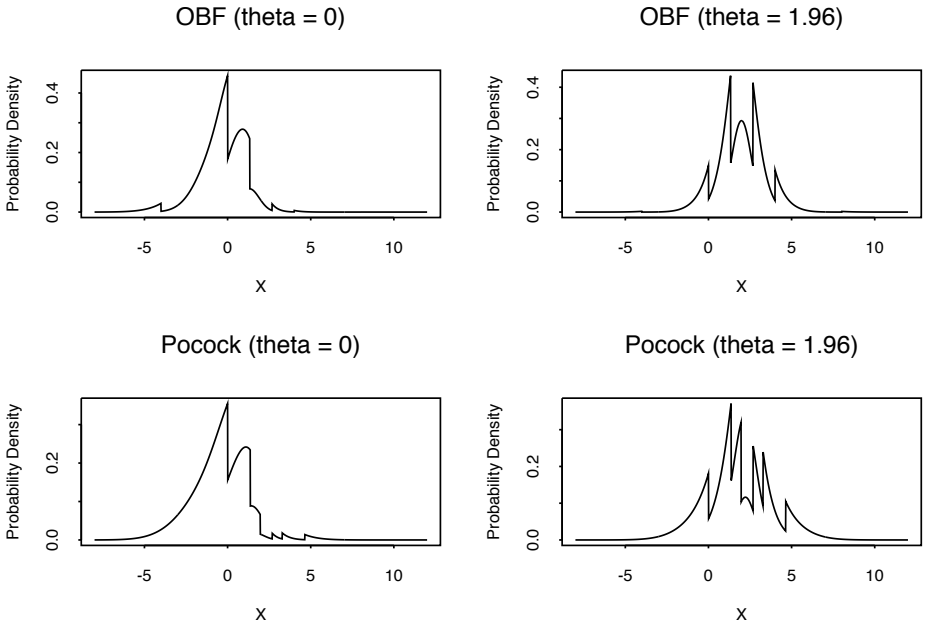

Illustration of statistical implications

Characteristics of the group sequential sampling density:

- Density is not shift invariant
- Jump discontinuities
- Requires numerical integration
- Sequential testing introduces bias:

	$E(\hat{\theta})$	
θ	OBF	Pocock
0.00	-0.29	-0.48
1.96	1.95	1.82
3.92	4.21	4.38

- (Recursive form of the sequential sampling density is computationally useful.)
- Fully discussed in sections 3 and 6 of this course.