

Introduction to the Design and Evaluation of Group Sequential Clinical Trials

Session 2 - Fixed Sample Trial Design & Motivating Examples

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SISCR - GSCT - 2 : 1

Introduction

Phases of the clinical trial process

► Phase I

- Exploratory trials concerned with toxicology and pharmacology
- Dosing trials
- Typically between 20-80 healthy volunteers

► Phase II

- Pilot studies to assess safety and efficacy
- Typically 100-300 diseased patients

► Phase III

- Confirmatory trials
- Often over 1000 diseased patients

► Phase IIIb/IV

- Post-marketing trials
- Observational monitoring of adverse events or new indications

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Where are we going?

- ▶ Group sequential methods build on the foundations of fixed sample clinical trial design
- ▶ As such, it is useful to review some of the key elements of fixed sample trial design
- ▶ This will lead to the specification of a fixed sample study
- ▶ From that foundation we can then build in group sequential procedures

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Defining the scientific hypotheses

Defining treatment(s)

- ▶ Treatment must be completely defined at the time of randomization
 - ▶ Dose(s)
 - ▶ Administration(s)
 - ▶ Frequency and duration
 - ▶ Ancillary treatments and treatment reduction protocol

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Defining the scientific hypotheses

Defining the target population

- ▶ Inclusion/exclusion criteria to identify a population for whom
 - ▶ A new treatment is needed
 - ▶ Experimental treatment is likely to work
 - ▶ Expected to work equally well in all subgroups
 - ▶ All patients likely to eventually use the new treatment are represented (safety)
 - ▶ Clinical experimentation with the new treatment is not unethical

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Defining the scientific hypotheses

Goals/discrimination of hypotheses

- ▶ A particular range of values that is of scientific interest for decisions is termed a "statistical hypothesis"
 - ▶ Example: Suppose θ is a scientifically appropriate summary measure of the distribution
 - ▶ Values of $\theta < 1.0$ indicate a beneficial treatment (e.g., a ratio)
 - ▶ Values of $\theta > 1.0$ indicate a harmful treatment (e.g., a ratio)

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Goals/discrimination of hypotheses

- ▶ Definitions of statistical hypotheses corresponding to scientific importance

-Tendency to be larger: $\theta > 1.0$

-No tendency to be smaller: $\theta > 0.9$

-Approximate equivalence: $0.8 < \theta < 1.2$

-No tendency to be larger: $\theta < 1.2$

-Tendency to be smaller: $\theta < 1.0$

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Goals/discrimination of hypotheses

- ▶ We describe statistical analyses that discriminate between several of these hypotheses

- ▶ One sided hypothesis tests
- ▶ Two sided hypothesis tests
- ▶ Two sided equivalence tests (e.g., bioequivalence)
- ▶ One-sided equivalence (noninferiority) tests

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Goals/discrimination of hypotheses

- ▶ Classically, hypotheses are considered as
 - ▶ Null hypothesis
 - ▶ Status quo
 - ▶ Decision in absence of evidence to the contrary
 - ▶ Alternative hypothesis
 - ▶ What is to be proven
 - ▶ Decision if evidence suggests null hypothesis is false

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Goals/discrimination of hypotheses

- ▶ One sided hypothesis tests discriminate between two hypotheses
 - ▶ null hypothesis
 - ▶ alternative hypothesis (greater or lesser)
- ▶ Two sided hypothesis tests discriminate between three hypotheses
 - ▶ greater alternative
 - ▶ null hypothesis
 - ▶ lesser alternative

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Defining the scientific hypotheses

Definitions of statistical hypotheses corresponding to scientific importance

1. One sided hypothesis tests:

▶ Lesser alternative

Superiority: $\theta < 1.0$ (reject $\theta > 1.0$)

Nonsuperiority: $\theta > 0.6$ (reject $\theta < 0.6$)

▶ Greater alternative

Inferiority: $\theta > 1.0$ (reject $\theta < 1.0$)

Noninferiority: $\theta < 1.8$ (reject $\theta > 1.8$)

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Definitions of statistical hypotheses corresponding to scientific importance

2. Two sided hypothesis tests:

Superiority: $\theta < 1.0$ (reject $\theta > 1.0$)

Equivalence: $0.6 < \theta < 1.8$ (reject $\theta < 0.6$; reject $\theta > 1.8$)

Inferiority: $\theta > 1.0$ (reject $\theta < 1.0$)

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Definitions of statistical hypotheses corresponding to scientific importance

3. One-sided equivalence tests (noninferiority):

Noninferiority: $\theta < 1.2$ (reject $\theta > 1.2$)

Nonsuperiority: $\theta > 0.8$ (reject $\theta < 0.8$)

4. Two sided equivalence tests (bioequivalence):

Superiority: $\theta < 1.0$ (reject $\theta > 1.0$)

Equivalence: $0.8 < \theta < 1.2$ (reject $\theta < 0.8$; reject $\theta > 1.2$)

Inferiority: $\theta > 1.0$ (reject $\theta < 1.0$)

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Defining the scientific hypotheses

Goals/discrimination of hypotheses

Choices of hypotheses

- ▶ One-sided hypothesis test (superiority)
- ▶ Two-sided hypothesis test (superiority/inferiority)
- ▶ Two-sided equivalence test (eg. bioequivalence)
- ▶ One-sided equivalence (non-inferiority) test

How to choose?

- ▶ Base decision on what conditions will change current practice by:
 - ▶ Adopting a new treatment
 - ▶ Discarding an existing treatment

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Conditions under which current practice will be changed

1. Adoption of a new treatment

- ▶ Superiority
 - ▶ Better than using no treatment (efficacious)
 - ▶ Better than existing treatment
- ▶ Equivalence or non-inferiority
 - ▶ Equal to some existing efficacious treatment
 - ▶ Not markedly worse than some existing efficacious treatment

2. Discarding an existing treatment

- ▶ Inferiority
 - ▶ Worse than using no treatment (harmful)
 - ▶ Markedly worse than another treatment

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Ethical issues when specifying hypotheses

- ▶ Clinical versus biological (surrogate) endpoints
 - ▶ Typically, subjects participating in a trial are hoping that they will benefit in some way from the trial
 - ▶ Clinical endpoints are therefore of more interest than purely biological endpoints
 - ▶ For late stage trials, how well does the proposed surrogate correlate with the targeted clinical endpoint?

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Statistical issues when specifying hypotheses

- ▶ Common pitfalls of experimentation are
 - ▶ Data driven hypotheses
 - ▶ Multiple comparisons
 - ▶ Poor selection of subjects
 - ▶ Over-fitting of data

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Statistical issues when specifying hypotheses

"When you go looking for something specific, your chances of finding it are very bad, because of all the things in the world, you're only looking for one of them.

"When you go looking for anything at all, your chances of finding it are very good, because of all the things in the world, you're sure to find some of them."

- Darryl Zero in "The Zero Effect"

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Statistical issues when specifying hypotheses

In Statistics-Speak “When you go looking for something specific, your chances of finding [a spurious association by chance] are very bad, because of all the things in the world, you’re only looking for one of them.

“When you go looking for anything at all, your chances of finding [a spurious association by chance] are very good, because of all the things in the world, you’re sure to find some of them.”

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Goals of statistical design

- ▶ Interested in identifying beneficial treatments in such a way as to maintain
 - ▶ Scientific credibility
 - ▶ Ethical experiments
 - ▶ Efficient experiments
 - ▶ Minimize time
 - ▶ Minimize cost
- ▶ Basic goal: Attain a high positive predictive value with minimal cost

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Predictive value of statistically significant result depends on

1. Probability of beneficial drug
 - ▶ Fixed when treatment is chosen
2. Specificity
 - ▶ Fixed by level of significance (alpha level)
3. Sensitivity
 - ▶ Statistical power made as high as possible by design

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Power is increased by

1. Minimizing bias
 - ▶ Remove confounding and account for effect modification
2. Decreasing variability of measurements
 - ▶ Homogeneity of population, appropriate endpoints, appropriate sampling strategy
3. Increasing sample size

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Statistical tasks

1. Definition of the probability model
 - ▶ Comparison group
 - ▶ Refinement of statistical hypothesis
 - ▶ Method of analysis
2. Definition of statistical hypotheses
3. Definition of statistical criteria for evidence

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Statistical tasks

4. Determination of sample size
5. Evaluation of operating characteristics
6. Planning for interim monitoring
7. Plans for analysis and reporting results

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Possible comparison groups

1. No comparison group

- ▶ Single arm clinical trial (cohort design)
- ▶ Appropriate when absolute criterion for treatment effect exists

2. Historical controls

- ▶ Single arm clinical trial
- ▶ Compare results to criteria defined from historical trial or sample from historical trial

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Possible comparison groups

3. Internal controls

- ▶ Subject serves as his/her own control (cross-over design)
- ▶ Different treatments at different times (washout period?)
- ▶ Different treatment for different body parts (eg. eyes)

4. Concurrent control group

- ▶ Two or more arms
- ▶ Active treatments or more than one level of same treatment

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Statistical hypotheses: Choice of summary measure

- ▶ Wish to determine the tendency for a new treatment to have a beneficial effect on a clinical outcome
- ▶ Consider the distribution of outcomes for individuals receiving intervention
 - ▶ Usually choose a summary measure of the distribution (eg. mean, median, proportion cured, etc)
 - ▶ Hypotheses then refined and expressed as values of the summary measure

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Statistical hypotheses: Choice of summary measure

- ▶ Typically have many choices for the summary measure to compare across treatment groups
- ▶ Consider the distribution of outcomes for individuals receiving intervention
 - ▶ Example: Treatment of high blood pressure with a primary outcome of systolic blood pressure at end of treatment
 - ▶ Possible analyses might compare:
 - ▶ Average, median, percent above 160 mmHg, or mean or median time until blood pressure below 140 mm Hg

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Statistical hypotheses: Choice of summary measure

- ▶ Choice of summary measure GREATLY affects the scientific relevance of the trial
- ▶ Summary measure should be chosen based on (in order of importance)
 - ▶ Most clinically relevant summary measure
 - ▶ Summary measure most likely to be affected by the intervention
 - ▶ Summary measure affording the greatest statistical precision

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Statistical hypotheses: Choice of summary measure

- ▶ In addition to choosing the summary measure within groups, also need to choose how to contrast measures across groups
- ▶ Again many choices are available with different implications
 - ▶ Ex: Difference in means or proportions
 - ▶ Ex: Ratio of odds, medians, or risks (probabilities)

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Software for evaluation/implementation of designs : RCTdesign

- ▶ Named `seqDesign` object (class)
 - ▶ Formatted output from RCTdesign
 - ▶ Predefined plotting functions and class routines

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Software for evaluation/implementation of designs : RCTdesign

- ▶ Sample size requirements
 - ▶ Printed with boundaries
 - ▶ X-axis with plots of boundaries
 - ▶ Plots of average sample size, quantiles of sample size distribution
- ▶ Stopping probabilities
 - ▶ Printed with operating characteristics
 - ▶ Plots with color coded decisions

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Software for evaluation/implementation of designs : RCTdesign

- ▶ Power curve
 - ▶ Hypotheses, size, power printed with boundaries
 - ▶ Tabled power with summaries
 - ▶ Plots of power curve
 - ▶ Plots versus reference power curve
- ▶ Decision boundary
 - ▶ Printed on specified boundary scale
 - ▶ Plots

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Software for evaluation/implementation of designs : RCTdesign

- ▶ Frequentist inference on the boundary
 - ▶ Printed with summary
 - ▶ Plots
- ▶ Bayesian inference on the boundary
 - ▶ Posterior probabilities implemented as a boundary scale
 - ▶ Median (mode) of posterior distribution
 - ▶ Credible intervals
- ▶ Futility measures
 - ▶ Implemented as boundary scale
 - ▶ Conditional and predictive approaches

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Background

- ▶ Critically ill patients often get overwhelming bacterial infection (sepsis), after which mortality is high
- ▶ Gram negative sepsis is often characterized by production of endotoxin, which is thought to be the cause of much of the ill effects of gram negative sepsis
- ▶ Hypothesis: Administering antibody to endotoxin may decrease morbidity and mortality
- ▶ Two previous randomized clinical trials showed a slight benefit
- ▶ There were no safety concerns at the inception of the trial

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Hodgkin's Trial (Survival Endpoint)

Definition of Treatment

- ▶ Single administration of antibody to endotoxin within 24 hours of diagnosis of sepsis
- ▶ Reductions in dose not applicable
- ▶ Ancillary treatments unrestricted

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Hodgkin's Trial (Survival Endpoint)

Defining the target population

- ▶ Patients in ICU with newly diagnosed sepsis
- ▶ Infected with gram negative organisms
 - ▶ culture proven
 - ▶ gram stain

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Defining the Comparison Group

- ▶ Need to ensure scientific credibility for regulatory approval
- ▶ Crossover designs impossible
- ▶ Ultimate decision:
 - ▶ Single comparison group treated with placebo
 - ▶ Not interested in studying dose response
 - ▶ No similar current therapy (still ethical to use placebo)
 - ▶ Randomized
 - ▶ Allow for causal inference
 - ▶ No blocking

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Defining the Outcomes of Interest

▶ Goals:

- ▶ Primary: Increase survival
 - ▶ Long term (always best)
 - ▶ Short term (many other processes may intervene)
- ▶ Secondary: Decrease morbidity

▶ Refinement of the primary endpoint

- ▶ Possible primary endpoints
 - ▶ Time to death
 - ▶ Mortality rate at a fixed point in time
 - ▶ Time alive out of ICU during fixed period of time

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Refinement of the primary endpoint

Sponsor's initial choice for primary endpoint: Mortality rate at a fixed point in time (binary data)

- ▶ Sponsor proposed 14 day mortality
- ▶ FDA countered with a suggestion of 28 day mortality

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Method of analysis

- ▶ Test for differences in binomial proportions
 - ▶ Ease of interpretation
 - ▶ 28 day mortality not a rare event
 - ▶ 1:1 correspondence with tests of odds ratio (for known baseline event rates)
- ▶ No adjustment for covariates
- ▶ Statistical information dictated by mean variance relationship of Bernoulli random variables:
 - ▶ Let Y_{ki} denote binary response (mortality at 28 days) for i -th subject in group k , $k = 0, 1$
 - ▶ $Y_{ki} \sim \mathcal{B}(1, \theta_k)$
 - ▶ $E[Y_{ki}] = \theta_k$ and $\text{Var}[Y_{ki}] = \theta_k(1 - \theta_k)$

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Definition of statistical hypotheses

Null hypothesis

- ▶ No difference in mortality between groups
- ▶ Estimated baseline rate
 - ▶ 28 day mortality: 30%
 - ▶ (needed in this case to estimate variability)

Alternative hypothesis

- ▶ One-sided test for decreased mortality
- ▶ Targeted 28 day mortality rate in antibody arm: 25%
 - ▶ 5% absolute difference in mortality

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Criteria for statistical evidence

- ▶ Type I error: Probability of falsely rejecting the null hypothesis Standards:
 - ▶ Two-sided hypothesis tests: 0.050
 - ▶ One-sided hypothesis test: 0.025
- ▶ Power: Probability of correctly rejecting the null hypothesis (1-type II error)
- ▶ Popular choice: 80% power

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Determination of sample size

- ▶ Sample size chosen to provide desired operating characteristics
 - ▶ Type I error : 0.025 when no difference in mortality
 - ▶ Power : 0.80 when 5% absolute difference in mortality
 - ▶ Statistical variability based on mortality rate of 30% in placebo arm

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Determination of sample size

- ▶ General sample size formula:
 - ▶ δ = standardized alternative
 - ▶ Δ = difference between null and alternative treatment effects
 - ▶ V = variability of a single sampling unit
 - ▶ n = number of sampling units

$$n = \frac{\delta^2 V}{\Delta^2}$$

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Determination of sample size

- ▶ Parameter values in the present case:
 - ▶ $\delta = (z_{1-\alpha} + z_{\beta})$ with $\alpha = 0.025$ and $\beta = 0.80$
 - ▶ $\Delta = \theta_{1,H_1} - \theta_{0,H_1} = -0.05$
 - ▶ $V = \theta_{1,H_1}(1 - \theta_{1,H_1}) + \theta_{0,H_1}(1 - \theta_{0,H_1}) = .25 \times .75 + .3 \times .7 = .3975$
 - ▶ n = sample size per arm

$$n = \frac{\delta^2 V}{\Delta^2} = \frac{(1.96 + .841)^2 \times .3975}{(-.05)^2} = 1247.97 \rightarrow 1248$$

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Evaluation of operating characteristics

Critical values:

- ▶ Observed value which rejects the null hypothesis
- ▶ Point estimate of treatment effect
 - ▶ Will that effect be considered important?
 - ▶ (Clinical and marketing relevance)

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Evaluation of operating characteristics

Confidence interval at the critical value:

- ▶ Observed value which fails to reject the null hypothesis
- ▶ Set of hypothesized treatment effects which might reasonably generate data like that observed
 - ▶ Have we excluded all scientifically meaningful alternatives with a negative study?
 - ▶ If not, study is underpowered...

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Case Study : Sepsis Trial

Computation of design in RCTdesign

- Primary function for defining any design in RCTdesign is `seqDesign()`

```
> binomFixed <- seqDesign( prob.model = "proportions", arms = 2,
+   null.hypothesis = .3, alt.hypothesis = 0.25,
+   ratio = c(1., 1.), nbr.analyses = 1,
+   test.type = "less", power = 0.80, alpha = 0.025 )
> binomFixed
```

PROBABILITY MODEL and HYPOTHESES:

```
Theta is difference in probabilities (Treatment - Comparison)
One-sided hypothesis test of a lesser alternative:
  Null hypothesis : Theta >= 0.00   (size = 0.025)
  Alternative hypothesis : Theta <= -0.05   (power = 0.800)
(Fixed sample test)
```

```
STOPPING BOUNDARIES: Sample Mean scale
                      Efficacy Futility
Time 1 (N= 2495.9)   -0.035   -0.035
```

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Case Study : Sepsis Trial

Inference on the boundary

- Confidence intervals resulting from an observation at the critical value can be computed with `seqInference()`

```
> seqInference( binomFixed )
      Ordering      *** a Boundary ***      *** d Boundary ***
Time 1      Boundary      -0.035      -0.035
           MLE           -0.035      -0.035
           BAM           -0.035      -0.035
           RBadj         -0.035      -0.035
           Mean MUE       -0.035      -0.035
           Mean P-value    0.025      0.025
           Mean 95% Conf Int (-0.07, 0) (-0.07, 0)
           Time MUE       -0.035      -0.035
           Time P-value    0.025      0.025
           Time 95% Conf Int (-0.07, 0) (-0.07, 0)
```

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Evaluation of operating characteristics

Operating characteristics with $N=2496$:

- ▶ Critical value : -0.035
- ▶ Corresponding p-value : 0.025
- ▶ 95% confidence interval : (-0.07, 0)
- ▶ Interpretation: Smallest magnitude of (observed) effect which would result in a significant result is a 3.5% decrease in mortality on the treatment arm with corresponding CI (-0.07, 0).

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Inference on the boundary

- ▶ Problem: Sponsor was concerned that 2496 patients would be logistically infeasible and want to consider a design with 1700 patients
- ▶ We can use the `update()` function to update the original design

```
> binomFixed.1700 <- update( binomFixed,  
                             sample.size=1700, power="calculate" )  
> binomFixed.1700
```

PROBABILITY MODEL and HYPOTHESES:

Theta is difference in probabilities (Treatment - Comparison)

One-sided hypothesis test of a lesser alternative:

Null hypothesis : $\Theta \geq 0.00$ (size = 0.0250)

Alternative hypothesis : $\Theta \leq -0.05$ (power = 0.6376)

(Fixed sample test)

STOPPING BOUNDARIES: Sample Mean scale

Efficacy Futility

Time 1 (N= 1700) -0.0424 -0.0424

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Inference on the boundary

- Confidence intervals on the boundary for the design with 1700 patients

```
> seqInference(binomFixed.1700)
      Ordering          *** a Boundary *** *** d Boundary ***
Time 1      Boundary          -0.042          -0.042
           MLE                -0.042          -0.042
           BAM                -0.042          -0.042
           RBadj              -0.042          -0.042
           Mean MUE           -0.042          -0.042
           Mean P-value       0.025           0.025
           Mean 95% Conf Int  (-0.085, 0)    (-0.085, 0)
           Time MUE           -0.042          -0.042
           Time P-value       0.025           0.025
           Time 95% Conf Int  (-0.085, 0)    (-0.085, 0)
```

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Effect of changing sample size

Operating characteristics with $N=1700$:

- Critical value : -0.0424
- Corresponding p-value : 0.025
- 95% confidence interval : (-0.085, 0)
- Interpretation: Smallest magnitude of (observed) effect which would result in a significant result is a 4.24% decrease in mortality on the treatment arm with corresponding CI (-0.085, 0).

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Sepsis Trial (Binary Endpoint)

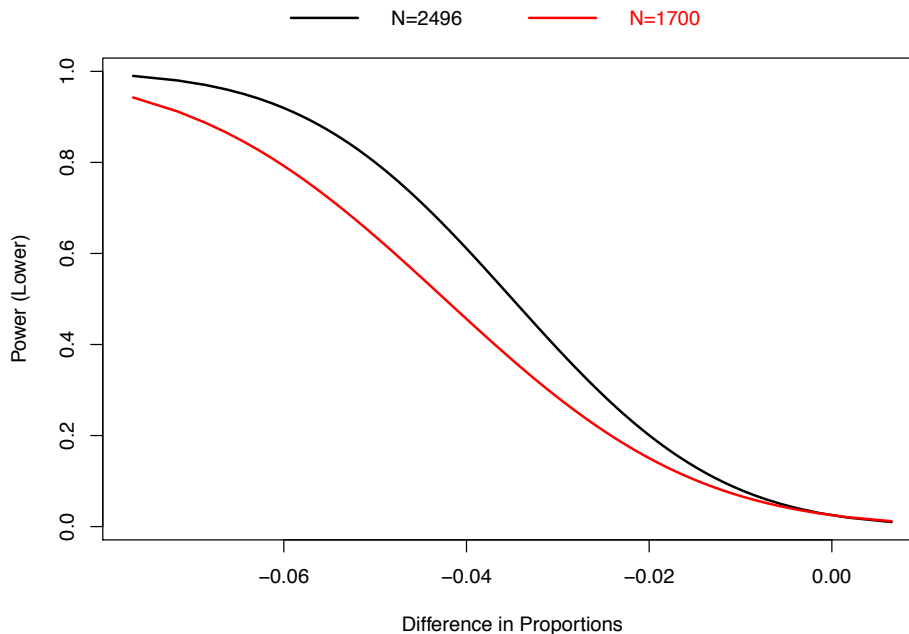
Hodgkin's Trial (Survival Endpoint)

Case Study : Sepsis Trial

Effect of changing sample size on power

- ▶ Power curve can be plotted with the `seqPlotPower()` function

```
> seqPlotPower( binomFixed, binomFixed.1700 )
```



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Case Study : Sepsis Trial

Effect of changing baseline event probability on power

- ▶ Because the statistical information is dictated by the baseline event probability for a binary outcome, should also assess potential impact on power if design assumptions are incorrect
- ▶ Again, this can easily be done with the `update()` function
- ▶ Let's explore the impact on power under a baseline event probability of 0.2, 0.3, and 0.4.

```
> Fixed.3 <- binomFixed.1700  
> Fixed.2 <- update( Fixed.3, null=.2, alt=.15 )  
> Fixed.4 <- update( Fixed.3, null=.4, alt=.35 )
```

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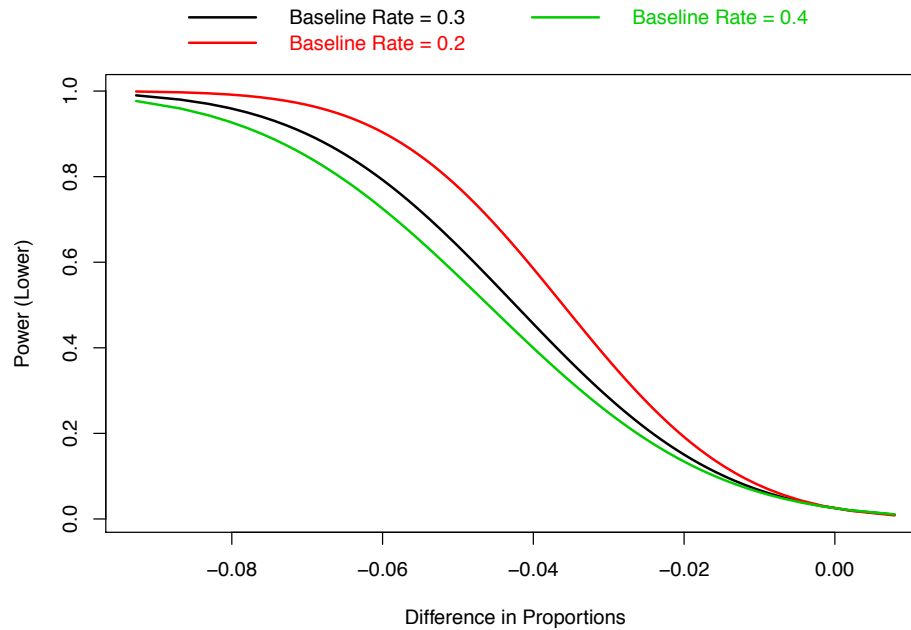
Sepsis Trial (Binary Endpoint)

Hodgkin's Trial (Survival Endpoint)

Case Study : Sepsis Trial

Effect of changing baseline event probability on power

```
> seqPlotPower( Fixed.3, Fixed.4, Fixed.5 )
```



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Sepsis Trial (Binary Endpoint)

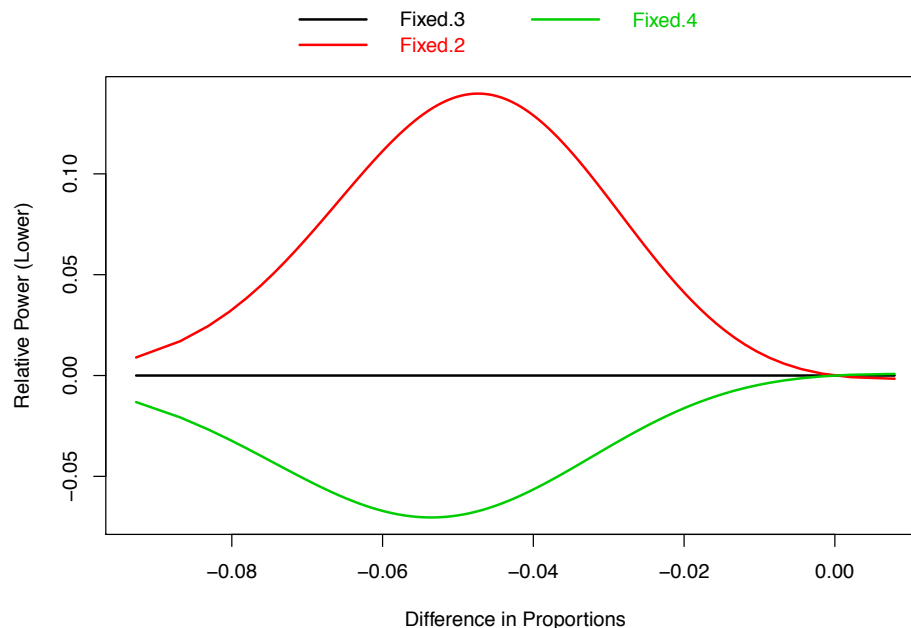
Hodgkin's Trial (Survival Endpoint)

Case Study : Sepsis Trial

Effect of changing baseline event probability on power

► Generally more useful to look at relative change in power

```
> seqPlotPower( Fixed.2, Fixed.4, reference=Fixed.3, lwd=2 )
```



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Hodgkin's Trial (Survival Endpoint)

Background

- ▶ Hodgkin's lymphoma represents a class of neoplasms that start in lymphatic tissue
- ▶ Approximately 7,350 new cases of Hodgkin's are diagnosed in the US each year (nearly equally split between males and females)
- ▶ 5-year survival rate among stage IV (most severe) cases is approximately 60-70%

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Background (cont.)

- ▶ Common treatments include the use of chemotherapy, radiation therapy, immunotherapy, and possible bone marrow transplantation
- ▶ Treatment typically characterized by high rate of initial response followed by relapse
- ▶ Hypothesize that experimental monoclonal antibody in addition to standard of care will increase time to relapse among patients remission

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Definition of Treatment

- ▶ Administered via IV once a week for 4 weeks
- ▶ Patients randomized to receive standard of care plus active treatment or placebo (administered similarly)
- ▶ Treatment discontinued in the event of grade 3 or 4 AEs
- ▶ Primary analysis based upon intention-to-treat

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Hodgkin's Trial (Survival Endpoint)

Defining the target population

- ▶ Histologically confirmed Hodgkin's lymphoma Grade 1-3
- ▶ Progressive disease requiring treatment after at least 1 prior chemotherapy
- ▶ Recovered fully from any significant toxicity associated with prior surgery, radiation treatments, chemotherapy, biological therapy, autologous bone marrow or stem cell transplant, or investigational drugs

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Case Study : Hodgkin's Trial

Defining the Comparison Group

- ▶ Scientific credibility for regulatory approval
- ▶ Concurrent comparison group
 - ▶ inclusion / exclusion criteria may alter baseline rates from historical experience
 - ▶ crossover designs impossible
- ▶ Final Decision
 - ▶ Single comparison group treated with placebo
 - ▶ not interested in studying dose response
 - ▶ no similar current therapy
 - ▶ avoid bias with assessment of softer endpoints
 - ▶ Randomize
 - ▶ allow causal inference

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Case Study : Hodgkin's Trial

Defining the Outcomes of Interest

- ▶ **Goals:**
 - ▶ Primary: Increase relapse-free survival
 - ▶ Long term (always best)
 - ▶ Short term (many other processes may intervene)
 - ▶ Secondary: Decrease morbidity
- ▶ **Refinement of the primary endpoint**
 - ▶ Definition of event
 - ▶ First occurrence of death or relapse (relapse defined as presence of measurable lesion at 3-month scheduled visits)
 - ▶ Possible primary endpoints
 - ▶ Event rate at fixed point in time
 - ▶ Quantile of time to event distribution
 - ▶ Hazard of event

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Refinement of the primary endpoint

Final Choice: Comparison of hazards for event (censored continuous data)

- ▶ Duration of followup
 - ▶ Wish to compare relapse-free survival over 4 years
 - ▶ Patients accrued over 3 years in order to guarantee at least one year of followup for all patients
- ▶ Measures of treatment effect (comparison across groups)
 - ▶ Hazard ratio (Cox estimate; implicitly weighted over time)
 - ▶ No adjustment for covariates
 - ▶ Statistical information dictated by number of events (under proportional hazards, statistical information is approximately $D/4$)

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Definition of statistical hypotheses

Null hypothesis

- ▶ Hazard ratio of 1 (no difference in hazards)
- ▶ Estimated baseline survival
 - ▶ Median progression-free survival approximately 9 months
 - ▶ (needed in this case to estimate variability)

Alternative hypothesis

- ▶ One-sided test for decreased hazard
 - ▶ Unethical to prove increased mortality relative to comparison group in placebo controlled study (always??)
- ▶ 33% decrease in hazard considered clinically meaningful
 - ▶ Corresponds to a difference in median survival of 4.4 months assuming exponential survival

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Criteria for statistical evidence

- ▶ Type I error: Probability of falsely rejecting the null hypothesis Standards:
 - ▶ Two-sided hypothesis tests: 0.050
 - ▶ One-sided hypothesis test: 0.025
- ▶ Power: Probability of correctly rejecting the null hypothesis (1-type II error) Popular choice:
 - ▶ 80% power

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Determination of sample size

- ▶ Sample size chosen to provide desired operating characteristics
 - ▶ Type I error : 0.025 when no difference in mortality
 - ▶ Power : 0.80 when 33% reduction in hazard
- ▶ Expected number of events determined by assuming
 - ▶ Exponential survival in placebo group with median survival of 9 months
 - ▶ Uniform accrual of patients over 3 years
 - ▶ Negligible dropout

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Determination of sample size

- ▶ General sample size formula:
 - ▶ δ = standardized alternative
 - ▶ Δ = log-hazard ratio
 - ▶ π_i = proportion of patients in group i , $i = 0, 1$
 - ▶ D = number of sampling units (events)

$$D = \frac{\delta^2}{\pi_0 \pi_1 \Delta^2}$$

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Determination of sample size

- ▶ Fixed sample test (no interim analyses):
 - ▶ $\delta = (z_{1-\alpha} + z_\beta)$ for size α and power β
- ▶ For current study, we assume 1:1 randomization
 - ▶ $\pi_0 = \pi_1 = 0.5$
- ▶ Number of events for planned trial:

$$D = \frac{(1.96 + 0.84)^2}{0.5^2 \times [\log(.67)]^2} = 195.75$$

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Case Study : Hodgkin's Trial

Specification of fixed sample design using RCTdesign

- ▶ Again, we can use the function `seqDesign()` for specifying the fixed sample design (`prob.model="hazard"`)

```
> survFixed <- seqDesign( prob.model = "hazard", arms = 2,
  null.hypothesis = 1, alt.hypothesis = 0.67,
  ratio = c(1, 1), nbr.analyses = 1,
  test.type = "less",
  power = 0.80, alpha = 0.025 )
```

```
> survFixed
```

Call:

```
seqDesign(prob.model = "hazard", arms = 2, null.hypothesis = 1,
  alt.hypothesis = 0.67, ratio = c(1, 1), nbr.analyses = 1,
  test.type = "less", power = 0.8, alpha = 0.025)
```

PROBABILITY MODEL and HYPOTHESES:

Theta is hazard ratio (Treatment : Comparison)

One-sided hypothesis test of a lesser alternative:

```
Null hypothesis : Theta >= 1.00      (size = 0.025)
Alternative hypothesis : Theta <= 0.67  (power = 0.800)
(Fixed sample test)
```

STOPPING BOUNDARIES: Sample Mean scale

```
          a          d
Time 1 (N= 195.75) 0.7557 0.7557
```

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Case Study : Hodgkin's Trial

Determination of sample size (cont.)

- ▶ In general, it necessary to know the expected number of patients required to obtain the desired operating characteristics
- ▶ This is given by:

$$N = \frac{D}{\pi_0 \Pr_0[\text{Event}] + \pi_1 \Pr_1[\text{Event}]}$$

where D is the total number of required events and π_i is the proportion of patients allocated to group i

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Determination of sample size (cont.)

- ▶ Under proportional hazards, Pr[Event] for each group depends upon
 1. The total followup (T_L) and accrual (T_A) time
 2. The underlying survival distribution
 3. The accrual distribution
 4. Drop-out

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Determination of sample size (cont.)

- ▶ From the above, if we assume a uniform accrual pattern we have:

$$\begin{aligned}\Pr[\text{Event}] &= \int_0^{T_A} \Pr[\text{Event \& Entry at } t] dt \\ &= \int_0^{T_A} \Pr[\text{Event} \mid \text{Entry at } t] \Pr[\text{Entry at } t] dt \\ &= 1 - \int_0^{T_A} \Pr[\text{No Event} \mid \text{Entry at } t] \Pr[\text{Entry at } t] dt \\ &= 1 - \frac{1}{T_A} \int_0^{T_A} \Pr[\text{No Event} \mid \text{Entry at } t] dt \quad (\text{unif acc}) \\ &= 1 - \frac{1}{T_A} \int_0^{T_A} S(T_L - t) dt\end{aligned}$$

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Specification of fixed sample design using RCTdesign

- ▶ In RCTdesign this is automated assuming exponential survival using the function `seqPHSubjects()`
- ▶ For the Hodgkin's trial we assumed
 - ▶ Median survival in the control arm of 9 months
 - ▶ Uniform accrual over 3 years with one additional year of followup

```
> seqPHSubjects( survFixed, controlMedian=0.75,  
                 accrualTime=3, followupTime=1 )
```

	accrualTime	followupTime	rate	hazardRatio	controlMedian	nSubjects
1	3	1	75.364	1.00	0.75	226.09
2	3	1	80.497	0.67	0.75	241.49

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Determination of sample size (cont.)

- ▶ Interpretation:
 - ▶ In order to desire the required number of patients we would need to accrue:
 - ▶ $N=76$ patients per year for 3 years if the null hypothesis were true (Total of 228 patients)
 - ▶ $N=81$ patients per year for 3 years if the alternative hypothesis were true (Total of 243 patients)

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Case Study : Hodgkin's Trial

Evaluating the operating characteristics

1. Critical values
 - ▶ Observed value which rejects the null
 - ▶ Point estimate of treatment effect (clinical and marketing relevance?)
2. Confidence interval at the critical value
 - ▶ Set of hypothesized treatment effects which might reasonably generate data like that observed
 - ▶ Have we excluded all scientifically meaningful alternatives with a negative study?
3. Statistical power across various alternatives
4. Bayesian posterior probabilities at the critical value (more later)
5. Sensitivity to design assumptions (sample size and/or baseline survival)

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Case Study : Hodgkin's Trial

Frequentist inference at the boundaries using RCTdesign

- ▶ In RCTdesign frequentist inference can be obtained with the `seqInference()` function
- ▶ Only required argument is the design to be used

```
> seqInference( survFixed )
      Ordering      *** a Boundary ***      *** d Boundary ***
Time 1      Boundary      0.756      0.756
           MLE           0.756      0.756
           BAM           0.756      0.756
           RBadj         0.756      0.756
           Mean MUE       0.756      0.756
           Mean P-value   0.025      0.025
           Mean 95% Conf Int (0.571, 1) (0.571, 1)
           Time MUE       0.756      0.756
           Time P-value   0.025      0.025
           Time 95% Conf Int (0.571, 1) (0.571, 1)
```

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Case Study : Hodgkin's Trial

Statistical power using RCTdesign

- ▶ Power can be computed using `seqOC()` or plotted using `seqPlotPower()`

```
> seqOC(survFixed, theta=seq(.4,1,by=.05) )
```

```
Operating characteristics
```

Theta	ASN	Power.lower
0.40	195.75	1.0000
0.45	195.75	0.9999
0.50	195.75	0.9981
0.55	195.75	0.9869
0.60	195.75	0.9467
0.65	195.75	0.8540
0.70	195.75	0.7037
0.75	195.75	0.5210
0.80	195.75	0.3450
0.85	195.75	0.2052
0.90	195.75	0.1107
0.95	195.75	0.0547
1.00	195.75	0.0250

```
Fixed design (one analysis time)
```

```
> seqPlotPower( survFixed, dsnLbls=c("survFixed") )
```

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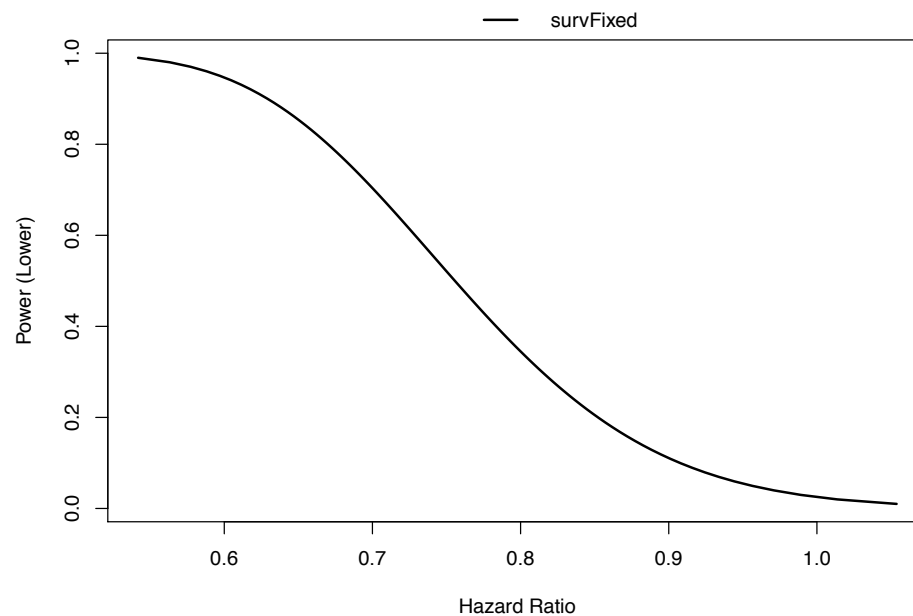
Hodgkin's Trial (Survival Endpoint)

Hodgkin's Trial (Survival Endpoint)

Case Study : Hodgkin's Trial

Statistical power using RCTdesign

- ▶ Power can be computed using `seqOC()` or plotted using `seqPlotPower()`



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Hodgkin's Trial (Survival Endpoint)

Re-designing the study

- ▶ Sponsor felt that attaining 75-80 patients per year would be unrealistic
- ▶ Wished to consider design operating characteristics assuming approximately uniform accrual of 50 patients per year while maintaining the same accrual time and follow up
- ▶ Problem: Need to determine the expected number of events if 50 subjects were accrued per year
- ▶ Solution: Solve backwards using the `nEvents` argument in `seqPHSubjects()`, substituting various numbers of events

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Re-designing the study

- ▶ After a (manual) iterative search, we find that if roughly 50 patients are accrued yearly (under the alternative), 121 events would be expected

```
> seqPHSubjects( survFixed, controlMedian = 0.75, accrualTime = 3,
                 followupTime = 1, nEvents = 121 )
```

	accrualTime	followupTime	rate	hazardRatio	controlMedian	nSubjects
1	3	1	46.584	1.00	0.75	139.75
2	3	1	49.757	0.67	0.75	149.27

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