SESSION 4:
SELECTED TOPICS

Module 9: Survival Analysis for Clinical Trials
Summer Institute in Statistics for Clinical Research
University of Washington
July, 2019

Ying Qing Chen, Ph.D.
Affiliate Professor
Department of Biostatistics
University of Washington

OVERVIEW

- Session 1
  - Review basics
  - Cox model for adjustment and interaction
  - Estimating baseline hazards and survival
- Session 2
  - Weighted logrank tests
- Session 3
  - Other two-sample tests
- Session 4
  - Choice of outcome variable
  - Power and sample size
  - Information accrual under sequential monitoring

CLINICAL TRIALS

- Goal: to find effective treatment indications
  - Primary outcome is a crucial element of the indication
- Scientific basis
  - Planned to detect the effect of a treatment on some outcome
  - Statement of the outcome is a fundamental part of the scientific hypothesis
- Ethical basis:
  - Ordinarily: subjects participating are hoping that they will benefit in some way from the trial
  - Clinical endpoints are therefore of more interest than purely biological endpoints

CHOICE OF PRIMARY OUTCOME

- Type I error for each endpoint
  - In absence of treatment effect, will still decide a benefit exists with probability, say, .025
- Multiple endpoints increase the chance of deciding an
  - ineffective treatment should be adopted
  - This problem exists with either frequentist or Bayesian criteria for evidence
  - The actual inflation of the type I error depends on
    1. the number of multiple comparisons, and
    2. the correlation between the endpoints

CHOICE OF PRIMARY OUTCOME

- **Primary endpoint: Clinical**
- Should consider (in order of importance)
  - The most relevant clinical endpoint (Survival, quality of life)
  - The endpoint the treatment is most likely to affect
  - The endpoint that can be assessed most accurately and precisely

OTHER OUTCOMES

- Other outcomes are then relegated to a “secondary” status
  - Supportive and confirmatory
  - Safety
  - Some outcomes are considered “exploratory"
  - Subgroup effects
  - Effect modification

CHOICE OF PRIMARY OUTCOME

- Should consider (in order of importance)
  - The phase of study: What is current burden of proof?
  - The most relevant clinical endpoint (Survival, quality of life)
    - Proven surrogates for relevant clinical endpoint (???)
  - The endpoint the treatment is most likely to affect
    - Therapies directed toward improving survival
    - Therapies directed toward decreasing AEs
  - The endpoint that can be assessed most accurately and precisely
    - Avoid unnecessarily highly invasive measurements
    - Avoid poorly reproducible endpoints

COMPETING RISKS

- Occurrence of some other event precludes observation of the event of greatest interest, because
  - Further observation impossible
    - E.g., death from CVD in cancer study
  - Further observation irrelevant
    - E.g., patient advances to other therapy (transplant)
- Methods
  - Event free survival: time to earliest event
  - Time to progression: censor competing risks (???)
  - All cause mortality

COMPETING RISKS

- Why not just censor observations that die from a different cause?

- Answer:

COMPETING RISKS

- Competing risks produce missing data on the event of greatest interest
  - There is nothing in your data that can tell you whether your actions are appropriate… but you might suspect that they are not….
- Are subjects with competing risk more or less likely to have event of interest?

PRIMARY OUTCOME

- Potentially long period of follow-up needed to assess clinically relevant endpoints
- Isn’t there something else that we can do?
- A tempting alternative is to move to “surrogate” endpoints...
- “progression free” is typically a “surrogate”

SURVIVAL ANALYSIS

- Composite outcome
  - “Progression free survival”
  - Composite of “no progression” and “no death”

SURROGATE ENDPOINTS

- Hypothesized role of surrogate endpoints
  - Find a biological endpoint which
    - can be measured in a shorter timeframe,
    - can be measured precisely, and
    - is predictive of the clinical outcome
  - Use of such an endpoint as the primary measure of treatment effect will result in more efficient trials
- Treatment effects on Biomarkers
  - Establish *Biological Activity*
  - But not necessarily *overall Clinical Efficacy*
    - Ability to conduct normal activities
    - Quality of Life
    - Overall Survival

SURROGATE ENDPOINTS

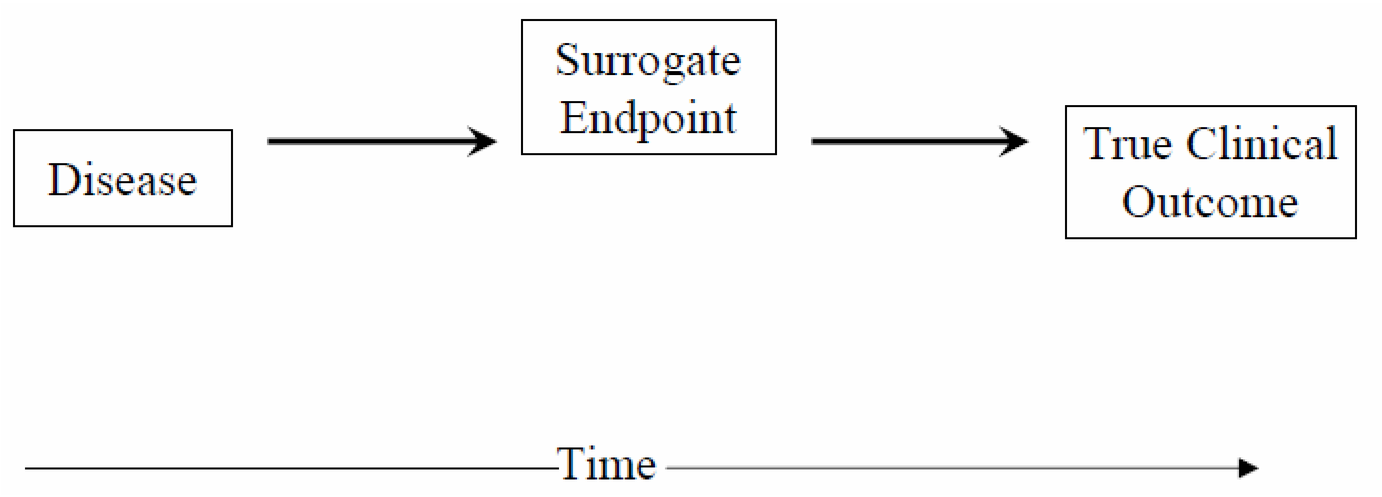
- Typically use observational data to find risk factors for clinical outcome
- Treatments attempt to intervene on those risk factors
- Surrogate endpoint for the treatment effect is then a change in the risk factor
- Establishing biologic activity does not always translate into effects on the clinical outcome
- May be treating the symptom, not the disease

EXAMPLES

- Example of surrogate endpoints
  - Cancer: tumor shrinkage
  - Coronary heart disease: cholesterol, nonfatal MI, blood pressure
  - Congestive heart failure: cardiac output
  - Arrhythmia: atrial fibrillation
  - Osteoporosis: bone mineral density
- Future surrogates?
  - Gene expression
  - Proteomics

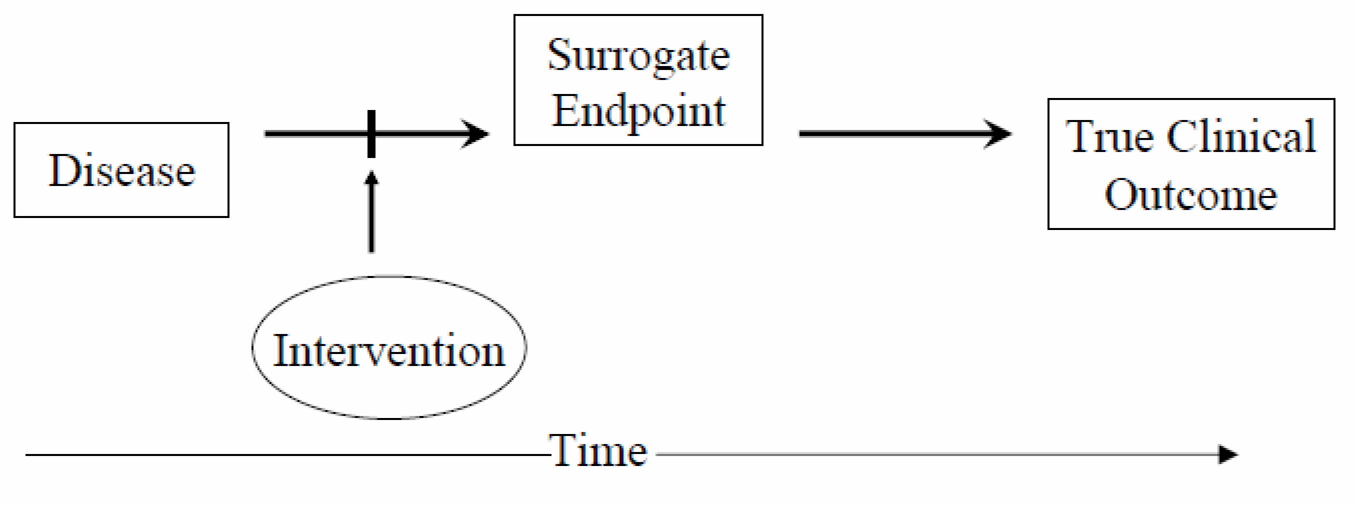
IDEAL SURROGATE

- Disease progresses to Clinical Outcome only through the Surrogate Endpoint



IDEAL SURROGATE USE

- The intervention's effect on the Surrogate Endpoint accurately reflects its effect on the Clinical Outcome

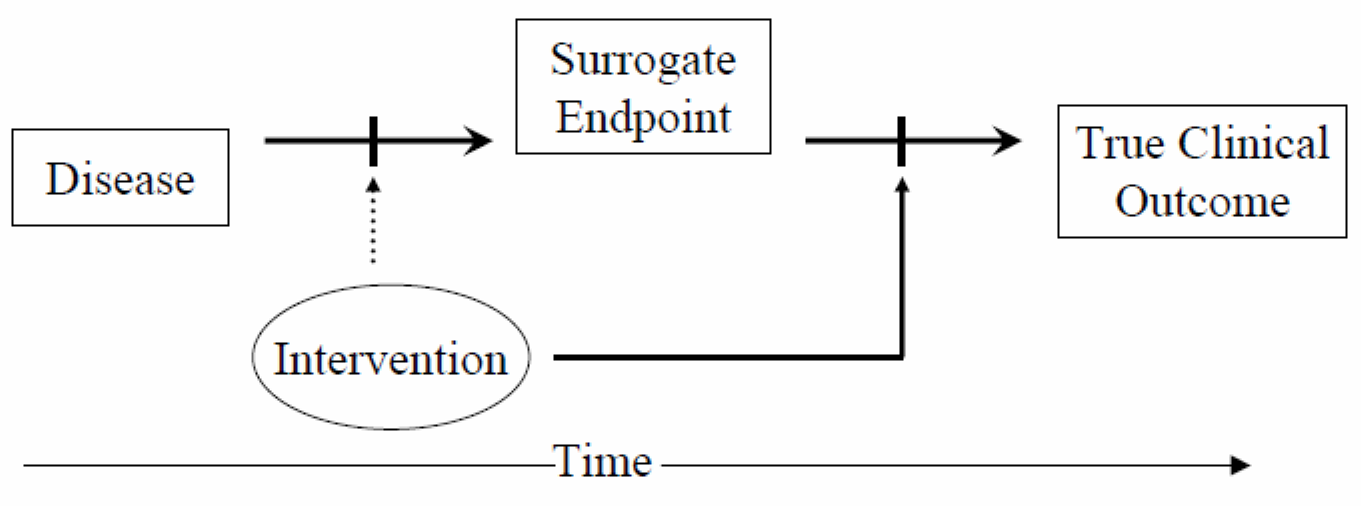


Typically

Too good to be true

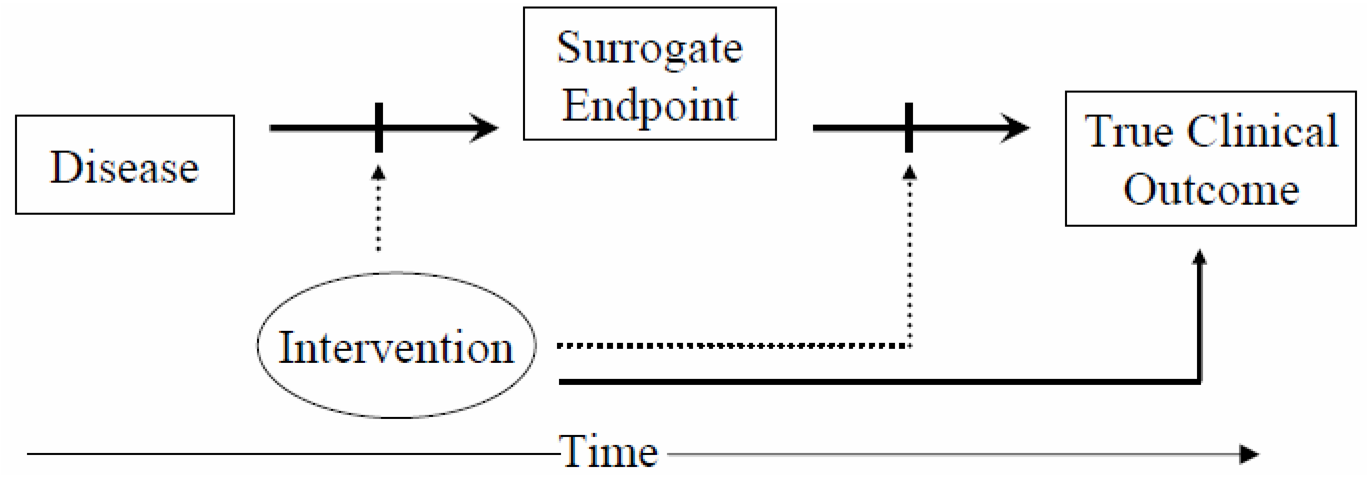
INEFFICIENT SURROGATE

- The intervention’s effect on the Surrogate Endpoint understates its effect on the Clinical Outcome



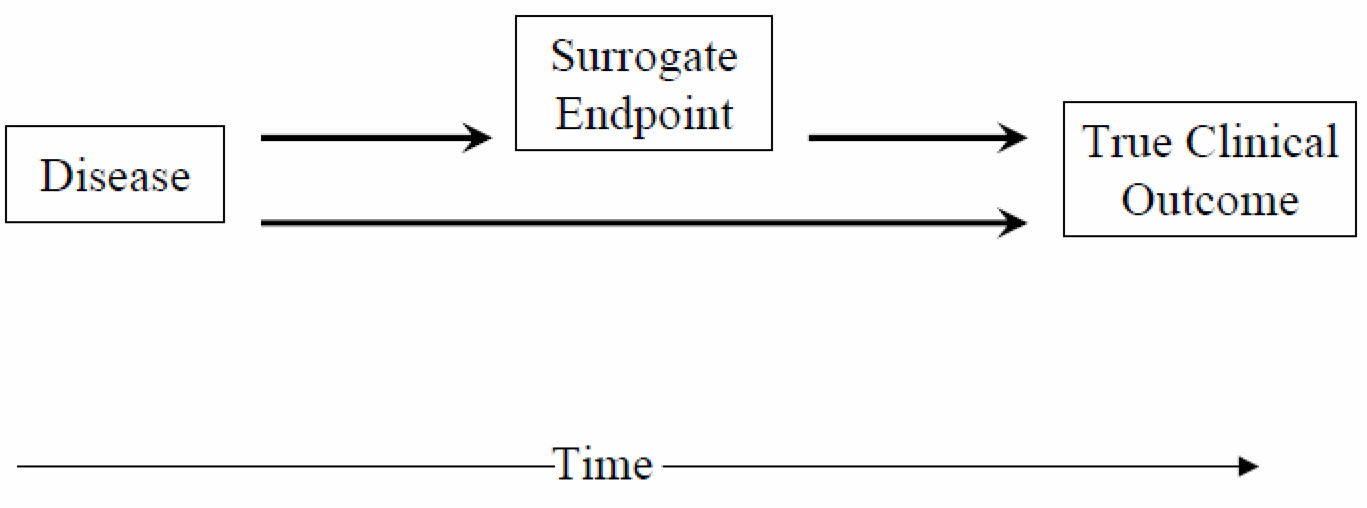
DANGEROUS SURROGATE

- Effect on the Surrogate Endpoint may overstate its effect on the Clinical Outcome (which may actually be harmful)



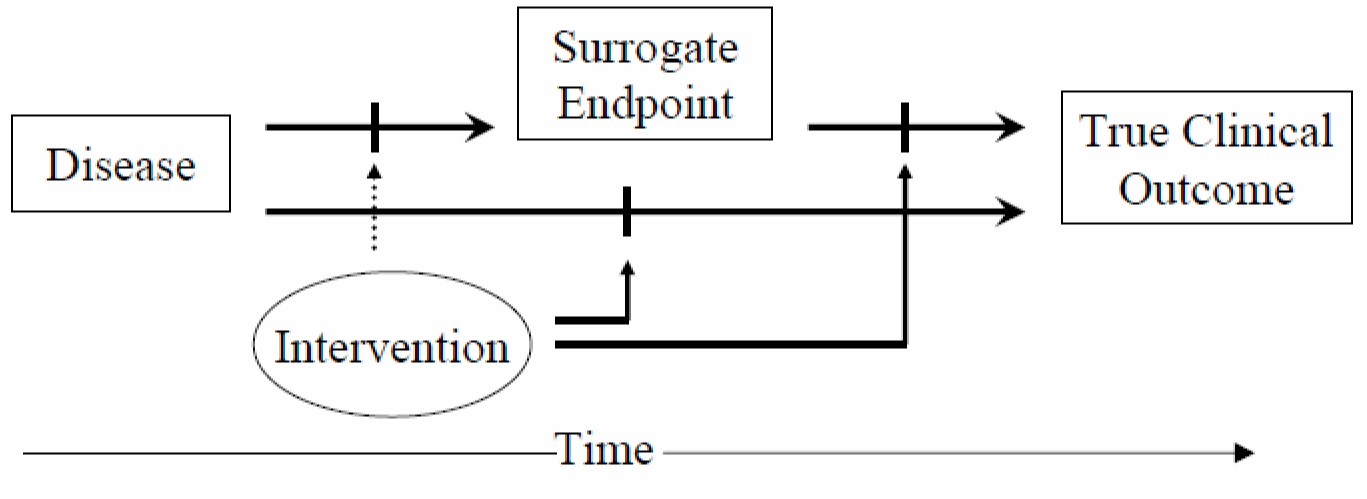
ALTERNATE PATHWAYS

- Disease progresses directly to Clinical Outcome as well as through Surrogate Endpoint



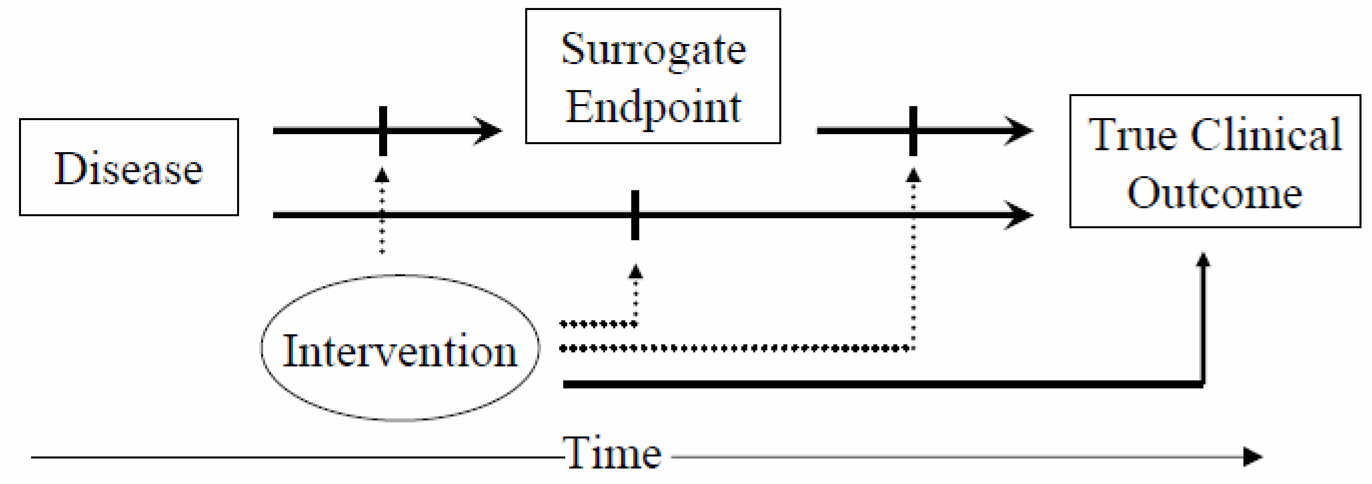
INEFFICIENT SURROGATE

- Treatment's effect on Clinical Outcome is greater than is reflected by Surrogate Endpoint



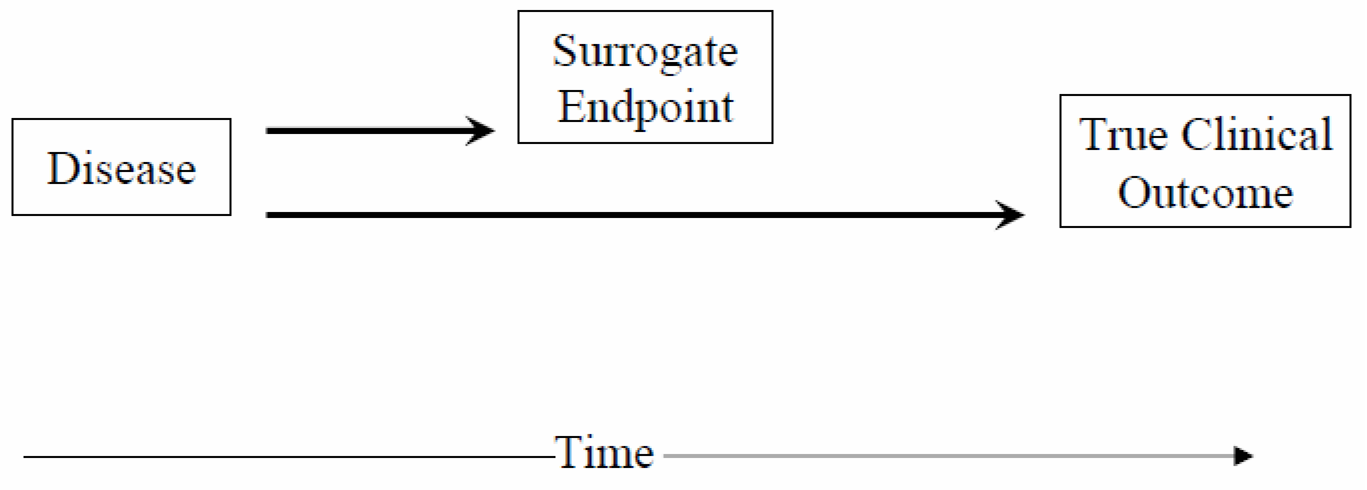
DANGEROUS SURROGATE

- The effect on the Surrogate Endpoint may overstate its effect on the Clinical Outcome (which may actually be harmful)



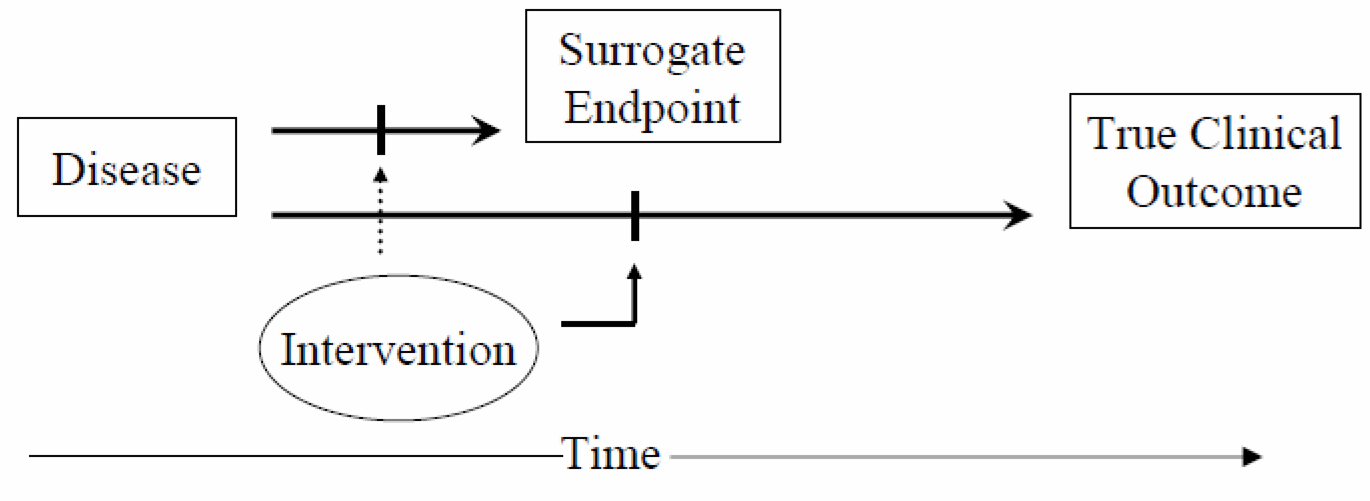
MARKER

- Disease causes Surrogate Endpoint and Clinical Outcome via different mechanisms



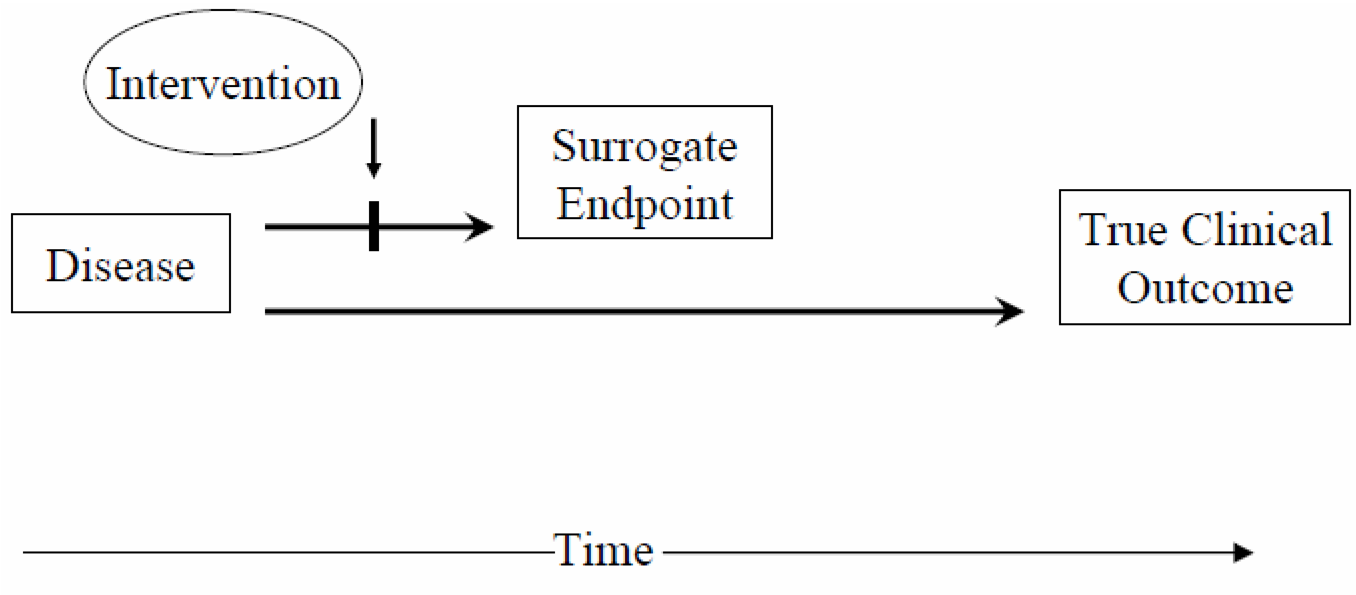
INEFFICIENT SURROGATE

- Treatment's effect on Clinical Outcome is greater than is reflected by Surrogate Endpoint



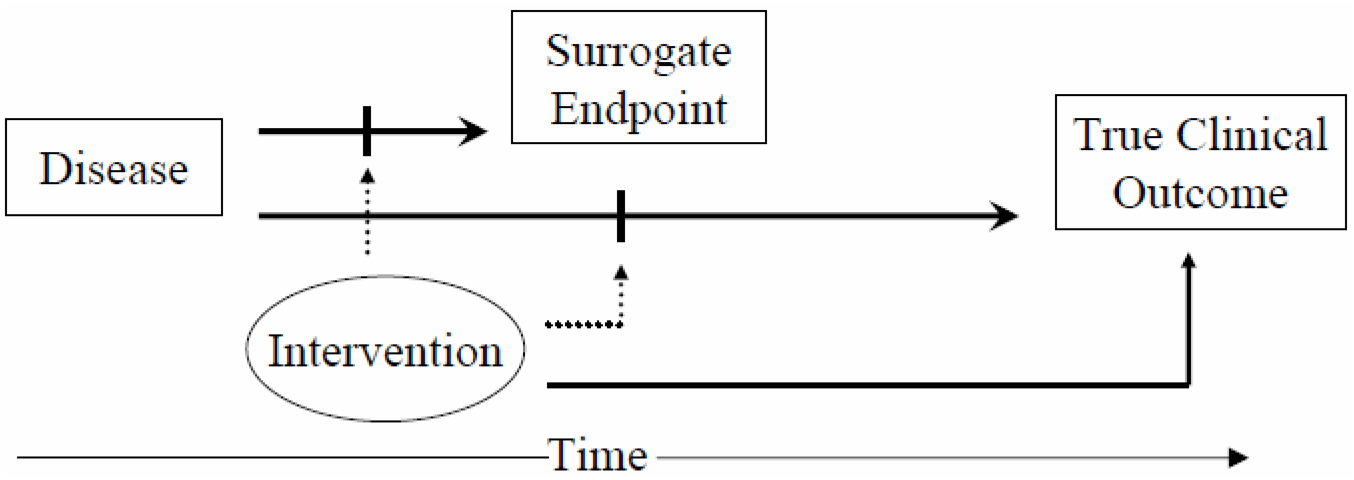
MISLEADING SURROGATE

- Effect on Surrogate Endpoint does not reflect lack of effect on Clinical Outcome



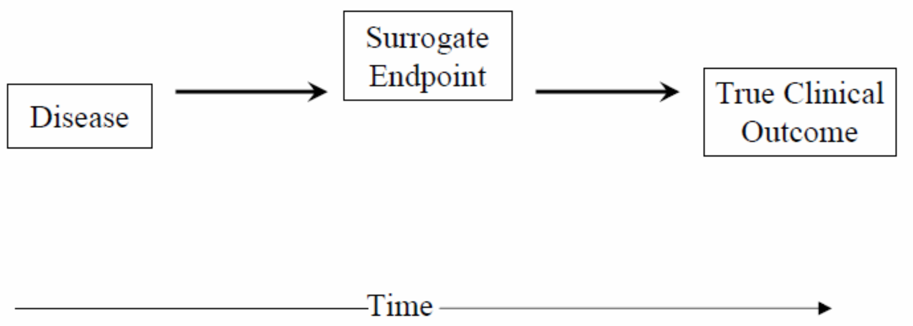
DANGEROUS SURROGATE

- Effect on the Surrogate Endpoint may overstate its effect on the Clinical Outcome (which may actually be harmful)



VALIDATION OF SURROGATE

- Prentice criteria (Stat in Med, 1989)
- To be a direct substitute for a clinical benefit endpoint on inferences of superiority and inferiority
  - The surrogate endpoint must be correlated with the clinical outcome
  - The surrogate endpoint must fully capture the net effect of treatment on the clinical outcome



HIERARCHY FOR OUTCOME MEASURES

- True Clinical Efficacy Measure
- Validated Surrogate Endpoint (Rare)
- *Non-validated Surrogate Endpoint that is “reasonably likely to predict clinical benefit”*
  - ⇨ *progression free survival*
- *Correlate that is solely a measure of Biological Activity*

SURROGATE OUTCOMES

- Surrogate endpoints have a place in screening trials where the major interest is identifying treatments which have little chance of working
- But for confirmatory trials meant to establish beneficial clinical effects of treatments, use of surrogate endpoints can (AND HAS) led to the introduction of harmful treatments

Questions?

OVERVIEW

- Session 1
  - Review basics
  - Cox model for adjustment and interaction
  - Estimating baseline hazards and survival
- Session 2
  - Weighted logrank tests
- Session 3
  - Other two-sample tests
- Session 4
  - Choice of outcome variable
  - Power and sample size
  - Information accrual under sequential monitoring

SAMPLE SIZE / POWER

- Hypothesis testing

The truth can only be: either H_0 true, or H_A true

	H_0 true	H_A true
We do not reject H_0	No error Prob = $1 - \alpha$	Type II error Prob = β
We reject H_0	Type I error Prob = α	No error Prob = $1 - \beta$

Type I error: falsely rejecting H_0 Probability: α
Type II error: falsely not rejecting H_0 Probability: β

$1 - \beta$ = Power of the test = Probability of rejecting H_0 when it is false.
(more on Power later)

GOAL

- Main goals of power / sample size calculations

- Avoid sample size that is TOO small
- Avoid sample size that is TOO large

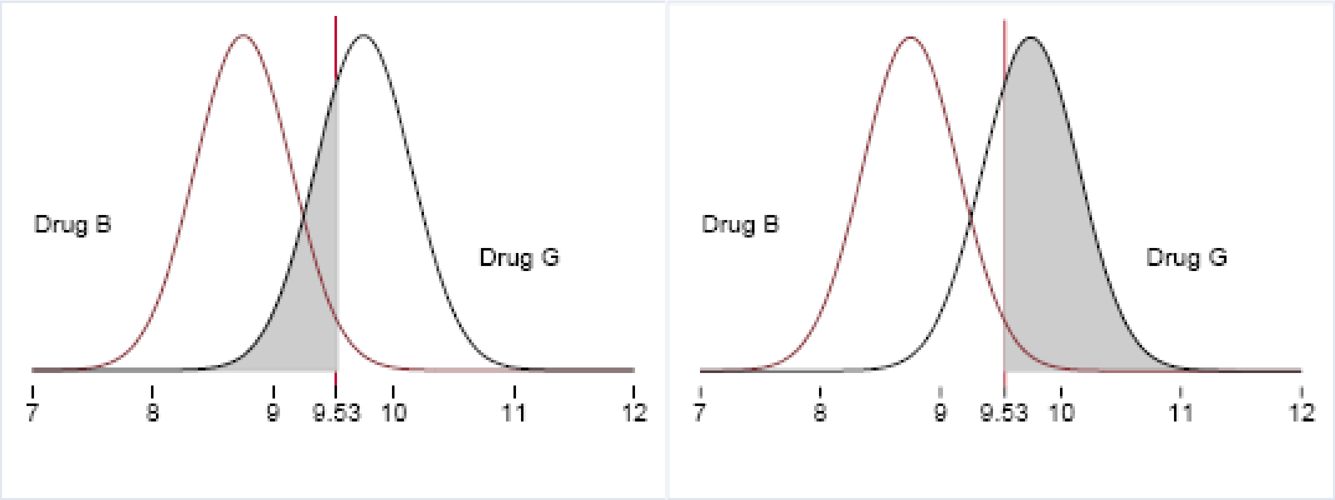
- Ethical issues
- Financial issues

SAMPLE SIZE / POWER

- Normally distributed outcome

Shaded area represents β,
the probability of type II error

$$n = \sigma^2 \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\left(\mu_a - \mu_0\right)^2}$$



Shaded area represents $1 - \beta$,
the power of the test.

SAMPLE SIZE / POWER

- How does this change for survival analysis?
  - Because of censoring
  - Two-step process
  - Determine total number of events
    - Specify hypothesis in terms of statistical parameters, their estimators and variance
    - Clinically important change in the parameters
    - Specify Type I and Type II error probabilities
    - Solve for sample size
  - Determine total number of observations
  - Length of recruitment and follow-up

SAMPLE SIZE / POWER

- Schoenfeld (1983)

$$m = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2}{\theta^2 \pi \left(1 - \pi\right)} \qquad HR = \exp\left(\theta\right)$$

- $z_{\alpha/2}$ corresponding percentage points from
  z_{β} the standard normal
  π fraction of subjects in the first group

With equal allocation ($m_1 = m_2$) $m = \frac{4\left(z_{\alpha/2} + z_{\beta}\right)^2}{\theta^2}$

EXAMPLE

- Assume: HR = 0.75
- Alpha = 0.05
- Power = 80%
- $\beta = 0.2$
- ⇨ $$379.5 = \frac{4(1.96 + 0.842)^2}{[\ln(0.75)]^2}$$

- Would be the right sample size if 380 subjects are randomized at time zero and all followed until the event occurs ⇨ not realistic

EXAMPLE

- Need to adjust *m* by dividing by an estimate of the overall probability of death by the end of the study
- Might have an estimate from past studies?
- Might have K-M estimate of baseline survival function

  $\hat{S}_0(t)$

- Estimate can be used to approximate the survival function under the new treatment and a PH model $\hat{S}_1(t) = \left[\hat{S}_0(t)\right]^{\exp(\theta)}$

EXAMPLE

- If subjects uniformly recruited over the first “a” years
- And then followed for an additional “f” years
- An estimate of the probability of death at the end of the study a + f is

$$\bar{F}(a+f)=1-\frac{1}{6}\left[\bar{S}(f)+4\bar{S}(0.5a+f)+\bar{S}(a+f)\right]$$

$$\bar{S}(t)=\pi\times\hat{S}_0(t)+(1-\pi)\times\hat{S}_1(t)$$

- π fraction of subjects in the standard tx

EXAMPLE

- The estimated number of subjects that must be followed is

$$n = \frac{m}{\bar{\bar{F}}(a+f)}$$

$$= \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2}{\bar{\bar{F}}(a+f)\theta^2\pi(1-\pi)}$$

SAMPLE SIZE / POWER

- Suppose we enroll subjects for 2 years
- And then follow them for an additional 3 years
- Also, we know (from previous research)

$$\hat{S}_0(3)=0.7, \hat{S}_0(4)=0.65 \text{ and } \hat{S}_0(5)=0.55$$

- Then

$$\hat{S}_1(3)=0.765=[0.7]^{0.75}$$
$$\hat{S}_1(4)=0.724=[0.65]^{0.75}$$
$$\hat{S}_1(5)=0.639=[0.55]^{0.75}$$

- And the average survival probabilities at these three time points are

$$\bar{S}_0(3)=0.733, \bar{S}_0(4)=0.687 \text{ and } \bar{S}_0(5)=0.595$$

EXAMPLE

- The average probability of death at the end of the study is estimated as

$$\bar{F}(5) = 0.321 = 1 - \frac{1}{6}[0.733 + 4 \times 0.687 + 0.595]$$

- And the total number of subjects that must be enrolled is

$$n_{total} = 1{,}183.8 = \frac{380}{0.321} \qquad n_{per-group} = 592$$

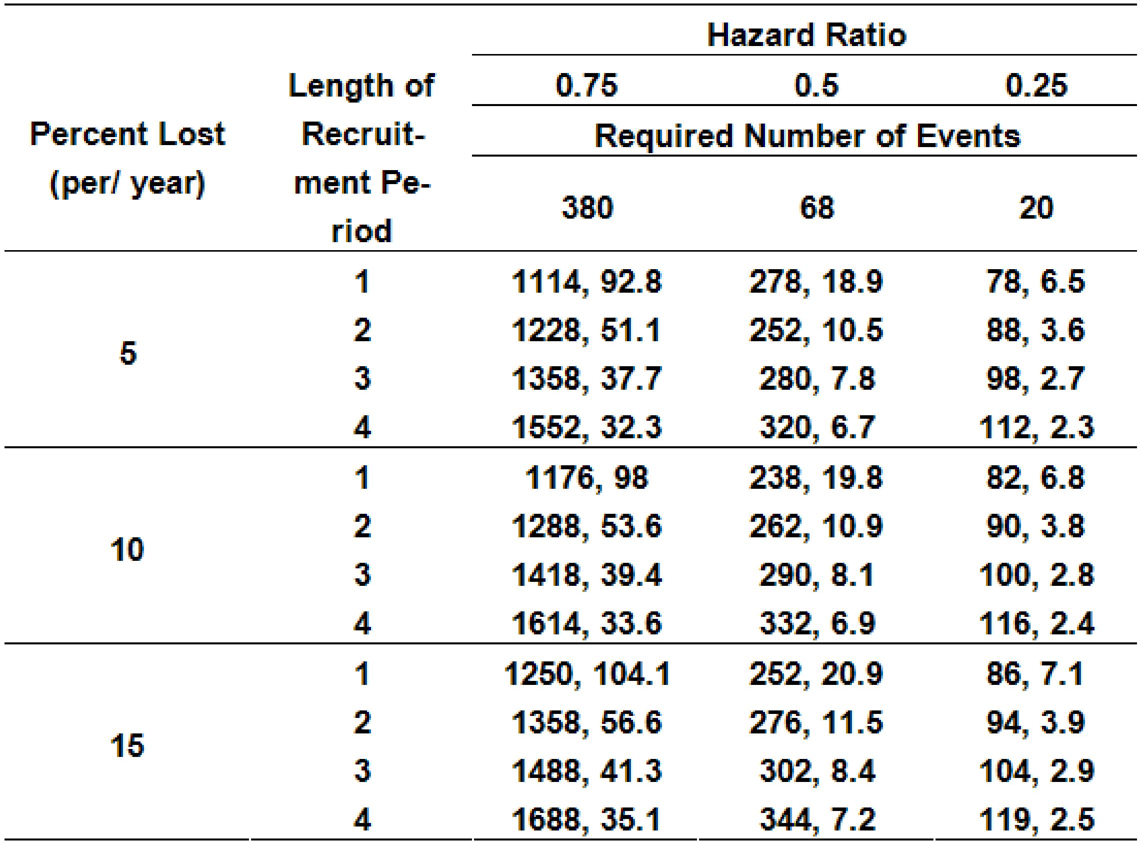
- ⇨ ~ 49-50 subjects per month need to be enrolled
- Slight differences in estimated numbers possible due to different approaches of different software packages

SAMPLE SIZE / POWER

- Factors
  - Effect size
  - Allocation ratio
  - Alpha
  - Power
  - Baseline survival distribution
  - Length of recruitment
  - Length of follow-up period
  - Loss to follow-up
  - Number of events/censored observations

EXAMPLE

- Total Sample Size and Required Number of Subjects to be Recruited per Month , Necessary to Detect the Stated Hazard Ratio Using a Two-Sided Log Rank Test with a Significance Level of 5 Percent and 80 Percent Power for a Total Length of Study of 5 Years.



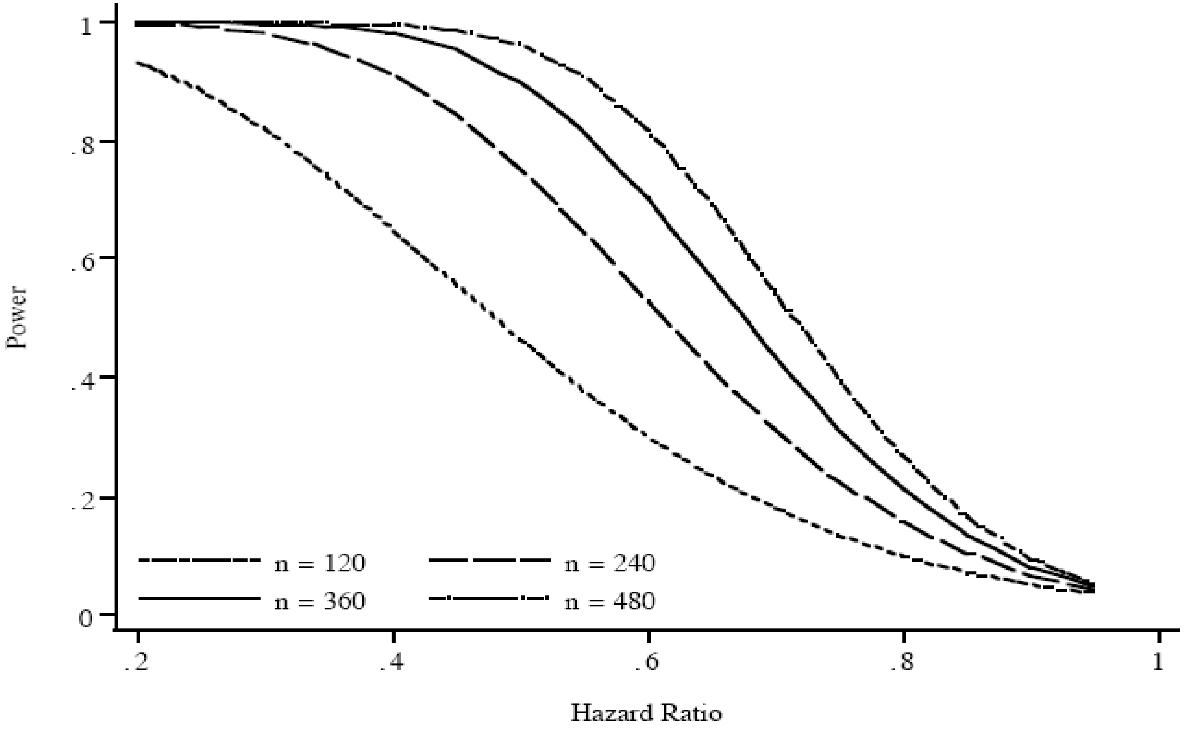
Percent Lost (per/ year)	Length of Recruitment Period	Hazard Ratio		
		0.75	0.5	0.25
		Required Number of Events		
		380	68	20
5	1	1114, 92.8	278, 18.9	78, 6.5
	2	1228, 51.1	252, 10.5	88, 3.6
	3	1358, 37.7	280, 7.8	98, 2.7
	4	1552, 32.3	320, 6.7	112, 2.3
10	1	1176, 98	238, 19.8	82, 6.8
	2	1288, 53.6	262, 10.9	90, 3.8
	3	1418, 39.4	290, 8.1	100, 2.8
	4	1614, 33.6	332, 6.9	116, 2.4
15	1	1250, 104.1	252, 20.9	86, 7.1
	2	1358, 56.6	276, 11.5	94, 3.9
	3	1488, 41.3	302, 8.4	104, 2.9
	4	1688, 35.1	344, 7.2	119, 2.5

SAMPLE SIZE / POWER

- Number of events depends only on the magnitude of the hazard ratio
- Estimated sample size depends heavily on the magnitude of the hazard ratio and length of recruitment period
- Less sensitive to the percent of loss to follow-up
- Also graphical representation of power

EXAMPLE

- Estimated power of a two sided five percent level of significance Log Rank test to detect the hazard ratio using the stated sample size



TWO-SIDED VS ONE-SIDED

- Symmetry?
- Two-sided $\alpha = 0.05$ ⇔ one-sided $\alpha = 0.025$

CHOICE OF ALPHA

- 0.20
- 0.10
- 0.05
- 0.01

- Risk – benefit ratio
- Phase of the trial

CHOICE OF POWER (1-BETA)

- 0.80
- 0.90
- 0.975

- “Translate” the effect size for different values of power

EFFECT SIZE

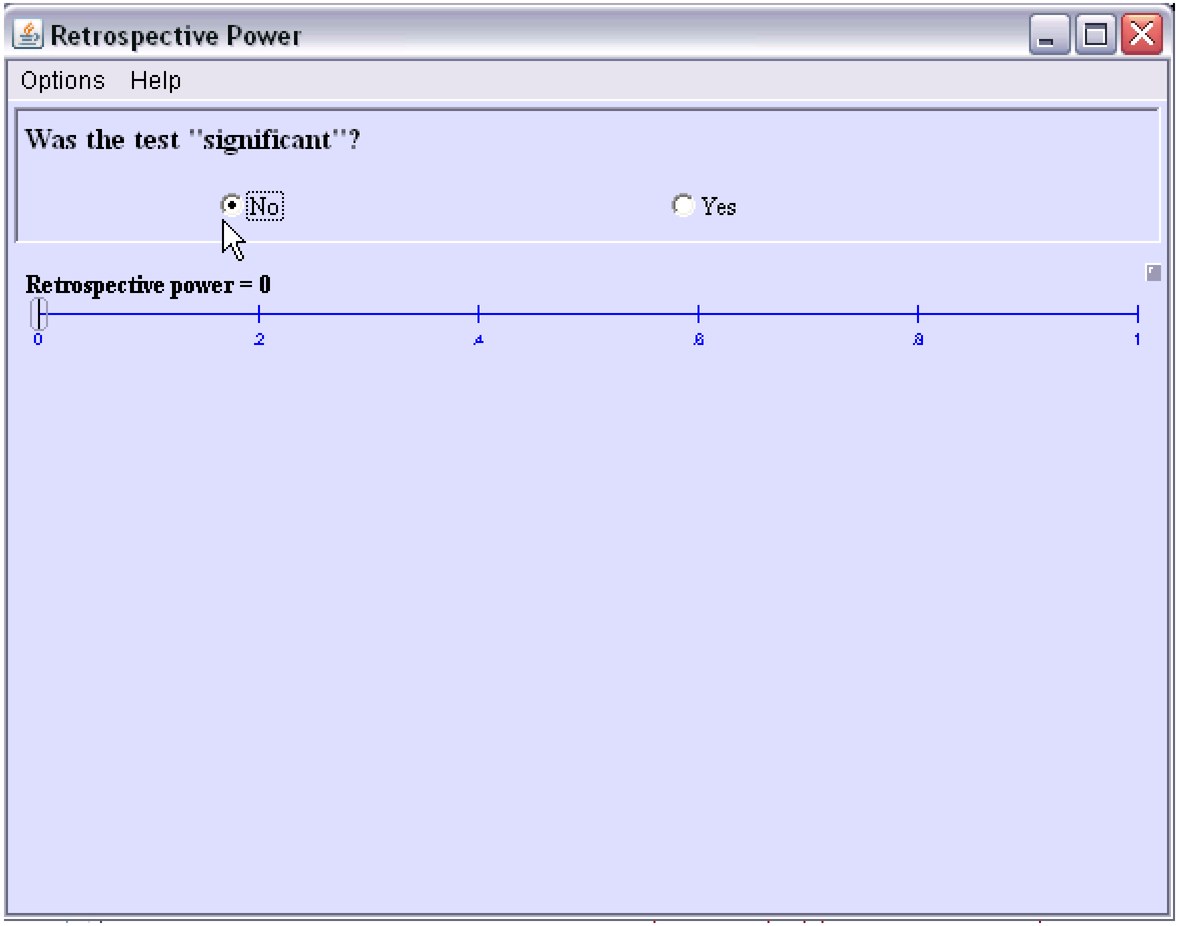
- **How to determine the "target" effect size?**
- Clinically meaningful
- Achievable

POST-HOC POWER

- After the study is done…. (usually) with a non-significant result….
- How much power did the study have to detect the result that was seen ….?

POST-HOC POWER

- <http://www.stat.uiowa.edu/~rlenth/Power/>



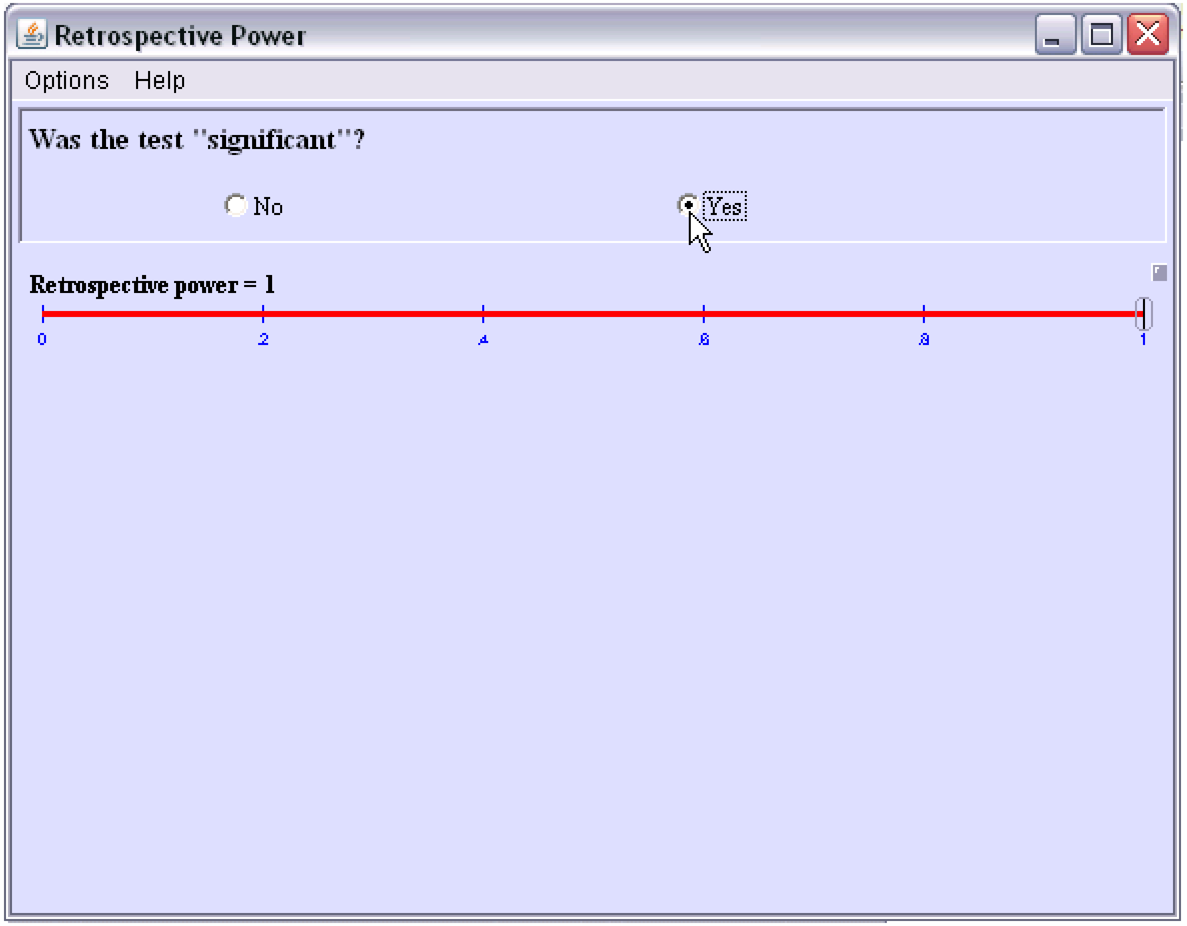
Was the test "significant"?

● No ○ Yes

Retrospective power = 0

POST-HOC POWER

- <http://www.stat.uiowa.edu/~rlenth/Power/>



Was the test "significant"?

○ No ● Yes

Retrospective power = 1

POST-HOC POWER

- Hoenig, John M. and Heisey, Dennis M. (2001), ``The Abuse of Power: The Pervasive Fallacy of Power Calculations for Data Analysis,'' *The American Statistician*, **55**, 19-24.
- CIs obtained at the end of the study are much more informative than post hoc power!

OVERVIEW

- Session 1
    - Review basics
    - Cox model for adjustment and interaction
    - Estimating baseline hazards and survival
- Session 2
    - Weighted logrank tests
- Session 3
    - Other two-sample tests
- Session 4
    - Choice of outcome variable
    - Power and sample size
    - Information accrual under sequential monitoring

GOAL OF SEQUENTIAL MONITORING

- Develop a design for repeated data analyses
  - which satisfies the ethical need for early termination if initial results are extreme
  - while not increasing the chance of false conclusions

GROUP SEQUENTIAL MONITORING

- Motivation: Many trials have been stopped early:
  - Physician health study showed that aspirin reduces the risk of cardiovascular death.
  - A phase III study of tamoxifen for prevention of breast cancer among women at risk for breast cancer showed a reduction in breast cancer incidence.
  - A phase III study of anti-arrhythmia drugs for prevention of death in people with cardiac arrhythmia stopped due to excess deaths with the anti-arrhythmia drugs.
  - Women’s Health Initiative: Hormones cause heart disease.

MONITORING ENDPOINTS

- Reasons to monitor study 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)

MONITORING ENDPOINTS

- If not done properly, monitoring of endpoints can lead to biased results:
  - Data driven analyses cause bias:
    - Analyzing study results because they look good leads to an overestimate of treatment benefits
  - Publication or 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

MONITORING ENDPOINTS

- 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

KEY ELEMENTS OF MONITORING

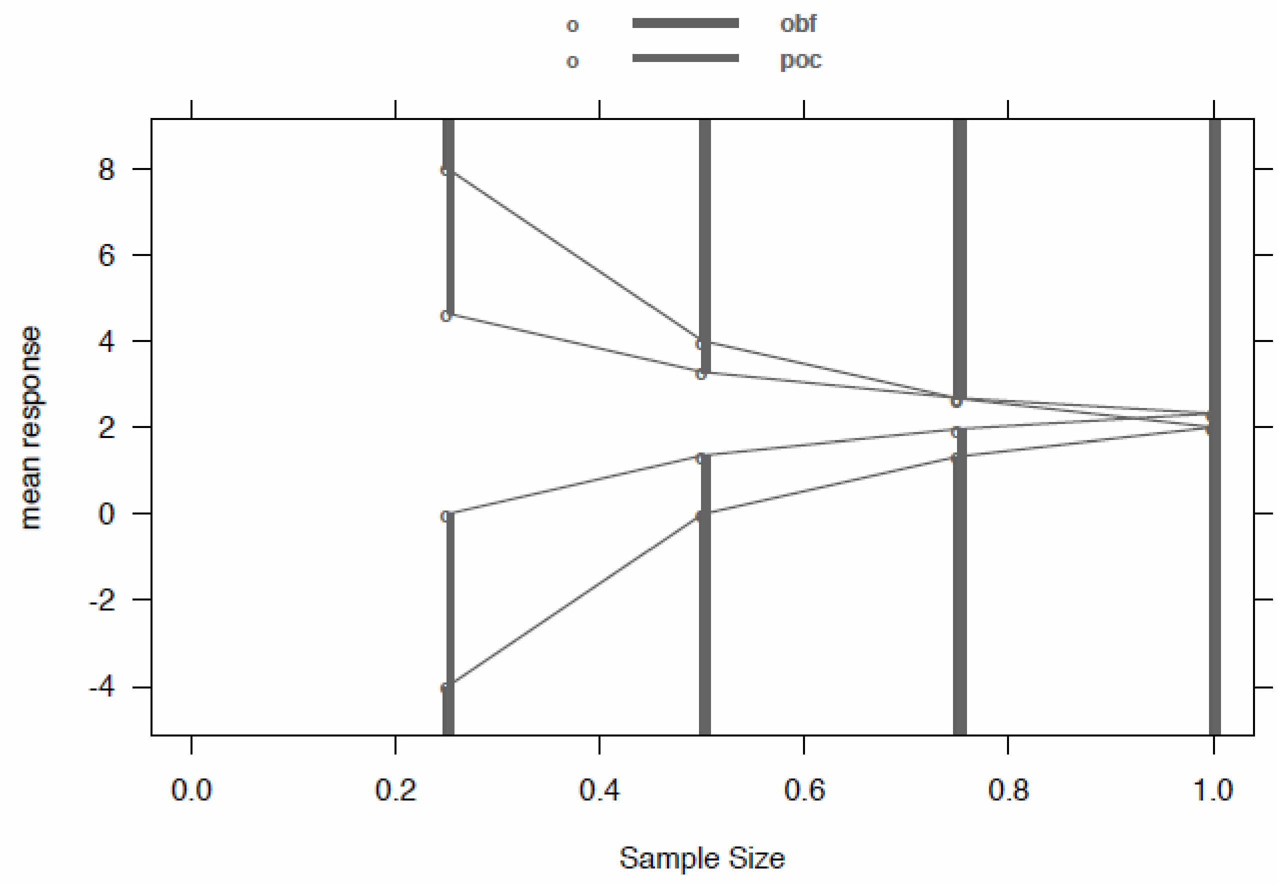
- How are trials monitored?
  - Investigator knowledge of interim results can lead to biased results:
    - Negative results may lead to loss of enthusiasm
    - Positive interim results may lead to inappropriate early publication
    - Either result may cause changes in the types of subjects who are recruited into the trial

INTERIM STATISTICAL ANALYSIS PLAN

- Typical content for ISAP:
    - Safety monitoring plan (if there are formal safety interim analyses)
        - Decision rules for formal safety analyses
        - Evaluation of decision rules (power, expected sample size, stopping probability)
        - Methods for modifying rules (changes in timing of analyses)
        - Methods for inference (bias adjusted inference)

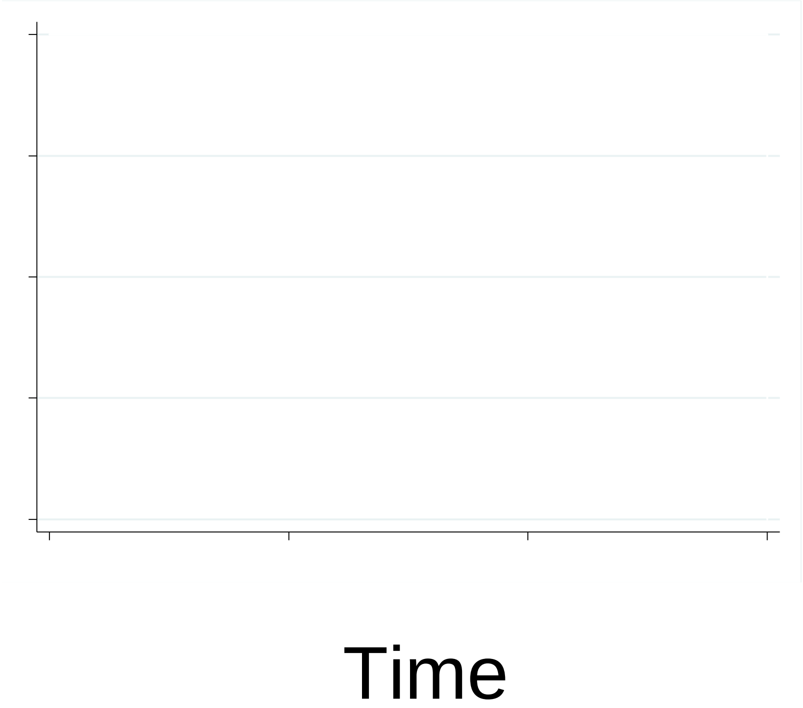
MONITORING BOUNDARIES

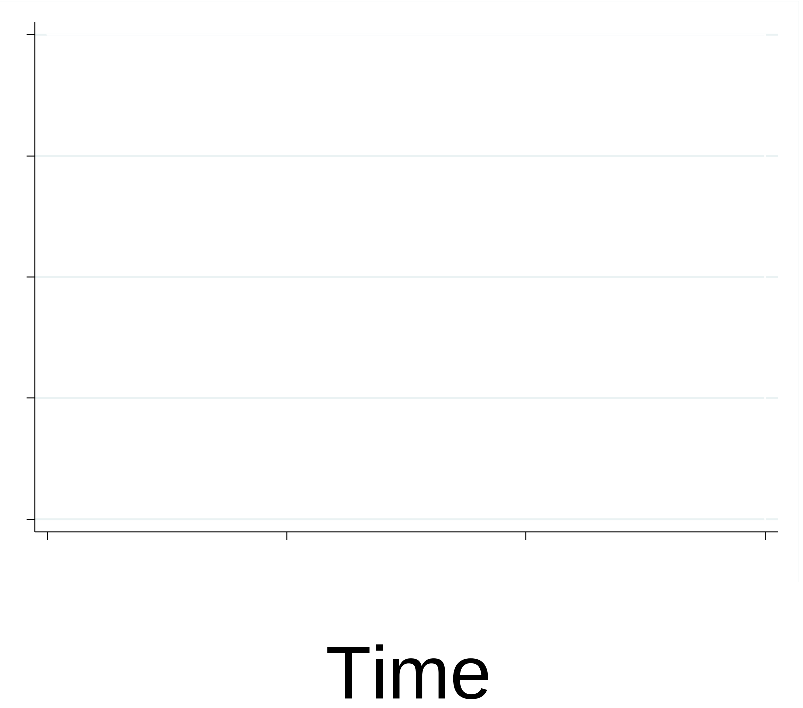
- Example of monitoring boundaries – note: scale



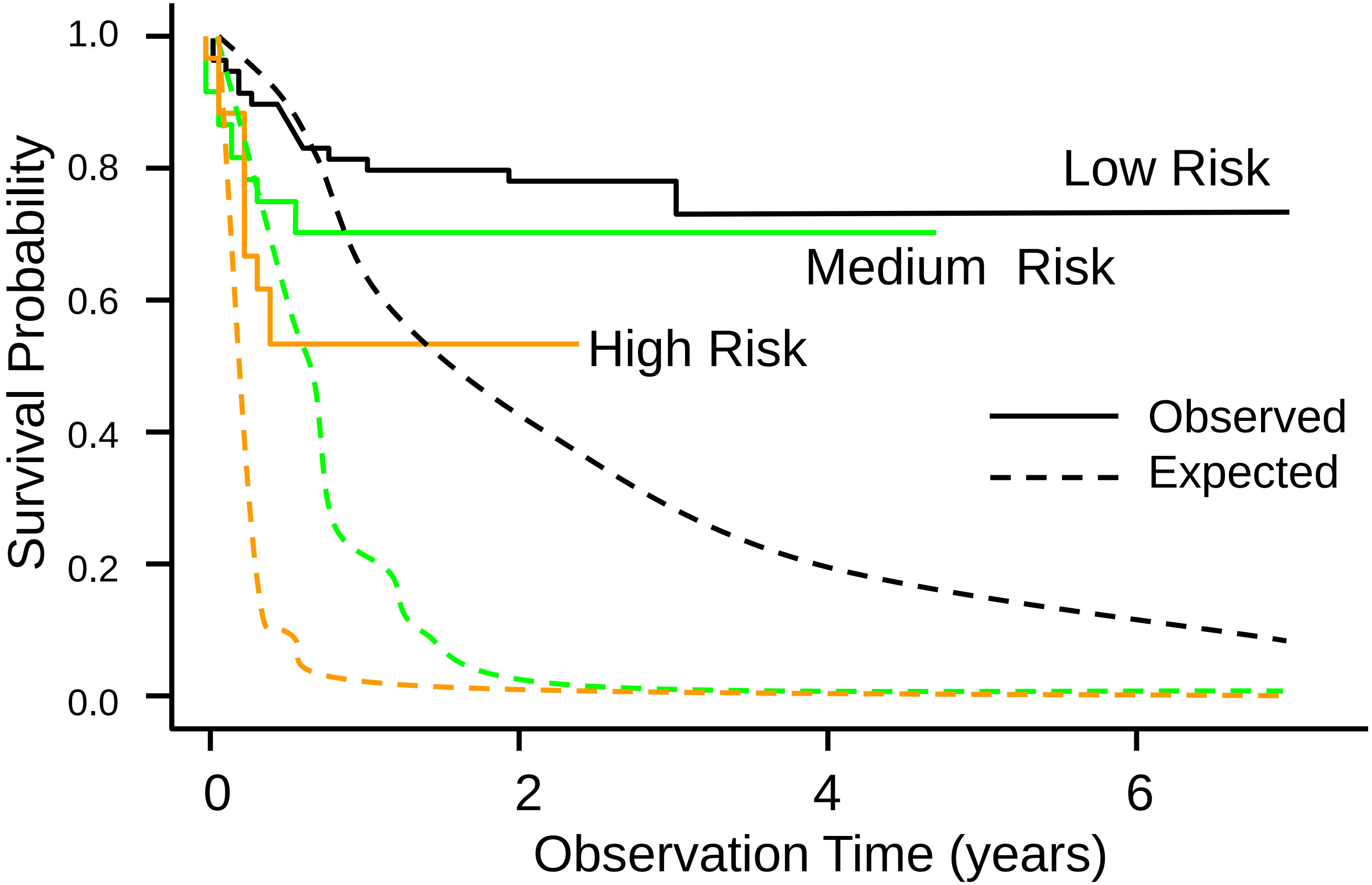
TRIAL WITH SURVIVAL ANALYSIS

- Accrual pattern and information growth





EXAMPLE


Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
Observation Time (years)
Low Risk
Medium Risk
High Risk
Observed
Expected

SAMPLE SIZE

- If the event rate of a trial is much lower than expected, and sample size adjustments are made to increase the number of individuals enrolled, will this affect the power of the study?

Questions ?