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Introduction to Clinical Trials - Day 2

Session 2 - Surrogate Endpoints

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
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Alternate Pathways
Surrogate Markers
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HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

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Choice of a Primary Outcome

Importance of primary outcome specification

- The goal of a RCT is to find effective treatment indications
  - The primary outcome is a crucial element of the indication
- Scientific basis:
  - A clinical trial is 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:
  - Generally, subjects participating in a clinical trial 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 a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
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Motivation and Examples
Examples of Problems with Surrogates
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Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Choice of a Primary Outcome

Multiple comparison issues

- 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 a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

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Multiple comparison issues

- Ex: Consider experiment-wise error rate when using level .05 per decision

Number Compared	Worst Case	Correlation 0.00	0.30	0.50	0.75	0.90
1	.050	.050	.050	.050	.050	.050
2	.100	.098	.095	.090	.081	.070
3	.150	.143	.137	.126	.104	.084
5	.250	.226	.208	.184	.138	.101
10	.500	.401	.353	.284	.193	.127
20	1.000	.642	.540	.420	.258	.154
50	1.000	.923	.806	.624	.353	.193

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Choice of a Primary Outcome

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

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

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
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Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Additional Endpoints

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

Choice of a Primary Outcome

Primary endpoint: Clinical

- 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 (????) More later...
  - 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

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
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Prentice's Criteria

Choice of a Primary Outcome

Multiple endpoints

- Sometimes we must consider multiple endpoints
- We then control experiment-wise error
- Possible methods include
  - Composite endpoint
    - AND: Individual success must satisfy all
    - OR: Individual success must only satisfy one
    - AVERAGE: Sum of individual scores
    - EARLIEST: e.g., event free survival
  - Co-primary endpoints
    - Must show improvement in treatment group on all endpoints
    - No guarantee that the same subjects are experiencing the improvement

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
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Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Choice of a Primary Outcome

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Competing risks

- Occurrence of some “nuisance" 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
  - “U statistics": define ranking based on both events

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Choice of a Primary Outcome

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Competing risks caveats

- Competing risks produce missing data on the event of greatest interest
- As with all missing data problems, there is nothing in your data that can tell you whether your actions are appropriate
  - Are subjects with competing risk more or less likely to have event of interest?
  - (the term “competing risk" has become shorthand for a setting in which your results are in doubt)

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Choice of a Primary Outcome

Issues with clinical outcomes

- Goal of clinical trial is to establish whether an experimental treatment will prevent a particular clinical outcome
  - Incidence of disease
  - Decreased quality of life
  - Mortality
- Relevant clinical outcomes are often relatively rare events that occur after a significant delay
  - Believe that earlier interventions have greater chance of benefit
- It can also be logistically difficult to measure a clinical outcome
  - Quality of life needs to be assessed over a sufficiently long period of time

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
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Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Choice of a Primary Outcome

Impact on trial design

- Large sample size required to assess treatment effect on rare events
- Long period of follow-up needed to assess endpoints
- Isn't there something else that we can do?
- A tempting alternative is to move to "surrogate" endpoints...

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Choice of a Primary Outcome
Clinical Endpoints
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Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
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Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Motivation for 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

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
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Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Identifying potential surrogates

- 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

Surrogate Endpoints

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Examples of surrogates

- Colon cancer prevention
  - Two-fold increase in risk of colon cancer for patients with adenomatous colon polyps
  - Prevention directed toward preventing colon polyps
  - Treatment effect measured by decreased incidence of colon polyps
  - True clinical outcome is preventing mortality

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

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Examples of surrogates

- HIV/AIDS
  - HIV leads to suppression of CD4 cells
  - Decreased CD4 levels correlates with development of AIDS
  - Treatment effects measured by following CD4 counts
  - True clinical outcome is prevention of morbidity and mortality

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

SISCR
UW - 2016

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Examples of surrogates

- Coronary heart disease
  - Poor prognosis in patients with arrhythmias following heart attack
  - Therapies directed toward preventing arrhythmias
  - Treatment effects measured by prevention of arrhythmias
  - True clinical outcome is prevention of mortality

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Examples of surrogates

- Liver failure
  - Poor prognosis in patients who develop renal failure
  - Therapies directed toward treating renal failure (dialysis)
  - Treatment effects measured by creatinine, BUN
  - True clinical outcome is prevention of mortality

Surrogate Endpoints

Examples of surrogates

- Other examples that have been used historically include
  - 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

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

Problem with surrogates

- Establishing biologic activity does not always translate into effects on the clinical outcome
- May be treating the symptom, not the disease
  - Concorde: ZDV improves CD4, not survival
  - CAST: encainide, flecainide prevents arrhythmias, worsens survival
- May be missing effect through other pathways
  - Intl CGD group: Gamma-INF no affect on biomarkers, decreases serious infections

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Examples of Problems with Surrogate Endpoints

Ex: Concorde Trial (Lancet, 1993)

- Asymptomatic HIV positive patients
- Randomize to
  - Immediate ZDV (n = 877)
  - Placebo then progression to ZDV (n = 872)
- Mean follow-up: 3 years

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Examples of Problems with Surrogate Endpoints

Ex: Concorde Trial (Lancet, 1993)

- Observed CD4 changes
- 3 mos relative to baseline
  - Immediate ZDV: +20 cells
  - Placebo: -10 cells
- Difference between treatment arms
  - 3 mos: 30 cells (P < .0001)
  - 6 mos: 35 cells (P < .0001)
  - 9 mos: 32 cells (P < .0001)

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: Concorde Trial (Lancet, 1993)

- However, more deaths observed on ZDV arm with roughly equal 3-year survival rate

	ZDV (n = 877)	Placebo (n = 872)
AIDS / Death	175	171
Death	95	76
3 year survival	92%	93%

"Results cast doubt on the value of using changes over time in CD4 count as a predictive measure for effects of antiviral therapy on disease progression and survival."

Ex: HIV Meta-Analysis

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: HIV Meta-analysis

- Review of ZDV, ddI and ddC on Surrogate Markers and Clinical Endpoints
  - 16 trials reviewed by NIAID S.O.T.A. Panel, Jun 93

		AIDS/Death		Survival			
		+	-	+	-	--	?
CD4	+	7	6	2	6	3	2
Effect	-	1	2	2	1	0	0

Ex: CAST

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: Cardiac Arrhythmia Suppression Trial (CAST)

- Arrhythmia a risk factor for sudden death following a myocardial infarction
- Antiarrhythmic drugs (encainide and flecainide) successfully decrease incidence of arrhythmias
- CAST
  - Placebo controlled trial using mortality as outcome
  - Encainide and flecainide TRIPLE the death rate

Ex: CGD

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
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Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: Chronic Granulomatous Disease (CGD)

- CGD leads to recurrent serious infections
- Gamma interferon increases bacterial killing and superoxide production?
- International CGD Study Group Trial of Gamma-INF
  - 70% reduction in recurrent serious infections
  - Essentially no effect on biological markers

Surrogate Endpoints

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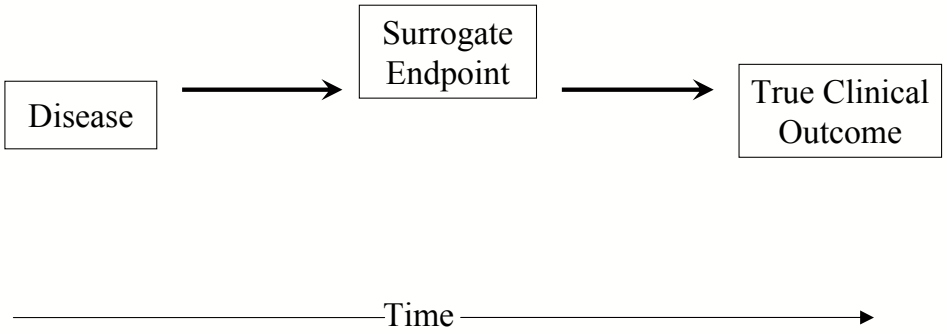
Scenario 1: Ideal Surrogate

- Disease progresses to Clinical Outcome only through the Surrogate Endpoint



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

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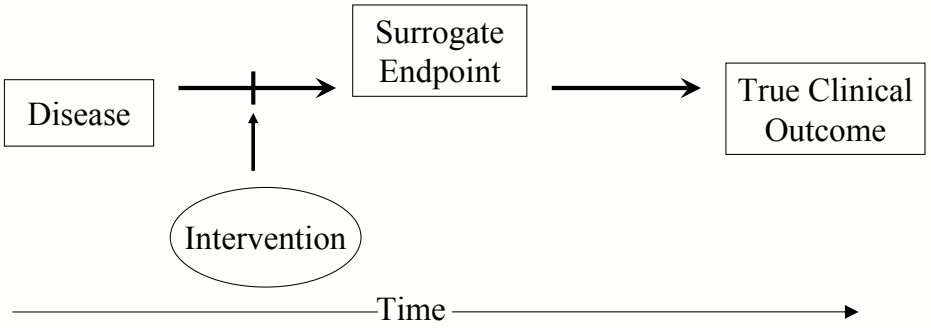
Scenario 1a: Ideal Surrogate Use

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



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

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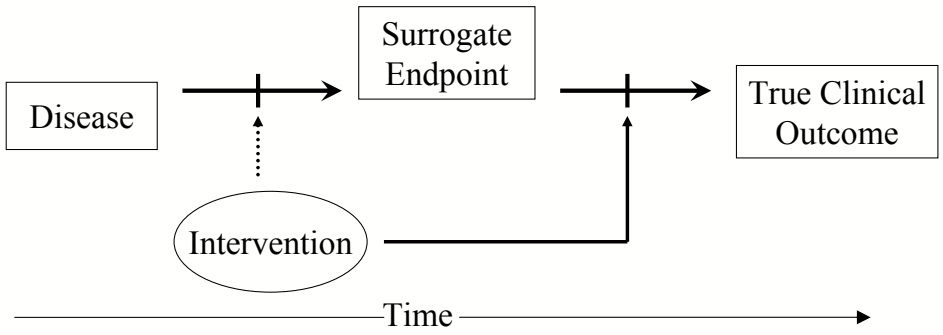
Scenario 1b: Inefficient Surrogate

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



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

SISCR
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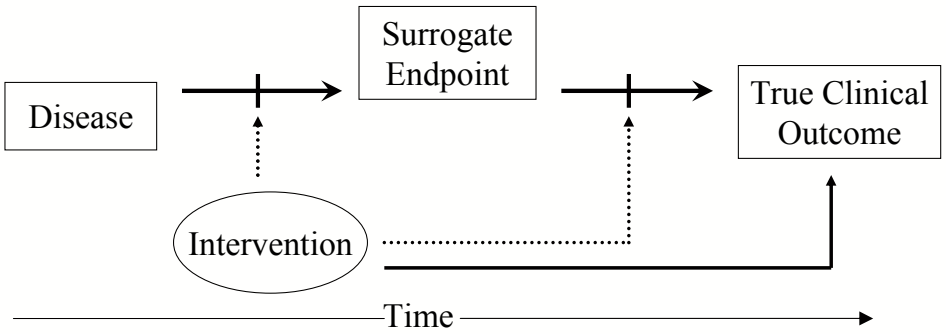
Scenario 1d: Dangerous Surrogate

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



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

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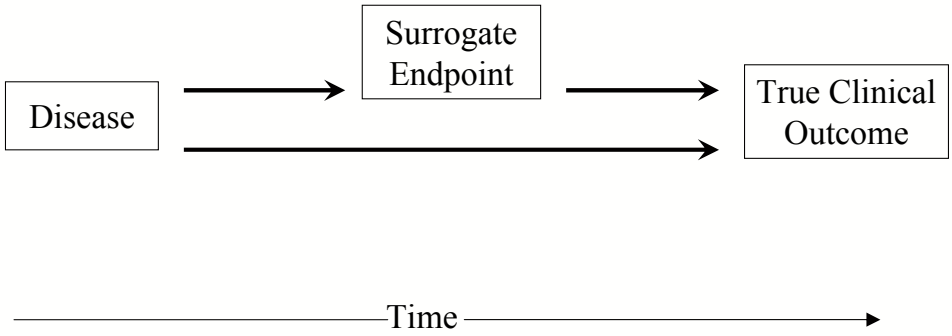
Scenario 2: Alternate Pathways

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



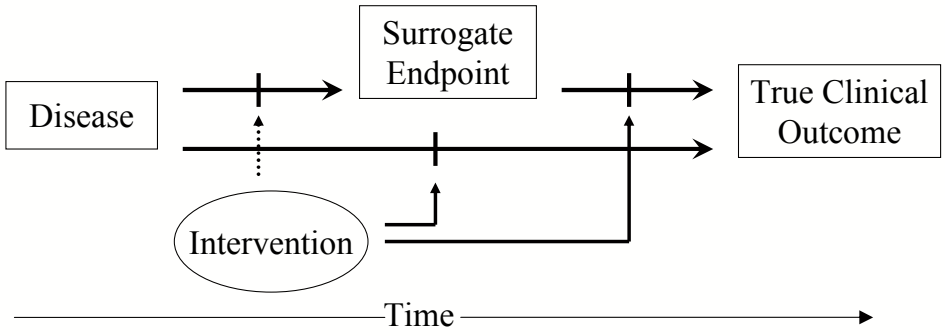
Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

SISCR
UW - 2016

Scenario 2b: Inefficient Surrogate

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



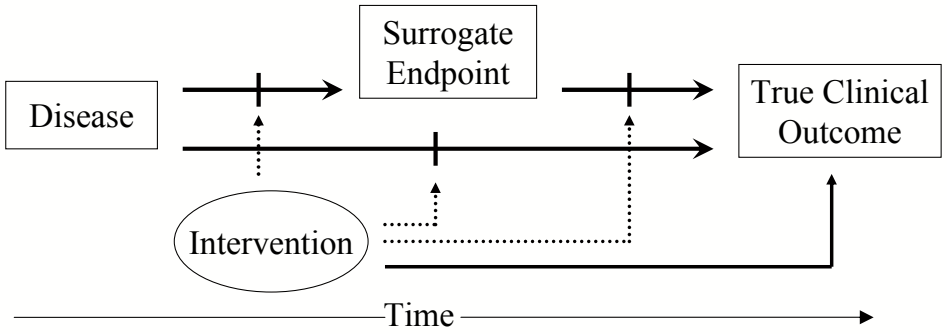
Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

SISCR
UW - 2016

Scenario 2d: Dangerous Surrogate

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



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

SISCR
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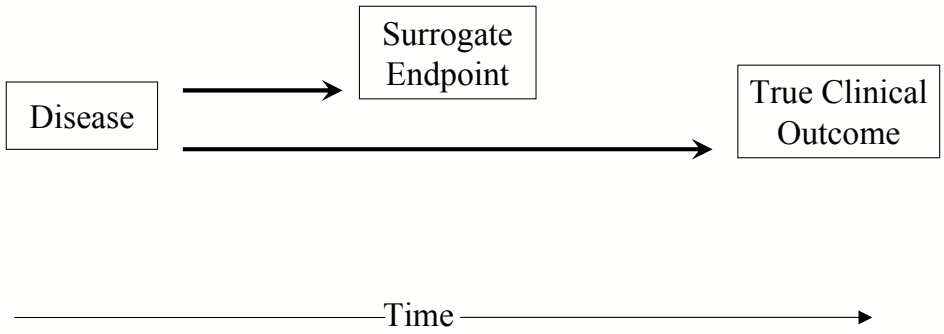
Scenario 3: Marker

- Disease causes Surrogate Endpoint and Clinical Outcome via different mechanisms



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

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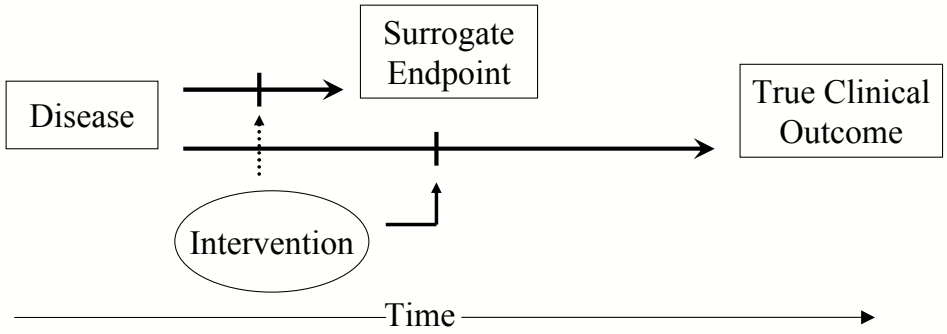
Scenario 3b: Inefficient Surrogate

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



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

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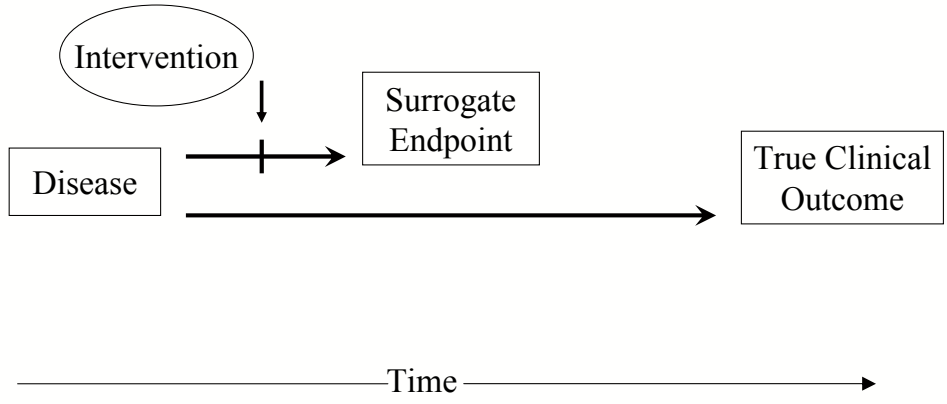
Scenario 3c: Misleading Surrogate

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

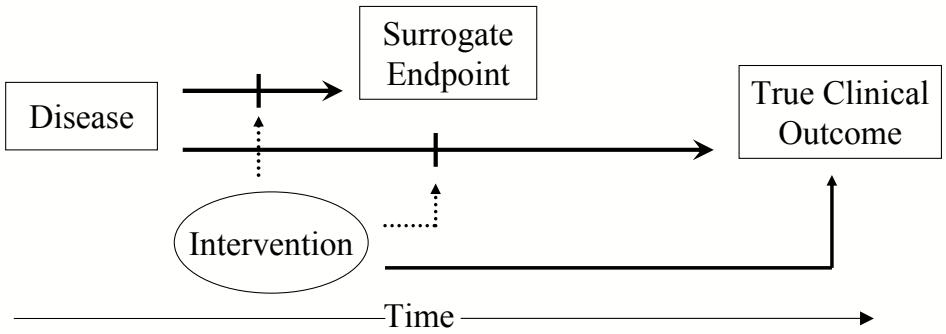


Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Surrogate Endpoints

Scenario 3d: Dangerous Surrogate

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



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
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Surrogate Markers
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HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: HIV Meta-Analysis

Ex: HIV Meta-analysis

- Review of ZDV, ddI and ddC on Surrogate Markers and Clinical Endpoints
  - 16 trials reviewed by NIAID S.O.T.A. Panel, Jun 93

		AIDS/Death		Survival			
		+	-	+	-	--	?
CD4	+	7	6	2	6	3	2
Effect	-	1	2	2	1	0	0

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
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HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: HIV Meta-Analysis

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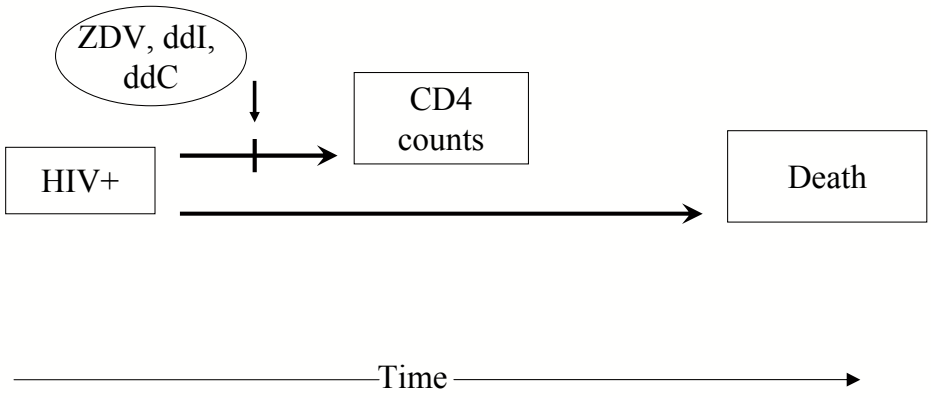
Scenario 3c: Misleading Surrogate



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Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: HIV Meta-Analysis

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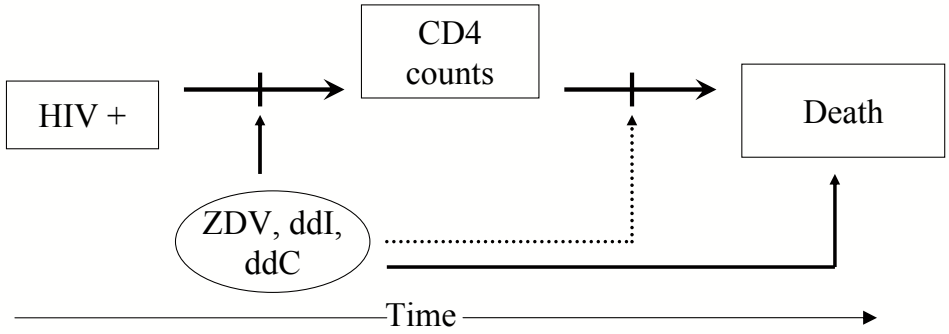
Scenario 1d: Dangerous Surrogate



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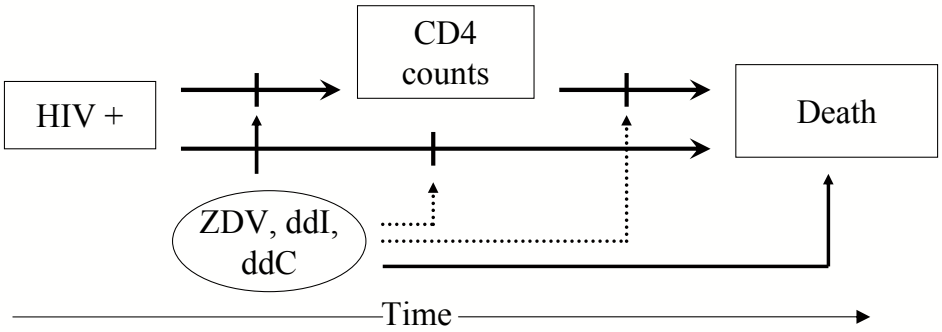
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: HIV Meta-Analysis

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Scenario 2d: Dangerous Surrogate



Ex: CAST

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
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Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: Cardiac Arrhythmia Suppression Trial (CAST)

- Arrhythmia a risk factor for sudden death following a myocardial infarction
- Antiarrhythmic drugs (encainide and flecainide) successfully decrease incidence of arrhythmias
- CAST
  - Placebo controlled trial using mortality as outcome
  - Encainide and flecainide TRIPLE the death rate

Ex: CAST

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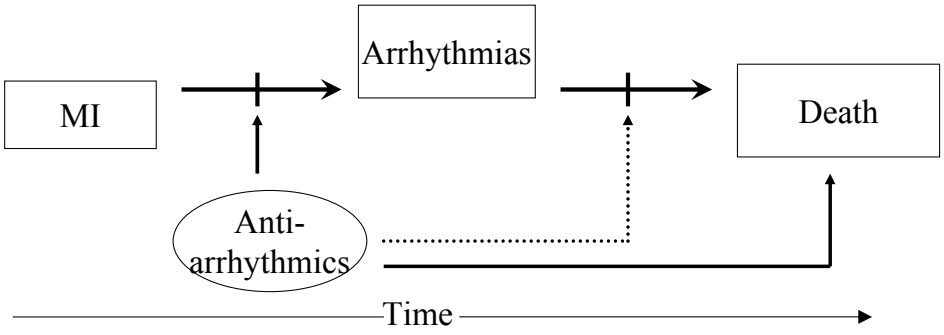
Scenario 1d: Dangerous Surrogate



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Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: CAST

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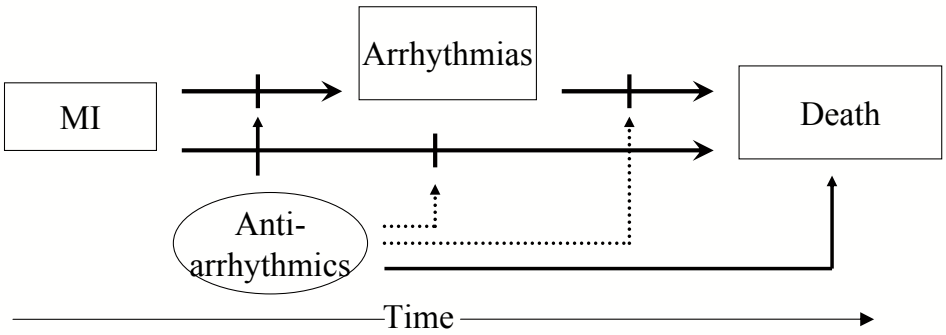
Scenario 2d: Dangerous Surrogate



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: CGD

Ex: Chronic Granulomatous Disease (CGD)

- CGD leads to recurrent serious infections
- Gamma interferon increases bacterial killing and superoxide production?
- International CGD Study Group Trial of Gamma-INF
  - 70% reduction in recurrent serious infections
  - Essentially no effect on biological markers

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: CGD

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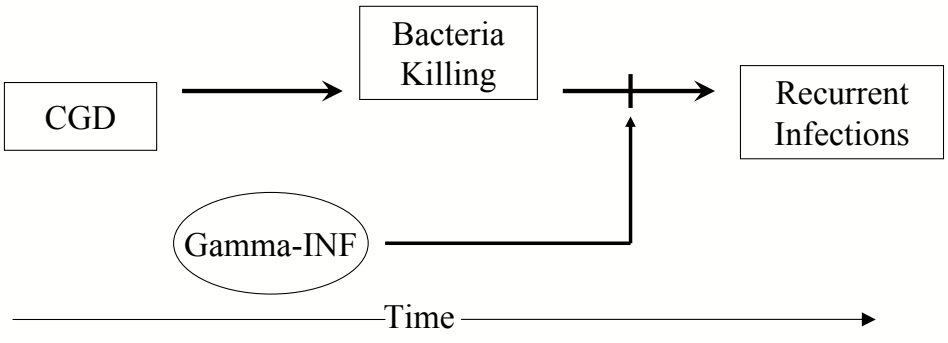
Scenario 1b: Inefficient Surrogate



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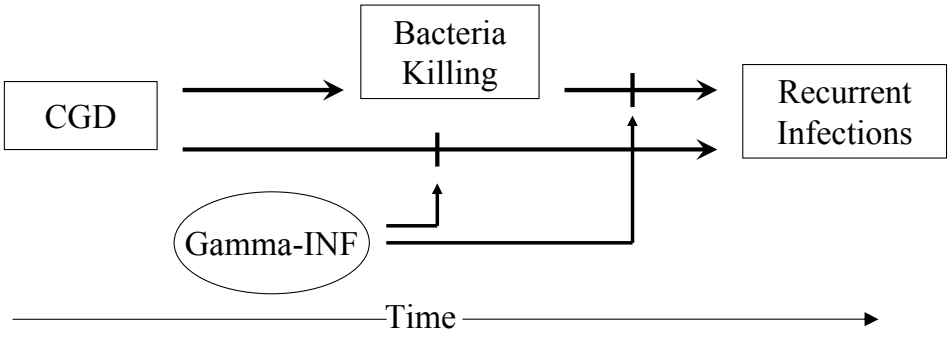
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Ex: CGD

Scenario 2b: Inefficient Surrogate



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Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Validation of Surrogate Outcomes

Can we validate a surrogate endpoint?

- Many proposed fixes for surrogate outcomes revolve around “validation" of particular surrogate outcomes
  - This is generally very difficult to do
- Is there a way to validate a surrogate endpoint by establishing which causal pathway holds?
- What doesn't work...
  - It is not sufficient to establish that the surrogate endpoint predicts the clinical outcome in each treatment group separately
  - Treatment can affect the distribution of the surrogate endpoint while increasing mortality in every level

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
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Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Validation of Surrogate Outcomes

What doesn't work...

- Consider the following hypothetical example

	Treatment		Control	
Surrogate	n	% die	n	% die
Low	30	50%	10	30%
Medium	40	60%	30	40%
High	30	70%	60	50%
Total	100	60%	100	45%

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
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HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
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Ex: CARET

- Beta-carotene supplementation for prevention of cancer in smokers
- Treatment group had excess cancer incidence and death
- Within each group, subjects having higher beta-carotene levels in their diet had better survival

Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Validation of Surrogate Outcomes

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Prentice's Criteria (SIM, 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

Validation of Surrogate Outcomes

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
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Alternate Pathways
Surrogate Markers
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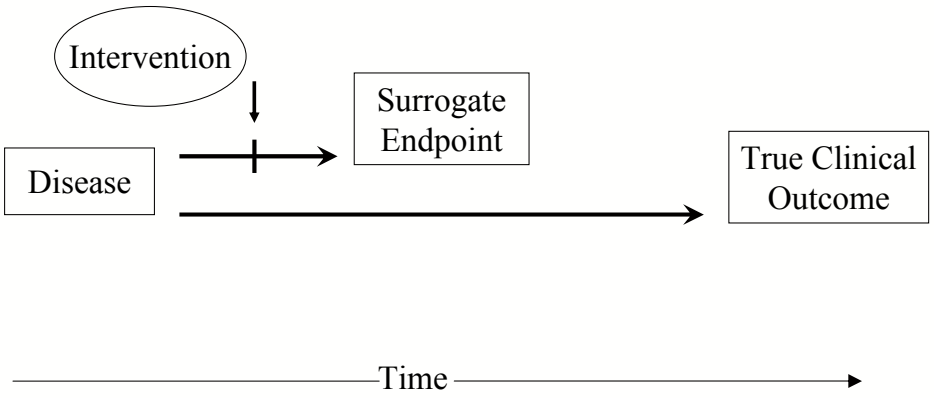
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Does Not Satisfy Criterion

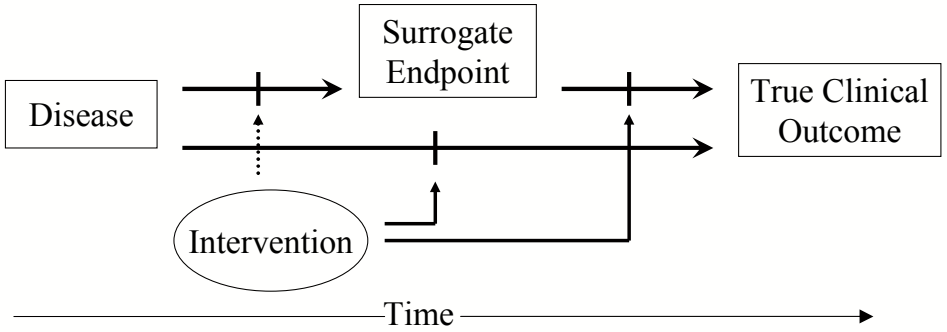
- Treatment has no effect on Clinical Outcome



Validation of Surrogate Outcomes

Does Not Satisfy Criterion

- Adjusting for Surrogate Endpoint will not capture all of Treatment effect



Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

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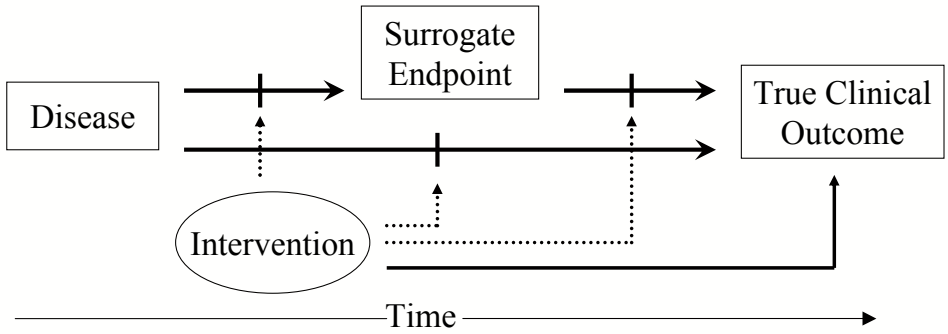

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
Surrogate Endpoints
Motivation and Examples
Examples of Problems with Surrogates
Ideal Surrogate
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CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

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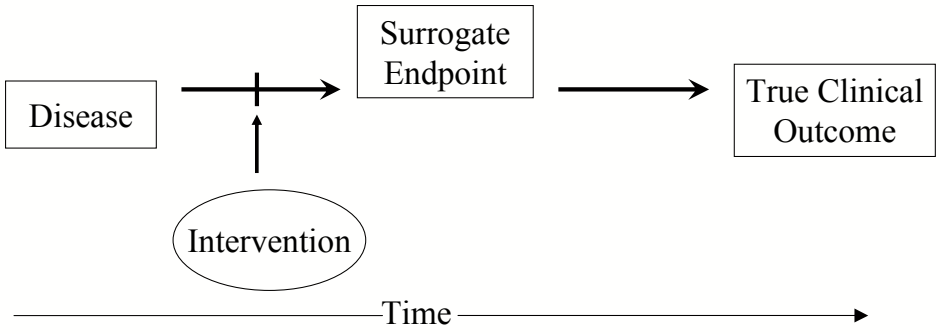
Satisfies Criterion

- Adjusting for Surrogate Endpoint will remove effect of Treatment on Clinical Outcome



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Clinical Endpoints
Multiple Endpoints and Competing Risks
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Examples of Problems with Surrogates
Ideal Surrogate
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Surrogate Markers
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HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Validation of Surrogate Outcomes

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What is the implication?

- The validity of a surrogate endpoint is dependent upon
  1. the disease
  2. the clinical outcome
  3. the treatment
- Thus it is not possible to validate a surrogate endpoint for every combination of treatment and disease without doing a trial looking at the clinical outcome

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Clinical Endpoints
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Surrogate Markers
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HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria

Validation of Surrogate Outcomes

What is the implication?

- When considering a number of treatments that can be presumed to act in a similar manner, meta-analyses of clinical trial results can sometimes be used to establish the suitability of a surrogate endpoint for other treatments in that class
  - Even then, we must watch for outliers within such a meta-analysis
  - Such outliers suggest that the presumption of similar action is violated

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Clinical Endpoints
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CAST
CGD
Validation of Surrogate Outcomes
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Validation of Surrogate Outcomes

At the end of the day

- 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

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Choice of a Primary Outcome
Clinical Endpoints
Multiple Endpoints and Competing Risks
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Alternate Pathways
Surrogate Markers
Examples Revisited
HIV Meta-Analysis
CAST
CGD
Validation of Surrogate Outcomes
Prentice's Criteria