Biost 524: Design of Medical Studies

Lecture 6:
Choice of Outcomes

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April 26, 2010

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Lecture Outline

- Criteria for Outcomes
- Surrogate Outcomes
  - Examples
  - Causal Pathways
  - Validation

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Primary Outcomes

Criteria

Where am I going?

- The goal of a RCT is to find effective treatment indications
- The primary outcome is a crucial element of the indication

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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

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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

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Statistics and Game Theory

- 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
    - the number of multiple comparisons, and
    - the correlation between the endpoints

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Ex: Level 0.05 per Decision

- Experiment-wise Error Rate
-

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

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Primary Endpoint: Clinical

- Consider (in order)
  - 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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Additional Endpoints

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

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Primary Endpoint: Clinical

- 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 the above
      - But how can we be sure?
  - 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

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Multiple Endpoints

- Sometimes we must consider multiple endpoints
- We then control experimentwise error
- Possible methods
  - 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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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

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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)

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Goal of Clinical Trial

- Establish whether an experimental treatment will prevent a particular clinical outcome
  - Incidence of disease
  - Decreased quality of life
  - Mortality

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Problems

- Relevant clinical outcomes are often relatively rare events that occur after a significant delay
  - Believe that earlier interventions have greater chance of benefit
- Difficulty in measuring clinical outcome
  - Quality of life needs to be assessed over a sufficiently long period of time

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Impact on Clinical 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?

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Surrogate Outcomes

Examples

Where am I going?

- The goal of a RCT is to find effective treatment indications
- Statistical and logistical constraints often lead to the desire for surrogate outcomes
  - But these have led us astray in the past

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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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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

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Examples

- 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

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Examples

- 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

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Examples

- 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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Examples

- 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

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Examples

- Other surrogate endpoints used historically
  - 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

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Problem

- Establishing biologic activity does not always translate into effects on the clinical outcome
- May be treating the symptom, not the disease
  - Examples
    - Concorde: ZDV improves CD_4, not survival
    - CAST: encainide, flecainide prevents arrhythmias, worsens survival
- May be missing effect through other pathways
  - Example
    - Intl CGD group: Gamma-INF no affect on biomarkers, decreases serious infections

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Example: Concorde Trial

- (Lancet, April 3, 1993)
  - Asymptomatic HIV positive patients
  - Randomize to
    - Immediate ZDV (n = 877)
    - Placebo then progression to ZDV (n = 872)
  - Mean follow-up: 3 years

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Concorde Trial: Surrogate Results

- 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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Concorde Trial: Clinical Results

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

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Concorde Trial: Conclusions

- "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."

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Example: 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

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Example: CAST

- Cardiac Arrhythmia Suppression Trial
  - 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

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Example: CGD

- 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

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Surrogate Outcomes

Possible Mechanisms

Where am I going?

- Understanding the pitfalls of surrogate outcomes requirese thinking about the mechanisms of treatments

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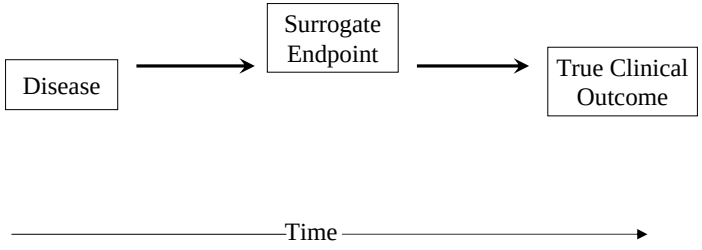
Scenario 1: The Ideal

- Disease progresses to Clinical Outcome only through the Surrogate Endpoint



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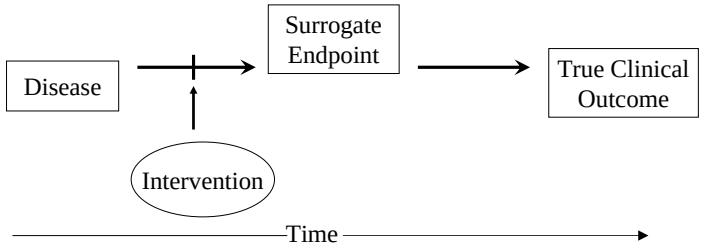
Scenario 1a: Ideal Surrogate Use

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



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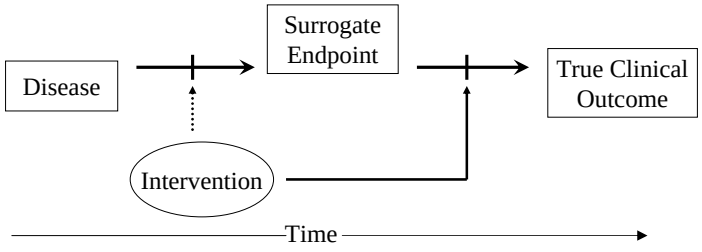
Scenario 1b: Inefficient Surrogate

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



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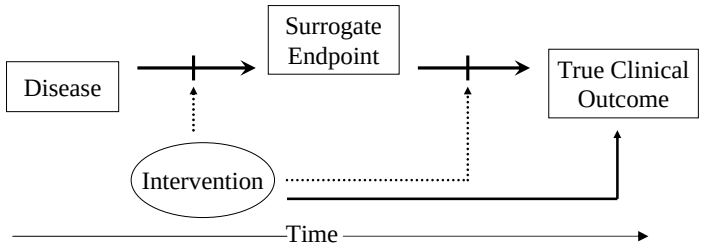
Scenario 1d: Dangerous Surrogate

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



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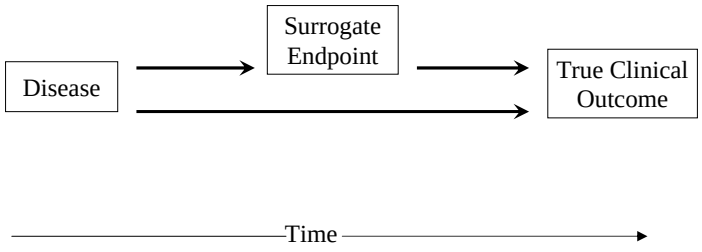
Scenario 2: Alternate Pathways

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



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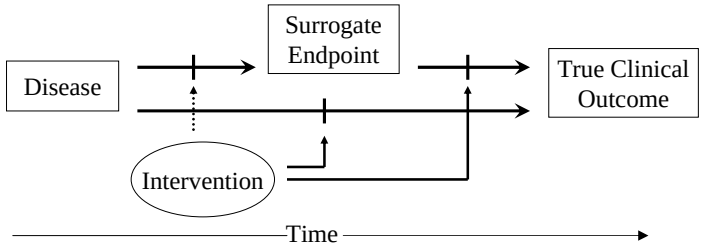
Scenario 2b: Inefficient Surrogate

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



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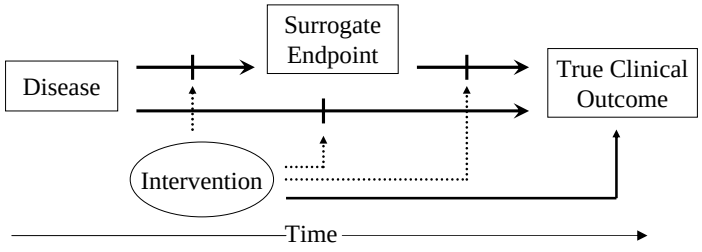

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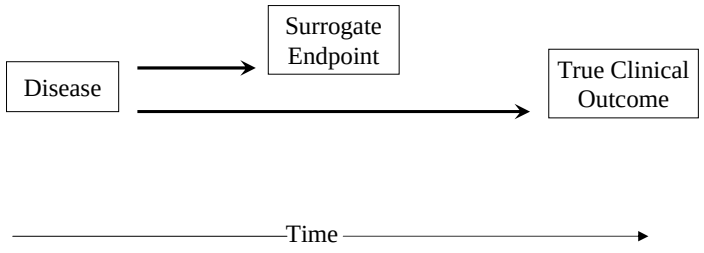
Scenario 3: Marker

- Disease causes Surrogate Endpoint and Clinical Outcome via different mechanisms



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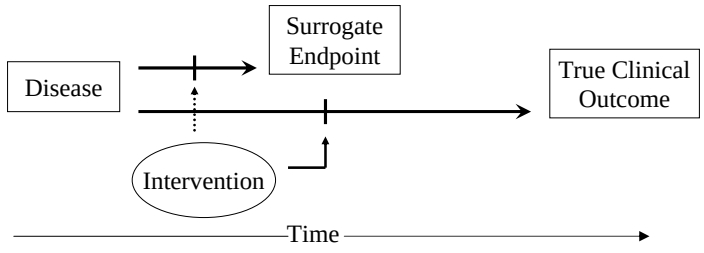

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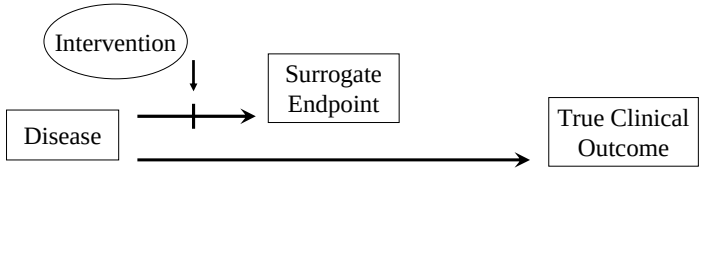
Scenario 3c: Misleading Surrogate

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



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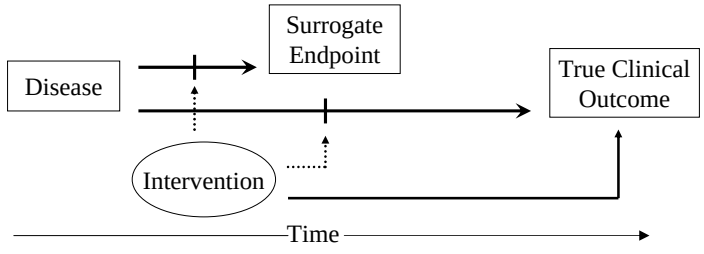

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Surrogate Outcomes

Examples Revisited

Where am I going?

- The goal of a RCT is to find effective treatment indications
- Statistical and logistical constraints often lead to the desire for surrogate outcomes
  - But these have led us astray in the past

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Illustration of the Problem

(Revisited)

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Example: Meta-analysis

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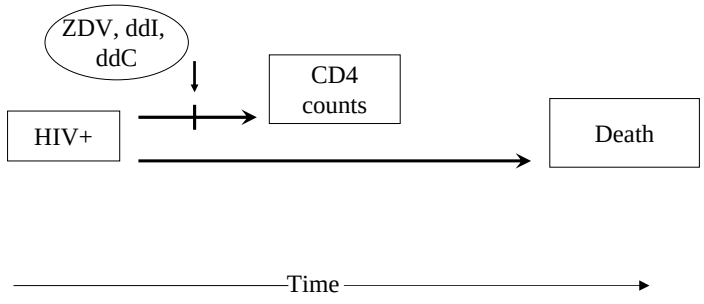

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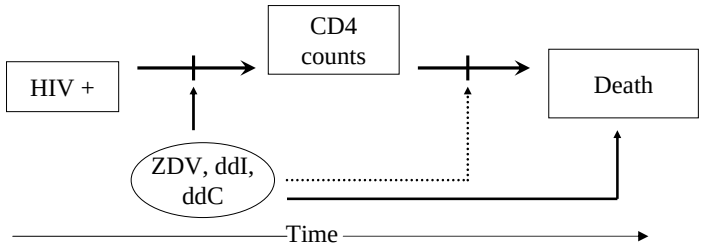
Scenario 1d: Dangerous Surrogate



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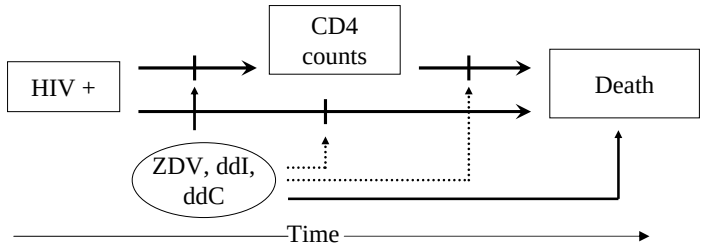
Scenario 2d: Dangerous Surrogate



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Example: CAST

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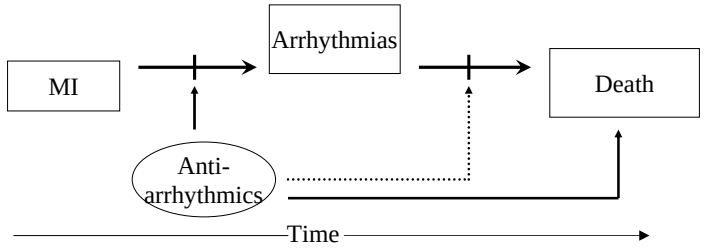

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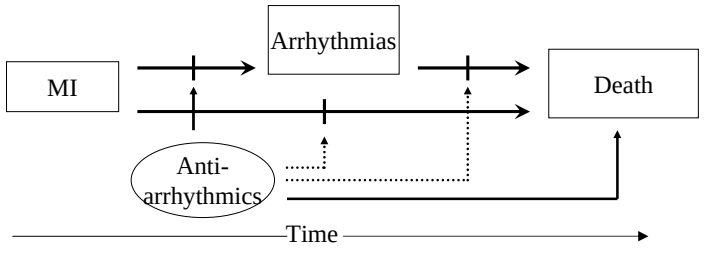

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Example: CGD

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  - CGD leads to recurrent serious infections
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    - 70% reduction in recurrent serious infections
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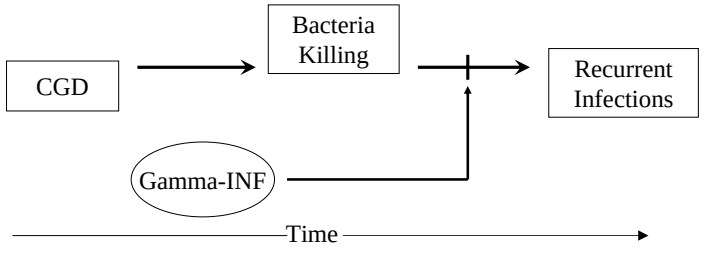
Scenario 1b: Inefficient Surrogate



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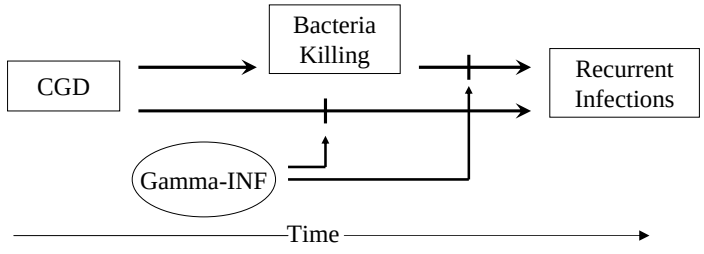
Scenario 2b: Inefficient Surrogate



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Surrogate Outcomes

Validation

Where am I going?

- Many proposed fixes for surrogate outcomes revolve around "validation" of particular surrogate outcomes
  - This is generally very difficult to do

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Question

- Is there a way to validate a surrogate endpoint by establishing which causal pathway holds?

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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

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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%

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Example: 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

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Prentice's Criteria

- A surrogate endpoint must be correlated with the clinical outcome
- A surrogate endpoint must fully capture the net effect of treatment on the clinical outcome
  - After adjustment for the surrogate endpoint, there must be no treatment effect on the clinical outcome

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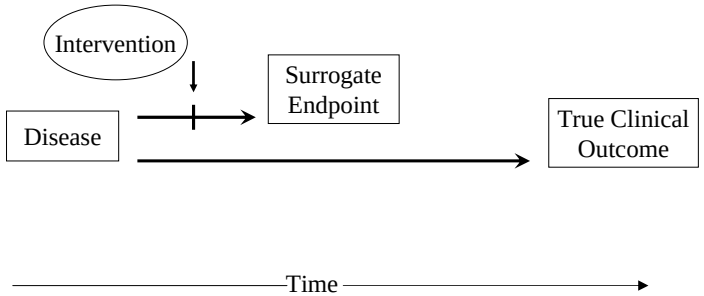
Does Not Satisfy Criterion

- Treatment has no effect on Clinical Outcome



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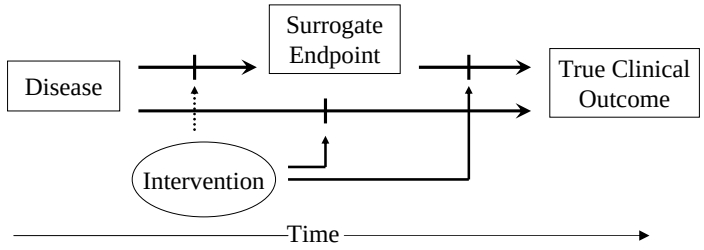
Does Not Satisfy Criterion

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



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Does Not Satisfy Criterion

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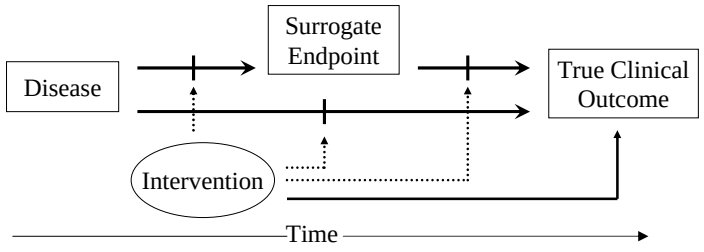

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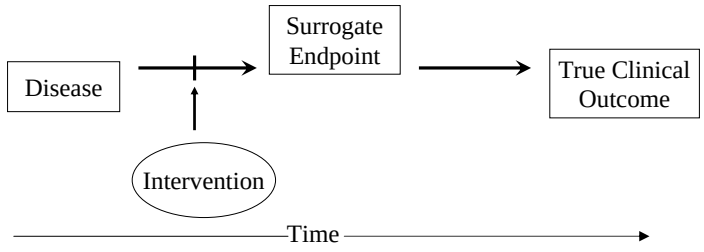
Satisfies Criterion

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



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However…

- The validity of a surrogate endpoint is dependent upon
  - the disease
  - the clinical outcome
  - 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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Hence…

- 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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Bottom Line

- 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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