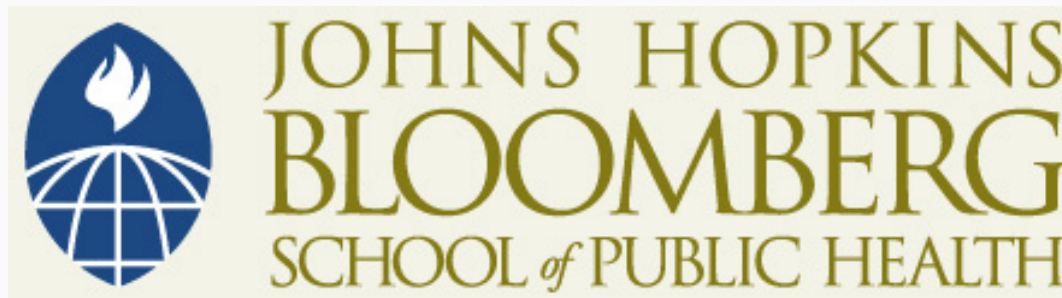


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Outcomes, Surrogates, Composite Endpoints

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Section A

Outcomes and Endpoints

What Are They?

- Synonyms
 - Response variables
 - Outcome measures
- Functional definition
 - What the trial is measuring
 - How it is measured

Definitions

- Outcomes measured during the course of the trial and they define and answer the question (Friedman, Furberg, and DeMets)
- A result, condition, or event associated with individual study patients that is used to assess the efficacy of the study treatment (Meinert)

Definitions

- . . . Evaluated on the basis of carefully defined criteria which are accurate and chosen to suit the aim of the trial (Spriet and Simon)
- a) An explanatory type, concerned essentially with the course of the disease and expressed as far as possible in strictly defined biological terms (Schwartz, Flamant, Lellouch)
- b) A pragmatic type, which may also be concerned with the course of the disease in an overall way (Schwartz, Flamant, Lellouch)

Before the Trial . . .

- Hypothesis: primary question
- Intervention and desired effect
- Measurement method
- Available safety data
- Missing data frequency
- Anticipated control group event rate or endpoint distribution

Endpoints vs. Objectives

- Endpoint \neq objective (but related)
- Objective = why do the trial
- Example
 - Objective: to test whether drug A is a superior analgesic to drug B
 - Endpoint: incidence of pain relief on VAS
 - Pick appropriate endpoint or trial might not meet objectives; but even with appropriate endpoint, trial may fail to meet objectives because A is inferior to B
 - So the right endpoint is crucial . . . but not necessarily a guarantee

Characteristics of a Good Endpoint

- Objective
- Reproducible
- Sensitive/specific
- Unbiased
- Clinically relevant
- Chosen a priori
- Active follow-up
- Easy to interpret
- Free of errors of ascertainment or measurement
- Stable
- Observable independent of Rx assignment

Appropriate Endpoints

- Depend on . . .
 - Phase of the trial
 - Disease
 - Therapy
 - Feasibility

Different Types of Endpoints

- Clinical vs. surrogate
- Landmark vs. time-to-event
- Binary vs. continuous
- Single event vs. composite
- Objective vs. subjective
- Cause-specific vs. all-cause

Binary vs. Continuous

- We can measure blood pressure in mmHg
 - We can measure hypertension as diastolic blood pressure $\geq 95\text{mmHg}$
- We can measure weight in Kg, or as a body mass index (BMI) in Kg/m^2
 - We can measure obesity as $\text{BMI} \geq 25\text{Kg}/\text{m}^2$
- We can measure survival as median survival time (months) or as a five-year survival rate

Binary vs. Continuous

- There are arguments in favour of continuous measurements
 - More efficient (need fewer patients)
 - Avoids arbitrary cut-off values
- There are arguments in favour of binary endpoints
 - Simpler to understand
 - More clinically relevant

Binary vs. Continuous

- If I am the patient, I want my outcome (blood pressure, body mass index, etc.) to be “as good as possible”
 - The continuous endpoint
- If I am the physician, I want to know which treatment will cure the patient “sufficiently” so that they need no further treatment
 - The binary endpoint

Objective vs. Subjective

- Objective
 - Assessment less likely to be influenced by other factors (bias)
 - Examples: mortality, culture + infection
- Subjective
 - Ways to minimize bias
 - ▶ Randomization, blinding
 - ▶ Central evaluation/adjudication committee
 - ▶ Clear case definition

Cause-Specific vs. All-Cause

- Cause-specific
 - Possible bias in ascertainment of causality
 - May exclude some events related to treatment in unknown ways
- All-cause
 - Advantages: objective and conservative
 - Disadvantages: may reflect events extraneous to the disease or treatment

Primary Endpoint

- Most trials will measure many endpoints
 - This makes efficient use of research effort
 - But leads to difficulties with the analysis
- It is important to pre-define a single, primary endpoint

Co-Primary Endpoints

- In some cases, benefit on one endpoint may not be sufficient
 - In acute cardiac failure, immediate (e.g., within two hours) relief of symptoms may be necessary
 - Mid-term (e.g., 14 days) mortality may also be necessary
- In such cases, we refer to co-primary endpoints
- Both are necessary; not either/or

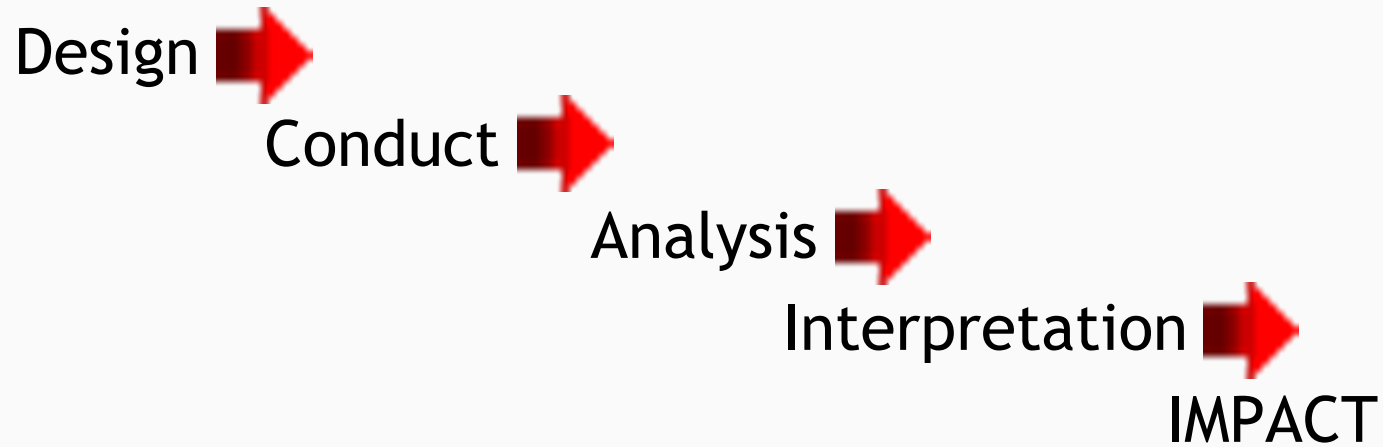
Composite Endpoints

- Different to co-primary
- Here, either of the separate endpoints may be sufficient
 - Common example in stroke . . . 28-day mortality or myocardial infarction or recurrent stroke
 - Having any one (or more) of these endpoints would be considered a treatment failure

Composite Endpoints

- Important to look at effects on each of the components
- Similar effects (certainly, direction of effects) should generally be seen on all components
- No one component should dominate the endpoint
 - If it does, this might limit the licensed indication

Choice of Endpoint Effects . . .



In the Next Section We'll Look at . . .

- Surrogate endpoints
 - Biomarkers
 - Reasons and benefits
 - Limitations



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Section B

Surrogate Endpoints

Endpoint Selection

- Why?
 - Need relevant endpoints
 - Yield reproducible scientific information
 - Reflect effect of intervention on study participants
 - Characterize clinical benefits
 - ▶ Directly
 - ▶ Surrogate

- FDA definition
 - Biomarker: “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”
- Although a biomarker can serve as a surrogate endpoint, the terms are not synonymous

Surrogate Endpoints

- Clinically important endpoint may be difficult to measure
 - Survival may be very long, such long term follow-up may not be practical
 - Small differences
- Change in surrogate may be much earlier
- Surrogate measures should predict/be correlated with benefit, but correlation alone is insufficient

Surrogate Endpoints

- May be more sensitive to intervention effects
 - Blood pressure (CVD)
 - Intraocular pressure (glaucoma)
 - PSA levels (prostate cancer)
 - Tumor size (cancer)
 - CD4+ count (progression to AIDS)
- May allow smaller/faster studies

Surrogate Endpoints

- May be more objective than clinical endpoints
 - X-rays of arthritic joints vs. assessment of inflammation or pain
 - Change on MRI scan vs. report of disability (MS)
 - Observer must be blinded to treatment even if neither patient nor physician is
- But be careful . . . surrogates are difficult to validate

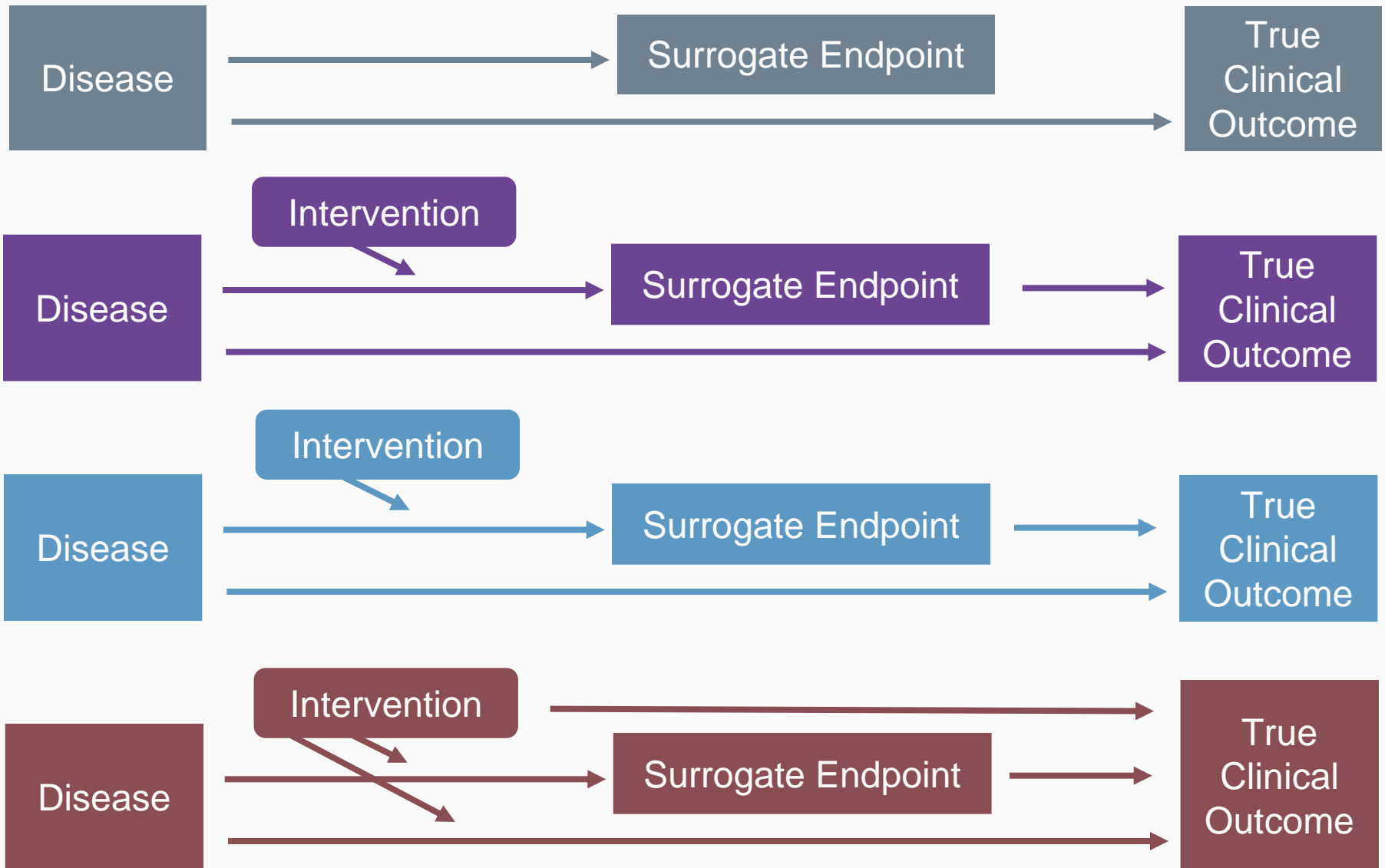
Surrogate Endpoints

- Validation
 - Correlated with clinical endpoint
 - Correlated with change in clinical endpoint
 - Both must be measured in same trial
 - Optimal to validate in phase II and apply in phase III
 - Often product is approved in phase III and surrogate validated in phase IV
 - ▶ This is not ideal

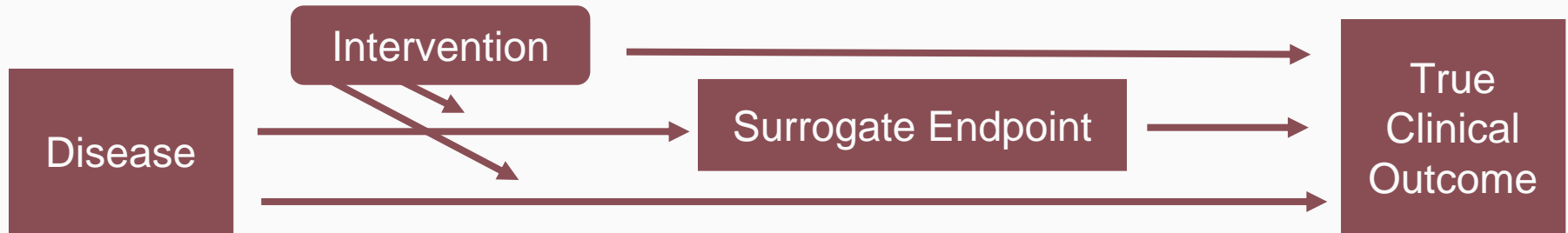
Characteristics

- Measured reliably, simply, and without invasive procedures
- In the causal chain
- Responsive/sensitive to intervention effects
- Same inferences
- Short latency

Surrogate Endpoints



Ideal Scenario



- The ideal scenario in which as surrogate endpoint is reliably used
- Sequence
 - Disease
 - As time progresses, treatment is given
 - Time progresses further, and the surrogate endpoint is measured
 - Time progresses further still, the true clinical outcome is observed

CVD Example

- Approval based on suppression of arrhythmias
- Surrogate—arrhythmias
- Clinical endpoint—mortality
- Encainide/flecainide in CAST
- Placebo-controlled survival study \Rightarrow three times mortality!

Biological Plausibility

- Epidemiological evidence
- Quantitative reliability
- Credible animal model
- Path understood
- Mechanism of action
- Surrogate late
- Inconsistent epidemiology
- No quantitative reliability
- No animal model
- Path not clear
- Novel action unstudied
- Surrogate remote

Success in Clinical Trials

- Effect on surrogate within class
- Effect on surrogate across classes
- Negative outcome without explanation
- Inconsistent across classes

Risk/Benefit and Public Health

- Serious or life-threatening with no alternative
- Large safety database
- Short-term use
- Difficulty studying clinical endpoint
- Non-serious disease with alternative therapies
- Little safety data
- Long-term use
- Easy to study clinical endpoint
- Long-delayed small effect

Risk/Benefit and Licensing Decisions

- All medicines should be beneficial (do positive good)
- All medicines have side effects
- Benefits must outweigh risks
- Difficult to know size of clinical benefit (if measured by a surrogate)
- So difficult to know if size of benefit outweighs size of risk

Evaluation of Surrogate

- Proportion of treatment effect explained (PTE) by surrogate
- PTE of one represents the ideal
- PTE near one only when the causal pathway and the intervention action through the surrogate are known

In the Next Lecture We'll Look at . . .

- Analysis issues
 - Intention to treat
 - Who wants to know the answer?