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 ≠ 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 BMI \( \geq 25\text{Kg/m}^2 \)
- 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
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
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
Biomarker

- 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
SurrogateEndpoints

- 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
The ideal scenario in which a 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 ⇒ 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
<table>
<thead>
<tr>
<th>Risk/Benefit and Public Health</th>
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<tr>
<td>Serious or life-threatening with no alternative</td>
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<td>Large safety database</td>
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<td>Short-term use</td>
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<td>Difficulty studying clinical endpoint</td>
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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

Source: Fleming, DeGruttola, and DeMets
In the Next Lecture We’ll Look at . . .

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