Primary Research Question and Definition of Endpoints

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Research Questions

Uncertainty that the investigator wants to resolve.

- Interesting, Novel, and Relevant:
  - Literature
  - Colleagues
  - Stakeholders

- Feasible: Concrete, researchable issue
Primary and Secondary Questions/Objectives

- Common error – Sinking ship: Avoid overloading the study with too many objectives and too much data collection

- A single primary question around which to focus the development of the protocol and sample size estimates

- Secondary research questions: can be related to the primary question or to other hypotheses
Main study variables

- Longitudinal Studies (cohort, RCT):
  - Endpoint
  - Outcome Measure
  - Response Variable

- Case-Control Study:
  - Exposure Variable
  - Case Definitions

- Other Study Designs:
  - Main Analysis Variables
Example

- Primary Objective: To assess the effectiveness of a new malaria vaccine
- Possible endpoints:
  - Occurrence of a malaria episode
  - Time to the occurrence of the first malaria episode
  - Occurrence of malaria related anemia
- Secondary objectives and endpoints
Example

- **Objective**
  - **Endpoint**
    - **Summary measure**
      - **Parameter**
        - Vaccine effectiveness
        - Occurrence of disease
        - VE = 1 - RR (Preventable Risk)
        - 95% CI for VE
Desired (Required) Characteristics

- **Clinical relevance** (clearly reflects research question, mechanism of action, impact on well-being of individuals).
Single primary endpoint:

- If more than one primary endpoint is used, the probability of getting a nominally significant result by chance alone is increased (Type I Error).
- If the analysis, based on several endpoints, gives conflicting results, interpretation becomes difficult.
Consistency. Primary endpoint must be capable of being assessed in all subjects consistently:

- Avoid having different endpoints for different subjects for the same primary objective.
- Avoid having different instruments or techniques applied for the measurement of the endpoint.
Desired (Required) Characteristics

- Validity of the comparisons. Unbiased ascertainment of endpoints across comparison groups:
  - The issue of blinding. Objective endpoints
  - The Misclassification problem:
    - Non-differential.
    - Differential.
Misclassification (Example)

Scenario: P. falciparum malaria in children living in holo-endemic area (EIR > 100)
- ~60% infected asymptptomatically
- MOI ~ 5 strains/child on average
- Clinical malaria diagnosis?

<table>
<thead>
<tr>
<th>Low</th>
<th>Specificity scale</th>
<th>High</th>
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<tr>
<td>Fever</td>
<td>fever+ parasitaemia</td>
<td>fever+ high parasitaemia</td>
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Misclassification (Non Differential)

Measured Treatment Effect After intervention: 25%

True Treatment Effect After intervention: 100%
Issue: Low specificity (Non-differential) in clinical outcomes = gross underestimation of true efficacy of intervention
Misclassification (Differential)

Measured Treatment Effect After intervention: 0%

True Treatment Effect After intervention: 50%
Misclassification (Differential)

**Issue:** Low specificity (Differential) in clinical outcomes = underestimation or overestimation of true efficacy of intervention
Misclassification

- **RCT:**
  - Misclassification can occur both before and after intervention. Usually non-differential due to randomization and blinding

- **Cohort:**
  - Misclassification can occur in the classification of exposure or disease

- **Case-Control:**
  - Misclassification can occur in the classification of disease or exposure
Desired (Required) Characteristics

- **Reliability.** The extent to which measurement obtained is reproducible in repeated administrations. Lack of random measurement error.
Desired (Required) Characteristics

- **Completeness.** Ascertainment of endpoints should be as complete as possible:
  - Consequences of Missing Data:
    - Sample size $\rightarrow$ Loss of power
    - Bias $\rightarrow$ Loss of validity
  - Data collection procedures and instruments
  - Follow up procedures. Participant retention
Desired (Required) Characteristics

- **Statistical Significance.** Selected endpoint should be such that it has the potential to show clinical significance statistically:
  - Clinical meaningful difference worth detecting (Effect size)
**Alternative Endpoint Definitions**

- **Surrogate Endpoints:**
  - Indicator of effect in lieu of the one of substantive interest,
    - e.g. CD4 counts for AIDS mortality
  - Rationale: Measuring effect sooner and/or for less cost
  - Highly correlated to the clinical outcome of interest:
    - Biological plausibility
    - Trial measuring both true and surrogate endpoint and studying their correlation
Surrogate Endpoints (Example)

- Cardiac Arrhythmia Suppression Trial (CAST) compared encainide and flecainide to placebo
- Trial established that the drugs were extremely beneficial in suppressing arrhythmia
- Surprisingly to cardiologists, CAST showed that the drugs tripled the death rate [Senn S. Statistical Issues in Drug Development. John Wiley, 1997.]
Alternative Endpoint Definitions

Composite endpoints:
- Combines multiple measurements into a single composite endpoint using a pre-specified algorithm
- Any one event occurs too infrequently
  - Sample size
  - Length of follow-up
- Meaningful interpretation
- Possibility of conflicting results
Composite endpoints (example):
- Primary endpoint. Occurrence of one or more of the following critical events associated with severe disease:
  - Death
  - Cardiac index less than or equal to 2.2
  - Ventricular tachycardia or fibrillation
  - Pulseless electrical activity
Final Remarks

- Choose your study endpoints (especially the primary endpoint) carefully by considering the desired characteristics discussed. Involve colleagues and recent research.
- Define endpoints in the protocol. Rationale and measurement procedures should be specified a priori.
  - “Redefinition of primary endpoints after unblinding will almost always be unacceptable,” ICH 9
Desired (Required) Characteristics

- Clinical Relevance
- Single Primary Endpoint
- Consistency
- Validity
- Reliability
- Completeness
- Statistical Significance