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
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).
Desired (Required) Characteristics

**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.
Desired (Required) Characteristics

- **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 asymptotically
- MOI ~ 5 strains/child on average
- Clinical malaria diagnosis?

**Specificity scale**

- **Low**
  - Fever
    - Fever + parasitaemia
- **High**
  - Severe anaemia
    - Cerebral Malaria
Misclassification (Non Differential)

**Issue:** Low specificity (Non-differential) in clinical outcomes

\[ = \quad \text{gross underestimation of true efficacy of intervention} \]
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)
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.]
Composite endpoints:
- Combines multiple measurements into a single composite endpoint using a \textit{pre-specified} algorithm
- Any one event occurs too infrequently
  - Sample size
  - Length of follow-up
- Meaningful interpretation
- Possibility of conflicting results
Alternative Endpoint Definitions

- 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