

Primary Research Question and Definition of Endpoints

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The Fundamentals of Clinical Research
Workshop
DMID/ICSSC

Research Questions

- Uncertainty that the investigator wants to resolve.
 - Interesting, Novel, and Relevant:
 - So What? Test
 - Consult Literature, Colleagues, Stakeholders
 - Feasible: Concrete, researchable issue
 - One study vs. several studies

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



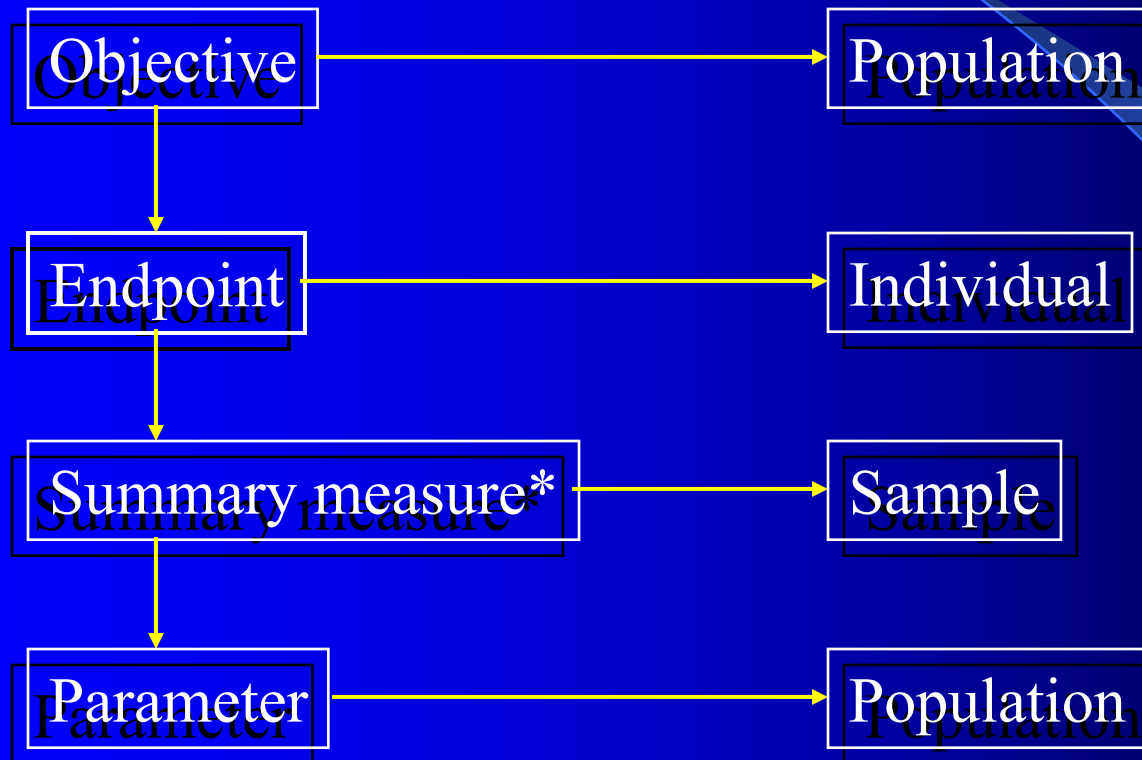
Main study variables

- Longitudinal Studies (cohort, RCT):
 - Endpoint
 - Outcome Measure
 - Response Variable
- Case-Control Study:
 - Exposure Variable
 - Case Definitions
- Other Study Designs:
 - Main Analysis Variables

Example

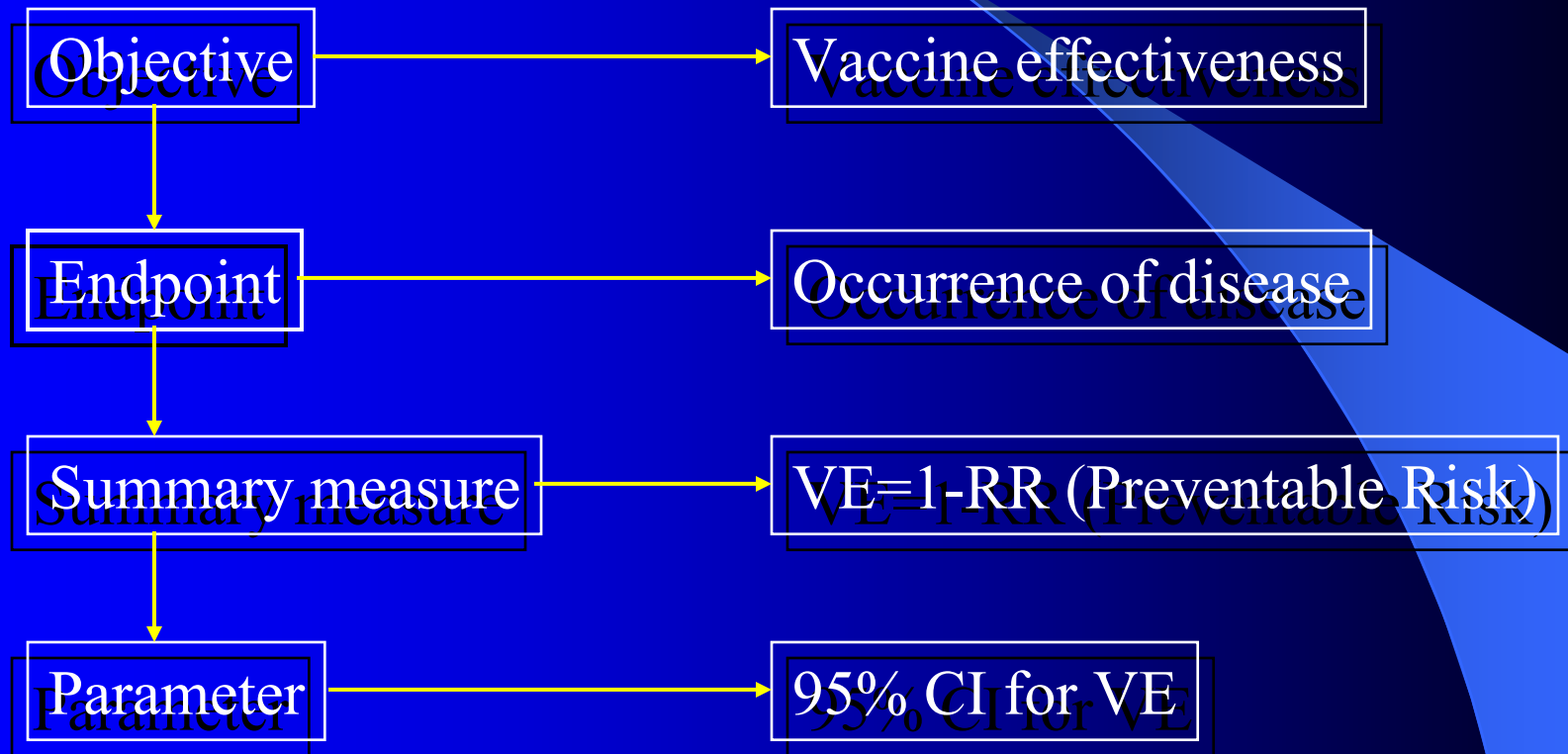
- Primary Objective: To assess the effectiveness of a new malaria vaccine
- Possible endpoints:
 - Occurrence of a malaria episode (or time to...)
 - Mortality
 - Occurrence of malaria related anemia
- Secondary objectives and endpoints
 - Acceptability

Framework



* Depends of primary analysis method

Example



Desired (Required) Characteristics

- **Clinical relevance:**
 - Endpoint should be a direct measure of how a patient feels, functions, or survives

What's Important to Patients?



Desired (Required) Characteristics

- **Single primary endpoint:**
 - Possible multiplicity problem (Increased Type I Error)
 - Interpretation may be difficult
- **Consistency**

Desired (Required) Characteristics

- **Validity**
 - **Measurement.** Lack of systematic error
 - **Comparisons.** The issue of blinding
- **Reliability**
 - Lack of random measurement error

Desired (Required) Characteristics

- **Completeness**

- Consequences of Missing Data:
 - Sample size → Loss of power
 - Bias → 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)

Example

- RCT to study the efficacy of prophylactic doxycycline at IUD insertion¹
- Primary Endpoint: Pelvic Inflammatory Disease (PID)
- Secondary Endpoint: Unscheduled Visit for an IUD-related Problem, e.g., bleeding, pain, or discharge

1. Sinei SKA, Schulz KF, Lamptey PR, et al. Preventing IUCD-related pelvic infection: the efficacy of prophylactic doxycycline at insertion. *Br J Obstet Gynaecol* 1990;97(5):412-19.

Estimating the Incidence of PID for Sample Size Calculations

- Government officials estimated 40%
- Ob/GYN from Med School estimated 12%
- We conservatively set initially at 6%
- Readjusted to 4% based on pilot trial
- And after all that, found 1.9% in placebo group
- Effect on power?

Results

Out- come	Doxy	Placebo	RR	95%CI	P-value
PID	1.3%	1.9%	0.69	.32-1.5	0.17
Unsch Visit	8.9%	13.0%	0.69	.52-.91	.004

Alternative Endpoint Definitions

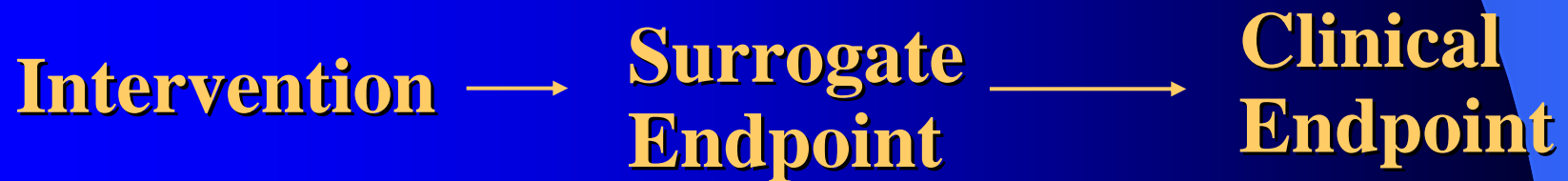
- **Surrogate Endpoints:**
 - Indicator of effect in lieu of the one of substantive interest
 - e.g CD4 counts for AIDS mortality
 - e.g. Blood pressure for CV disease
 - Surrogate endpoint by itself does not confer direct clinical benefit to the patient

Surrogate Endpoints

- Rationale: Measuring effect sooner and/or for less cost
 - Lost-to-follow up less of a problem
 - Smaller sample size
 - Ethical issues

Surrogate Endpoints

- Highly correlated to the clinical outcome of interest:
 - Biological plausibility
 - Surrogate must be on causal path of disease
 - Requires Validation



Surrogate Endpoints

- **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

- **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

- “Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.”

John W. Tukey (1962)

Annals of Mathematical Statistics

1962;33:1-67.

Final Remarks

- 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