Protocol Development: The Guiding Light of Any Clinical Study

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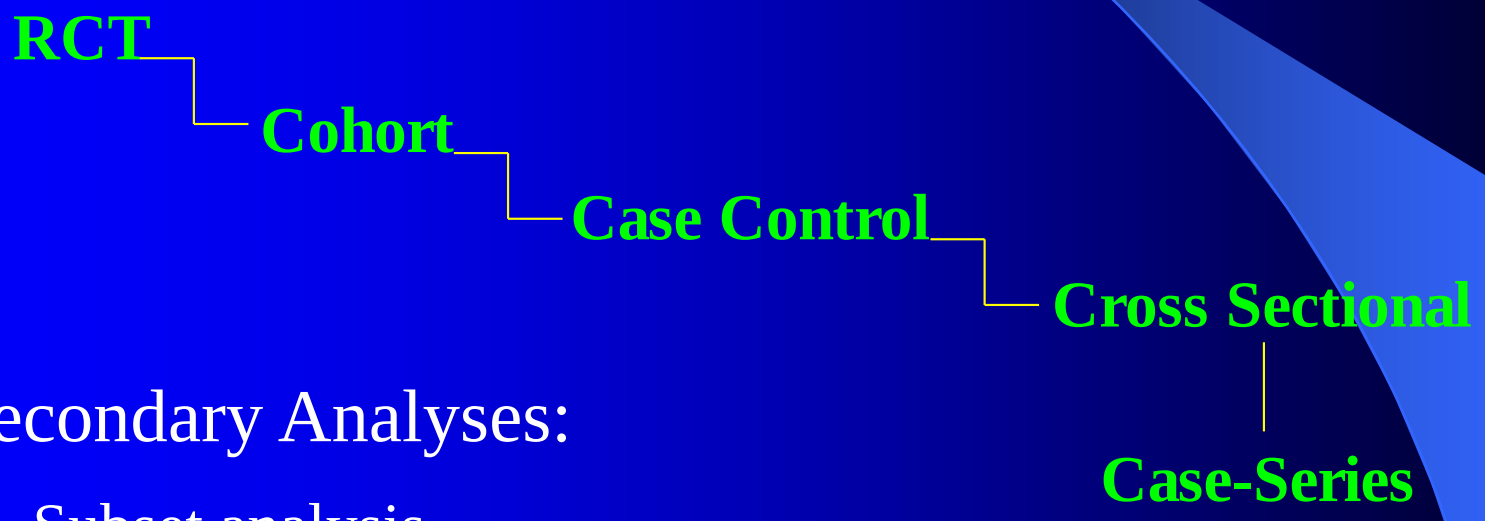
Introduction

- Importance/ relevance/ gaps in knowledge
- Specific purpose of the study
  - Describe an observation or population
  - Test a biologic hypothesis
  - Demonstrate drug efficacy
  - Develop a prognostic model
- Identify a primary independent factor (exposure) and a dependent factor (outcome)
- Identify the population of interest

Methods - Study Design

- Critical component in assessing the validity of a study
- Primary Designs (experimental & observational)



- Secondary Analyses:
  - Subset analysis
  - Meta analysis
  - Re-analysis: New question / old data

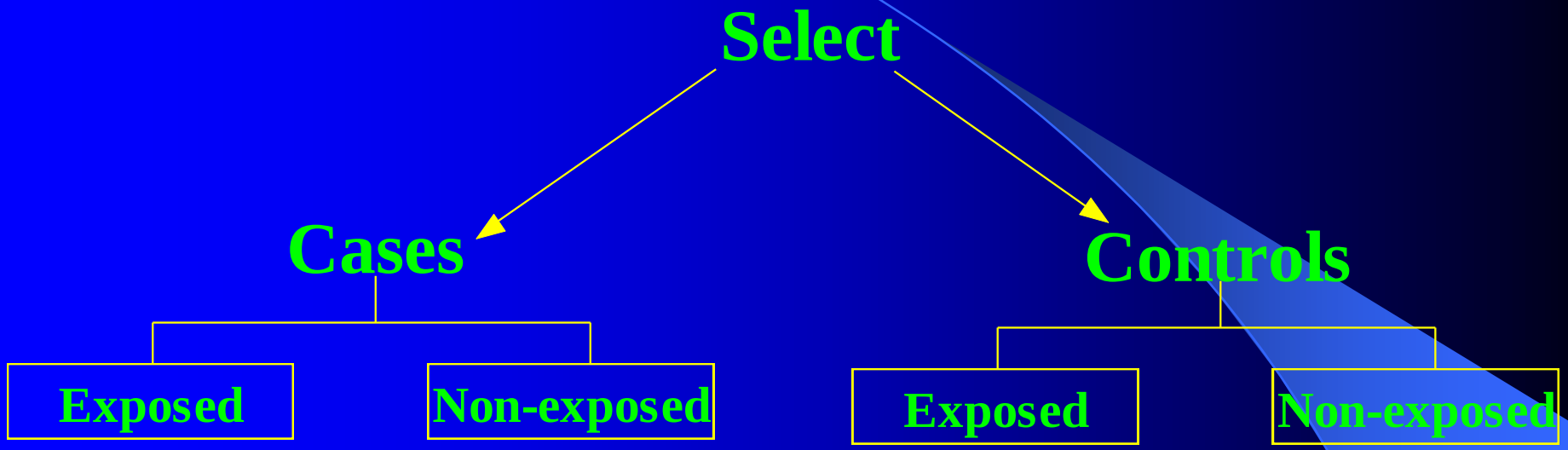
Case Series

- Descriptive account of an occurrence in one individual or a cluster
- Retrospective; quick & easy
- No control group
- No research hypothesis

Cross-sectional Studies

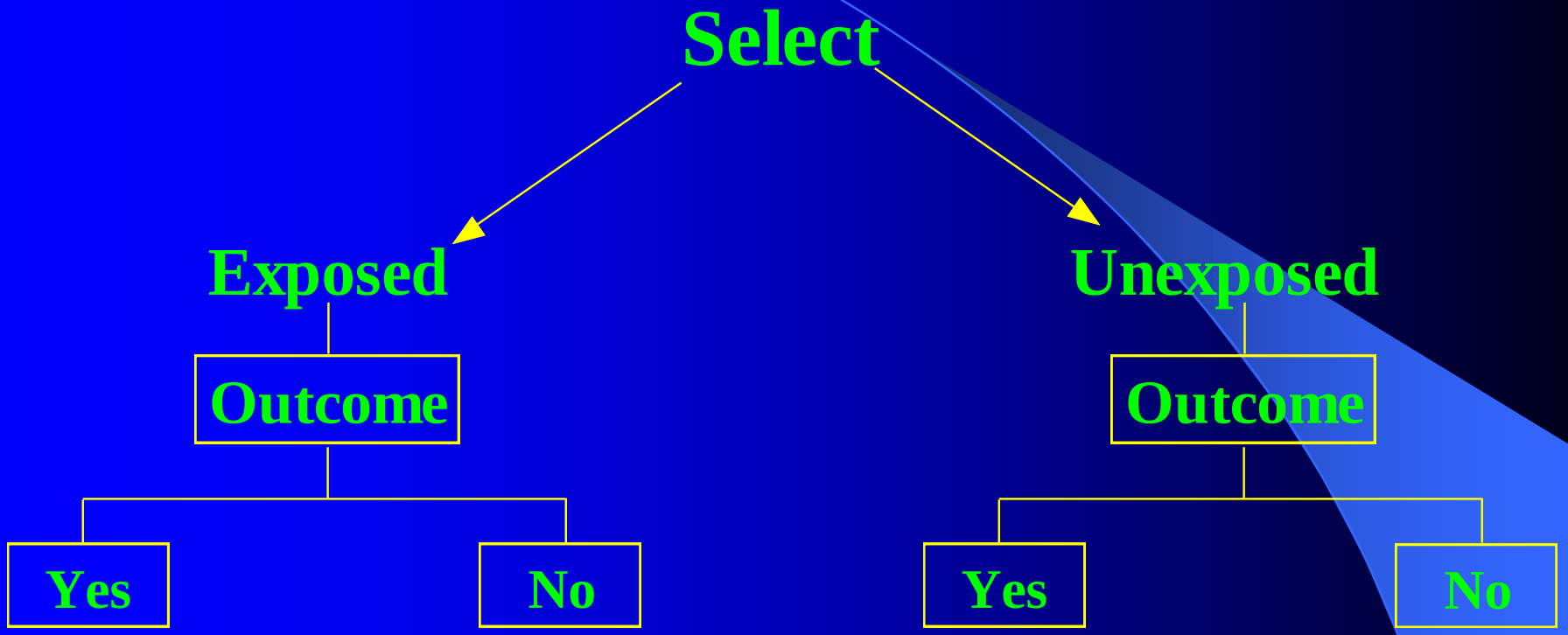
- Designed to describe the frequency of an event or an association
- Data collected from 1 group of subjects at one point in time
- Quick, easy, low cost
- Does not address temporality of association

Case Control Study



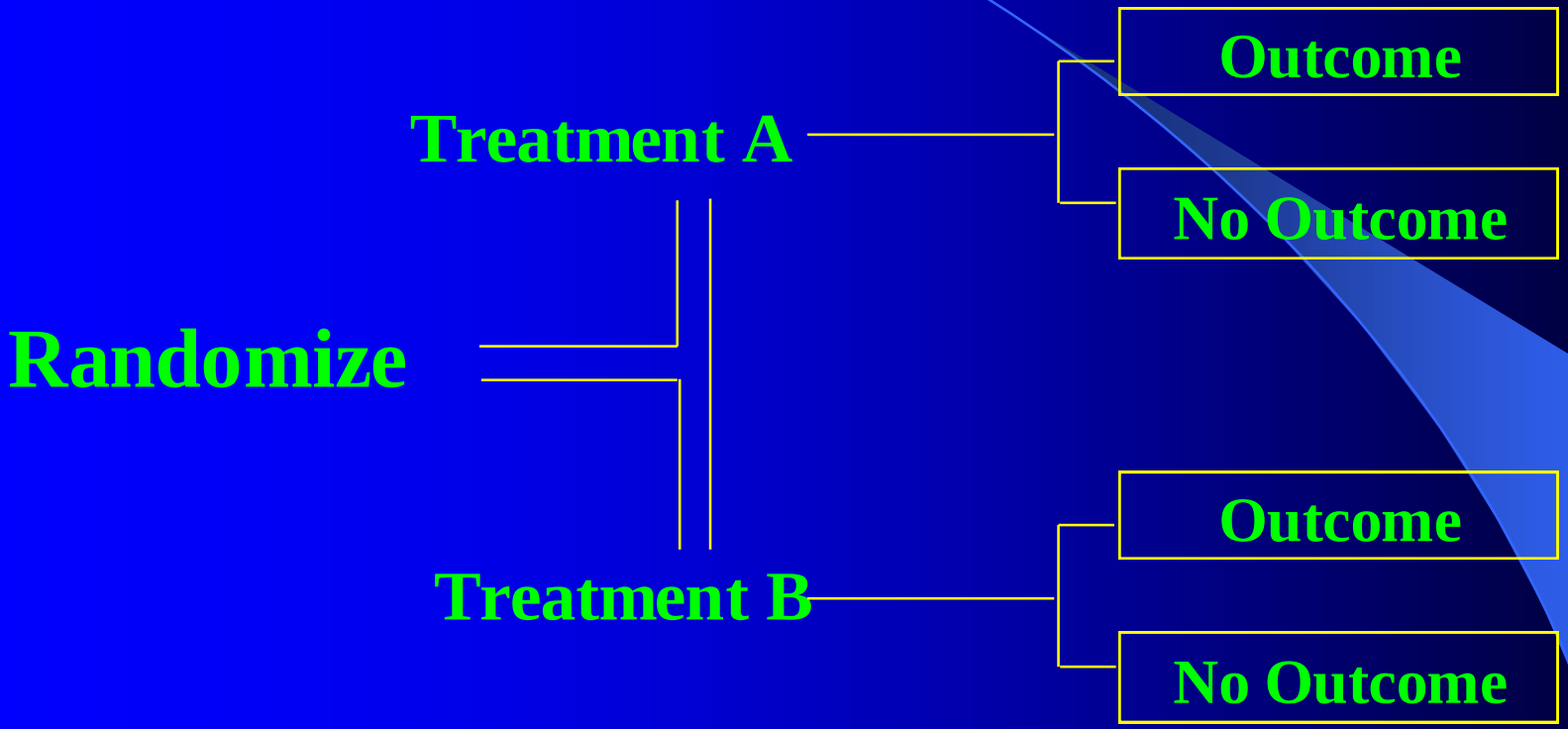
- Addresses a specific hypothesis
- Select a group with outcome of interest and group without outcome
- Retrospectively examine presence of risk factor

Cohort Study



- Addresses a specific hypothesis
- Select subjects with and without risk factor of interest
- Prospectively document outcome of interests

Randomized Clinical Trial



- Select subjects of interest
- Randomly assign subjects to one of two or more treatments
- Usually includes a ‘new’ treatment and a comparison treatment
- Follow subjects to document outcome of interest

Methods - Study Population

. . . Who, where, when, how

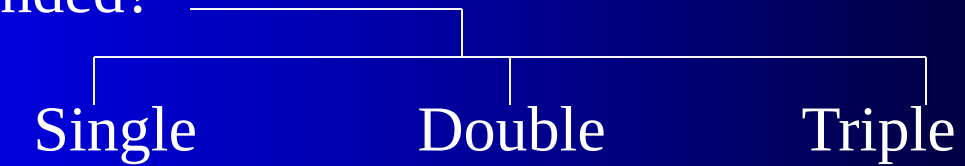
- Inclusion and Exclusion criteria
  - Who will most likely benefit from study findings?
  - Generalizability of study results
- Setting
  - Geographic area
  - Type of Institution
  - Referral pattern
- Time Frame
  - Recruitment
  - Follow-up

Methods – Study Sample

- Is this the "right" target population to answer the question?
- Do the participants represent this target population?
  - How were they recruited? (Volunteers, convenience sample, random sample)
- Who was excluded?

Methods - Treatment Allocation

- Natural occurrence
- Individual choice
- Physician decision
- Randomized assignment
  - Method should be described
  - Was study sample stratified prior to randomization?
  - Is treatment blinded?



Methods - Sample Size

- Sample size criteria should be specified
- Sample size requirements driven by:
  - Magnitude of effect – difference you wish to detect
  - Type I Error – p value: probability of a false positive
  - Type II Error – (1-power): probability of a false negative
- Impact of less than planned sample size should be discussed related to power of a negative study

Methods - Statistical Analysis

- Approaches should be planned *a priori* and reported
- Outline details of analysis including:
  - Categorization of variables
  - Univariate tests
  - Multivariate tests
  - Model building approaches
- Definition of statistical significance
  - One versus two-sided tests

Methods - Statistical Analysis

continued

- Use of interim monitoring techniques
- Intention to treat
- Methods to control for bias
  - Internal quality control steps
  - Determination of outcomes (blinded, formal guidelines, committee consensus)

Methods - Follow Up & Outcomes

- Follow-up time: min, max, median
- Allowable medical care and screening
- Ascertainment of outcomes and verification
- Subject adherence by group
  - Treatment
  - Attrition

Study Results

- Early, interim or planned final analysis
- Do the patient numbers add up?
- Actual measures of outcome by group
- Summary of treatment experiences
  - Completed
  - Early termination
  - Protocol deviation
  - Toxicity

Results *continued*

- Do they address the aims of the study?
  - Are they clinically meaningful?
  - Are they valid?
- Tables/Figures (general format):
  - Table One- Description of Participants
  - Table Two- Main findings (unadjusted)
  - Table Three- Adjusted and/or refined findings
  - Figures- Often the best (most intuitive) way to present important findings

Subgroup analyses

- Primary analysis of a trial is usually an overall comparison of treatments for all patients

- If a statistically significant difference between treatments is found
  - Is the difference the same within meaningful subgroups of patients?
  - In statistical terms: is there an *interaction* ?

Discussion & Interpretation

- Are conclusions justified?
  - Do they match the statistical results?
  - Are they generalizable?
  - Are they constrained to the parameters of the study?
- Are findings placed in context of other scientific work?
- Are limitations and shortcomings reported and discussed?
- Are implications for future clinical practice and future investigations delineated?