Research Design

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HERC
Health Economics Resource Center

VA
U.S. Department of Veterans Affairs
Veterans Health Administration
Health Systems Research

Overview

1. Overview of Research Design
2. Pros & Cons of Commonly Used Study Designs
3. Measurement Error and Bias (Endogenous & Exogenous Variables)

Focus will be on human subjects research and quantitative designs.

Poll

- What is your background?
  - Clinical
  - Biostatistics
  - Epidemiology
  - Economics
  - Data Science
  - Other Mathematics or Science Background
  - Other non-Mathematics or non-Science Background

Poll

- How many years have you been working in research?
  - <2 years
  - 2-5 years
  - 5-10 years
  - >10 years

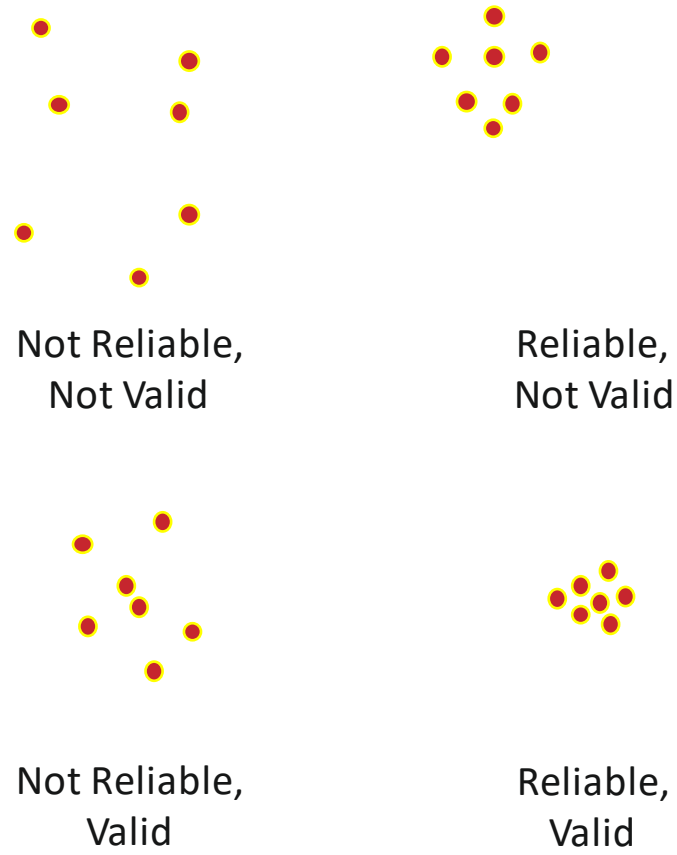
What is Research Design?

- **Framework** or **strategy** to conduct research
  - Study Methods

- **Why** is research design important?
  - Minimizes bias and errors while maximizing reliability
  - Provides a blueprint for replication, enhancing the credibility of findings

Goals of Research Design

- Optimize **validity** and **reliability** of results
  - **Validity** refers to how accurately a method measures what it is intended to measure
  - **Reliability** refers to the consistency or stability of a measurement method over time or across raters



Guidelines for Research Design

- **Equator network**: Enhancing the Quality and Transparency Of health Research (https://www.equator-network.org/)

Consolidated Health Economic Evaluation Reporting Standards (CHEERS)

- Target Population
- Setting and Location
- Study Perspective
- Comparators
- Time Horizon
- Discount Rate
- Choice of Health Outcomes
- Measurement of Effectiveness
- Preference Based Outcomes
- Estimating Resources and Costs
- Current, Price Date, and Conversion
- Choice of Model
- Assumptions
- Analytic Methods

https://www.equator-network.org/reporting-guidelines/cheers/

Consolidated Health Economic Evaluation Reporting Standards (CHEERS)

Study Design

- Comparators
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Data

- Preference B
- Estimating Re Costs
- Current, Price Date, and Conve n

Analyses

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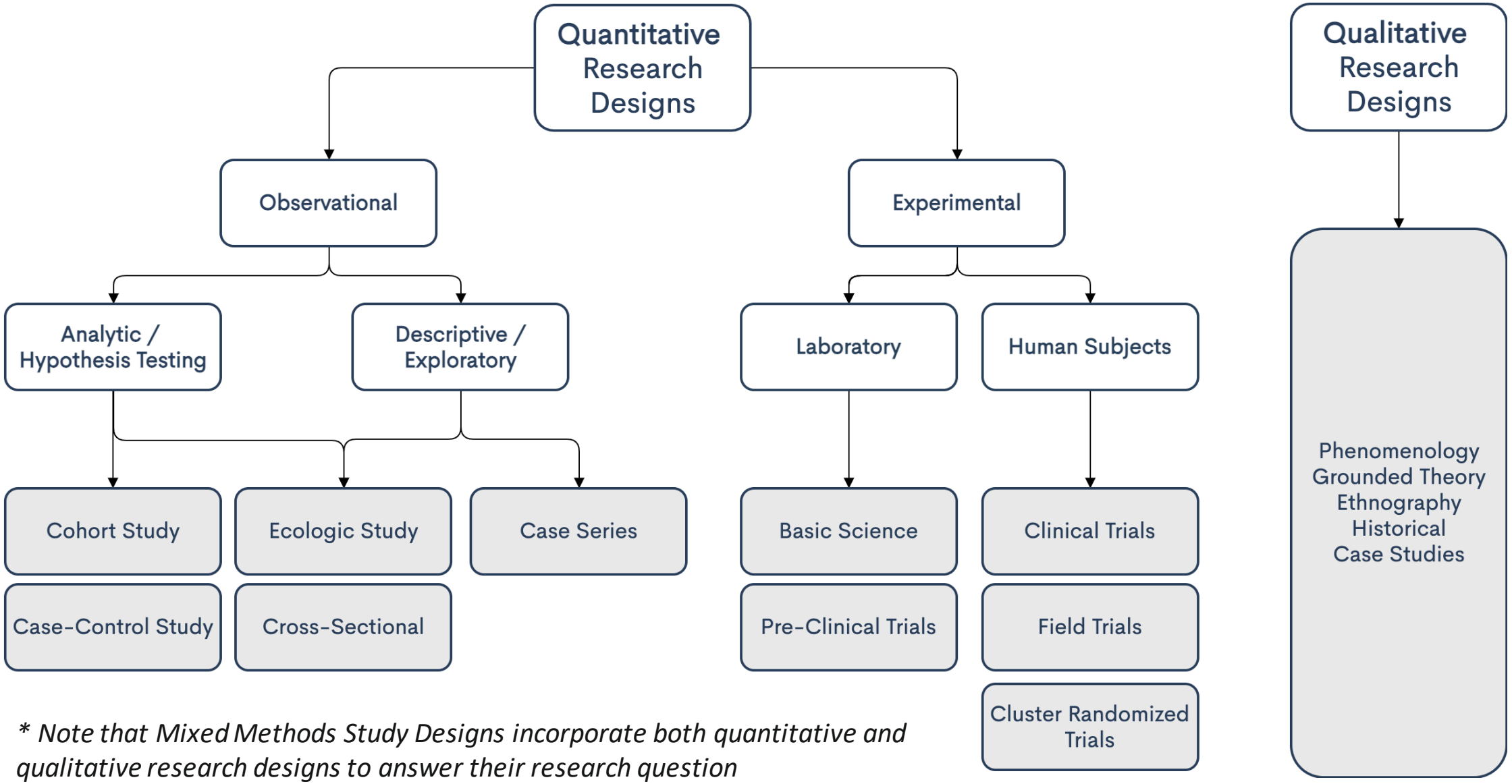
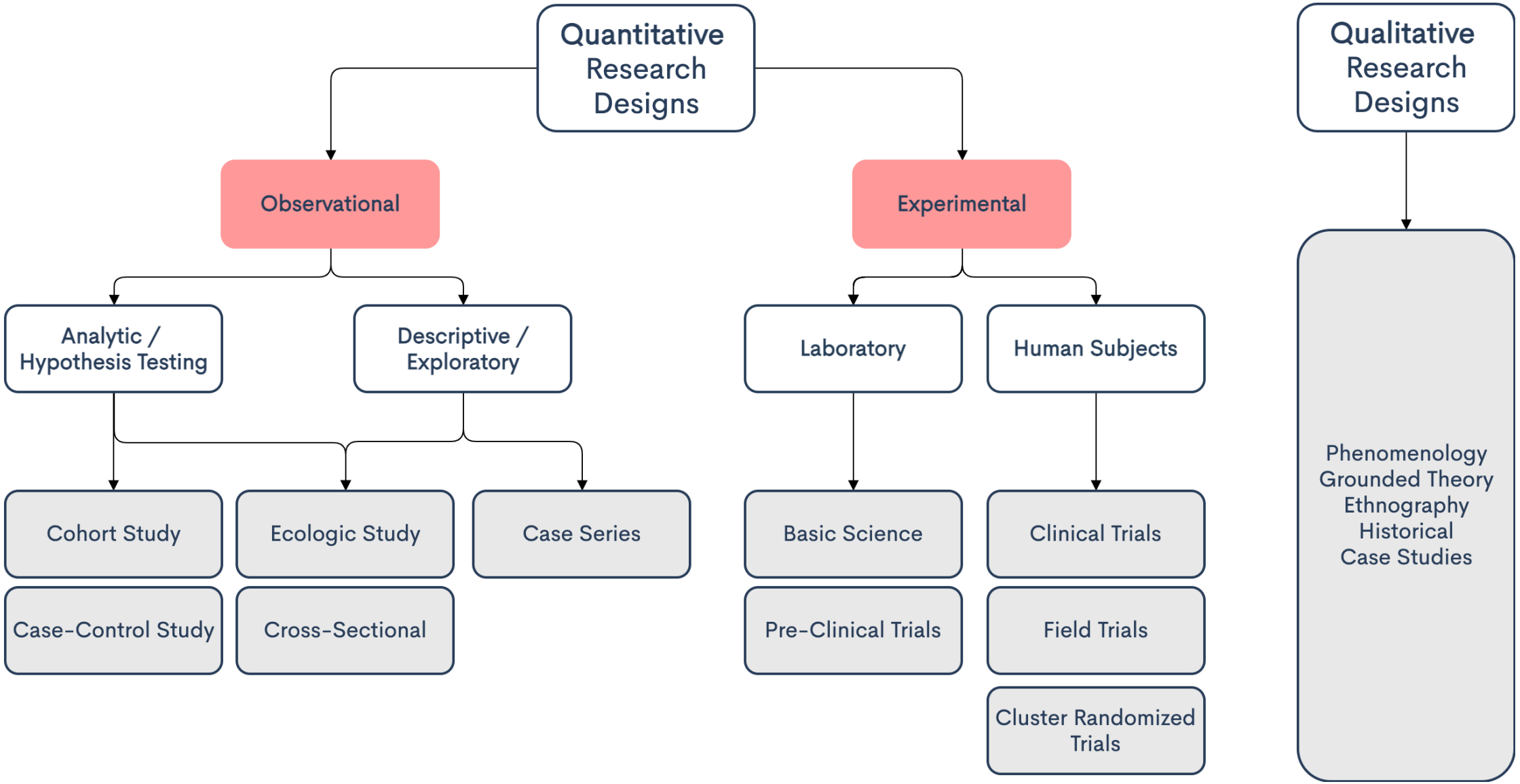


** Note that Mixed Methods Study Designs incorporate both quantitative and qualitative research designs to answer their research question*

Quantitative vs. Qualitative

Quantitative	Qualitative
Formal, **objective**, systematic process for obtaining information about the world	Systematic **subjective** approach used to describe life experiences and give them meaning
Test relationships and describes or **examine** causal associations	Gain insight, **discover** frameworks, or **explore** a particular phenomenon
Tests theory	**Develops** theory

** Note that Mixed Methods Study Designs incorporate both quantitative and qualitative research designs to answer their research question*


Quantitative Research Designs
Observational
Experimental
Analytic / Hypothesis Testing
Descriptive / Exploratory
Laboratory
Human Subjects
Cohort Study
Ecologic Study
Case Series
Basic Science
Clinical Trials
Case-Control Study
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Grounded Theory
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Case Studies

Experimental Research Designs

- **The Gold Standard**

- Ideal for establishing cause-and-effect relationships
  - Controlled settings and manipulation of variables
- May not always be feasible due to research objectives, ethical considerations, and available resources

Experimental vs. Observational

Experimental	Observational
High internal validity due to control over confounding factors and randomization	**Higher risk of bias** (e.g., confounding variables) but often greater external validity
Investigator **manipulates the exposure** (Randomization)	Investigator **does not control the exposure** (Subjects self-select into groups)
Only **ethically permissible** when "adherence to the protocol does not conflict with the subject's best interest"	Generally more ethical, as there is no intervention or manipulation of participants
May be impractical for studying long-term effects or rare phenomena	Suitable for studying long-term trends, rare events, or phenomena that cannot be ethically manipulated

Quasi-experimental Designs

- Aim to approximate experimental conditions while maintaining applicability in real-world settings
  - Time-Series Designs
  - Regression Discontinuity
  - Natural Experiments
  - Instrumental Variable Analyses

- Allows for **causal inferences** but with less certainty than true experiments due to lack of randomization

Observational Research Design

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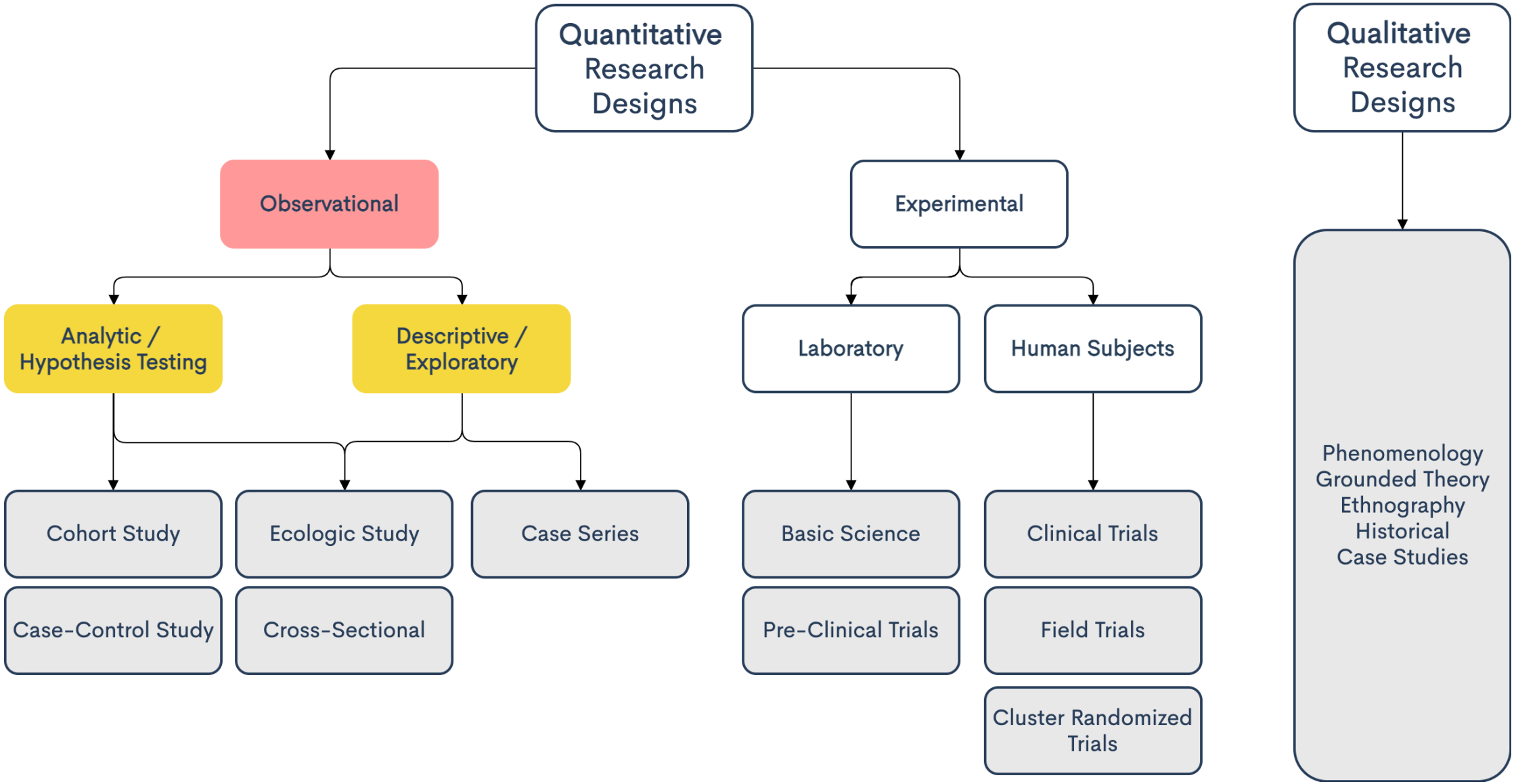
Observational Research Design

- Unlike experimental designs ….
  - The investigator **does not assign exposure status**
  - Rely heavily understanding the **selection of subjects** into treatment groups
    - Source of A LOT of our research design concerns.
  - **Less valid** than experimental designs but also **less resource-intensive** (time, money, data, etc.)
  - May be better for **rare outcomes**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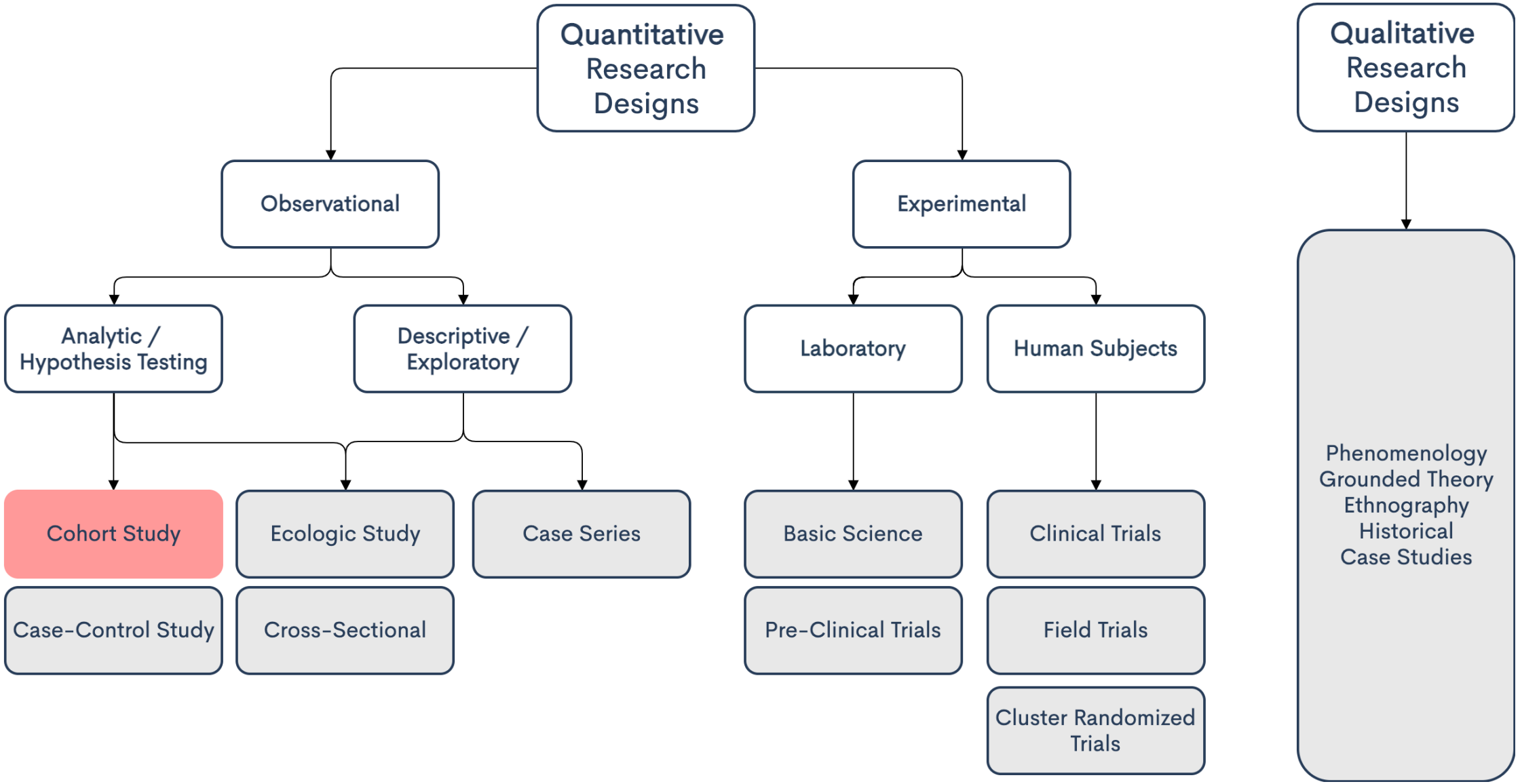
Analytic vs. Descriptive

Analytic	Descriptive
Test hypotheses	**Generate hypotheses**
Quantify the direction and magnitude of associations.	Identifies and describes patterns by place, time, and/or person in a population
	Lacks a comparison group!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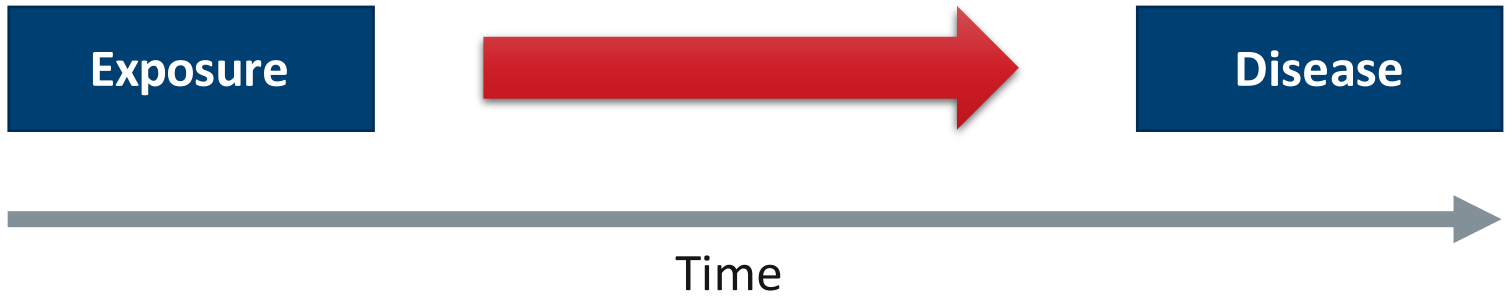
Cohort Studies

- Well-defined group of subjects that are followed over time for an outcome of interest.
- Research subjects are identified by their **exposure status**.



Cohort Studies

- **Prospective**
  - Exposure is assessed before the disease develops

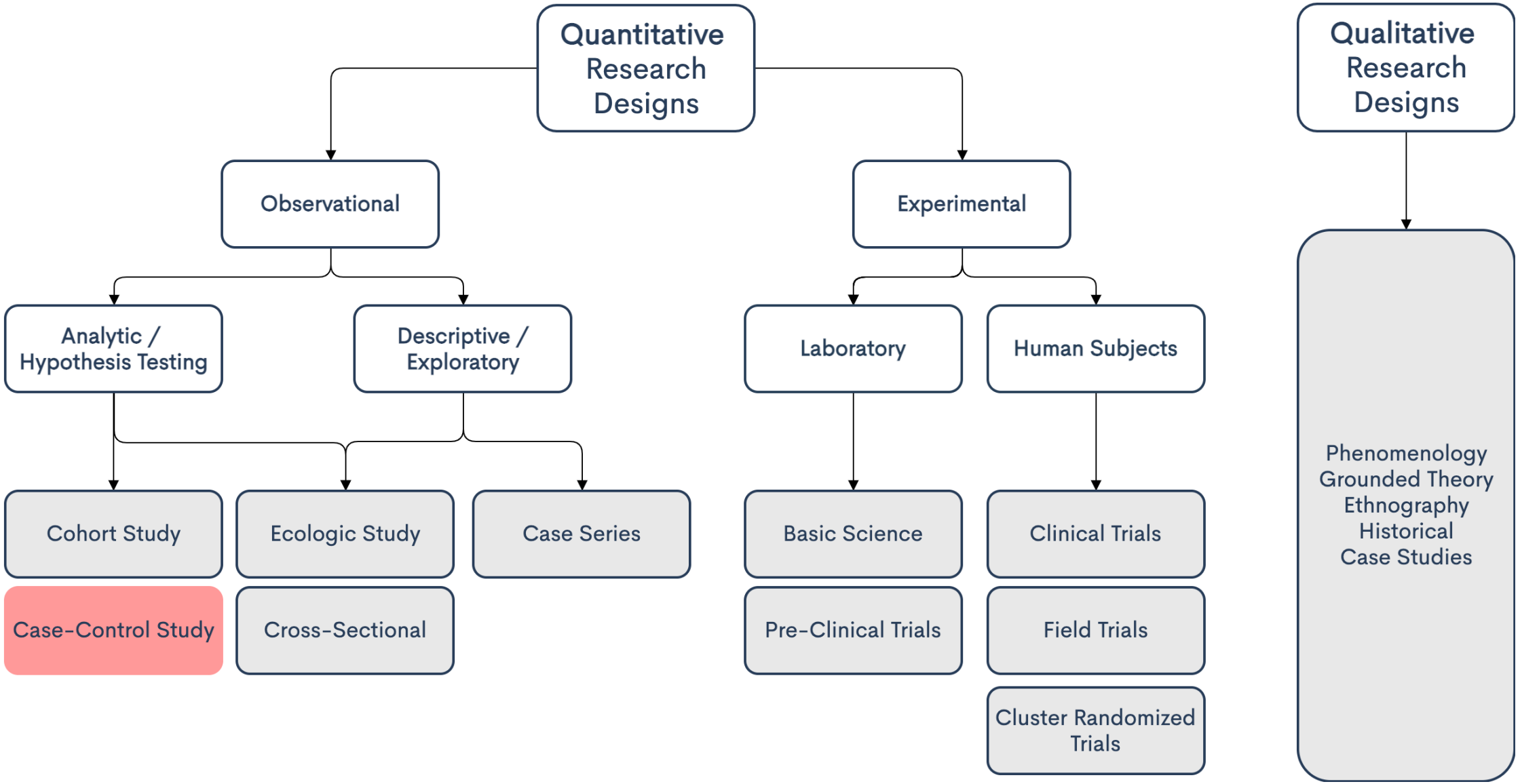
- **Retrospective**
  - Exposure is assessed after some people have already developed disease

Cohort Studies

- **Strengths**
  - Establishes a **temporal association** between exposure and disease
  - Can measure **incidence**
  - Good for **rare exposures** and common diseases
  - Can look at **multiple outcomes**
  - Prospective studies allow better control over sampling and **better-quality assessments** over time.
    - Existing data may be incomplete, inaccurate, or measured in ways that are not ideal for answering the research question.

Cohort Studies

- **Weaknesses**
  - **Recall bias** can be an issue for retrospective studies
  - **Loss-to-follow-up** can also become an issue in long prospective studies
  - Prospective cohort studies can be **resource-intensive** (large sample size, long follow-up)
  - Not good for rare diseases/outcomes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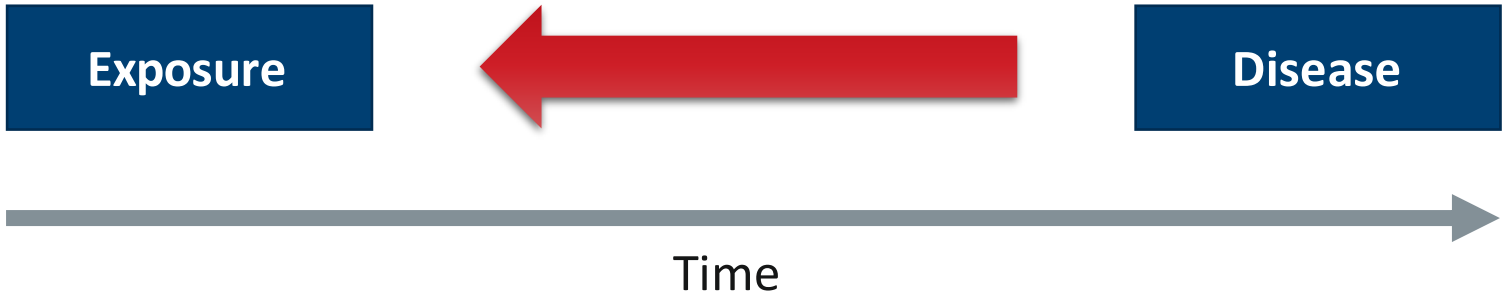
Case-Control Studies

- Research subjects are identified by their **disease status**
- **Always retrospective**

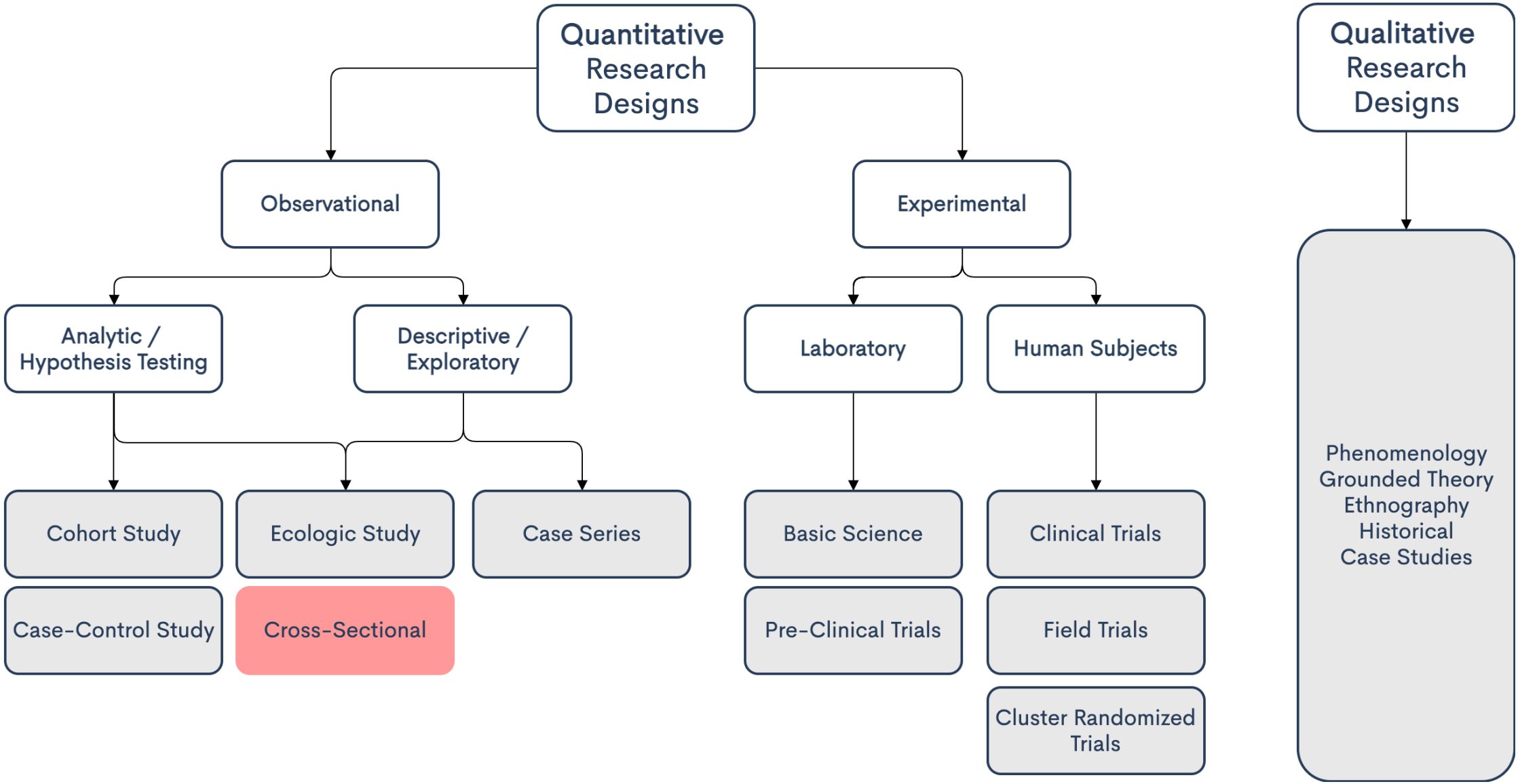


Case-Control Studies

- Key considerations
  - Case selection
    - Cases should be **representative of all diseased subjects** in the community
  - Control selection
    - Controls should be similar to the cases in all respects other than the disease in question
    - Should be representative of all persons without the disease in the population from which the cases are selected
    - **Should have the potential to become cases**

Case-Control Studies

- **Strengths**
  - Good for **rare outcomes**
  - Can be less resource-intensive
  - Can assess **multiple exposures**
    - Case-control studies are useful for generating hypotheses about the causes of an outcome variable.
- **Weaknesses**
  - **More prone to bias (recall bias, selection bias, etc.)**
  - Do not estimate incidence or prevalence
  - Examine only one outcome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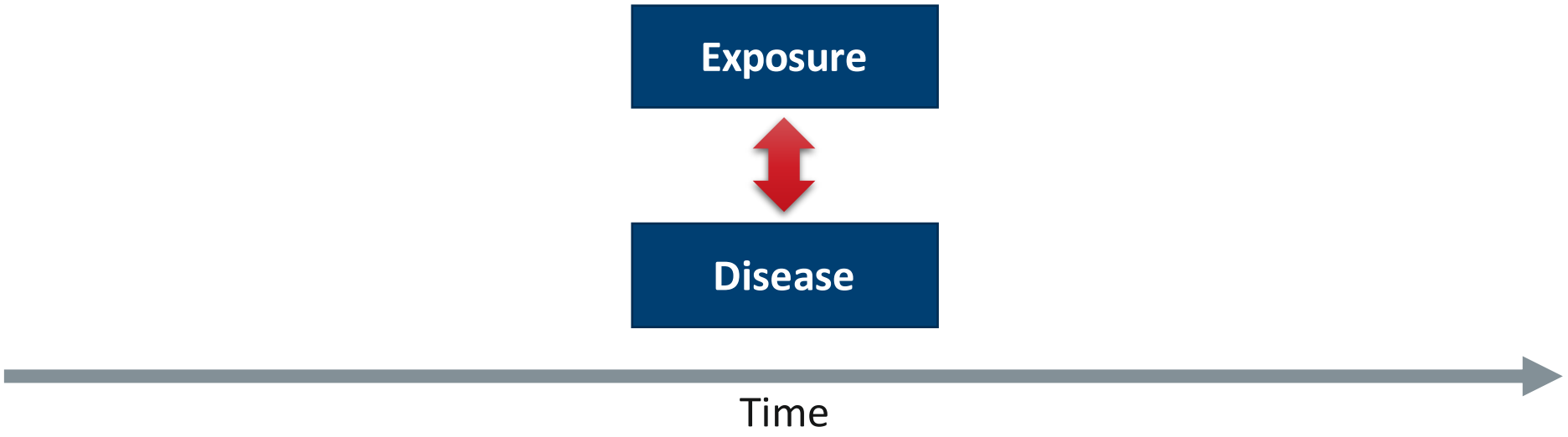
Cross-Sectional Studies

- Both the exposure and outcome are assessed at the **same point in time or over a short period of time**.



Cross-sectional Studies

- **Strengths**
  - Provide a point-in-time **prevalence** estimate
  - Require less time to complete and **avoids the problem of loss to follow-up**
  - Can be used at the beginning of a cohort or clinical trial to provide baseline characteristics
- **Weaknesses**
  - Does not estimate incidence
  - Provides **less evidence of a causal relationship** because temporality cannot be confirmed

Ecological Studies

- Unit of analysis is a **group**, not the individual.
- Result in aggregate measures that are reported (descriptive) or compared (analytic).
- Also, good for rare diseases or to study the effect large-scale public health interventions.
- Should always consider the potential **ecologic fallacy**
  - When the relationship observed at the group level does not represent the relationship at the individual level (ex. relationship may differ based on grouping levels)

Case Series

- Useful for:

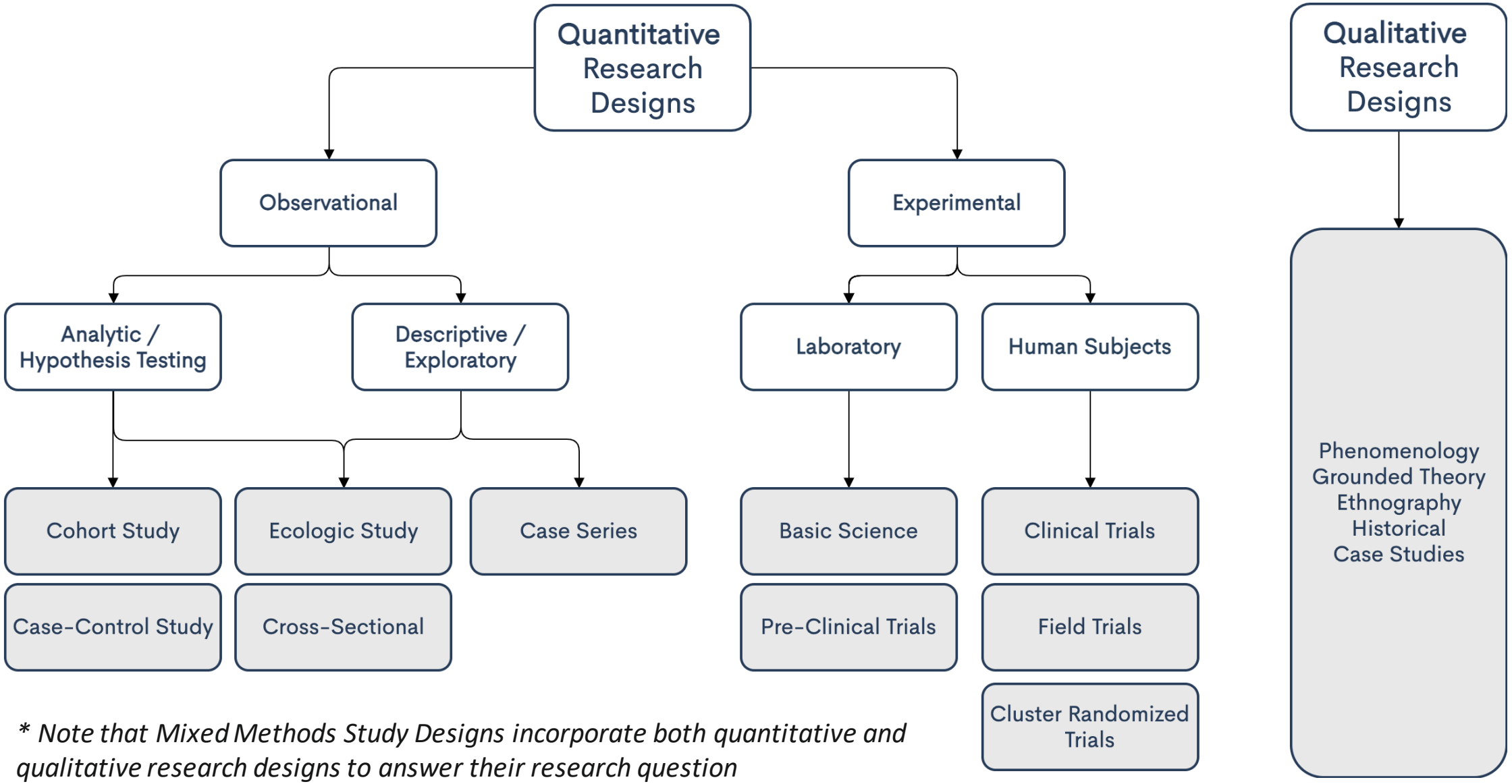
1. Describing a **new disease** processes
2. Identifying and describing **rare manifestations**
3. Identifying **emerging** health conditions

- Example. A case series of the **first 1000 patients with AIDS**. 72.7% were homosexual or bisexual males and 23.6% were injection drug users. It did not require a formal control group to conclude that these groups were at higher risk.

Case Series

- **Strengths**
  - Cost-effective method to describe rare manifestations and new/emerging diseases

- **Weaknesses**
  - Purely descriptive
  - Weakest form of evidence
  - Misleading and may suggest a plausible causal relationship where none exists in real population



** Note that Mixed Methods Study Designs incorporate both quantitative and qualitative research designs to answer their research question*

Guess the Study Design

- I want to know if aspirin is associated with postoperative bleeding. I ask patients on the day of surgery if they took an aspirin that morning or the day before. Later, I query the medical records for postoperative bleeding events in those patients.

- What type of study is this?

Guess the Study Design

- I want to know if aspirin reduces your risk of becoming infected with SARS-CoV-2. I send out a survey that asks about daily aspirin use and also asks about history of SARS-CoV-2 infection.

- What type of study is this?

Hybrid Study Designs

- Combine elements of **different designs**
  - A nested case control study within a cohort study
  - A study that incorporates both a qualitative and quantitative design (Mixed Methods Study)

- Can be used to address some of issues of a single study design

Hybrid Study Designs

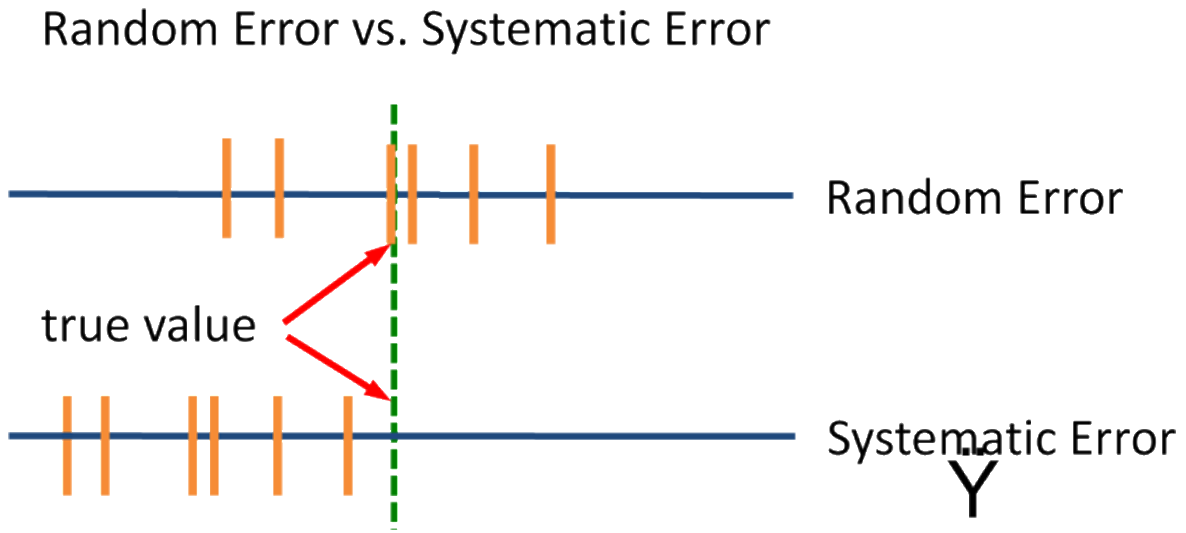
Design Concern	Hybrid Study Suggestion
Underlying hypothesis is not well-supported	Use a qualitative design to support and guide findings in a quantitative study
Retrospective cohort data does not include **detailed disease information**	Nested case-control or case-cohort to get more granular data that is not already collected
Concern about **case and control selection**	Nested case-control design can ensure all cases and controls come from the same population

Measurement Error and Bias

Measurement Error

- **Error**: difference between the observed result and the truth
- The goal of a good research design is to **minimize error**

- Random Error
- Systematic Error



Measurement Error

- **Random Error** (Precision / Reliability)
  - The degree to which our research methods produce consistent results
  - Example. Blood pressure measurements when there is not standardized protocol
  - Exists in ALL Research Design

- **Systematic Error** (Accuracy / Validity)
  - Closeness of a measured value to the truth
  - The degree to which a method/study actually measures what it is supposed to measure

Systematic Error

- Bias is a **systematic error** in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease — (Schlesselman and Stolley, 1982)

  - Selection bias
  - Information bias
  - Confounding
  - Endogeneity

Selection Bias

- Method of **participant selection** that distorts the exposure-outcome relationship from that present in the target population

  - Surveying by phone may systematically exclude patients without phones (**non-response bias**)
  - Patients without the exposure may be more likely to not complete the study (**loss-to-follow-up bias**)
  - Healthier patients may be more likely to get a certain risky treatment (**confounding by indication**)
  - Patients affected by the disease may be more likely to participate (**volunteer bias**)

Information bias

- Information bias occurs when **information is collected differently between two groups (misclassification)**, leading to an error in the conclusion of the association

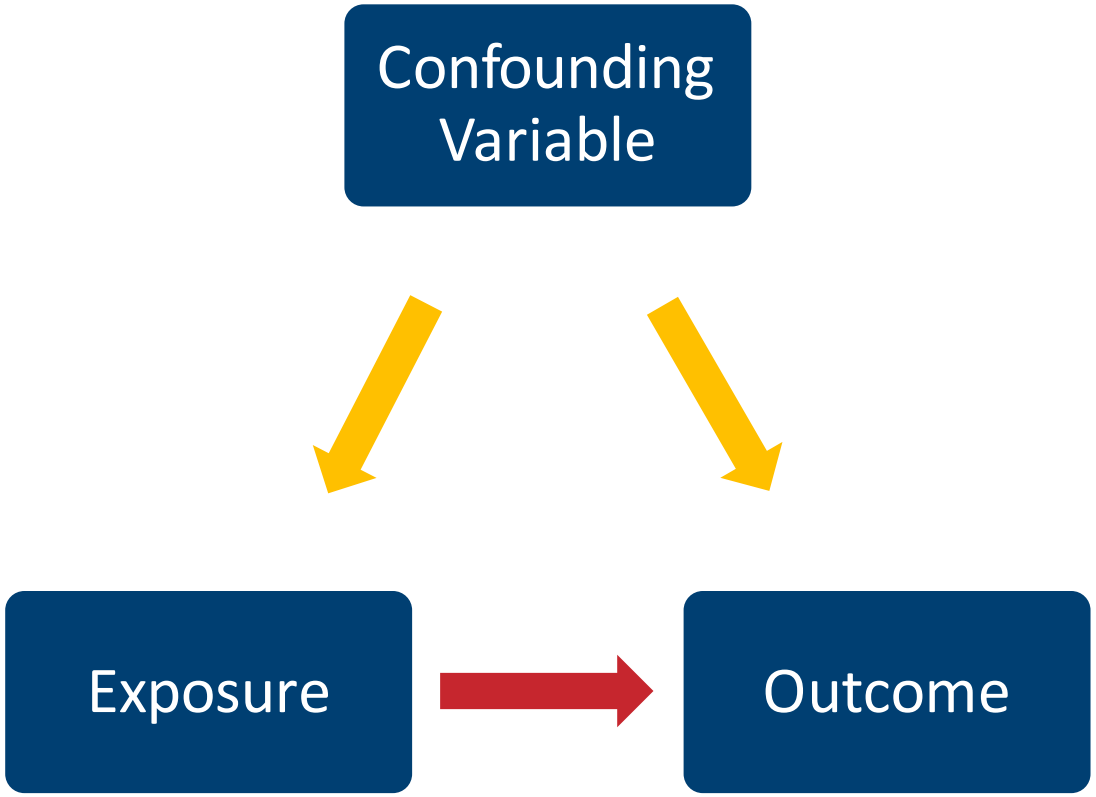
  - **Differential** misclassification occurs when the level of misclassification differs between the two groups
  - **Non-differential** misclassification occurs when the level of misclassification does not differ between the two groups

Confounding

- Confounding occurs when the **observed result** between exposure and disease **differs from the truth** because of the influence of the third variable

- In contrast, effect modification is when the effect of the exposure is different among subgroups – not a distortion of the effect due to a systematic error.

Confounding



- Associated with both exposure and outcome
- Distributed **unequally** among comparison groups
- **NOT in the causal pathway** from exposure to outcome

Confounding & Endogeneity

- **Not the same**
- **Endogeneity** occurs when a variable in a multiple regression model is **correlated with the error term**
- May be due to:
  - An omitted variable/residual confounding
  - Measurement error of collected variables
  - Simultaneity
    - X causes Y but Y also causes X

Confounding & Endogeneity

- Research Design Solutions
  - **Restrict** the cohort
  - **Instrumental variables**
  - **Match** comparison groups
  - Covariate **adjustment** (statistical control)
  - **Randomize** subjects (experimental design)

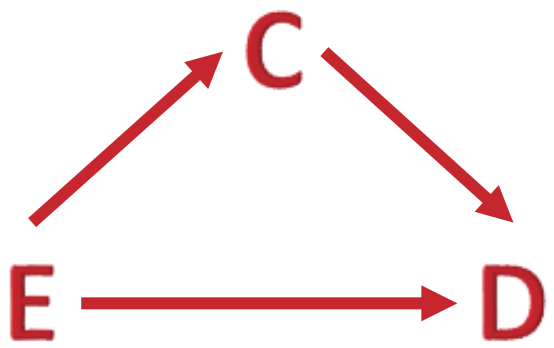
Directed Acyclic Graphs (DAGs)

- Visual representation of causal **assumptions** of your research question
  - A conceptual framework unique to your research question
  - **Directed**: Factors are connected with arrows, the arrows represent the direction of the causal relationship
  - **Acyclic**: no directed path can form a closed loop, a factor cannot cause itself

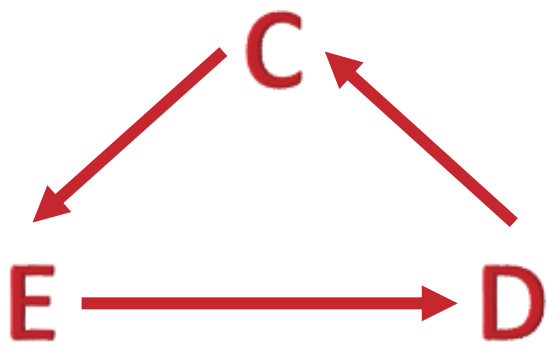
- Illustrate sources of bias

Directed Acyclic Graphs (DAGs)

DAG

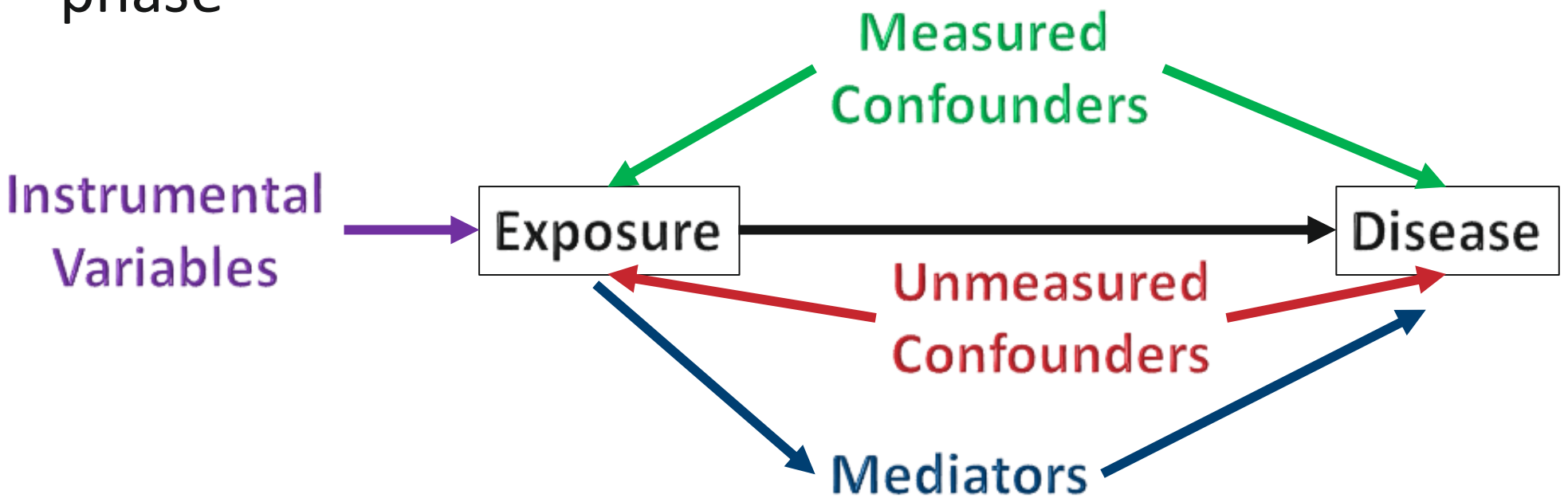


Not a DAG



Directed Acyclic Graphs

- **Directed acyclic graphs (DAGs)** can help to identify confounding and endogeneity during the study design phase



References & Resources

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- **Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement.** http://www.equator-network.org/reporting-guidelines/cheers/
- **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.** https://www.equator-network.org/reporting-guidelines/strobe/

Thank you!

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“We are all apprentices in a craft where no one ever becomes a master.”—Ernest Hemingway

Questions?

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