Research Design

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Health Economics Resource Center

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

Overview

1. Overview of Research Design
2. Pros & Cons of Commonly Used Study Designs
3. Measurement Error and Bias Considerations

Focus will be on human subjects research and quantitative designs.

Poll 1

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

Poll 2

- 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

What is 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

Data

Analyses

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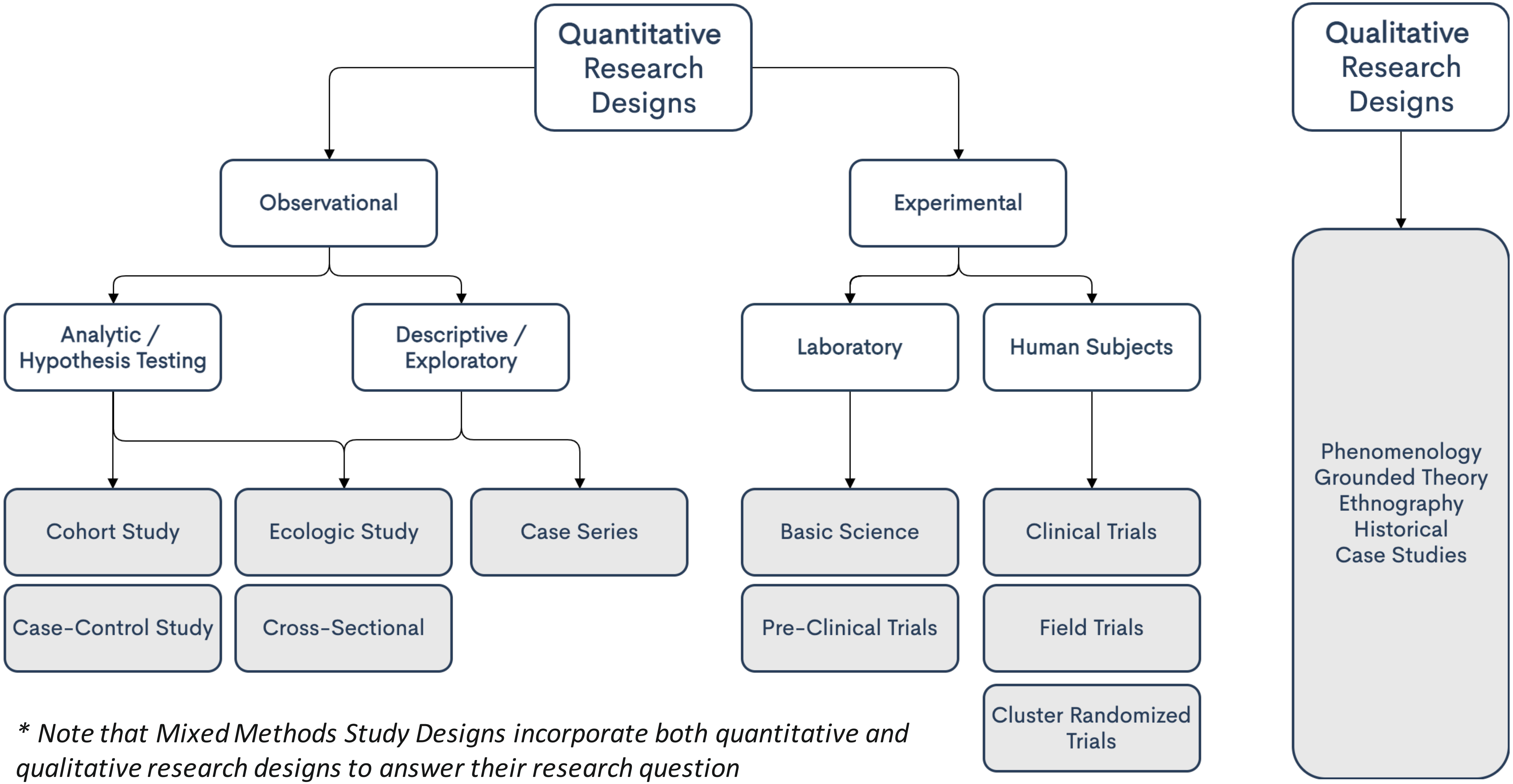

** Note that Mixed Methods Study Designs incorporate both quantitative and qualitative research designs to answer their research question*

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

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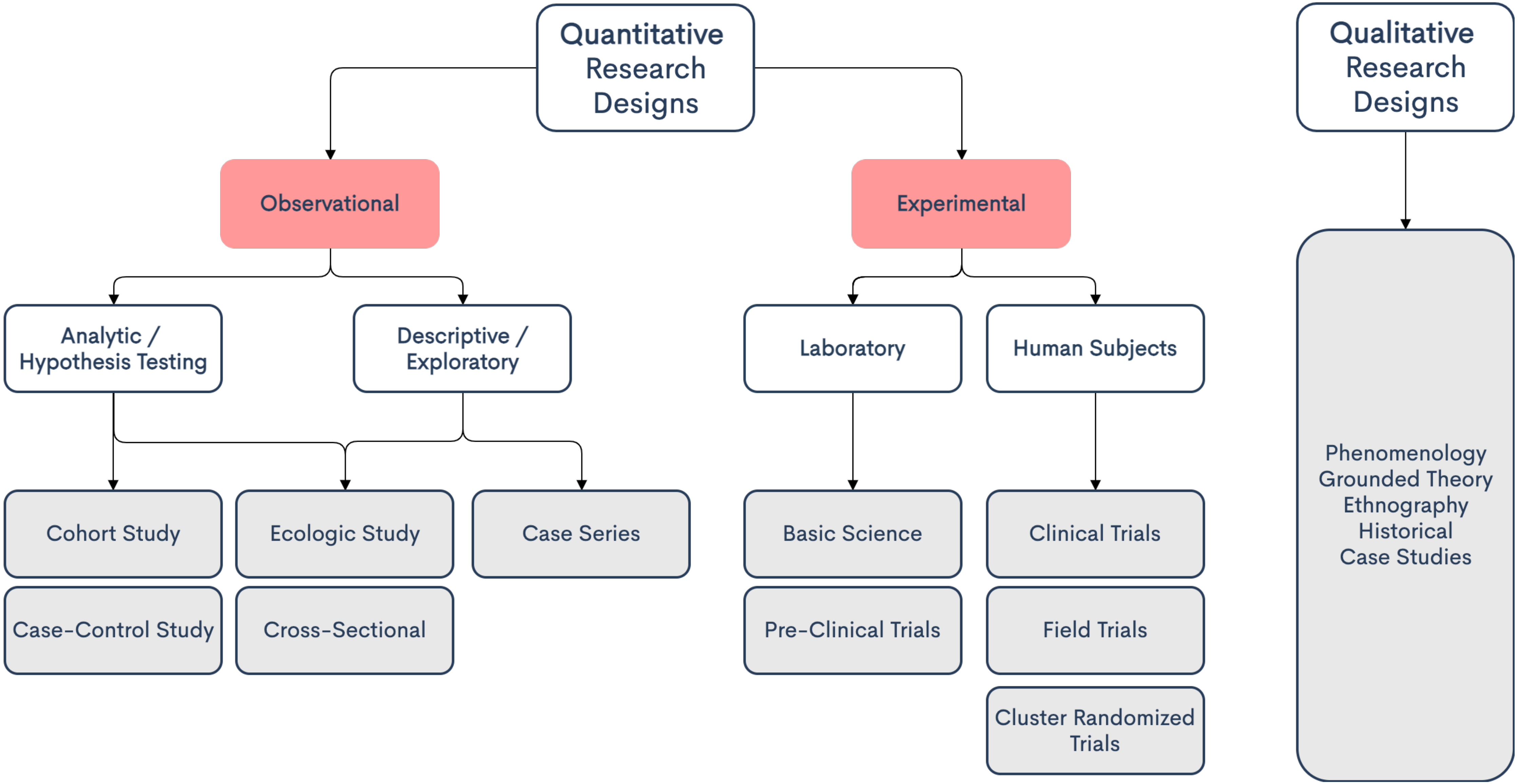
Quantitative Research Designs
Observational
Experimental
Analytic / Hypothesis Testing
Descriptive / Exploratory
Laboratory
Human Subjects
Cohort Study
Ecologic Study
Case Series
Basic Science
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Grounded Theory
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Case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

Experimental vs. Observational

- **Experimental / Interventional**
  - Higher quality evidence → Better validity
  - Investigator manipulates the conditions (i.e. Assigns treatment groups)
  - Experimental studies are only ethically permissible when “adherence to the protocol does not conflict with the subject’s best interest.”

- **Non-experimental / Observational**
  - Came about due to ethical and cost restrictions of experimental studies
    - i.e. It is unethical to force some patients to smoke and others not to smoke
  - Investigator does not control the exposure (i.e. Subjects self-select into group)

Observational Research Design

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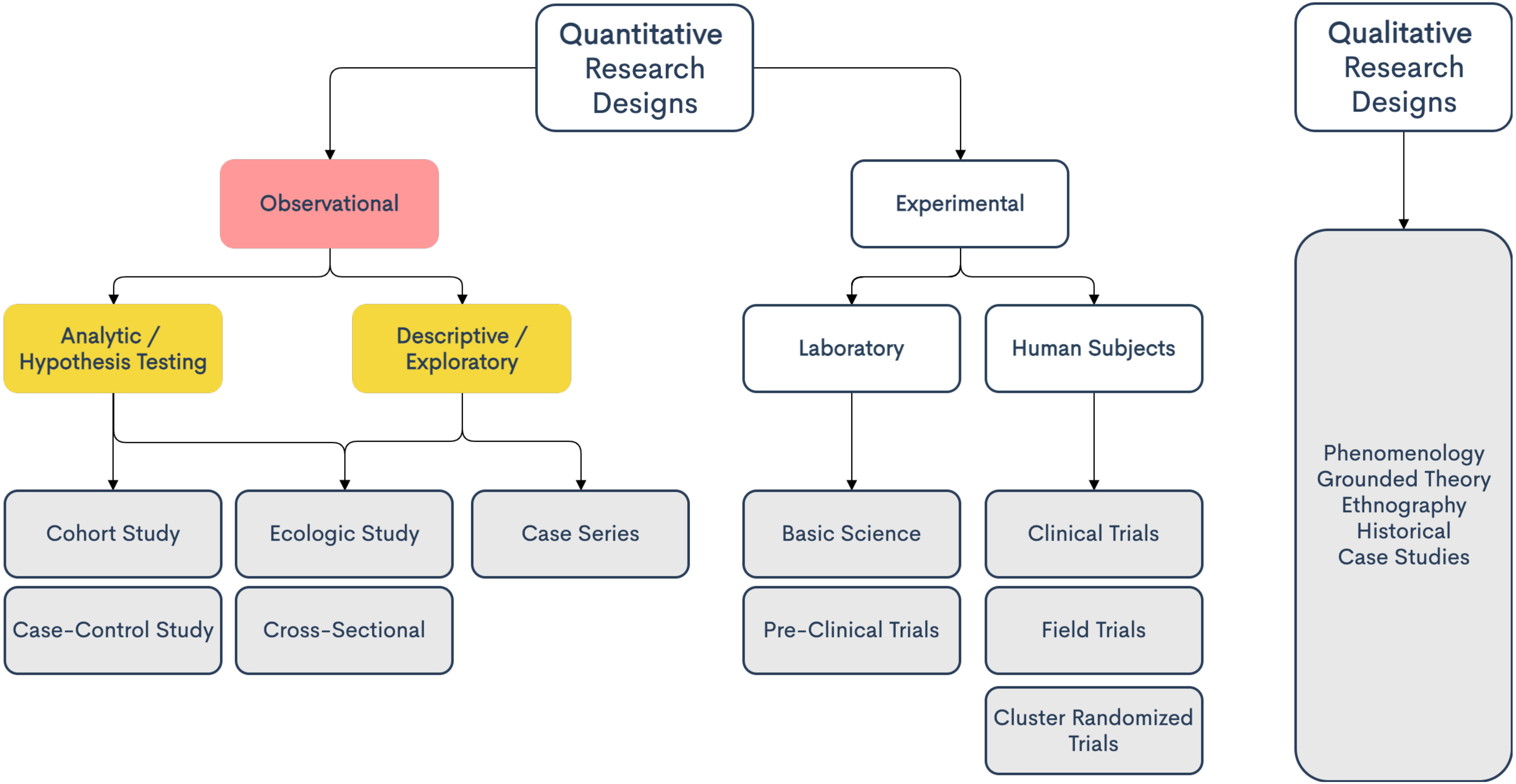
Observational Research Design

- 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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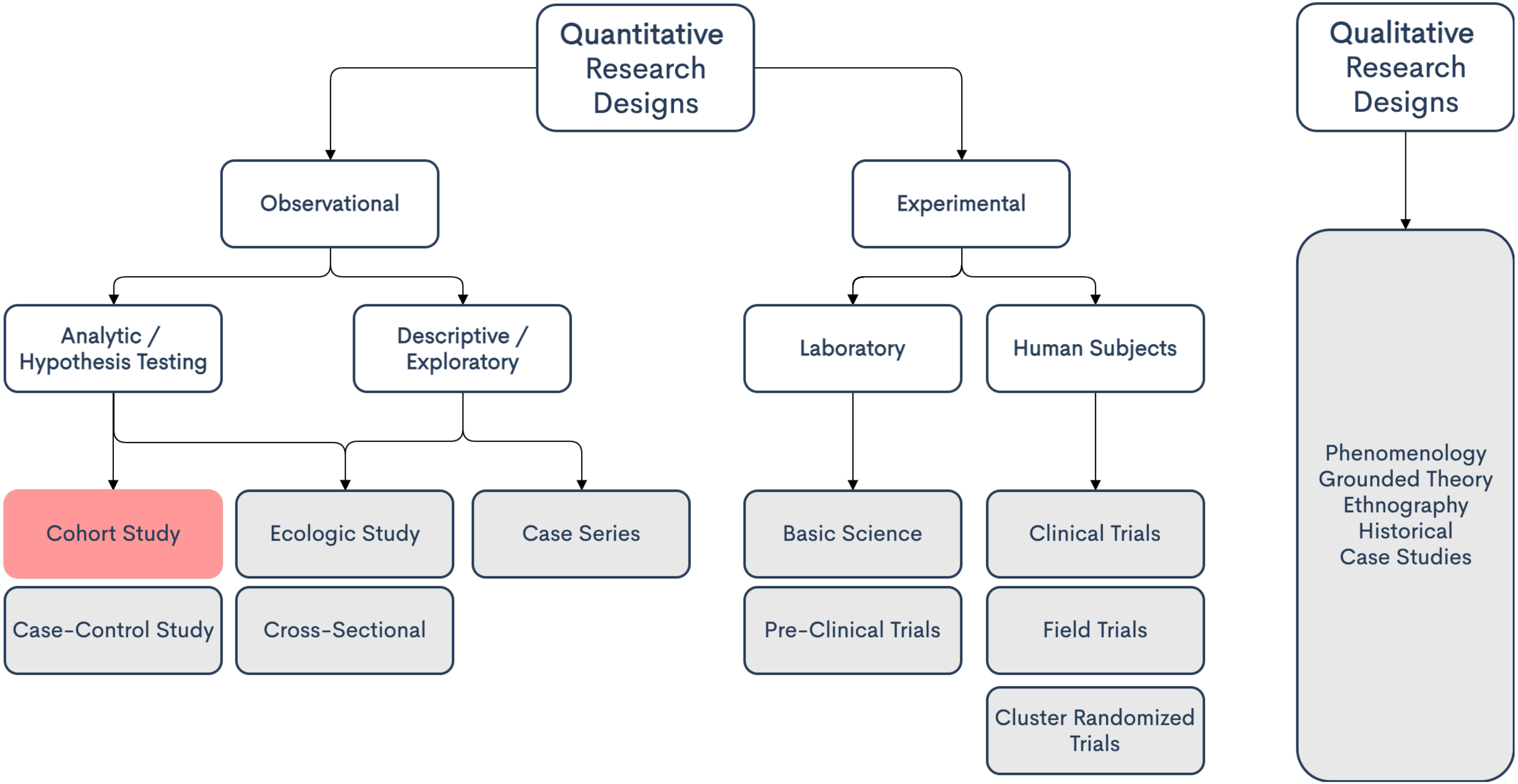
Analytic vs. Descriptive

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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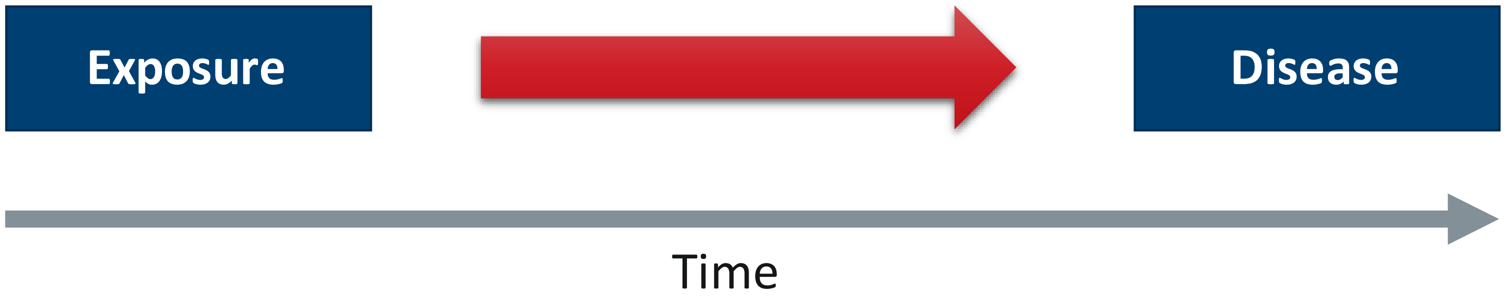
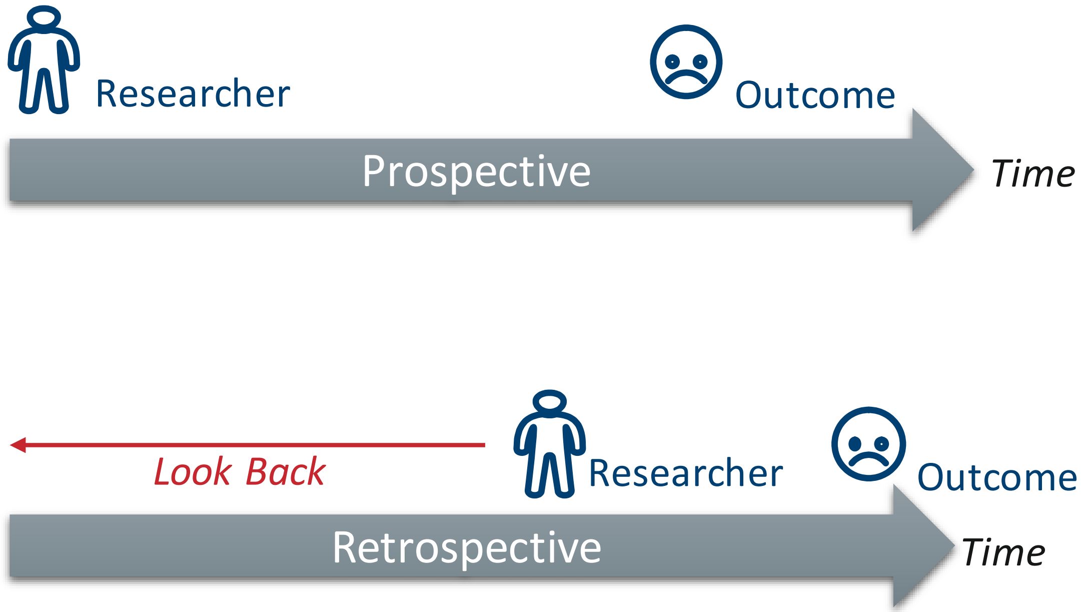
Cohort Studies

- 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

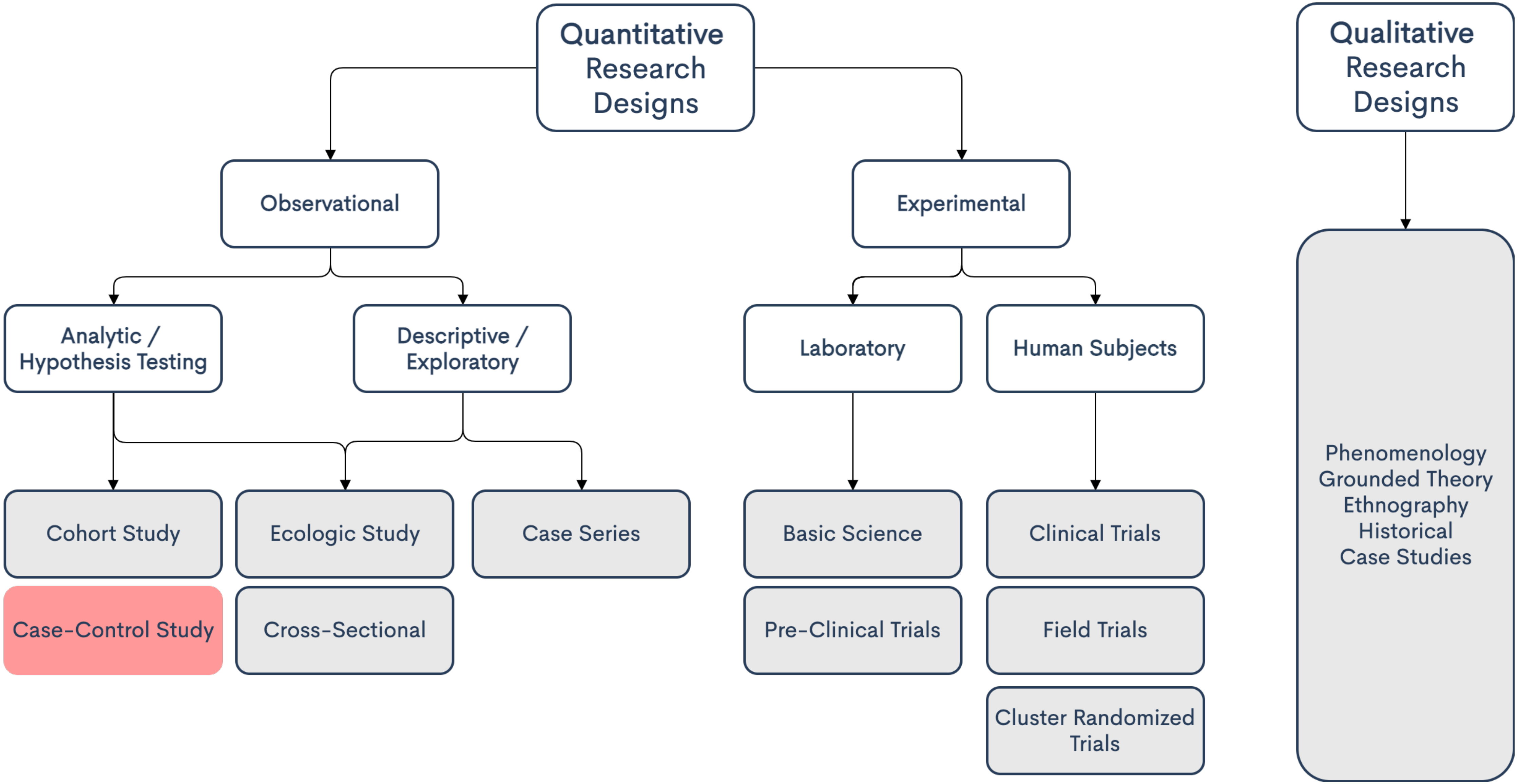


Cohort Studies

- **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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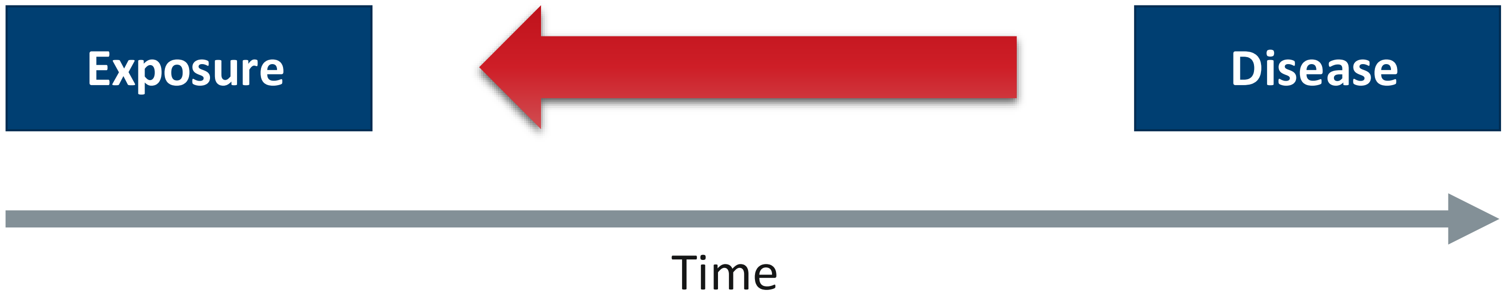
Case-Control Studies

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

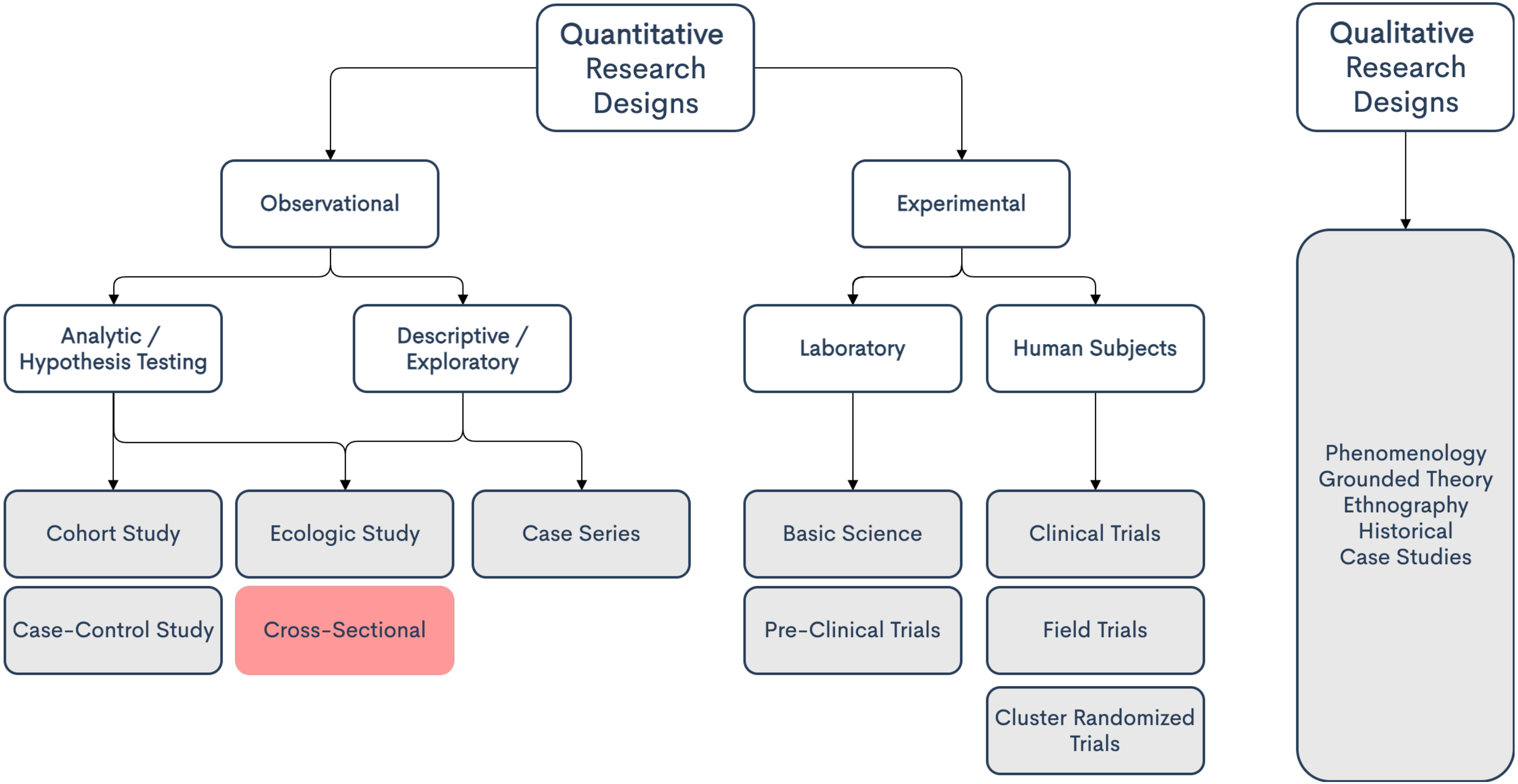


Case-Control Studies

- Key considerations
  - Case selection
    - Cases should be **representative of all of 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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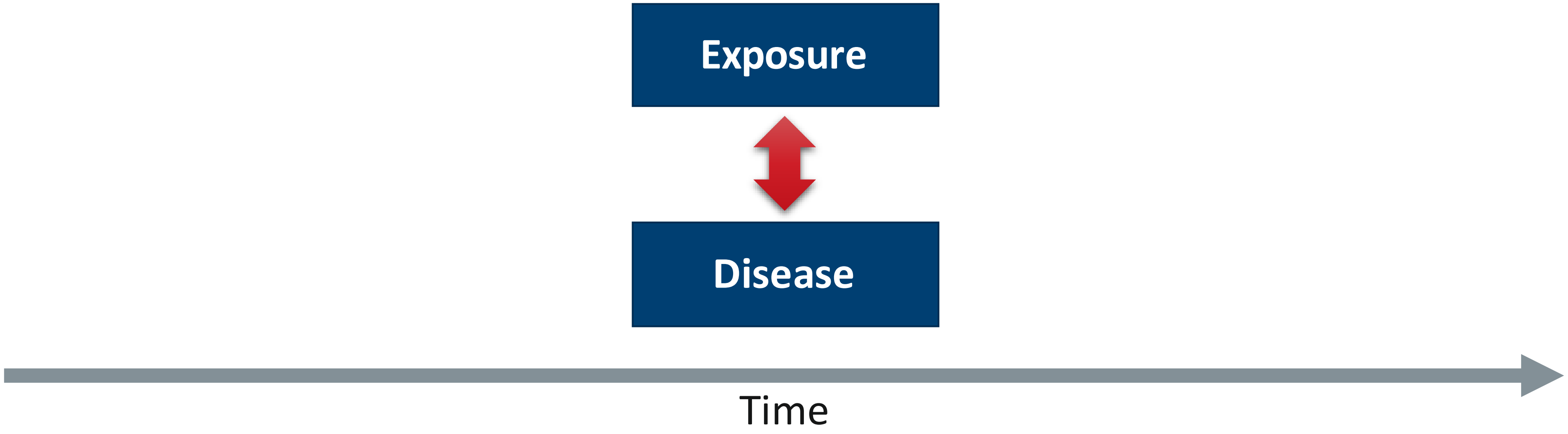
Cross-Sectional Studies

- 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

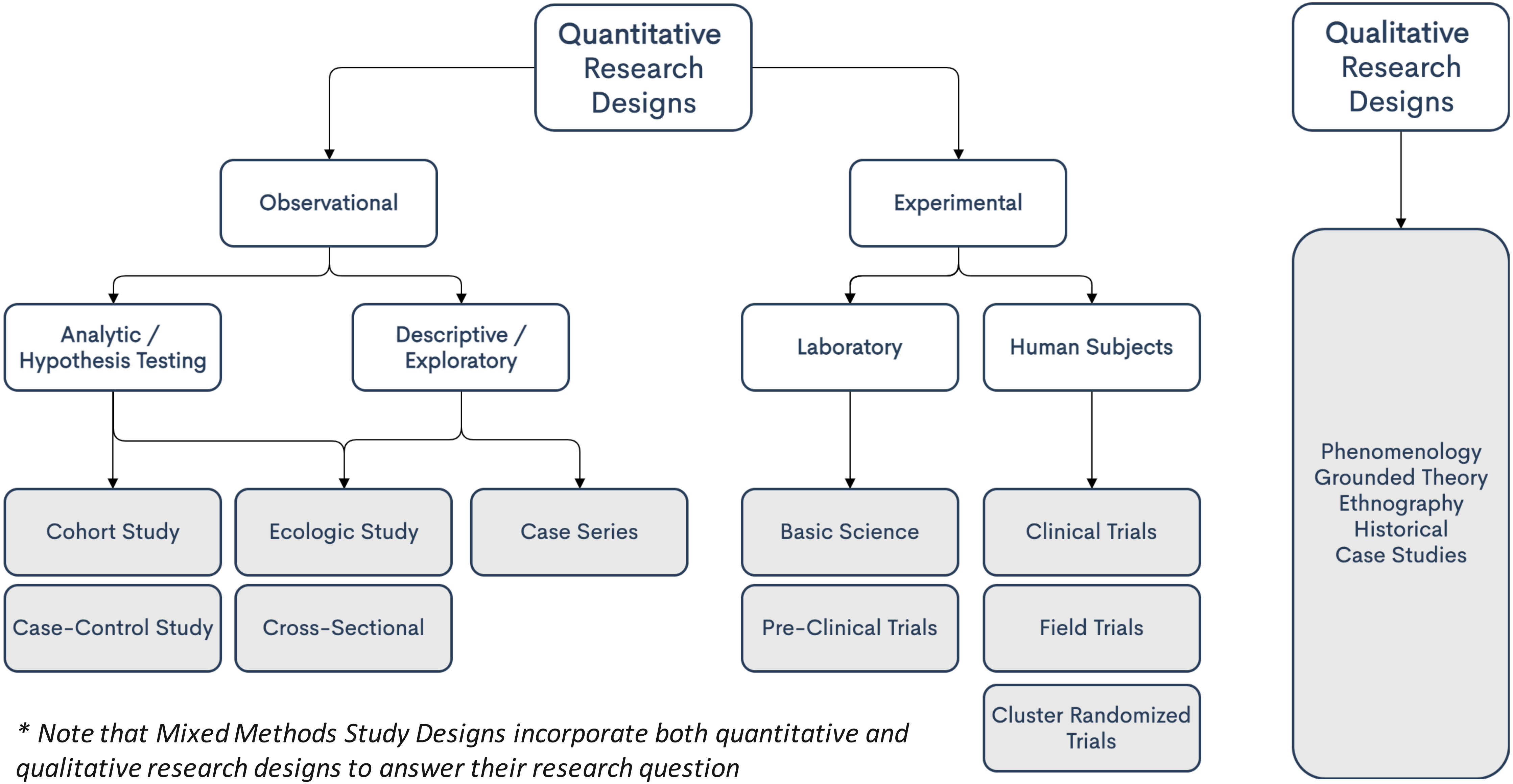
- Useful for:

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

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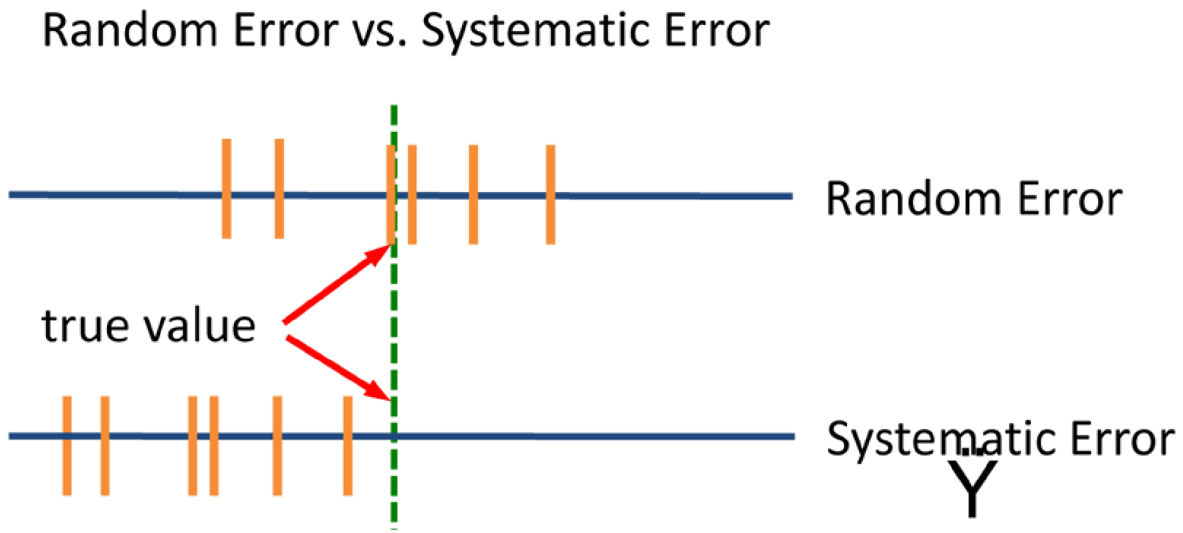
Measurement Error

- **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 an 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

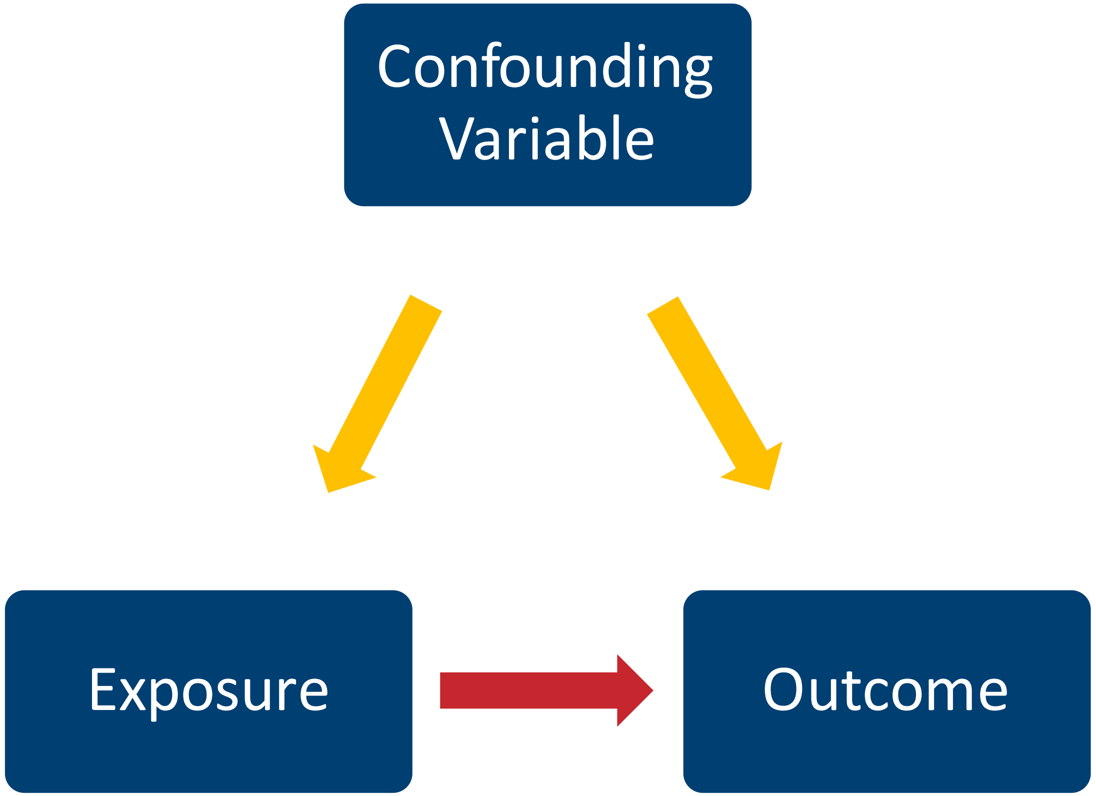
- Information bias occurs when **information is collected differently between two groups (misclassification)**, leading to an error in the conclusion of the association
  - **Differential** misclassification occurs when the level of misclassification differs between the two groups
  - **Non-differential**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

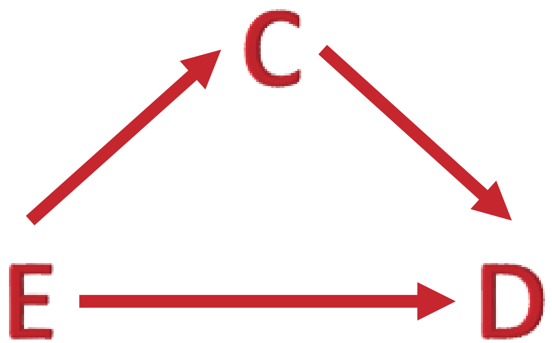
Directed Acyclic Graphs (DAGs)

- Visual representation of causal **assumptions** of your research question
  - A conceptual framework unique to your research question
- Illustrate sources of bias

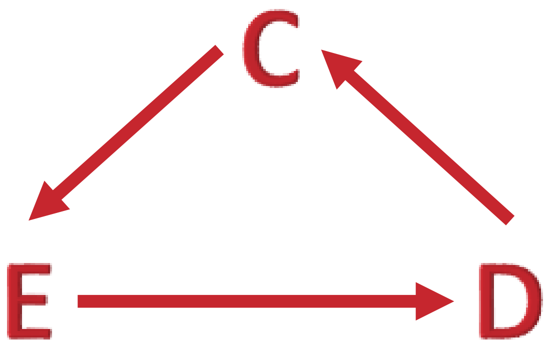
- **Directed**: Factors are connected with arrows, the arrows represent the direction of the causal relationship
- **Acyclic**: no directed path can form a closed loop, a factor cannot cause itself

Directed Acyclic Graphs (DAGs)

DAG

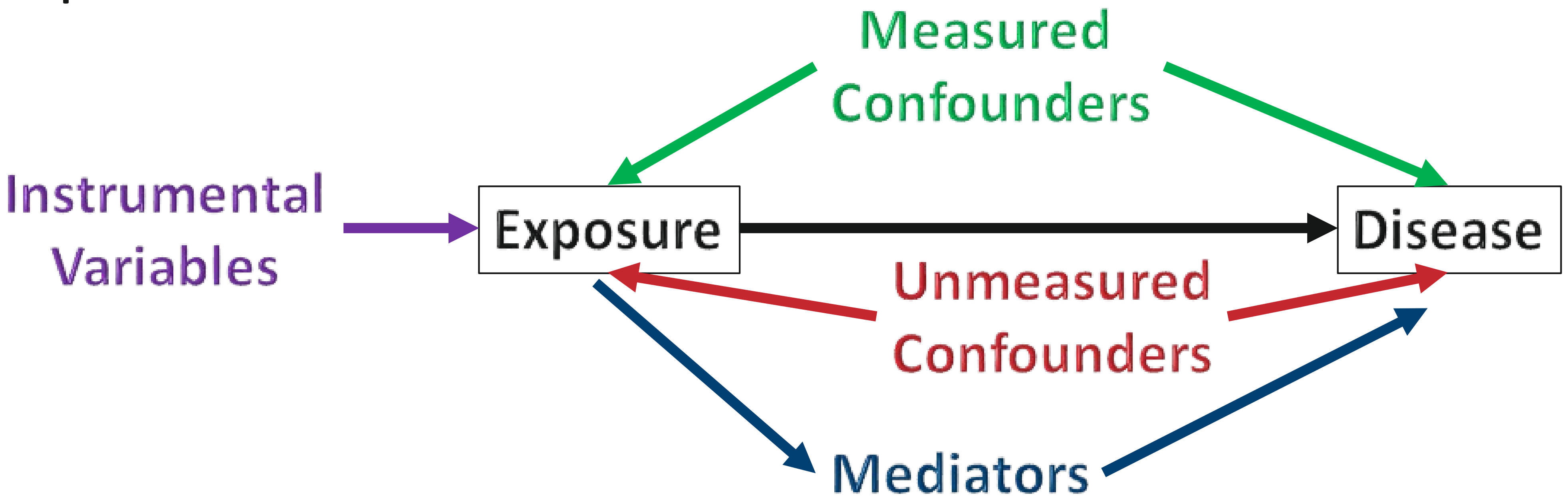


Not a DAG



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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- Gunasekara FI, Carter K, & Blakely T. Glossary for econometrics and epidemiology. J Epidemiol Community Health 2008;62;858-861
- Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999:37-48.

- **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