Assessment and Education in Rigor and Reproducibility

ASPET Teaching Symposium • EB2017

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Why are we talking about this?

Some evidence suggests that we haven't been doing so well at conducting experiments reproducibly.

News and Analysis

Nature Reviews Drug Discovery **10**, 643-644 (September 2011) | doi:10.1038/nrd3545

Reliability of 'new drug target' claims called into question

Asher Mullard

top

Bayer halts nearly two-thirds of its target-validation projects because in-house experimental findings fail to match up with published literature claims, finds a first-of-a-kind analysis on data irreproducibility.

Bayer: Findings of 53/67 target validation studies in cardiovascular disease, women's health, and oncology could not be reproduced using the published methods

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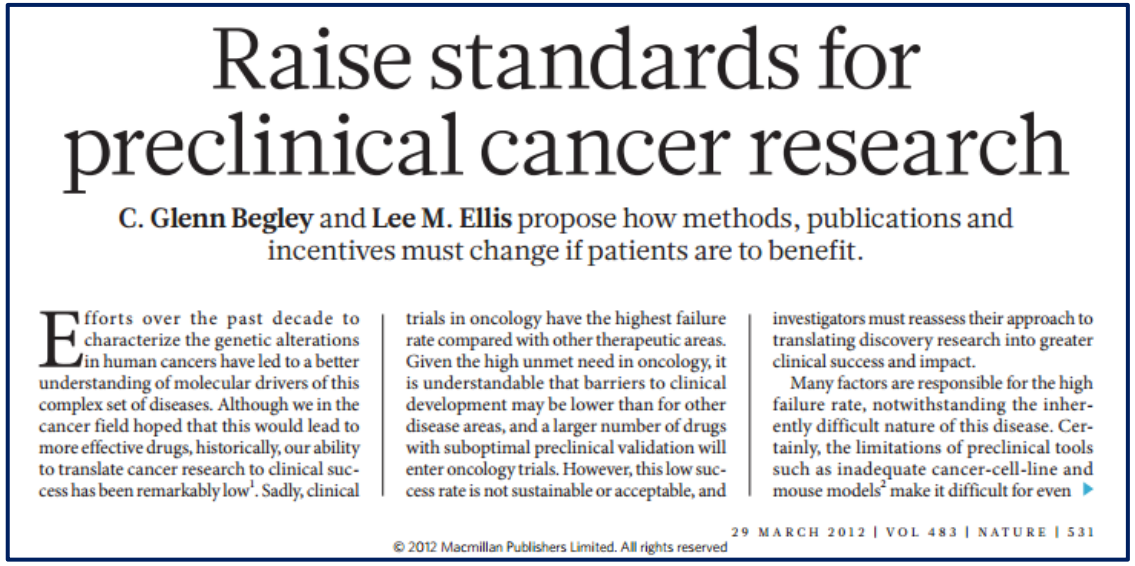

Raise standards for preclinical cancer research

C. Glenn Begley and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

Efforts over the past decade to characterize the genetic alterations in human cancers have led to a better understanding of molecular drivers of this complex set of diseases. Although we in the cancer field hoped that this would lead to more effective drugs, historically, our ability to translate cancer research to clinical success has been remarkably low[1]. Sadly, clinical trials in oncology have the highest failure rate compared with other therapeutic areas. Given the high unmet need in oncology, it is understandable that barriers to clinical development may be lower than for other disease areas, and a larger number of drugs with suboptimal preclinical validation will enter oncology trials. However, this low success rate is not sustainable or acceptable, and investigators must reassess their approach to translating discovery research into greater clinical success and impact.

Many factors are responsible for the high failure rate, notwithstanding the inherently difficult nature of this disease. Certainly, the limitations of preclinical tools such as inadequate cancer-cell-line and mouse models[2] make it difficult for even ▶

Amgen: Findings of 47/53 "landmark" papers in cancer biology could not be reproduced using the published methods

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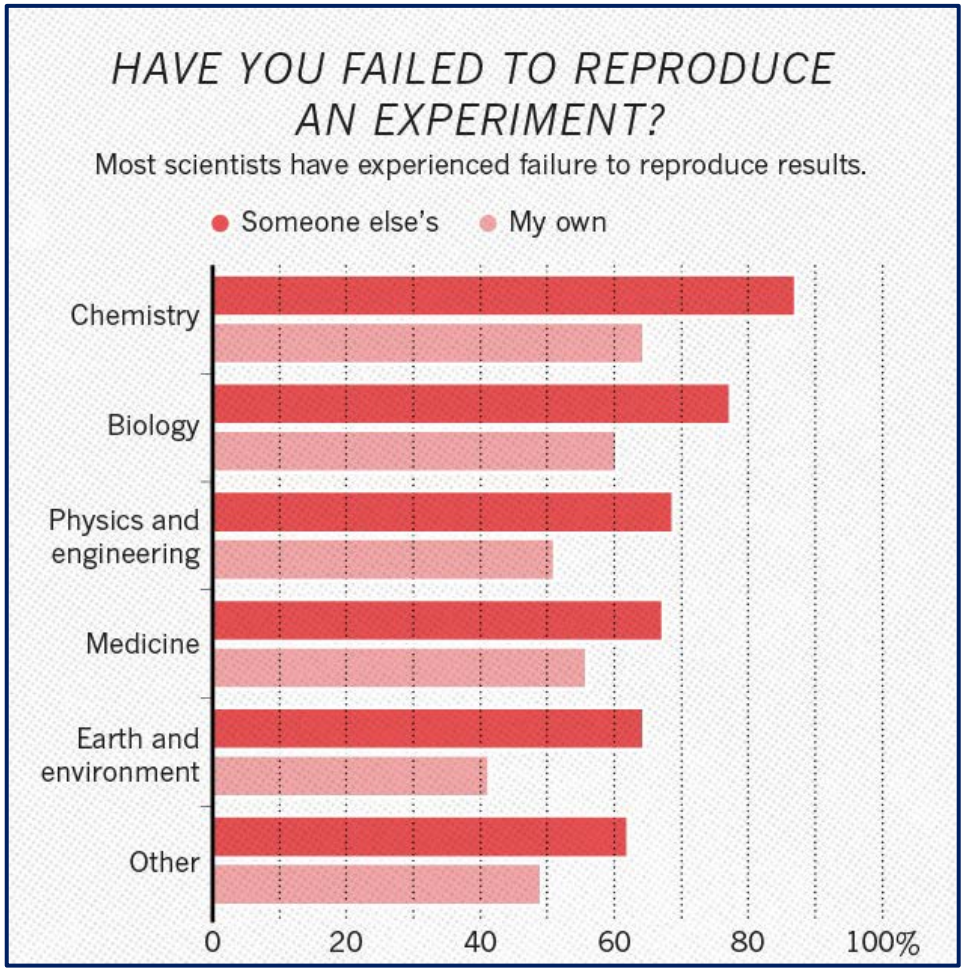


Poll of 1500 scientists, published in *Nature* News & Comments, 25 May 2016

Why are we talking about this?

Consequences to society

- Slowed progress of science
- Waste of resources
- Erosion of public trust

Why are we talking about this?

Proposed reasons why:

Not an RCR issue per se

- It is unethical to conduct a poorly designed experiment
- Data fabrication and falsification do lead to irreproducibility
- These forms of misconduct are only a small fraction of the problem

Culture of science

- Increased emphasis on making provocative statements
- Incentivizing publications in high-profile journals
- Emphasizing innovation over replication and rigor
- Publication bias

Why are we talking about this?

Proposed reasons why:

Lack of transparency

- Difficulty of accessing data
- Failure to report basic elements of experimental design or key methodological details

Failures of experimental design

- Ignoring crucial experimental design elements
- Poor training of researchers in experimental design

NIH Response has Included Support for Education

Supplements to NIGMS Predoctoral Training Grants

- Provide exposure to tools, expertise, and experiences that support rigor and reproducibility.
- Change the culture to support best practices in design and management.
- Identify and disseminate effective tools to the broader scientific community.

Formal training in the philosophy and methods of experimental design is fundamental to PhD training in the sciences.

Why a Course in Experimental Design?

Relationship to your training needs as PhD scientists

Consider the following:

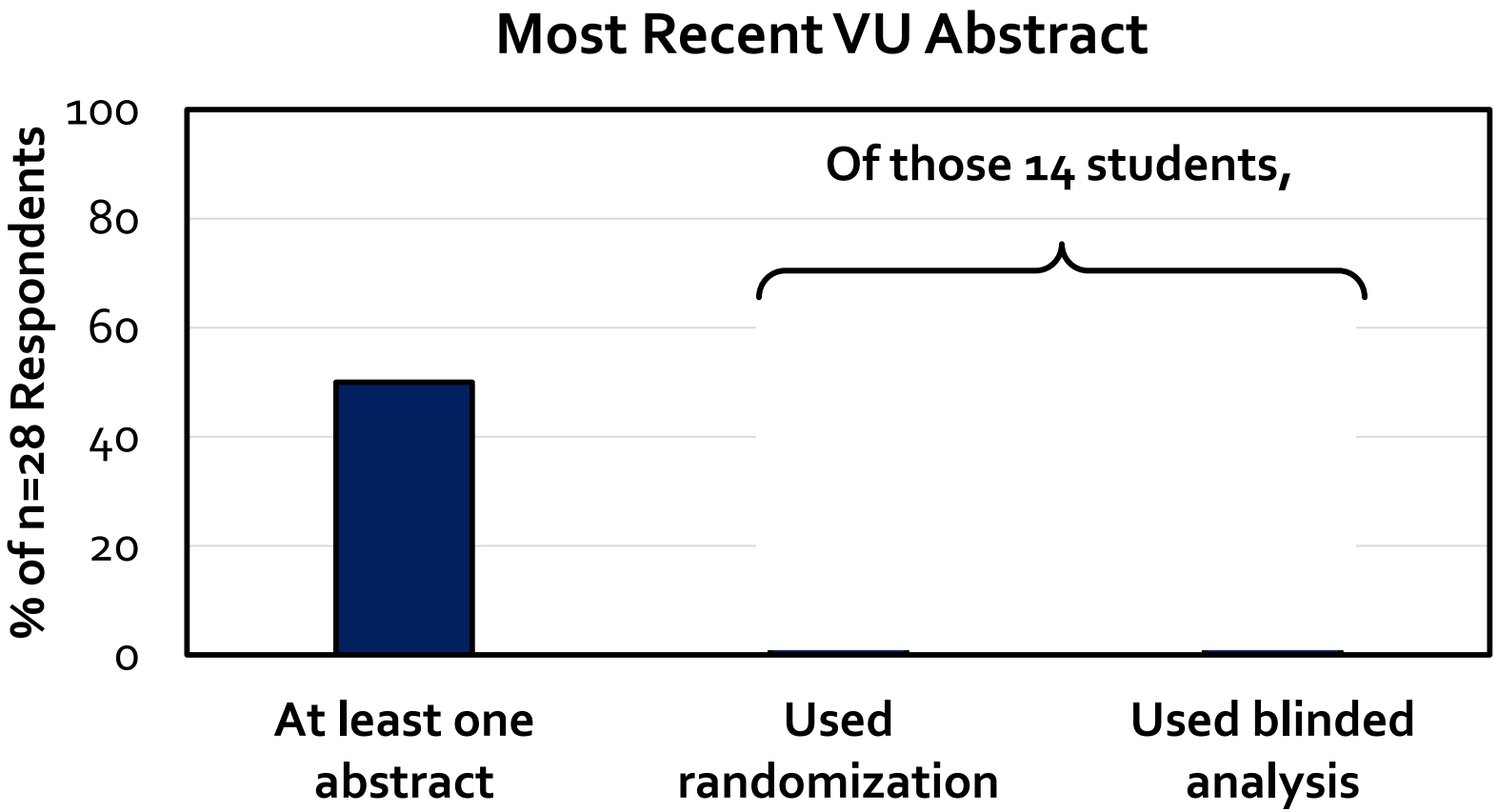
- There are three types of RNA: mRNA, tRNA, rRNA
- 90% of the human genome is junk. It's just there to prevent damage to, and act as scaffolding for, the important parts.

This is a PhD degree

- Facts will evolve, change, be disproven, etc.; to be a scientist, what you need to know and practice are the philosophy and methods of scientific experimentation
  - Adapt to changes in knowledge
  - Generate new knowledge in the most rigorous way

Current Model for Graduate Education is Incomplete

Behaviors related to rigorous experimental design



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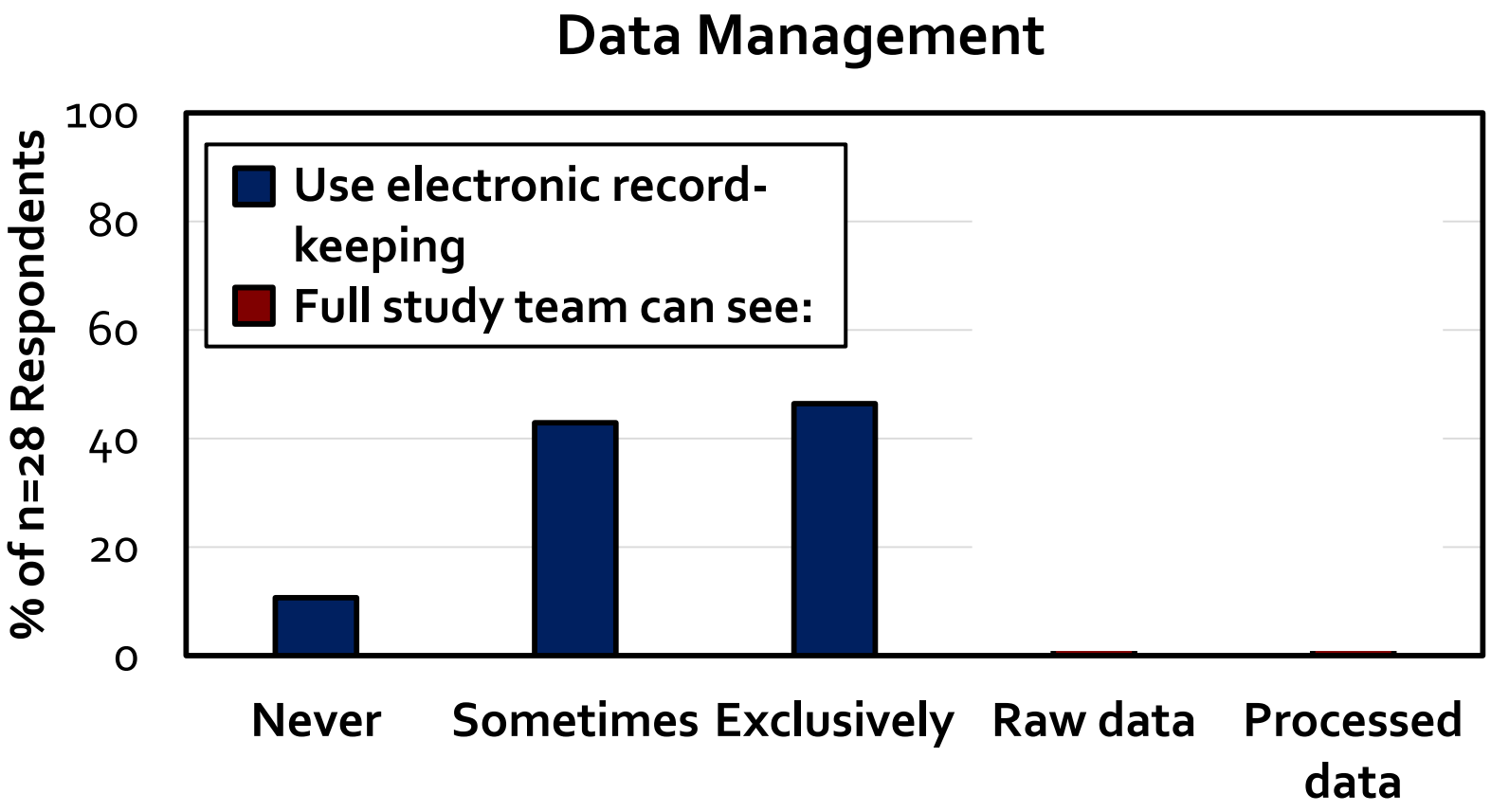

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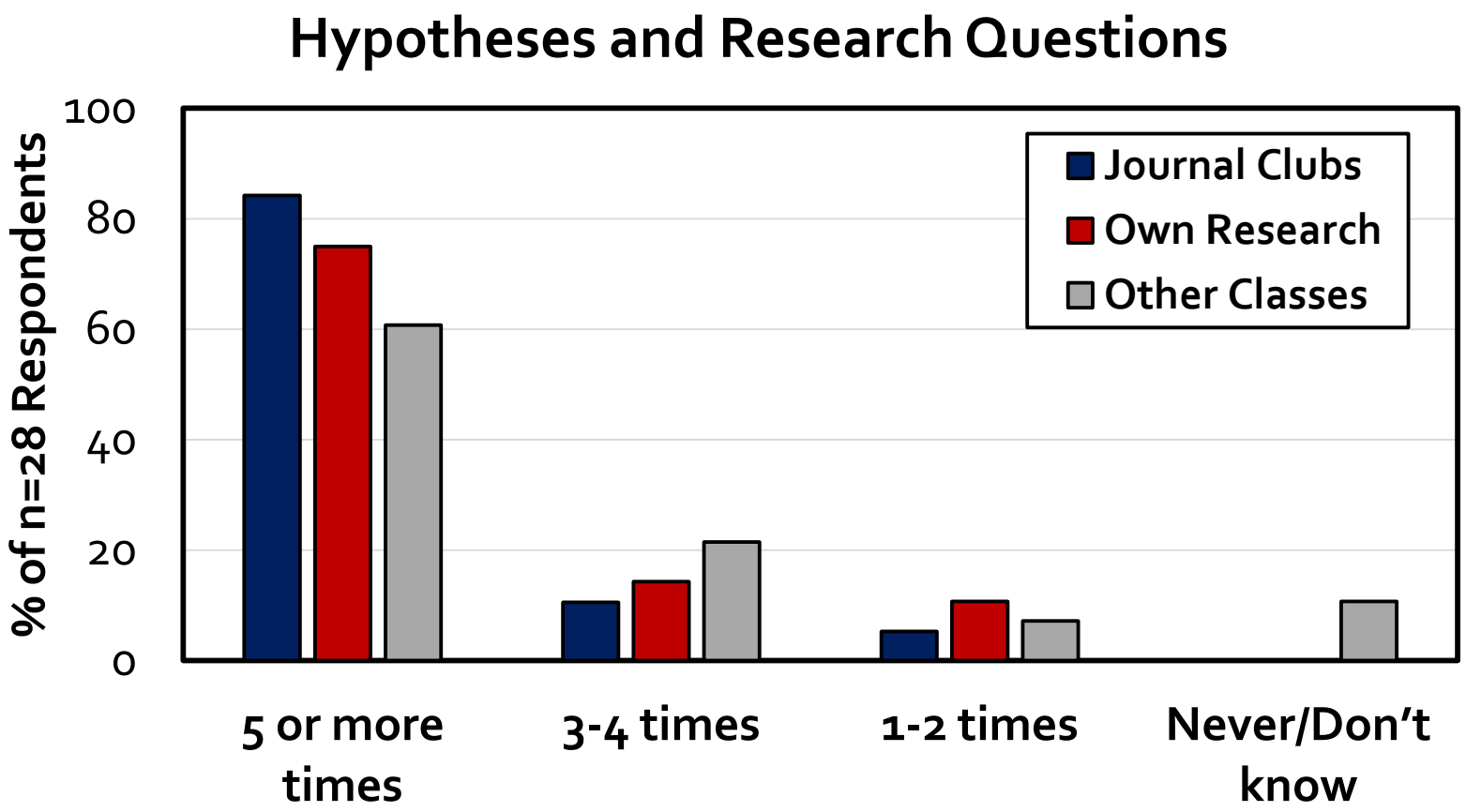
Sources of knowledge in experimental design



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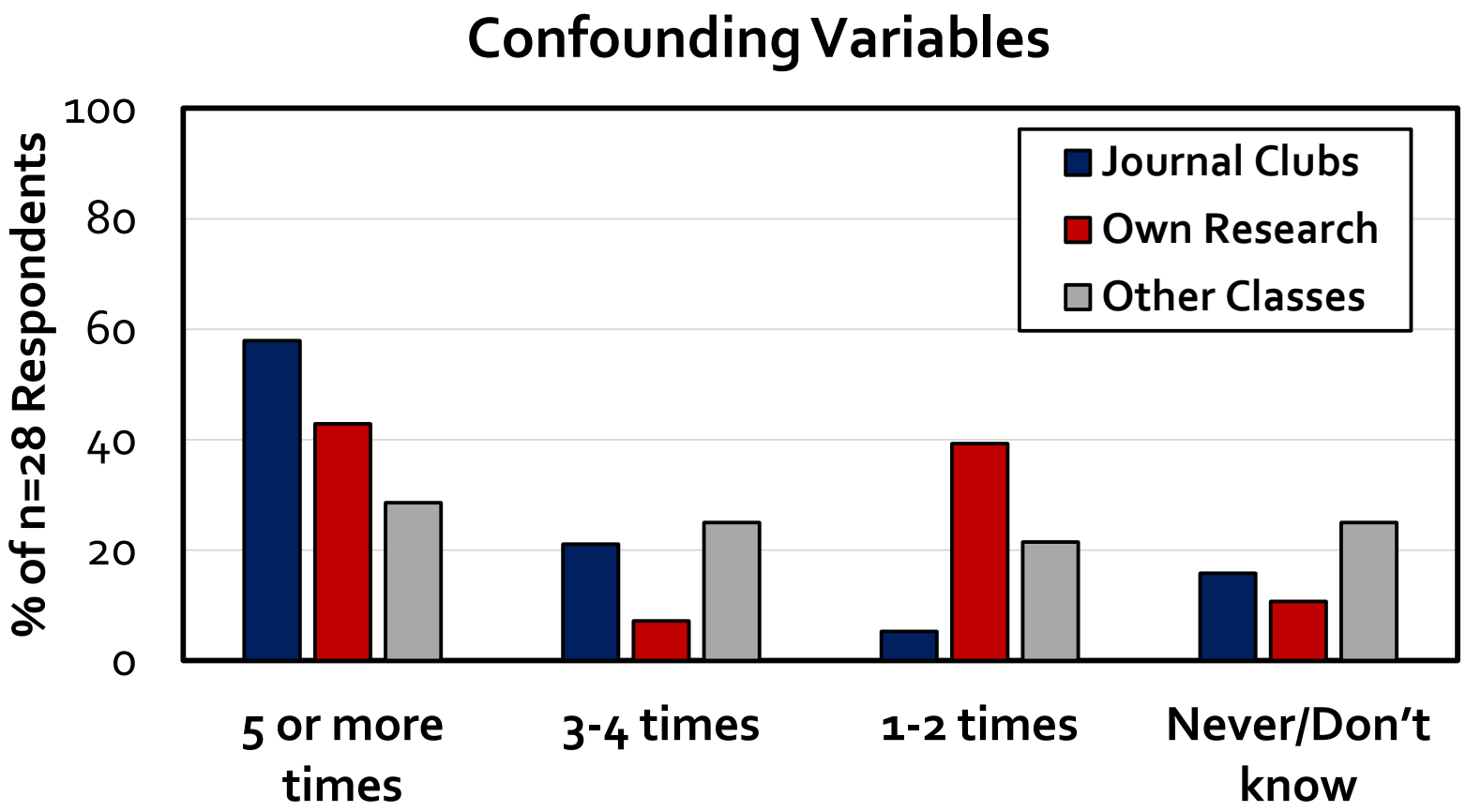

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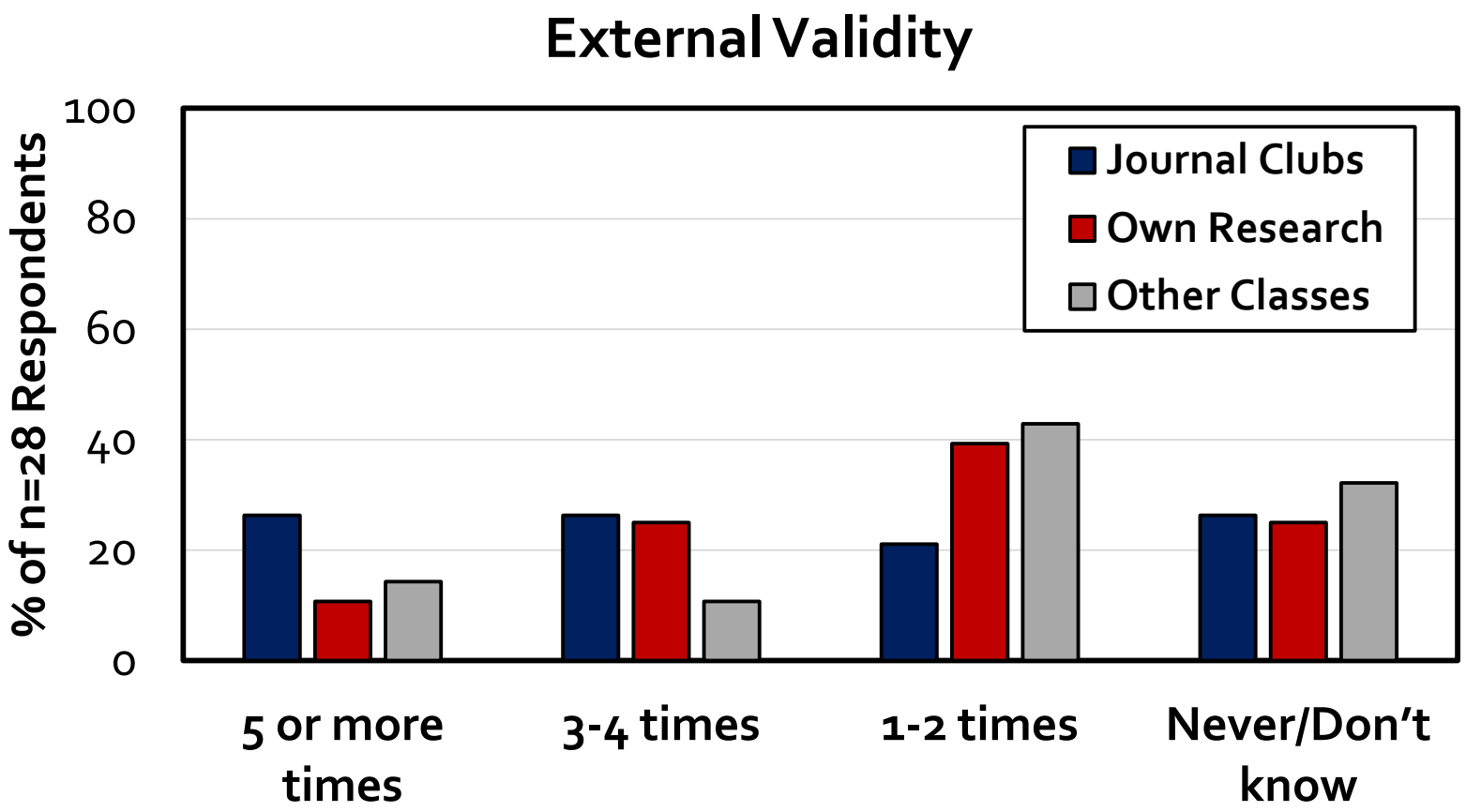

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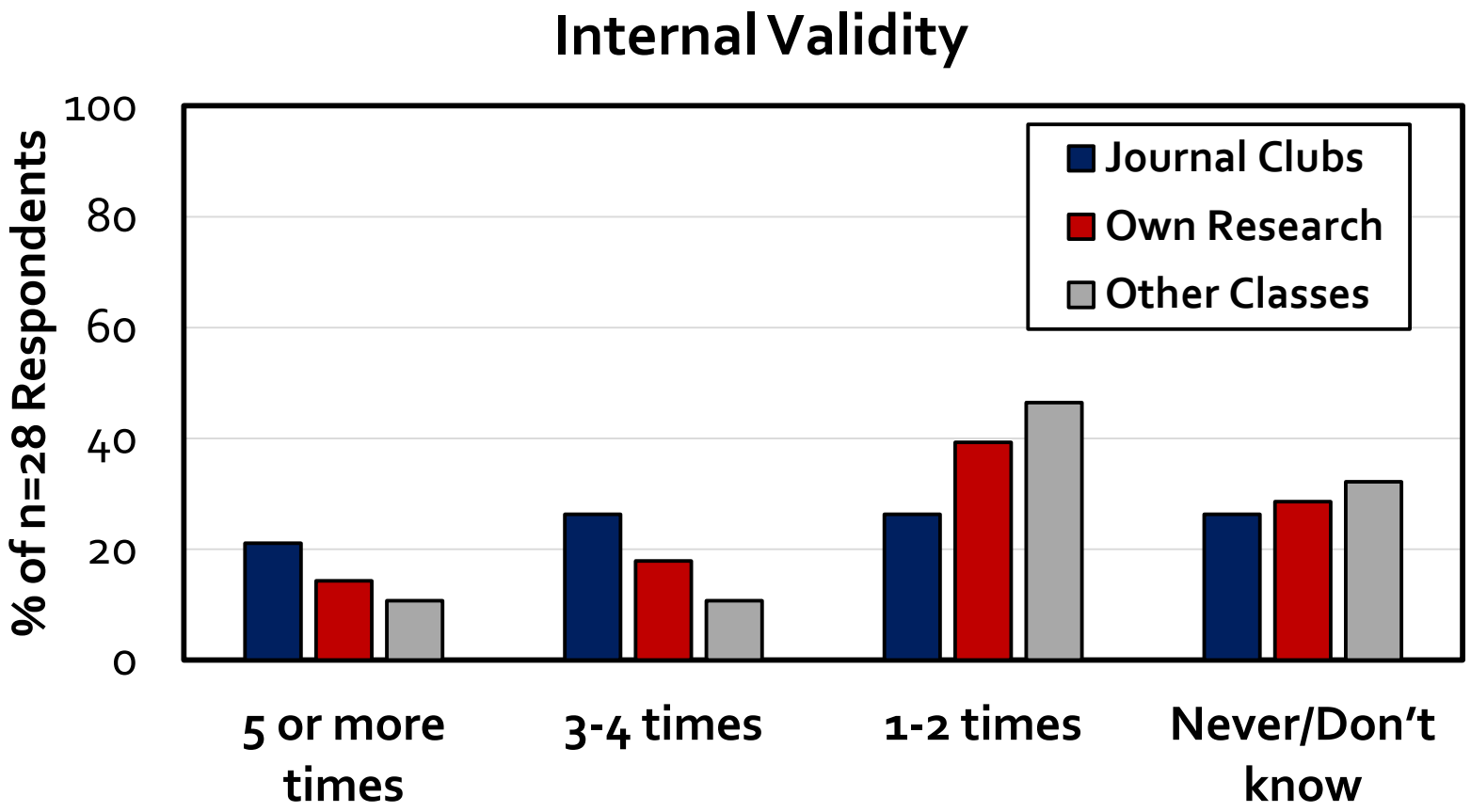

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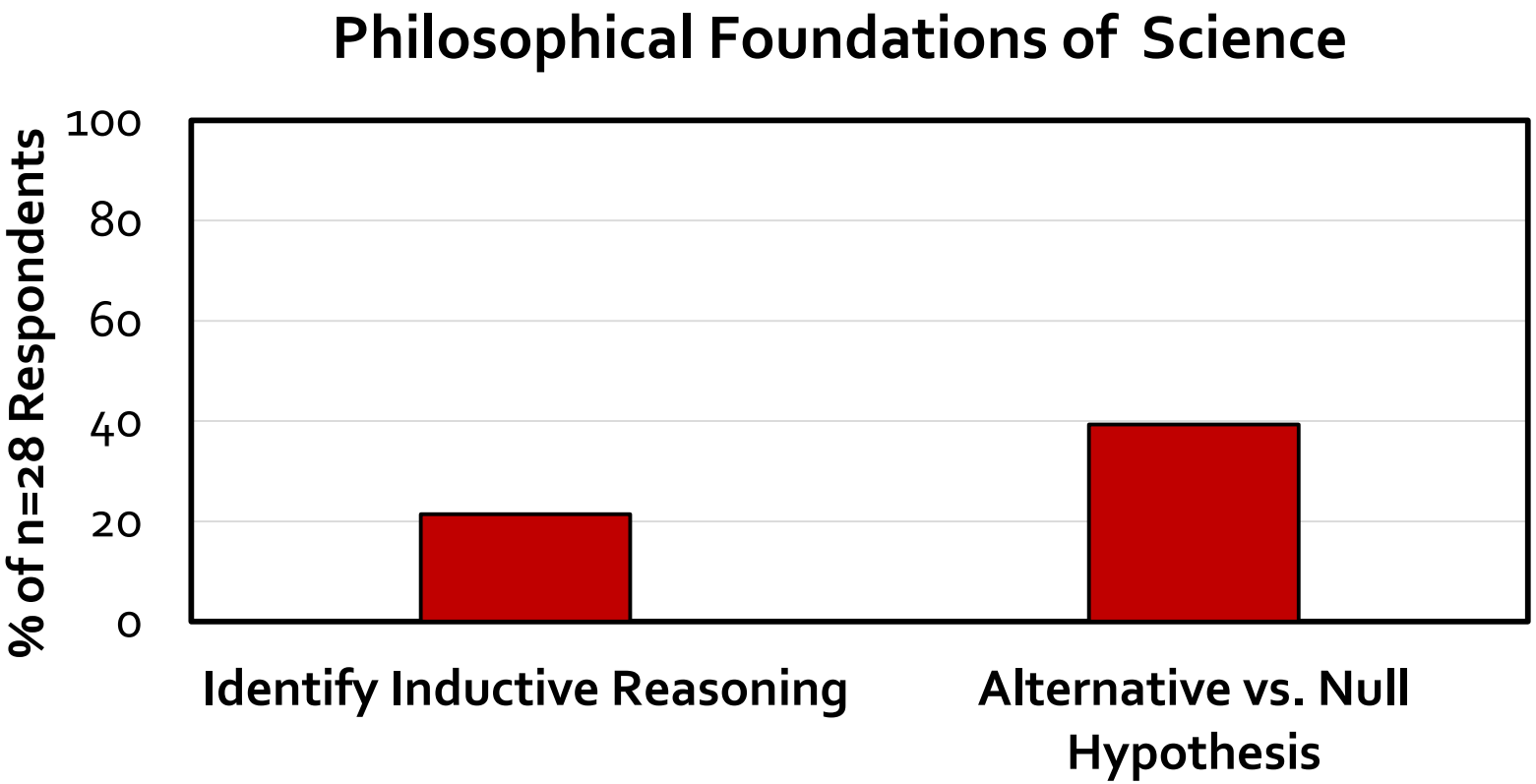
Knowledge of experimental design



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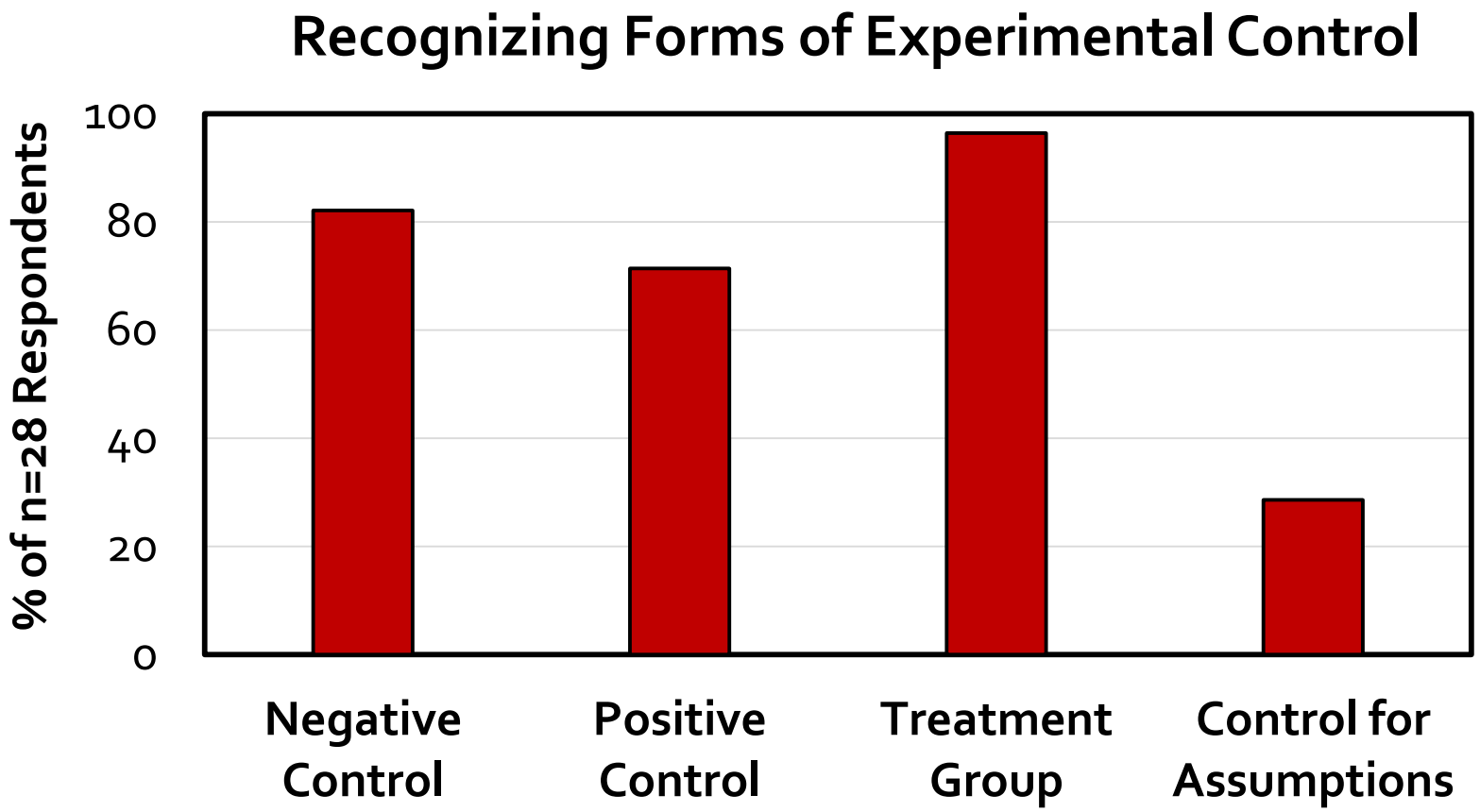

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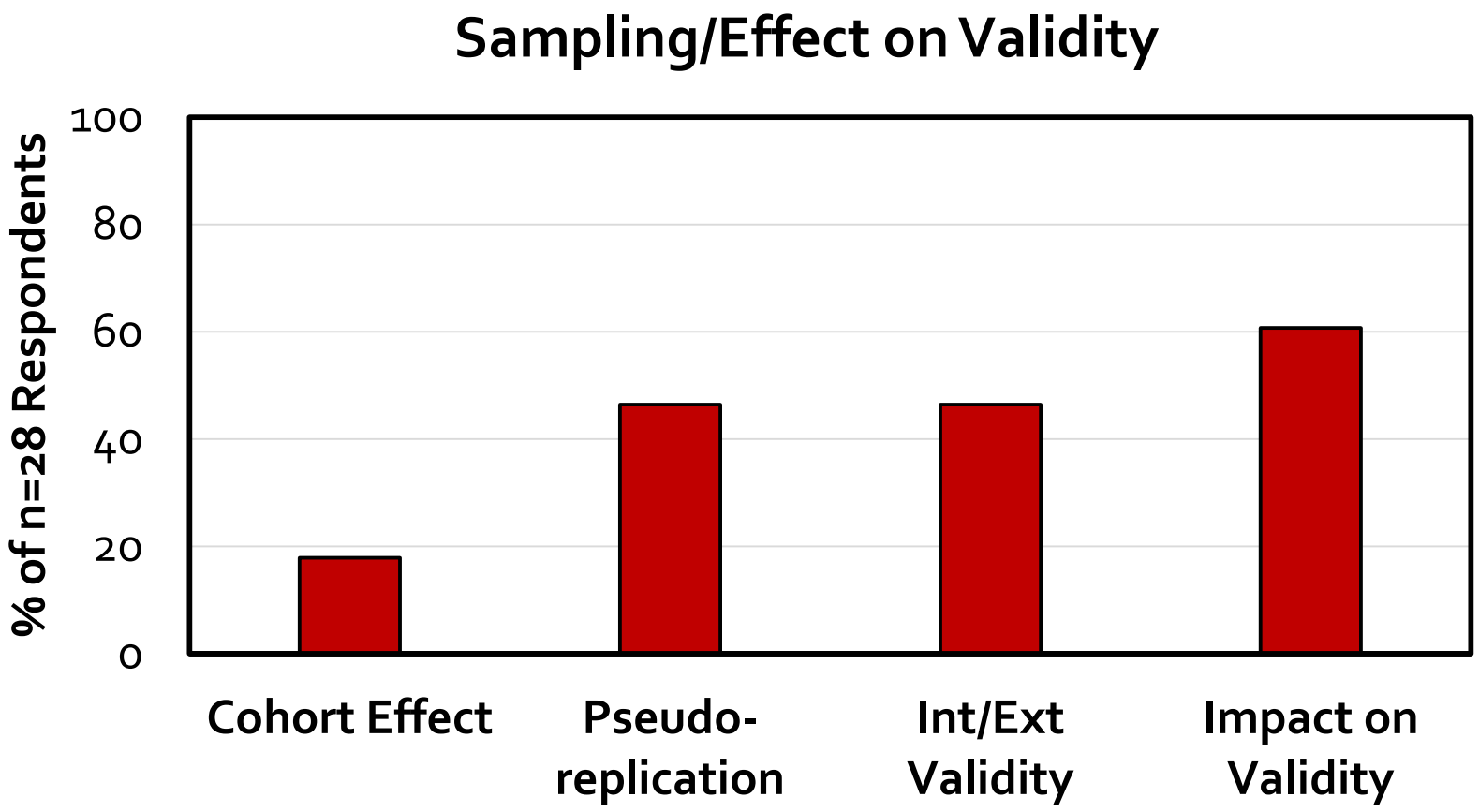

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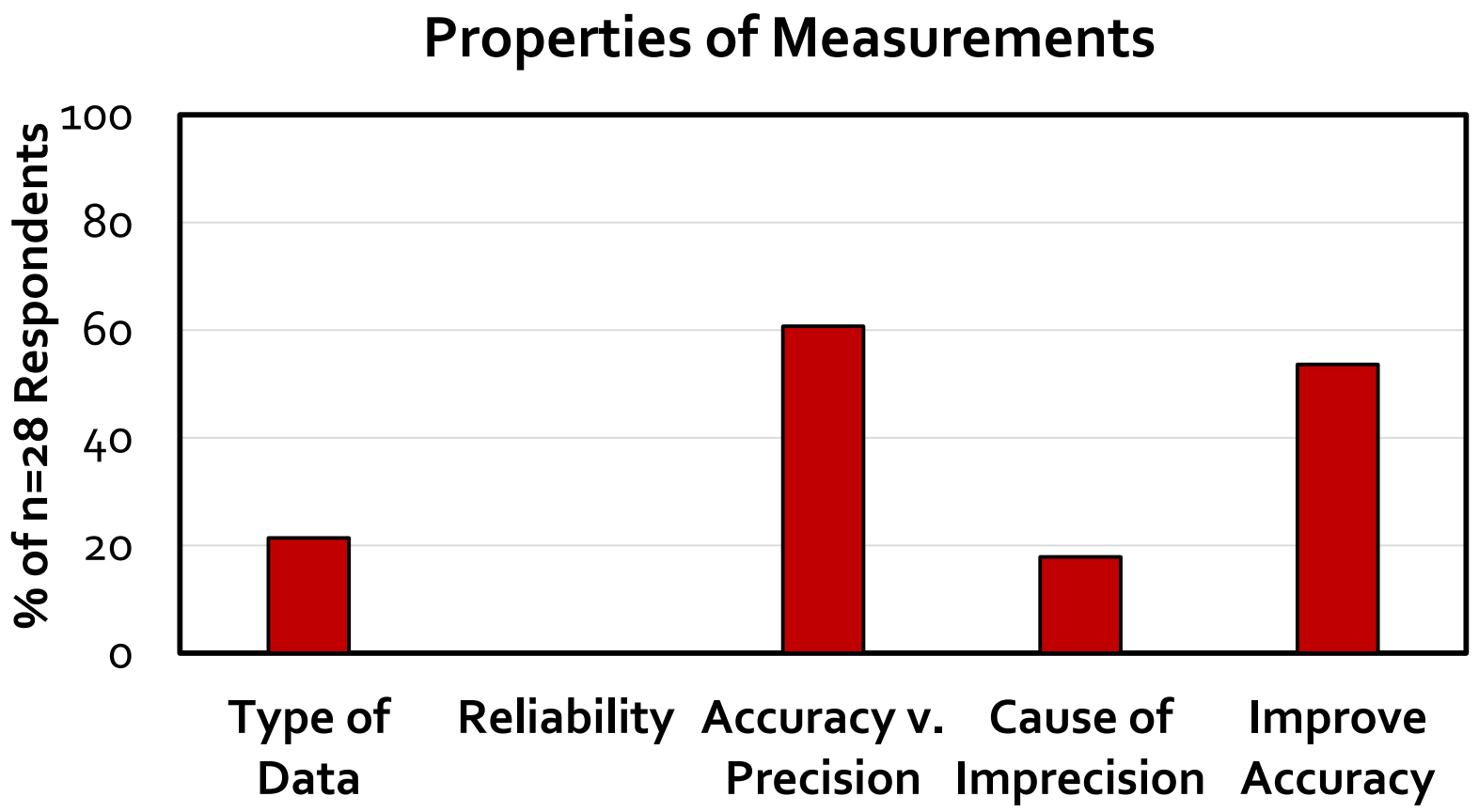
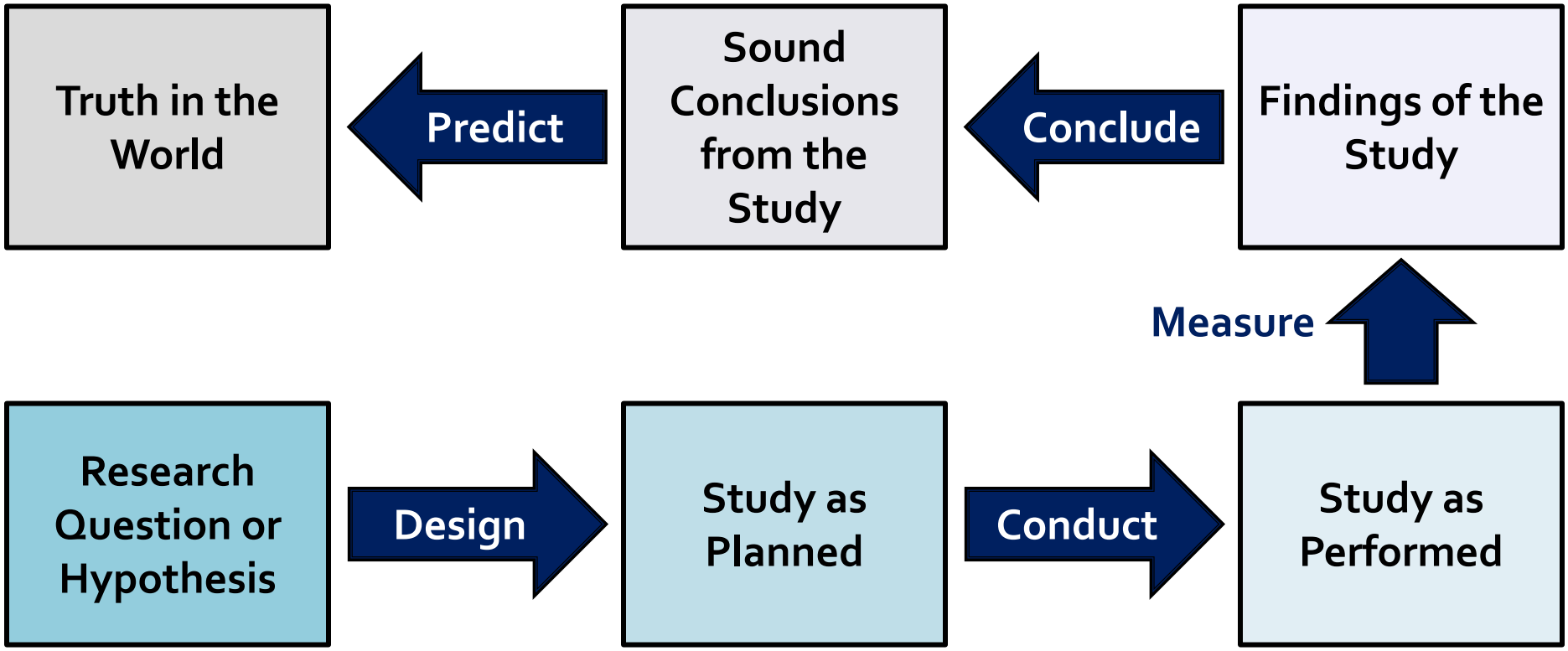


Course Structure

Mix of didactic and practical elements



Adapted from Hulley et al. (2013). Designing Clinical Research. Philadelphia, PA: Lippincott, Williams, and Wilkins.

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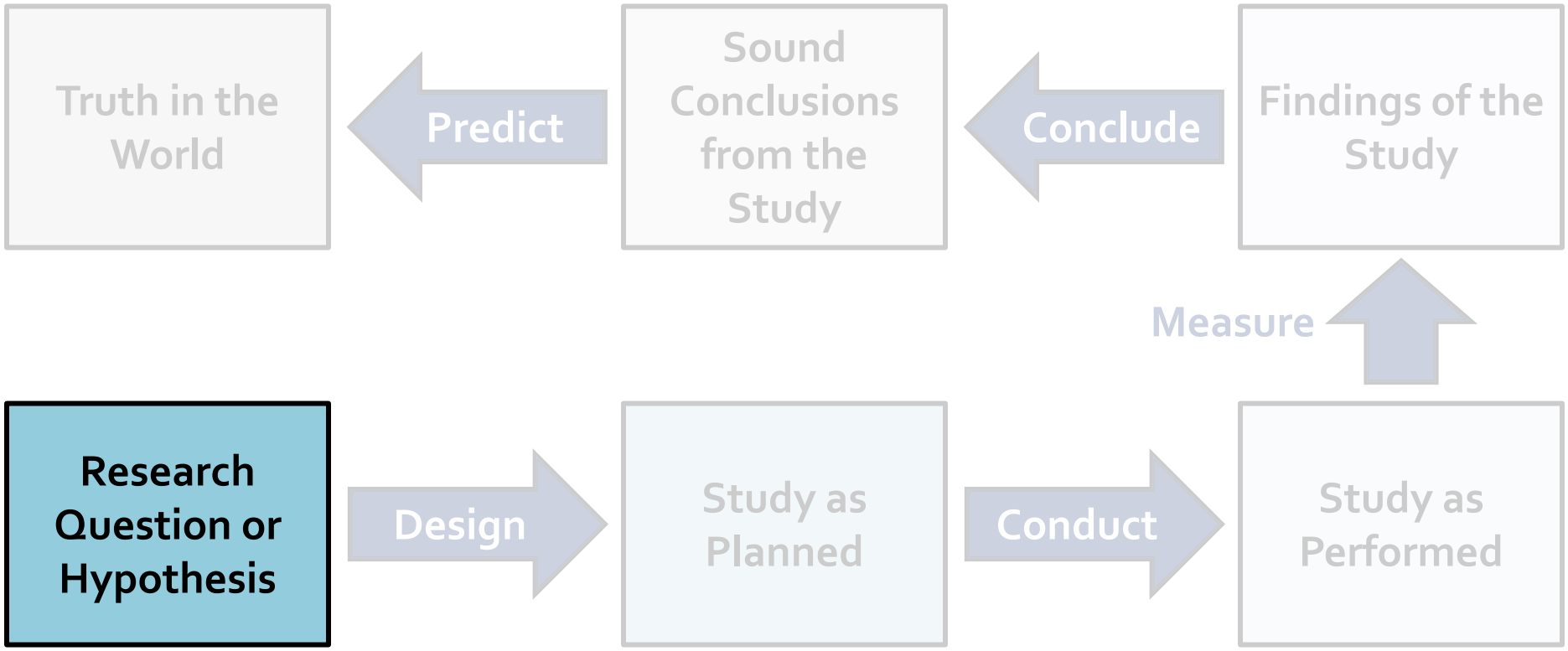

Specificity and Testability

Falsifiability; Alternative vs. Null hypotheses

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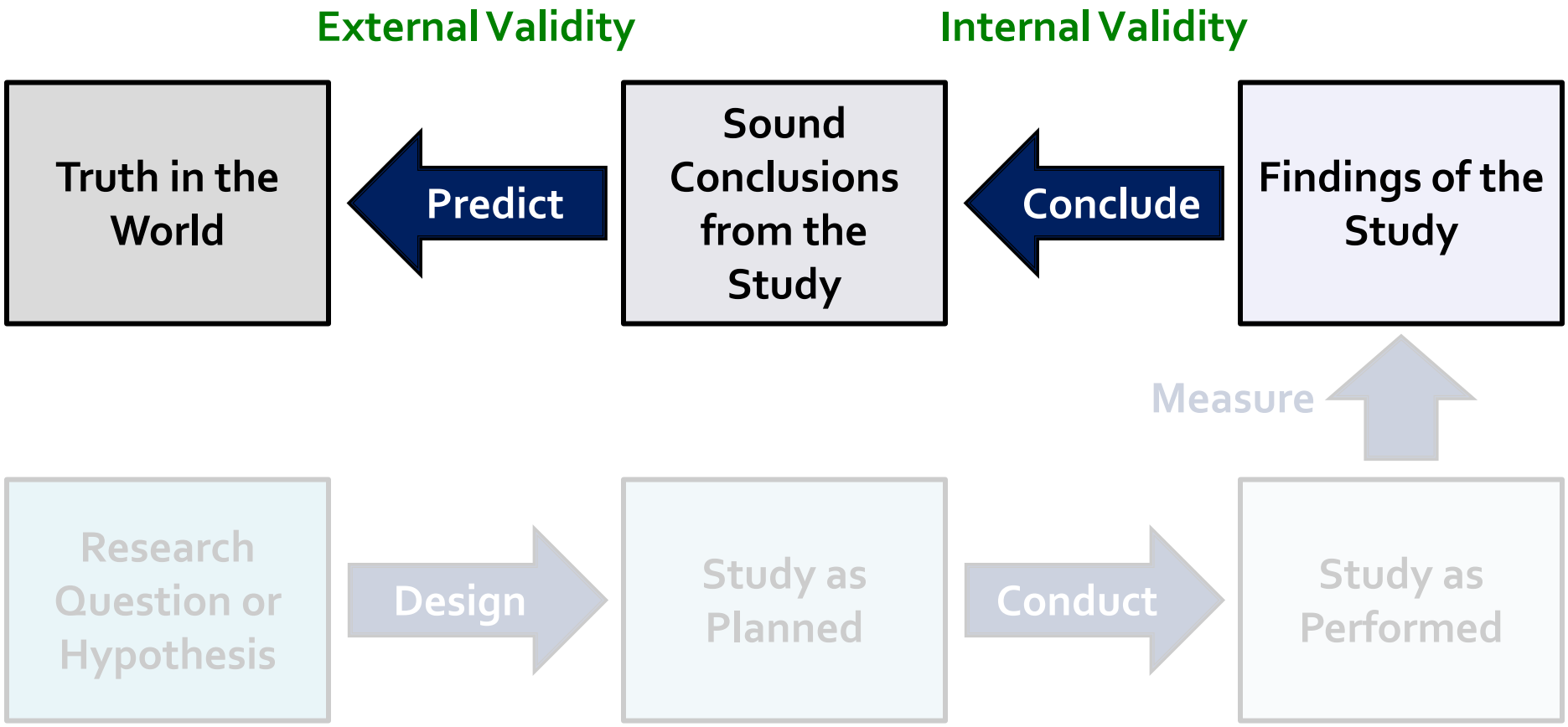

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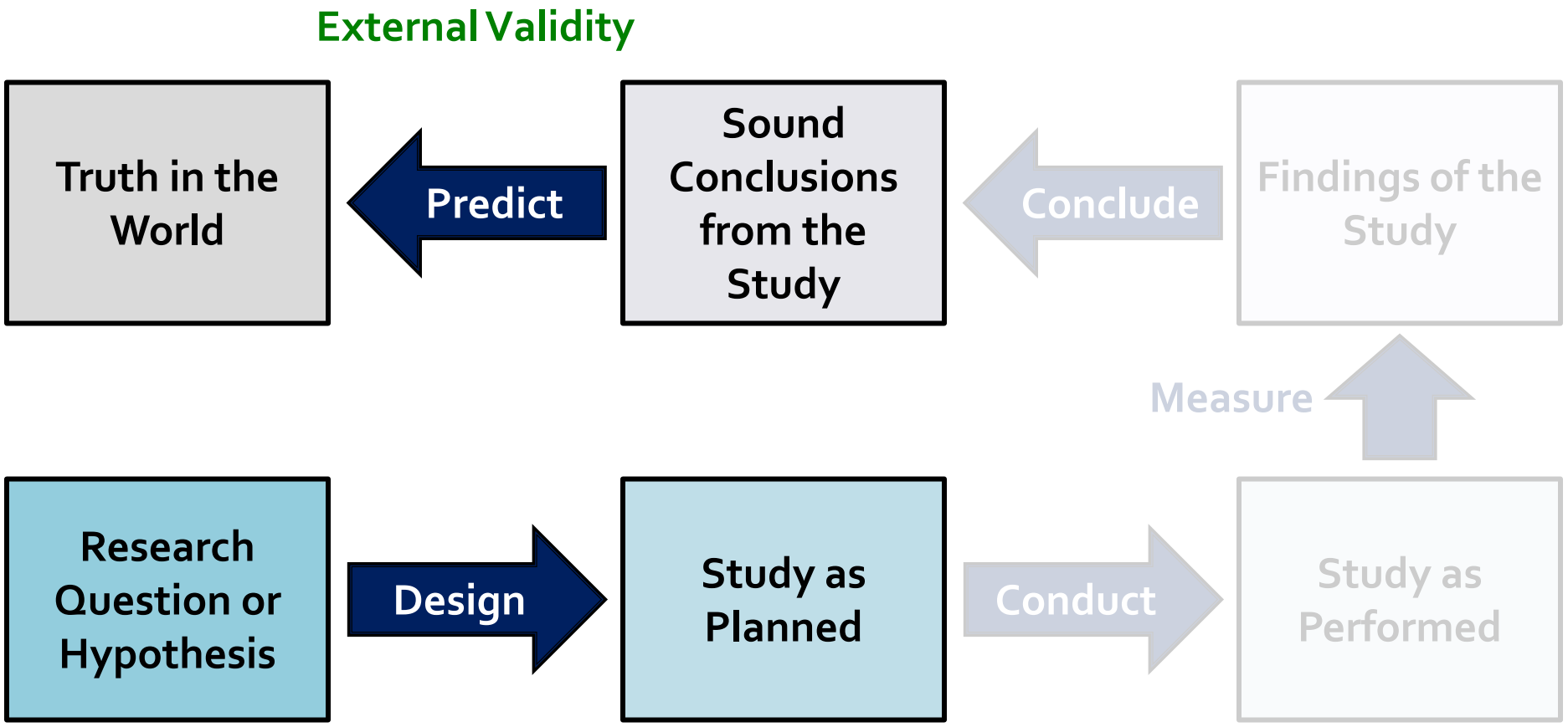

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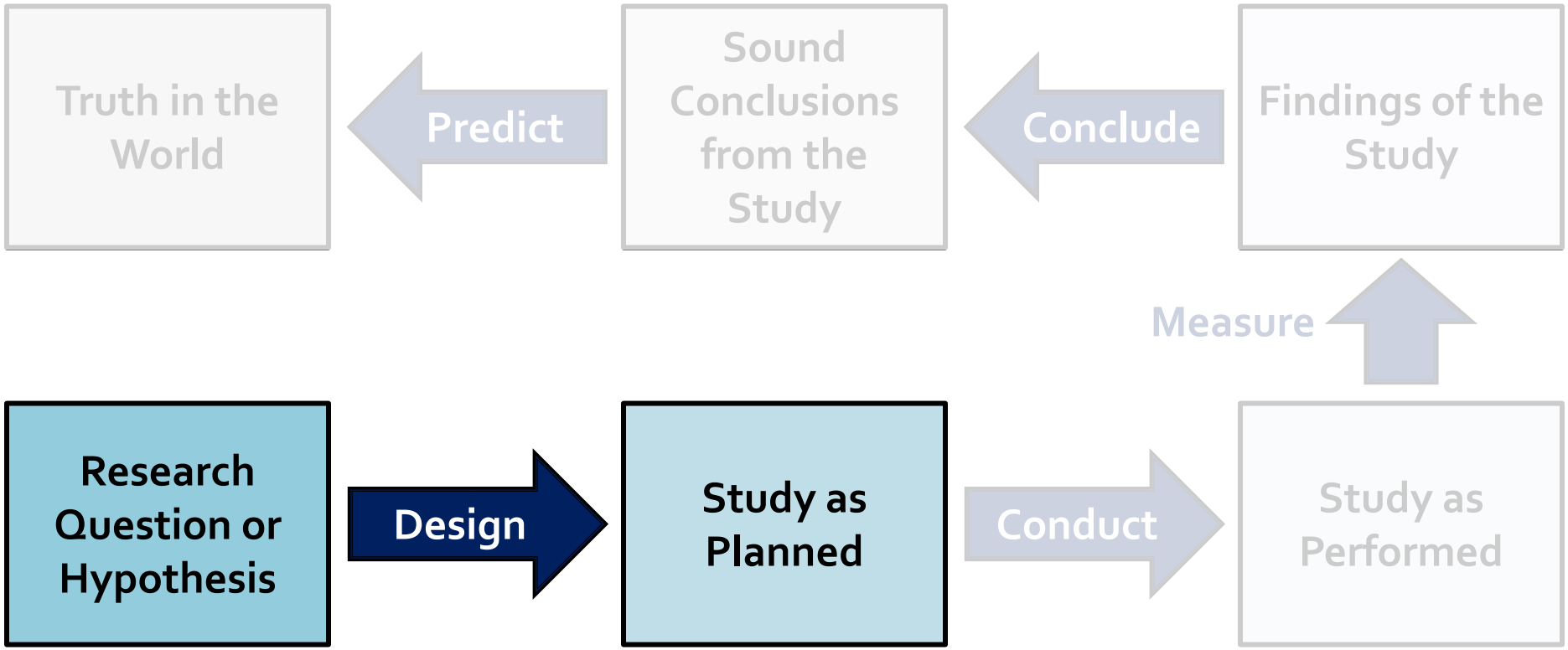
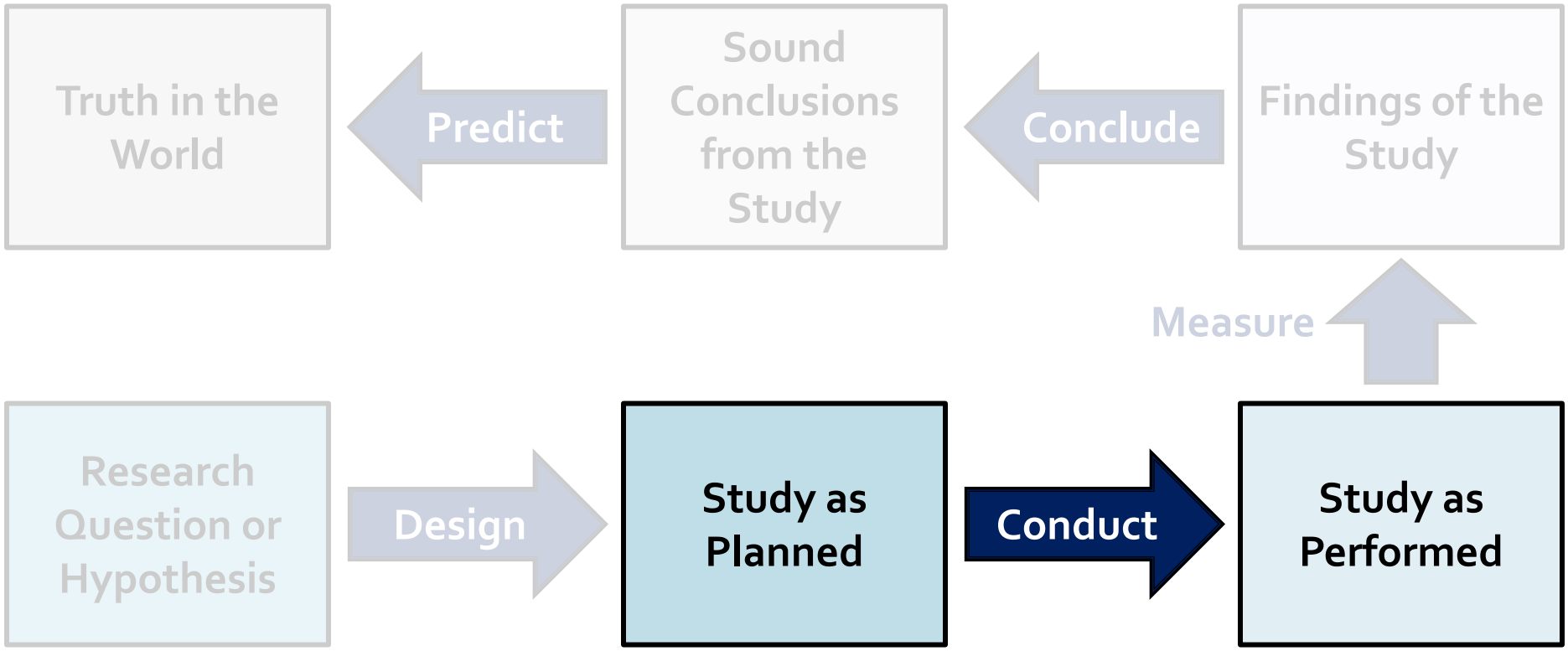


Necessity and sufficiency

Forms of experimental control

Types of experimental designs

Course Structure



Data management

Recording system validation and experimental control

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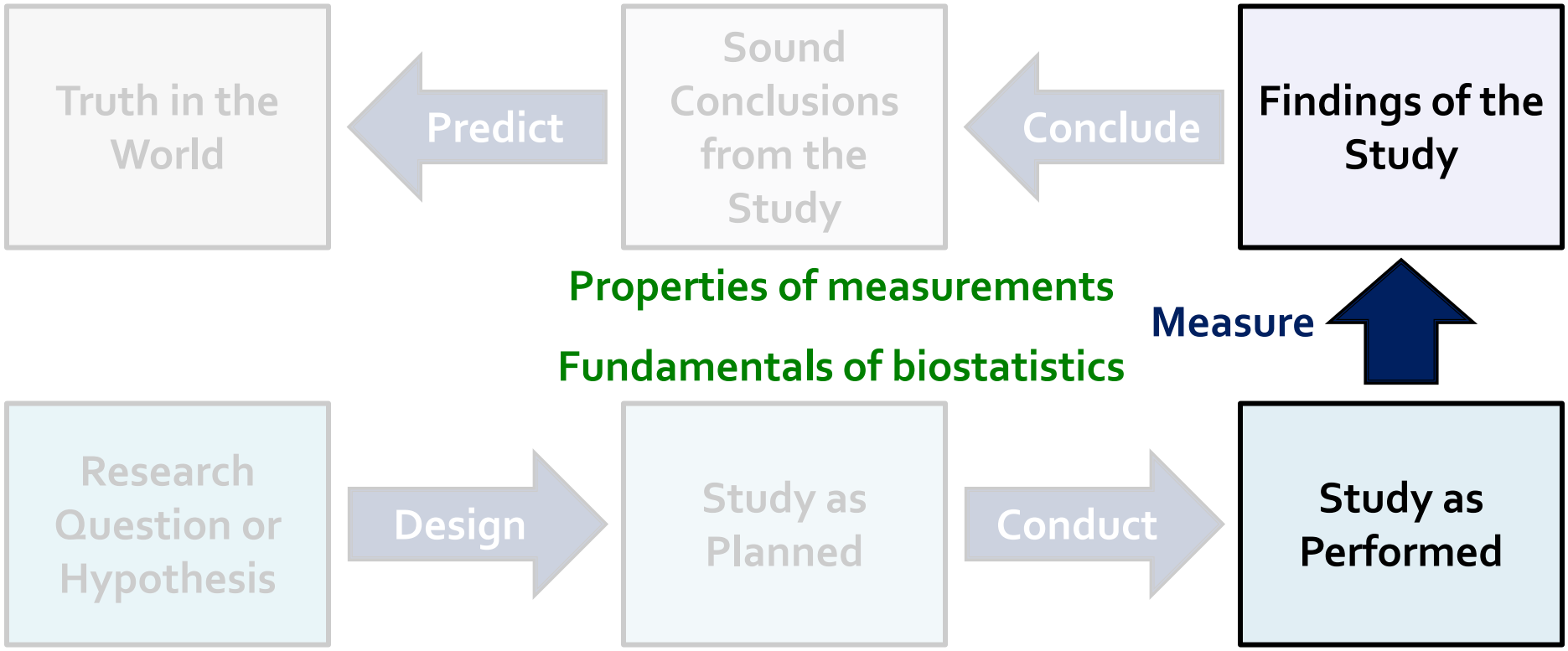

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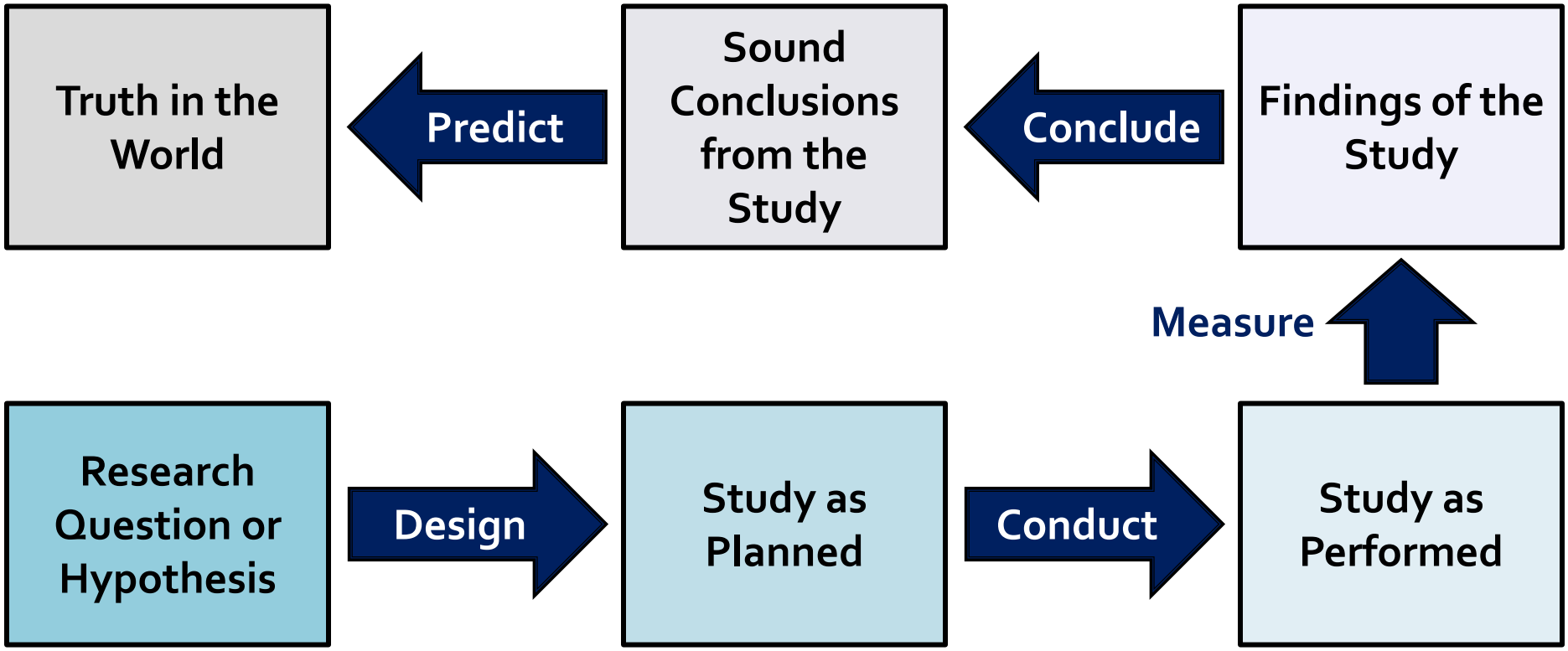

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Summary and Conclusions

Coursework is needed that specifically teaches experimental design

- Support objective of rigorous, reproducible science
- Ethical requirement
- Fundamental to PhD training

Curriculum should assess, teach, and reinforce

- Knowledge
- Behavior

Future plans

- Expansion and validation of assessment instrument
- Assess long-term outcomes

Lastly, thanks go to

People

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- Abigail Brown , PhD
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- Larry Marnett, PhD

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