Research Management in Clinical Study, CTR

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Research:

is a scientific process of investigation and/or experimentation that involves the systematic collection, analysis and interpretation of data to answer a certain question or solve a problem

Basic Research:

is to generate new knowledge, theories and technologies to deal with major unresolved health problems

Applied Research:

is to establish new knowledge and the results can be applied to practical settings.

Clinical Research:

is to be improving treatment of diseases.

Clinical Trial:

An experiment designed to assess the efficacy of a test treatment by comparing its effects with those produced using some other test or control treatment in comparable groups of human beings.

Public Health Research:

is to be providing tools for prevention of disease

Basic Ingredients of Clinical Research

Two viewpoints, setting up themes that run together;

The Anatomy of research—what it's made of.

- This includes the tangible elements of the study plan: research question, design, subjects, measurements, sample size calculation, and so forth.
- The goal is to design these components in a fashion that will make the project feasible and efficient.

The Physiology of research—how it works.

- Studies are useful to the extent that they yield valid inferences, first about what happened in the study sample and then about how these findings generalize to people outside the study.

- The goal is to minimize the errors, random and systematic, that threaten conclusions based on these inferences.

- Separating the two themes is artificial in the same way that the anatomy of the human body doesn't make much sense without some understanding of its physiology.

- But the separation has the same advantage: It clarifies our thinking about a complex topic.

ANATOMY OF RESEARCH: WHAT IT'S MADE OF

- The structure of a research project is set out in its **protocol**, the written plan of the study.

- Protocols are well known as devices for seeking grant funds and Institutional Review Board (IRB) approval.

- Also have a vital scientific function: helping the investigator organize her research in a logical, focused, and efficient way.

Anatomy of Research: The Study Plan

Design Components	Purpose
•**Research questions**	What questions will the study address ?
•**Background and significance**	Why are these questions important ?
• **Design** Time frame Epidemiologic design	How is the study structured ?
•**Subjects** Selection criteria Sampling design	Who are the subjects and how will they be selected ?

Anatomy of Research: The Study Plan

Design Components	Purpose
•**Variables** Predictor variables Confounding variables Outcome variables	What measurements will be made ?
•**Statistical issues** Hypotheses Sample size Analytic approach	How large is the study & how will it be analyzed ?

Research Question

- The research question is the objective of the study, the uncertainty the investigator wants to resolve.

- Often begin with a general concern that must be narrowed down to a concrete, researchable issue.

  For example, the general question:

  Should people eat more fish?

- This is a good place to start, but the question must be focused before planning efforts can begin.

- Often this involves breaking the question into more specific components, and singling out one or two of these to build the protocol around:
- How often do Americans eat fish?
- Does eating more fish lower the risk of cardiovascular disease?
- Is there a risk of mercury toxicity from increasing fish intake in older adults?
- Do fish oil supplements have the same effects on cardiovascular disease as dietary fish?
- Which fish oil supplements don't make your breath smell like fish?

FINER Criteria for a Good Research Question and Study Plan

•Five essential characteristics : It should be feasible, interesting, novel, ethical, and relevant

1. **Feasible**
   - Adequate number of subjects
   - Adequate technical expertise
   - Affordable in time and money
   - Manageable in scope

2. **Interesting**
   - Getting the answer intrigues the investigator and her colleagues

FINER Criteria ;

3. Novel

- Provides new findings
- Confirms, refutes, or extends previous findings
- May lead to innovations in concepts of health and disease, medical practice, or methodologies for research

4. Ethical

- The institutional review board will approve

5. Relevant

- Likely to have significant impacts on scientific knowledge, clinical practice, or health policy
- May influence directions of future research

Background and Significance

- A brief background and significance section in a protocol sets the proposed study in context and gives its rationale:
- What is known about the topic at hand ?
- Why is the research question important ?
- What kind of answers will the study provide ?

- To cites relevant previous research and indicate the problems with the prior research and what uncertainties remain

- **Mastering the Literature**

It is important to master the published literature in an area of study:

- should conduct a thorough search of published literature in the areas pertinent to the research question and critically read important original papers
- mastery of a subject entails participating in meetings and building relationships with experts in the field.

- **Being Alert to New Ideas and Techniques**

In addition to the medical literature as a source of ideas for research questions, it is helpful to attend conferences in which new work is presented

Design

- To take a passive role in making measurements on the study subjects in an observational study or
- To apply an intervention and examine its effects in a clinical trial

Among observational studies, two common designs are;

- Cohort studies, in which observations are made in a group of subjects that is followed over time, and
- Cross-sectional studies, in which observations are made on a single occasion.

Cohort studies

- Prospective studies that begin in the present and follow subjects into the future, and
- Retrospective studies that examine information collected over a period of time in the past.

- A third common option is the Case–Control design, In which the investigator compares a group of people who have a disease or other outcome with another group who do not.

- Among clinical trial options, the randomized blinded trial is usually the best design but nonrandomized or unblinded designs may be all that are feasible for some research questions.

•Descriptive studies

What is the average number of servings of fish per week in the diet of Americans with a history of coronary heart disease (CHD)?

• Analytic studies

Do people with a CHD who eat a lot of fish have a lower risk of recurrent myocardial infarction than people with a history of CHD who rarely eat fish?

•Clinical trial to establish the effects of an intervention:

Does treatment with fish oil capsules reduce total mortality in people with CHD?

Study Subjects

Two major decisions

1. To specify inclusion and exclusion criteria that define the target population: the kinds of people best suited to the research question.
2. To recruit an appropriate number of people from an accessible subset of this population to be the subjects of the study.

   Eg. The study of fish intake in people with CHD

Decisions about which patients to study often represent trade-offs; studying a random sample of people with CHD from the entire country (or at least several different states and medical care settings) would enhance generalizability but be much more difficult and costly.

Variables

- The choice of which variables to measure;
- A study of fish intake in the diet,

for example, might ask about different types of fish that contain different levels of omega-3 fatty acids, and include questions about portion size, whether the fish was fried or baked, and use of fish oil supplements.

- In an analytic study the investigator studies the associations among variables to predict outcomes and to draw inferences about cause and effect.
- Association between two variables , on biologic grounds to be causal is called the predictor variable; the other is called the outcome variable.

Most observational studies have

- predictor variables (age, race, sex, smoking history, fish and fish oil supplement intake) and
- outcome variables (heart attacks, strokes, quality life, unpleasant odor).

Clinical trials examine the effects of an intervention;

- A special kind of predictor variables that the investigator manipulates, such as treatment with fish oil capsules.
- Using randomization to minimize the influence of confounding variables ;

  Other predictors of the outcome such as smoking or income level that could be associated with dietary fish and confuse the interpretation of the findings.

•Statistical Issues

Hypothesis: 50- to 69-year-old women with CHD who take fish oil supplements will have a lower risk of recurrent myocardial infarction than those who do not.

This is a version of the research question that provides the basis for testing the statistical significance of the findings.

Purely descriptive studies (what proportion of people with CHD use fish oil supplements?) do not involve tests of statistical significance, and thus do not require a hypothesis

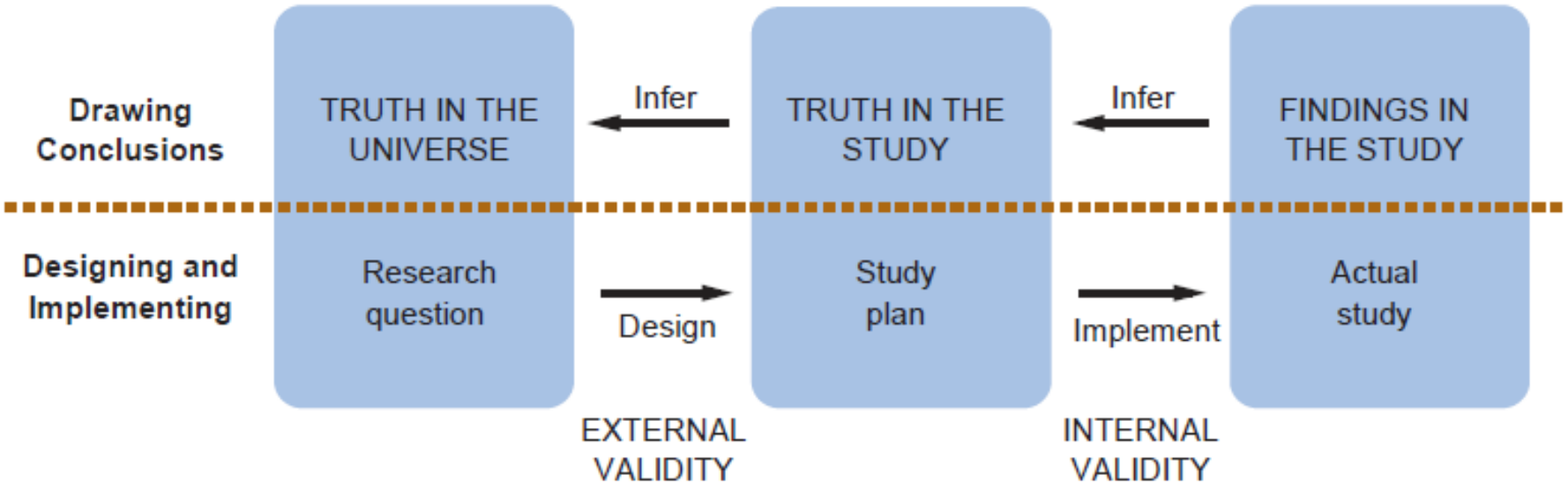
Sample size; To observe expected diff: in outcome b/t study groups with reasonable probability(power)
To produce acceptably narrow confidence interval

PHYSIOLOGY OF RESEARCH: HOW IT WORKS

The goal of clinical research is to draw inferences from findings in the study about the nature of the universe around it.

Inference #1 concerns **internal validity**, the degree to which the investigator draws the correct conclusions about what actually happened in the study

Inference #2 concerns **external validity** (also called generalizability), the degree to which these conclusions can be appropriately applied to people and events outside the study.



- Process of designing and implementation; drawing conclusion based on inference from the findings

Designing the Study

- Consider this simple descriptive question:
- What is the prevalence of daily ingestion of fish oil supplements among people with CHD?
- This question cannot be answered with perfect accuracy because it would be impossible to study all patients with CHD and our approaches to discovering whether a person has CHD and is taking fish oil are imperfect.

- To settle for a related question that can be answered by the study:

- Among a sample of patients seen in the investigator's clinic who have a previous CHD diagnosis and respond to a mailed questionnaire, what proportion report taking daily fish oil supplements?

- The transformation from research question to study plan

Major components of the transformation ;

The choice of a sample of subjects that will represent the population. The group of subjects specified in the protocol can only be a sample of the population

The choice of variables that will represent the phenomena of interest.

however, is the risk that design choices may cause the study to produce a wrong or misleading conclusion because it is designed to answer a somewhat different question from the research question of interest.

Implementing the study;

Causal Inference

- A special kind of validity problem arises in studies that examine the association between a predictor and an outcome variable in order to draw causal inference.

- If a cohort study finds an association between fish intake and CHD events, does this represent cause and effect, or is fish intake just an innocent bystander in a web of causation that involves other variables?

- Reducing the likelihood of confounding

The Errors of Research

- Recognizing that no study is entirely free of errors, the goal is to maximize the validity of inferences from what was observed in the study sample to what is happening in the population.

- **Random error** is a wrong result due to chance—sources of variation that are equally likely to distort measurements from the study in either direction.

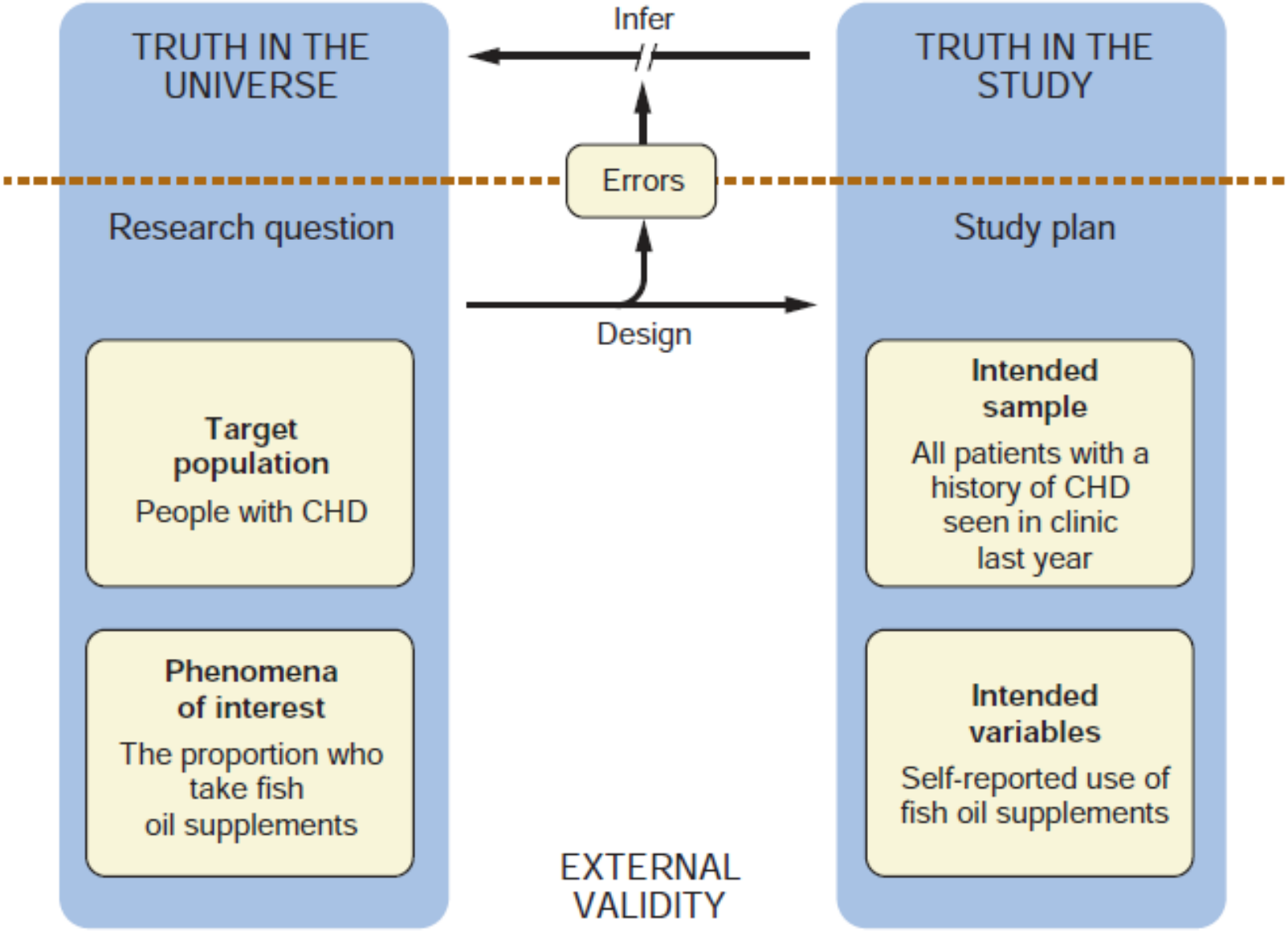
- Among several techniques for reducing the influence of random error, the simplest is to increase the sample size. The use of a larger sample diminishes the likelihood of a substantially wrong result by increasing the precision of the estimate.

- **Systematic error** is a wrong result due to bias—sources of variation that distort the study findings in one direction.

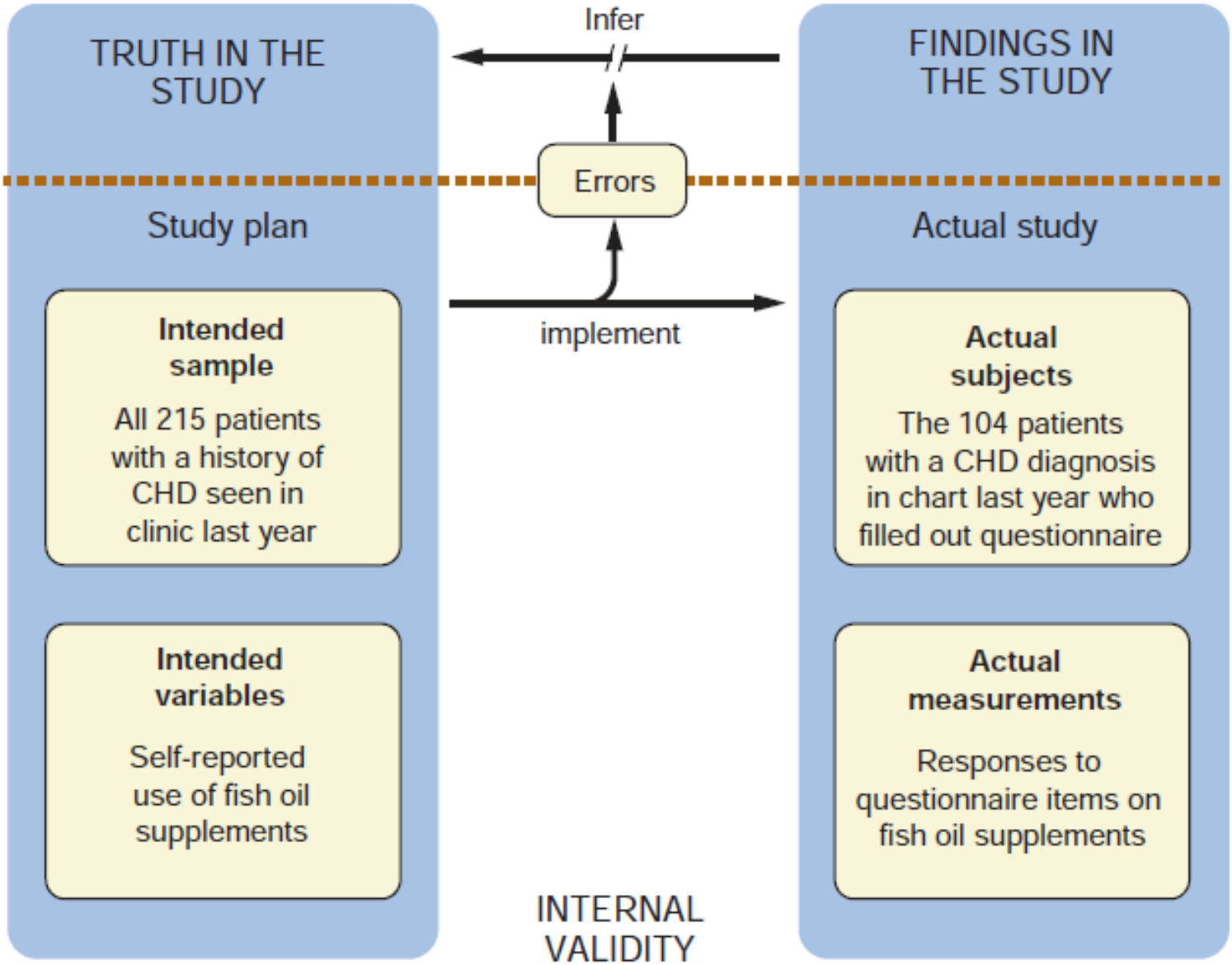
- The best way to improve the accuracy of the estimate (the degree to which it approximates the true value) is to design the study in a way that reduces the size of the various biases.

- Alternatively, the investigator can seek additional information to assess the importance of possible biases

- Random and systematic error are components of sampling error, which threatens inferences from the study subjects to the population

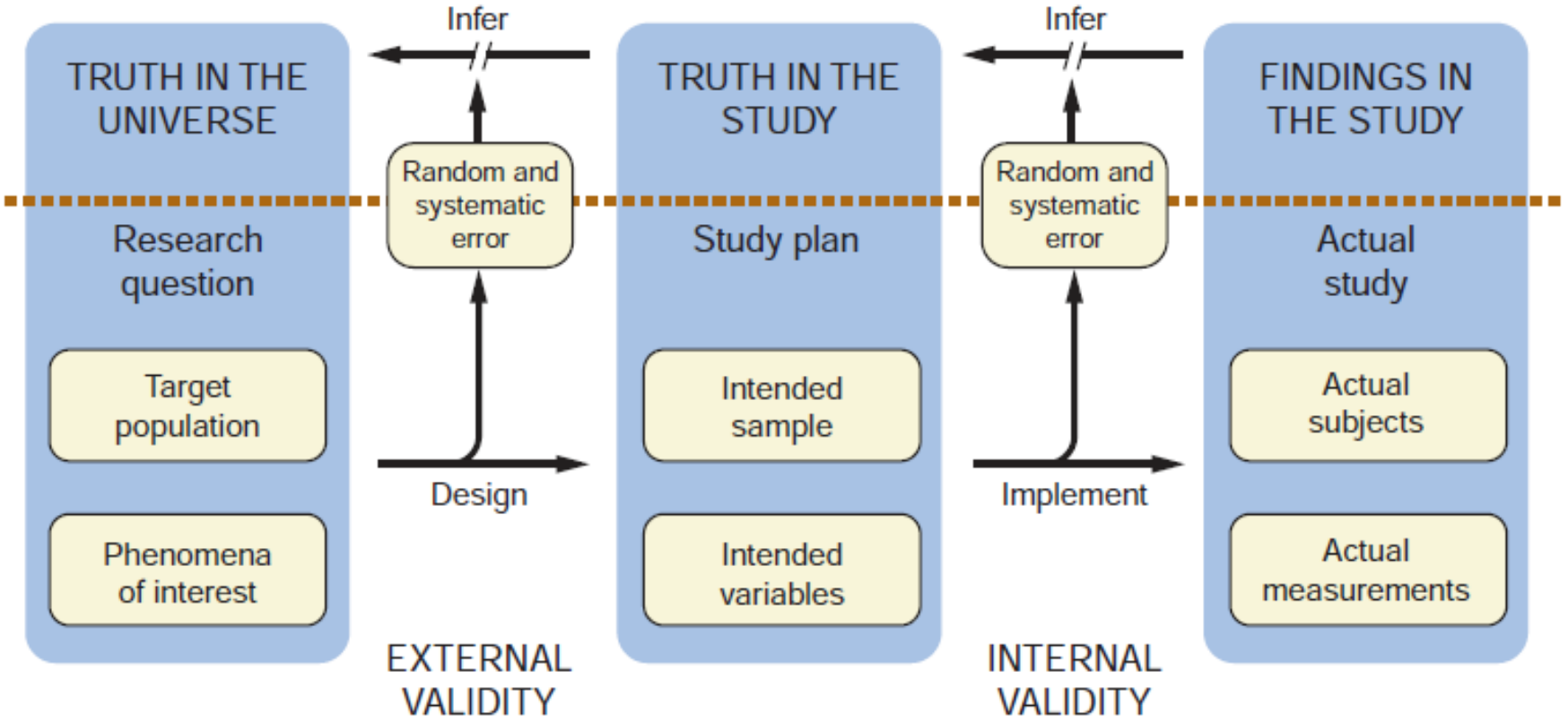


Intended samples and variables do not sufficiently represent the target population & phenomenon of interest, these errors may distort inferences about what actually happens in the population.



The actual subjects and measurements do not sufficiently represent the intended sample & variables, these errors may distort inferences about what happened in the study.

Physiology of research:
How it works



Attributes of a good research worker

- Imaginative
- Observant
- Honest
- Patient
- Dedicated
- Persistent
- Industrious
- Wise
- Ethical

Special Issue in Research

- Conflict of interest

The Institution/ Research sponsors/ The Researcher

- Scientific misconduct

Includes willful Fabrication/ Falsification/ Plagiarism

- Publication of research results

Authorship

- All qualified authors to be listed
- Specific author to assume responsibility for integrity of the whole
- Qualified author – participated sufficiently to be publicly responsible for specific parts

Not valid grounds for authorship credit

- Acquisition of Fund
- Collection of data
- General supervision

Budget estimation

Consideration for termination of trial

- Results trends overtime
- Internal consistency
- Importance of tested- treatment
- Risk and benefits of testing
- Size and clinical significance of the treatment observed
- Statistical significance

Reference

Stephen B. Hulley, Steven R. Cummings, Warren S. Browner, Deborah G. Grady, Thomas B. Newman. 2013, Designing Clinical Research, 4th ed, School of Medicine, University of California, San Francisco

Thank you