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Plenary 2

Overview of Study Design and Formulating the Research Question

Santiago Moreno
Hospital Ramón y Cajal
Madrid

Outline of Session

- Introduction
- Overview of Study Design
- The Research Question
- A real example

Introduction – Clinical Research

- Clinicians often face problems in the care of patients that are still unresolved
- The answers to most of these unresolved issues can be obtained by the own clinician, transformed into a clinical investigator
- The most important tasks for a clinical researcher are **being creative** and applying **common sense**:
  - Recognizing important research question
  - Devising clever approaches

Introduction – Goal of Research

- To draw inferences about truth in the universe from events observed in the study sample

Introduction – Investigator's Goals

- To **create the elements of the study plan** (research question, type of study, subjects, measurements, sample size calculation,……) in a form that will make the project fast, inexpensive, and easy to do
- To **minimize the errors** that threaten conclusions based on the inferences about the events that happened in the study sample and then about generalizing these events to people outside the study

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The sequence and cycle of research

The structure of research projects

- The protocol is the written plan of the study
- The protocol has important functions
  - It helps the investigator to organize the research in a logical, focused, and efficient way
  - It is the device needed for seeking grant fund

Outline of the study protocol

Element	Purpose
Research questions (objectives)	What question will the study address?
Significance (background)	Why are these questions important?
Design Time frame Epidemiologic approach	How will the study be carried out?
Subjects Selection criteria Sampling design	Who are the subjects, and how will they be selected?
Variables Predictor variables Outcome variables	What measurements will be made?
Statitiscal issues Hypotheses Sample size estimation Analytical approach	How large is the study, and how will it be analyzed?

Some design decisions I

Decision #1
Alter the events under study?

Design	Example
Observational Study	
The investigator observes the events without altering them	A case-control study comparing the needle-sharing history of i.v. drug-users who have HIV antibodies with the history of those who do not
Experiment	
He applies an intervention, and observes the effect on the outcome	A randomized trial of the impact of a health-education program on needle-sharing habits

Some design decisions II

For Observational Studies
DECISION #2
Make measurements on more than one occasion?

Design	Example
Cross-sectional Study	
Each subjects is examined on only one occassion	A cross-sectional study of needle-sharing habits and HIV antibodies measured at the same exam
Longitudinal Study	
Each subject is followed over a period of time	A cohort study that assesses current needle-sharing habits of a group of i.v. drug abusers, then observes who subsequentlly develops HIV antibodies

Sequence for studying a topic

Study	Example
Descriptive Studies (distribution of diseases and health-related characteristics in the population)	What is the prevalence of antibodies to HIV in i.v. drug users?
↓	
Analytic Studies (associations to discover cause-and-effect relationships)	What risk factors increase the likelihood of HIV infection in this population?
↓	
Experiment (effects of an intervention)	Does a health education program alter the incidence of infection?

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How does research work?

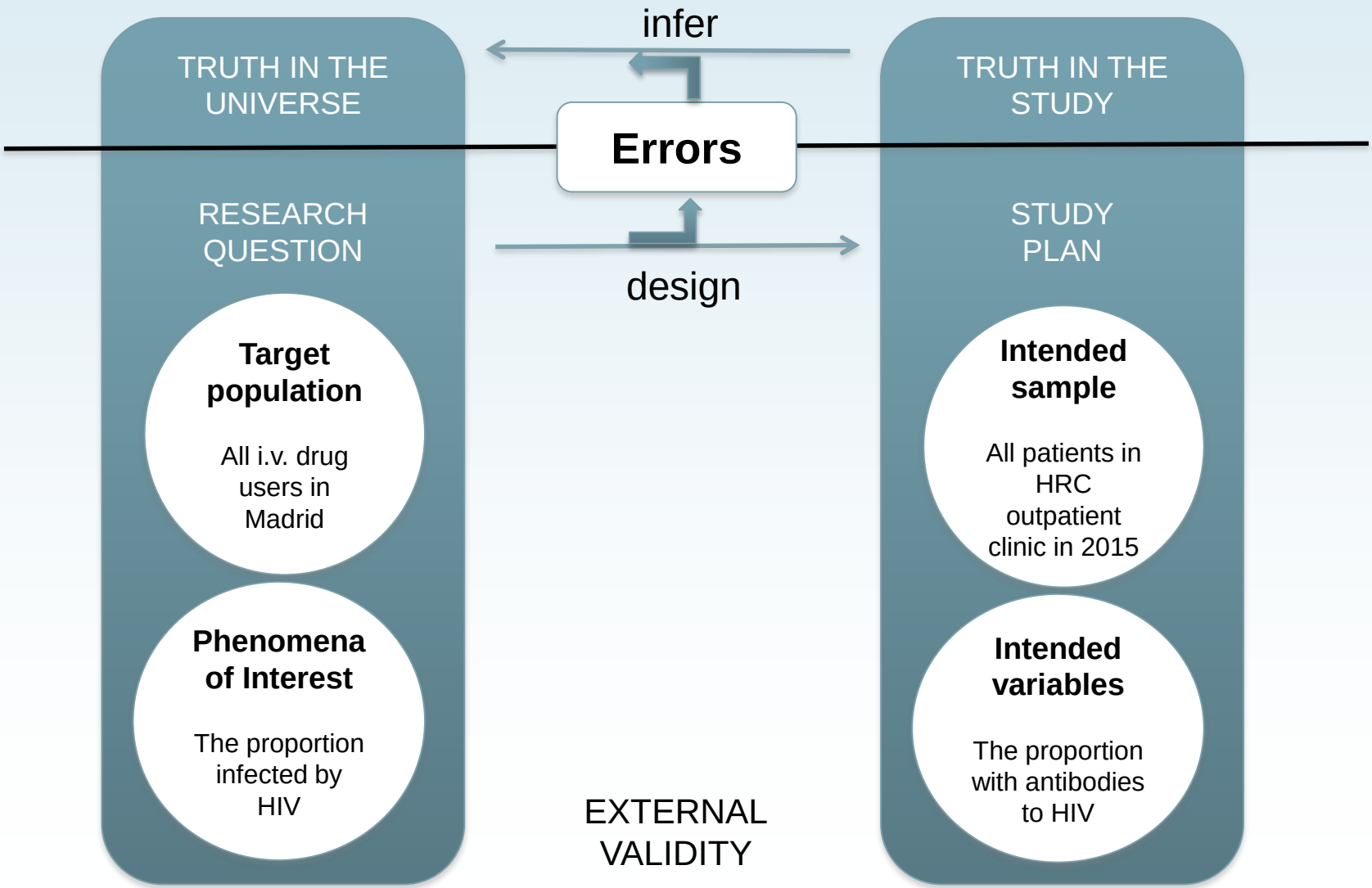
EXTERNAL VALIDITY (Generalizability)

INTERNAL VALIDITY

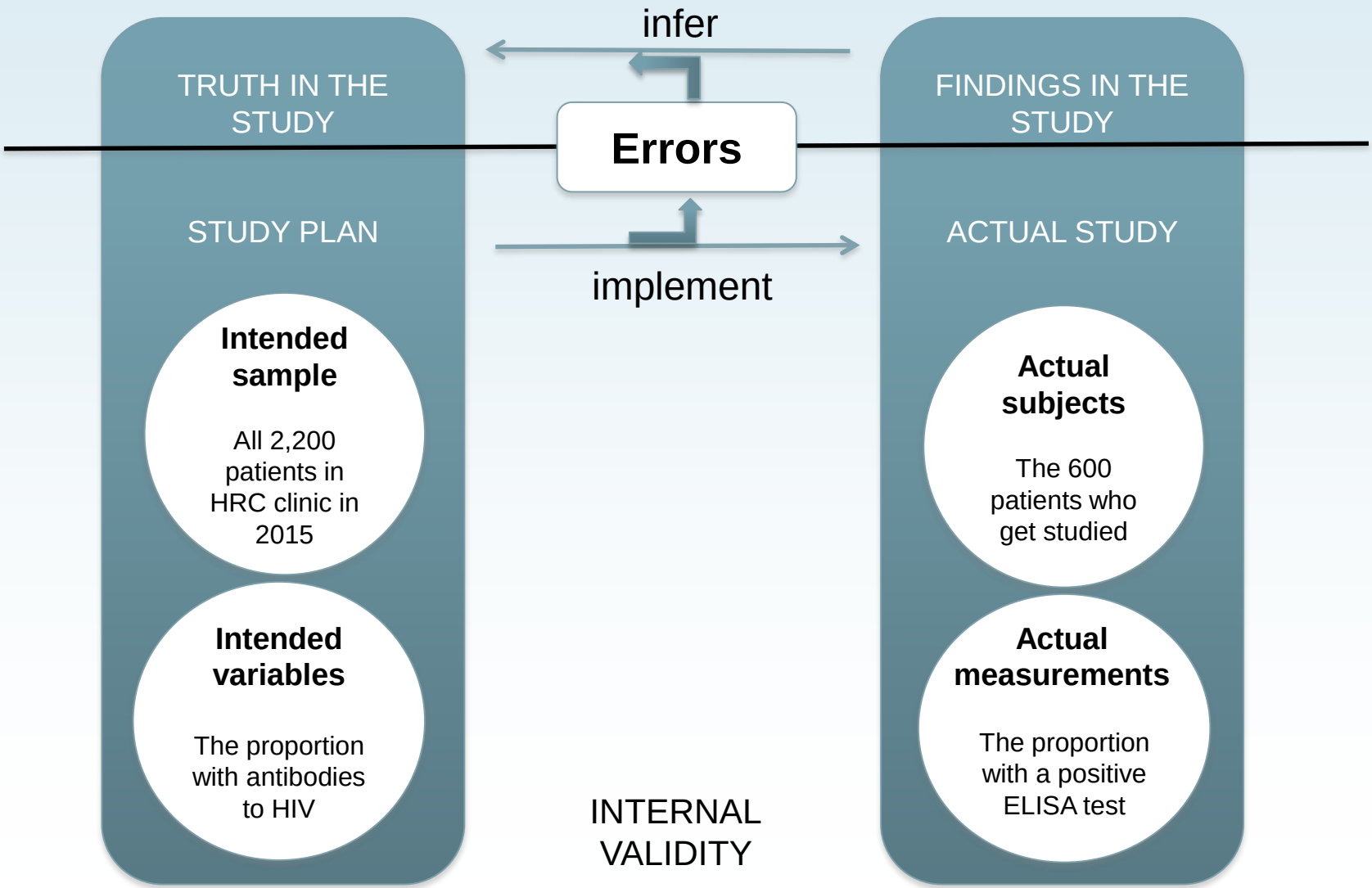
Errors in research

- No study is free of errors
- The main issue is whether the errors will be large enough to change the conclusions in important ways
- Our goal is to control the errors
  - In the design and implementation phases
  - In the analysis phase

Design errors



Implementation errors



Types of errors

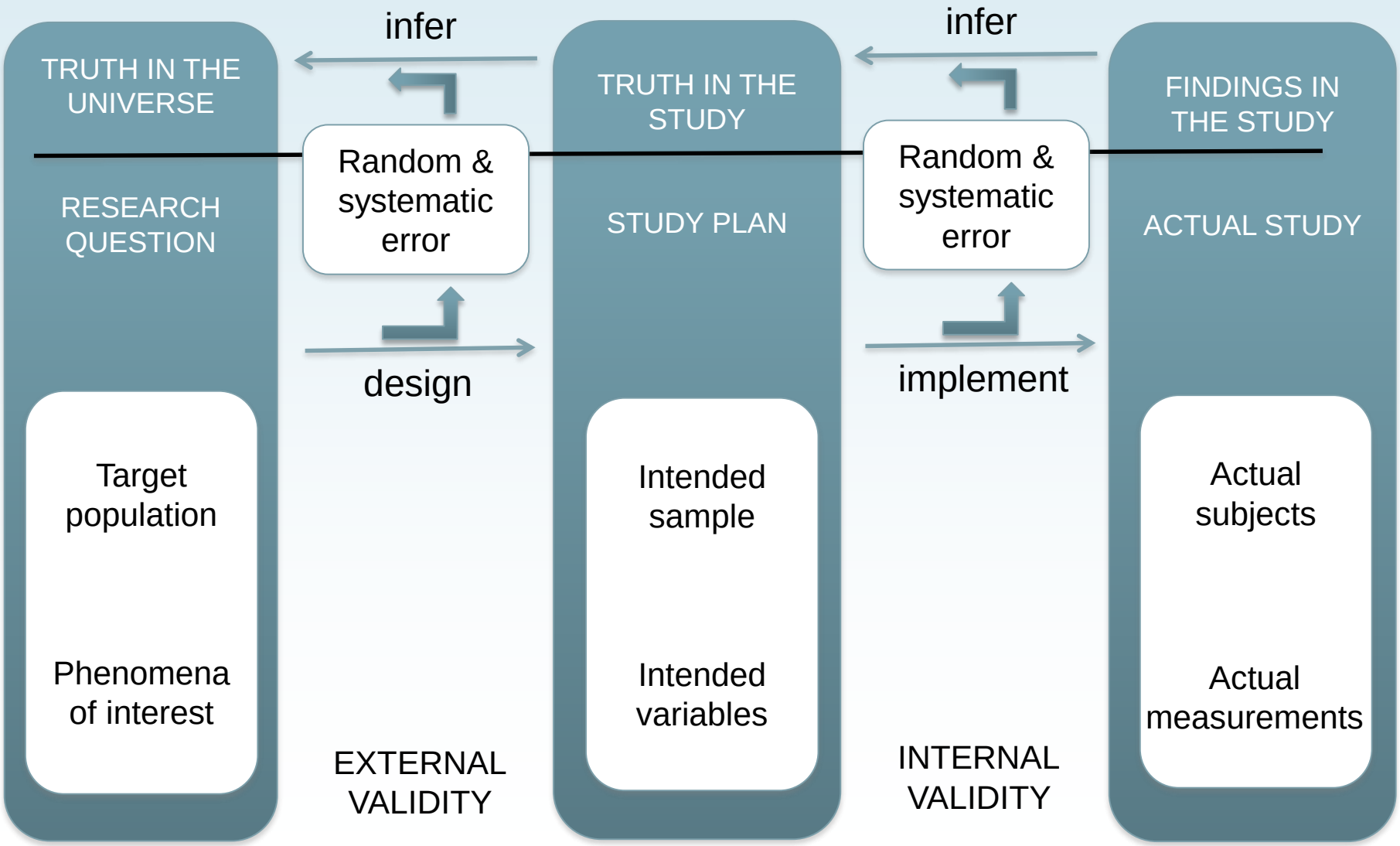
Type	Example	Solution
Random error (wrong result due to chance)	By chance, patients tested for HIV have a lower prevalence of HIV antibodies than the real one	Increase the sample size (increase in the precision)
Systematic error (wrong result due to bias)	The patients attended at the HRC clinic do not represent all i.v. drug users in Madrid	Design the study in a way that either reduces the size of the biases or gives some information about them
Measurement error (random or systematic)	Variation in the titer of HIV antibody titer when a single specimen is tested repeatedly (random), testing for antibodies may not include patients with recent infection (systematic)	Choose the best measurements and acknowledge their limitations

The importance of errors

“On being asked to talk on the principles of research, my first thought was to arise after the chairman’s introduction, to say ‘be careful’, and to sit down ……..”

Cornfield J. Principles of research. Am J Ment Deficiency 1959; 64:240-252.

Summary of how research works



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Introduction

- The research question is the uncertainty about something in the population that the investigator wants to resolve by making measurements on the study subjects
- There is no shortage of questions in the universe
- The challenge is the difficulty of finding an important question that can be transformed into a feasible and valid study plan

Origins of a research question

- **Build on experience**
  - Established vs. new investigator
  - For a new investigator, the single most important decision to make is ……. the choice of a mentor!!!!
- **Be alert to new ideas**
  - Medical literature, journal clubs
  - National and international meetings
  - Observation of patients
  - Skeptical attitude
- **Keep the imagination roaming**
  - Creativity and tenacity

Characteristics of a good research question (FINER)

- **F**easible
  - Adequate number of subjects
  - Adequate technical expertise
  - Affordable in time and money
  - Manageable in scope
- **I**nteresting to the investigator
- **N**ovel
  - Confirms or refutes previous findings
  - Extends previous findings
  - Provides new findings
- **E**thical
- **R**elevant (the “so what” test)
  - To scientific knowledge
  - To clinical and health policy
  - To future research directions

Primary and secondary questions

- Many studies have more than one research question
- Designing a study with several questions has
  - Advantages: efficiency (several answers emerge from a single study)
  - Disadvantages: complexity of designing and implementing the study
- Solution: establish a single primary research question and supplement with secondary research questions
- Focus the development of the study plan around the primary research question

Final considerations

- Get good advice
  - Research team (including at least one senior scientist)
  - Consult with specialists
  - Local and national/international experts
- The study plan should gradually emerge from an iterative process of designing, reviewing, pretesting and revising

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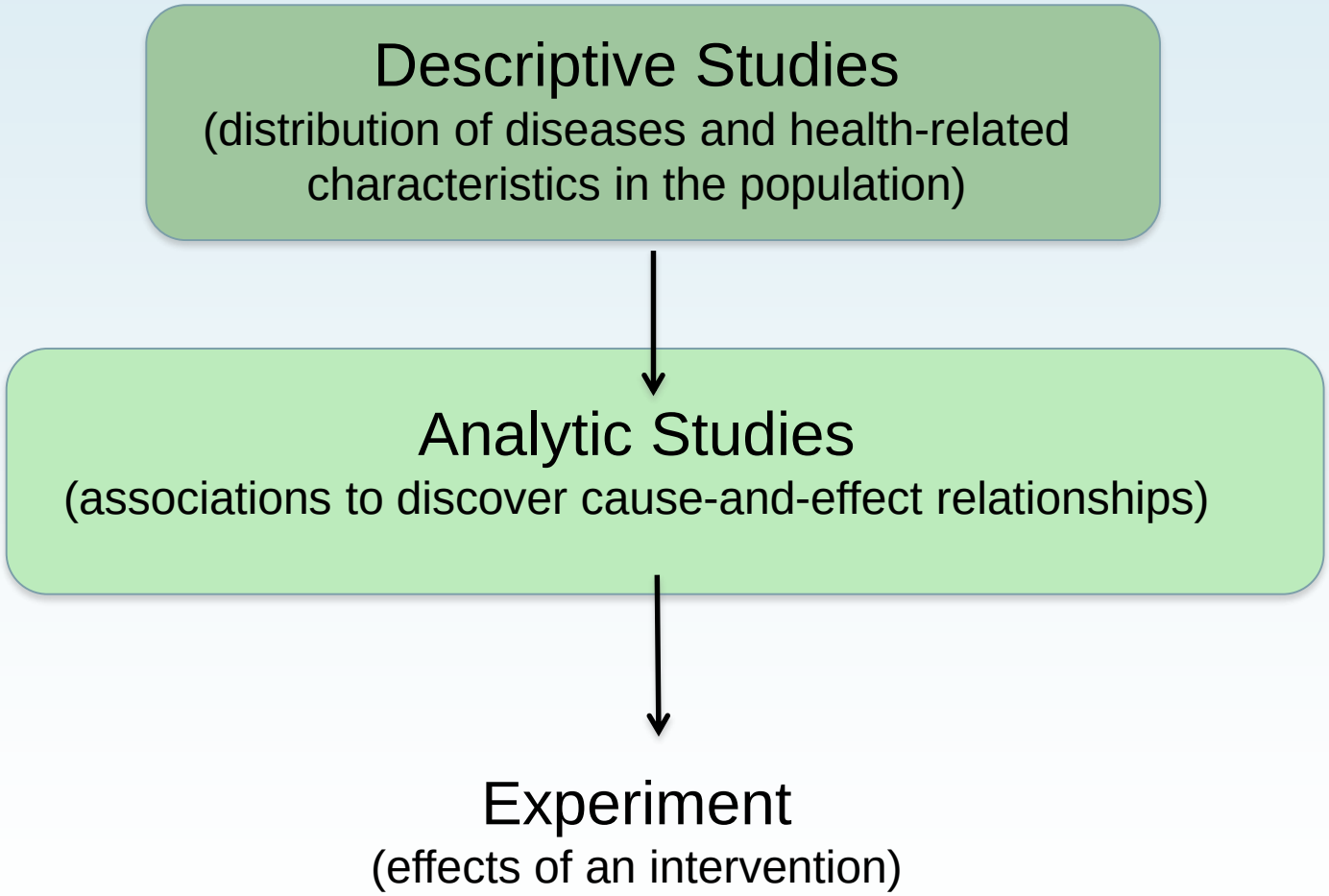
Developing the research question: A real example I

- **The origin of the research question.**
  - In 1987, we began to see an extraordinarily high number of HIV patients with tuberculosis in Spain
  - HIV-infected patients had atypical presentation of tuberculosis with high mortality
  - Risk factors for developing tuberculosis in the HIV infected population were not known, so preventive measures could not be adopted
  - Of great concern, most patients who developed tuberculosis had a negative tuberculin skin test (TST) before and after the development of the disease

Sequence for studying a topic



Developing the research question: A real example II

- **The origin of the research question.**
  - It was identified that being drug user, a positive TST, and having AIDS or a low CD4 count were associated with a higher risk of developing TB
  - With these observations, we thought that perhaps the development of tuberculosis could happen in patients with a previous negative TST who were anergic and with low CD4 count
  - The initial research question was: Are anergic patients at high risk of developing TB?

Developing the research question: A real example III

- **Translating the research question into a study plan**
  - Discussion of the idea with my advisor and colleagues
  - We agreed that the question was novel and relevant
  - A search of the literature confirmed the high risk of development of TB associated with HIV infection but information on the risk of anergic patients was lacking
  - We decided to develop a study plan
  - The initial research question still was: Are anergic patients at high risk of developing TB?

Developing the research question: A real example IV

- **Making the research question FINER**
  - The variables “anergic”, “high risk” and “developing TB” are too ambiguous and broad
    - For **anergy**, there was no clear consensus, but most author agreed that a battery of negative skin tests, in addition to TST, could identified anergic patients. Intradermal administration of different antigens by the Mantoux method was preferred to the multipuncture device.
    - For **high risk**, we decided that anergic patients had to be compared with patients with a positive TST (identified as being at very high risk) and, if possible, with TST-negative, non-anergic patient.
    - For **development of TB**, the gold-standard was culture-proven TB, although clinically and/or radiologically and/or histologically documented TB had also to be considered.

Developing the research question: A real example IV

- **Making the research question FINER**
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Developing the research question: A real example IV

- **Making the research question FINER**
  - We wrote the study plan that specified the approaches to selecting study subjects and decided on the type of study.
  - We decided that a retrospective, cohort study was the best type of study at that time for our purposes.
  - To be certain that there would be enough subjects, we consulted the Immunology Department to check the number of HIV-infected subjects that had undergone "anergy testing" at the same time that the CD4 count was measured.
  - We evaluated a small sample of patients (25) to be sure that the outcome could be documented in most of them.

Developing the research question: A real example V

- **Making the research question FINER**
  - Having determined that the project was important and feasible, the research question was written in its final specific form: *Among HIV-infected patients seen in our hospital, do the results of intradermal administration of multiple antigens predict the risk of developing confirmed TB?*
  - The question meets all the criteria for a good research question: it provides a clear focus for the study, describes the variables in terms that can be measured, and specifies the population that will be studied
  - A detailed proposal was submitted for funding.
  - The results of the research were published.