Clinical Research Methods

Thinking about and designing clinical research studies

Presented by
Dr. Alexander Weber, PhD
Imaging Staff Scientist,
BC Children's Hospital Research Institute

aweber@bcchr.ca

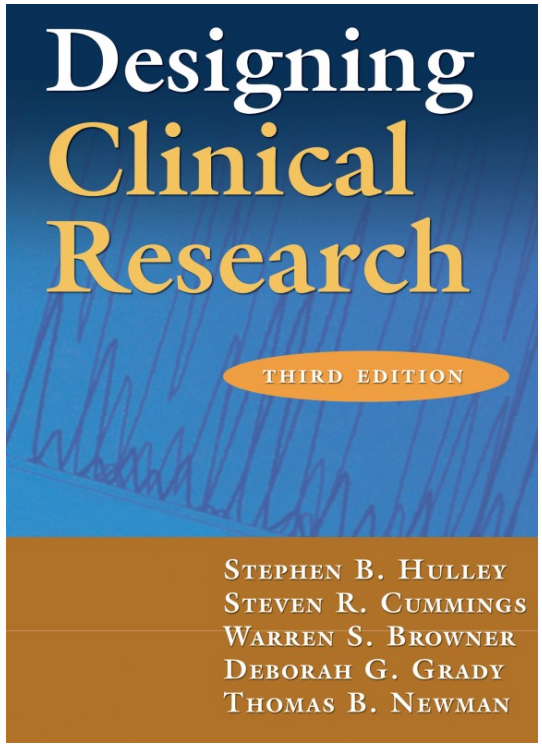
Course Overview

What is clinical research?

Study of health and illness in people
How to prevent, diagnose and treat illnesses/injuries
Translates basic research into new treatments and information to benefit patients
Examples: Treatment (intervention such as medicine or psychotherapy, new devices, new surgeries,etc.), Prevention (better ways to prevent disorders: medicines, vitamins, vaccines, lifestyle), Diagnostic (how to identify disorder or condition, and its severity), Screening (how to detect), Quality of Life (comfort, happiness, meaning, etc.), Genetic, Epidemiological (patterns, causes, and control of disorders)

Course Overview

- Discussion driven seminar
- Readings: first 12 (maybe 13) Chapters of Designing Clinical Research by Stephen Hulley and friends
- **Section I**: Basic Ingredients
  Clinical Research, Research Question, Subjects, Measurements, Sample Size
- **Section II**: Study Designs: Cohort, Cross Sectional and Case-Control, Causal Inference, Randomized Blinded



Course Goals

1) Thoroughly explore what is clinical research and its best practices

2) Cultivate your own thinking around research issues: What is worth studying? What is feasible? What is ethical?

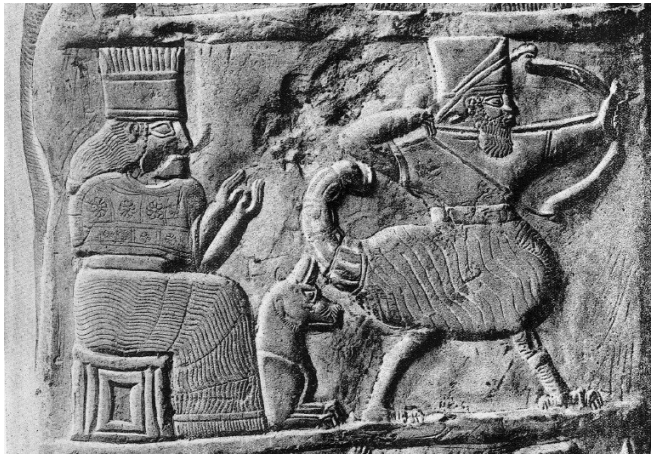
3) Improve your skills at designing a research study, which includes: a) recognizing best practices; b) understanding when and how to use them; c) critiquing your own and others works in order to improve clinical research as a whole

Reading Schedule

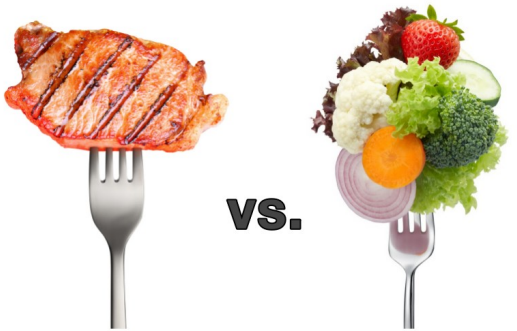
Jan 13	Intro and Chpt 1
Jan 27	Chpt 2 and 3
Feb 10	Chpt 4 and 5
Mar 09	Chpt 6
Mar 23	Chpt 7
Apr 06	Chpt 8
Jun 01	Chpt 9
Jun 15	Chpt 10
Jun 29	Chpt 11 & 12

Some History

- Biblical Times: King Nebuchadnezzar orders his people to eat only meat and drink only wine, but allows a few who objected to follow a vegetarian diet -> found the vegetarians better nourished in the end



https://en.wikipedia.org/wiki/Nebuchadnezzar_I#/media/File:Nabu-Kudurri-Usur.jpg



https://medium.com/@olracsnabayac/meat-or-veggies-40a9653fd881

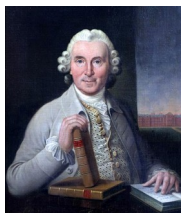
Some History

https://en.wikipedia.org/wiki/Ambroise_Par%C3%A9#/media/File:Ambroise_Par%C3%A9.jpg

- 1537: Ambroise Pare **compared** one group of battlefield patients who were treated in the traditional manner with boiling elder oil and cauterization, and the remainder with a recipe made of egg yolk, oil of roses and turpentine -> next morning he found the egg yolk patients in much better health (likely due to antiseptic properties of turpentine)

Some History

- 1747: James Lind performs perhaps the **first controlled clinical trial**. Appalled by the high mortality of sailors dying of scurvy, planned a comparative trial of the most promising cures for scurvy:



”On the 20th of May 1747, I selected twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of the knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all, viz. water gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times light puddings, boiled biscuit with sugar, etc., and for supper, barley and raisins, rice and currants, sago and wine or the like. Two were ordered each a quart of cyder a day. Two others took twenty-five drops of elixir vitriol three times a day … Two others took two spoonfuls of vinegar three times a day … Two of the worst patients were put on a course of sea-water … Two others had each two oranges and one lemon given them every day … The two remaining patients, took … an electary recommended by a hospital surgeon … The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty … The other was the best recovered of any in his condition; and … was appointed to attend the rest of the sick. Next to the oranges, I thought the cyder had the best effects …” (Dr James Lind's “Treatise on Scurvy” published in Edinburgh in 1753)

Some History

https://upload.wikimedia.org/wikipedia/commons/a/a8/Austin_Flint%2C_Sr.jpg

- 1863: Austin Flint plans first clinical study comparing a dummy remedy (**placebo**) to an active treatment. Treated 13 hospital inmates who had rheumatic fever with dummy treatment: diluted quassia. Results: no difference compared to active treatment (note: not compared directly)

Ch 1: The ‘Anatomy’ and ‘Physiology’ of Clinical Research

Anatomy of Clinical Research: What is it made of?

Study Protocol: written plan of a study

- needed for seeking grant funds

- help investigator organize research

TABLE 1.1 Outline of the Study Protocol

Element	Purpose
Research questions	What questions will the study address?
Background and significance	Why are these questions important?
Design	How is the study structured?
Time frame	
Epidemiologic approach	
Subjects	Who are the subjects and how will they be selected?
Selection criteria	
Sampling design	
Variables	What measurements will be made?
Predictor variables	
Confounding variables	
Outcome variables	
Statistical issues	How large is the study and how will it be analyzed?
Hypotheses	
Sample size	
Analytic approach	

Anatomy: Research Question

Research Question: objective of the study; what the investigator wants to resolve

General concern -> broken down to concrete, researchable issue

Example?

What makes a good question?

Does it pass the ‘So What?’ test?

Anatomy: What Makes a Good Question?

F – Feasible: affordable, doable, resources available, realistic

I – Interesting: useful, important, funding,

N – Novel: new, different, exciting

E – Ethical: honesty, recruitment, consent, safety, risks, benefits

R – Relevant: improve lives, safety, generalizeable,

Anatomy: Background and Significance

Start with doing research on the background literature and significance

- Gives context and rationale:
  - What do we already know?
  - Why is it important to answer this question?
  - What kind of answers will the study provide?
- This is similar to the introduction to a paper or grant

Anatomy: Design - Types of Studies

Two types of studies:

1.Observational (passive)

2.Clinical (active)

Observational can be further broken down:

1) Cohort Studies: observations are made on group that is followed over time

2) Cross-sectional: observations/data (usually from population) are taken at a specific point in time (cross-section)

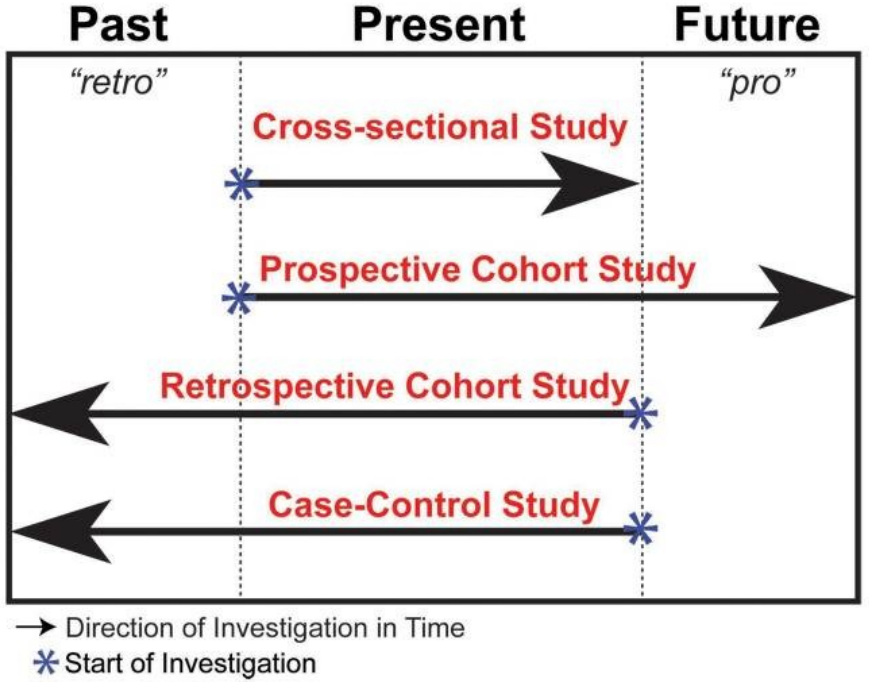
3) Case-control: compare groups with and without condition; usually to find cause of condition

Anatomy: Types of Studies

Cohort can be further broken down:

a) prospective: begin in the present, follow into future

b) retrospective: collect data from or about the past



Clinical Trial: as opposed to observational, one or more factors are actively altered and effects examined. Much better at delineating cause

Most common: randomized (allocated to intervention or control group randomly) blinded (both experimenter and subjects don't know which group they belong in order to prevent influencing results)

Song & Chung (2011) Observational Studies: Cohort and Case-Control Studies. *Plast Reconstr Surg.* 126(6): 2234-2242

Types of Studies

If randomized blinded trial is ‘gold standard’ why would we bother with observational studies?

- Cost
- Initial pilot study
- Rare outcomes

TABLE 1.2 Examples of Common Clinical Research Designs Used to Find Out Whether Fish Intake Reduces Coronary Heart Disease Risk

Study Design	Key Feature	Example
	Observational Designs	
Cohort study	A group followed over time	The investigator measures fish intake at baseline and periodically examines subjects at follow-up visits to see if those who eat more fish have fewer coronary heart disease (CHD) events
Cross-sectional study	A group examined at one point in time	She interviews subjects about current and past history of fish intake and correlates results with history of CHD and current coronary calcium score
Case-control study	Two groups selected based on the presence or absence of an outcome	She examines a group of patients with CHD (the “cases”) and compares them with a group who did not have CHD (the controls), asking about past fish intake
	Clinical Trial Design	
Randomized blinded trial	Two groups created by a random process, and a blinded intervention	She randomly assigns subjects to receive fish oil supplements or placebo, then follows both treatment groups for several years to observe the incidence of CHD

Anatomy: Types of Studies

Typical sequence for studying a topic:

- Descriptive: observational studies that ‘explore the lay of the land’

- Analytic: observational studies that look for associations to permit inferences about cause-and-effect

- Clinical Trial: establish effects of intervention

Anatomy: Subjects & Variables

Subjects

Specify inclusion and exclusion in order to define target population

Then decide how you will recruit them

Variables

Predictor variables vs Outcome variable

ex. an intervention can be the predictor variable (fish oils) that may or may not effect the outcome variable (heart attacks)

Randomization used to reduce confounding variables (alternate predictors)

Anatomy: Statistical Issues

Hypothesis: provides basis for testing statistical significance, and calculating sample size

Sample size: number subjects needed to observe expected difference in outcome btw study groups with reasonable probability; for descriptive studies: number subjects need to produce sufficiently narrow confidence intervals

Physiology: Designing Study

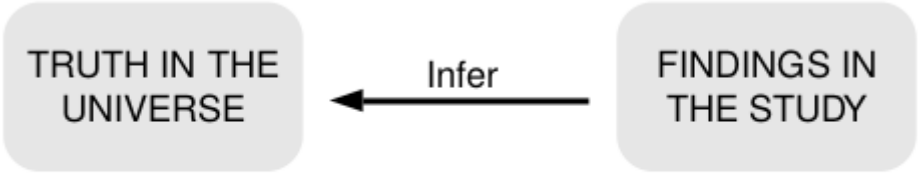


FIGURE 1.1. The findings of a study lead to inferences about the universe outside.

Design study plan with question, subjects, and measurements that enhance external validity (generalization) and conducive to implementation with high degree of internal validity (degree to which correct conclusion drawn from study)

Choose sample that will represent population (external validity)

Choose variables that will represent phenomena of interest (internal validity)

Each are practical compromises from the truth

Physiology: Designing Study

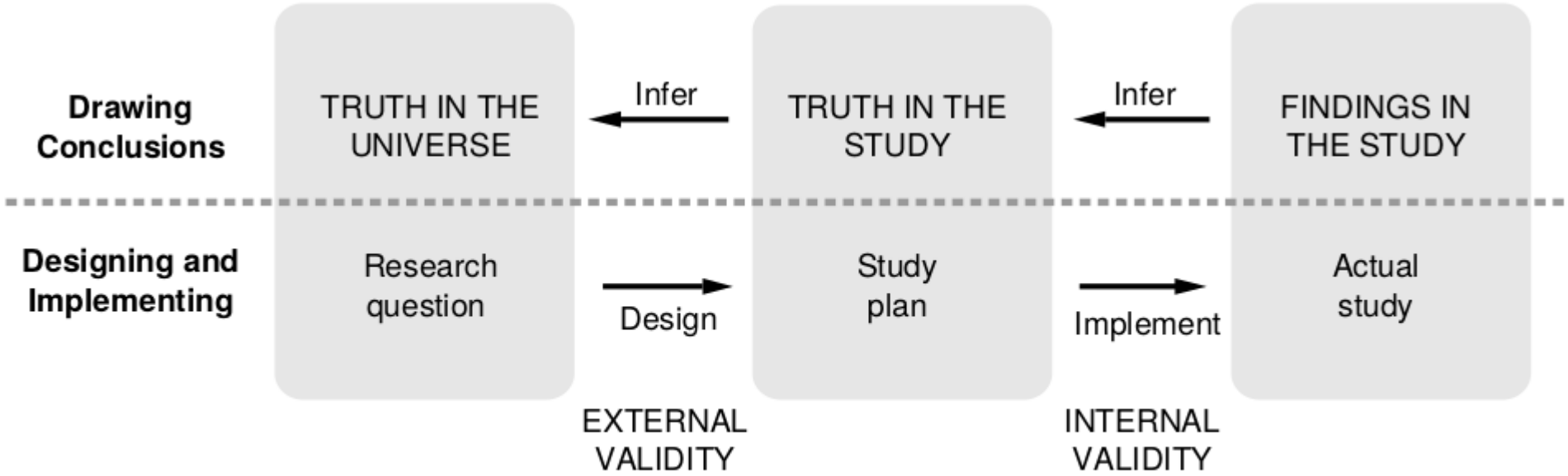


FIGURE 1.2. The process of designing and implementing a research project sets the stage for drawing conclusions from the findings.

Physiology: Implementing Study

Probably won’t go as planned

Causal inferences are hard to draw, due to problems of association

Important to reduce **confounding factors**

Errors:
Random Errors: wrong result due to chance / natural variability. Best way to solve: increase sample size -> increase precision

Systematic Errors: wrong result due to bias. Best way to solve: reduce bias or give information about biases -> increase accuracy

Physiology: Errors

Sampling error: threatens inferences from the study subjects to the population

Measurement error: threatens inferences from the study measurements to the phenomena of interest

Both types of errors can have systematic and/or random errors

Physiology: Implementing Study

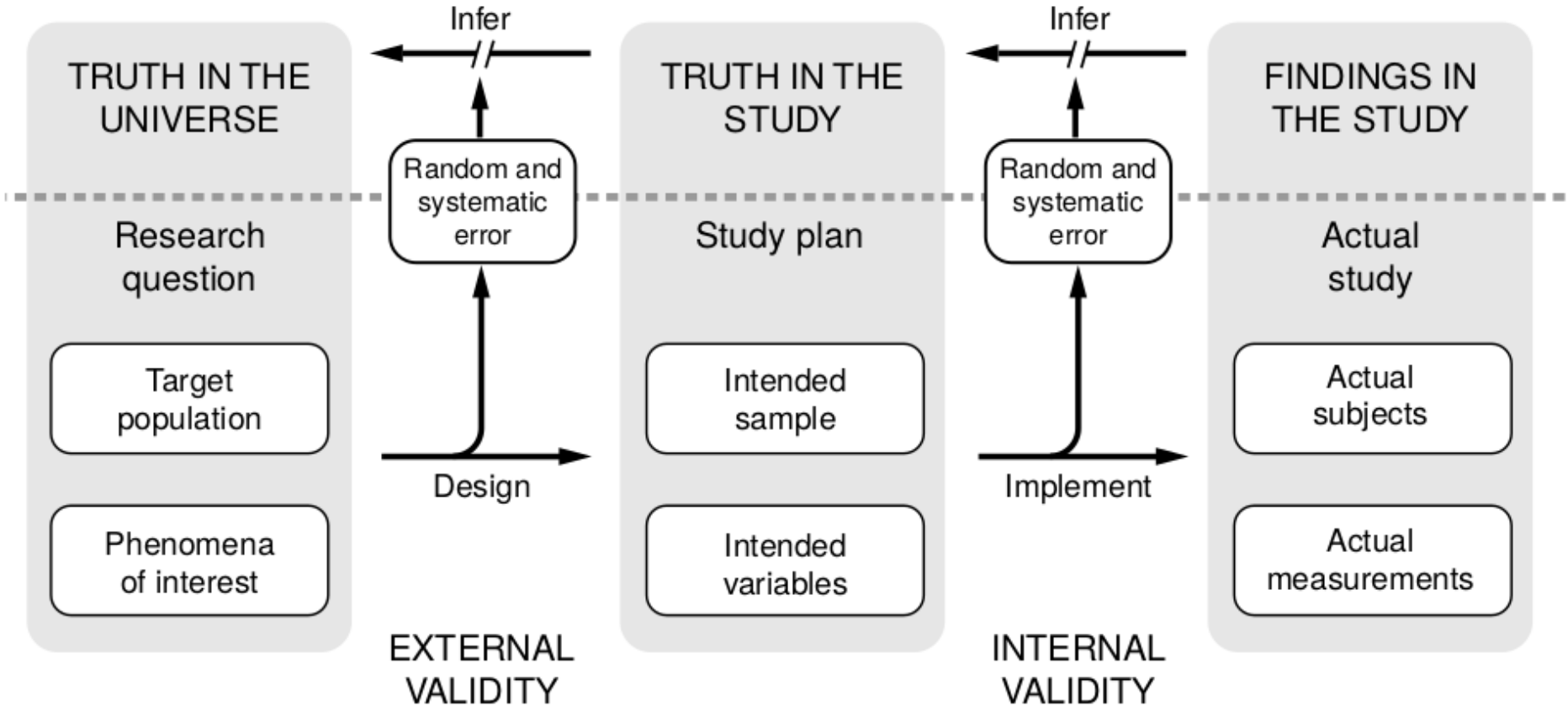


FIGURE 1.6. Summary of the physiology of research—how it works.

Physiology: Study Protocol

Study protocol:

begins with a research question... then:

- outline: standardized checklist; acts as reminder to include all components
- study protocol: expansion of outline; used to plan study and apply for grants
- operations manual: specific procedural instructions, questionnaires: ensure uniform and standardized approach

Trade-offs: internal and external validity vs feasibility

Concessions must be made when transforming research question to study plan

Appendix 1.1

APPENDIX 1.1

Outline of a Study*

Element	Example
Title	Relationship between Level of Experience and Degree of Clinical Utility of Third Heart Sound Auscultation.
Research question	Do auscultatory assessments of third heart sound by more experienced physicians result in higher sensitivity and specificity for detecting left ventricular dysfunction than assessments by less experienced physicians?
Significance	1. Auscultation of third heart sounds is a standard physical examination indicator of heart failure that all medical students have learned for 100 years. 2. The degree to which this clinical assessment, which many physicians find difficult, actually detects abnormal left ventricular function has not been studied. 3. There are no studies of whether auscultatory measurements of third heart sounds by cardiology fellows and attendings are more accurate than those of residents and medical students.
Study design	Cross-sectional analytic study
Subjects	
• **Entry criteria**	Adults referred for left heart catheterization
• **Sampling design**	Consecutive sample of consenting patients
Variables	
• **Predictor**	Level of experience of physicians
• **Outcome**	1. Area under the receiver operating characteristic curve for third heart sound score (AUC) in relation to higher LV diastolic pressure by catheterization 2. AUC in relation to lower ejection fraction by cardiac echo 3. AUC in relation to B natriuretic protein
Statistical issues	Hypothesis: More experienced physicians will have more favorable AUCs Sample size (to be filled in after reading Chapter 6)

Summary

Research question and its significance
Design, study subjects, and measurement approaches

Study findings draw inferences about what happened in the study sample (internal validity), about the world (external validity)
Want to reduce random error (chance) and systematic error (bias)

Research Question > Study Plan > Actual Study

Research Question < Outline < Protocol < Operations Manual