

Clinical Research Methods

Thinking about and designing clinical research studies
Day Two: Chapters 2 and 3

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Recap - Chapter 1

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



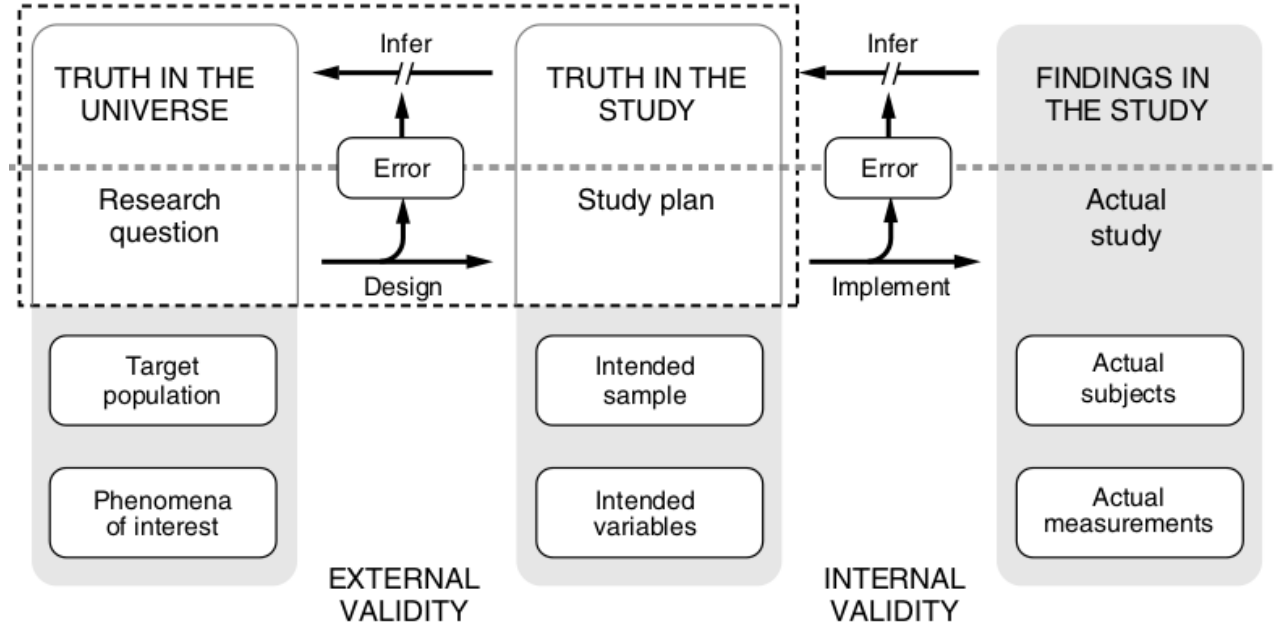
Chapters 2 & 3: Research Question and Study Subjects

Learning Objectives:

- Understand what makes a good research question and study plan
- List best practises for developing these
- How to consider these through F.I.N.E.R. acronym
- Explain the two types of translational research
- Explain the difference between a sample and a population
- How to best include and exclude in order to generalize to target population
- Describe the three types of sampling and when they are used

Chapter 2 – Conceiving the Research Question

“The challenge in searching for a research question is not a shortage of uncertainties; it is the difficulty of finding an important one that can be transformed into a feasible and valid study plan.”



Research Question: Where to start?

Literature review and scholarship: master the background of the problem
(can also serve as background for grant proposals & research reports)

Other ingredients:

- Skeptical attitude; new technologies; apply concept from one field into another; observation; teaching; creativity; tenacity; courage (don't be afraid of criticism or seeming weird); a mentor

F.I.N.E.R.

TABLE 2.1

FINER Criteria for a Good Research Question

Feasible

- Adequate number of subjects
- Adequate technical expertise
- Affordable in time and money
- Manageable in scope

Interesting

- Getting the answer intrigues the investigator and her friends

Novel

- Confirms, refutes or extends previous findings
- Provides new findings

Ethical

- Amenable to a study that institutional review board will approve

Relevant

- To scientific knowledge
 - To clinical and health policy
 - To future research
-

Developing Research Question and Study Plan

Helps to write out research question

Then brief one-page study plan

Afterwards, look for advice: choose a team of diverse experts with at least some senior scientists

Establish a primary question, with some secondary ones: asking too many questions increases complexity of designing and implementing study (F - Feasible)

Translational Research

Studies of how to translate findings from the ivory tower to the real world

Two types:

1. apply basic science findings to clinical studies of patients (T1)
2. apply findings from clinical studies to alter health practices in community (T2)

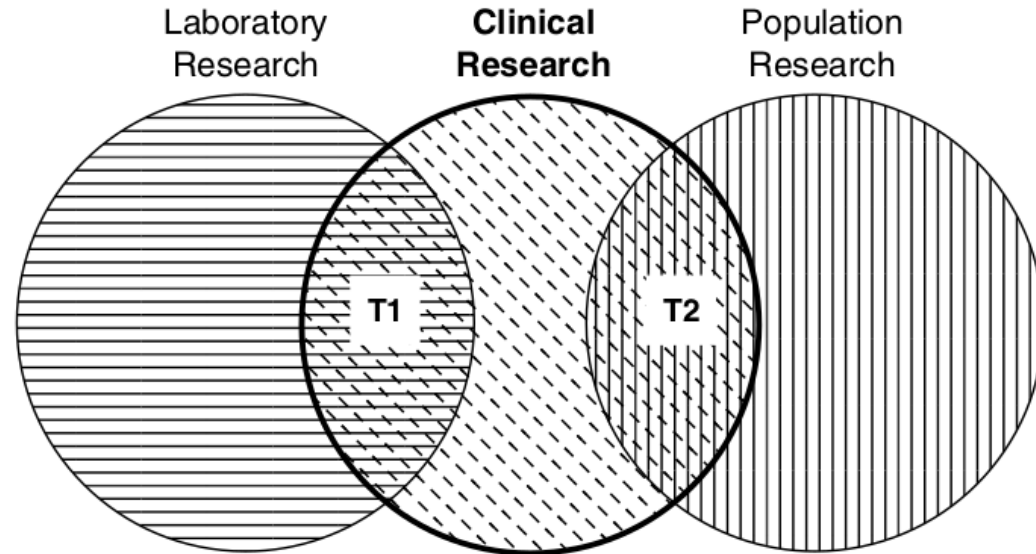


FIGURE 2.2. Transitional research is the component of clinical research that interacts with basic science research (hatched area T1) or with population research (hatched area T2).

Translational Research

T1: Bench-to-bedside requires a thorough understanding of the underlying basic science

- test – retest reliability
- receiver operating curves
- sampling and blinding
- effects of prior probability of disease

T2: need access to large group of patients

When wanting to generalize to general population, be sure to actually sample the general pop. (seems obvious, doesn't it?)

Chapter 3: Choosing Study Subjects

Subjects should represent the population of interest

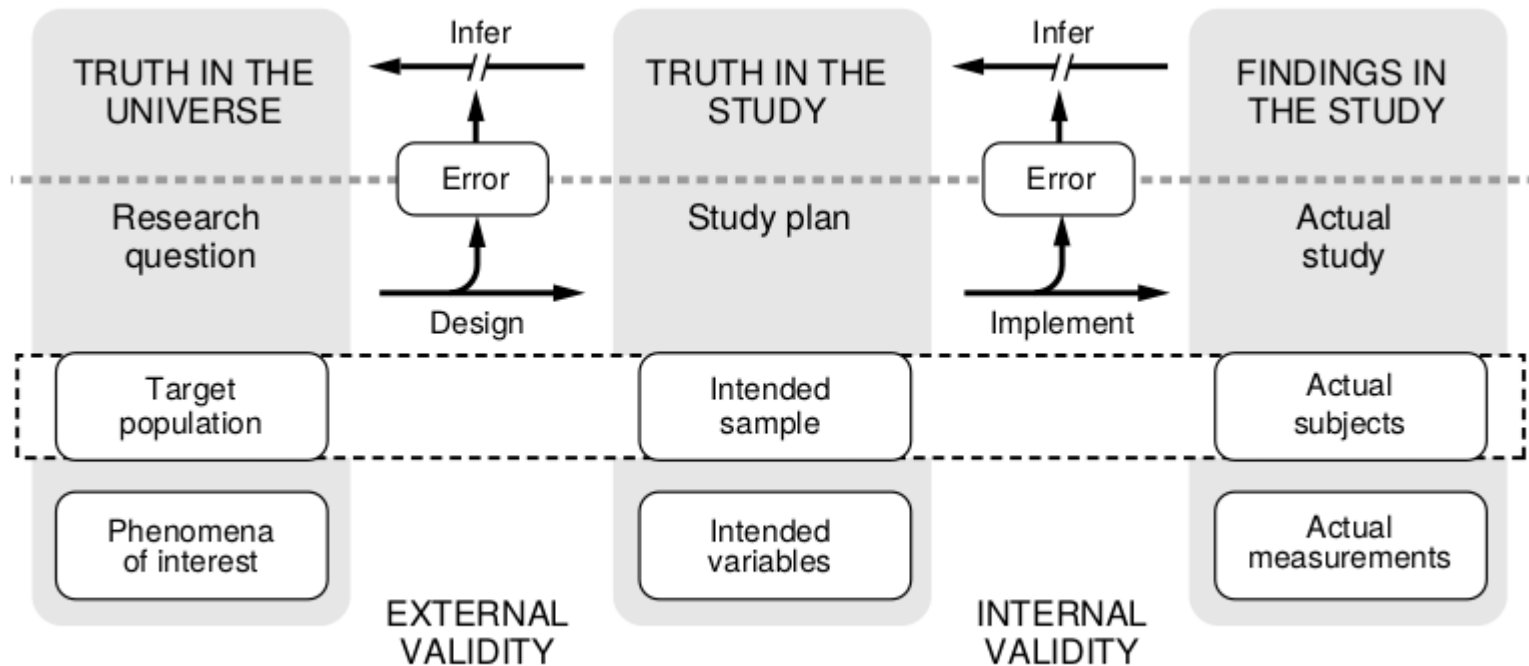


FIGURE 3.1. Choosing study subjects that represent the population.

Basic Terms and Concepts

Target Population:

large set of people throughout the world to which the results are to be generalized

Accessible Population:

geographically and temporally defined subset of the target pop. that is available to study

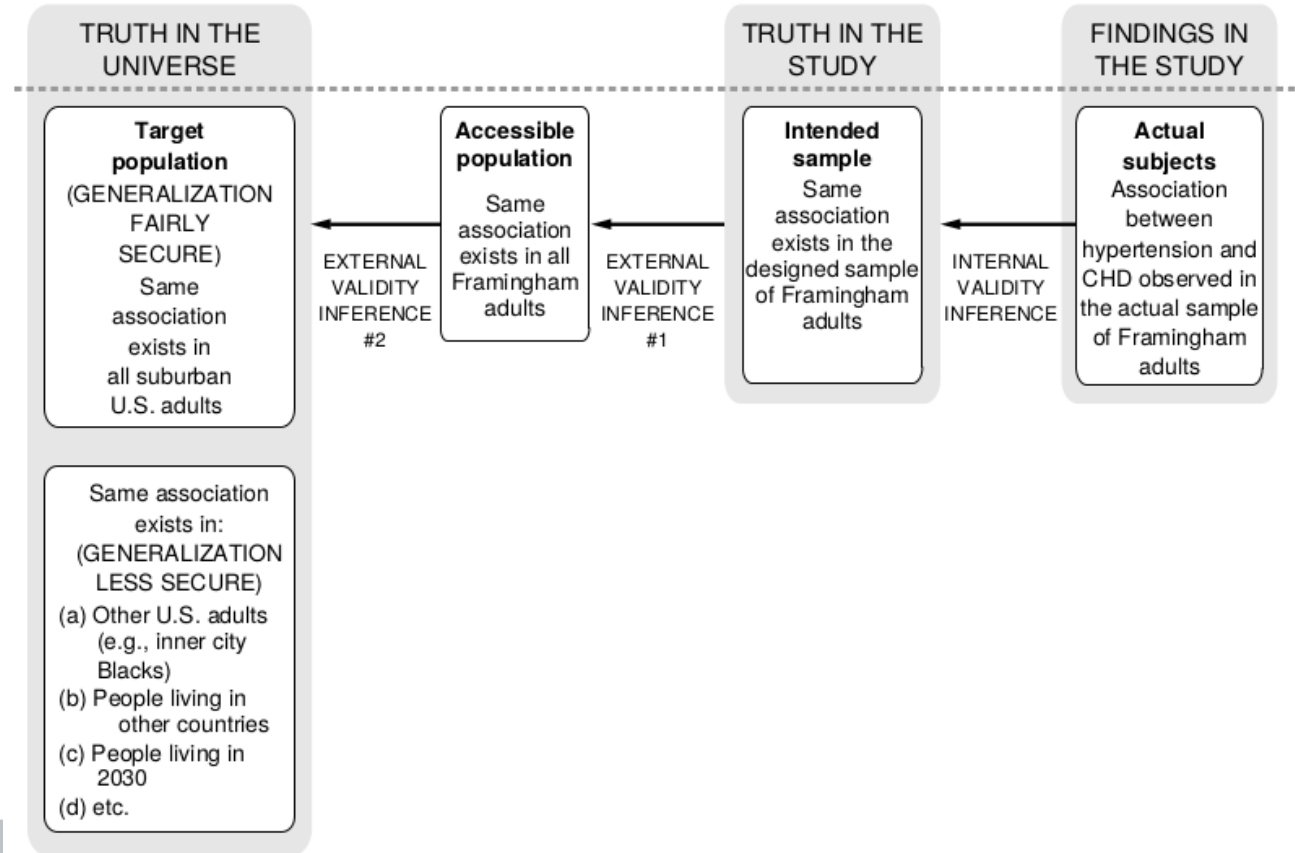
Study sample:

subset of the accessible pop.

Inferences:

findings in a sample that can be applied to a population

Populations and Samples



Selection Criteria

Inclusion criteria:

main characteristics of target pop. that you are interested in

Exclusion criteria:

characteristics that might interfere with: follow up; quality of data; acceptability of randomized treatment.

Good rule: have as few exclusion criteria as possible.
Why?

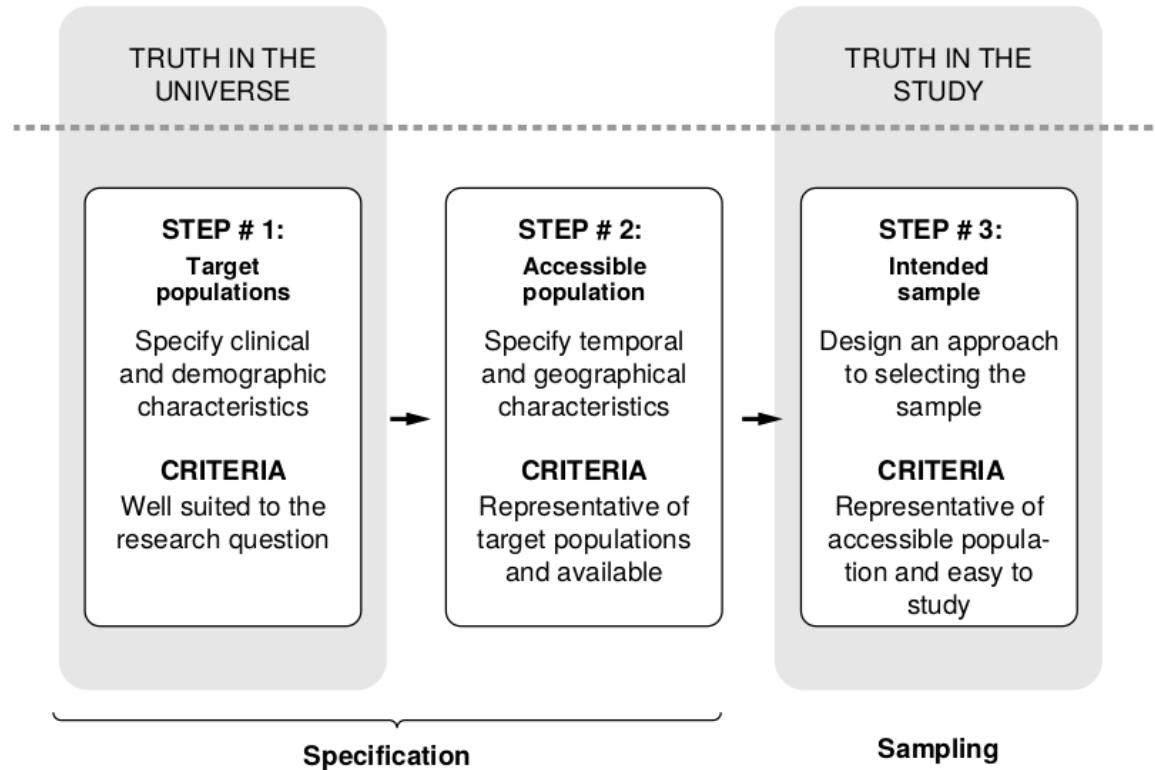


FIGURE 3.3. Steps in designing the protocol for choosing the study subjects.

Clinical vs Community Pop

Clinical vs Community Pop.:

Clinical: make sure you're not introducing bias (for example, a specialty clinic at a tertiary care medical centre)

Community: expensive

TABLE 3.1

Designing Selection Criteria for a Clinical Trial of Low Dose Testosterone to Enhance Libido in Menopause

	Design Feature	Example
Inclusion criteria (be specific)	Specifying populations relevant to the research question and efficient for study:	
	Demographic characteristics	White women 50 to 60 years old
	Clinical characteristics	Good general health Has a sexual partner
	Geographic (administrative) characteristics	Patients attending clinic at the investigator's hospital
Exclusion criteria (be parsimonious)	Temporal characteristics	Between January 1 and December 31 of specified year
	Specifying subsets of the population that will <i>not</i> be studied because of:	
	A high likelihood of being lost to follow-up	Alcoholic or plan to move out of state
	An inability to provide good data	Disoriented or have a language barrier*
	Being at high risk of possible adverse effects	History of myocardial infarction or stroke

* Alternatives to exclusion (when these subgroups are important to the research question) would be collecting nonverbal data or using bilingual staff and questionnaires.

Sampling

Convenience Sample: easily accessible to investigator. Can minimize volunteerism

Consecutive sample: consecutively selecting every accessible person who meets the entry criteria

Pros: expedited, easy, readily available, cost effective

Cons: bias, under-powered

Sampling

Probability (or Random) Sample: simple random sample: enumerating the units of the pop. & selecting a subset at random

Systematic sample: random sample but selected by a preordained periodic process (note: offers no logistic advantage)

Stratified random sample: divide pop. into subgroups then take random sample from each strata

Cluster sample: random sample of natural groupings (clusters) of individuals in the pop.

disadvantages: naturally occurring groups are often relatively homogeneous for variables of interest

Recruitment

Two goals: a) recruit sample that adequately represents the target pop.
b) recruit enough subjects

Achieving a Representative Sample:

Non-response: people who refuse to participate tend to be different from those who do (introduces bias)

A non-reponse rate of 25% can seriously distort the observed prevalence of a disease when the disease itself is the reason for non-response

Try to improve efficiency and attractiveness of study

Recruitment

Recruiting Sufficient Numbers:

- estimate magnitude of recruitment problem with a pretest
- accessible pop. that is larger than the believed necessary amount
- contingency plans should the need arise for additional subjects

Summary: Chapter 2

- 1) Start with a research question, one that follows F.I.N.E.R.: feasible, interesting, novel, ethical, and relevant
- 2) Do your background research; find a good senior scientist advisor/mentor
- 3) Read medical articles, attend conferences, think critically about clinical practices, applying new methods to old problems, teach and daydream
- 4) Write a one page study plan: how many subjects, how they will be recruited
- 5) Research question and study plan will go through multiple iterations after consultation with experts, pilot studies, reading literature
- 6) Focus on a single primary question
- 7) Translational Research: basic science to clinical studies of patients (T1); apply findings from T1 to improve health in community (T2)

Summary: Chapter 3

- 1) Use of a sample to represent population
- 2) Why? Efficient and Realistic. Downside: introduces error; may not generalize
- 3) First step: conceptualize population with inclusion criteria; use accessible population. Exclude subjects that would be unethical or inappropriate to study
- 4) Second step: how to sample population: convenience sample; simple random sample; probability sampling
- 5) Final step: recruitment: minimize bias due to nonresponse and loss to follow-up