Seminar 1 Lecture

"CTS Research Project **Preparation**"

Year 1 (2012-13)

Clinical and Translational Science (CTS) Initiative

University of New England

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1. CTS at UNE

From the CTS Initiative webpage at http://www.une.edu/research/cts/index.cfm:

Welcome! … You will see that the website is divided into these seven sections:

- Founding Document
- Programs: The Faculty seminar (Year 1, 2012-13)
  - Fall seminar (2012) Lectures and Exercises and Dates
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- CTS Initiative Records

CTS at UNE

From the CTS Initiative "Founding document," first of seven sections at http://www.une.edu/research/cts/index.cfm: By the NIH definition,

Clinical research is "Research with human subjects that is:

1. *Patient-oriented research* … conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes: mechanisms of human disease, therapeutic interventions, clinical trials, development of new technologies.

2. *Epidemiological and behavioral studies*. And

3. *Outcomes research and health services research*. Studies falling under 45 CFR part 46.101(b) (4) (Exemption 4) are not considered clinical research by this definition." (http://grants.nih.gov/grants/glossary.htm)

CTS at UNE

For Exemption 4: see FAQ 5 ff at
http://grants.nih.gov/grants/policy/hs/faqs_aps_exempt.htm

From the CTS Initiative "Founding document," first of seven sections at http://www.une.edu/research/cts/index.cfm: By the NIH definition,

Translational research "includes *two areas of translation*.

One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans.

The second area of translation concerns research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies also is an important part of translational science." (http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-10-020.html)

CTS at UNE

From the CTS Initiative "Founding document," first of seven sections at http://www.une.edu/research/cts/index.cfm:

Vision: The University is known to recruit, retain, promote, and tenure health sciences faculty whose teaching and service is informed and refreshed by the sponsored (extramural) pre-clinical, clinical, and translational science research they conduct.

Mission: To support and promote the clinical and translational science research capacity of University of New England faculty.

Goals: The CTS Initiative's goals are: ***Year 1 (2012-13)*** and carried into subsequent years, to design and conduct a well-enrolled, well-attended, high-performance, two-semester, eight-topic Faculty seminar and a well-advertized, well-implemented, well-reviewed, two-call per annum Awards program. Undergirding the Faculty seminar and Awards program will be the CTS Initiative Proposal Workshop, convened regularly for the constructive critique of UNE faculty grant proposals nearing submission deadline.

CTS at UNE

From the CTS Initiative "Founding document," first of seven sections at http://www.une.edu/research/cts/index.cfm:

Objectives. ***Year 1 (2012-13)*** objectives are to implement (September 2012-April 2013), evaluate (May 2013), and report (June 2013) the first-year Faculty seminar and Awards program. The Awards program will solicit proposals for the 1) Pilot Project Award … and 2) … Mentored Career Development Award.

- The purpose of the Pilot Project Award is to position UNE investigators to leverage extramural R series (http://grants.nih.gov/grants/funding/funding_program.htm#RSeries) and related research awards.
- The purpose of the Mentored Career Development Award is to position UNE investigators to leverage extramural K series (http://grants.nih.gov/training/careerdevelopmentawards.htm) and related career development and research awards.

2. CTS Initiative Faculty seminar

From the CTS Initiative "Programs: The Faculty seminar (Year 1, 2012-13)," second of seven sections at http://www.une.edu/research/cts/index.cfm:

The Faculty seminar (Year 1, 2012-13). A two-semester, eight-topic **Faculty seminar** will be offered in Year 1. Each seminar will have two parts, a one-hour Lecture and a one-hour Exercise, separated by one week, and each part will be offered on Thursday, 12:00-1:00pm (Portland campus location to be announced).

- The purpose of the Lecture will be to introduce interested UNE faculty to one defining dimension of doing CTS research.
- The purpose of the Exercise, which follows the Lecture by one week, will be to provide each seminar participant the opportunity to "work-up" a part of that lecture and then to report back that work in an interactive manner with other participants and the lecturer/s.

CTS Initiative Faculty seminar

From the CTS Initiative "Programs: The Faculty seminar (Year 1, 2012-13)," second of seven sections at http://www.une.edu/research/cts/index.cfm:

- The Seminar's first six topics proceed from CTS research project preparation through design, implementation, measurement and measures, proposal preparation and submission, and results reporting and dissemination.

- The Seminar's final two lectures take up the "special topics" chosen for Year 1: Community Engagement and Research and Research using Existing Data.

CTS Initiative Faculty seminar

Fall seminar (2012) Lectures and Exercises and Dates

- **Seminar 1 lecture and exercise**: CTS research project Preparation (Ross, Mittal, Rudolph: Lecture September 20, 2012; Exercise September 27, 2012)
- **Seminar 2 lecture and exercise**: CTS research project Design (Ross and Li: Lecture October 11, 2012; Exercise October 18, 2012)
- **Seminar 3 lecture and exercise**: CTS research project Implementation (Ross and Li: Lecture November 1, 2012; Exercise November 8, 2012)
- **Seminar 4 lecture and exercise**: CTS research project Outcomes measurement, measures, Controls (Ross and Joshi: Lecture November 29, 2012; Exercise December 6, 2012)

CTS Initiative Faculty seminar

Spring seminar (2013) Lectures and Exercises and Dates

- **Seminar 5 lecture and exercise**: CTS Research Project Sponsorship, Proposal preparation, Submission (Rudolph and Herrick, February 7, 2013; Exercise February 14, 2013)
- **Seminar 6 lecture and exercise**: CTS Research Project Results reporting and dissemination (Rudolph, February 28, 2013; Exercise March 7, 2013)
- **Seminar 7 lecture and exercise**: CTS Research Special topic: Community Engagement and Research (Ford, March 28, 2013; Exercise April 4, 2013)
- **Seminar 8 lecture and exercise**: CTS Research Special topic: Research using Existing Data (Cattabriga and Ochs, April 18, 2013; Exercise April 25, 2013)

3. CTS at NIH

From The NIH Common Fund (http://commonfund.nih.gov/) at http://commonfund.nih.gov/about.aspx:

"The NIH Common Fund was enacted into law by Congress through the 2006 NIH Reform Act to support cross-cutting, trans-NIH programs that require participation by at least two NIH Institutes or Centers (ICs) or would otherwise benefit from strategic planning and coordination.

"The requirements for the Common Fund encourage collaboration across the ICs while providing the NIH with flexibility to determine priorities for Common Fund support. To date, the Common Fund has been used to support a series of short term, exceptionally high impact, trans-NIH programs known collectively as the NIH Roadmap for Medical Research."

CTS at NIH

From The NIH Common Fund (http://commonfund.nih.gov/) at http://commonfund.nih.gov/clinicalresearch/overview-translational.aspx:

"Growing barriers between clinical and basic research … are making it more difficult to translate new knowledge to the clinic - and back again to the bench. … Through discussions with deans of academic health centers, recommendations from the Institute of Medicine, and meetings with the research community, the NIH recognized that a broad re-engineering effort is needed … to catalyze the development of a new discipline of clinical and translational science. [Thus] the launch of the Clinical and Translational Science Awards (CTSA) Consortium in October 2006. … The purpose of the CTSA Program, which NCRR [National Center for Research Resources] is leading on behalf of the NIH Roadmap for Medical Research, is to assist institutions to forge a uniquely transformative, novel, and integrative academic home for Clinical and Translational Science…."

CTS at NIH

From The Clinical and Translational Science Awards (CTSA)® webpage **"CTSA Institutions"** at https://www.ctsacentral.org/:

"Currently, about 60 medical research institutions in 30 states and the District of Columbia are active members of the CTSA consortium. … The list of institutions can be sorted by Institution Name (default), Year or State by clicking on the respective heading." https://www.ctsacentral.org/ctsa-institutions

"Below are publications that have been endorsed by Consortium leadership as CTSA Consortium publications. They reflect group efforts within the consortium, involving at least two or more CTSA institutions. The Consortium is pleased to share its … recent contributions to the clinical and translational research and training community." https://www.ctsacentral.org/content/ctsa-consortium-publications

CTS at NIH

CTS at NIH

The Clinical and Translational Science Awards (CTSA)® webpage (https://www.ctsacentral.org/), at **"Resources for Researchers"** (https://www.ctsacentral.org/content/resources-researchers), reads

- "Resources for Researchers provides webpage links to publically available information for basic, clinical, and translational research communities. Information is organized by source and subcategorized by topic.
- "The following links to resource tools, portals, funding opportunities and subheadings such as **drug discovery, Prevention and Personalized Medicine, Comparative Effectiveness Research (CER), global health, and pharmacogenetics/pharmacogenomics**.
- "For reference, here are links to the NIH Office of Extramural Research Glossary & Acronym List, Research Portfolio Online Reporting Tool (RePORT), **CTSA Collaboration Opportunities**, and the Office of Research Services NIH Library."

CTS at NIH

The Clinical and Translational Science Awards (CTSA)® webpage (https://www.ctsacentral.org/), at **"Resources for Researchers"** (https://www.ctsacentral.org/content/resources-researchers) lists **three sets of CTSA resources** (CTSA Consortium, NIH, other Government Agency), e.g. in

- **Drug Discovery**
- **Translational Research 1: Basic Science, Translational, and Clinical Research**
- **Translational Research 2: Clinical, Translational, and Community Based**
- **Biostatistics, Epidemiology, and Research Design**
- **Prevention and Personalized Medicine**
- **Public Private Partnerships**
- **Regulatory Affairs and Ethics**
- **Research Education, Training, and Career Development**
- **Comparative Effectiveness Research/Patient Centered Research Outcomes Research**

CTS at NIH

The Clinical and Translational Science Awards (CTSA)® webpage (https://www.ctsacentral.org/), at "**Thematic Special Interest Groups**" (https://www.ctsacentral.org/content/thematic-special-interest-groups) reads,

- "CTSA Thematic Special Interest Groups (TSIG) have self-formed across the consortium. With NIH participation, their direction is driven by CTSA and non-CTSA interests. The TSIGs are in varying levels of formation, and their range of activities includes: Developing collaborations with existing networks, societies and organizations; Identifying specific research proposals for collaboration; Obtaining support from NIH Institutes and Centers ICs), research institutions, and societies; Organizing workshops and meetings with support from NIH ICs, research institutions, and NIH conference grants; Meeting regularly in informal settings (teleconferences and at other pre-existing meetings) to share and collaborate.
- "Organizationally, the **TSIGs are currently outside of the CTSA consortium** structure…."

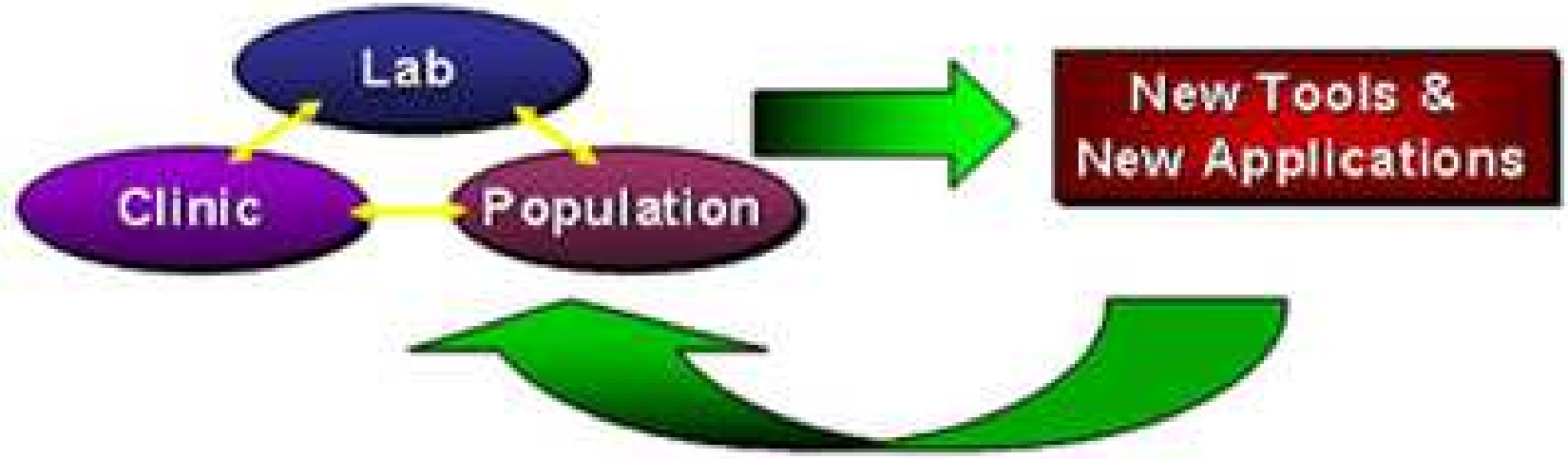
CTS at NIH

The Clinical and Translational Science Awards (CTSA)® webpage (https://www.ctsacentral.org/), at "**Thematic Special Interest Groups**" (https://www.ctsacentral.org/content/thematic-special-interest-groups) lists,

Topic	NIH Contact	Email
Sleep Research Network	Rosemarie Filart	filartr@mail.nih.gov
Dentistry and Oral Health	Andrea Sawczuk	sawczuka@mail.nih.gov
Emergency Care Researchers	Rosemarie Filart	filartr@mail.nih.gov
Neuroscience Researchers	Rosemarie Filart	filartr@mail.nih.gov
CTSA Nurse Scientist	Donna Jo McCloskey	mccloskd@mail.nih.gov
VA Research Collaboration	François Boller	bollerf@mail.nih.gov
CTSA Pain Research Interest Group	Andrea Sawczuk	sawczuka@mail.nih.gov
Women in Clinical and Translational Research	Andrea Sawczuk	sawczuka@mail.nih.gov
CTSA TEAM (TElemed, TeleheAlth, Mhealth)	Rosemarie Filart	filartr@mail.nih.gov
CTSA-USCIITG Critical Care Scientific Interest Group	Mary Purucker	puruckerm@mail.nih.gov

CTS at NIH

To conclude: From The Translational Research Working Group (TRWG) of the National Cancer Institute
http://www.cancer.gov/researchandfunding/trwg/TRWG-definition-and-TR-continuum: "Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality."



4. CTS Basic Ingredients

CTS Basic Ingredients (Hulley and Cummings* chapters 1-6)

Chapter 1: Getting started: Anatomy and physiology of clinical research (Ross 20Sept12)
Chapter 2: Conceiving the research question (YOU week of 20Sept12)
Chapter 3: Choosing the study subjects (YOU week of 20Sept12)
Chapter 4: Planning the measurements (YOU week of 20Sept12)
Chapter 5: Getting ready to estimate Sample size (Mittal 20Sept12)
Chapter 6: Estimating sample size and power (Mittal 27Sept12)

*Hulley SB, Cummings SR et al., Designing Clinical Research: An Epidemiologic Approach (Philadelphia PA: Lippincott Williams & Wilkins, 2001, 2nd edition)

At UNE: http://0-www.r2library.com.lilac.une.edu/marc_frame.aspx?ResourceID=464

4.1. Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

1. The Anatomy of Research

"The structure of a research project is set out in its **protocol**, the written plan of the study. Protocols [help] the investigator to organize her research in a logical, focused, and efficient way.

"The research question is the objective of the study, the uncertainty that the investigator wants to resolve. Research questions often begin with a general concern that must be narrowed down to a concrete, researchable issue. For example … **Should women take hormones after menopause?** … the question must be focused before planning efforts can begin … breaking the whole question into its constituent parts and singling out one or two of these to build a protocol around[, e.g. into] **Does taking estrogen after menopause lower the likelihood of developing coronary heart disease (CHD)?**

"The acronym *FINER* denotes five essential characteristics of a good research question: that it be *feasible, interesting, novel, ethical,* and *relevant (Chapter 2).*"

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"The **significance section** of 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? This section cites previous research that is relevant (including the investigator's own work) and indicates the problems with that research and what questions remain. It makes clear how the findings of the proposed study will help resolve these uncertainties, leading to new scientific understanding and influencing clinical and public health policy.

"**The design** of a study is a complex issue. A fundamental decision is whether to take a passive role in observing the events taking place in the study subjects in an observational study or to apply an intervention and examine its effects on these events in a clinical trial (Table 1.2). Among observational studies, two of the most common designs are cohort studies, in which a group of subjects is followed over time, and cross-sectional studies, in which the observations are made on a single occasion.

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"A third common option is the case-control design, in which the investigator compares a group of subjects who have a disease or condition with another group of subjects who do not.

"Another design decision is whether to deal with past events in a retrospective study or to follow study subjects prospectively for events that have not yet occurred. Among clinical trial options, the randomized blinded trial is often the best design but unblinded or time-series designs may be more suitable for some research questions.

"No one approach is always better than the others, and each research question requires a judgment about which design is the most efficient way to get a satisfactory answer. The randomized blinded trial is often held up as the gold standard for establishing causality and the effectiveness of interventions, but there are many situations for which an observational study is a better choice or the only feasible option."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chap 1, Table 1.2)

Study Design	Key Feature	Example
Observational Designs		
Cohort study	A group followed over time	The Investigator examines a cohort of women yearly for several years, observing the incidence of heart attacks in hormone users and nonusers.
Cross-sectional study	A group examined at one point in time	She examines the group of women once, observing the prevalence of a history of heart attacks in hormone users and nonusers
Case-control study	Two groups, based on the outcome	She examines a group of women with heart attacks (the "cases") and compares them with a group of healthy women (the controls), asking about hormone use.
Experimental Design		
Randomized blinded trial	Two groups created by a random process and a blinded intervention	She randomly assigns women to receive hormone or identical placebo, then follows both treatment groups for several years to observe the incidence of heart attacks.

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"A typical sequence for studying a topic begins with observational studies of a type that is often called **descriptive**. These studies explore the lay of the land, for example describing distributions of diseases and health-related characteristics in the population (*How common is estrogen treatment in women after menopause?*) or the sensitivity and specificity of a diagnostic test.

"Descriptive studies are usually followed or accompanied by **analytic** studies that evaluate associations to discover cause-and-effect relationships (*Is taking estrogen after menopause associated with lower risk of CHD?*). The final step is often a clinical trial to establish the effects of an intervention (*Does hormone treatment alter the incidence of CHD?*).

"Experiments usually occur later in the sequence of research studies, because they tend to be more difficult and expensive, and answer more narrowly focused questions…."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"It is useful to characterize the design in a single sentence that begins with its name. Some studies do not easily fit into these molds, however….

"It is worth the effort-a precise description of the type of study clarifies the investigator's thoughts and is useful for orienting colleagues and consultants. (This single sentence is the research analogue of to the opening sentence of a medical resident's report on a new hospital admission" This 62-year-old white policewoman was well until ….) If the study has two major phases, the design for each should be mentioned.

> ***"Research design*: This is a cross-sectional study of the prevalence of estrogen treatment among women aged 50 to 69 years, followed by a prospective cohort study of whether estrogen treatment is associated with low risk of subsequent heart attacks."**

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"Two major decisions must be made in choosing the **study subjects** (Chapter 3). The first is to specify selection criteria that define the target population: the kinds of patients best suited to the research question. The second decision concerns how best to recruit enough women from an accessible aspect of this population who will be the actual subjects of the study.

"For example, the study of hormones and CHD in women might select women aged 50 to 69 years attending primary care clinic at the investigator's hospital, and the investigator might decide to invite the next 1,000 such patients. These design choices represent trade-offs; studying a random sample of all U.S. women of that age would enhance generalizability but be formidably difficult and costly.

"Another major set of decisions in designing any study concerns the choice of which **variables** (characteristics that vary from one study subject to another) to measure (Chapter 4)."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"**In a descriptive study** the investigator looks at individual variables one at a time. A study of the prevalence of hormone treatment, for example, might record the presence or absence of the self-report of taking estrogen. **In an analytic study** the investigator studies the associations among two or more variables in order to predict outcomes and to draw inferences about cause and effect. In considering the association between two variables, the one that precedes (or is presumed on biologic grounds to be antecedent) is called the **predictor variable**; the other is called the **outcome variable**.

"Most observational studies have many predictor variables (e.g., estrogen treatment, blood cholesterol, age, race), and several outcome variables (e.g., heart attacks, strokes). Experiments study an intervention (a special kind of predictor variable that the investigator manipulates), such as treatment with estrogen or placebo. This design allows her to observe the effects on the outcome variable, often using randomization to control for the influence of confounding variables (... that could confuse the interpretation of findings)."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"The investigator must develop **plans for managing and analyzing the study data**. For experiments this always involves specifying a hypothesis, a version of the research question that provides the basis for testing the statistical significance of the findings (Chapter 5).

> *Hypothesis*: Women who receive estrogen treatment after menopause will have fewer heart attacks than those who do not.

"The hypothesis also allows the investigator to estimate the sample size, the number of subjects needed to observe the expected difference in outcome between study groups with a reasonable degree of probability, or power (Chapter 6). …

"For purely descriptive studies (e.g., the prevalence of CHD in women 50 to 69 years of age), an analogous approach estimates the number of subjects needed to produce an acceptable level of precision when confidence intervals are calculated for the means, proportions, or other descriptive statistics."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

2. The Physiology of Research

"The goal of clinical research is to draw **inferences** from the study results about the nature of truth in the universe…. Beginning with a decision about what health problem the investigator wishes to address, the investigator undertakes a study that will answer this research question. This undertaking involves two distinct steps…. The **first is to *design*** a study plan with subjects and measurements chosen to enhance the process of appropriately answering the research question and generalizing these conclusions to the people and phenomena addressed by the research question.

"The **second step is to *carry out*** the study in a fashion that enhances the likelihood of getting the right answer; in other words, to draw the correct conclusions about what actually happened in the study."

"[You] first address the **design side** … then the **implementation side** … then turn to the **errors** that threaten the validity of clinical research inferences."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

2.1. Designing the Study. "For the purpose of illustration, we will use a simple descriptive question: ***How common is it for women to take estrogen after menopause?*** This question cannot be answered with perfect accuracy because it would be impossible to study all postmenopausal women and because our instruments for discovering whether a woman is taking estrogen are imperfect. So the investigator must settle for a related question that can be answered by the study, such as the following: "**Among postmenopausal women seen for the first time in her primary care clinic, what proportion report on a questionnaire that they are taking estrogen?**"

"One major component of this transformation is 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 of interest because there are practical barriers to studying the entire population. The decision to study patients entering the UCSF primary care clinics is a compromise. This is a sample that is feasible to study but one that may produce a different prevalence of estrogen treatment than that found in all women.

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"The other major component …of the transformation is the choice of variables that will represent the phenomena of interest. The variables specified in the study plan are usually proxies for these phenomena. The decision to use a self-report questionnaire to assess estrogen treatment is a fast and inexpensive way to collect information, but it will not be perfectly accurate. Some women will not give the right answer because they know they're taking hormones but don't recognize the phrase *estrogen treatment* that appears in the questionnaire, or because they may have forgotten what they are taking.

"In short … differences … between the research question and the study plan [reflect the need for] making the study more practical. The cost of this increase in practicality, however, is the risk that the study may produce a wrong answer to the research question. [Here] errors in designing the study are a common reason for getting the wrong answer to the research question."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

2.2. Implementing the Study. Now consider "the problem of a wrong answer to the research question [which may result from differences, for example, between] the actual sample of study subjects [and] the intended sample.

"The plans to study all age-eligible women entering primary care clinics, for example, would probably be disrupted by incomplete attendance (say only 150 of the 278 patients who are scheduled for first visits ever show up during the year of the study) and by refusal to participate (say only 100 of these consent to be studied). The 100 patients who agree to be studied may have a different prevalence of estrogen treatment from those who do not show up or refuse.

"[And so too differences between] the actual [and] intended measurements. If the format of the questionnaire is unclear, the women may get confused and check the wrong box, for example, or they may simply omit the question by mistake. [In this way] errors in implementing the study [join] errors of design [as reasons] for getting the wrong answer to the research question."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

Drawing 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 the study finds an association between hormone therapy and heart attacks, does this represent cause and effect, or is there some other explanation? Reducing the likelihood of confounding and other rival explanations is one of the major challenges in designing an observational study (Chapter 9).

Errors of Research. "No study is free of errors, and the inferences that have been described are never perfectly valid. The goal is simply to maximize the validity of drawing inferences from what happened in the study sample to reach conclusions about the nature of things in the population. Erroneous inferences can be addressed in the analysis phase of research, but the best strategies are focused on design and implementation[, on p]reventing errors from occurring in the first place, to the extent that it is practical and economic to do so."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"The two main kinds of error that interfere with research inferences are random error and systematic error. The distinction is important because the strategies for minimizing them are quite different.

"**Random error** is a wrong result due to **chance**-unknown sources of variation that are equally likely to distort the sample in either direction. If the true prevalence of estrogen treatment in 50- to 69-year-old women is 20%, a well-designed sample of 100 patients from that population might contain exactly 20 patients with this disease. More likely, however, the sample would contain a nearby number such as 18, 19, 21, or 22. Occasionally, chance would produce a substantially different number, such as 12 or 28.

"Among several techniques for reducing the influence of random error, the simplest and best known is to increase the sample size. The use of a larger sample diminishes the likelihood of a wrong result by increasing the **precision** of the estimate-the degree to which the observed prevalence approximates 20% each time a sample is drawn."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"**Systematic error** is a wrong result due to **bias** (sources of variation that distort the study findings in one direction). An illustration is the decision … to use patients who come to the primary care clinic, who might be more likely than average to adopt medical treatments. Increasing the sample size has no effect on systematic error.

"The only 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 either reduces the size of the various biases or gives some information about them.

"An example would be to draw a second sample of women from a setting that may be less likely to bias the proportion of women treated with estrogen (e.g., employees in a corporation), and to compare the observed prevalence in the two samples."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

"The examples of random and systematic error in the preceding two paragraphs are components of **sampling error**, which threatens inferences from the study subjects to the population. Both random and systematic errors can also contribute to **measurement error**, threatening the inferences from the study measurements to the phenomena of interest.

"An illustration of **random measurement error** is the variation in the response when a questionnaire is administered on several occasions.

"An example of **systematic measurement error** is the underestimation of the prevalence of estrogen treatment due to lack of clarity in how the question is phrased. Additional strategies for controlling all these sources of error are presented in Chapters 3 and 4."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

Developing the Study Protocol. "The first step in designing a study is to establish the research question. This task is discussed at length in Chapter 2. Once the research question is in hand, the process of developing the study plan can begin. There are three versions of the study plan that are produced in sequence, each larger and more detailed than the preceding one.

"A **one- to two-page outline** of the elements of the study. … It serves as a standardized checklist to remind the investigator to include all the components. Just as important, the sequence has an orderly logic that helps clarify the investigator's thinking on the topic.

"The **study protocol**, an expansion on the one- to two-page outline that can range from five to 25 or more pages. The full protocol is the main document used to plan the study and to apply for grant support; we discuss parts of it throughout this book and put them all together in Chapter 19.

"The **operations manual**, a collection of specific procedural instructions, questionnaires, and other materials designed to ensure a uniform and standardized approach to carrying out the study… (Chapters 4 and 17)."

Getting started: Anatomy and physiology of clinical research (Hulley and Cummings, chapter 1)

Outline of the Study Protocol	
Element	Purpose
Research questions	What questions will the study address?
Significance (background)	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	

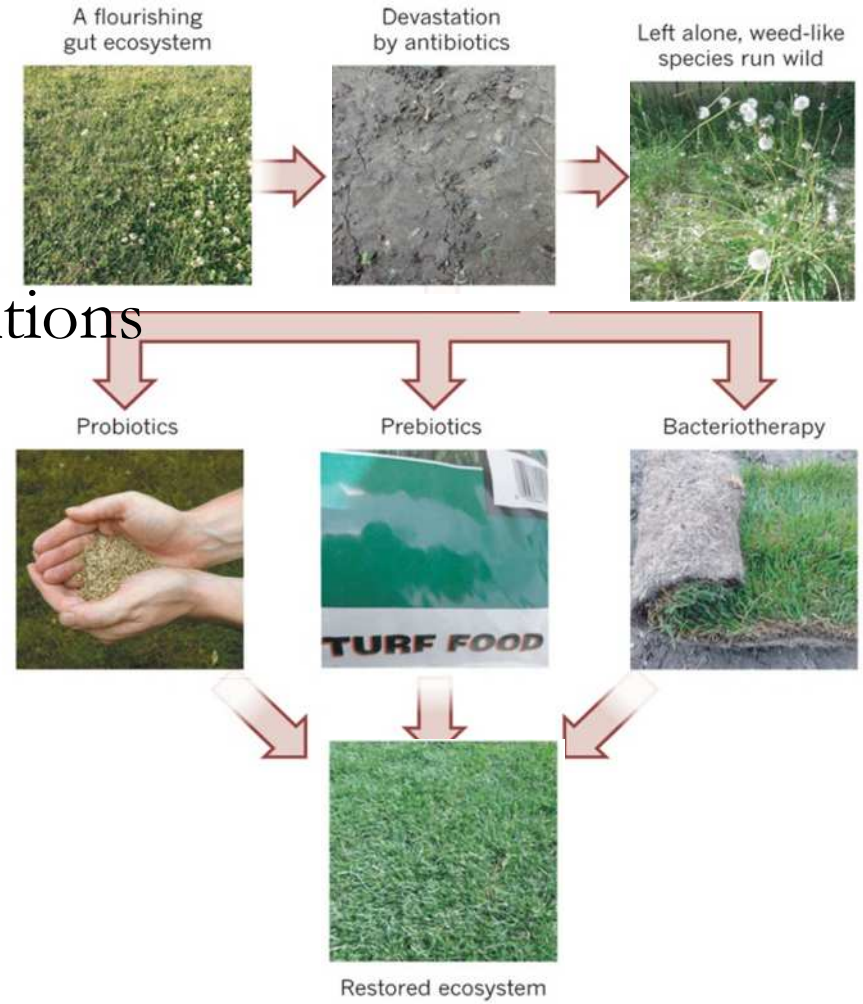
Sample size and Power

Lies, damned lies and statistics

- Chapter 5: Browner, Newman and Hulley
- Assumptions:
  - Statistics is not an exact science
  - Absence of evidence is not evidence of absence
  - One short lecture may not be enough

The case of human Microbiome

- Trillions of microbes
- Perform Vital functions
- Disruption causes health conditions
- Antibiotics
- Farm animals
- Restoring Microbiome



Two Statistical Hypotheses

- Null Hypothesis

(No association between predictor(s) and outcome)

There is no association between low dosage of antibiotics and obesity

$P_l = P_n$ **(two sided)**	$\mu_l = \mu_n$ **(two sided)**

Two Statistical Hypotheses

- Alternative Hypothesis (Association exists)

There is an association between low dosage of antibiotics and obesity

Quantify low dosage and obesity rate increase (Effect size)

$P_l \neq P_n$ **(two sided)**	$\mu_l \neq \mu_n$ **(two sided)**
$P_l < P_n$ **(One sided)**	$\mu_l < \mu_n$ **(One sided)**
$P_l > P_n$ **(One sided)**	$\mu_l > \mu_n$ **(One sided)**

Types of errors

To reject or not to reject a Null hypothesis

Truth in the population

Study conclusion	**No association between predictor and outcome**	**Association between predictor and outcome**
No association between predictor and outcome	**Correct decision**	**Type II error** β (Beta)
Association between predictor and outcome	**Type I error** α (alpha)	**Correct decision (Power = 1- β)**

Type I and II errors

- Acceptable range:
  - Type 1: 0.01 to 0.1
  - Type 2: 0.2 or less
- Both can not be reduced together.
- Increasing sample size is an acceptable way of reducing type II error.

Sample size (n)

- The best sample size.
- A technically sound study vs Unplanned study
- Power estimation after collecting data.

Other topics

- P-value
- Post-hoc analysis