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DESIGNING CLINICAL RESEARCH

Fourth Edition

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FOURTH EDITION

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To our families and our students

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Introduction

This fourth edition of *Designing Clinical Research* (DCR) marks the 25th anniversary of the publication of our first edition. It has become the most widely used textbook of its kind, with more than 130,000 copies sold and foreign language editions produced in Spanish, Portuguese, Arabic, Chinese, Korean, and Japanese. We designed it as a manual for clinical research in all its flavors: clinical trials, observational epidemiology, translational science, patient-oriented research, behavioral science, and health services research. We used epidemiologic terms and principles, presented advanced conceptual material in a practical and reader-friendly way, and suggested common sense approaches to the many judgments involved in designing a study.

Many of our readers are physicians, nurses, pharmacists, and other health scientists who, as trainees and junior faculty, are developing careers in clinical research and use this book as a guide in designing and carrying out their studies. Many others are clinicians in residency programs and pre-doctoral students in professional schools—medicine, nursing, pharmacy, and public health among others—who use DCR to help them become discerning readers with a grasp of the strengths and limitations of the research studies that inform evidence-based clinical practice. A third audience consists of undergraduate students preparing to apply to these schools who are interested in looking ahead at the world of clinical research.

What's new in the fourth edition? The most visible innovation is color, which, in addition to improving the esthetics, will speed comprehension of the color-coded components. A larger innovation that accompanies each purchase of the paperback text is an interactive digital experience powered by Inkling®, viewable through a browser or as a download to tablet or smartphone. Its features include rapid index-based search options that link to a newly created glossary; bookmarking, highlighting, and annotating capability; cross-linking of relevant content; the ability to cut-and-paste figures or text into PowerPoint presentations; and live Internet links to jump instantly from citations to articles on PubMed, and to Google topics.

The substantive revisions to the fourth edition include updated and tightened text, figures, and tables in every chapter; many new examples and references; and new sections covering recent advances in the field. For example:

- The chapters on observational studies have been reorganized with an entire chapter now devoted to various case–control designs, including the incidence-density approach for addressing changes in risk factor levels and differences in follow-up time.
- The chapters on clinical trials have an expanded section on the non-inferiority trials that have become popular in comparative effectiveness research, and they address subgroup analysis and effect modification more fully.
- The chapter on studying medical tests has a new section on the growing practice of developing clinical prediction rules.
- The chapter on utilizing existing data sets emphasizes attractive options for beginning investigators to publish rapidly and inexpensively.
- The chapter on research ethics is updated to reflect current policy on whole genome sequencing and other topics, with new cases that illustrate the resolution of ethical dilemmas in clinical research.

- The chapter on data management has been extensively updated with the latest Web-based approaches.
- The chapter on getting funded has strategies for addressing the new NIH grant-writing requirements, as well as updates on funding by foundation and corporate sponsors.

The fourth edition is accompanied by an upgraded DCR website at www.epibiostat.ucsf.edu/dcr/ that contains materials for teaching DCR, including links to a detailed syllabus for the 4- and 7-week DCR workshops that we present to 300 trainees each year at UCSF. There are also instructor's notes for the workshops that faculty who teach this material will find useful, and links to our Training In Clinical Research (TICR) master's degree program at UCSF, with more than 30 other courses and their materials. In addition, there are useful tools for investigators, including an excellent interactive sample size calculator.

Many things have *not* changed in the fourth edition. It is still a simple book that leaves out unnecessary technicalities and invites the investigator to focus on the important things: how to find a good research question and how to plan an efficient, effective, ethical design. The chapters on estimating sample size continue to demystify the process and enable readers with minimal training in statistics to make these calculations themselves, thoughtfully, and without needing to wrestle with formulas. The book still works best when combined with the essential ingredient of one or more long-term mentors. It still *does not* address the important areas of how to analyze, present, and publish the findings of clinical research—topics that our readers can pursue with other books (e.g., 1–4). And we still *do* use the feminine pronoun in the first half of the book, masculine in the second, the goal (besides avoiding the passive tense) being to symbolically empower clinical investigators of both genders.

The process of becoming an independent clinical scientist can be challenging, especially getting over the hump of acquiring a substantial grant for the first time. But it is gratifying that many of our former trainees who used this book have achieved this goal, discovered that they *like* doing research, and settled into a great career. For those with inquiring minds, the pursuit of truth can become a lifelong fascination. For perfectionists and craftsmen, there are endless challenges in creating elegant studies that conclusively answer questions, large and small, at an affordable cost in time and money. Investigators who enjoy teamwork will develop rewarding relationships with colleagues, staff, and students, as well as friendships with collaborators working in the same field in distant places. And for those with the ambition to make a lasting contribution to society, there is the prospect that with skill and tenacity they will participate in the incremental advances in clinical and public health practice that is the natural order of our science.

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Contents

SECTION I

Basic Ingredients

CHAPTER 1

Getting Started: The Anatomy and Physiology of Clinical Research

Stephen B. Hulley, Thomas B. Newman, and Steven R. Cummings

This chapter introduces clinical research from two viewpoints, setting up themes that run together throughout the book. One is 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. An investigator's goal is to design these components in a fashion that will make the project feasible and efficient.

The other theme is 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, but they also have a vital scientific function: helping the investigator organize her research in a logical, focused, and efficient way. Table 1.1 outlines the components of a protocol. We introduce the whole set here, expand on each component in the ensuing chapters of the book, and return to put the completed pieces together in Chapter 19.

Research Question

The research question is the objective of the study, the uncertainty the investigator wants to resolve. Research questions often begin with a general concern that must be narrowed down to a concrete, researchable issue. Consider, 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?

TABLE 1.1 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	How is the study structured?
Time frame	
Epidemiologic design	
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	

A good research question should pass the "So what?" test. Getting the answer should contribute usefully to our state of knowledge. The acronym FINER denotes five essential characteristics of a good research question: It should be feasible, interesting, novel, ethical, and relevant (Chapter 2).

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? This section cites relevant previous research (including the investigator's own work) and indicates the problems with the prior research and what uncertainties remain. It specifies how the findings of the proposed study will help resolve these uncertainties, lead to new scientific knowledge, or influence practice guidelines or public health policy. Often, the literature review and synthesis done for the significance section will lead the investigator to modify the research question.

Design

The design of a study is a complex issue. A fundamental decision is whether 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 (Table 1.2). 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 can be further divided into 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

TABLE 1.2 EXAMPLES OF CLINICAL RESEARCH DESIGNS TO FIND OUT WHETHER FISH INTAKE REDUCES CORONARY HEART DISEASE RISK

EPIDEMIOLOGIC DESIGN	KEY FEATURE	EXAMPLE
	Observational Designs	
Cohort study	A group of subjects identified at the beginning and followed over time	The investigator measures fish intake in a group of subjects at baseline and periodically examines them 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 a group of 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 do 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 a placebo that is identical in appearance, then follows both treatment groups for several years to observe the incidence of CHD.

usually the best design but nonrandomized or unblinded designs may be all that are feasible 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 best design 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. The relatively low cost of case–control studies and their suitability for rare outcomes makes them attractive for some questions. Special considerations apply to choosing designs for studying diagnostic tests. These issues are discussed in Chapters 7 through 12, each dealing with a particular set of designs.

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 health-related characteristics and diseases in the population:

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

Descriptive studies are usually followed or accompanied by analytic studies that evaluate associations to permit inferences about cause-and-effect relationships:

- 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?

The final step is often a clinical trial to establish the effects of an intervention:

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

Clinical trials usually occur relatively late in a series of research studies about a given question, because they tend to be more difficult and expensive, and to answer more definitively the narrowly focused questions that arise from the findings of observational studies.

It is useful to characterize a study in a *single sentence that summarizes the design and research question*. If the study has two major phases, the design for each should be mentioned.

- This is a cross-sectional study of dietary habits in 50- to 69-year-old people with a history of CHD, followed by a prospective cohort study of whether fish intake is associated with lower risk of subsequent coronary events.

This sentence is the research analog to the opening sentence of a medical resident's report on a new hospital admission: "This 62-year-old white policewoman was well until 2 hours before admission, when she developed crushing chest pain radiating to the left shoulder."

Some designs do not easily fit into the categories listed above, and classifying them with a single sentence can be surprisingly difficult. It is worth the effort—a concise description of the design and research question clarifies the investigator's thoughts and is useful for orienting colleagues and consultants.

Study Subjects

Two major decisions must be made in choosing the study subjects (Chapter 3). The first is to specify **inclusion** and **exclusion criteria** that define the target population: the *kinds* of people best suited to the research question. The second decision concerns how to **recruit** an appropriate *number* of people from an accessible subset of this population to be the subjects of the study. For example, the study of fish intake in people with CHD might identify subjects seen in the clinic with diagnostic codes for myocardial infarction, angioplasty, or coronary artery bypass grafting in their electronic medical record. 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

Another major set of decisions in designing any study concerns the choice of which variables to measure (Chapter 4). 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. In considering the association between two variables, the one that occurs first or is more likely on biologic grounds to be causal is called the **predictor variable**; the other is called the **outcome variable**.[1] Most observational studies have many predictor variables (age, race, sex, smoking history, fish and fish oil supplement intake) and several outcome variables (heart attacks, strokes, quality of life, unpleasant odor).

Clinical trials examine the effects of an **intervention**—a special kind of predictor variable that the investigator manipulates, such as treatment with fish oil capsules. This design allows her to observe the effects on the outcome variable 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.

[1]Predictors are sometimes termed independent variables and outcomes dependent variables, but the meaning of these terms is less self-evident and we prefer to avoid their use.

Statistical Issues

The investigator must develop plans for estimating sample size and for managing and analyzing the study data. This generally involves specifying a hypothesis (Chapter 5).

> **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. The hypothesis also allows the investigator to calculate the sample size—the number of subjects needed to observe the expected difference in outcome between study groups with reasonable probability (an attribute known as power) (Chapter 6). 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; instead, the number of subjects needed to produce acceptably narrow confidence intervals for means, proportions, or other descriptive statistics can be calculated.

■ 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. Two major sets of inferences are involved in interpreting a study (illustrated from right to left in Figure 1.1). 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.

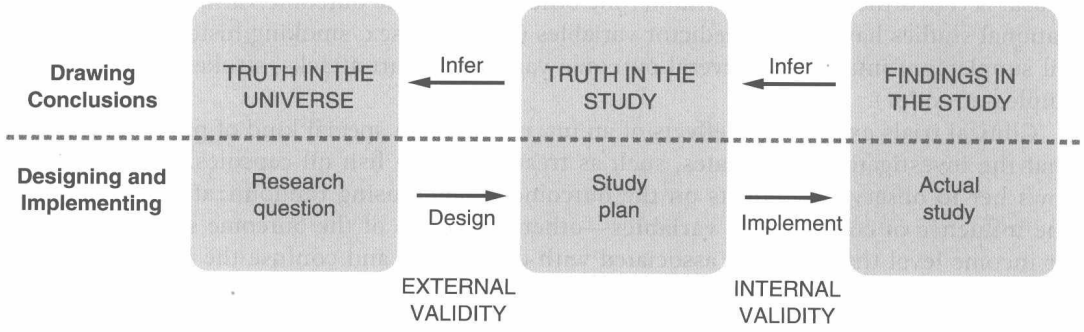
When an investigator plans a study, she reverses the process, working from left to right in the lower half of Figure 1.1 with the goal of maximizing the validity of these inferences at the end of the study. She designs a study plan in which the choice of research question, subjects, and measurements enhances the external validity of the study and is conducive to implementation with a high degree of internal validity. In the next sections we address design and then implementation before turning to the errors that threaten the validity of these inferences.

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



■ FIGURE 1.1 The process of designing and implementing a research project sets the stage for drawing conclusions based on inferences from the findings.

and is taking fish oil are imperfect. So the investigator settles 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?

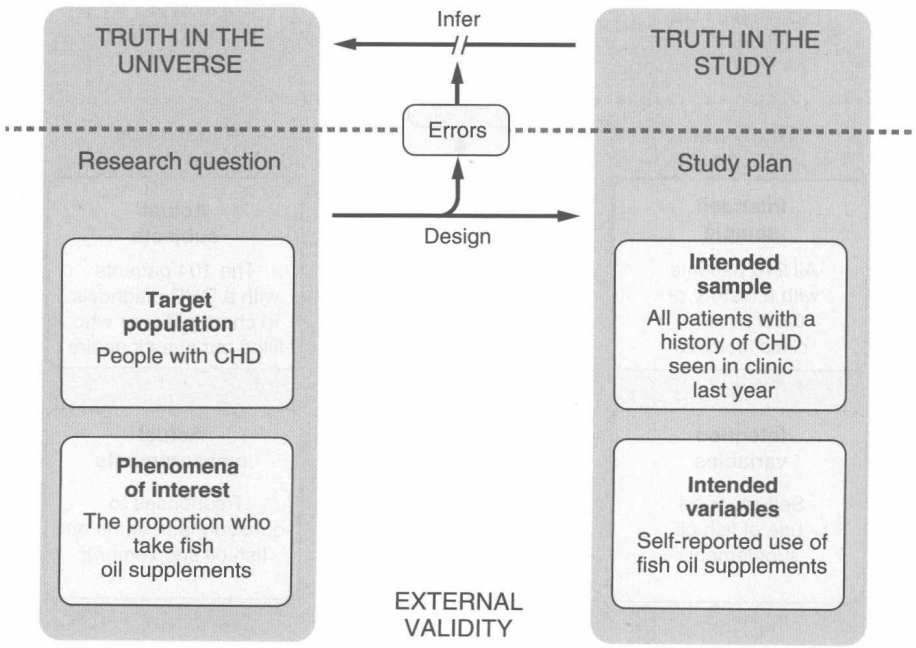
The transformation from research question to study plan is illustrated in Figure 1.2. One major component of this transformation is the choice of a sample of subjects that will represent the population. The group of subjects specified in the protocol can only be a sample of the population of interest because there are practical barriers to studying the entire population. The decision to study patients in the investigator's clinic identified through the electronic medical record system is a compromise. This is a sample that is feasible to study but has the disadvantage that it may produce a different prevalence of fish oil use than that found in all people with CHD.

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 fish oil use is a fast and inexpensive way to collect information, but unlikely to be perfectly accurate because people usually do not accurately remember or record how much they take in a typical week.

In short, each of the differences in Figure 1.2 between the research question and the study plan has the purpose of making the study more practical. The cost of this increase in practicality, 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

Returning to Figure 1.1, the right-hand side is concerned with implementation and the degree to which the actual study matches the study plan. At issue here is the problem of a wrong answer



■ **FIGURE 1.2** Design errors and external validity: If the intended sample and variables do not sufficiently represent the target population and phenomena of interest, these errors may distort inferences about what actually happens in the population.