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CHAPTER 1

Getting Started: The Anatomy and Physiology of Research

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INTRODUCTION

This chapter introduces clinical research from two viewpoints, setting up themes that run together through the book. One theme is the anatomy of research—what it's made of. This includes the tangible elements of the study plan: the research question, design, subjects, measurements, sample size calculation, and so forth. An investigator's goal is to create these elements in a form that will make the project fast, inexpensive, and easy to do.

The other theme is the physiology of research—how it works. Studies are useful to the extent that they yield valid inferences, first about the events that happened in the study sample (*internal validity*), and then about generalizing these events to people outside the study (*external validity*). The goal is to minimize the errors, random and systematic, that threaten conclusions based on these inferences.

Separating these 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 also has the same advantage: it simplifies our thinking about a complex topic.

THE 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, but they also have a vital scientific function: helping the investigator to organize his research in a logical, focused, and efficient way. Table 1.1 outlines the components of a protocol. We will introduce the whole set here, expand on each of them in the ensuing chapters of the book, and return in Chapter 17 to put the completed pieces together.

The research question

The research question is the objective of the study, the uncertainty about a health issue

Table 1.1
Outline of the study protocol

Element	Purpose
Research questions (objectives)	What questions will the study address?
Significance (background)	Why are these questions important?
Design	How will the study be carried out?
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	
Outcome variables	
Statistical issues	How large is the study, and how will it be analyzed?
Hypotheses	
Sample size estimation	
Analytic approach	

that the investigator wants to resolve. Research questions often begin with a vague and general concern that must be narrowed down to a concrete, researchable issue. For example,

> *Initial research question:* Are intravenous (i.v.) drug abusers likely to spread the AIDS epidemic to the general population?

This is a good place to start, but the question must be focused before planning efforts can begin. Often this involves breaking the whole question into its constituent parts, and singling out one or two of these to build the protocol around.

> *More specific research questions:*
> 1. What proportion of i.v. drug abusers have been infected by the AIDS virus?
> 2. What risk factors increase the chance of transmitting the infection?

A good research question should pass the "so what" test—getting the answer should contribute usefully to our state of knowledge. The question must also be feasible to study. Deciding what is feasible is a complicated issue that we will come to in the second, physiologic half of this chapter.

The significance

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, and 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 and influence clinical and public health policy.

The design

The design of a study is a complex topic that involves a number of decisions (Fig. 1.1). The most fundamental is whether to stand apart from the events taking place in the study subjects (in an observational study), or to test the effects of an intervention on these events (in an experiment). If the investigator chooses an observational design, his next decision is whether to make the measurements on a single occasion (in a cross-sectional study) or over a period of time (in a longitudinal study). A third aspect of the design decision (not shown explicitly in the figure) is whether to deal exclusively with past and present events in a retrospective study, or to follow study subjects prospectively for events that have not yet occurred when the study begins.

No one approach is always better than the others; for each research question a judgment must be made as to which design is the most efficient way to get a satisfactory answer. The randomized trial is often held

up as the ultimate standard, but there are many situations for which an observational study is a better choice. The relatively low cost of retrospective case-control studies, for example, makes them particularly attractive for questions they can answer satisfactorily. Figure 1.1 shows how four of the most basic study designs—the *case-control study*, the *randomized control trial*, the *cross-sectional study*, and the *cohort study*—could be used to study four different AIDS-related research questions. These designs, and others, are presented in Chapters 7-11.

A typical sequence for studying a topic begins with relatively easy and open-ended observational studies of a type that is often called **descriptive**; these studies explore the lay of the land, describing distributions of diseases and health-related characteristics in the population (What is the prevalence of antibodies to AIDS virus in i.v. drug abusers?). Descriptive studies are usually followed or accompanied by analytic studies that analyze associations in order to discover cause-and-effect relationships (What risk factors increase the likelihood of AIDS virus infection in this population?). The final step is often an **experiment** to establish the effects of an intervention (Does a health education program alter the incidence of infection?). Experiments usually occur later in the sequence of research studies because they tend to be more difficult and expensive, and to answer more narrowly focused questions.

It is useful to characterize the design in a single sentence that begins with its name, as illustrated in Figure 1.1. Some studies do not easily fit into these molds, however, and classifying them can be a surprisingly difficult exercise. It is worth the effort—a precise description of the type of study helps to clarify the investigator's thoughts and is useful for

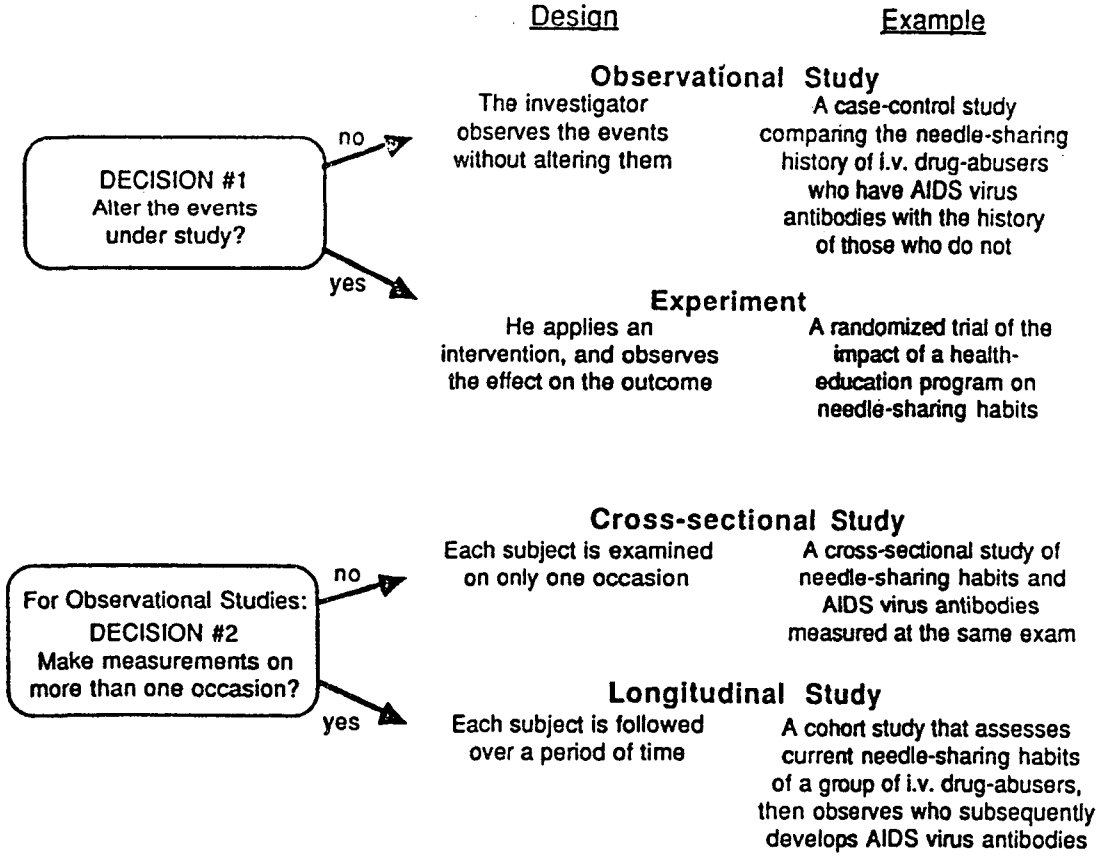

Figure 1.1. Some design decisions, illustrated by the four major epidemiologic prototypes: the case-control study, the randomized trial, the cross-sectional study, and the cohort study.

orienting colleagues and consultants. (This single 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 policeman was well until 2 hours prior to admission, when he developed crushing chest pain radiating to the left shoulder.") 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 antibodies to the AIDS virus among methadone clinic patients, followed by a prospective cohort study of the risk factors for seroconversion among those initially free of antibodies.

The subjects

There are two major decisions to be made in choosing the study subjects (Chapter 3). Specifying the selection criteria is the process of defining the study population: the kinds of patients best suited to the research question and where to recruit them. Sampling is the process of picking the subgroup of this population who will actually be the subjects of the study. An AIDS study might specify as selection criteria patients in the methadone program at San Francisco General Hospital, and sample consecutively the next 100 patients entering that program. These design choices represent trade-offs; drawing the same number of i.v. drug abusers from street sources might expand generalizability but be more difficult and costly.

The variables

Another major set of decisions in designing any study concerns the choice of which variables—characteristics of the study subjects—to measure (Chapter 4). In a descriptive study the investigator looks at individual variables, one at a time. A study of the prevalence of AIDS virus infection, for example, focuses on the distribution of a single variable: The presence or absence of AIDS virus antibodies in the study sample.

In an analytic study the investigator analyzes the relationships 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 the other (or is presumed on biologic grounds to be antecedent) is called the predictor variable, and the other is called the outcome variable.[a] Most observational studies have many predictor variables (e.g., needle-sharing habits, socioeconomic status, age, race), and several outcome variables (AIDS virus antibodies, symptoms of AIDS).

Experiments have a special kind of predictor variable, termed the intervention, which the investigator manipulates (e.g., a health education program about needle-sharing). This design allows him to observe the effects on the outcome variable (seroconversion) while controlling for the influence of confounding variables—other predictors like socioeconomic status that can confuse the interpretation of the outcome (Chapter 10).

Statistical issues

The investigator must develop plans for managing and analyzing the study data. For analytic studies and experiments this always includes a hypothesis-testing component: specifying in advance at least one main hypothesis. A hypothesis is a version of the research question that has the purpose of providing the basis for testing the statistical significance of the findings.

> *Hypothesis*: I.v. drug abusers who cleaned their needles with bleach during the past year will be less likely to have antibodies to AIDS virus than those who did not.

Descriptive studies do not require a hypothesis because their purpose is to describe how variables are distributed (e.g., the prevalence of AIDS virus antibodies) rather than how they are associated with each other.

All studies should also have a sample size estimation (Chapters 12 and 13). For studies with prior hypotheses, this means estimating the number of subjects needed to consistently observe the expected difference in outcome between study groups. For descriptive studies, an analogous approach considers the number of subjects needed to

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[a] Predictor variables are often termed "independent" and outcome variables "dependent", but we find this usage confusing, particularly since "independent" means something quite different in the context of multivariate analyses.

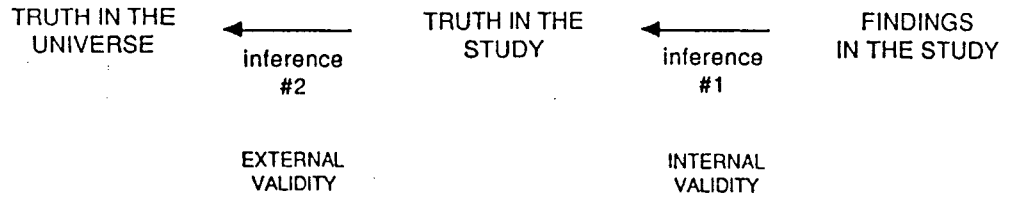

Figure 1.2. The two inferences involved in drawing conclusions from the findings of a study and applying them to the universe outside.

produce descriptive statistics (means, proportions, etc.) of adequate precision.

THE PHYSIOLOGY OF RESEARCH: HOW IT WORKS

One way to think about how research works is to consider the end result of a research project, the process of drawing and applying the study conclusions. Two major sets of inferences are involved (illustrated from right to left in Figure 1.2). One of these concerns the internal validity of the study, the degree to which the investigator's conclusions correctly describe what actually happened in the study. The other concerns the external validity (also called generalizability), the degree to which these conclusions are appropriate when applied to the universe outside the study.

When an investigator plans and carries out a study he needs to keep these two inferences in mind; the overall goal is to maximize their validity at the end of the study. The logical order of the planning process is reversed, however, now going from left to right (bottom panel of Fig. 1.3). The first step is to settle on the health problem in the universe that is of interest (the research question). The investigator then designs a research plan that will provide inferences of satisfactory validity, and implements the study in a way that enhances these inferences.

In this section we will first address the design side of Figure 1.3, then turn to the implementation side, and finally consider the errors that threaten the validity of these inferences.

Designing the study

The research question, as noted earlier, is what the investigator really wants to answer (What proportion of i.v. drug abusers in San Francisco have been infected with the AIDS virus?). This question cannot be answered explicitly because it would be impossible to study all the i.v. drug abusers in San

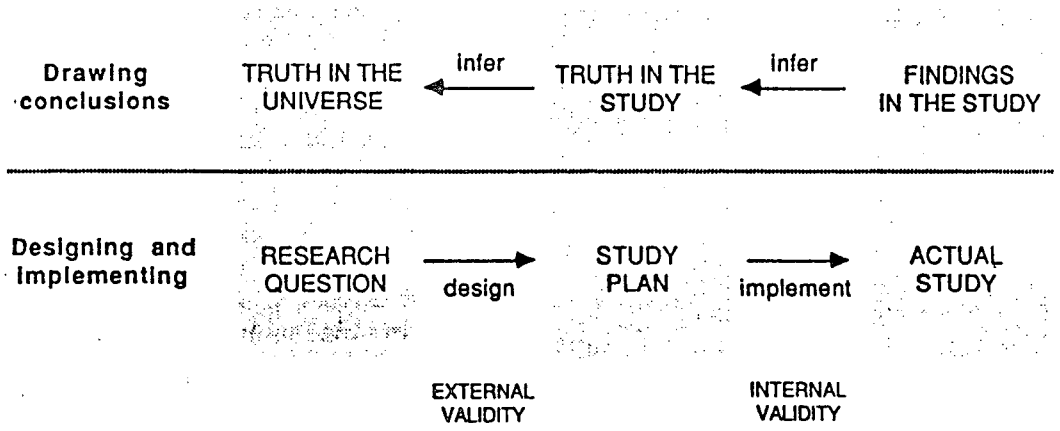

Figure 1.3. The process of designing and implementing a research project sets the stage for the process of drawing conclusions from it.

Francisco, and because our tests for infection are imperfect. So the investigator must settle for a related question that *can* be answered by the study (What proportion of the patients attending methadone clinics at San Francisco General Hospital have antibodies to the AIDS virus?). The transformation from research question to study plan is illustrated in Figure 1.4.

One major component of this transformation is the *choice of a sample of subjects that will represent the target population*. The group of subjects specified in the protocol can only be a subset of the population of interest because there are practical barriers to studying the entire population. In this example, the very large numbers of i.v. drug abusers (about 12,000 in San Francisco) would make it enormously expensive to study all of them, and their inaccessibility (most i.v. drug abusers are not known to medical authorities) would make it impossible. The decision to study patients in the San Francisco General Hospital methadone clinic is a compromise: this is a sample that is feasible to study, but one that may produce a falsely low prevalence of AIDS virus infection if the i.v. drug abusers who come to the methadone clinic tend to have fewer high-risk habits than those who do not come there.

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 antibodies as a proxie for AIDS virus infection provides a feasible way to measure this infection, but it may result in a falsely low prevalence because antibodies do not appear until several months after infection.

In short, each of the differences in Figure 1.4 between the research question and the study plan has the purpose of making the study more practical. The cost of this in-

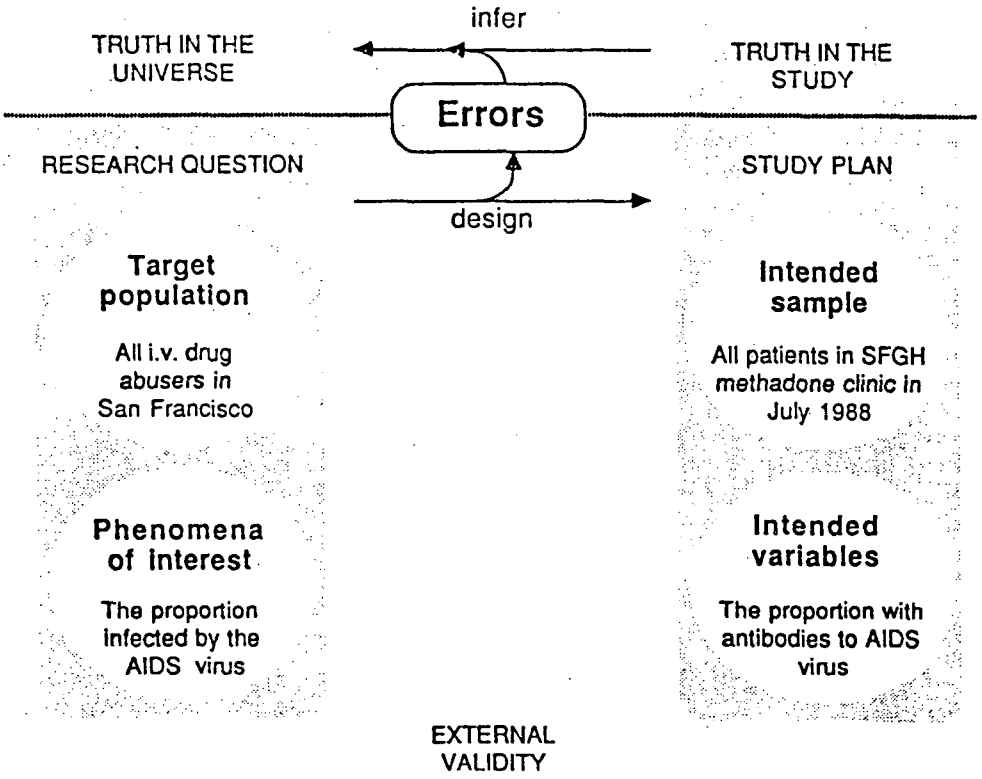

Figure 1.4. Design errors: if the intended sample and variables do not represent the target population and phenomena of interest, the errors that result will threaten the validity of drawing inferences about what is happening in the universe.

crease in practicality, however, is the risk that the study may produce a wrong answer to the research question—for example, a prevalence of AIDS virus antibodies in methadone clinic patients of 15%, when the prevalence of infected i.v. drug abusers in the population is really 30%. Figure 1.4 illustrates the important fact that errors in designing the study are a common reason for getting the wrong answer to the research question.

Implementing the study

Returning to Figure 1.3, 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 to the research question because the way the sample was actually drawn and the measurements made differed in important ways from the way they were designed (Fig. 1.5).

The actual sample of study subjects is almost always different from the intended sample. The plans to study all methadone clinic patients, for example, would probably be disrupted by incomplete attendance (say only 150 of the 200 patients who are registered in the clinic show up during the month of the study), and by noncompliance (say only 100 of these agree to be studied). The 100 patients who volunteer to be tested may have a different prevalence of AIDS infection from those who do not show up or refuse to have the test. In addition to these problems with the subjects, the actual measurements often differ from the intended measurements. The ELISA assay is a reasonably sensitive and specific test for AIDS virus antibody in most populations, for example, but i.v. drug abusers often have biologically false-positive results—antibodies acquired nonspecifically, without any exposure to the AIDS virus. There can also be technical errors, such as a mix-up in the labeling of the specimens, or in carrying out the assay.

These differences between the study plan and the actual study could further distort the answer to the research question—for

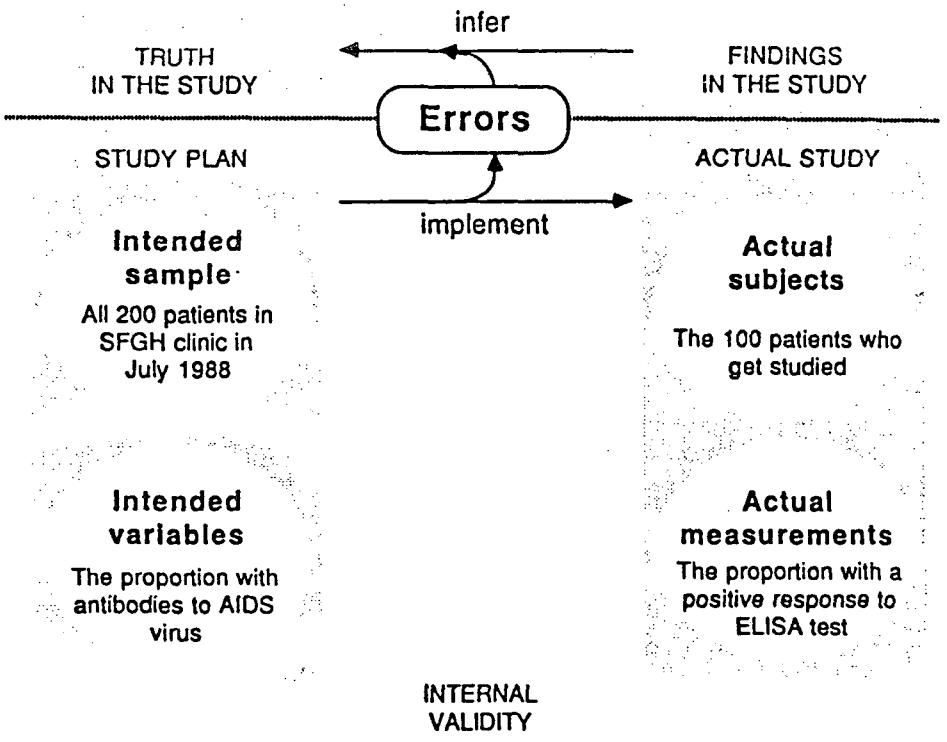

Figure 1.5. Implementation errors: if the actual subjects and measurements do not represent the intended sample and variables, the errors that result will threaten the validity of drawing inferences about what actually happened in the study.

example, the observed prevalence of positive ELISA tests might be 7.5% when the actual prevalence in all clinic patients is 15%. Figure 1.5 illustrates the important fact that errors caused by difficulties in implementing the study are the other common reasons (besides errors of design) for getting the wrong answer to the research question.

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 cleaning needles with bleach and the ELISA test result, does this represent a cause and effect relationship, or is there some other explanation? Reducing the likelihood of spurious associations and other rival explanations is one of the major challenges for the architect of an observational study (Chapter 10).

The 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 internal and external validity so that the inferences about what happened in the study sample can be usefully applied to the population. Erroneous inferences can be controlled either in the analysis phase of research or in the design and implementation phases (Fig. 1.6). This book deals mainly with design and implementation phase strategies: preventing errors from occurring in the first place, to the extent that it is practical and economic to do so.

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 antibodies to AIDS virus in the population is 30%, a well-designed sample of 100 patients from that population might contain exactly 30 patients with antibodies. More likely, however, the sample would contain some

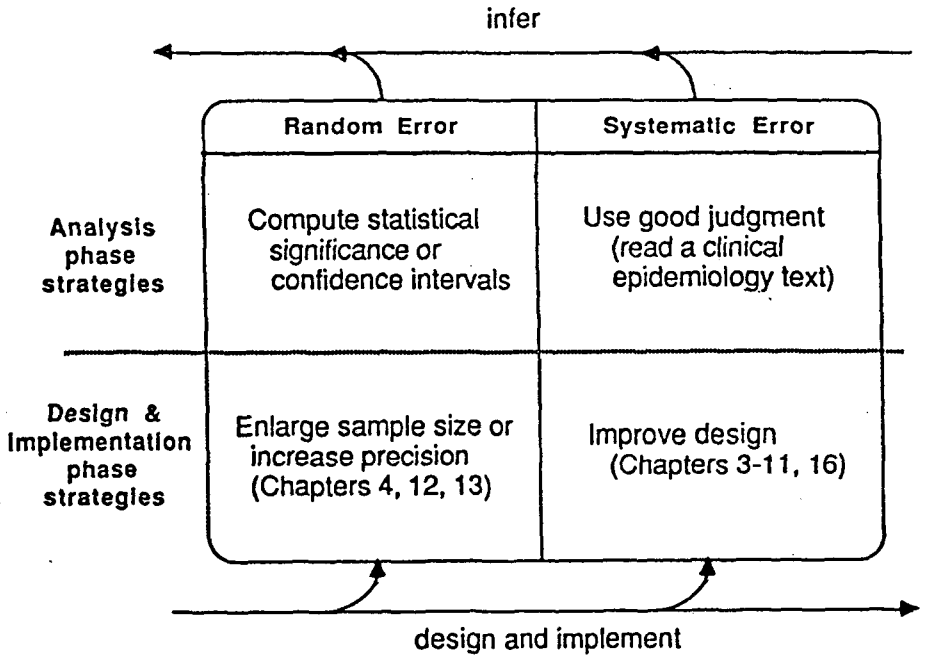

Figure 1.6. Research errors can have both random and systematic elements, as indicated in this blown up version of the error box in Figures 1.4 and 1.5; the box summarizes the strategies for minimizing the effects of these errors that are available in the design and analysis stages of research.

nearby number like 28, 29, 31, or 32. Occasionally chance would produce a substantially different number, like 19 or 42. Among several techniques for reducing the influence of random error (Chapter 12), 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 30% each time a sample is drawn.

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 in Figure 1.4 to use patients who come to the methadone clinic to represent all i.v. drug abusers. 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 i.v. drug abusers by advertising for volunteers through street sources, and to compare the observed prevalence in the two samples.

The examples of random and systematic error in the preceding two paragraphs are components of sampling error, threatening the inference from the study subjects to the population. Both random and systematic errors can also be components of measurement error, threatening the inference from the study measurements to the phenomena of interest. An example of random measurement error is the variation in the titer of AIDS virus antibody observed when a single specimen is tested repeatedly. An example of systematic measurement error is the fact that testing for antibodies will consistently underestimate the prevalence of AIDS virus infection because patients who have been infected for less than 3 months will not yet have antibodies.

The concepts presented in the last several pages are summarized in Figure 1.7. Here is an important bottom line: Getting the right answer to the research question is a matter of designing and implementing the study in a fashion that keeps the extent of the inferential errors at an acceptable level.

DESIGNING THE STUDY

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 four versions of the study plan

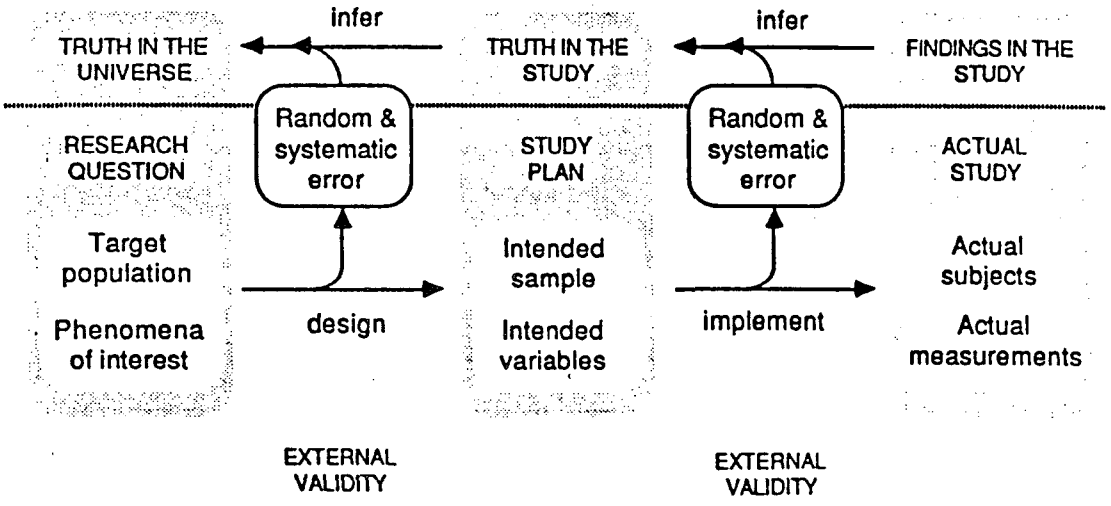

Figure 1.7. Summary of how research works.

that are produced in sequence, each larger and more detailed than the preceding one.

The first version is the study question, a one-sentence analogue of the research question that specifies what the study will actually answer if it is successful.

The second version is a 1-2 page outline of the elements of the study. We recommend the sequence in Table 1.1. It does what the review of systems does in a clinical examination—serves as a standardized checklist that reminds 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 third version is the study protocol, a fleshed in version of the 1-2 page outline that can range from 5 to several hundred 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 17.

The fourth version is the operations manual, a collection of specific procedural instructions, questionnaires, and other materials designed to assure a uniform and standardized approach to carrying out the study with good quality control (Chapters 4 and 16).

The study question and 1-2 page outline should be written out at an early stage. Putting thoughts down on paper leads the way from vague ideas to specific plans, and provides a concrete basis for getting advice from colleagues and consultants. It's a challenge to do it—ideas are easier to talk about than to write out—but the rewards are a faster start and a better project.

Appendix 1 illustrates the 1-2 page study plan using the AIDS example discussed in this chapter. As usual, this study plan deals more with the anatomy of research (Fig. 1.1) than with its physiology (Fig. 1.7), so the investigator must remind himself to worry about the internal and external validity that will result when it comes time to draw inferences about what happened in the study sample and formulate conclusions for the population. A study's virtues and problems can be revealed by explicitly considering how the question the study is likely to answer differs from the research question, given the plans for acquiring subjects and making measurements, and given the likely problems of implementation.

With the 1-2 page outline in hand and the internal and external validity inferences in mind, the investigator can proceed with fleshing out the details of his protocol. He will discover that this includes getting advice from colleagues, drafting specific recruitment and measurement methods, changing the study question and outline, pretesting specific recruitment and measurement methods, making more changes, getting more advice, and so forth. This iterative process is the nature of research design and the topic of the rest of this book.

Trade-offs

We have seen that errors are an inherent part of all studies, and that the main issue is whether the errors will be large enough to change the conclusions in important ways. The investigator, when designing a study, is in much the same position as a labor union official bargaining for a new contract. The union official begins with a wish list—shorter hours, more pay, parking spaces, and so forth. He must then make concessions, holding onto the things that are most important and relinquishing those that are not essential. At the end of the negotiations is a vital step: he must look at the best contract he was able to negotiate and decide if it has become so bad that it is no longer worth having.

The same sort of concessions must be made by an investigator when he transforms the research question to the study plan and considers the potential problems in implemention. On the one side is the issue of scientific validity, on the other, feasibility. The last step of the union negotiator is all too often omitted. Once the study plan has been formulated, the investigator must decide whether it adequately addresses the research question, and whether it can be implemented with acceptable levels of error. Often, the answer is "no," and the investigator must begin the process anew. But take heart!

Good scientists distinguish themselves not so much by their uniformly good research ideas as by their tenacity in turning over those that won't work at an early stage and trying again.

SUMMARY

1. The *anatomy of research* is the set of tangible elements that make up the study plan: the research question, design, study subjects, measurement approaches, and statistical plans. The challenge is to design a study plan with elements that are fast, inexpensive, and easy to implement.
2. The *physiology of research* is how the study works: the study findings are used to draw *inferences* about what actually happened in the study sample (*internal validity*), and about events in the world outside (*external validity*). The challenge here is to design and implement a study plan with adequate control over two major threats to these inferences: *random error (chance)* and *systematic error (bias)*.
3. A good way to develop the study plan is to write a *one-sentence* summary and to expand this into a *1-2 page outline* that sets out the study elements in a standardized sequence. Later on the study plan will be expanded into the *protocol* and the *operations manual*.
4. The next step is to consider the main inferences that will be drawn from the study subjects to the population, and from the study measurements to the phenomena of interest. At issue here are the relationships between the *research question* (what the investigator really wants to answer in the world outside), the *study plan* (what the study is designed to answer), and the *actual study* (what the study will actually answer, given the errors of implementation that can be anticipated).
5. Good judgment by the investigator and advice from colleagues are needed for the many *trade-offs* involved and for determining the overall viability of the project.

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CHAPTER 2

Conceiving the Research Question

Steven R. Cummings, Warren S. Browner, and Stephen B. Hulley

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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 his study subjects (Fig. 2.1). There is no shortage of questions in the universe. Even as we succeed in producing good answers to some questions, we remain surrounded by others. Recent clinical trials, for example, have established that β-blockers reduce mortality for at least the first 2 years after a myocardial infarction (1). But now there are new questions: Are some β-blockers more effective than others? Do all patients benefit (2)? How long should treatment be continued after the infarction?

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

ORIGINS OF A RESEARCH QUESTION

Build on experience

For an established investigator, the best research questions usually emerge from the findings and problems he has observed in his own prior studies and in those of other workers in the field. A new investigator has not yet developed this base of experience. Although a fresh perspective can sometimes be useful, allowing a creative person to conceive new approaches to old problems, lack of experience is largely an impediment.

A good way to start is to master the published literature in an area of study; *scholarship* is a necessary ingredient to good research. But no amount of reading can substitute for first hand experience in guiding the many judgments of clinical research. Therefore an essential strategy for a young investigator is to apprentice himself to an experienced senior scientist who has the time and interest to work with him regularly. A good relationship of this sort also provides the tangible resources a young investigator needs—office space, computer facilities, support for supplies and laboratory tests, etc. The *choice of a mentor* is the single most important decision a new investigator makes.

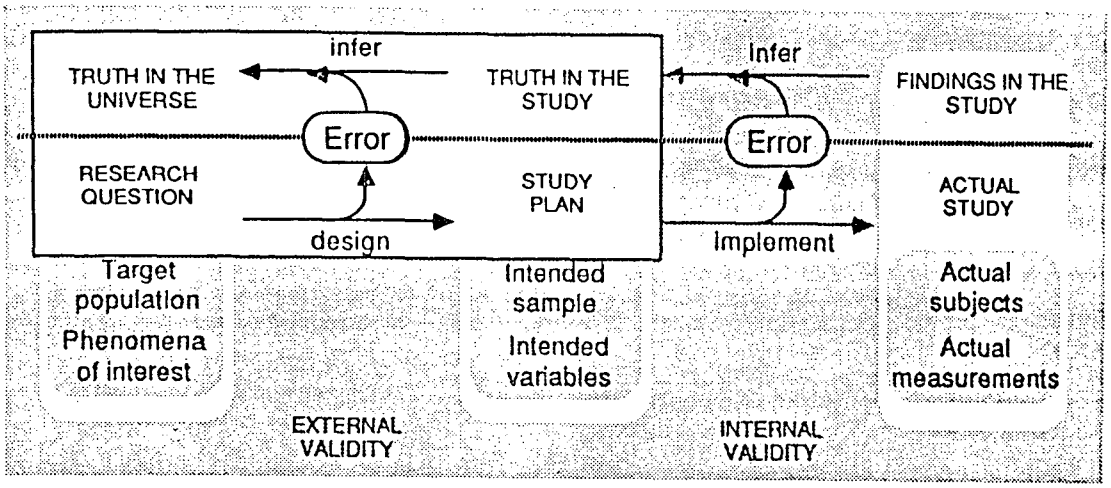

Figure 2.1. Choosing the research question and designing the study plan.

Be alert to new ideas

In addition to the medical literature and journal clubs as a source of ideas for research questions, all investigators find it very helpful to attend national meetings in which recent work is presented. The discussion of the work in the meeting can be supplemented by informal conversations with other scientists during the breaks. A new investigator who overcomes his shyness and engages a speaker over coffee will often find the experience richly rewarding.

A skeptical attitude about prevailing beliefs can stimulate good research questions. For example, surgery was formerly recommended for patients with asymptomatic gallstones because studies had claimed that up to 50% of such patients eventually developed symptoms or complications. However, one research group critically reviewed these studies and observed that some had included patients with symptomatic gallstones. Other studies had counted symptoms that were probably not due to gallstones. Using better criteria for gallstone-related symptoms in a well-defined cohort of patients with asymptomatic gallstones, the investigators found that only 15% of the patients suffered any biliary pain during 15 years of follow-up (3).

The application of new technologies often helps generate new research questions about familiar clinical problems. The development of assays that measure very small concentrations of cotinine (a metabolite of nicotine) in urine, for instance, has stimulated new questions and studies about the effects of second-hand exposure to cigarette smoke (see Appendix 2). Similarly, taking a concept or technique from one field and applying it to a problem in a different field can lead to new insights and advances. One recent study applied the concept of "social support," developed primarily in social science research, to the study of survival after myocardial infarction. It found that patients with less social support had a higher mortality rate during the three years following their infarctions (4).

Careful observation of patients has historically been one of the major sources of descriptive studies and is still a fruitful source of research questions. Teaching is also an excellent source of inspiration; ideas for studies often occur while preparing presentations or during discussions with inquisitive students. Because there is usually not enough time to develop these ideas on the spot, it is useful to keep them in a notebook for future reference.

Keep the imagination roaming

There is a major role for creativity in the process of conceiving the research question, imagining new answers to old questions and having fun with ideas. There is also a need for tenacity, for returning to a troublesome

problem repeatedly until there is a resolution that feels comfortable. Some creative ideas come to mind during informal conversations with colleagues over lunch, and others occur in brainstorming sessions. Many inpirations are solo affairs that strike while preparing a lecture, showering, or just sitting and thinking. The trick is to put an unresolved problem clearly in view and turn on the mental switch that lets the mind run freely toward it.

CHARACTERISTICS OF A GOOD RESEARCH QUESTION

The characteristics of a good research question, which have the mnemonic FINER, are summarized in Table 2.1.

Table 2.1.
Criteria for a good research question

Feasible
Adequate number of subjects
Adequate technical expertise
Affordable in time and money
Manageable in scope
Interesting to the investigator
Novel
Confirms or refutes previous findings
Extends previous findings
Provides new findings
Ethical
Relevant
To scientific knowledge
To clinical and health policy
To future research directions

Feasible

It is best to know the practical limits and problems of studying a question early on, before wasting much time and effort along unworkable lines.

The number of subjects: Many studies do not achieve their intended purposes be cause they are unable to enroll enough subjects. The first step is to make a preliminary estimate of the sample size requirements of the study (Chapter 13). The next step is to estimate the number of subjects likely to be available for the study, the number who would be excluded or refuse to participate, and the number who would be lost to follow-up. Even careful planning often produces estimates that are overly optimistic, and the investigator should be very certain that there are enough willing subjects. It is sometimes necessary to carry out a pilot survey to be sure. If the number of subjects appears insufficient, there are a number of strategies the investigator can consider. These include expanding the inclusion criteria, eliminating unnecessary exclusion criteria, lengthening the time-frame for enrolling subjects, acquiring additional sources of subjects, developing more precise measurement approaches (Chapter 4), and using a different study design.

Technical expertise: The investigators must have the skills, equipment and experience needed for recruiting the subjects, measuring the variables, and managing and analyzing the data. The easiest strategy is to use familiar and established approaches, because the process of developing new methods and skills is time consuming and uncertain. When it is necessary to develop an approach such as a new questionnaire for the study, expertise in how to accomplish the innovation should be available. Consultants can help to shore up technical aspects that are unfamiliar to the investigators, but for *major* areas of the study it is better to have an experienced colleague as a co-investigator. For example, it is often wise to include a statistician as a regular part-time member of the research team from the beginning of the planning process.

Cost in time and money: It is important to estimate the costs of each component of the project, bearing in mind that the time and money needed will generally exceed the amounts projected at the outset. If the costs are prohibitive, the only options are to consider a less expensive design or to develop additional sources of funding. If the study will be too expensive or time-consuming it is best to know this early, when the question can be modified or abandoned before a great deal of effort has been expended.

Scope: Problems often arise when an investigator attempts to accomplish too much, making many measurements on a

large group of subjects in an effort to answer too many research questions. The solution is to narrow the scope of the study and focus only on the most important goals. Many scientists find it difficult to give up the opportunity to answer interesting side questions, but the reward will be a better answer to the main question at hand.

Interesting

An investigator may have many motivations for pursuing a particular research question: because it will provide financial support, because it is a logical or important next step in building a career, or because getting at the truth of the matter seems interesting. We like this last reason; it is one that grows as it is exercised, and that provides the intensity of effort needed for overcoming the many hurdles and frustrations of the research process.

Novel

Good clinical research is novel; it contributes new information. A study that merely reiterates what is already established is not worth the effort and cost. On the other hand, a question need not be totally original in order to be worth studying. It may ask whether a previous observation can be replicated, whether the findings in one population also apply to a different group of subjects, or whether improved measurement techniques can clarify the relationship between known risk factors and a disease. A confirmatory study is particularly useful if it avoids the weaknesses of previous studies.

Ethical

A good research question must be ethical. If the study poses unacceptable physical risks or invasion of privacy (Chapter 14), the investigator must seek other ways to answer the research question. If there is uncertainty about whether the study is ethical, it may help to discuss it with the institutional review board that will ultimately review the study plans.

Relevant

Among the characteristics of a good research question, none is more important than its relevance. A good way to decide about relevance is to imagine the various outcomes that are likely to occur and consider how each possibility might advance scientific knowledge, influence clinical management and health policy, or guide further research.

DEVELOPING THE RESEARCH QUESTION AND STUDY PLAN

It is important to write down the research question and a 1-2 page outline of the study plan at an early stage. This requires some self-discipline, but it forces the investigator to clarify his own ideas about the plan and to discover specific problems that need attention. The 1-2 page outline also provides a basis for colleagues to react to with specific suggestions.

Problems and solutions

The potential problems in choosing the research question and developing the study plan are recapped, with their solutions, in Table 2.2. Two general kinds of solutions deserve special emphasis. The first is the importance of getting good advice. We recommend a research team that includes representatives of each of the major aspects of the study, and that includes at least one senior scientist. In addition, it is a good idea to consult with specialists who can guide the discovery of previous research on the topic and the choice and design of measurement techniques. Sometimes a local expert will do, but it is often useful to contact individuals in other institutions who have published pertinent work on the subject. A new investigator may be intimidated by the prospect of writing or calling someone he knows only as an author in the *New England Journal of Medicine*, but most scientists respond favorably to such requests for advice.

The second thing to emphasize is the way the study plan should gradually emerge from an iterative process of designing, reviewing, pretesting and revising (Chapter 16). Once the 1-2 page study plan is written, advice from colleagues will usually result in important changes. As the protocol gradually takes shape, a small pretest of

Table 2.2.
The research question and study plan:
Problems and solutions

Potential problem	Solutions
1. Vague or inappropriate	• Write the research question at an early stage • Get specific in the 1-2 page study plan about - how the subjects will be sampled - how the variables will be measured • Think about ways to make - the subjects more representative of the population - the measurements more representative of the phenomena of interest
2. Not feasible	
Too broad	• Specify a smaller set of variables • Narrow the question
Not enough subjects available	• Expand the inclusion criteria • Eliminate exclusion criteria • Add other sources of subjects • Lengthen the time frame for entry into study • Use more efficient variables or designs
Methods inadequate or beyond the skills of the investigator	• Consult experts and review the literature for alternative methods • Learn the skills • Collaborate with colleagues who have the skills
Too expensive	• Consider less costly study designs and measurement methods • Seek additional financial support
3. Not relevant or novel	• Modify the research question
4. Uncertain ethical suitability	• Consult with institutional review board • Modify the research question to avoid potentially unethical elements

the number and willingness of the potential subjects may lead to a new accessible population. The preferred blood test may turn out to be prohibitively costly, and a less expensive alternative must be sought. And so on. This iterative process, which requires tenacity and attention to detail, is illustrated in Appendix 2.

Primary and secondary questions

Many studies have more than one research question. Experiments often address the effect of the intervention on several outcomes (for example, the Multiple Risk Factor Intervention Trial [MRFIT] asked whether lowering risk factors would prevent heart attacks *and* whether it would lower total mortality (6)). It is also common to look separately at the results in various subgroups of study subjects (the MRFIT investigators decided in advance to look at the effects of treatment in the healthiest subgroup—those with normal electrocardiograms at the outset (6)). Many research projects also include ancillary studies (the MRFIT contained a study of the relationship between psychologic factors and heart disease (7)).

The advantage of designing a study with several research questions is the efficiency that can result, with several answers emerging from a single study. The disadvantages are the increased complexity of designing and implementing the study, and of drawing statistical inferences from a study with multiple hypotheses (see Chapter 12). A sensible strategy is to establish a single primary research question around which to focus the development of the study plan. This can be supple-

mented with secondary research questions that may also produce valuable conclusions.

SUMMARY

1. All studies should start with a *research question* that addresses what the investigator would like to know. The goal is to find an *important* one that can be transformed into a *feasible and valid study plan.*
2. Two important ingredients for developing a research question are *scholarship* and *experience*. The single most important decision for an investigator who is not yet experienced is his *choice of a senior scientist* to serve as his mentor.
3. Good research questions often *arise* from medical articles and conferences, from critical thinking about clinical practices and problems, from applying new concepts or methods to old issues, and from alert observations during patient care and teaching.
4. Before committing much time and effort to writing a proposal or carrying out a study, the investigator should consider whether the research question and study plan are "FINER": *feasible, interesting, novel, ethical* and *relevant.*
5. Early on, the research question should be developed into a written 1-2 page *study plan* that specifically describes how the subjects will be selected and the measurements made.
6. Developing the research question and study plan is an *iterative process* that includes consultations with advisors and friends, a growing familiarity with the literature, and pilot studies for testing the recruitment and measurement approaches. The qualities needed in the investigator are *judgment, tenacity* and *creativity.*
7. Most studies have more than one question, but it is useful to focus on a *single primary* question in designing and implementing the study.

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ADDITIONAL READINGS

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