The research question is the uncertainty about something in the population that the investigator wants to resolve by making measurements on her study subjects (Fig. 2.1). There is no shortage of good research questions, and even as we succeed in producing answers to some questions, we remain surrounded by others. Recent clinical trials, for example, have established that treatments that block the synthesis of estradiol (aromatase inhibitors) reduce the risk of breast cancer in women who have had early stage cancer (1). But now there are new questions: How long should treatment be continued, what is the best way to prevent the osteoporosis that is an adverse effect of these drugs, and does this treatment prevent breast cancer in patients with BRCA 1 and BRCA 2 mutations?

The challenge in searching for a research question is not a shortage of uncertainties; it is the difficulty of finding an important one that can be transformed into a feasible and valid study plan. This chapter presents strategies for accomplishing this in arenas that range from classical clinical research to the newly popular translational research.
Origins of a Research Question

For an established investigator the best research questions usually emerge from the findings and problems she has observed in her 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 by allowing a creative person to conceive new approaches to old problems, lack of experience is largely an impediment.

Mastering the Literature

It is important to master the published literature in an area of study; scholarship is a necessary ingredient to good research. A new investigator should conduct a thorough search of published literature in the area of study. Carrying out a systematic review is a great first step in developing and establishing expertise in a research area, and the underlying literature review can serve as background for grant proposals and research reports. Recent advances may be presented at research meetings or just be known to active investigators in a particular field long before they are published. Thus, mastery of a subject entails participating in meetings and building relationships with experts in the field.

Being Alert to New Ideas and Techniques

In addition to the medical literature as a source of ideas for research questions, all investigators find it helpful to attend conferences in which recent work is presented. As important as the presentations are the opportunities for informal conversations with other scientists during the breaks. A new investigator who overcomes her shyness and engages a speaker at the coffee break will often find the experience richly rewarding, and occasionally will find she has a new senior colleague. Even better, for a speaker known in advance to be especially relevant, it may be worthwhile to look up her recent publications and contact her in advance to arrange a meeting during the conference.

A skeptical attitude about prevailing beliefs can stimulate good research questions. For example, it has been widely believed that lacerations that extend through the dermis require sutures to assure rapid healing and a satisfactory cosmetic outcome. Alternative approaches that would not require local anesthetics and be faster, less expensive, and produce as good a cosmetic result were widely believed to be unachievable. However, Quinn et al. noted personal experience and case series evidence that wounds repair themselves regardless of whether wound edges are approximated. They carried out a randomized trial in which patients with hand lacerations less than 2 cm in length all received tap water irrigation and a 48-hour antibiotic dressing, but one group receive conventional sutures while the other did not. The group treated with sutures had a more painful and time-consuming treatment but subsequent blinded assessment revealed similar time to healing and cosmetic results (2).

The application of new technologies often generates new insights and questions about familiar clinical problems, which in turn can generate new paradigms (3).

Recent advances in imaging and in techniques for molecular and genetic analyses, for example, have spawned a large number of clinical research studies that have informed extraordinary advances in the use of these technologies in clinical medicine. Similarly, taking a new concept or finding from one field and applying it to a problem in a different field can lead to good research questions. Low bone density, for example, is widely recognized as a risk factor for fractures. Investigators applied this technology to other populations and found that women with low bone density have higher rates of cognitive decline (4), perhaps due to low levels of estrogen over a lifetime.

Keeping the Imagination Roaming

Careful observation of patients has led to many descriptive studies and is 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 computer file or notebook for future reference.

There is a major role for creativity in the process of conceiving research questions, imagining new methods to
address old questions and having fun with ideas. There is also a need for tenacity, for returning to a troublesome problem repeatedly until a resolution is reached that feels comfortable. Some creative ideas come to mind during informal conversations with colleagues over lunch; others occur in brainstorming sessions. Many inspirations are solo affairs that strike while preparing a lecture, showering, perusing the Internet, or just sitting and thinking. Fear of criticism or seeming unusual can prematurely quash new ideas. The trick is to put an unresolved problem clearly in view and allow the mind to run freely toward it.

Choosing a Mentor

Nothing substitutes for experience in guiding the many judgments involved in conceiving and fleshing in a research question. Therefore an essential strategy for a new investigator is to apprentice herself to an experienced mentor who has the time and interest to work with her regularly. A good mentor will be available for regular meetings and informal discussions, encourage creative ideas, provide wisdom that comes from experience, help ensure protected time for research, open doors to networking and funding opportunities, encourage the development of independent work, and put the new investigator's name first on grants and publications whenever appropriate. Sometimes it is desirable to have more than one mentor, representing different disciplines. Good relationships of this sort can also provide tangible resources that are needed—office space, access to clinical populations, datasets and specimen banks, specialized laboratories, financial resources, and a research team. Choosing a mentor can be a difficult process, and is perhaps the single most important decision a new investigator makes.

Characteristics of a Good Research Question

The characteristics of a good research question, assessed in the context of the intended study design, are that it be feasible, interesting, novel, ethical, and relevant (which form the mnemonic FINER; Table 2.1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasible</td>
<td>Adequate number of subjects, Adequate technical expertise, Affordable in time and money, Manageable in scope</td>
</tr>
<tr>
<td>Interesting</td>
<td>Getting the answer intrigues the investigator and her friends</td>
</tr>
<tr>
<td>Novel</td>
<td>Confirms, refutes or extends previous findings, Provides new findings</td>
</tr>
<tr>
<td>Ethical</td>
<td>Amenable to a study that institutional review board will approve</td>
</tr>
<tr>
<td>Relevant</td>
<td>To scientific knowledge, To clinical and health policy, To future research</td>
</tr>
</tbody>
</table>

Feasible

It is best to know the practical limits and problems of studying a question early on, before wasting much time and
Number of subjects. Many studies do not achieve their intended purposes because they cannot enroll enough subjects. A preliminary calculation of the sample size requirements of the study early on can be quite helpful (Chapter 6), together with an estimate of 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 assure that there are enough eligible willing subjects. It is sometimes necessary to carry out a pilot survey or chart review to be sure. If the number of subjects appears insufficient, the investigator can consider several strategies: 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, inviting colleagues to join in a multicenter study, and using a different study design.

Technical expertise. The investigators must have the skills, equipment, and experience needed for designing the study, recruiting the subjects, measuring the variables, and managing and analyzing the data. 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 steadily involved as a coinvestigator; for example, it is wise to include a statistician as a member of the research team from the beginning of the planning process. It is best to use familiar and established approaches, because the process of developing new methods and skills is time-consuming and uncertain. When a new approach is needed, such as a questionnaire, expertise in how to accomplish the innovation should be sought.

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 projected costs exceed the available funds, the only options are to consider a less expensive design or to develop additional sources of funding. Early recognition of a study that is too expensive or time-consuming can lead to modification or abandonment of the plan before expending a great deal of effort.

Scope. Problems often arise when an investigator attempts to accomplish too much, making many measurements at repeated contacts with 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 may 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 is 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. However, it is wise to confirm that you are not the only one who finds a question interesting. Speak with mentors and outside experts before devoting substantial energy to develop a research plan or grant proposal that peers and funding agencies may consider dull.

Novel

Good clinical research contributes new information. A study that merely reiterates what is already established is not worth the effort and cost. The novelty of a proposed study can be determined by thoroughly reviewing the literature, consulting with experts who are familiar with ongoing research, and searching lists of projects that have been funded using the NIH Computer Retrieval of Information on Scientific Projects (CRISP). Although novelty is an important criterion, a research question need not be totally original—it can be worthwhile to ask whether a previous observation can be replicated, whether the findings in one population also apply to others, 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 question. If there is uncertainty about whether the study is ethical, it is helpful to discuss it at an early stage with a representative of the institutional review board.

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 practice guidelines and health policy, or guide further research. When relevance is uncertain, it is useful to discuss the idea with mentors, clinicians or experts in the field.

Developing the Research Question and Study Plan

It helps a great deal to write down the research question and a brief (one-page) outline of the study plan at an early stage (Appendix 1.1). This requires some self-discipline, but it forces the investigator to clarify her ideas about the plan and to discover specific problems that need attention. The outline also provides a basis for specific suggestions from colleagues.

Problems and Solutions

Two general solutions to the problems involved in developing a research question 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 disciplines involved in 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 she knows only as an author in the Journal of the American Medical Association, but most scientists respond favorably to such requests for advice.

The second solution is to allow the study plan to gradually emerge from an iterative process of designing, reviewing, pretesting, and revising. Once the one-page study plan is specified, advice from colleagues will usually result in important changes. As the protocol gradually takes shape, a small pretest of the number and willingness of the potential subjects may lead to changes in the recruitment plan. The preferred imaging test may turn out to be prohibitively costly and a less expensive alternative sought. The qualities needed in the investigator for these planning stages of research are creativity, tenacity, and judgment.

Primary and Secondary Questions

Many studies have more than one research question. Experiments often address the effect of the intervention on more than one outcome; for example, the Women's Health Initiative was designed to determine whether reducing dietary fat intake would reduce the risk of breast cancer, but an important secondary hypothesis was to examine the effect on coronary events (5). Almost all cohort and case–control studies look at several risk factors for each outcome. 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 when there are multiple hypotheses (Chapter 5). A sensible strategy is to establish a single primary research question around which to focus the study plan and sample size estimate, adding secondary research
questions about other predictors or outcomes that may also produce valuable conclusions.

## Translational Research

Translational research refers to studies of how to translate findings from the ivory tower into the “real world.” Translational research (6) comes in two main flavors (Fig. 2.2):

- Applying basic science findings from laboratory research in clinical studies of patients (sometimes abbreviated as T1 research), and
- Applying the findings of these clinical studies to alter health practices in the community (sometimes abbreviated as T2 research).

Both forms of translational research require identifying a “translation” opportunity. Just as a literary translator first needs to find a novel or poem that merits translating, a translational research investigator must first identify a worthwhile scientific finding. Translational research projects are usually limited by the quality of the source material, so think “Tolstoy”: the more valuable the result of a laboratory experiment or a clinical trial, the more likely a translational project will have merit. Pay attention to colleagues when they talk about their latest findings, to presentations at national meetings about novel methods, and to speculation about mechanisms in published reports.

### Translating Research from the Laboratory to Clinical Practice (T1)

A host of new tools have become available for clinical investigations, including analysis of single nucleotide polymorphisms (SNPs), gene expression arrays, imaging and proteomics. From the viewpoint of a clinical investigator, there is nothing intrinsically different about any of these measurements or test results. The chapters on measurements will be useful in planning studies involving these types of measurements, as will the advice about study design, population samples, and sample size. Especially relevant will be the information about multiple hypothesis testing.

![Figure 2.2](image.png)

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

Compared with ordinary clinical research, being a successful T1 translational researcher requires having an additional skill set or identifying a collaborator with those skills. Bench-to-bedside research necessitates a thorough
understanding of the underlying basic science. Although many clinical researchers believe that they can master this knowledge—just like many laboratory-based researchers believe doing clinical research requires no special training—in reality, the skills hardly overlap. For example, suppose a basic scientist has identified a gene that affects circadian rhythm in mice. A clinical investigator has access to a cohort study with data on sleep cycles in people and a bank of stored DNA, and wants to study whether there is an association between polymorphisms in the human homolog of that gene and sleep in people. In order to propose a T1 study looking at that association she needs collaborators who are familiar with that gene and with the advantages and limitations of the various methods of genotyping.

Similarly, imagine that a laboratory-based investigator has discovered a unique pattern of gene expression in tissue biopsy samples from patients with breast cancer. She should not propose a study of its use as a diagnostic test for breast cancer without collaborating with someone who understands the importance of test-retest reliability, receiver operating curves, sampling and blinding, and the effects of prior probability of disease on the applicability of her discovery. Good translational research requires expertise in more than one area. Thus a research team interested in testing a new drug needs scientists familiar with molecular biology, pharmacokinetics, pharmacodynamics, Phase I clinical trials, and the practice of medicine.

Translating Research from Clinical Studies to Populations (T2)

Studies that attempt to apply findings from clinical trials to larger and more diverse populations often require expertise in identifying high-risk or underserved groups, understanding the difference between screening and diagnosis, and knowledge of how to implement changes in health care delivery systems. On a practical level, this kind of research usually needs access to large groups of patients (or clinicians), such as those enrolled in health plans. Support and advice from the department chair, the chief of the medical staff at an affiliated hospital, or the leader of the local medical society, may be helpful when planning these studies.

Some investigators take a short cut when doing this type of translational research, studying patients in their colleagues’ practices (e.g., a housestaff-run clinic in an academic medical center) rather than involving practitioners in the community. This is a bit like translating Aristophanes into modern Greek—it will still not be very useful for English-speaking readers. Chapter 18 emphasizes the importance of getting as far into the community as possible.

The sampling scheme is often a problem when studying whether research results can be applied in general populations. For example, in a study of whether a new office-based diet and exercise program will be effective in the community, it may not be possible to randomly assign individual patients. One solution would be to use physician practices as the unit of randomization; this will almost certainly require collaborating with an expert on cluster sampling and clustered analyses. Many T2 research projects use proxy “process” variables as their outcomes. For example, if clinical trials have established that a new treatment reduces mortality from sepsis, a translational research study might not need to have mortality as the outcome. Rather, it might examine different approaches to implementing the treatment protocol, and use the percentage of patients with sepsis who were placed on the protocol as the outcome of the study.

Summary

1. All studies should start with a research question that addresses what the investigator would like to know. The goal is to find one that can be developed into a good study plan.

2. One key ingredient for developing a research question is scholarship that is acquired by a thorough and continuing review of the work of others, both published and unpublished. Another key ingredient is experience, and the single most important decision a new investigator makes is her choice of one or two senior scientists to serve as her mentor(s).

3. Good research questions arise from medical articles and conferences, from critical thinking about clinical practices and problems, from applying new methods to old issues, and from ideas that emerge from teaching and daydreaming.
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 one-page written study plan that specifically describes how many subjects will be needed, and 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 of the recruitment and measurement approaches. The qualities needed in the investigator are creativity, tenacity, and judgment.

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.

8. Translational research is a type of clinical research that studies the application of basic science findings in clinical studies of patients (T1), and how to apply these findings to improve health practices in the community (T2); it requires collaborations from laboratory to population-based investigators, using the clinical research methods presented in this book.

References


