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Questions before Starting on the Details

The later chapters in this book discuss details. These details matter: we have spent most of our professional lives helping researchers improve details. These details determine whether a grant will be funded and increase the chance that an investigation, once begun, succeeds in obtaining the data needed with acceptable accuracy so that valid conclusions can be drawn from the research. There are, however, broad questions that you should consider *before* you worry about the details. These questions are so fundamental that they are rarely even recognized, let alone addressed. At times these questions may seem too personal, but they are intended to force you to think carefully about yourself, your motivations, ideas, and goals before you invest your time, energy, and effort in doing clinical research. It is important that you answer the first question (Why are you doing research?) for your own benefit, while you need answers to all the other questions to convince others that you can do the research you propose.

1.1 What Are the Broad Issues?

We have identified five questions you must consider before developing a detailed research plan. Although most questions focus on the specific project, the first question is broader:

Question 1. Why are you doing research?

You must understand why you are doing research to decide how important research is to you. Doing good research is very, very hard.

Doing good clinical research is even harder: you have to deal with human beings on top of everything else. To do research at all, you must invest your energy, effort, and time in the project. You should answer this question before doing your first project – and at least briefly consider it every time you are thinking about starting a new project. For each project requires you to invest part of your life in it – and that is a trade-off that you should consciously be making, not drifting into it because you "ought to do some research."

To this, we add four more questions, based on ideas in Cochran and Cox (1957), which are usually posed by funding agencies as part of a grant application. There questions are:

Question 2. What is your question?

Specifically, what do you hope to learn once the project is over? In grant language, these are the specific aims of the project and may include innovation aspects as well.

Question 3. Why does answering this question matter?

This is the justification for someone to pay you to answer your question (if resources are needed), and part of your rationale for investing your time, energy, and effort into the project. In grant language, this is the significance section, which needs to be buttressed by the background information, and again may include innovation as well.

Question 4. Why are you the person to answer this question?

This is a demonstration that you are capable of achieving your goal. In grant language, this is the investigator and the environment aspects of the grant.

Question 5. How will you know whether you have answered your question?

This provides an objective measure, when the project is over, to assess whether you have succeeded. Grants do not seem to consider this as part of the evaluation at all – but if you cannot succinctly state this, others will wonder whether your approach is actually complete.

1.2 Question 1: Why Do You Want to Do Research?

This question would seem to be none of our – or anyone else's – business. But it is a lot of other people's business, including your coworkers and especially your family. You are taking time away from all of them to indulge yourself in doing research. For research *is* an indulgence. You are planning to invest a considerable amount of your effort, energy, and time in doing research. Research takes time – far more than you would expect. Even experienced researchers find that research almost always takes more effort than they expected.

We have no desire to make you feel good or bad about your reasons, nor do we actually care why our collaborators are doing research. But it is only by knowing your reasons for doing research that you can decide how much of your energy, effort, and time you should invest in doing research. We emphasize that you are spending precious resources on research: your emotional energy, your physical energy, and your time. Your time has value both in terms of what you can achieve and how you focus your life. You have other responsibilities, a personal life and interests, perhaps students or a family. The time you spend on research is taken from these other areas. Generally, your responsibilities stay the same even when your research commitments increase. Thus, the cost to you of doing research is being paid, at least in part, by reducing the time available for your personal activities and your relationships. There may not be a dollar cost associated with this loss, but there is a cost, a cost that might not be apparent to you today but a real one nonetheless.

It may be that the real reason you are doing research is one or more of the following, which focus on specific projects:

- I want to do this research project studying this disease because I want to find a cure for a specific disease which has affected me personally in some way.
- I want to do this research project studying this disease because the disease fascinates me.
- I want to do this research project because I want to know the answer to this question.
- I want to do this research project because it would be a challenge to pull it off.

- I want to do this research project because it would be fun.
- I want to do this research project because if I am right, it would be exciting and maybe have an important impact.

Some of our favorite colleagues do research for these very reasons. We work in medical research because of some underlying altruism (we want to "help humankind" through better health), but on a day-to-day basis we work with medical researchers because it is (usually) a challenge, it is (sometimes) fun, and it is (often) neat. Unlike many physicians, however, neither of us feel "called" to study a specific disease, or do a specific research project, although we have both been "called" to be biostatisticians.

Sometimes, though, the reasons for doing research, while still very personal, are more generic or professional, such as:

- I would like to do a research project because I have never done research and would like to try something new.
- I would like to do a research project because I want to expand human knowledge.
- I would like to do a research project because I want to develop, maintain, or enhance my professional reputation.
- I would like to do a research project because I want to cut back on clinical hours or on administrative responsibilities.

Finally, you may need to do research for some external reason, such as:

- I need to do a research project as part of my fellowship program.
- I need to do a research project because my mentor wants me to.
- I need to do a research project because my advisor wants me to.
- I need to do a research project because I am at an academic institution and I am expected to do research.
- I need to do a research project because I need it for a promotion (or retention).
- I need to do a research project because I need to bring in salary support for my staff.
- I need to do a research project because I need to bring in salary support for myself.

Often there is a combination of the "want," "would like," and "need" issues. One common combination among our successful colleagues is:

"I want to study this disease because …" and "I need external support to keep all my staff."

1.3 Question 2: What Is Your Question?

It is only after you have some background in an area that you can hope to develop the goals for your study. The reality is that every study has several specific goals, some scientific and technical, and some personal to the investigators. Question 1 should have helped you identify the personal goals for this and all your studies. Question 2 should help you focus on the scientific and technical goals of your study.

A standard framework of science – taught in many elementary and secondary schools – is that science is hypothesis-driven, that is, observations leads to an idea (a hypothesis), and one then conducts experiments to test the hypothesis by collecting new data, which allow one to provide support for or evidence against the hypothesis. This fits the current notion of hypothesis-driven research as essential for funding. Although successful grant writers will honor the conventions and frame their grants as hypothesis-driven research, the reality appears to be that investigators start by asking interesting questions. What happens if …? Why does this …? Does this affect …? We believe that the scientific goal of a study is to answer one or more such questions. The hypothesis-driven approach formalizes this approach into a testable question and is discussed in Section 1.6.

Although no one can be certain of the outcome of research, and the most interesting and important results are frequently serendipitous, you should be able to be specific and unambiguous in terms of the major questions that the project is intended to answer. One of the most effective ways to do this is to draft an abstract for a paper addressing each of the major questions. Putting your ideas down on paper is the most effective way we know to help define the questions concretely, to ensure that you express what you hope to achieve. Investigators often have an idea of what they hope to find. By drafting the abstract you are communicating a clear idea of the aims of your study, even if you have question marks for all the numbers. The abstract helps you identify the primary endpoints for the study, which dictate the data you need to collect. This abstract is for personal use

when planning the study; it is not for publication. It provides you a framework for developing the study design and implementation.

Doing the study is a necessary step in answering your questions, but it is not the goal itself. The goal is not to do, for example "a randomized double blind clinical trial of two specified treatments to assess the effect of the treatments on a specific outcome," although many investigators initially describe their goal in these terms. The goal is to find the answer to a specific research question, in this case, probably, "Which treatment works better?"

You may not be able to formulate the research question immediately. It may be helpful to work with others while you develop clear and concrete goals. Others can help by providing you a sounding board, an opportunity for you to talk through your ideas, by pointing out to you when your ideas are fuzzy or vague. Sometimes, others can even help you figure out what you are attempting to do, providing an initial version of what your abstract might be. Eventually, however, you have to be able to identify your questions, otherwise you will never be able to design a study to answer them. If you undertake a study without a clear idea of what you are trying to achieve – and both of us have worked with investigators who have done this – you run a major risk of achieving nothing, of having nothing to show despite the effort you spent on the study. We do not want this to happen to you.

If you really do know the questions you are attempting to answer, you should have little difficulty in stating these questions clearly. Since you do not have to hone the language and fit within a 250 word limit, writing an abstract should not be very hard, if you know what you are trying to do. It should help you identify the reasons why a sponsor should fund the study (Section 1.4). In our experience, investigators who know what they want to do have little trouble actually writing such an abstract, while those most resistant to doing so often have no clear idea of what they are planning to do.

On occasion, investigators feel that this "prejudges" the study and prevents them from being "objective" when assessing the results from the study. Nonsense! The results you hope to find are the reason you undertake a study. The results from the study are what you report, whether they match your hopes or not.

1.4 Question 3: Why Does Answering This Question Matter?

This question is addressed in the Significance and Background sections of a grant application. We assume that you know enough about the research area to know that the question has not already been answered or, if there is a conventional answer, that you can put together a persuasive argument that the conventional answer might be wrong or inadequate. Here we focus on another aspect of whether the project is worthwhile: Who cares?

No matter what question you are trying to answer, we hope that you feel that the question is important. But if no one else would care what the result was, why are you spending your time and effort doing the study? Given all your investment in a research project, you must feel that the results will matter to others and possibly will matter a lot. If not, should you be doing the study?

The Significance section of the proposal hopefully convinces someone that such research should be funded. Although wanting to do it "because it will be fun" might be adequate for you, regrettably payers who fund studies, whether internal or external, rarely find fun fundable. Thus, you must tell why the question matters to other people. Without some type of support, it usually is impossible to complete any but the simplest studies. Except for a record review, some resources are likely to be needed for any study; even for a record review, there may be charges associated with record retrieval, data abstraction and management, analysis, and publication. You must know why your question matters if you hope to get support to answer it.

Although it may be difficult to accept, knowledge per se is not always valued. Possible ways to show the value of the knowledge include the magnitude of the problem being addressed (in human or financial terms, preferably both) or a display of how this new knowledge may lead (directly or indirectly) to new or improved therapies (more effective, less expensive, or more cost-effective approaches).

Personally, we have a lot of problems with such questions. We started writing this book because we thought that writing a book would be fun (naive, innocent biostatisticians that we were) and that it would be useful. We still hope it will be useful.

1.5 Question 4: Why Are You the Person to Answer the Question?

The fact that the question is important is not in itself sufficient. In addition to being important, is it reasonable to expect that the question can be answered? And is it reasonable to expect that *you* can answer the question?

You might have a fantastic idea that is clearly worthwhile. To answer the question, however, you might need a large number of participants, need a large number of expensive measurements, or need to follow participants for many years. Thus, the study cannot be done without substantial resources. Even if you have the financial resources, do you have the other resources needed for the study? Do you have access to the participants you need, in the quantity you need? Do you have access to the personnel you will need for the study team, the measuring instruments and assays you need, access to sufficient infrastructure for the study (such as a place to meet participants), and sufficient time to do the study? If you have all the necessary resources, is the study feasible? Even with an adequate number of potential participants, is it possible to recruit enough participants into the study? Recruiting and retaining participants becomes increasingly difficult as the length of the study increases and as it becomes more difficult for a participant to be involved in your study, whether because of the frequency of visits, invasiveness of procedures, duration of measurements, or challenges in following an assigned intervention. If the study will require many years to complete, are you willing to make that commitment? What impact will the inevitable personnel changes have? Will the funding agency be willing to wait so long for results? Sometimes the ideal study cannot realistically be done by you or anyone else.

You also need to consider whether you are the right person to do the study. Even small studies usually require a variety of skills and abilities. Do you have the skills necessary to complete the study single-handedly, or have you put together a team that could answer the question? Without such skills and knowledge, it is very unlikely that you can successfully complete a project; learning skills on the fly while doing research is hardly optimal, and at best might lead to having to redo much of your initial work. Possession of the necessary knowledge and skills – either by

you or by the study team – is thus a prerequisite to carrying out a project successfully, of achieving your goal and answering your question.

If you are seeking support for the research, moreover, you must have more than knowledge. You are asking someone to give you support, provide you with *their* resources. They usually will expect some evidence that you will use their resources appropriately, that by giving you resources the research will be successful. If you are requesting only a relatively small amount of resources, sponsors may settle for "potential" as adequate proof. For more substantial support, however, you will have to provide evidence that you can complete the project and achieve the goal. At the highest levels of support, you will have to show that you have previously carried out work of a similar complexity successfully and that you have the experience to perform the necessary procedures.

You must be able to answer this question – at least to yourself – before you start a study, and must present your answer persuasively in the grant application if you submit one.

1.6 Question 5: How Will You Know Whether You Have Answered Your Question?

At the end of the study, you will have some information. If the study were designed appropriately (which we hope this book will teach you), and your study worked out reasonably well, you should have enough information to answer your question. After the study is done, will the answer to your question be:

- clear-cut?
- precise?
- reliable?
- convincing?

It is in this context that we feel that the hypothesis-driven view of research makes sense. This view implies that there is an underlying hypothesis being tested, which then allows the machinery of statistics, particularly the formal framework of hypothesis testing, to quantify statistically how clear-cut your answer is. (Appendix A provides

an introduction to hypothesis testing.) Statistics also provides tools to quantify the precision of your answer. But statistical methods cannot assess how reliable your answer is – how free your answer is from bias and confounding – nor can statistical methods assess whether your answer is convincing or useful to others.

You may feel that you yourself can judge the validity and credibility of your study, so that you will be the ultimate arbiter of this question. Even if you could do this objectively (which we question), what possible use would the information be *unless* you disseminate it to your peers? We believe that information must be used, must be incorporated into the pool of knowledge, before it can be considered reliable and convincing. Thus, we do not believe that you can know whether your study is reliable and convincing unless you disseminate your results and see whether the study you have done and the answers you have obtained are accepted by your peers as convincing. By disseminating the results of your study you have a concrete result that you and others can use to assess whether or not you have answered the question. This might be a final report on a project to the sponsor, a presentation at a scientific meeting, or publication in a peer-reviewed journal. We use presentations and publications because they are the most common means of disseminating results we encounter, but in other environments your answer might help develop a patent application or marketable product, improve a process with specific measurable objectives such as reducing cost or downtime, or fill in specific gaps in knowledge required for one of these achievements.

1.7 Ethical Issues

You might think that there are no ethical issues involved in any of these questions, since these questions really do not involve any of the details of what you might propose. If you think this, you are wrong.

First, unless it is likely that you will be able to achieve your goal, you have no right to impose anything, no matter how trivial it may seem to you, on any participant. Second, if your goal does not matter, you have no right to impose anything, no matter how trivial it may seem to you,