

## RESEARCH: DOING IT AND WRITING THE PAPER

### ARAŞTIRMA: YAPMAK VE YAZMAK

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I have been doing medical research for about 45 years. During this time I have done much research myself and have mentored many young researchers. The following is a summary of what I have learned during this period.

#### Why Do Research?

The first question that one might ask is why would anyone ever do research. There are several possible reasons. One might want to get rich, but most researchers do not end up rich. One might want to get famous, but only a rare researcher gets famous. One might want to get a free trip. Certainly, if you perform research and your abstract is accepted for presentation, you might get a free trip to an interesting place. One might want to get a good professional position. Certainly a research background with publications can help one obtain a good professional position. One might want to answer a question about the diagnosis or treatment of a disease. This a rational reason to perform research. One might want to help patients. Again this is a rational reason to perform research. Lastly, one might want to discover something that is unknown.

#### What is necessary to perform research?

A genius level of IQ, a lot of money, an inquisitive mind, dedication, persistence, or organization. In my opinion, the most important element is persistence. I have worked with many individuals who start a project but never complete it. They may stop while they are writing the protocol, doing the research and most

commonly while writing the paper. To be a successful researcher one must be persistent. In my opinion, the second most important element is organization. By organization I mean arranging one's life so time is not wasted. Have things organized so you do not spend an hour looking for a paper. Do not waste time complaining about things. I keep a list of things that I need to do on my computer. When I have x number of minutes free, I look at the list and see what I can accomplish in that x number of minutes. I believe that dedication is the third most important element. If you are not dedicated to your research and watch football games or go to movies rather than work on your research, you are less likely to be successful. The fourth most important element is to have adequate money. If you do not have adequate money to perform your research, obviously it will fail. However, it should be noted that many of the research projects that I have completed did not require any money. The fifth most important element is to have an inquisitive mind. This element is important to aid the researcher in formulating the research and analyzing the data. Lastly, one need not have a genius level of IQ to perform research. It helps to be smarter than the average person, but a genius level of IQ is not necessary.

#### What are the different types of research?

Case reports are frequently the type of research that one starts with. However, it is difficult to get case reports published unless the case is distinctly unique. Medical journals do not like to publish case reports because case reports decrease their impact factor.

Reviews of the literature are worthwhile but again are hard to get published unless one is invited to write the review. Retrospective reviews of case series generally do not cost any money and are certainly useful. However, the downside of retrospective reviews of the cases is that frequently important data is missing. Prospective reviews of case series again do not cost any money and if they are organized, missing data should not be a problem. However, it may take time to accumulate the appropriate number of patients. Evaluation of new diagnostic tests is an important part of medical research. It is important to compare the new diagnostic test with the test that has previously been used as the gold standard. Evaluation of new therapies is one of the most commonly performed types of research. Ideally evaluation of new therapies should be done with randomized double-blind controlled studies. If the study is not blinded, the researcher probably believes in his new therapy and is biased in evaluating results. Evaluation of new medical devices is important in advancing medical science. Again it is best to do randomized controlled studies but frequently with medical device studies it is difficult to design the study so it is blind. Lastly, a large percentage of medical research has to do with basic science. I did no basic science or animal studies until 1988. When I started doing animal studies I found that animals were much easier than patients to recruit. Subsequently I found that cells were easier to recruit. However, basic science research requires more resources than do many types of human research.

### **How do you get started to do research?**

The first thing you need to do is to develop an idea including a hypothesis. How do you develop the idea? It can be a question raised when taking care of a patient. It can be a question raised by an associate, an attending or a subordinate. It can be a question raised while attending a lecture or while reading the medical literature. It can also be a question raised while dreaming or even while drinking.

Once you have the question posed, it is important to review the literature. Medline is a good place to start. On Medline you should narrow your search as far as is practical. One should obtain a copy or download to your computer all pertinent reference papers. Do not rely on review papers. Do not use Wikipedia.

It is important to organize the pertinent references. I recommend transferring all abstracts to your computer. Keep them organized by putting them in alphabetical order by the first author's last name. Make

notes on the abstracts as pertinent. Make an outline of what you have found in your review.

Once you have your idea formulated and have the literature reviewed, then discuss the proposal with your associates. In addition, you should evaluate the resources necessary to complete your project? How many patients do you need to answer your question? How much money will it take to conduct the study? Take into account money for personnel, Elisa kits, animals, pharmaceuticals, pipettes, etc. What personnel is needed for the study? What space including office space and laboratory space is necessary for the study? How long will it take to complete the project? In general it is a good idea to multiply your estimate by at least a factor of two.

### **Is the research ethical?**

For human subjects, the question I ask myself is as follows: Would I volunteer for this project if I qualified to participate. If you answer no to this question, the research should not be performed.

### **Writing the Protocol**

Before the research can be conducted, a research protocol needs to be written. You should start with the specific objectives and hypothesis. Then set the stage for your protocol by writing the background information which is essentially a review of the literature in the context of your research. Then describe the actual research protocol. Make this very detailed. Do not leave anything open to question. Include the statistical method of analysis and perform a power analysis. Include references in the protocol.

### **Necessary Approvals Before Research Can Begin**

If the project involves humans, approval must be obtained for the Institutional Review Board (IRB) before the study can be started. If blood or tissue is obtained for present or future studies, a written informed consent is required. IRB approval is necessary even if you are doing a chart review but this does not require a written informed consent. Most journals will not accept a paper for publication if the project has not been approved by an IRB. If animals are being studied, the animal studies committee must approve the project. If radioisotopes are used in the study, the radioisotope committee must approve the project. If biohazards are being used, e.g. Staph. aureus or asbestos, the biohazard committee must approve the project. If you are studying a new drug or an old drug for

a new indication, you may have to submit your proposal to the National Health Service (NIH in the United States).

### Eliciting Cooperation of Collaborators

In order to elicit the cooperation of collaborators, one needs to create a WIN WIN situation. By this I mean you need to create a situation in which you win (your project gets done) but the collaborator also needs to benefit. The main difficulty is creating the win for the collaborator. This can be in the form of a co-authorship on the manuscript, saving the collaborator work, a dinner, a book or money. It is best to avoid the following: direct payment for patient referred is unethical, avoid competition for patients that the collaborator wants to study, do not make extra work for the collaborator where he gets nothing in return.

### Performing the Research

Before you actually start the research, have everything organized. Effort is wasted if everything is not done on the first patients. It is best to develop forms for all the data which will be collected. The forms should be such that the data is easily transcribed to a computer. The responsibilities of all co-investigators and collaborators should be well defined. Once the research is started, one should be patient, persistent, and compulsive. If the research is going poorly and the chances for success appear minimal, the research should be stopped.

**Reasons for Failure of Research Projects:** The most common causes for failure of a research project are a lack of persistence or a lack of organization. Other reasons for failure include the following: Inadequate literature review - after the research has been started it becomes apparent that the study has already been done or that the hypothesis is completely different from what is accepted in the medical literature. It is also possible that someone completes an identical project before your project is completed, but this is uncommon. Inadequate numbers of patients can lead to failure or a project as can lack of the required cooperation. In some instances, there is not enough time to complete the project. This is particularly likely to happen when residents, fellows or visiting researchers are primarily responsible for the project. And lastly, and very importantly, the research is done but the paper never gets written. This has happened to me numerous times in my career.

**Analyzing the Data:** Once the research project is finished, it is time to analyze the data. Many individuals are frightened by statistics. However, data analysis is easy if data is organized. The actual statistical analysis will depend upon the design of the project. In general one desires to discover whether the results in two groups differ significantly. Basic terms in statistics are the mean (the average value), the median (the value with an equal number of observations above and below), and the variance which is a measure of the variability of the results in one group. Most studies involve comparing the mean levels in two or more different groups.

### Minimize the Variance

The formula for the variance is shown in the following equation:

$$\text{Variance} = \text{Sum } (x_i - x_{\text{mean}})^2 / (n-1)$$

Where  $x_i$  is the value of the  $i$ th observation,  $x_{\text{mean}}$  is the average of all observations and  $n$  is the total number of observations in the group. The standard deviation (SD) is the square root of the variance. The standard error of the mean (SEM) is the SD divided by the square root of  $n$ . In order for two means to be different with a probability ( $p$ ) value less than 0.05, the two means need to be separated by 2 SEMs. From the above discussion, it is apparent that if the variance is minimized, the two means are more likely to differ significantly. In performing research, it is important to do everything possible to minimize the variance. This means paying careful attention to details to decrease the randomness in the results.

### Writing the Manuscript

The main sections of the manuscript are the abstract (summary), the introduction (why?), the materials and methods (how?), the results (what you found), and the discussion (so what). When I write a manuscript, I write the sections in the following order. First I write the material and methods section. This section is the easiest to write - just cut and paste from the protocol (remember to change tenses from future to past). I then write the results with the liberal use of tables and graphs. I then write the introduction again relying heavily on the protocol. I do not write the introduction initially because the results of the study may alter the introduction somewhat. I then write the discussion. Lastly I write the abstract. I write the abstract last so that it will be consistent with the remainder of the paper.

## Writing the Discussion

Without a doubt this is the most difficult part of the paper to write. Before I start writing the discussion, I always make an outline of what I want to include in the discussion. In the outline, the first paragraph is a brief summary of the results of the study and the last paragraph is the conclusion of the study. Then other paragraphs in the discussion should compare the results of the present study with those reported previously, the clinical implications of the study, and the limitations of the study.

## Tips on Writing

Write in a simple manner. Keep sentences short. The first sentence in each paragraph should say what that paragraph is going to say. This makes it easy for the reader to speed read the paper. If the reader agrees with and knows about what is said in the first sentence, he/she can skip the rest of the paragraph. If you have difficulty writing one paragraph, go to a different paragraph. Writing the manuscript is a big task. Count your successes as paragraphs, not entire papers. If you write one paragraph per day, you will have at least 12 manuscripts per year.

## Submitting the Paper

Before you submit the manuscript, have someone whose first language is English and who is knowledgeable about medicine review the manuscript and edit it. Next you need to choose the journal for submission of your paper. One should look at previous editions of the journal to see if they have accepted similar papers on similar subjects. It is best to select a journal with a high impact factor. After the journal is selected, read the instructions to the authors carefully and follow these instructions. If the journal states the upper limit is 2500 words, do not submit a paper with 3500 words. If they say that they do not accept animal experiments and your research involves animals, do not submit to that journal. If you do not follow the directions, the reviewers will think that you are not a careful researcher.

## When Paper is Accepted Provided Revisions Are Done

The goal of revising the paper is to get it accepted for publication. A rebuttal letter should be written where the critiques of each of the reviewers is addressed. List each criticism by a reviewer and then formulate a response. It is best to use different fonts when listing criticisms and making responses. When the reviewer requests an explanation of something, he wants it explained in the manuscript - not in the rebuttal letter. Make simple requested changes without argument. Remember the reviewer is trying to make the paper better. Thank the reviewers for their constructive criticisms whether or not you like them.

## When the Paper Is Rejected

If the paper is rejected, do not give up but rather plan on resubmitting. Remember that submitting a paper is a little like playing the lottery - sometimes you get favorable reviewers and sometimes you get unfavorable reviewers. Remember that reviewers frequently do not agree - maybe you were just unlucky or alternatively maybe the paper is really bad. There are many medical journals and some have higher standards than others. Before you submit to another journal, look carefully at the criticisms of the reviewers and answer as many as possible. You may get the same reviewer upon resubmission and nothing irritates a reviewer more than seeing the same paper again without any changes.

## Conclusions

Persistence and organization are the most important factors for success. Before the research is started, review the literature and write a detailed protocol before you start the research. Create win win situations to elicit cooperation of collaborators. Write the paper one paragraph at a time. Respond to reviewers and change paper as suggested.