

OPT 6111

Research Methodology

Basic Principles of Medical Research

This lecture mostly taken from the following reference:
Designing Clinical Research (2nd Edition)
By Hulley, Cummings, Browner, Grady, Hearst and Newman
2001; Lippincott Williams & Wilkins

I. DEVELOPING THE RESEARCH PROTOCOL

An important word you will probably hear in formal research is “the protocol.” This is a document that describes your research plan in detail.

The Apple computer dictionary gives 3 definitions for protocol. The one that applies to us is: “A formal or official record of scientific experimental observations: A procedure for carrying out a scientific experiment ...”

Table 1 summarizes the main elements that should be included in the protocol.

Table 1. Main parts of a research protocol.

Element	Purpose
Research question	What questions will the study address?
Significance (background)	Why are these questions important?
Design	How you organize and carry out the study?
Hypothesis	
Time frame	
Methods	
Subjects	Who are the subjects and how will you selected them?
Variables	What will you measure and what will your data look like?
Predictor variables	
Confounding variables	
Outcome variables	
Statistical analysis	What will you do with the data?
Sample size calculation	
Data analysis method	

You will be working on your research protocol this semester and next. It is very beneficial to write out a formal research protocol because it will help organize your research in a logical, focused and efficient way.¹ That is, it helps you think out and prepare for you project. Let’s look at parts of a protocol in more detail.

A. The research question

Your first important task is to decide on the topic of your research, and eventually focus on a specific research question. That will be the objective of your study. At first your ideas will be broad and general. As you study more about the topic you’ll focus your research question. The textbook uses the example of medical research about estrogen. It lists three specific example questions:

- *How commonly do women take estrogen after menopause?*
- *Does taking estrogen after menopause lower the likelihood of developing coronary heart disease (CHD)?*
- *Are there other benefits and harms of estrogen treatment?*

As an exercise, you should brainstorm some example research questions in your area of interest.

Deciding on the research question

Perhaps you've been wondering how to decide on a research question. Here's one approach:

- First choose a general area of interest; for example, your favorite area in optometry, such as contact lenses.
- Within that field, try to get some ideas of general topics that are "hot" for research in that field. For example, within contact lenses, dry eye, silicone hydrogels, or acanthamoeba.
- Then begin reading about that topic to develop a good understanding of the background science and recent research in that field.

Textbooks and course notes

A good place to start is with your textbooks or lecture notes relevant to that topic. You can also talk to the faculty member who teaches that course. **A solid knowledge of the underlying principles is very important**, but keep in mind that scientific knowledge published in a textbook usually lags 5-10+ years behind current research.

Journals

In order to be reasonably up to date, you must also review the current scientific literature, that is, review journal articles. From this you will learn things such as:

- What do we already know about this topic?
- What are the **hot topics** in that field?
- What are the **methods** that may be used to study this?
- They may give you new ideas for a research project.

How do you find relevant articles? You can begin by scanning relevant journals. For example, if you're interested in contact lenses, you should peruse copies of the CLAO journal (Contact Lens Association of Ophthalmologist; *Eye & Contact Lens*). The journal of the American Academy of Optometry, **Optometry and Vision Science (OVS)** is also a good source. Every research project should include a search of OVS. Essentially all the major eye research journals are available through the NSU John Vaughn Library.

Q. What other eye related journals can you think of?

Q. What's the difference between a peer-reviewed journal and non peer-reviewed journal?

Q. Can you think of examples of each?

Sandra Martin, the Optometry librarian, has compiled a list of eye research journal available through our library. Find and view the list.

As you read articles you should review the references at the end of the article to find other articles to read. After reading several articles, you'll probably begin to notice that there are a few particular papers that are almost always mentioned. They are the "classic" papers in that field. You should identify them, and definitely read those. Failure to find and read the classic papers is an indication of inadequate background research.

In a subsequent lecture, Sandra Martin will teach two sessions on how to use the reference tools available online through our library.

Other sources of ideas

a. Experts

Scientists regularly attend scientific meetings where they hear presentations of the latest research before it's been published. They also swap ideas during their conversations. It doesn't take long before you will get to know many of the world's leading scientists who are working in your area. Once you get to know them, you can swap ideas at meetings or over the internet.

Most students don't attend scientific meetings, although I encourage you, if possible, to attend the annual meeting of the American Academy of Optometry. If you can't attend a meeting, how can you find an expert to talk to? In your case, one expert will be a faculty member who has expertise in that field.

You can also talk to fourth year students who did similar research in their project last year.

As you read papers, you may learn of an expert who has written important articles. If input would be helpful, you can email him or her for advice or suggestions. Many of the scientists whose articles you read are nice people who would be happy to help. Of course, you should be sure you've "done your homework" before you contact the scientist.

b. Observation

You may come up with new ideas, or notice a particular clinical problem that leads to a research project. Sometimes an idea may pop into your mind when you don't have time to pursue it. If possible, you should jot down the idea before you forget it.

c. New technologies

New technologies are rapidly being introduced into medicine and sometimes technologies from another field can be applied to medical problems in a novel

way. For example, one project two years ago studied the use of podcasts to teach neurophysiology.

Characteristics of a good research question

The book mentions 5 important characteristics of a good research question. It should be

- Feasible
- Interesting
- Novel
- Ethical
- Relevant

1. Feasible

Will it be feasible to complete the project in terms of

- Scope,
- Time,
- Expense,
- Number of subjects,
- Technical expertise,
- Equipment?

2. Interesting

The project should definitely be something you can “get into.” Your interest in the topic “provides the intensity of effort needed for overcoming the many hurdles and frustrations of the research process.”²

3. Novel

Your research should be something that no one has ever done before. It is OK to do a study similar to what has been done before, but there should be something unique and different about your research question. “A study that merely reiterates what is already established is not worth the effort and cost.”³

4. Ethical

Any research should not place the subject at undue risk or violate his or her privacy. Dr. Alexandria Miller, former chairman of the NSU Institutional Review Board (IRB), will speak about this in a subsequent lecture.

5. Relevant

You should think ahead and ask yourself, “If I am able to complete this study and get a definitive answer to my research question, so what?” You should also consider all other possible outcomes of your project and see if it will

- Advance scientific knowledge
- Influence clinical management
- Affect health policy
- Lead to future research

Table 2.2 in the book list problems with a poorly designed research question and suggested solutions.

Significance or background

The next major part of the research protocol document is a section that states the significance or background for your proposed study. It should answer the following questions.

- What is known about this topic? It should summarize previous research.
- What are the important unanswered questions in this field of research?
- Why is the research question important?
- What will we learn from this study, or what important answers will this study provide for current problems?

Design

There are two broad approaches to clinical research.

1. Passively observe some phenomenon or condition, and then report what you see. This is an **observational study**.
2. Actively manipulate some variable, or apply some treatment and study its effects. This is a **clinical trial or experimental study**.

Observational studies can be divided into 3 subtypes.

- **Cohort study**. A group of subjects (the **cohort**) is followed over time. “For example, an investigator examines a cohort of women yearly for several years, observing the incidence of heart attacks in hormone users and non-users.”⁴
- **Cross-sectional study**. The group or groups of subjects are observed on just one occasion. This gives a “snap-shot” of a particular condition. For example, the investigator “examines the group of women once, observing the prevalence of a history of heart attacks in hormone users and nonusers.”⁴
- **Case-control study**. The investigator compares two group of subjects, for example, subjects with heart attacks (the **cases**) and compares them with a group of healthy women (the **controls**), asking about hormone use.”⁴

When observing a group of subjects, you can do so in a **retrospective** manner (survey past history or diagnoses) or in a **prospective** manner, in which you follow them over time.

In a clinical trial (or experimental study), the best method is to randomly select two groups that are very similar (age matched, etc.) and provide the medical treatment to members of one group, and a placebo to the other in a random masked (or blinded) manner. This is called a **randomized masked trial**. Masking (or blinding) means that the subject does not know if he’s receiving the treatment or the placebo. In a **double masked** or **double blind** study, the

investigator who collects the data also doesn't know whether the subject is receiving the treatment of the placebo.

Subjects

You should consider the following questions about your subject.

Decide what kind of subjects you will need and the inclusion and exclusion criteria.

How many subjects will you need? You may need to do a sample size calculation. You should assume that some subjects will not complete the study.

How will you recruit the subjects?

Variables

What will you be measuring? Perhaps more than one thing. Try to keep it narrowly focused. If appropriate in your research project, you should develop a hypothesis, which you will test. An example is given in the book:

*Hypothesis: Women who receive estrogen treatment after menopause will have fewer heart attacks than those who do not.*⁵

A hypothesis will help you better understand exactly what variables you will need to measure and know what your raw data will look like.

In a simple observational study, you will study just one variable. Most observational studies are more complex, and may study numerous variables, including **predictor variables** and **outcome variables**. For example, predictor variables such as age, medication dosage, amount of exercise, and outcome variables such as IOP, or optic nerve head blood flow. You may be trying to find an association between variables to draw inferences about a possible cause and effect.

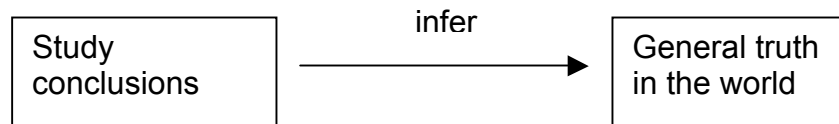
In a **clinical trial/experimental study**, you will be studying an intervention, such as the use of a certain medication or treatment versus a placebo. Then you will observe the effect on the outcome variables.

Statistical issues

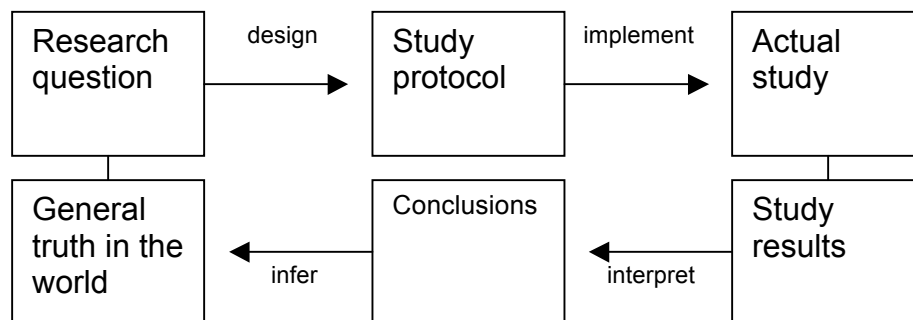
In your protocol, you should think through and plan exactly how you will process and analyze your data. Depending on the nature of your question and nature of the data, a particular kind of statistical analysis may be indicated. Later this semester we will have two lectures that summarize statistics, including a discussion of both **descriptive** and **inferential** statistics.

II. OVERVIEW OF THE RESEARCH PROCESS

The ultimate purpose of research is to learn about how something works in the world. That is, to infer some general clinical truth, based on the conclusions drawn from your study. This is illustrated by Figure 1, which was taken from the book.



The process can be shown in more detail by Figure 2, below.



At each stage in the process, it's possible to introduce errors that can lead, in the end to an erroneous conclusion or inference about the truth in the world. For example, you may have design flaws such as

- poor choice of variables
- inadequate sample size
- poorly chosen subjects
- poorly designed study

Additional errors can come in at the implementation level, in spite of a good research protocol. For example,

- Subjects don't show up
- Equipment fails
- Poor technique in collecting data
- Errors in data analysis

Similarly problems in the interpretation of results or inferences drawn from the study finding can lead to erroneous conclusions.

One of the best ways to avoid errors is to have a well thought out research question and well-prepared study protocol. However, even the best study will invariably encounter problems and errors. There are two general types of errors.

- **Random errors** are due to random circumstances that can occur at any stage of the study. They can influence the results in either direction. One way to minimize random error is to increase sample size. This increases the **precision** of the study.
- **Systematic errors** are errors that tend to bias the results in a particular direction. The solution is to improve the study design, in order to improve **accuracy**.

Q. What is the difference between precision and accuracy?

As a preliminary step to developing the research protocol, the book recommends developing a 1-2 page outline of the major elements of the study. An example is given in Appendix 1.1 of the book, which is reproduced below.

Table 2. Example of a study outline.

Element	Example
Project title	Effects of Hormone Treatment after Menopause on Lipoprotein (a)
Research question	What are the effects of treatment with estrogen plus progestin (compared with placebo) on Lp(a) levels in postmenopausal women?
Significance	<ol style="list-style-type: none"> 1. Epidemiologic studies suggest that hormone treatment after menopause may help prevent coronary heart disease, the largest cause of death in women. 2. Lp(a) is an understudied lipoprotein that has been found to be an independent risk factor for coronary disease in several studies. 3. Among conventional lipid-lowering drugs, only nicotinic acid in high doses lowers Lp(a) levels; however previous studies have suggested that hormone treatment may have this effect. 4. There is a need to confirm this finding for the estrogen plus progestin treatment that is now commonly used after menopause, and to extend it to women with existing coronary disease.
Design	<p>Randomized masked clinical trial with one year follow-up.</p> <p>Hypothesis. There will be a greater decrease in Lp(a) levels in the hormone-treated group than in the placebo group.</p>

Subjects

1. Entry criteria. Postmenopausal women with documented coronary disease (evidence of prior myocardial infarction or coronary surgery, or 50% obstruction on angiography).
2. Recruitment. Consecutive sample of all women who qualify in 20 clinical centers, recruited in cardiology clinics and by mailings and advertisements.

Variables

1. Predictor. Randomization to a daily tablet containing conjugated equine estrogen (0.65 mg) and medroxy-progesterone acetate (2.5 mg), or to a placebo identical in appearance.
2. Outcome. Change in serum levels of Lp(a) between baseline and 1 year, after randomization, measured immunochemically with a sandwich ELISA assay that uses a monoclonal antibody to apo(a) as the capture antibody (Strategic Diagnostics, Newark, DE)

Statistical issues

1. Sample size. The number of women in the existing HERS trial available for this ancillary study was 2,763. This allows detection of a reduction in Lp(a) at 2mg/dL with a power of 90% using a t-test and two-tailed alpha of 0.05.
2. Change in serum Lp(a) levels for two groups. Two-tailed t-test.

As an exercise, you should complete a similar outline for a hypothetical study about some optometry-related topic. Later in the semester you will prepare a similar outline for your specific projects.

Citations refer to the reference book.