



# Continuing Education



## Pharmaceutical research methodology

### Learning Objectives

**Describe** the steps in the scientific method.

**Identify** the components of a research protocol.

**Describe** the different types of experimental designs.

**Explain** how research results are interpreted.

**Identify** the standard sections of a research report.

This second article in a three-part series discusses methodology and design of pharmaceutical research. Topics include the scientific method, research protocols, experimental designs, interpreting results and the research report.

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**M**odern research follows a method of inquiry called the scientific method, which emphasizes observable, objective evidence and avoids drawing conclusions by common sense alone. The steps in the scientific method are problem definition, hypothesis formulation, hypothesis testing and development of theories.

**Problem definition.** Scientists begin by observing reality, asking questions about the relationships among conditions that cannot be answered with evidence already on hand. Modern scientists also collect evidence in the problem definition stage by reading about the issue in scientific literature.

**Hypothesis formulation.** Scientists use the available information and observations to predict relationships between factors. The patterns that appear to be true are the basis for a hypothesis. The hypothesis predicts what will be found through the experiment. Scientists usually write the hypothesis in two forms: the null hypothesis and the alternative hypothesis. The null hypothesis states that there is no difference between factors. The alternative hypothesis states that a true difference exists between factors that cannot be explained by

chance alone.

**Hypothesis testing.** Hypothesis testing involves the following concepts:

**Reliability and validity.** These are easy to confuse, but both are desirable. Reliability means that the same results will be found again if the study is repeated. Validity means that the measuring instrument accurately detects the characteristic of interest and that any differences found in the study are real differences in the characteristic the scientist intended to evaluate.

**Controlled experiments.** Controlled experiments usually involve two or more similar groups that are treated differently. The researcher forms the groups and administers the treatment in such a way that the effects of the treatment are distinguishable from the effects of other factors.

**Epidemiological studies.** These are studies of the occurrence of disease in a population and can also be used to test a hypothesis. For example, the Japanese have a low incidence of heart disease and also eat low-fat diets, while Americans have a high incidence of heart disease and eat high-fat diets. This relationship was revealed by measuring factors within the two populations and comparing them.

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*Interpretation of results.* Interpretation of results requires a statistical description and logical interpretations. The analyst must determine whether variables are related causally or are associated in some random or nonpredictive way. Causation requires an association of factors and an appropriate sequence – that is, the cause must precede the effect.

**Development of theories.** The final step in the scientific method is the development of theories, or the generalization of research results to explain other phenomena. Basic scientists are especially interested in bringing together many truths about how systems work. Applied scientists generalize when they find new applications for existing products or procedures.

## The research protocol

The research protocol documents the plans for a clinical trial or a long-term toxicity test. Well before a clinical trial begins, the research team plans the research, including the following components:

**Population of interest.** The group of people identified in the hypothesis is the population of interest. They all have a characteristic in common, such as a disorder, a genetic characteristic or a history of an experience.

**Sample selection.** If a population of interest is too large or too difficult to access to be included in a study in its entirety, a sample must be selected. The sample is a finite number of individuals who represent the entire population. One of the best methods for ensuring that the sample represents the population is random selection.

**Hypothesis.** The hypothesis should be written in both forms – “the treatment makes no difference” (the null hypothesis form) and “the treatment produces an effect” (the alternative hypothesis form). Writing the hypothesis seems like a formality, but it forces the researchers to commit themselves to the decision they will make using the research results.

**Experimental design.** The purpose of experimental design is to control the influence of extraneous variables. Variables are measurable characteristics of the sample. The treatment is a variable, and the effect or outcome of treatment is a variable. The researchers are mainly interested in the relationship between these two variables, but in order to evaluate cause and effect, they must control the effects of other variables. A common control method is the use of a control group, which is identical to the experimental group and is treated identically to the experimental group, except in the administration of the experimental treatment. When the results are analyzed, the researchers can tell how much of the outcome is due to the treatment variable.

**Measurement techniques.** The research protocol must describe how the variables will be measured, including measurement instruments, criteria and schedule. The measurements that are taken

## Components of a research protocol

Components	Contents
Population of interest	Common characteristics of the group of people identified in the hypothesis
Sample	Number of individuals to be selected to represent the population; selection technique, such as randomization; sample size
Hypothesis	Null hypothesis (“the treatment makes no difference”) and alternative hypothesis (“the treatment produces an effect”)
Experimental design	Strategy for isolating the effects of experimental treatment; methods for controlling effects of extraneous variables
Measurement techniques	Measurement instruments, criteria, schedule
Data analysis	Statistical tests; how sources of error will be controlled; level of confidence required

before treatment is administered are important in the measurement specifications.

**Data analysis.** The research protocol describes the statistical tests that will be used, how the sources of error will be controlled and the level of confidence the researchers require to make a decision about the hypothesis. The biostatistician plans and performs the data analysis.

## Experimental designs

Research studies can be characterized by their orientation (whether they look ahead or backward), as well as their design.

**Prospective studies.** These studies observe or measure variables over time into the future. Experimental treatments may or may not be administered in prospective studies. If an experimental treatment is administered and controls are employed, the study is a prospective controlled experiment.

**Retrospective studies.** These studies look backward in time. The researchers begin by finding a group of people who have the condition they are investigating. Then they look in the people’s past for the presence of other conditions. This type of study reveals factors that may be associated. A major limitation of retrospective studies is that new measurements cannot be taken. If a piece of data does not exist or is not in the form the researchers need, they have to use a substitute measure or get along without it.

**Cohort studies.** A cohort is a group of subjects who share a common characteristic. The study seeks to identify other variables associated with the characteristic. If the common characteristic is an outcome variable, the researchers will look backward to see what other variables may have been associated with that outcome. If the common characteristic is a treatment variable, the researchers will follow the subjects to see what the treatment’s future effects will be.

Commonly used experimental designs include:

**Single-group designs.** Single-group designs are not controlled experiments. The experimental treatment is given to one group of subjects, and there is no control group. This design is inexpensive and easy to manage but is rarely recommended because, without a control group, it does not manage the effects of extraneous variables. It is difficult to

tell whether the beneficial or adverse effects result from the treatment or from other causes.

**Parallel designs.** Parallel design is the classic or standard controlled experiment. Two or more homogeneous groups of subjects are studied concurrently. The groups are treated equally except for one variable: the experimental treatment. In these studies, the use of random selection to form treatment groups is important in preventing selection bias.

**Crossover designs.** Two or more groups of subjects are studied concurrently in a crossover design, but unlike the parallel design, in which the subjects get only one treatment, the groups' treatments are switched at a prescribed point during the study.

**Crossover-with-washout-period designs.** These designs solve – or improve – the problem of residual effects from one treatment contaminating the effects of the subsequent treatment. A period of no treatment separates the first and second treatments for each group.

## Interpreting results

Research results do not tell what is true; they tell what is probably true. Data analysis evaluates whether differences in outcomes occurred by chance or because of a nonchance influence. Research results are the basis for inferences, which are estimates about the population from which the sample was taken. There is always a chance that the inference is wrong and the sample misrepresented the population.

Statistics are measurements taken of the sample, and statistical tests are used to estimate the likelihood of the sample measurements reflecting the population. A statistically significant difference in a sample is one that is unlikely to have shown up just by chance. The same difference probably exists throughout the population.

Research always entails the risk of errors. Errors in decisions may be of two types: false-positive error (that is, a difference is found when, in reality, no difference exists) and false-negative error (when a difference is not found even though, in reality, one does exist). Research designers try to minimize these risks, but they cannot eliminate errors completely. Statistics are designed to keep the risk of error in perspective. If a study shows something to be true at a 0.01 level of significance, there is only a 1% chance of being wrong and a 99% chance of being right. Ninety-nine times out of 100, if the research is done well and the statistical estimates are followed, the decisions will be correct.

Notice that the terms “false negative” and “false positive” do not imply that a result is favorable or unfavorable. They simply refer to whether there is a difference (positive) or no difference (negative).

## The research report

The research report must set the scientific context for the study and assure the reader that the results

## Article Summary

- Modern research follows an established method of inquiry called the scientific method, which emphasizes observable, objective evidence and avoids drawing conclusions by common sense alone.
- The research protocol documents the plans for a clinical trial or a long-term toxicity test and includes standard components.
- Research studies may be characterized by their orientation (prospective or retrospective), as well as their design (single group, parallel, crossover, crossover with washout period).
- Data analysis evaluates whether differences in outcomes occurred by chance or because of a nonchance influence.
  - Research always entails the risk of errors.
- The research report, which is written in a standardized format, sets the scientific context for the study and assures the reader that the results can be taken seriously.

can be taken seriously. By following the standard format of scientific articles, the author helps the reader in both regards. Further, the report should be detailed enough so that other scientists would be able to repeat the study with the same accuracy. A standard research report contains the following sections:

**Abstract.** The abstract is a brief summary of all the information being presented in the report. It should tell the purpose of the study, the methods, the results and the implications.

**Introduction.** In the introduction, the author states the hypothesis clearly and simply and also restates it as a research question. The introduction describes the issues behind the study, including a justification of how the study helps illuminate these issues.

**Methods.** The procedures used to measure the effect of the experimental treatment are described here. This section includes information on the experimental design, the selection of subjects and their assignment to groups, the variables of interest and methods for controlling extraneous variables, and the measurement techniques.

**Analysis.** The analysis section covers the statistical techniques used to analyze the data. In some journals, methods and analysis are combined in one section.

**Results.** The results section is an objective summary of the data obtained in the study. Here, the author reports the facts without expressing any opinions. All findings must be reported, not just the ones that support the author's hunches. In most cases, the author reports summary statistics, such as the average and the range.

**Discussion/summary.** Here the author discusses the meaning of the research findings. The results of the study may be compared with similar or dissimilar results of other studies. The author will state a final conclusion, whether it is a positive statement about the effects of a treatment or a negative statement that no significantly different effects could be found. The conclusion may also point out areas where further study is needed.

**References.** This section lists the research used as background. Depending on the standards of the publication, the references are listed in alphabetical order or in the same order they were cited in the article.

The final article in this series will discuss research costs and constraints.