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Testing Ephedra: Using Epidemiologic Studies to Teach the Scientific Method

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Lesson Plan

TITLE: Testing Ephedra: Using Epidemiologic Studies to Teach the Scientific Method

SUBJECT AREA: Science, particularly biology, health education

OBJECTIVES:

- To familiarize students with some examples of epidemiologic studies, mainly the randomized controlled clinical trial and, to a lesser extent, the cohort study
- To use epidemiologic study to help students develop a strong understanding of the scientific method and how science experiments are conducted
- To help students understand why it is important to test the safety and effectiveness of over-the-counter and prescription drugs that are sold on the market
- To help students understand that the dietary supplements and herbal remedies on the market are not heavily regulated and required to be tested for safety and effectiveness

TIME FRAME: Two separate lessons are in this instructional unit. The first lesson will take two to three 40-minute periods to do. The second lesson should take one to two 40-minute periods. The lessons do not need to be taught together, although the two lessons complement each other very well.

PREREQUISITE KNOWLEDGE: A basic knowledge of the scientific method and experimentation helps, although the lesson could also be an exploratory one. The first lesson has a more advanced version for students who have a stronger background in scientific literacy.

MATERIALS NEEDED:

- Worksheets that are included in this unit
- Selected articles from different newspapers, which can be acquired from the Web; the URLs for these articles have been included in this unit.

PROCEDURE:

Students will be given copies of the worksheet that will correspond to the particular lesson. Students will work in groups to answer the questions. The discussion questions that follow the first lesson and the assessment assignment that follows the second lesson can be done either in class or as homework for teachers who do not enough class time to devote to these lessons.

ASSESSMENT:

- The first lesson will be followed by a series of discussion questions, after which both versions of the lesson/worksheet will be presented. As mentioned before, these questions can be answered either in class or for homework
- The second lesson has an assignment that asks students to decide whether they should carry out a clinical trial or cohort study, and then to justify their decision. Once they decide on their method, they must construct an outline of their anticipated study that will take into account all the protocols of carrying out an epidemiologic study.
- Additional extra credit assignments have also been included to give students the opportunity to apply what they have learned in these lessons. The first assignment discusses the procedure for receiving approval from the Food and Drug Administration (FDA) to manufacture a drug. The second assignment focuses on the controversial issue of dietary supplements and herbal remedies and why they are not regulated the same way that prescription drugs or even over-the-counter drugs are.

LINK TO STANDARDS:

Science Education Standards

- **IDENTIFY QUESTIONS AND CONCEPTS THAT GUIDE SCIENTIFIC INVESTIGATIONS**
 - Students should formulate a testable hypothesis and demonstrate the logical connections between the scientific concepts guiding a hypothesis and the design of an experiment.
- **DESIGN AND CONDUCT SCIENTIFIC INVESTIGATIONS:** Students must use evidence, apply logic, and construct an argument for their proposed explanations.
- **FORMULATE AND REVISE SCIENTIFIC EXPLANATIONS AND MODELS USING LOGIC AND EVIDENCE:** In the process of answering questions, students should engage in discussions and arguments that result in the revision of their explanations.
- **COMMUNICATE AND DEFEND A SCIENTIFIC ARGUMENT:** Students in school science programs should develop the abilities associated with accurate and effective communication. This includes:
- **PERSONAL AND COMMUNITY HEALTH:** Students should understand that:
 - Personal choice concerning fitness and health involves multiple factors. Personal goals, peer and social pressures, ethnic and religious beliefs, and understanding of biological consequences can all influence decisions about health practices.

- **SCIENCE AS A HUMAN ENDEAVOR**

- Scientists have ethical traditions. Scientists value peer review, truthful reporting about the methods and outcomes of investigations, and making public the results of work. Violations of such norms do occur, but scientists responsible for such violations are censured by their peers.
- Individuals and teams have contributed and will continue to contribute to the scientific enterprise. Doing science or engineering can be as simple as an individual conducting field studies or as complex as hundreds of people working on a major scientific question or technological problem. Pursuing science as a career or as a hobby can be both fascinating and intellectually rewarding.

A more detailed description of the science education standards can be found in the National Academy Press Web site, which is available at: <http://www.nap.edu/readingroom/books/nse/html/6e.html>

Health Education Standards

- Students will demonstrate the ability to access valid health information and health-promoting products and services: Identification of valid health information, products, and services including advertisements, health insurance and treatment options, and food labels.
- Students will analyze the influence of culture, media, technology, and other factors on health: Describing and analyzing how one's cultural background, messages from the media, technology, and one's friends influence health

Social Studies Standards

- Social studies programs should include experiences that provide for the study of relationships among science, technology, and society. Standard #8
- Social studies programs should include experiences that provide for the study of interactions among individuals, groups, and institutions. Standard #5
 - Institutions, such as churches, families, and government agencies, and the courts all play an integral role in our lives. These and other institutions exert enormous influence over us, yet institutions are no more than organizational embodiments to further the core social values of those who comprise them.

All information from the National Council for the Social Studies Web site, which is available at: <http://www.socialstudies.org/standards/2.0.html>

Introduction

Objective

The goal of this module is to familiarize students with the design of epidemiologic studies, particularly the randomized controlled clinical trial that is often used in experimental epidemiology.

Background

Given the new age of multimedia advertising, the public is inundated with advertisements for all types of products that make many different health claims, such as promising one to lose weight or improve memory. Many Americans are also turning to herbal remedies, which are often not regulated as well as over-the-counter or prescription drugs are by the Food and Drug Administration (FDA).

Many teenagers are also significant consumers of this market. They watch television, surf the Web, and read magazines, so they are constantly bombarded with ads for products that claim to make one thinner or stronger or have more endurance on the athletic field. As a biology teacher, I am constantly being asked by my students if these products they see on television work, and my response is "Think about what you have learned in biology and tell me whether it makes sense."

In these lessons students will have the opportunity to design their own experiment to test the effectiveness of popular nutritional supplements that are taken by many teenagers, such as ephedra, creatine, PowerBars, and androstenedione, or andro (which was made popular by baseball player Mark McGwire). Students will become familiar with the protocols that must be set up when designing a clinical trial, as well as a cohort study. They will learn about concepts such as hypothesis testing, experimental and controlled variables, independent and dependent variables, randomization of subjects into groups for comparison, placebo, dosage and measurement of outcomes. Other topics that could be explored include information and selection bias and confounding variables.

These lessons could be easily taught in a survey biology course in high school. This would be a very good way to help students grasp basic concepts of the scientific method. **These activities are designed so that teachers do not need to teach all the lessons. Instead, they may choose those they find most suitable for their classroom and curriculum.** However, each lesson is related to the next in the hope that students will see the big picture in the end.

The first lesson, for example, is an introductory lesson that will help students learn how a randomized controlled clinical trial is set up. Students are given a scenario in which they can design their own experiment. They will determine what the experimental variable is, learn why it is important for randomization into groups to take place, and be able to explain what the characteristics of the control and experimental group should be. A second lesson will then focus on the different approaches to testing for the health risks of using some of these supplements.

These lessons will focus on the herbal supplement ephedra, which is derived from the plant *Ephedra sinica*. Ephedra is the herbal form of the amphetamine-like stimulant ephedrine, which is sold as an over-the-counter bronchodilator for people with asthma. The herbal form of this substance is sold as a dietary supplement that promises its customers to help them burn fat, build muscle and increase their available energy. Often supplements that contain ephedra will also contain caffeine that is derived from guarana or green tea extract.

The FDA is having difficulty regulating the manufacturing and marketing of products that contain ephedra, as it does with many other nutritional supplements because they are sold as supplements and not as drugs. Ephedra-containing products were the first dietary supplement that was banned by the FDA. Even then, it took a vast amount of scientific data to prove that the product was unsafe to get it banned because of a loophole in the law that is given to dietary supplements. When the product was available for sale, there were questions of whether there was enough empirical data to support what the manufacturer claims for these products. (FDA Website, 2003) Although these products are banned, ephedra can still be used as subject to discuss how clinical trials are done, since it is a subject that may spark the interests of high school students. Also, banning a product does not mean it will disappear from use. The product may still be sold illegally.¹

The benefit of using experimental and observational epidemiologic studies to teach the scientific method to high school students is that the students do not need a strong background in science to learn how to design an experiment or a study. Designing a clinical trial or a cohort study often requires common sense and aptitude in critical reasoning, which are skills students need both in science and in life in general. Lessons such as this help students not only become more familiar with science but also become citizens who learn how to make wiser health decisions.

Organization

The lessons in this module are designed to be broken up into individual 40-minute lessons, although one can certainly elaborate on each of these lessons and stretch it into one 80-minute period or two 40-minute periods, depending on how one's class schedule works. The first lesson is the most fundamental one in this module. It introduces students to the foundations of experimental epidemiology.

We recommend that teachers first review the scientific method with students before they begin this lesson. However, the lesson could also be used as an activity to introduce students to the scientific method. There are two versions of the first lesson. The first version is designed for students who do not have a strong background in science. The lesson has been made into a worksheet, and the student is walked through it. The second version is designed for more advanced science students who have a fairly good understanding of the scientific method and who do not need as much hand holding.

A series of discussion questions is given to help students reflect on the activity they have just done. These questions emphasize the importance of following proper protocol when designing a clinical trial or any other experiment. They also focus on the importance of limiting and decreasing experimental errors, and include the concept of bias.

The second lesson centers on the potential health risks of taking ephedra. Teachers can add this lesson to build on the first one. This lesson focuses on the two types of epidemiologic study, experimental and observational. It compares the advantages and disadvantages of using either a randomized controlled clinical trial or a cohort study, which would be considered a type of observational epidemiologic study. It helps students learn why a clinical trial is considered more scientifically valid, and when it might be more acceptable to conduct a cohort study.

The last two assignments are enrichment lessons. Teachers who have a more rigid curriculum can assign these for extra credit. The first of these lessons focuses on the procedures a company must follow to seek approval to manufacture and market a drug. An assignment such as this helps students become familiar with how government agencies like the FDA protect consumers from products that are unsafe and ineffective in what they claim to do and how the system is not always perfect. The second assignment helps students learn why products like ephedra are not regulated under the same standards applied to many prescription and over-the-counter drugs. This lesson helps them realize how some manufacturers get away with making extravagant health claims and what we, as informed citizens, can do to make better health decisions.

Lesson Outcome

The scientific method is the most fundamental concept that students of all sciences should understand very well. Such understanding entails being familiar with the design of an experiment, which is why there are always questions about the scientific method and experimentation in many standardized tests. For example, the New York State Living Environment Regents exam always has a question that asks students to develop their own experiment for a particular scenario. The questions are written similarly to the way the questions in these lessons are given.

The College Board's SAT® II Subject Test™ in Biology E/M also stresses interpretation and application of data. Thirty-five percent of the exam tests how well students are able to interpret and

analyze data. Students are asked to “infer and deduce quantitative and qualitative data, integrate information, form conclusions, and recognize unstated assumptions.” Another 35% of the exam tests how well students can apply the knowledge they have learned in biology to different situations, particularly practical ones, and this often requires solving problems by “using mathematical relationships.”²

By working on these lessons, students will have the opportunity to become familiar with the proper procedures of scientifically testing the safety and effectiveness of a product while developing a better understanding of the scientific method. They will also begin to understand why a standardized system is needed to regulate the proper labeling and responsible marketing of medications, which include herbal supplements as well as over-the-counter and prescription medications.

References

1. FDA Web site. 2003. FDA announces plans to prohibit sales of dietary supplements containing ephedra. Available at: <http://www.fda.gov/oc/initiatives/ephedra/december2003>. Accessed May 11, 2004.
2. College Board. *College Board SAT II: Subject Test, Biology E/M Test Bulletin*. New York: College Entrance Examination Board and Educational Testing Service; 1998:2.

Teacher's Guide to Epidemiologic Studies and These Lessons

When epidemiologists suspect associations between two factors such as cholesterol and heart disease, epidemiologic studies are often done to confirm whether these associations are real. These types of studies can be classified as either experimental or observational. The key difference between these two types is that experimental epidemiologists can control the conditions in the study by assigning the participants to either the experimental or the comparison (also known as control) group and by determining the dosage given to members of the experimental group.¹ In observational studies the assigning of participants to either of the two groups is based on preexisting conditions and characteristics of the participants. For example, participants who smoked would be compared with participants who do not, in a study in which smoking is considered the risk factor. Another example would be participants who already have heart disease and are being compared with those who do not.

The randomized controlled trial, commonly known as a clinical trial, is a widely used type of experimental epidemiologic study. It can be used to test the safety and effectiveness of a drug or medical device or procedure, the efficacy of a vaccine, or the effectiveness of a health education/intervention program.¹ In these types of experiments participants are assigned randomly to either the experimental group or the comparison group. Members of the experimental group are sometimes referred to as the intervention or treatment group because they are given the newly developed method of intervention or treatment, whereas members of the comparison group are given either the traditional method of treatment or a placebo.

The lessons in this module will focus mostly on the proper procedures and protocols of a randomized controlled clinical trial. Students will become familiar with how this particular type of study is done, and they will learn why the clinical trial is considered the gold standard of epidemiologic studies. They will learn how the process of randomization limits the occurrence of potential sources of bias and confounding because the participants do not know whether they are in the experimental or comparison group, and there is no selection criterion, other than random assignment, to place members into either of the two groups. The protocols that students will learn about in experimental epidemiology can reinforce many of the basic principles and concepts of the scientific method.

The second lesson in this module will also cover the design of a cohort study, which would be an example of an observational epidemiologic study. Cohort studies are done to determine if there is an association between exposure to a particular factor and a particular health outcome. A risk factor could be a particular type of food or nutrient, a type of behavior or environmental exposure to a particular substance. An example of a cohort study is a study done by two British epidemiologists who first examined the association between smoking and lung cancer.² In this study doctors

who smoked were placed in the exposure group, and doctors who did not smoke were placed in the comparison group. The incidence rates of lung cancer were then recorded in both groups. Cohort studies can also be conducted to determine whether exposure to a particular factor may improve one's health and prevent one from getting a particular disease. Such factors are referred to as protective factors. Cohort studies were done to determine whether there was an association between increased fiber intake and a decreased risk of colon cancer. This question still has not been adequately answered.

The problem with cohort studies and other types of observational studies is that they are more susceptible to sources of bias. There is also a greater chance for confounders to exist in these studies because the researchers cannot control the conditions of the study, as they can in clinical trials. To begin with, participants already know whether they are in the exposure or comparison group, whereas those in a randomized controlled trial would not know whether they are receiving the placebo or the new method of intervention or treatment. Furthermore, there may be certain underlying qualities found within either the exposure or the comparison group that the researchers may not know of in a cohort study. The process of randomization in clinical trials limits this from occurring. These qualities or characteristics can be considered confounders because they may distort the results of the study. Simply, the data being collected may not always give an accurate picture of the actual situation.

To give an example, observational studies have been done to determine whether there is an association between drinking wine and decreased health problems, such as heart disease and certain types of cancers, because there is a lower rate of these diseases among wine drinkers. Health experts are now questioning the validity of these studies. They believe that the lower incidence rates of health problems among wine drinkers is influenced by the fact that wine drinkers tend to have healthier lifestyles. A study published in the *American Journal of Clinical Nutrition* supports this hypothesis. The healthier lifestyle that exists among wine drinkers would therefore be the confounding variable in many of these previous studies.³

The second lesson assigns students to design a study that will determine the potential risks of taking ephedra. They have the option of conducting either a cohort study or a randomized controlled trial. This lesson helps them realize why cohort studies are done, even though clinical trials are considered more scientific. Learning about the cohort study and the randomized controlled clinical trial helps students become familiar with different types of health studies that are done to determine the possible effects of certain factors on particular outcomes of health. These are the types of epidemiologic studies that help researchers determine whether eating certain types of food will improve or worsen their health or whether abstaining from certain behaviors will reduce the risk of certain diseases. Associations that are found in epidemiologic studies do not always demonstrate that one factor causes the other, but they help lead researchers to possible causes, prevention methods and cures for a disease. To make these activities more relevant, the teacher can explain that these are the types of studies that students may often read or hear about in the news. Included with these lessons is a glossary of terms often used in epidemiologic studies that will help students work on this assignment.

References

1. Lilienfeld DE, Stolley PD. Experimental epidemiology: randomized clinical trials. In: *Foundations of Epidemiology*. 3rd ed. New York: Oxford University Press; 1994: 155–166.
2. Doll R, Hill AB. Lung cancer and other causes of death in relation to smoking. *British Medical Journal*. November 10, 1956: 1071–1081.
3. Associated Press. Yahoo Health News Web site. Wine drinkers lifestyle may explain better health. July 25, 2002. Available at: <http://story.news.yahoo.com/news?tmpl=index2&cid=534>

Glossary

Clinical trial	A research activity that involves the administration of a test regimen to humans to evaluate its efficacy and safety.
Cohort study	A research design in which populations exposed to a substance or possessing a particular attribute are followed forward over time and compared with a population not exposed or not possessing the attribute of interest. The rates of disease are then compared in the two groups. An example is the American Cancer Society's 10-year follow-up of smokers versus nonsmokers. The incidence rates of lung cancer and heart disease were higher in the smokers.
Confounding	An outside factor that may distort the results of a study that is determining a possible association between exposure to a particular factor and the consequent development of a disease. ¹ For instance, the annual mortality rate in Michigan is much lower than the annual mortality rate in Florida. This is not to say that one is more likely to die in the state of Florida; it is just that Florida has a higher proportion of elderly residents (a confounding factor), so the state winds up having a higher annual mortality rate.
Dosage	A quantitative value that measures how much the subjects in the experimental group are being exposed to a particular factor, as different levels of exposure can result in variations of health outcome. In a clinical trial that is testing the safety and effectiveness of a drug, researchers must determine how much of that drug should be given to the patients to achieve the anticipated results. Dosage can also represent the number of cigarettes a person smokes per day or the amount of fiber a person consumes in a given day, depending on the variable being studied.
Exposure	In epidemiologic studies this often represents the experimental variable of the study. Epidemiologists determine whether exposure to a particular factor is associated with the outcome of a particular health condition. Exposure factors can include those that can improve one's health or those that can increase the risk of getting a disease or illness. In studies that determine the association between exposure to a particular factor and health outcome, exposure would be considered the independent variable, and the health outcome would be labeled the dependent variable.

Health outcome	The health condition that is being studied. Epidemiologists determine if valid associations are found between exposure to a particular factor and a particular disease or health condition. An epidemiologic study determines if a direct or inverse association can exist between the exposure factor and the health outcome.
Informed consent	Voluntary consent given by the participant in a research study to join the study after being fully informed about risks, benefits, ability to withdraw without compromising care, etc.
Intervention group	In a clinical trial, this is the group that is getting the newly developed type of treatment, medication or health education/disease prevention program. Members of this group are therefore considered to be the experimental group in a controlled clinical trial.
Randomization	The allocation or assignment of individuals to groups in a study by chance alone so as to ensure comparability of groups. A simple coin toss or table of random numbers, or computer programs written expressly for this purpose, can be used for the allocation. Randomization eliminates bias in assignment as well as distributing prognostic factors equally between the groups to be compared.
Risk factor	An exposure factor that may have a positive association with a particular disease, in which this factor may increase one's chances of getting that disease. Risk factors include certain types of behavior, food, medications and other substances, and exposure to certain environmental pollutants.

Reference

1. Lilienfeld DE, Stolley PD. *Foundations of Epidemiology*. 3rd ed. New York: Oxford University Press; 1994.

Sample Advertisements for Ephedra-Containing Products

Nature's SUPER CAP

850 mg Ephedra Extract

Because of Super Cap's high yield of ephedrine, it has many of the benefits of a bronchodilator, opening the airway and dramatically enhancing breathing performance. It is also a preferred product among serious bodybuilders looking to achieve greater endurance and greater strength levels.

8% Ephedra Alkaloids per Capsule,
delivering 68 mg of naturally occurring Ephedrine

Supplement Facts

Serving size: One capsule

Amount per serving: *Ephedra sinica* extract (aerial parts)—883 mg

* Daily value not established

Other Ingredients: Calcium sulfate, gelatin, maltodextrin, magnesium stearate, and silica

Directions (adults only): Take one capsule daily as a dietary supplement. **Not for use by minors.**

Warning: Ephedra contains naturally occurring ephedrine. If you are pregnant or nursing, or if you have heart disease, thyroid disease, diabetes, high blood pressure, depression or other psychiatric conditions, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder, consult a health care provider before using this product. Do not use if you are using monoamine oxidase inhibitors (MAOI) or for two weeks after stopping an MAOI drug; certain drugs for depression, psychiatric or emotional conditions; drugs for Parkinson's disease; methyldopa; or any product containing ephedrine, pseudoephedrine, or phenylpropanolamine (ingredients found in allergy, asthma, cough/cold, and weight control products). Stop use and call a health care professional immediately if dizziness, severe headache, rapid and/or irregular heartbeat, chest pain, shortness of breath, nausea, tremor, loss of appetite, sleeplessness, noticeable change of behavior or loss of consciousness occurs. Do not exceed recommended serving.

Manufactured under authority of D&E Pharmaceuticals, Inc.

Source: From the D&E Pharmaceuticals, Inc. Web site. Available at: <http://d-n-e.com/epsucap85.html>

*From the bottle label of the product Ephedra: Nature's Super Caps (24 capsules).

Ultimate Energizer, High Potency Ephedra and Caffeine

(Young Again 2002 Web site)

The Ultimate Energizer has 100 capsules with 257 mg of ephedra and 100 mg of caffeine and a proprietary blend of fat melting herbs. It packs a wallop, and it is not for everyone! Read our cautions and full description. This fat burning supplement is 3 times more potent than Metabolife.

Please note the following cautions about the ULTIMATE ENERGIZER and other products that contain ephedra:

Ephedra, also known as ma huang, is a common ingredient in herbal weight-loss products. It has been shown to be generally safe and effective. It is also used to treat depression, asthma, colds, and other respiratory complaints. Ephedra should not be used by people with anxiety disorders such as panic attacks, or by those with glaucoma, heart disease or high blood pressure. Avoid this herb if you are taking medication for depression. Since it stimulates the central nervous system, avoid caffeine, St. John's Wort, and over-the-counter decongestant medications while taking ephedra.

Source: From the Young Again 2000 Web site, Available at:
<http://www.youngagain2000.com/marcella75/ulen50100cap.html> 2002 Version*

*The most recent version of this Website includes another weight loss product that is "Ephedra-free", since the Food and Drug Administration has recently banned all products containing ephedrine alkaloids.

Lesson 1:

Clinical Trial for Testing the Effectiveness of Ephedra

Lesson Plan

A worksheet is included to supplement the lesson.

Objective: To reinforce the concepts of the scientific method by introducing students to the design of a randomized controlled clinical trial.

Motivation: Pass out copies of the advertisements for ephedra products. Ask students if they know anyone who takes these products. Ask how many question if these products actually work.

Aim: How can we test to see if these products that contain ephedra work?

1. In setting up an experiment, what principles and guidelines should we follow?

(Prompt: The scientific method.)

2. Every experiment requires a hypothesis. How would we formulate the hypothesis?
3. What would the experimental variable be in this experiment?
4. What would the independent and dependent variables be?
5. When we select people to be placed in an experimental group, why is it important to select another group of people and place them into a comparison group?
6. Why is it important that members of both the experimental and the comparison groups have certain similar characteristics?

Potentially confounding variables need to be controlled.

7. What would be some examples of similar characteristics that both groups must have in this experiment?

Some acceptable answers would be age, sex, fitness level, etc.

8. Members of the comparison group would have to take a placebo, whereas members of the experimental group would take the actual drug. However, all participants would not know whether they are in the experimental group or comparison group. This procedure is called blinding or masking. Why must the process of masking occur in an experiment?

9. All participants would be randomly placed in either the experimental group or the comparison group. This procedure is called randomization. How does this procedure keep the experiment valid?

It limits potential sources of selection bias.

10. How would we collect the data?
11. How can we measure the outcome of our experiment?
12. How would we determine if the data we collect support our hypothesis?

SUMMARY: This experiment that you have just designed is called a randomized controlled clinical trial. It is an experiment that must be conducted by all pharmaceutical companies to get approval from the FDA to market a drug. Important experiments such as these have to follow all the principles of the scientific method, and many of the basic concepts that are part of the scientific method, such as hypothesis testing and experimental variable, must be applied in all experiments and studies.

Teacher's Notes

The activity would have more substance if your students were presented with some empirical data that would correspond to the experiment they are going to design. Unfortunately, there are not too many published studies.

One example of a published study would be an article found in the *International Journal of Obesity*. The citation for this journal is as follows:

Boozer CN, Daly PA, Homel P, et al. Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. *Int J Obes* 2002;26:593–604.*

It should be noted that the study done by Boozer et al. (2002) demonstrated several types of bias. One example would be a large percentage of study participants who no longer continued with the study. This high percentage was, however, found in both the experimental and the comparison groups, distributing characteristics (in this case, likelihood of dropping out of the study) equally between the two groups is one reason why randomized controlled clinical trials are more valid than other types of epidemiologic study. It could also be debated whether the numbers the authors presented actually show a significant difference in weight loss and fat reduction. Statistical analysis was not used to determine whether the difference between the two groups was significant.

*Special acknowledgments to Carol Chang and the other interns at The Robert Wood Johnson Foundation who conducted these literature searches.

On the other hand, reviewing a study such as this can help students understand how even a randomized controlled clinical trial can be vulnerable to sources of bias and confounding—not as much as with observational studies, such as cohort and case-control studies, but the potential sources are certainly there. The dearth of studies may also illustrate how products such as those with ephedra can be marketed to the public without any substantial scientific research.

Another reference that can be used is an article from the *Journal of the American Medical Association (JAMA)*. The citation for this article is as follows:

Shekelle PG, Hardy ML, Morton SC, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance, meta-analysis. *Journal of the American Medical Association*. 2003;289:1537–1545.

This journal article is a literature review of different studies of ephedra that were conducted. Students should be informed that the marketing of Ephedra products as a dietary supplement has been banned.

The discussion questions included in this module should be answered by students who have been working on either version of the Clinical Trials (Lesson 1) worksheet.

Testing the Effectiveness of Ephedra: How Do We Know It Works? (Student Version)

Ephedra is one of the many herbal supplements that claim to help people burn fat, build muscle and increase endurance. As a result, many athletes are taking it, in the hope it will give them a cutting edge against their competitors. The question is “are these claims really true?” If they are, by how much? If they are not, why are these manufacturers allowed to make these claims? Look at the advertisements that are included. Both were taken from the Internet.

In this activity you and your group members will have the opportunity to design your own experiment that can determine if these claims are true. You and your partners are research scientists, and you are being paid by an independent consumer rights advocate group to see if this product really does what it claims to do. This type of experiment is called a randomized controlled trial, commonly known as a clinical trial. These types of experiments must be done by drug manufacturers in order to get approval from the Food and Drug Administration (FDA). Manufacturers must prove that their product is both safe and effective (effective means that the product does what it claims to do). However, supplements have a loophole to evade these requirements because they are regulated more like a food product than a drug.

1. In every experiment, a scientist must have a hypothesis and a method of testing the hypothesis. To test a hypothesis, a scientist must understand what the experimental variable is. In the space below write a hypothesis and **briefly** describe how to test this hypothesis. In this explanation indicate what your experimental variable is.

2. When testing the experimental variable, a researcher must understand the possible association of one factor with another—in this case the effect of taking ephedra and its effect on the body’s metabolism, body weight and available energy. These associations that may be found are labeled as the independent and dependent variables. What is the independent variable in this experiment? What are the dependent variables? Explain the relationship between the independent and dependent variables.

3. Clinical trials are experiments that involve human test subjects. Because of this there are ethical issues that must be dealt with. What are the ethical issues that a researcher must face when conducting an experiment such as this? How can these issues be resolved?

4. Every experiment requires a comparison (control) group and an experimental group, which receives the intervention. What characteristic distinguishes members of the comparison group from those of the experimental group? What similar characteristics should both the control group and the experimental group members have? Why is it important for the groups to have similar characteristics? What are some characteristics of participants who should be excluded from this study? (Hint: Read the labels of the product.)

5. In a clinical trial, subjects are randomly assigned to either the experimental or the comparison group. Another requirement is that the participants do not know which group they are placed in, so the participants do not know whether they are taking the placebo or the actual drug. This procedure is called **blinding**. In addition to the subjects of the experiment not knowing which group they are in, the researchers may not know who is in each group. This is known as **double blinding**. Why is it important to use double blinding and randomization, when feasible?

6. How would you measure the outcome of your experiment? (Hint: Refer back to Question 2, which asked you about the dependent and independent variable). How would you determine whether your hypothesis was confirmed? How does research such as this help the public learn more about the products they buy and use?

Testing the Effectiveness of Ephedra: How Do We Know It Works? (Teacher's Answer Key)

Ephedra is one of the many herbal supplements that claim to help people burn fat, build muscle and increase endurance. As a result, many athletes are taking it, in the hope it will give them a cutting edge against their competitors. The question is “are these claims really true?” If they are, by how much? If they are not, why are these manufacturers allowed to make these claims? Look at the advertisements that are included. Both were taken from the internet.

In this activity you and your group members will have the opportunity to design your own experiment that can determine if these claims are true. You and your partners are research scientists, and you are being paid by an independent consumer rights advocate group to see if this product really does what it claims to do. This type of experiment is called a randomized controlled trial, commonly known as a clinical trial. These types of experiments must be done by drug manufacturers in order to get approval from the Food and Drug Administration (FDA). Manufacturers must prove that their product is both safe and effective (effective means that the product does what it claims to do). However, supplements have a loophole to evade these requirements because they are regulated more like a food product than a drug.

1. In every experiment, a scientist must have a hypothesis and a method of testing the hypothesis. To test a hypothesis, a scientist must understand what the experimental variable is. In the space below write a hypothesis and **briefly** describe how to test this hypothesis. In this explanation indicate what your experimental variable is.

Acceptable answers are that ephedra will increase weight loss, burn fat or increase the amount of available energy during exercise. This would be done by giving one group ephedra and another group a placebo, and the results of both groups would be recorded. The experimental variable would be taking ephedra.

2. When testing the experimental variable, a researcher must understand the possible association of one factor with another—in this case the effect of taking ephedra and its effect on the body's metabolism, body weight and available energy. These associations that may be found are labeled as the independent and dependent variables. What is the independent variable in this experiment? What are the dependent variables? Explain the relationship between the independent and dependent variables.

The independent variable is the use of ephedra. The dependent variable is either body mass, percentage of body fat or available energy, depending on what the students listed as their hypothesis. If ephedra has an effect on the body mass, percentage of body fat or available energy, then the group taking ephedra (experimental group) should have better results in one or all of those factors mentioned above, compared with the group taking the placebo (control group).

3. Clinical trials are experiments that involve human test subjects. Because of this there are ethical issues that must be dealt with. What are the ethical issues that a researcher must face when conducting an experiment such as this? How can these issues be resolved?

Students should understand the importance of informed consent. Participants should know that they could be given either the placebo or the actual drug, but they will not know which one they have. They should also be told about all the risks of taking the drug. Finally, they should be informed that they can drop out of this experiment any time they wish, and they cannot be coerced to continue with this experiment if they do not wish to.

4. Every experiment requires a comparison (control) group and an experimental group, which receives the intervention. What characteristic distinguishes the members of the comparison group from those of the experimental group? What similar characteristics should both the control group and the experimental group members have? Why is it important for the groups to have similar characteristics? What are some characteristics of participants who should be excluded from this study? (Hint: Read the labels of the product.)

The experimental and the comparison groups should have people of similar body mass and percentage of fat, as well as fitness level. The age and sex distributions should also be very similar. Other factors that your students find relevant to the results of the experiment could also be considered. Participants who should be excluded from this experiment could be those with heart problems, those with high blood pressure and those who suffer from depression or anxiety disorders, including those who take MAO inhibitors. People in both the experimental and the comparison groups should be advised not to use caffeine or take nasal decongestants while taking the ephedra supplement.

5. In a clinical trial, subjects are randomly assigned to either the experimental or the comparison group. Another requirement is that the participants do not know which group they are placed in, so the participants do not know whether they are taking the placebo or the actual drug. This procedure is called **blinding**. In addition to the subjects of the experiment not knowing which group they are in, the researchers may not know who is in each group. This is known as **double blinding**. Why is it important to use double blinding and randomization when feasible?

The purpose of randomizing is to make sure that the experimental and comparison groups are as similar as possible, in terms of the factors mentioned in the previous questions. Randomization helps prevent selection bias. Double blinding limits sources of information bias. If the participants don't know if they are taking either the actual drug or the placebo, it will not encourage them to act differently and will not have an effect on their attitude toward the experiment (placebo effect). It is beneficial for

those administering the drug to not know who is in either the comparison group or the experimental group because they may be tempted to inaccurately record the results of those in the experimental group and comparison group.

6. How would you measure the outcome of your experiment? (Hint: Refer back to question 2, which asked you about the dependent and independent variables.) How would you determine whether your hypothesis was confirmed? How does research such as this help the public learn more about the products they buy and use?

Those in the experimental group should have a greater average weight loss than those in the comparison group. The same should apply if percentage of body fat or fitness level were also tested in this experiment. Weight loss, reduction in body fat or increase in fitness level of those in the experimental group should be significantly different from those in the comparison group. Statistical analysis could be done to determine if this difference is significant. This kind of research helps consumers know if the products they use have actually been tested for effectiveness.

Using a Clinical Trial to Test the Effectiveness of Ephedra (Student Handout)

(More Advanced Version)

A clinical trial is an experiment that all pharmaceutical companies must conduct in order to get FDA approval to sell their products. For the FDA to approve the drug, the manufacturer has to show scientific data that will prove that the product is not only safe but also effective, effective meaning that the product does what it claims to do. Often, many of the herbal remedies seem to escape the standard regulations that most over-the-counter and prescription drugs, as a whole, are governed by. One could have a separate discussion of why this happens and if there is any scientific rationale for more lax standards.

You and your colleagues are research scientists who are being paid by an independent consumer rights advocate group who wants to confirm that ephedra does exactly what it claims to do. Ephedra is an herbal supplement that claims to increase one's available energy, help build muscle and help burn fat. For a more detailed description, read the advertisements that have been included. How would you go about this investigation? Recall that when designing an experiment, you must first formulate a hypothesis and determine how to test this hypothesis. Remember the fundamentals of experimentation and the scientific method. What is the experimental variable, and what would the independent and dependent variables be? What is the relationship between them? What are some variables that would have to be controlled?

Also, keep in mind that in a clinical trial one is dealing with human test subjects. What are some ethical issues that must be considered in this experiment? How can these issues be resolved so that they do not violate any ethical standards? What are some characteristics of participants who should be excluded from this study? Read the advertisement and labels again.

Consider the participants who would be in your experimental and comparison groups. Why is it important to randomly assign participants the placebo or the actual drug? This process is called randomization. Explain why participants should be unaware of whether they are taking the placebo or the actual drug. Why is it important, in some cases, for the research scientists implementing the study to not know whether the participants are in the experimental or comparison group? What are some similar characteristics that participants in both the experimental and the control groups should have? Why are these similar characteristics important?

Finally, determine how you would measure the outcome of this experiment. How would you determine whether the results and data you anticipate will confirm your hypothesis? Think back to what the dependent and independent variables are in this experiment. Are there any other factors that must be considered, even after one has collected all the data? How will the results of these experiments help the public learn more about some of the products they purchase and use?

Create an outline that will help describe and diagram the experiment you anticipate designing for this study. The outline must address all of the questions and issues mentioned above, and it must also be written in a format that is easy to follow. Following this sheet is an outline to make sure that you have addressed all of the protocols that are required for a clinical trial. Good luck with your endeavor.

General Outline of a Protocol for a Clinical Trial

1. Rationale and background for study
2. Specific objectives of study
3. Concise statement of study design (masking, randomization, types and duration of treatments, number of patients)
4. Criteria for including and excluding subject
5. Outline for treatment procedures
6. Methods of assuring the integrity of the data
7. Major and minor outcomes
8. Procedures for obtaining the informed consent of patients
9. Procedures for analyzing results; a conclusion should be drawn in the end

Source: Bearman JE. Writing the protocol for a clinical trial. *American Journal of Ophthalmology*. 1975;79:775–778.

More Advanced Version

(Teacher's Answer Key)

This exercise is a review of the scientific method and experimentation. Therefore, students must include all of the components of making an experiment valid. The outline of their experiment should have the following:

1. A hypothesis should be clearly stated. Ephedra is effective in promoting weight loss, reducing body fat and increasing available energy during exercise. The alternate hypothesis is that it is not. Ephedra is the experimental variable. Taking ephedra or not taking ephedra is the independent variable, whereas weight loss, reduction in body fat and fitness level are the dependent variables.
2. There should be an experimental group, those taking ephedra, and a control group (or comparison group), those who are taking the placebo.
3. The participants in this clinical trial should be randomly placed in either the experimental group or the comparison group. This limits the potential for selection bias.
4. Neither the participants in the experiment nor those conducting the experiment will know who is getting the drug and who is not until the end of the experiment. This process is called double blinding and limits the potential for information bias.
5. The clinical trial should have a reasonable number of participants in both the experimental and the comparison groups. The larger the number, the more valid are the data collected from the experiment. On the other hand, students also have to be realistic about the number of people who are willing to participate.
6. The characteristics of both the experimental group and the comparison group should be as similar as possible. These characteristics include distribution of age, sex, weight, percentage of body fat, fitness level and any other factors that your students may find relevant. Randomization should help to make the groups as similar as possible, but it is not always guaranteed.
7. Participants who may be excluded include those taking MAO inhibitors, those suffering from either depression or anxiety disorders, or those with heart problems and high blood pressure. The problem with excluding these participants is that many people who have these problems may also be taking ephedra-containing products, so an experiment such as this may not represent all of the people taking ephedra.
8. Since this is a clinical trial, ethics is another important issue. The participants of the experiment should be told what the experiment is about, the risks of taking ephedra, and that

they will be randomized to take either the actual drug or the placebo, but they will not know what they are taking until the end of the experiment. Participants must be counseled about why this procedure is done. They should also know that they are allowed to drop out of the clinical trial whenever they want. An informed consent form must be signed by all participants.

9. The procedure of the experiment should include how often the participants will be taking the drug and for how long. The weight, percentage of body fat and endurance of participants can be measured in the beginning. Physical exams can be given regularly to monitor the progress of the participants. Participants can be instructed to exercise or not to exercise, but if participants are instructed to exercise, then all participants must follow a similar exercise regimen. Participants can be told to avoid products that contain caffeine because many ephedra-containing products already contain caffeine. They should also be advised to avoid nasal decongestants because the chemical composition of ephedra is similar to that of ingredients found in nasal decongestants.
10. At the end of the clinical trial, the results for all patients will be determined. The weight of each participant can be measured and compared with the weight recorded before the clinical trial. Percentage of body fat can be measured with machines that calculate body fat. Fitness level can be measured by having each participant perform endurance tests.
11. Once the researchers know who is in the experimental group and who is in the comparison group, they can determine an average in weight loss, reduction in percentage of body fat and increased level of energy during exercise. A statistical analysis should be done to determine if the difference between the two groups is significant. They should also look at the characteristics of the participants at the start of the trial in both the experimental and the comparison groups. Remember, the researchers were not aware of which participants were in the experimental and comparison groups until the end of the experiment. If there is any significant difference between the participants of the experimental group and those of the comparison group, then it should be noted, as this would be an example of selection bias.
12. Analysis of the data should help the researchers draw their final conclusion.

Students are allowed to expand more on this. What is important is that they understand that every experiment involves following a series of protocols, and these protocols must be followed to make the experiment and the data that are collected from the experiment valid.

Discussion Questions

1. Read the advertisements carefully once again and think of other products that are taken by athletes, such as creatine and androstenedione. Although many herbal remedies and nutritional supplements have been scientifically found to be safe and effective, many products do not have scientific proof that they work and are safe. Why do you think some of these herbal remedies and nutritional supplements seem to get away with making such claims? What do you think should be done to protect consumers from ineffective and unsafe products?
2. Why are issues such as correct dosage of the medication important? Why is it important to have a large number of subjects in both the experimental and the comparison groups?
3. In addition to testing the effectiveness of the product, what else must be tested? (Read the labels again for a hint.) Remember that you are testing this for a consumer rights advocate group. Give a brief summary of how you would test this other factor.
4. When you read an article or watch the news about a new health study confirming how some types of food or nutritional supplement can be beneficial or perhaps detrimental to one's health, what are some questions you should ask yourself about how the study was conducted?
5. Bias can be defined as "any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect" on a particular health outcome.¹ Bias can be classified as either selection or information bias. Selection bias occurs when an error is made in the method of selecting test subjects or when errors are made in placing test subjects into either the experimental or the comparison group. *How do randomized controlled clinical trials decrease the potential for selection bias? Are there still possibilities of selection bias occurring in a randomized controlled trial? If so or if not, explain.*
6. Information bias occurs when information obtained from the subjects is considered inadequate in some way. This results in incorrect information about exposure or the health outcome being studied, which may lead to misinterpretation of the data collected. A manufacturer, for example, may overreport beneficial health outcomes in the intervention group and underreport the same beneficial health outcomes in the comparison group, which may help the manufacturer get approval to market its product. *How do randomized controlled trials limit the occurrence of some potential sources of information bias? How does the practice of blinding and double blinding help decrease the possibilities of information bias in a study? Do these practices eliminate all possibilities of information bias? Explain.*

Reference

1. Gordis L. Bias, confounding, and interactions. In: *Epidemiology*. 2nd ed. Philadelphia: WB Saunders; 2000:204–212.

Discussion Questions

(Teacher's Answer Key)

1. Read the advertisements carefully once again and think of other products that are taken by athletes, such as creatine and androstenedione. Although many herbal remedies and nutritional supplements have been scientifically found to be safe and effective, many products do not have scientific proof that they work and are safe. Why do you think some of these herbal remedies and nutritional supplements seem to get away with making such claims? What do you think should be done to protect consumers from ineffective and unsafe products?

Many of the labels are very vague. The promises and claims that they make are not very clear, and they are often followed by this disclaimer: "This statement has not been evaluated by the FDA." This is how the manufacturers of herbal remedies and dietary supplements get around these claims. Laws could be passed to make the labels easier to understand.

2. Why are issues such as correct dosage of the medication important? Why is it important to have a large number of subjects in both the experimental and the comparison groups?

Correct dosage is important because dosage can play a role in how well the drug works. High dosage could also be dangerous for certain patients. Having a large number of participants is important because the effectiveness of drugs varies with different people and, with large numbers of participants, differences in outcomes in the experimental and comparison groups are less likely to be due to chance.

3. In addition to testing the effectiveness of the product, what else must be tested? (Read the labels again for a hint.) Remember that you are testing this for a consumer rights' advocate group. Give a brief summary of how you would test this other factor.

Safety is another important factor to test for. This could be done by either conducting a clinical trial for safety or conducting a cohort study of people who are already taking ephedra and comparing them with those who are not. Side effects from taking the drug are then recorded. Lesson 2 deals with the issue of safety.

4. When you read an article or watch the news about a new health study confirming how some types of food or nutritional supplement can be beneficial or perhaps detrimental to one's health, what are some questions you should ask yourself about how the study was conducted?

Some questions to ask would be as follows: How was the study conducted? How long did the study take? How were the participants selected? How were they placed in either the exposure or comparison group? How were the results of the experiment collected and analyzed? Other questions might include who was funding

the experiment. Many other relevant questions could be asked as well. Answers should not be limited to the factors mentioned, but these are some of the important questions that should be asked.

5. Bias can be defined as “any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure’s effect” on a particular health outcome.¹ Bias can be classified as either selection or information bias. Selection bias occurs when an error is made in the method of selecting test subjects or when errors are made in placing test subjects into either the experimental or the comparison group. *How do randomized, controlled clinical trials decrease the potential for selection bias? Are there still possibilities of selection bias occurring in a randomized controlled trial? If so or if not, explain.*

Randomization decreases the potential for selection bias because it randomly places participants in either the experimental group or the comparison group. This process increases the chances of making the experimental group and the comparison group as similar as possible. However, equality is not guaranteed. Even with randomization, there may be some important differences between the characteristics of those in the experimental group and the characteristic of those in the comparison group. However, the chances for this are much less than with other selection processes.

6. Information bias occurs when information obtained from the subjects is considered inadequate in some way. This results in incorrect information about exposure or the health outcome being studied, which may lead to misinterpretation of the data collected. A manufacturer, for example, may overreport beneficial health outcomes in the intervention group and underreport the same beneficial health outcomes in the comparison group, which may help the manufacturer get approval to market its product. *How do randomized controlled trials limit some potential sources of information bias? How does the practice of blinding and double blinding help decrease the possibilities of information bias that may occur in a study? Do these practices eliminate all possibilities of information bias? Explain.*

When neither the participants nor the researchers know who is taking the drug and who is taking the placebo, the chance for information bias is much reduced. If participants who are receiving the drug are told that they are, this may motivate them to exercise more than they should. When researchers know who has the placebo and who has the drug, they may overreport the progress of one group and underreport the progress of another group. Double blinding prevents both of these situations from occurring. Participants may still be motivated to exercise more than they are supposed to, even if they do not know whether they are taking the placebo or the actual drug, but the potential for information bias would be much greater if the participants knew whether they were taking the drug or not.

Reference

1. Gordis L. Bias, confounding, and interactions. In: *Epidemiology*. 2nd ed. Philadelphia: WB Saunders; 2000:204–212.

Lesson 2:

Clinical Trial Versus Cohort Study for Determining the Safety of Ephedra

Lesson Plan

A handout is included to supplement this lesson.

Objective: To compare the randomized controlled clinical trial with the cohort study.

Do now: Distribute articles from *USA Today* and the *New York Times* and have students read them. (Citations are found in the reference section of the handout.)

Motivation: Discuss articles and review the warning labels found on the bottle and advertisements.

Aim: How can we test for the potential risks of taking the herbal supplement ephedra?

1. The FDA reviewed 140 filed reports of adverse reactions that were believed to be linked to taking the herbal supplement ephedra. The reports were filed between 1997 and 1999. By developing and using a standardized rating system, 31% of the adverse reactions filed were classified as “definitely” or “probably” related to taking ephedra, and another 31% of the adverse reactions filed were classified as “possibly” related to taking the supplement. What are the limitations to studies such as these?

Adverse reactions may be underreported, only serious conditions may be reported, different doctors may have different diagnoses of the conditions and the situations, etc.

2. How can we develop a study that would allow for a more accurate strategy for scientifically determining the potential risks of taking ephedra?

Some students may remember the randomized controlled trial.

3. If we were to develop a clinical trial to test for the risks of adverse reactions, how would this be set up?

Students should give a brief summary of the sequential procedures for implementing a clinical trial, in which testing the risks of ephedra is used as an example.

4. Experiments such as these can be done and are considered a more precise method of testing the hypothesis scientifically, but these studies are very costly. What if an institution has a limited amount of funds to conduct an epidemiologic study?

Get students to brainstorm and come up with some ideas to segue into a discussion of cohort studies. Introduce the concept of the cohort study to them.

5. Why do you think cohort studies are not considered as scientific as randomized controlled clinical trials?

There are more sources of potential bias and extraneous factors. Researchers cannot control conditions.

6. Why are cohort studies done, even though randomized controlled trials are considered the gold standard of epidemiologic studies?

One reason was already given; have students give other reasons.

You and your group will design a study that will determine the potential risk of taking ephedra. You have the option of designing either a randomized controlled clinical trial or a cohort study. Whatever type of study you plan to design, justify why you decided on that type of study, especially if you have chosen a cohort study.

Teacher's Notes*

Just as there was difficulty finding published clinical trials that tested the safety and effectiveness of ephedra, there was also difficulty finding cohort studies on this topic. The controversial death of Baltimore Orioles pitcher Steve Bechler has brought a lot of publicity to this subject. Public officials are debating the safety of taking ephedra and are discussing whether it should be banned altogether. Many supplement manufacturers are now selling products that are ephedra free, although the manufacturers do not advertise the active ingredient that has replaced ephedra in the products.

Currently, the International Olympic Committee and the National College Athletic Association have banned the use of ephedra in all of their sports competitions. The National Football League is the first professional sports association in the United States to ban ephedra. NFL athletes are required to be tested for ephedra, as they are also tested for anabolic steroids.¹ On December 30, 2003, the FDA released a consumer alert that warns against the purchase of ephedra-containing products.² The FDA has also issued a statement to manufacturers of the product that it will publish a final report that will include the unreasonable risks of injury or illness that are associated with taking ephedra. This led to a ban of the sales of all dietary supplements containing ephedrine alkaloids on April 12, 2004.³

References

1. NFL News. National Football League Web site. NFL adds ephedra to testing program. May 10, 2002. Available at: <http://www.nfl.com/multi/0,3738,5321457,00.html>. Accessed August 15, 2002.
2. Food and Drug Administration (FDA) Web site. FDA Announces Plans to Prohibit Sales of Dietary Supplements Containing Ephedra. Available at: <http://www.fda.gov/oc/initiatives/ephedra/december2003>. Accessed January 11, 2003.

*Acknowledgments to Dr. Philip Alcabes, professor of epidemiology at Hunter College, City University of New York, whose educational materials helped develop the Notes on Clinical Trial and Cohort Studies review sheet.

3. Food and Drug Administration (FDA) Web site. FDA Announces Rule Prohibiting Sale of Dietary Supplements Containing Ephedrine Alkaloids Effective April 12, 2004. Available: <http://www.fda.gov/bbs/topics/NEWS/2004/NEW01050.html>. Accessed: May 11, 2004.

Other Helpful Sources

FDA Web site. Dietary supplements containing ephedra alkaloid resource page. Available at: <http://www.fda.gov/ohrms/dockets/00n1200/index.htm>

U.S. Department of Health and Human Services, HHS New. 1997. FDA Web site. FDA proposes safety measures for ephedrine dietary supplements resource page. Available at: <http://www.cfsan.fda.gov/~lrd/hhsephed.html>

The citations for the *USA Today* and *New York Times* articles are found in the references section of the worksheet. We recommend that your students read these articles before or at the beginning of the lesson. This gives students an idea of the situation and the issues involved in the lesson activity.

Designing a Cohort Study or Randomized Controlled Trial to Test the Safety of Ephedra

Recently, there have been many reported cases of illness and even deaths that have been linked to using the herbal supplement ephedra. Ephedra is an amphetamine-like stimulant, after all. The supplement has been linked to side effects such as anxiety, sleeplessness, migraines, seizures, high blood pressure, irregular heartbeats, heart attacks and strokes.¹⁻³ One of the advertisements also includes a warning stating that the product “should not be used by people with anxiety disorders such as panic attacks, or by those with glaucoma, heart disease, or high blood pressure.” It also warns consumers to “avoid this herb if you are taking medication for depression. Since it stimulates the nervous system, avoid caffeine, St. John’s Wort, and over-the-counter decongestant medication while taking Ephedra.” Remember that caffeine is added by some of the manufacturers that sell this herbal supplement.

In a study published in the *New England Journal of Medicine*¹, 140 reports of adverse reactions filed by the FDA that were related to the use of ephedra were reviewed; these reports were filed between June 1, 1997, and March 31, 1999. This study set up a standardized review system to classify the adverse effects filed from these reports as “definitely,” “probably” or “possibly” related or unrelated to the use of ephedra. In this review it was found that 31% of the reports filed had adverse effects that were classified as either definitely or probably related to ephedra, and another 31% of the reports filed were found to be possibly related to the use of ephedra. Hypertension, heart palpitations, tachycardia, stroke and seizures were some common adverse effects reported among the cases that were found to be definitely, probably or possibly related to the use of ephedra.

The limitation of a study such as this is that it does not give an accurate picture of all individuals who may be at risk for the adverse health reactions associated with taking the supplement, especially when the adverse effects that were related to the drug may be underreported. Also, manufacturers continue to claim that the product is safe and that many of the adverse reactions linked to ephedra resulted from people not taking the supplement properly as instructed. Some of these manufacturers have formed the Ephedra Education Council as a result, and they question the methods used in this study that was published in the *New England Journal of Medicine*.⁴ How would one go about using a different method to test whether this supplement is correlated to all of these adverse health conditions and diseases?

A clinical trial is one type of experiment that is often done by pharmaceutical companies when they are seeking approval from the FDA to market a drug. Another type of study that can be done is a cohort study. In cohort studies the participants’ assignment to either the comparison group or the exposure group is based on the participants’ exposure or lack of exposure to the risk factor, in this case taking ephedra. Those who already take ephedra would be placed into the exposure group, whereas those who do not take ephedra would be placed into the comparison group. The participants are therefore not randomly assigned, as they are in randomized controlled clinical trials, because members of both groups are already determined.

The disadvantage of cohort studies is that they do not eliminate potential sources of bias, particularly selection bias, because the participants are already predetermined to be placed in either the exposure group or the comparison group. Confounding is another factor that researchers conducting this type of study should be concerned about. These are outside factors that may have a distorted influence or effect on the results of the study. There are many precautions that can be taken to control for these sources of bias. However, even the most meticulously designed cohort studies cannot eliminate all of these intervening factors. On the other hand, clinical trials are often costly, and this is an issue if there is a limited budget. There is also the issue of ethics, because one is dispensing a drug that may be unsafe to the participants.

The same consumer rights advocate group is now hiring you to test the potential risks and dangers of taking ephedra. You must decide whether your group should conduct a randomized controlled clinical trial or a cohort study. Before you decide which type of study to do, prepare a list of all the disadvantages and advantages of using a cohort study and a clinical trial. Think of why cohort studies are done, even though randomized controlled trials are considered more scientific. Once you have prepared this list, then select which type of study you and your colleagues will conduct. If you decide to design a clinical trial, what would be the drawbacks of this type of study? Then think of all the difficulties that are associated with implementing a randomized controlled clinical trial. Once you have listed the difficulties and complications of designing a clinical trial, come up with solutions to address them. Do the same if you decide to design a cohort study.

Read the warning labels from the bottle again. People with certain medical conditions are warned against taking the supplement. Those who take this supplement are also warned to avoid certain substances. How would these warnings affect the criteria that would be used to reject some of the participants in this study? If you design a clinical trial, there is an ethical issue of excluding participants with certain conditions because issuing the drug may put them at risk of endangering their health. Even though there is an ethical responsibility to do this, would this possibly invalidate the experiment you are conducting, as you are not including all consumers who use this product? This could be a source of bias and certainly would limit the generalizability of the results of the trial. On the other hand, if you are designing a cohort study, you may reject participants who take ephedra but have the medical conditions that the product warns against. Would this practice possibly invalidate the data?

Finally, would you test for all of the health conditions or just one or maybe a few? How would you measure these health outcomes? How would you determine if there is an increased risk of, let us say, increased blood pressure from taking ephedra? How would you test for the other health conditions mentioned? Also, remember to consider potential bias or confounders that may cause the data to become invalid, especially in cohort studies. How would you go about following up on the health of your participants in both the comparison and experimental groups? How often would you follow up on your participants to keep the validity of the data you anticipate collecting? Additional notes and a worksheet on cohort studies and clinical trials have been included to help you set up your research plans.

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Notes on Clinical Trials and Cohort Studies

Clinical Trials

When Are They Most Often Used?

- Evaluating the effectiveness of medical treatments, therapies and procedures.
- Determining the effectiveness of health education and disease prevention programs.

Basic Principles and Characteristics

- Test subjects are randomly placed in either the exposure or the comparison group.
- The exposure group is given the newly developed treatment; the comparison group is given a placebo or the traditional method of treatment.
- Conditions of the study, such as how much the subjects should be exposed to the factor, are controlled by the researchers.

Cohort Studies

When Are They Most Often Used?

- Determining the risks or benefits of being exposed to a particular factor and its relation to a particular health condition (e.g., high cholesterol and heart disease, exercise and heart disease).
- Useful in determining rare exposures and their potential risks or benefits for certain health conditions.

Basic Principles and Characteristics

- Placing participants into the exposure and comparison groups is predetermined.
- Participants who are already exposed to the factor are placed in the exposure group; participants not exposed are placed in the comparison group.

Clinical Trials Versus Cohort Studies

Similarities Between the Two Types of Studies

- Both make comparisons between the exposure and comparison groups, in which the exposure group is being exposed to the factor being studied and the comparison group is not.
- Both involve systematic approaches to measuring outcome.
- Both are determining an association and correlation between the exposure and the outcome.

Differences Between the Two Types of Studies

- Clinical trials are considered to have a higher standard of scientifically proving the stated hypothesis.
- Clinical trials are experiments that are designed by researchers; researchers can create certain conditions.
- Cohort studies are not experiments; they are observational studies designed by researchers; researchers are only recording results of the participants.
- Cohort studies usually require a larger sample population and a longer period of time.
- Clinical trials are often more costly, requiring a greater number of facilities and personnel.
- Ethical issues involving clinical trials are much more complicated.

Outline for Testing Possible Risks of Ephedra

1. List the advantages and disadvantages of implementing a clinical trial.

Advantages

Disadvantages

2. List the advantages and disadvantages of conducting a cohort study.

Advantages

Disadvantages

3. After reviewing the advantages and disadvantages of both types of studies, your group must decide what type of study would be more suitable for your research. In the space below, indicate the type of study you have decided to conduct and explain why your group has reached this decision.

4. Depending on what type of study you choose, what are some complications and difficulties associated with this anticipated study? What are some factors that may invalidate the results of this anticipated study? Include any possible sources of bias or confounding variables that may occur in the study.
5. Referring back to Question 4, how would you address, alleviate and possibly resolve any of the problems and complications mentioned before? For example, what would be some ways of limiting the potential sources of information and selection bias? How would you address outside factors that may affect the results of the experiment?

Preparing a Plan for Your Anticipated Research

On a separate sheet of paper create an outline or draw a diagram that demonstrates how your group plans to set up this anticipated study. When you design this study, do not forget all the basic principles of the scientific method. What is your hypothesis? How do you plan to test this hypothesis? What is your experimental variable? What are the independent and dependent variables, and what are their relations? What type of relevant data would you plan to collect? How would you measure the outcome of the experiment? How would you determine whether you should confirm or refute your hypothesis?

Also, remember the protocols of designing an experiment. Consider the proper procedures that must be carried out in both kinds of studies. Suggest what could be done to control possible sources of error, mentioned in Questions 4 and 5, that may exist in your study.

Extra Credit Assignments

Assignment 1

As mentioned before, the FDA requires all pharmaceutical companies to go through a series of protocols to prove scientifically and empirically that the product they have developed is safe and effective. Drug manufacturers must go through a series of procedures to demonstrate that their medications can be sold to the public. These procedures are divided into four phases. Write a report about the steps that are required to seek FDA approval to market a drug to the public.

Use this information to analyze recent controversial cases, such as the increased risks of using hormone replacement therapy, or estrogen supplements that are taken after menopause. Studies have found that this hormone therapy increases the risk of breast cancer, stroke and heart disease in women.¹ Another recent study found that osteoarthritis patients really do not much benefit from arthroscopic knee surgery, a procedure that can cost as much as \$5,000, yet for years this was a standard procedure recommended to many patients who have osteoarthritis.^{2,3} Is there any type of government procedure that makes sure that medications and medical procedures are properly analyzed and evaluated to determine if they are safe and effective and are being properly implemented?

Assignment 2

The activities in these lessons focused on the product ephedra, which is classified as an herbal supplement. Although Ephedra has been banned by the FDA for several reasons, there have been other herbal remedies and nutritional supplements are sold over the counter. However, they are not regulated under the same standards that traditional over-the-counter drugs are because these supplements are classified more as a food than as a drug. The manufacturers of supplements that contain ephedra, for example, do not need to register and apply for approval from the FDA to market their product.

Under the Dietary Supplement Health and Education Act of 1994, it is the manufacturer's responsibility to ensure that its product is safe and effective. The FDA has authority only to monitor the claims made by the manufacturer to ensure that the product labels contain accurate information, especially when dealing with the safety of the product. The FDA is also responsible for monitoring reports of adverse reactions that have been linked to these herbal remedies, as they are also responsible for monitoring adverse side effects associated with traditional over-the-counter and prescription drugs, and they can take action to issue a recall if the product is

proven to be unsafe.⁴ Products that contained ephedra, for example, were sold for years, even though there were many cases of adverse reactions that may have been attributed to these products. It was finally banned in 2004 by the FDA, and it was the first herbal remedy to be banned by the FDA since the passing of the Dietary Supplement Health and Education Act of 1994.

On the basis of the activity that you have just done and the articles that you have read, as well as what you may know about other dietary supplements that are on the market, write an essay about how effective this system of giving responsibility to the manufacturer is. Should the FDA be given more authority to regulate the marketing of these products? Should the information found on the labels of the products be more descriptive, or should the public be more responsible for the products that they take? These are some of the issues that must be dealt with in your essay.

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