LESSON 5:
Clinical Trials

INTRODUCTION

In this lesson, students learn about the purpose and structure of **clinical trials** by simulating three phases of a clinical trial. Using colored beads to represent a local population that could be involved in research, students recruit participants for a study researching the effects of a medication on high blood pressure, a fairly common condition. After students complete three clinical trial phases for this drug, they consider the challenges of running a clinical trial testing medication for a **rare disease**. Students will also be introduced to elements of clinical trial study design including the use of **placebos**, **randomization**, and **blinded studies**.

CLASS TIME

About one class period of 55 minutes.

KEY CONCEPTS

- Clinical trials are systematic research studies for health-related benefits that involve human participants.
- Clinical trials consist of three or four phases, each with a different purpose and structure. The end goal is to find out whether a study medicine or treatment is safer and/or more effective than no treatment at all.
- Clinical trials have strict **inclusion** and **exclusion criteria** which can, at times, make it difficult to enroll enough participants to run the trial.
- A randomized, **double-blind**, placebo-controlled study is designed to yield scientifically valid results and to decrease bias in both researchers and participants. It is considered a highly reliable form of gathering evidence.
- Successful clinical trials require support and participation from the community.

Vocabulary words used in each lesson are in **bold**. Definitions can be found at the end of each lesson and in the *Master Glossary* in the *Appendix*.

LEARNING OBJECTIVES

Students will know:

- The purpose and structure of each phase of a clinical trial.
- The challenges of recruiting participants for a study.
- Elements of clinical trial study design.

Students will be able to:

- Simulate three phases of a clinical trial.

MATERIALS

Materials	Quantity
Student Handout 5.1—*Clinical Trial Study Design Flap Book*	1 per student
Student Handout 5.2—*Understanding Clinical Trials*	1 per student
Possible Answers to Student Handout 5.2—*Understanding Clinical Trials*	1
Student Handout 5.3—*Clinical Trial Phases* [**Note:** These can be reused in subsequent classes.]	1 per student
Container such as a gallon-size baggie to hold classroom bead population (see *Teacher Preparation*)	1
Container such as a shoebox lid, beaker, or paper cup to hold beads	1 per group
Six-sided die	1 per group
"Drug Discovery & Development Overview" PowerPoint slide (Found under the ***Resources*** tab at http://www.nwabr.org/curriculum/humans-research.)	1
Computer with PowerPoint and overhead projection	1
Teacher Resource 5.1—*Clinical Trial Study Designs* [**Note:** Teachers should be prepared to project these pages for the whole class to see.]	1 of each
Possible Answers to Class Discussion Questions	1

FRAMING THE LESSON

In previous lessons, students have considered historic case studies involving humans in research, learned about the involvement of review boards in research, and contemplated their own participation in research. In this lesson, students learn how this research is actually conducted and what elements constitute good study design.

Clinical trials are research studies for health-related benefits that involve human participants. Make sure students understand that clinical trials are part of a larger system of biomedical research that extends from "[laboratory] bench to bedside." Clinical trials are preceded by **pre-clinical** research that involves basic discovery science, **computer simulation**, **cell and tissue cultures**, and **animal trials**. The end goal of this lengthy process (sometimes lasting years, sometimes decades) is better health for both humans and animals through new drugs, devices, treatments, procedures, and prevention techniques.

To further explore the use of animals in research, teachers may be interested in the Northwest Association for Biomedical Research's curriculum, *The Science and Ethics of Animal Research*, which may be downloaded free from http://www.nwabr.org.

TEACHER PREPARATION

- Make copies of *Student Handouts*.
- Make and fill in a model flap book using Student Handout 5.1—*Clinical Trial Study Design Flap Book*.
- For showing PowerPoint slide, prepare computer and projection unit.
- For projecting Teacher Resource 5.1—*Clinical Trial Study Designs*, prepare overhead projection unit.
- Create a representative population using pony beads by combining the quantities outlined in the chart below in the gallon-size baggie. Each student group will choose a representative to go to the container and scoop out a subset of the classroom population to use in their small group. For smaller classes (20 students or less), halve the bead volumes. The following chart percentages accurately represent the occurrence of high blood pressure (HBP) in the U.S.

  Combine into one container for a class of 25–32 students (eight groups):

Volume/color of pony beads	Representing	% of population
440 mL of green beads	Children without HBP	22%
60 mL of yellow beads	Children with HBP	3%
1,120 mL of blue beads	Adults without HBP	56%
380 mL of red beads	Adults with HBP	19%

  These beads represent a population of approximately 4,500 individuals. To simulate a U.S. population including individuals with a rare disease (*Part III* of this lesson), add three beads of any one new color to the classroom population container. These beads represent the approximately 1 in 1,500 people in the U.S. who have any rare disease. [**Note:** Color a yellow bead with a marker to make a new color, if necessary.]

  (See *Resources* at the end of this lesson for information on where to order pony beads.)

PROCEDURE

Activity One: Simulating a Clinical Trial

Part I: Setting the Scenario and Introducing Vocabulary

1. Set the simulation scenario by explaining to students:

   - You are on a team of biomedical researchers made up of doctors, nurses, **social workers**, clinical coordinators, and other staff.
   - A researcher from the local university has approached your team with a molecule labeled NW234, a potential drug to treat high blood pressure.
   - NW234 has already been in the drug development pipeline for more than five years—it tested well in cell and tissue cultures, and was shown to be effective and safe in both rodents and non-human primates with high blood pressure.
   - The molecule has been approved by the **FDA (Food and Drug Administration)** to begin a clinical trial to find out how safe and effective it is for humans. It is your organization's job to take the potential drug through human clinical trials.
   - High blood pressure is the most common type of cardiovascular disease. Cardiovascular disease and other heart diseases are the ***leading cause of death*** in the U.S., and are projected to be the leading cause of death worldwide by 2030. You and your team see the value in the potential drug and want to begin the clinical trial process.

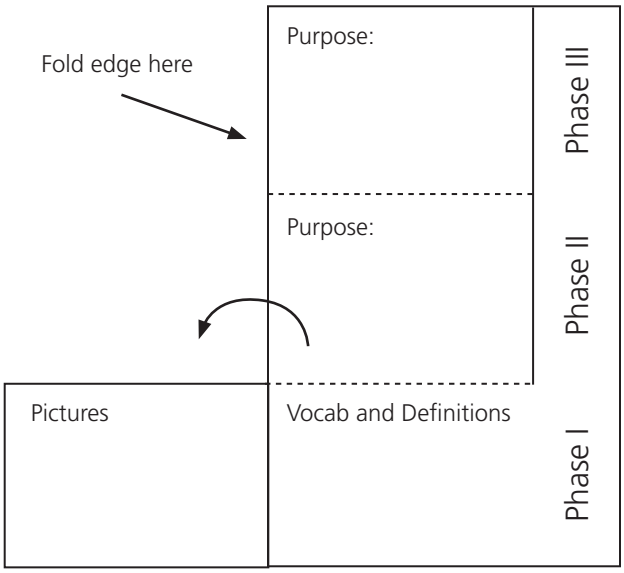
2. Explain to students that humans participate in research through a system of highly regulated and controlled processes called clinical trials. Clinical trials are broken down into a series of phases, and each phase has a different purpose and a different research population.

3. Tell students that in this lesson they will be simulating **Phase I**, **Phase II**, and **Phase III clinical trials** for NW234.

4. Before beginning the simulation, explain to students that they need to become familiar with the design and purpose of each clinical trial phase, as well as know the meaning of some important vocabulary words. They will incorporate new vocabulary into a flap book, as described below.

5. Give each student a copy of Student Handout 5.1—*Clinical Trial Study Design Flap Book*, and allow them a few minutes to fold and cut the paper as directed. [**Note:** Alternately, teachers may guide students in how to create a flap book using a blank piece of white paper.]

6. After students have completed folding and cutting, display your master flap book with proper labeling as shown below:



7. Use the Teacher Resource 5.1—*Clinical Trial Study Designs* overviews to walk students through the study design of each phase and the associated vocabulary words. [**Note:** Vocabulary words are highlighted in bold.] As you present the material, ask students to work on their flap books by filling in the front of each tab with the purpose of each phase of the clinical trial. Have them use the inside back cover of each tab for vocabulary words and short definitions as they relate to each phase. Direct students to draw a visual representation of each phase on the inside of each tab. Ask students to use their own phrasing and language as they fill in their flap books, rather than copying from the master. Some vocabulary words to know include:

   Double-blind study: A study in which neither the participants *nor the researchers* know which participants are receiving the treatment being researched and which are receiving a placebo. This information is not available to anyone working with study participants.

   Efficacy: Effectiveness as measured in a controlled clinical trial.

   Multicenter: A study conducted through more than one research center.

   Open label: The term for a study in which participants and staff know which study arm (treatment or the placebo) participants are in; there is no "blinding."

Pharmacokinetics: The study of how the body absorbs, distributes, metabolizes, and eliminates a drug or vaccine.

Placebo: A pill or liquid that is made to look like the treatment being researched but has no active ingredients (e.g., "sugar pill" or saline solution).

Randomization (randomized): The process of assigning study participants to two or more alternative treatments by chance, such as by flipping a coin or rolling a die.

8. ***Make sure that students understand that a randomized, double-blind, placebo-controlled study is considered the "gold standard" of study design.*** These studies are designed to yield scientifically valid results and to decrease bias in both researchers and participants. This study design is considered a highly reliable form of gathering evidence.

An alternative activity for introducing clinical trial vocabulary can be found in *Module Five* of the *Exploring Bioethics* NIH curriculum supplement at: http://science.education.nih.gov/supplements/nih9/bioethics/default.htm.

Part II: Simulation—Conducting a Clinical Trial for a Common Disease

9. Remind students that clinical trials are undertaken ***only after*** years of preliminary research (pre-clinical research), which may include basic discovery science, the use of computer modeling, and cell and tissue cultures. Pre-clinical research also involves animals as model organisms and as research subjects.

10. Tell students that in the simulation, they will need to recruit individuals (represented by beads) who qualify for the study. To qualify, participants must fulfill all of the **inclusion criteria** (conditions that a participant ***must meet***), and exhibit none of the **exclusion criteria** (any condition that would ***disqualify*** a participant).

11. Divide students into small groups and distribute to each student one copy each of Student Handout 5.2—*Understanding Clinical Trials* and Student Handout 5.3—*Clinical Trial Phases*.

12. As a class, read the purpose and title of the Phase I study and go over the meaning of vocabulary words, referring students to the flap book they created in *Part I*. Although study titles can be dense, they are very descriptive if each word is defined and understood individually.

13. Tell students that they will repeat the following steps for each clinical trial phase:

- Read through the phase description as a group and make sure everybody understands the vocabulary words.
- Draw a bead from the population (the color will differ depending on each phase of the trial—see Student Handout 5.3—*Clinical Trial Phases*). Determine whether the person represented by your bead qualifies for the study by rolling the die and referring to the inclusion/exclusion criteria.
- Record information about the study on Student Handout 5.2—*Understanding Clinical Trials*.

14. Have one student representative from each group go to the classroom population bead baggie and scoop out a population of beads for their group. [**Note:** Each group should receive approximately the same number of beads by volume, but beads should be distributed randomly.]

15. ***Conducting the Trials:*** In the same small groups, have students go through the steps outlined in #13 above for each clinical trial phase. Ask students to fill out Student Handout 5.2—*Understanding Clinical Trials* as they do the activity, using Student Handout 5.3—*Clinical Trial Phases* as a guide.

Students may wonder why only male participants are being recruited for the Phase I study. While today most studies strive for gender diversity in their participant pool, men have historically been the primary participants in Phase I and early Phase II clinical trials. From 1977 through the early 1990s, women of childbearing age were excluded from many studies to protect a potential fetus. Women were also left out due to concerns over how potential hormonal changes might affect study results. Leaving women out of studies led to gaps in data for diseases and conditions common in women. This exclusion has been addressed by the National Institutes of Health (NIH) and other funding agencies, and has led to an increase in the participation of women in all phases of clinical trials (Siang, 2000).

16. When students have completed all three trial phases, as a class discuss the answers to Student Handout 5.2—*Understanding Clinical Trials*. Possible answers are provided in Possible Answers to Student Handout 5.2—*Understanding Clinical Trials*.

17. Lead a more in-depth discussion using the following questions. Possible answers are provided in *Possible Answers to Class Discussion Questions*.

    a) How long did the clinical trial process take? How long did the whole process (from idea to the completion of Phase III) take?

    b) Is this medicine ready to be approved for the public? Would you like to first test the drugs on any other populations?

    c) What ethical issues need to be considered if a doctor recruits his or her own patients for a clinical trial that he/she is leading?

    d) If a person has high blood pressure and is interested in having effective and safe medications available for public use, how could they get involved?

    e) If a healthy person is interested in having effective and safe medication available to the public, how could they get involved?

    f) What are some limitations to this model of conducting clinical trials?

18. Tell students that at this point in the development of NW234, the clinical trial results would be presented to the FDA to seek approval for licensure. If licensed, the drug could then be prescribed by a physician for the treatment of high blood pressure for the same groups of people who participated in the human clinical trials (i.e., males and females between the ages of 18 and 55). Patients who are taking the drug would be followed in a **Phase IV trial**, with continued monitoring of the drug for safety, effectiveness, and long-term benefits and/or risks.

Part III: Conducting a Clinical Trial for a Rare Disease

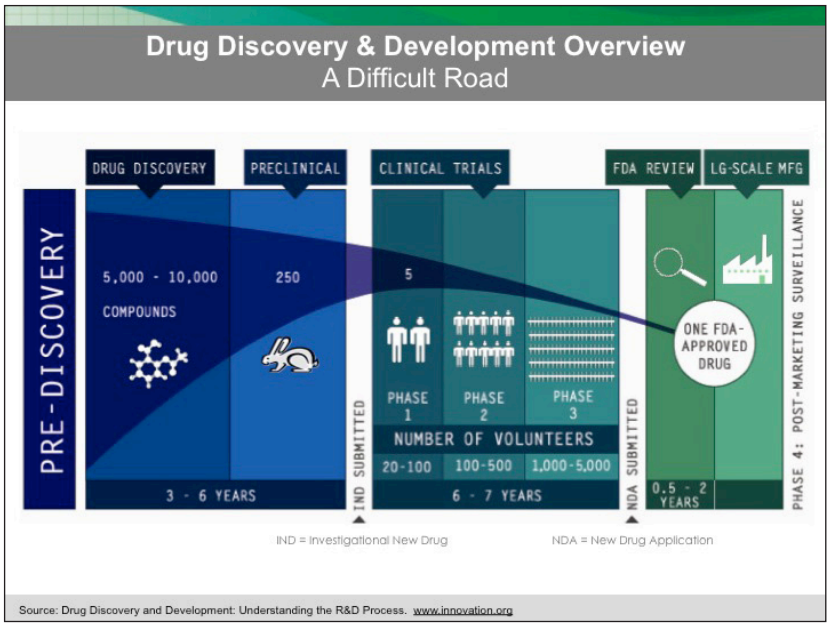
19. Tell students that they have just simulated a trial for a very common disease—high blood pressure—and even with so many people affected by this condition, it can be difficult to recruit enough participants for such a study. How then would a researcher conduct a trial for a rare disease?

20. Ask students what they think defines a rare disease. Tell them that in the U.S., a rare disease is one that affects fewer than 1 in 1,500 people; they are mostly genetic conditions, passed from parent to child.

21. Model the 1/1,500 frequency by dropping ***three beads of a new color*** into the full classroom set of pony beads as explained in *Teacher Preparation*. If the population is still distributed among student groups, teachers may mix the three beads randomly among the groups, or put all three beads into one group's sub-population to demonstrate an uneven distribution of the rare condition.

22. Ask students, "How would a researcher conduct a clinical trial for a rare disease or condition?" Incorporate the following points into the discussion:

    - As a local population, your class will need to join other communities around the country or even the world to find and recruit just a few participants for the trial.
    - **Patient advocacy groups** are critical to rare disease research. These groups are often founded by family members who seek to unite people with rare diseases and propel research forward. The website from one such group, which will be explored in *the RARE* Film Guide, can be found at http://www.hpsnetwork.org.
    - It is difficult for researchers and pharmaceutical companies to spend time, money, and effort getting a drug for an "**orphan**" (rare) **disease** to market because very few people will eventually buy the drug. The **Orphan Drug Act** of 1983 provides incentives to researchers and pharmaceutical companies for developing drugs for rare disorders.
    - Though it is tempting to discount rare diseases as too uncommon to warrant the spending of research dollars, remind students that every bead represents a real person, and in the case of a rare disease, the person is usually a sick child with a family desperate for a cure or treatment.



Closure

23. Show students the "Drug Discovery & Development Overview" PowerPoint slide found under the ***Resources*** tab at http://www.nwabr.org/curriculum/humans-research. Have students turn to a neighbor and share three pieces of information on the slide that they understand, then have the partner share three things. Now ask these pairs to share with the class the ideas they shared with each other. Tell students that for every FDA-approved drug that goes to market, between 5,000 and 10,000 compounds are studied and dismissed.

CONNECTION TO FORMATIVE ASSESSMENT

Revisit the statements students sorted in the *Formative Assessment*. After completing this lesson, students should understand that Statement A is accurate, and that Statements B and F are not accurate.

EXTENSION

Invite students to further their understanding of how clinical trials work by researching and writing about three new things they learned using one of these resources/topics:

- *The New York Times* ran a noteworthy article about cousins with the same disease who chose to participate in a clinical trial. One man was randomized into the placebo group, and the other man received the drug.

  New Drug Stirs Debate on Rules of Clinical Trials, Sept. 18, 2010 http://www.nytimes.com/2010/09/19/health/research/19trial.html?ref=targetcancer.

- The NIH has an informative website covering clinical trial basics: http://www.nih.gov/health/clinicaltrials/basics.htm.

- Students may be interested in reading more about the actual high blood pressure drug on which NW234 was based. The original drug was designated PS433540.

  - Students can see the original study designs for two Phase II trials by going to http://www.clinicaltrials.gov and entering "PS433540" into the search box.

  - An abstract containing PS433540 study results can be found here: http://circ.ahajournals.org/cgi/content/meeting_abstract/118/18_MeetingAbstracts/S_886.

- Students may go to http://www.clinicaltrials.gov to search for trials found in their geographic area, or for trials focused on a specific condition.

GLOSSARY

Animal trial: A medical research trial using non-human animals. Together with cell and tissue cultures, also known as pre-clinical trials.

Blinded study: A study in which participants do not know whether they are receiving the treatment being researched or a placebo.

Cell and tissue cultures: Biological samples used in a preliminary study stage (that precedes animal and human clinical trials) to evaluate whether a new treatment is a good candidate for further study. Together with animal trials, also known as pre-clinical trials.

Clinical trials: Systematic research studies for health-related benefits that involve human participants.

Clinical trial phases: Clinical trials are conducted in three or four phases. Each phase has a different purpose to help researchers answer different questions. Following is an overview of each phase:

Phase I—An experimental drug or treatment is tried on a small group of people (fewer than 100). The purpose is to evaluate its safety and identify any side effects.

Phase II—The experimental drug or treatment is administered to a larger group of people (several hundred) to further assess safety, and to assess questions such as optimal dosing and frequency of dose administration.

Phase III—The experimental drug or treatment is administered to large groups of people (several thousand) to determine its effectiveness, further monitor safety, and compare it with standard or equivalent treatments.

Phase IV—After a drug is licensed by the FDA, researchers track its safety, seeking more information about its risks, benefits, and best use in "real world" settings.

Computer simulation: A technique used in preliminary research that precedes animal and human clinical trials. Computer simulations can help scientists evaluate whether a new treatment is a good candidate for further study.

Diuretic: A drug that promotes the production of urine; a common treatment for hypertension.

Double-blind study: A study in which neither the participants *nor the researchers* know which participants are receiving the treatment being researched and which are receiving a placebo. This information is not available to anyone working with study participants.

Efficacy: Effectiveness as measured in a controlled clinical trial.

FDA (Food and Drug Administration): The U.S. national authority ultimately responsible for the licensure of new drugs and treatments, as well as supervision of clinical trials.

Hypertension: Abnormally high blood pressure.

Inclusion/exclusion criteria: Factors that allow someone to participate in a clinical trial are inclusion criteria. Those that exclude or do not allow participation are exclusion criteria.

Metabolize: To break down or synthesize within the body.

Multicenter: Conducted through more than one research center.

Open label: The term for a study in which participants and staff know which study arm (treatment or the placebo) participants are in; there is no "blinding."

Orphan disease: See "Rare disease."

Orphan Drug Act: The *Orphan Drug Act* of 1983 provides incentives to researchers and pharmaceutical companies for developing drugs for rare disorders.

Patient advocacy group: Often founded by family members, these groups seek to connect people who have rare diseases and move research forward.

Pharmacokinetics: The study of how the body absorbs, distributes, metabolizes, and eliminates a drug or vaccine.

Placebo: A pill or liquid that is made to look like the treatment being researched but does not have any active ingredients (e.g., "sugar pill" or saline solution).

Pre-clinical: Describes stages of preliminary research involving basic discovery science, computer simulation, cell and tissue cultures and animal trials. These stages precede clinical trials (with human participants).

Randomization (randomized): The process of assigning study participants to two or more alternative treatments by chance, such as by flipping a coin or rolling a die.

Rare disease: A disease that affects fewer than 1 in 1,500 people (in the U.S.). They are mostly genetic conditions passed on from parent to child.

Social worker: A professional who deals with the social, emotional, and environmental problems associated with a disease or disability.

RESOURCES

Where to buy pony beads

Pony beads are available at craft stores such as Michael's Craft Stores and Jo-Ann's, or online through many vendors (e.g., http://www.consumercrafts.org).

One package of *Creatology* brand 6 x 9 mm beads (720 beads per package) has a volume of about 325 mL. For the *RARE* Film Guide activity (following the volumes listed in *Teacher Preparation*), you will need:

RARE Film Guide Pony Bead Needs

Yellow	1 package
Red	2 packages
Green	2 packages
Blue	4 packages

At around $3.99/package, the approximate total cost for beads is $36.

SOURCES

Information about clinical trial phases was found at: http://clinicaltrials.gov/ct2/info/understand#Q19.

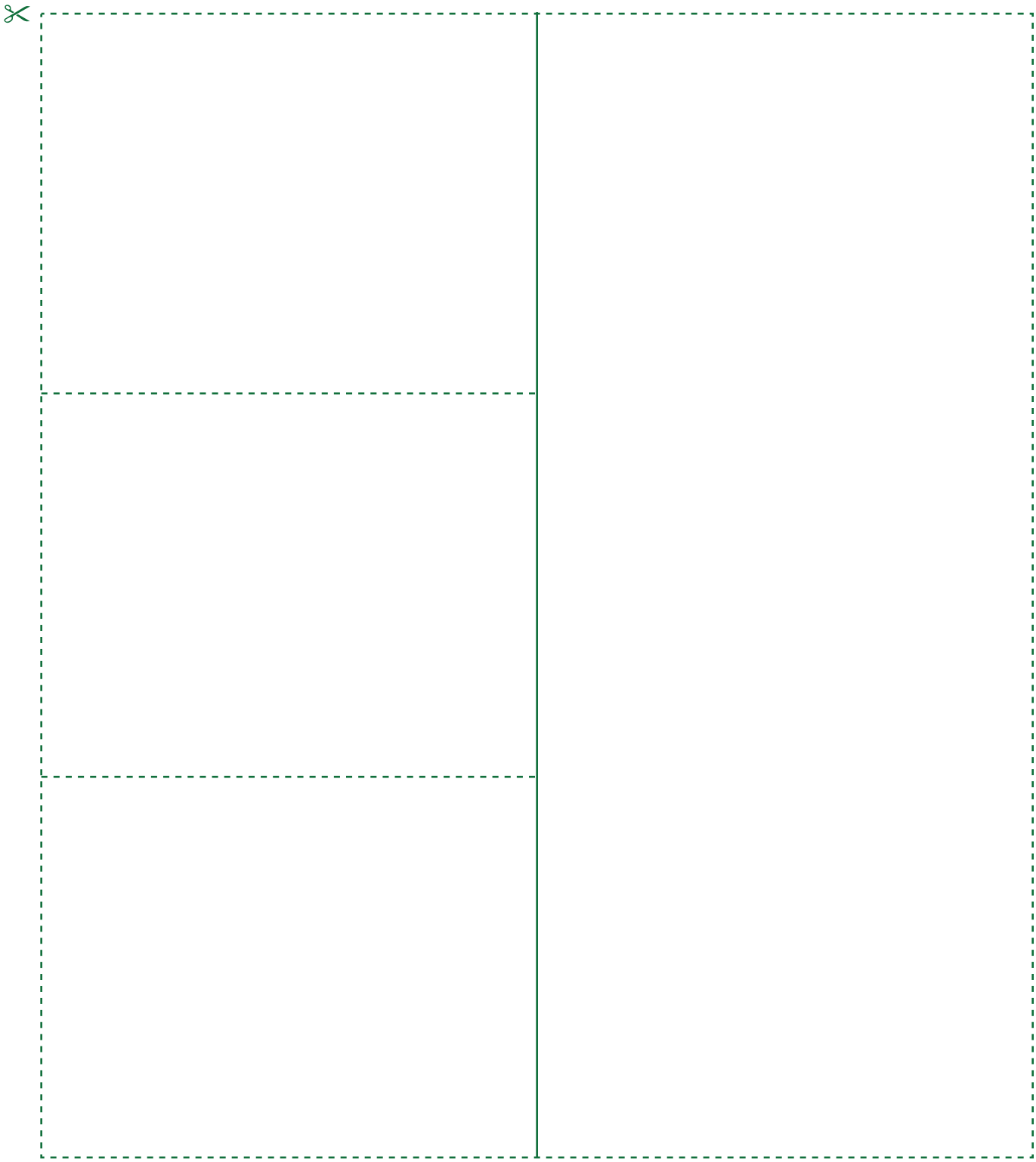
Siang, S. (2000, July 20). The mismeasure of woman: Women and clinical trials. *BioMedNet.com*. Retrieved from: http://www.anapsid.org/cnd/gender/genderdrug2.html.

STUDENT HANDOUT 5.1

Clinical Trial Study Design Flap Book

Name_____ Date_____ Period_____

Directions: Cut along all dotted lines. Fold on all solid lines.



HANDOUT

STUDENT HANDOUT 5.2
Understanding Clinical Trials

Name_____ Date_____ Period_____

	Phase I		Phase II		Phase III	
1. What color bead represents the population in which you are interested?						
2. How did your team recruit volunteers?						
3. Tally the number of times you roll the die in order to enroll 10 participants.	Excluded	Included	Excluded	Included	Excluded	Included
4. How difficult (or easy) was it to recruit enough participants for this phase? Why?						
5. Will the participants in the trial directly benefit from the research taking place?						
6. Who volunteered in this phase of the study? What do you think motivated the volunteers?						
7. How many people total do you need to recruit in this phase						
8. If it took 10 minutes to get 10 participants, how long would it take to get the number you need for the trial?						
9. How many years did this phase take?						

HANDOUT

Possible Answers for STUDENT HANDOUT 5.2
Understanding Clinical Trials

	Phase I	Phase II	Phase III
1. What color bead represents the population in which you are interested?	*Blue*	*Red*	*Red*
2. How did your team recruit volunteers?	*Room and board for week. Additional pay for time. Free health screening and care.*	*Building relationships with doctors who treat patients with high blood pressure to increase patient referrals. Free health screening/ healthcare. Compensation for time.*	*Need for international coordination. Building relationships with doctors who treat patients with high blood pressure to increase patient referrals. Free health screening/healthcare. Compensation for time.*
3. Tally the number of times you roll the die in order to enroll 10 participants.			
4. How difficult (or easy) was it to recruit enough participants for this phase? Why?	*Fairly easy—large pool of healthy people from which to choose.*	*There are a lot of people with high blood pressure, but many were excluded from the trial. The community could support all 250 participants but it would require tremendous community support and additional funding for recruitment efforts.*	*There is no way your community could support a trial for 2,500 participants. It is **multicenter** because you will need to join other research teams. This will likely take place in many countries.*
5. Will the participants in the trial directly benefit from the research taking place?	*Unlikely. They don't even have the condition for which the drug is being developed (at this point in their lives).*	*Unlikely. The drug, if successful, may not be approved for sale for many years. Participant has 50% (1 in 2) chance of getting the placebo.*	*Possibly. Drug approval may still be far off. Participant has 50% (1 in 2) chance of getting the placebo.*
6. Who volunteered in this phase of the study? What do you think motivated the volunteers?	*Young men who could be away from work/ school/family for one week. Possibly motivated by money.*	*People with high blood pressure. Motivated by possible benefits and/or altruism. Free healthcare during the study may be motivating.*	*People with high blood pressure, particularly if current medicine isn't working well. Motivated by possible benefits and/or altruism. Free healthcare during the study may be motivating.*
7. How many people total do you need to recruit in this phase	*50*	*250*	*2,500*
8. If it took 10 minutes to get 10 participants, how long would it take to get the number you need for the trial?	*50 minutes*	*250 minutes (more than 4 hours)*	*2,500 minutes (more than 41 hours)*
9. How many years did this phase take?	*2 years*	*3 years*	*7 years*

RESOURCE

STUDENT HANDOUT 5.3
Clinical Trial Phases

PART I — PHASE I CLINICAL TRIALS

Phase I **clinical trials** are conducted with a small group of volunteers. To test NW234 in this phase, you are looking for ***50 healthy adult volunteers*** who ***do not*** have high blood pressure to participate in your study.

The purpose of this phase is to determine whether NW234 is safe to give humans and to identify any side effects that may exist. In this phase, varying doses of the drug will be given to adult male participants to find out how well the drug is **metabolized** (**pharmacokinetics**), and to determine the range and severity of possible side effects (safety and tolerability).

Study title: *A* **Randomized**, **Open Label**, **Single Dose**, *Study to Evaluate Pharmacokinetics and Safety After Oral Administration of NW234 in Healthy Male Volunteers.*

1. First, get to know the population of your mid-sized city. Each bead represents one person, as described below:

Bead color	Age and condition of individual	Percentage of population
Green	Children (ages 0–17) ***without*** high blood pressure	22%
Yellow	Children (ages 0–17) ***with*** high blood pressure	3%
Blue	Adults (18 and up) ***without*** high blood pressure	56%
Red	Adults (18 and up) ***with*** high blood pressure	19%

2. On Student Handout 5.2—*Understanding Clinical Trials*, record the color of the bead representing a healthy adult.
3. Discuss with your team how you will recruit healthy adult male volunteers who do not have high blood pressure. Where will you recruit volunteers? What do volunteers stand to gain by participating in the trial? Record some of your ideas on the *Student Handout*.
4. To simulate obtaining volunteers, scoop out one container of beads from the classroom population set (the teacher's baggie). These beads represent the part of the population that contacted you in response to your advertisement for study participants.
5. Read the following inclusion and exclusion criteria:

   Inclusion criteria (all of these conditions must be met):

   - Ages 18–55.
   - Male.
   - Gives informed consent to participate.
   - Willing to spend one week at the clinical trial facility without leaving.
   - Must be willing and able to comply with study requirements and restrictions.

   Exclusion criteria (any of these conditions would disqualify someone from participation):

   - Has a history of hypersensitivity to ingredients used in making the drug.
   - Has been diagnosed with low blood pressure or high blood pressure.
   - Has a history of acute infection within 14 days of screening.

6. Pull out a bead that represents a healthy adult male volunteer from your possible participants; assume that only males responded to your recruitment efforts.

HANDOUT

7. Roll the die to determine whether the individual can participate in the study:

If you roll:	Take this action:
1	Just getting over the flu. Cannot participate.
2	Fulfills all inclusion and exclusion criteria. Can participate in trial.
3	Fulfills all inclusion and exclusion criteria. Can participate in trial.
4	Fulfills all inclusion and exclusion criteria. Can participate in trial.
5	Reads over informed consent and objects to required time away from family. Chooses not to participate.
6	An initial physical examination reveals high blood pressure. Cannot participate.

8. Draw individuals (beads) from the pool and roll the die until you have 10 eligible participants who are willing to enroll. Remember, even though you are only drawing until you have 10 qualified beads, Phase I will require 50 participants. Tally the number of times you roll the die on the *Student Handout*.
9. Congratulations! It took two years to recruit participants, run the research study, and analyze your results. The data show that NW234 is well-tolerated, **metabolized** easily by healthy male participants, and has no significant side effects. Answer the rest of the questions on the *Student Handout*. You may now move on to Phase II.
10. Return the Phase I trial participant beads to your group's total population before beginning Phase II.
11. Stop here until your teacher asks you to begin *Part II*.

PART II — PHASE II CLINICAL TRIALS

Phase II clinical trials are conducted with a larger group of volunteers than Phase I. You will need ***250 adult participants*** for this study. In this phase, you will be recruiting adults with high blood pressure, not healthy volunteers, to judge the effectiveness of NW234.

The purpose of this study is to see whether NW234 lowers blood pressure more effectively than the **placebo**, and to see how safe NW234 is compared to the placebo.

Study title: Randomized, **Double-Blind**, **Placebo-Controlled** *Study to Evaluate the Safety and* **Efficacy** *of NW234 in Subjects with* **Hypertension**

1. You are still working in the same mid-sized city and your population remains the same. Each bead represents one person, as described below:

Bead color	Age and condition of individual	Percentage of population
Green	Children (ages 0–17) ***without*** high blood pressure	22%
Yellow	Children (ages 0–17) ***with*** high blood pressure	3%
Blue	Adults (18 and up) ***without*** high blood pressure	56%
Red	Adults (18 and up) ***with*** high blood pressure	19%

2. On Student Handout 5.2—*Understanding Clinical Trials*, record the color of the bead that represents an adult with high blood pressure.
3. Discuss with your team how you will recruit volunteers. Where will you recruit? What do volunteers stand to gain by participating in the trial? Record some of your ideas on the *Student Handout*.

HANDOUT

4. Read the following inclusion and exclusion criteria:

Inclusion criteria (all of these conditions must be met):

- Males or females 18–55 years old.
- Moderately high blood pressure.
- Subjects must have a daytime work schedule; nightshift workers cannot participate.
- Women of child-bearing potential and male subjects must use two reliable forms of contraception if they are sexually active in a manner that could lead to pregnancy. Alternatively, female subjects must be postmenopausal (for at least one year) or show documentation of hysterectomy.
- Must be willing and able to comply with study requirements and restrictions.

Exclusion criteria (any of these conditions would disqualify someone from participation):

- Subjects with ongoing, serious medical disorders; this includes diseases of the kidney, lungs, gastrointestinal or nervous systems, current history of cancer, or psychiatric disease.
- Subjects with a history of heart attack or heart failure within the last six months.
- Subjects with a history of a head injury or stroke within the last year.
- Subjects with diabetes.

5. Pull out a bead representing an adult with high blood pressure from your population; assume that only people within the correct age range responded to your recruitment efforts.

6. Roll the die to determine whether the individual fits the study criteria:

If you roll:	Take this action:
1	Blood pressure too low. Cannot participate.
2	Fulfills all inclusion and exclusion criteria. Can participate in trial.
3	Fulfills all inclusion and exclusion criteria. Can participate in trial.
4	Fulfills all inclusion and exclusion criteria. Can participate in trial.
5	Reads over informed consent and objects to treatment. Chooses not to participate.
6	Blood pressure too high. Cannot participate.

7. Draw individuals from the pool and roll the die until you have 10 volunteers. Tally the number of times you roll the die on the *Student Handout*.

8. Remember, you need 250 participants for this phase. Do you think recruiting enough participants will be a problem given your current population?

9. Congratulations! The results of your trial show that the drug significantly lowers blood pressure, is safe and well-tolerated, and has no side effects different from those found with the placebo. It took three years to recruit participants, run the research study, and analyze your results. Answer the questions on the *Student Handout* and proceed to Phase III clinical trials.

10. Return the Phase II trial participant beads to your group's total population before beginning Phase III.

PART III — PHASE III CLINICAL TRIALS

In Phase III, NW234 will be given to a large group of people (***2,500*** for this study). You will be recruiting adults with high blood pressure, not healthy volunteers, to participate in this phase.

The purpose is to determine the effectiveness of NW234, monitor side effects, further assess safety, and compare the drug to commonly used treatments.

Study title: *A* **Multicenter**, **Double-blind**, **Randomized**, **Placebo-controlled** *Study to Assess the* **Efficacy** *and Safety of NW234 in Subjects with Hypertension Currently Receiving Treatment with a* **Diuretic**

[**Note:** A diuretic is a common type of blood pressure medication. Participants will continue taking their diuretic during this study.]

1. You are still working in the same mid-sized city and your population remains the same. Each bead represents one person, as described below:

Bead color	Age and condition of individual	Percentage of population
Green	Children (ages 0–17) ***without*** high blood pressure	22%
Yellow	Children (ages 0–17) ***with*** high blood pressure	3%
Blue	Adults (18 and up) ***without*** high blood pressure	56%
Red	Adults (18 and up) ***with*** high blood pressure	19%

2. On Student Handout 5.2—*Understanding Clinical Trials*, record the color of the beads that represent an adult with high blood pressure.
3. Discuss with your team how you will recruit adult volunteers. Where will you recruit? What do volunteers stand to gain by participating in the trial? Record some of your ideas on the *Student Handout*.
4. Read the following inclusion and exclusion criteria:

   Inclusion criteria (all of these conditions must be met):

   - Males or females, ages 18–55.
   - Diagnosed high blood pressure.
   - Subjects have been taking a diuretic to control elevated blood pressure for at least 90 days.
   - Women of child-bearing potential and male subjects must use two reliable forms of contraception if they are sexually active in manner that could lead to pregnancy. Alternatively, female subjects must be postmenopausal (for at least one year) or show documentation of hysterectomy.
   - Must be willing and able to comply with study requirements and restrictions.

   Exclusion criteria (any of these conditions would disqualify someone from participation):

   - Subjects taking two or more medications to control high blood pressure (not including diuretics).
   - Subjects with severe high blood pressure.
   - Subjects with previous experience of heart failure.
   - Subjects with diabetes.
   - Pregnant or nursing women.
   - Subjects with ongoing, serious medical disorders including diseases of the kidney, lungs, gastrointestinal or nervous systems, current history of cancer, or psychiatric disease.
5. Pull out a bead representing an adult with high blood pressure from your population; assume that only people within the correct age range responded to your recruitment efforts.

HANDOUT

6. Roll the die to determine whether the individual fits the study criteria:

If you roll:	Take this action:
1	Blood pressure too low. Cannot participate.
2	Pregnant or wishes to become pregnant in next three years. Cannot participate.
3	Fulfills all inclusion and exclusion criteria. Can participate in trial.
4	Fulfills all inclusion and exclusion criteria. Can participate in trial.
5	Reads over informed consent and objects to treatment. Chooses not to participate.
6	Blood pressure too high. Cannot participate.

7. Draw individuals (beads) from the pool and roll the die until you have 10 volunteers. Tally the number of times you roll the die on the *Student Handout*.

8. Remember, you need 2,500 participants for this study. Do you think recruiting enough participants will be a problem given your current population? What word in the title of the study addresses this?

9. Congratulations! The results of your trial show that the drug significantly lowers blood pressure for those people taking a diuretic, is safe and well-tolerated, and has no side effects different from those found with the placebo. It took seven years to recruit participants, run the research study, and analyze your results. You are now ready to submit your results to the FDA to seek licensure, which may take up to two years.

10. You are feeling exceptionally fortunate. NW234 is one of 5,000 to 10,000 (on average) compounds tested in the laboratory to progress through **pre-clinical research** and all three phases of human trials to be ready for a New Drug Application to the FDA.

11. Answer the remaining questions on the *Student Handout*.

12. As a challenge, name your drug—NW234 is not going to appeal to the public!

Clinical trials: Systematic research studies for health-related benefits that involve human participants.

Diuretic: A drug that promotes the production of urine; a common treatment for hypertension.

Efficacy: Effectiveness as measured in a controlled clinical trial.

Exclusion criteria: Any of the conditions that would disqualify someone from participating in a study.

Hypertension: Abnormally high blood pressure.

Inclusion criteria: All of the conditions that must be met for someone to participate in a study.

Metabolize: To break down or synthesize within the body.

Multicenter: Conducted through more than one research center.

Open label: The term for a study in which participants and staff know which study arm (treatment or placebo) participants are in; there is no "blinding."

Pharmacokinetics: The study of how the body absorbs, distributes, metabolizes, and eliminates a drug or vaccine.

Placebo: A pill or liquid that is made to look like the treatment being researched but has no active ingredients (e.g., "sugar pill" or saline solution).

Pre-clinical: Describes stages of preliminary research involving basic discovery science, computer simulation, cell and tissue cultures, and animal trials. These stages precede clinical trials (with human participants).

Randomization (randomized): The process of assigning study participants to two or more alternative treatments by chance, such as by flipping a coin or rolling a die.

TEACHER RESOURCE 5.1
Clinical Trial Study Designs

PHASE I STUDY DESIGN

Purpose of Phase I: To determine whether NW234 is safe for use in humans, and to learn more about how NW234 works in order to design future trials.

Study title: *A* **Randomized**, **Open Label**, *Single Dose Study to Evaluate* **Pharmacokinetics** *and Safety After Oral Administration of NW234 in Healthy Male Volunteers*

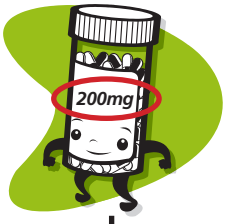
Qualified Study Participants

Randomized
Those who qualify are randomly put into one of the two study "arms" (groups).

Participants are monitored to see how the body **metabolizes** this dose of NW234. Side effects are noted.

Participants are monitored to see how the body metabolizes this dose of NW234. Side effects are noted.

Open Label
Participants and staff know which study arm participants are in.



All data are analyzed.

Participants are monitored to see how the body metabolizes the second administration of this dose of NW234. Side effects are noted.

Participants are monitored to see how the body metabolizes the second administration of this dose of NW234. Side effects are noted.

RESOURCE

PHASE II STUDY DESIGN

Purpose of Phase II: To see whether NW234 lowers blood pressure better than a placebo, and to see how safe NW234 is compared to a placebo.

Study title: Randomized, Double-Blind, Placebo-Controlled *Study to Evaluate the Safety and Efficacy of NW234 in Subjects with Hypertension*

Qualified Study Participants

Randomized
Those who qualify are randomly put into one of the two study "arms" (groups).

Participants are monitored to see how the drug works. Side effects are noted. Repeated for 28 days.

Participants are monitored to see how the drug works. Side effects are noted. Repeated for 28 days.

All data are analyzed.

Blind Study
Participants do not know which level of medicine or placebo they are receiving.

Double-blind
Neither participants ***nor the researchers*** know which treatment the participant is receiving.

?

Placebo-controlled
Placebos contain no medicine or treatment. They serve as a control for the research study.

RESOURCE

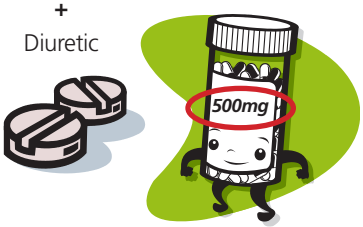
PHASE III STUDY DESIGN

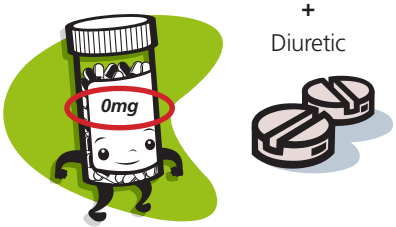
Purpose of Phase III: To assess the effectiveness of NW234, to assess safety, and to compare NW234 to commonly used treatments.

Study title: *A* **Multicenter**, **Double-blind**, **Randomized**, **Placebo-controlled** *Study to Assess the Safety and Efficacy of NW234 in Subjects with Hypertension Currently Receiving Treatment with a Diuretic*
[**Note**: a diuretic is a common type of blood pressure medication. Participants will continue taking their diuretic during this study.]

Qualified Study Participants

\+ Diuretic





\+ Diuretic

Randomized
Those who qualify are randomly put into one of the two study "arms" (groups).

Participants are monitored for safety. Side effects are noted.

Health checks done after six weeks; then every 12 weeks for three years.

Participants are monitored for safety. Side effects are noted.

All data are analyzed.
Drug **efficacy** is determined.

Multicenter
This study requires too many participants to be run in one location, so several research centers are involved to enroll the required number of participants.

RESOURCE

Possible Answers for
Class Discussion Questions (From *Part II: Simulation*, step 17)

a) How long did the clinical trial process take? How long did the whole process (from idea to completion of Phase III) take?

The three clinical trial phases took 12 years to complete. Early drug discovery and animal studies took five years. The total time is 17 years.

b) Is this medicine ready to be approved for the public? Are there any other subjects on whom you would like to test the drug?

This drug may be licensed for certain people in the public, but this drug has not yet been tested on pregnant women or children, both of whom may have high blood pressure. NW234 would need to undergo more trials before being licensed for all groups.

c) What ethical issues might arise if a doctor recruits his or her own patients for a clinical trial that he or she is leading?

As a personal physician, the doctor's focus should be on his or her patients' health and welfare. When enrolling patients into a clinical trial, the focus is finding out if the drug is safe and effective. The individual patient should not expect to benefit personally from participation in the trial since the drug may not be effective, or the patient may be randomized into the placebo group. **Conflicts of interest** *may also arise if the doctor has a financial interest in the outcome of the research study.*

d) If a person has high blood pressure and is interested in having effective and safe medications available to the public, how could that person get involved?

A robust system of clinical trials requires community participation and support. New drugs and treatments cannot become available to the public without people enrolling in clinical trials. People are also needed to be part of community advisory boards, to help advertise and promote clinical trials to the public, and to assist with public education and outreach.

e) If a healthy person is interested in having effective and safe medication available to the public, how could that person get involved?

A robust system of clinical trials requires community participation and support. New drugs and treatments cannot become available to the public without people enrolling in clinical trials. You do not have to have a disease or condition to enroll in clinical trials. People are also needed to be part of community advisory boards, to help advertise and promote clinical trials to the public, and to assist with public education and outreach.

f) What are some limitations to this model of clinical trials?

Our simulation made a number of assumptions that would not be true in the real world. Two major assumptions are:

- *Any "red bead" (person with high blood pressure) could be drawn and possibly participate. In reality it is much harder to enroll study participants. Researchers and clinical coordinators work very hard to identify, engage, and recruit individuals who might qualify for a study. It is common for trials to be delayed or even canceled due to lack of enrollment.*
- *Nobody drops out of a study once it begins. In reality, a person can drop out of a trial at any time for any reason, and studies lose people in this way. Poor retention of study participants can undermine the validity of study results.*