The Science and Ethics of **Humans in Research**

Grades 7-12 | First Edition

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The Science and Ethics of Humans in Research

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Credits

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The Science and Ethics of Humans in Research

CURRICULUM OVERVIEW

Why do scientists involve human participants in biomedical research? Who participates in research and why? Furthermore, how does the complex—and sometimes difficult—history of humans in research influence current attitudes, policies, and practices?

This curriculum introduces students to the way research is conducted with human participants, the related rules and regulations, and the bioethical principles that guide scientists when working with humans in research. Lesson strategies and bioethical discussions engage students in science content and promote an understanding of the role of science in society.

RESEARCH ETHICS SERIES ENDURING UNDERSTANDINGS

- The biomedical research process is interconnected, complex and dynamic, requiring information and tools of reasoning.
- The biomedical research process is driven by the future benefit to people and animals.
- The biomedical research process has evolved due to analytical reflection by society and scientists regarding accepted practices and continues to do so as our knowledge expands.
- The biomedical research process requires active participation by scientists, consumers, clinicians, citizens, and research participants.

The Science and Ethics of Humans in Research curriculum is part of NWABR's Research Ethics Series, which also includes *The Nature of Scientific Research*, and *The Science and Ethics of Animal Research* (see page 8).

INSTRUCTIONAL COMPONENTS

Elements: The curriculum consists of a formative assessment, five sequential lessons, a film guide for the movie *RARE*, and a summative assessment.

Time:

Element	Approximate Time Required
Formative Assessment	20 minutes
Lessons One through *Five*	1 class period of 55 minutes each
RARE Film Guide	1–2 class periods of 55 minutes each
Summative Assessment	1 class period to begin; additional time depends on how much in-class time is given for writing the paper.

Targeted Audiences: Grades 7–12

Systems Thinking

Science is a human enterprise conducted in a social context; science and its technological applications clearly have interconnected ethical implications. This curriculum seeks to integrate elements of the research endeavor and impact student learning in the following ways:

- Students learn to look at the interconnections between parts in a system rather than looking at qualities of separate objects.
- Students see a "web" of interconnection between a set of events, rather than thinking linearly about the events.
- Students understand that a whole system may have different properties than the parts of the system.

Fostering a Safe Classroom Environment

It is especially important to foster a safe classroom atmosphere when students must consider and discuss possibly controversial issues. The ethical issues addressed throughout this curriculum may involve conflicting moral choices. Please review or create classroom discussion ground rules ("norms") before beginning the unit (*see Appendix, Creating Discussion Ground Rules*).

THE SCIENCE AND ETHICS OF HUMANS IN RESEARCH

Essential Questions

1. How does the history of research with humans influence attitudes, policies, and current practices?
2. Why do scientists involve humans in research? How do scientists recruit, engage, and partner with study participants?
3. What is the process used to make decisions regarding humans in research, and how are costs and benefits evaluated?
4. How does the process of carrying out ethical trials involving humans influence the amount of time needed to develop new cures and treatments?
5. How can my actions reflect my position on research involving humans?

LESSON OVERVIEW

The ***5 E Learning Cycle Model***, as publicized through its use in the BSCS (Biological Sciences Curriculum Study) science program, incorporates five phases of learning: engagement, exploration, explanation, elaboration, and evaluation. The lessons in this curriculum follow the 5 E Model to guide students through this powerful cycle of learning. In the lesson plan descriptions provided below, notes indicate which stage of the 5 E Learning Cycle Model aligns with each lesson plan.

Formative Assessment: Identifying Misconceptions

"Engage"
Students begin the unit with an activity in which they sort their prior knowledge and any misconceptions about research involving human participants. In the *Human Research Background Sort*, students decide whether research statements are accurate or not by sorting them into two categories and explaining their reasoning. This helps teachers elicit student ideas about research involving human participants and take into consideration the students' prior knowledge for the remainder of the unit. Students will revisit these statements throughout the unit to confirm or refute their positions.

Lesson One: Historical Context of Humans in Research

"Explore & Explain"
In this lesson, students gain insight into the historical context of human participants in research. Students participate in an activity in which they analyze four historically notable case studies where ethics remain unclear. Students develop their own list of ethical guidelines by creating a concept map and then comparing their guidelines to the principles outlined in the Belmont Report: Respect for Persons (including autonomy), Beneficence, and Justice. This lesson provides a preliminary understanding of the difficulties and considerations that need to be taken into account when involving humans in research.

Lesson Two: Applying the Belmont Principles

"Elaborate"
In this lesson, students apply the principles outlined in the Belmont Report to complex case studies involving human participants as research subjects. Students analyze a case using the concept map they produced in *Lesson One*. They then work together in mixed-case groups to present their findings and evaluate each other's work using a peer evaluation process.

Lesson Three: Institutional Review Boards—The Nitty Gritty

"Explore"
Students are introduced to the concept of an Institutional Review Board (IRB), also known as an Ethics Committee (EC), and perform a skit to learn about the regulations and membership requirements of an IRB. Students use the information learned from the skit to further discuss the rationale for having IRBs evaluate research studies involving humans. In small groups, students visit different stations to perform three activities typical of the work of IRBs. They work together to 1) simplify the language of a section of an informed consent document to be more easily understood, 2) analyze three advertisements made for fictional clinical trials to assess whether they are accurate and/or coercive, and 3) examine a segment of a research proposal written by an investigator describing the process for obtaining informed consent. Students report back to the class on their experience and discuss the benefits and limitations of the rigorous IRB process. Lastly, students read an article in which bioethicists encourage shorter, easier to understand consent forms.

Lesson Four: Participating In Research

"Explore & Elaborate"
Students begin by gathering their own behavioral, medical, and genetic information, and prepare a cheek swab DNA sample. Next, students consider using their information to participate in a number of simulated research projects. This leads to a discussion about how the amount of time, degree of involvement, level of risk, and reasons for participation can vary for different types of research studies. Finally, students think about the ramifications of the fast-growing technology of biobanking in the context of clinical research and discuss their personal views.

Lesson Five: Clinical Trials

"Explore & Explain"
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.

RARE Film Guide: Curriculum Supplement—Exploring Rare Disease Research

"Elaborate"
This activity is designed to be used with the film *RARE*, a documentary that explores the major issues affecting people living with a rare genetic disorder, Hermansky-Pudlak Syndrome (HPS). Before the film, students explore and share their ideas about general themes in the film by responding to statements in a *Silent Chalk Talk*. Students are then asked to view the film from the perspective of a stakeholder in regard to a clinical trial testing a new drug for HPS. Stakeholders include Donna Appell, a mother working to find a cure for her 21-year-old daughter who has HPS; Heather Kirkwood, a woman with HPS who is involved in a clinical trial for a drug to treat people with HPS; and Dr. William Gahl, a researcher from the National Institutes of Health (NIH) who works with people with HPS and runs the clinical trial in which Heather is enrolled. After watching the film, students gather for another *Silent Chalk Talk*, and meet in small groups to discuss the film's ethical issues from different perspectives.

Summative Assessment: Position Paper

"Evaluate"
Students demonstrate what they have learned over the course of the unit by identifying and justifying their personal position regarding their own participation in a real clinical trial. Students evaluate a trial using a decision-making model to consider ethical protections, the scientific and social value of the trial, and the potential risks and benefits of their possible participation in the trial. Students then write a paper detailing how their decision to participate or not reflects their position on research involving humans.

RESEARCH ETHICS SERIES

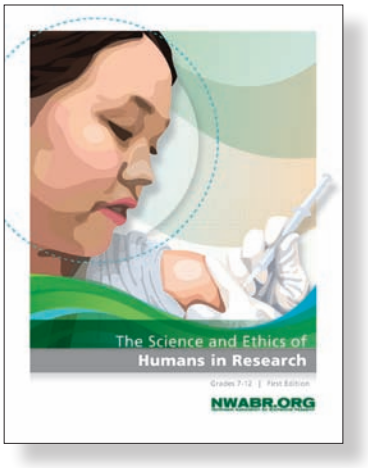
The Science and Ethics of Humans in Research is part of the following curricular set:

The Social Nature of Scientific Research

- How is scientific research different from other ways of discovery and learning about the world?
- How does the ethical conduct of scientific research lead to a process that promotes accountability, integrity, and intellectual honesty?
- How are scientific research and society shaped and influenced by each other?
- How does scientific research develop and change in response to new evidence, knowledge, and the application of new tools?
- What is my role and responsibility in being a scientifically literate citizen?

The Science and Ethics of Animal Research

- Why do scientists use animals in research?
- How does the history of animal research influence current views and policies?
- How do ethical considerations influence the use of animals in research?
- How can my actions reflect my position on the use of animals in research?



The Science and Ethics of Humans in Research

- How does the history of research with human participants influence attitudes, policies, and current practice?
- Why do scientists involve humans in research? How do scientists recruit, engage, and partner with study participants?
- What is the process used to make decisions regarding humans in research, and how are costs and benefits evaluated?
- How does the process of carrying out ethical trials involving humans influence the time needed to develop new cures and treatments?
- How can my actions reflect my position on research involving humans?

Each unit is designed to be used independently or as part of a larger curricular set.
All three units are available from http://www.nwabr.org.

CORRELATION TO NATIONAL LEARNING STANDARDS

National Standards Alignment: Science (Grades 5–12)

	Lesson One: Historical Context	**Lesson Two:** Applying the Belmont Principles	**Lesson Three:** IRBs—The Nitty Gritty	**Lesson Four:** Participating in Research	**Lesson Five:** Clinical Trials	***RARE* Film Guide**
Science as Inquiry						
Abilities necessary to do scientific inquiry				•	•	•
Understandings about scientific inquiry	•	•		•	•	•
Science and Technology						
Abilities of technological design.					•	
Understandings about science and technology.	•	•	•			
Science in Personal and Social Perspectives						
Personal and community health.	•	•	•	•	•	•
Science and technology in local, national, and global challenges.	•	•	•	•	•	•
History and Nature of Science						
Science as human endeavor.	•	•	•	•	•	•
Nature of scientific knowledge.	•	•		•	•	•
Historical perspectives	•	•				

Source: National Research Council. 1996. *National Science Education Standards*. Washington, D.C.: National Academies Press.

Common Core State Standards

For English Language Arts & Literacy in History/Social Studies, Science, and Technical Subjects

	Lessons 1–5
Comprehension and Collaboration, Grades 9–10	
1. Initiate and participate effectively in a range of collaborative discussions (one-on-one, in groups, and teacher-led) with diverse partners on topics, texts, and issues, building on others' ideas and expressing their own clearly and persuasively.	•
a. Come to discussions prepared, having read and researched material under study; explicitly draw on that preparation by referring to evidence from texts and other research on the topic or issue to stimulate a thoughtful, well-reasoned exchange of ideas.	•
b. Work with peers to set rules for collegial discussions and decision-making (e.g., informal consensus, taking votes on key issues, presentation of alternate views), clear goals and deadlines, and individual roles as needed.	•
c. Propel conversations by posing and responding to questions that relate the current discussion to broader themes or larger ideas; actively incorporate others into the discussion; and clarify, verify, or challenge ideas and conclusions.	•
d. Respond thoughtfully to diverse perspectives, summarize points of agreement and disagreement, and, when warranted, qualify or justify their own views and understanding and make new connections in light of the evidence and reasoning presented.	•

Source: National Governors Association Center for Best Practices, Council of Chief State School Officers. 2010. *Common Core State Standards for English Language Arts & Literacy in History/Social Studies, Science, and Technical Subjects*. Washington, D.C.: National Governors Association Center for Best Practices, Council of Chief State School Officers.

Framework for K–12 Science Education

	Lesson One: Historical Context	**Lesson Two:** Applying the Belmont Principles	**Lesson Three:** IRBs—The Nitty Gritty	**Lesson Four:** Participating in Research	**Lesson Five:** Clinical Trials	***RARE* Film Guide**
Scientific Practices						
1. Asking Questions	•	•		•		•
2. Developing and Using Models	•			•	•	
3. Planning and Carrying Out Investigations				•	•	•
4. Analyzing and Interpreting Data	•	•	•	•	•	•
5. Using Mathematics, Information and Computer Technology, and Computational Thinking						
6. Constructing Explanations	•	•	•		•	•
7. Engaging in Argument From Evidence	•	•	•		•	•
8. Obtaining, Evaluating, and Communicating Information	•	•	•	•	•	•
Crosscutting Concepts						
Patterns	•	•				
Systems and System Models	•	•		•	•	•
Energy and Matter: Flows, Cycles, and Conservation						
Core Ideas: Life Sciences						
LS 1: From Molecules to Organisms: Structures and Processes						•
LS 2: Ecosystems: Interactions, Energy, and Dynamics D: Social Interactions and Group Behaviors	•	•				•
LS 3: Heredity: Inheritance and Variation of Traits						•

Source: National Research Council. 2011. *A Framework for K-12 Science Education: Practices, Crosscutting Concepts, and Core Ideas*. Washington, D.C.: National Academies Press.

Formative Assessment
Identifying Misconceptions

INTRODUCTION

Students begin the unit with an activity in which they consider their prior knowledge and identify misconceptions they may have about research involving human participants. In the *Human Research Background Sort*, students decide whether research statements are accurate or not by sorting them into two categories and explaining their reasoning. This helps teachers elicit student ideas about research involving human participants and take into consideration the students' prior knowledge for the remainder of the unit. Students will revisit these statements throughout the unit to confirm or refute their positions.

CLASS TIME

About 20 minutes.

KEY CONCEPTS

- Human participation in research studies is part of a multi-step process in which new medicines, prevention tools, treatments, and medical devices are made available to the public.
- Involving humans in research brings up a number of ethical considerations.

ASSESSING AND ADDRESSING STUDENT MISCONCEPTIONS

In order to advance student scientific thinking process, it's important for teachers to ask thought-provoking questions about the topic and acknowledge any student misconceptions. The concepts presented in this *Formative Assessment* are relevant to the entire *Understanding Research and Ethics* curriculum series, which includes this module on humans in research. In *Benchmarks for Scientific Literacy: The Research Base*, the American Association of the Advancement of Science (AAAS) revealed some common misconceptions about the history of science pertinent to this curriculum:

- Research has shown that when students are exposed to the history of science, they view science as a "more philosophical, historical, and humanitarian discipline than they had thought." (AAAS, 2009).
- Students may have difficulty understanding the points of view of people in the past, and think that these people were "dumb" or "just didn't get it." It's important for students to grasp that historic values, beliefs, and attitudes may differ from those of today (AAAS, 2009).
- Students show little regard for the thinking of scientists whose theories they know are no longer supported by the data (AAAS, 2009).
- Students don't realize that values, beliefs, and attitudes may be different between cultures within a given population or between populations (AAAS, 2009).

LEARNING OBJECTIVES

Students will:

- Express their ideas about humans in research.

MATERIALS

Materials	Quantity
Student Handout FA-1—*Formative Assessment: Humans in Research Background Sort* [**Note:** Alternatively, you may project the *Student Handout* and ask students to write the answers in their notebooks.]	1 per student
Possible Answers for Student Handout FA-1—*Formative Assessment: Humans in Research Background Sort*	1

NOTE TO THE TEACHER

The National Research Council (NRC) has done extensive research on the cognitive and developmental aspects of learning. Their research shows that students learn science best when certain principles are met. These are a deliberate acknowledgement of and connection to prior knowledge, a connection between what they are learning and "big ideas," and a meta-cognitive reflection on the learning accomplished. Basically, students need to know what they thought before a concept was introduced, what they are being taught *and* why, followed by time for reflection back on what they learned and *how their thinking changed*. Without this reflection, many students will revert back to their prior knowledge even after direct instruction and activities. Sometimes students will remember the information long enough to take a test on it before reverting back to prior knowledge (NRC, 2005).

Before beginning this activity, review the Possible Answers for Student Handout FA-1—*Formative Assessment: Humans in Research Background Sort*.

TEACHER PREPARATION

- Make copies of *Student Handout*.

PROCEDURE

Activity One: Humans in Research Background Sort

1. Pass out one copy of the Student Handout FA-1—*Humans in Research Background Sort* to each student, and ask students to work on it for about 10 minutes. [**Note:** Alternatively, you may project the *Student Handout* and ask students to sketch a chart and write the answers in their notebooks.]
2. As a class, invite students to share their thoughts, expressing how they sorted the statements and why.
3. Work together as a class to decide whether each statement is accurate or not and record this on a class chart, PowerPoint, overhead transparency, or other visual aid. Fill in the chart with answers from the class as a whole; this chart will be revisited throughout the unit. At this point in the unit, the goal is not to have all of the statements in the correct place, but to have students decide as a group whether each statement is accurate or inaccurate.

Closure

4. Tell students that you will be referring back to these answers throughout the unit.

You will revisit the *Formative Assessment* statements at the end of each unit lesson using the class statement sort chart as a reference. Use this as a time for reflection, when students have a chance to confirm or refute/change where statements are placed on the class chart.

SOURCES

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STUDENT HANDOUT FA-1

Formative Assessment: Human Research Background Sort

Name_____ Date_____ Period_____

Instructions:
Sort the following statements (identifying them by A, B, C, D, E, or F) into "accurate" or "not accurate" and explain why you sorted the answers the way you did.

A) Most of our medicines and modern medical treatments would not be available without experiments that were done on people.

B) Because the general public is pushing for new treatments, medications, and prevention methods, researchers often have to turn away qualified people who want to participate in studies because the studies are full.

C) Scientists follow several established guidelines to respect the privacy, dignity, and culture of their human participants.

D) Cells or tissue samples left over from medical tests performed by doctors or nurses can be used in experiments without patient permission.

E) All of the current regulations for research involving humans today, compared to years past, means there are few or no ethical problems or debates about research involving humans.

F) Computer simulations are making research with humans unnecessary.

These statements are accurate (EXPLAIN WHY).	These statements are not accurate (EXPLAIN WHY).

HANDOUT

Possible Answers for STUDENT HANDOUT FA-1
Formative Assessment: Human Research Background Sort

Instructions:
Sort the following statements (identifying them by A, B, C, D, E, or F) into "accurate" or "not accurate" and explain why you sorted the answers the way you did.

A) Most of our medicines and modern medical treatments would not be available without experiments that were done on people.

B) Because the general public is pushing for new treatments, medications, and prevention methods, researchers often have to turn away qualified people who want to participate in studies because the studies are full.

C) Scientists follow several established guidelines to respect the privacy, dignity, and culture of their human participants.

D) Cells or tissue samples left over from medical tests performed by doctors or nurses can be used in experiments without patient permission.

E) All of the current regulations for research involving humans today, compared to years past, means there are few or no ethical problems or debates about research involving humans.

F) Computer simulations are making research with humans unnecessary.

These statements are accurate (EXPLAIN WHY).	These statements are not accurate (EXPLAIN WHY).
A) Most medicines and modern medical technologies would not be available without experiments that were conducted with humans. This includes insulin used to treat diabetes, prosthetic limbs, birth control hormones, etc. *C) There have been many unethical studies done on humans in the name of "scientific progress." Many times these studies were a result of scientists dehumanizing their subjects. As a result, scientists follow ethical guidelines (i.e., The Belmont Report) developed to explain how subjects should be treated during the research process.* *D) There are different rules regarding cells or tissues in different medical settings and different states, but often after a medical or clinical test (like a biopsy, a Pap Smear, a simple surgery, or blood draw), leftover cells are considered "medical waste" and can be used by scientists without patient permission. Many times the patient will have signed a form that says s/he understands that the tissues/cells could be used, although the patient may or may not understand what they are agreeing to.*	*B) It is common for research studies relying on human participants to be behind schedule or even canceled because researchers can't recruit enough qualified people to participate in the studies.* *E) Even though there is more research regulation from Institutional Review Boards and scrutiny from the public due to the internet, research studies often bring up ethical questions.* *F) Although computer simulations may be a part of the experimental process, human volunteers are required for all levels of clinical research. Computer modeling is usually considered part of "pre-clinical" research (studies that do not involve human participants). Typically, successful computer modeling and research with animals are used to justify why a study should move forward into the human trial phase.*

RESOURCE

LESSON 1:
Historical Context of Humans in Research

INTRODUCTION

In this lesson, students gain insight into the historical context of human participants in research. Students participate in an activity in which they analyze four historically notable case studies where **ethics** remain unclear. Students develop their own list of ethical guidelines by creating a concept map and then comparing their guidelines to the principles outlined in the **Belmont Report**: Respect for Persons (including autonomy), **Beneficence**, and Justice. This lesson provides a preliminary understanding of the difficulties and considerations that need to be taken into account when involving humans in research.

CLASS TIME

One to two class periods of 55 minutes.

KEY CONCEPTS

Ethics is a discipline that focuses on questions of values, and a practice that requires reasoned judgments. Some ethical considerations related to human participation in research include:

- **Autonomy**.
- **Informed consent**.
- Assessment of risks and benefits.
- Selection of subjects.
- Identification of **vulnerable populations**.
- Possible compensation for participants.

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

Student will know:

- Ethical judgments are required when research is done with human participants.
- Researchers must follow ethical guidelines that result in the consideration of populations that are used for research.

Students will be able to:

- Formulate a set of "rules that should guide the use of humans in research," compare the list against current internationally used principles, and summarize key ethical principles.
- Analyze and discuss the ethical use of human participants in historical research cases, select the principle that was most violated, and defend their choice.

MATERIALS

Materials	Quantity
Student Handout 1.1a—*Case Study A: Henrietta Lacks and HeLa Cells*	3–4 per group
Student Handout 1.1b—*Case Study B: The Havasupai Indians*	3–4 per group
Student Handout 1.1c—*Case Study C: The Tuskegee Syphilis Study*	3–4 per group
Student Handout 1.1d—*Case Study D: The Willowbrook Study*	3–4 per group
Student Handout 1.2—*Guiding Questions for Historical Case Studies*	1 per student
Student Handout 1.3—*Concept Mapping*	1 per student
Possible Answers for Student Handout 1.3—*Concept Mapping*	1
Student Handout 1.4—*The Belmont Report*	1 per student

NOTE TO THE TEACHER

To teach this unit, knowledge of ethical theories is helpful but not necessary. Additional background, one-page summaries, and a comparison chart on ethical theories can be found in *An Ethics Primer: Lesson Ideas and Ethics Background* at http://www.nwabr.org.

The Belmont Report (http://ohsr.od.nih.gov/guidelines/belmont.html) provides the ethical guidelines governing human research as a result of committee deliberations after the National Research Act was signed in 1974. These documents were crafted, in part, in response to the emerging public understanding of the treatment of the men involved in the *U.S. Public Health Service Study* (Tuskegee Study). The basic ethical principles outlined are: respect for persons (including autonomy), beneficence, and justice (see Student Handout 1.4—*The Belmont Report*).

The historical case studies used in this lesson are U.S. cases and span a time period from the 1930s to the 1970s. However, the issues surrounding each case continue to be discussed today. To further study different vulnerable populations, consider using the following studies:

- Elderly patients—Jewish Chronic Disease Hospital Study.
- Prisoners—Guatemalan Syphilis Study/Nazi concentration camp studies leading to the Nuremberg Trials.
- Decision-impaired individuals—The Terri Schiavo case. [**Note:** This case is not research-oriented, but provides a clinical decision-making context.]

FRAMING THE LESSON

In this activity students will use case studies to explore the ethical implications of humans in research. Explain to students that the case study stories are real historical situations where researchers involved human participants in their studies. Stress that these particular cases are included because they illustrate questionable practices involving humans in research. Though the methods may (or may not) have been acceptable at the time, they do not represent current ethical practices. [**Note:** Information on supplementary resources and additional case studies can be found in *Resources* at the end of the lesson.]

TEACHER PREPARATION

- Make copies of *Student Handouts*.

PROCEDURE

Activity One: Guiding Questions

1. Tell the students that in this lesson they will use real-life medical case studies to explore the ethical implications of humans in research.
2. Have the students form groups of three or four.
3. Pass out one copy of the Student Handout 1.2—*Guiding Questions for Historical Case Studies* to each student and assign each group a case study to read together. Ask each group to answer the *Student Handout* questions for their case. [**Note:** Teachers may also choose to run a "jigsaw" exercise using the case studies (where one case study is passed out to each group for in-depth discussion, then new groups are formed in which students familiar with each case share what they have learned with the others in the new group).]
4. Now ask each student group to share information from their case study with the class. Encourage the class to ask clarifying questions.
5. As a class, ask students to help brainstorm a list of shared themes among the studies. To help students generate their list, have them review their notes on Student Handout 1.2—*Guiding Questions for Historical Case Studies* and use these prompts:
   - What similarities did you notice between two or more cases?
   - Did anything repeat itself?
   - What was fair/not fair?
   - How should study participants expect to be treated?
6. Record student answers on the board.

The full title of the Tuskegee Syphilis Study is "U.S. Public Health Service Tuskegee Study of Untreated Syphilis."

Activity Two: Creating a Concept Map

7. Tell students that they will now create a concept map that shows relationships among the common ideas found in the case studies.

8. Ask students to group the answers to the questions in *Step Five* into similar themes, working either individually or in their small groups. Have them use Student Handout 1.3—*Concept Mapping* to record the major concepts from the class discussion, case study table, and brainstorming activity. Ask students to consider what they recorded on Student Handout 1.2—*Guiding Questions for Historical Case Studies*, and have them organize the guidelines further, possibly narrowing them down to three or four major categories complete with ***specific examples*** from each of the case studies to support their themes. The goal is to arrive at themes that parallel those of the Belmont principles (see Possible Answers for Student Handout 1.3—*Concept Mapping*).

9. Working as a class, invite students to share their concept map themes. Generate a class concept map that includes examples from each of the case studies. [**Note:** A useful website for how to turn a text outline into a concept map can be found at http://www.text2mindmap.com. Teachers may use this resource to create their class concept map.]

10. Ask students to go back and fill in any missing elements on their own concept maps (Student Handout 1.3—*Concept Mapping*). Remind students to include specific examples from each of the case studies to support their themes.

Activity Three: The Belmont Report

11. Pass out Student Handout 1.4—*The Belmont Report*. Have students compare their concept map guidelines to these ethical principles that were developed to guide human research.

12. Review each of the Belmont principles with the class, and encourage students to note similarities or differences between these principles and those on their concept maps.

13. Using Student Handout 1.4—*The Belmont Report*, ask students to give a concrete example from one of the case studies for each of the principles found in the Belmont Report.

Closure

14. Have students compare their class concept map principles to those found in the Belmont Report. Tell students that the principles described in the Belmont Report are sometimes referred to as the Belmont principles.

CONNECTION TO FORMATIVE ASSESSMENT

Revisit the statements students sorted in the *Formative Assessment*. After completing *Lesson One*, students should understand that *Statement C* is accurate. Careful reading of the Henrietta Lacks case also shows *Statement D* to be accurate (this concept will be revisited in the next lessons).

GLOSSARY

Antibody: A substance made by the body as an immune response that attacks and destroys foreign agents, such as viruses and bacteria.

Autonomy: A person's freedom and ability to make his or her own decisions.

Autopsy: An examination conducted on a dead body to determine the cause of death.

Belmont Report (Belmont principles): Created in 1978 by the U.S. Department of Health, this report established three basic ethical principles to be considered when humans participate in research.

Beneficence: Minimizing all potential harms and maximizing all potential benefits to the subject as well as to society.

Cervical cancer: Cancer of the cervix, which is the lower, narrow end of the uterus.

Clinical research: Medical research involving human participants to test new medications, treatments, methods of prevention, and therapies.

Coercion: The act of pressuring someone to do something using force, intimidation, or threats without respect for individual choice. This includes the idea that a person with few choices may find participation in a study to be so appealing that they feel they cannot decline, even if being in the study is not a good decision for other reasons.

Conflict of interest: A situation in which someone is responsible for making a decision in an official capacity (e.g., someone holding public office) that could benefit them personally.

Ethics: A field of study that looks at the moral basis of human behavior and attempts to determine the best course of action in the face of conflicting choices.

Hepatitis: Inflammation of the liver caused most frequently by viruses.

Human cell line: A continuously dividing set of cells used in medical research that are derived from a single human cell.

Inbreeding: When closely related people have children together, generation after generation.

Incidence: The percentage of newly diagnosed cases of a disease in a population.

Informed consent: A process that outlines required elements of research participation, including its risks and potential benefits, to help someone decide whether to participate. An informed consent form is used to convey essential information and is signed by the participant if he or she decides to join the study.

Penicillin: An antibiotic drug made from penicillium mold (or produced synthetically) used to treat infections and diseases.

Schizophrenia: A mental illness resulting in greatly impaired thinking, emotional responses, and behaviors.

Stakeholder: A person with an interest or concern in something.

Stories of origin: Stories that recount how something (or a people) came into being.

Syphilis: A sexually transmitted disease caused by bacteria, which can cause skin lesions. Left untreated, syphilis can cause inflammation, meningitis, and other central nervous system damage, as well as cardiovascular damage. Syphilis can remain in the body undetected for many years (latency), and symptoms can appear more than 40 years later.

Tissue sample: Bodily fluids (e.g., blood or saliva) or tissue (e.g., cells, skin, bone, or muscle) for use in research.

Type II Diabetes: A chronic medical condition that affects how the body metabolizes sugar (glucose). Type II Diabetes typically begins in adulthood and patients are not usually dependent on the use of insulin to control their sugar levels.

Undue influence: Is exerted when a person of higher power or authority takes advantage of another person; undue influence can often include coercion.

Vulnerable (populations): Groups that may be exploited for use in research, e.g., children, people who are illiterate, and prisoners.

RESOURCES

Additional notes on the Henrietta Lacks case study (optional for teacher to share):

The Lacks family was contacted by researchers many years after the HeLa cells had been established in culture and were asked to voluntarily provide biological samples. Researchers obtained consent from the family, but the family's understanding was that the researchers would be testing them for cancer. The Lacks then donated samples but did not hear further from the researchers.

Johns Hopkins University received the original HeLa tumor cells for research after they were collected from Henrietta Lacks. The university used them for research but did not sell or make any profit from the cell line. Cells were also given free of charge to many labs around the world for research purposes.

As of 2012, it is legally permissible for clinicians, institutions, or researchers to store patients' biological samples for research without their consent if the tissue is considered medical waste and all information that identifies the sample with a person has been removed. When a patient undergoes routine medical procedures, etc., he or she often signs an informed consent form that enables doctors or researchers to use tissues for further study.

Additional notes on the Havasupai case study (optional for teacher to share):

A six-minute film from *The New York Times* about the importance of informed consent and the Havasupai Indians can be found here: http://video.nytimes.com/video/2010/04/21/us/1247467672743/blood-journey.html.

Additional historical case studies involving humans in research can be found in *Lesson Four* of *The Science and Ethics of HIV Vaccine Clinical Trials*, available from http://www.nwabr.org.

The case studies are:

- *Yellow Fever in Cuba* (Walter Reed's early use of informed consent)
- *Prisoner Experiments* (Nazi experimentation on concentration camp victims)
- *AZT and Pregnant Women in Developing Countries* (the use of placebos in the absence of existing proven therapy)
- *Behavior in Young Boys* (using young boys to study the effects of fenfluramine on behavior)

Additional notes on The Willowbrook Study (optional for teacher to share):

Hepatitis A is a mild inflammation of the liver that causes flu-like symptoms; it can be contracted through contact with feces that contains the virus. Hepatitis B is a more severe form of the disease that also affects the liver; it is contracted through the exchange of infected body fluids. Approximately 50% of patients who have Hepatitis B are unable to overcome it and have what is called chronic hepatitis. These people must monitor their medications so they won't develop liver failure, a potentially deadly condition.

EXTENSION

Ask students to choose from the suggested list of cases involving vulnerable populations in the *Teacher Background* section of this lesson, or have them research another case study online.

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STUDENT HANDOUT 1.1a
HeLa Cells

Case Study A: Henrietta Lacks and HeLa Cells

Henrietta Lacks died when she was 31 years old in a segregated hospital ward for "coloreds" in Baltimore, Maryland on October 4, 1951. Lacks was a poor, black woman from an uneducated family who had worked in the tobacco fields in Virginia almost all of her life. She married young and had five children.

Soon after the birth of her youngest child in 1950, Henrietta discovered a lump in her body. A doctor at a free clinic ward for colored people examined her lump and the diagnosis was **cervical cancer**. The doctor performed a routine medical procedure to collect **tissue samples** from her cancerous tumor. At the time, it was common for doctors to send tissue samples to research facilities so that cells could be studied to learn more about many diseases. The rules for getting **informed consent** from patients were much less strict than they are today. Henrietta's doctors did not inform her about what they were doing or get her permission for the tissue collection, though they did get consent from her husband to perform an **autopsy** after her death.

On the same day that Henrietta passed away, Dr. George Gey [pronounced "guy"], a leading researcher who had been trying to establish the successful growth of a stable **human cell line**, appeared on television to present his contribution to the fight against cancer. Dr. Gey introduced to the world the first successfully grown human cell line, which he termed "HeLa" in honor of the human patient who had unknowingly donated to the cause— Henrietta Lacks.

As Dr. Gey was presenting his discovery, scientists all over the world were being given HeLa cells for free to conduct their own studies. The HeLa cell line became an essential resource for medical research in many labs worldwide. Soon, many companies began mass producing HeLa cells for commercial research use, reaping millions of dollars in profits that would never have been possible without Henrietta's cells. HeLa cells have since been used in many ways, including testing vaccines, learning about genetics, research into cancer and AIDS, and developing drugs. It took decades, and the help of a journalist, for the family to learn what had happened to their mother's cells.

Henrietta was buried in an unmarked grave for almost 60 years, until 2010. Her headstone has now been marked with her name and an inscription that reads "In loving memory of a phenomenal woman, wife, and mother who touched the lives of many. Here lies Henrietta Lacks (HeLa). Her immortal cells will continue to help mankind forever."

Henrietta's family never received any part of the billions of dollars that HeLa cells brought (and continue to bring) to many companies. In fact, since Henrietta was never informed that her tissue had been collected, for more than 20 years after her death, her family was unaware of the robust industry Henrietta's cells helped launch or her "immortal" status.

The Lacks' family and children are still economically disadvantaged. Many of Henrietta's descendants can't afford health insurance or treatments that have been made possible by direct work with the HeLa cell line. Deborah, the fourth of Lacks' children, describes the situation: "Truth be told, I cannot get mad at science, because it helps people live and I'd be a mess without it. But I won't lie. I would like some health insurance so I don't got to pay all that money every month for drugs my mother's cells probably helped make."

This summary is based on a true story. Please see the Sources *section for reference information.*
Contributed by Myra Arnone, Redmond High School, Redmond, WA.

Autopsy: An examination conducted on a dead body to determine the cause of death.

Cervical cancer: Cancer of the cervix, which is the lower, narrow end of the uterus.

Human cell line: A continuously dividing set of cells used in medical research that are derived from a single human cell.

Informed consent: A process that outlines required elements of research participation, including its risks and potential benefits, to help someone decide whether to participate. An informed consent form is used to convey essential information and is signed by the participant if he or she decides to join the study.

Tissue sample: Bodily fluids (e.g., blood or saliva) or tissue (e.g., cells, skin, bone, or muscle) for use in research.

HANDOUT

STUDENT HANDOUT 1.1b
The Havasupai Indians

Case Study B: The Havasupai Indians

The Havasupai Indian tribe lives in the state of Arizona, deep in the Grand Canyon, relatively isolated from the rest of U.S. society. The tribe's language, called Pai, is spoken by all of its approximately 639 members. Only a few members of the tribe have graduated from an English-speaking high school. Unemployment is very high in the community and income is mostly dependent on seasonal tourism. To access medical facilities, tribal members must either hike for miles on a steep trail or leave the canyon via horse or helicopter.

In the 1960s, the tribe began seeing a very high **incidence** of **Type II Diabetes** among their members. As a result, many of the members suffered poor health, and some needed to have limbs amputated to treat the disease. In 1989, members of the tribe contacted researchers at Arizona State University (ASU) to figure out how to control the disease and treat members of the tribe.

Researchers had already established that a neighboring tribe, the Pima Indians, had a genetic link to diabetes. The researchers sought to investigate whether the Havasupai had a similar genetic link to the condition. The researchers from ASU received money in 1990 from the university to carry out the investigation. From 1990 to 1994, many tribe members were recruited for the study. To participate, the members signed a general consent form that stated the research they would be participating in would "study the causes of behavioral/medical disorders." The Havasupai research subjects provided blood samples. In turn, the tribe received limited medical care.

In 1991, the research study yielded a paper that showed that there was no direct evidence to link the tribe's genes to diabetes.

After the initial study was conducted, researchers continued to use the Havasupai's blood for research on **schizophrenia**, **inbreeding**, and patterns of human migration. The migration research is notable because the Havasupai never agreed to the use of tribal members' blood for research that might contradict the tribe's traditional **stories of origin**. The tribe became aware of this additional research in 2003, when one of the tribe members was invited to a talk at ASU where a doctoral student presented information from a study that used Havasupai blood samples. Carletta Tilousi, a tribe member who attended the ASU presentation, remarked, "I'm not against scientific research. I just want it to be done right. They used our blood for all these studies, people got degrees and grants, and they never asked our permission."

The tribe members who contributed blood samples for research purposes did not know that their blood was being used to study other conditions in addition to diabetes. The Havasupai tribe sued ASU and received $700,000, several forms of additional support and resources for the tribe, and in 2010, the return of all their remaining blood samples.

This summary is based on a true story. Please see the Sources *section for reference information.*
Contributed by Myra Arnone, Redmond High School, Redmond, WA.

HANDOUT

Type II Diabetes: A chronic medical condition that affects how the body metabolizes sugar (glucose). Type II Diabetes typically begins in adulthood and patients are not usually dependent on the use of insulin to control their sugar levels.

Inbreeding: When closely related people within an isolated group have children together, generation after generation.

Incidence: The percentage of newly diagnosed cases of a disease in a population.

Schizophrenia: A mental illness resulting in greatly impaired thinking, emotional responses, and behaviors.

Stories of origin: Stories that recount how something (or a people) came into being.

STUDENT HANDOUT 1.1c
The Tuskegee Syphilis Study

Case Study C: The Tuskegee Syphilis Study

(Formally known as the U.S. Public Health Service Tuskegee Study of Untreated Syphilis)

From 1932 to 1972, the U.S. government conducted a study that focused on understanding the long-term effects of untreated syphilis, a sexually transmitted disease caused by bacteria. The original intent of the study was to show that the disease was "potentially…the same in African Americans and Caucasians." The government claimed it wanted to study the effects of the disease so that it could develop programs to help treat syphilis in the local community.

The Tuskegee Syphilis Study, named after a college for black people called the Tuskegee Institute, took place in Macon County, Alabama. The study involved the active recruitment of poor, black, male sharecroppers. The researchers conducting the study told the men that they would be treated for "bad blood," a term that was used in the local community to describe the symptoms of syphilitic disease—fatigue, fever, sores, and muscle aches.

The study, which was supposed to last up to nine months, continued for more than 40 years. Initially the study was approved by the Alabama state government with the expectation that the men would be treated for the disease. Researchers treated the men with the standard use of mercury and bismuth. These highly toxic remedies were sometimes fatal, and were only slightly effective since the cure rate was less than 30 percent and the treatment lasted several months.

Of the 600 men who enrolled and who consented, 399 men had syphilis and 201 did not have the disease. Although the men gave their consent, they were never informed about the research itself or that some of them actually had syphilis. In exchange for their cooperation, the men were promised free medical care, free meals, free travel to and from the clinics, and insurance for burials so that their families would not need to worry about the cost of their deaths.

In 1947, **penicillin** became available and was widely distributed as a highly effective treatment for syphilis; it became the standard of medical care for this disease. Although the researchers were aware that penicillin was effective against syphilis, they wanted to observe the consequences of the disease over time. The infected men in the study were never made aware of nor offered penicillin treatment.

In 1972, the study ended when a reporter wrote about the research in *The New York Times*. An advisory committee was formed to look into the study and strongly advised the researchers to stop the study. The men and their families received $10 million in a settlement, and received healthcare for their wives and children. More than 100 men in the study died from syphilis-related complications, and some of the patients' wives and children also contracted syphilis, which is sexually transmitted and can be passed to the fetus during pregnancy. The patients and their families did not receive a formal public apology from the U.S. government until President Bill Clinton apologized in 1997.

This summary is based on a true story. Please see the Sources *section for reference information.*

Contributed by Myra Arnone, Redmond High School, Redmond, WA.

HANDOUT

Penicillin: An antibiotic drug made from penicillium mold (or produced synthetically) used to treat infections and diseases.

Syphilis: A sexually transmitted disease caused by bacteria, which can cause skin lesions. Left untreated, syphilis can cause inflammation, meningitis, and other central nervous system damage, as well as cardiovascular damage. Syphilis can remain in the body undetected for many years (latency) and symptoms can appear more than 40 years later.

STUDENT HANDOUT 1.1d
The Willowbrook Study

Case Study D: The Willowbrook Study

Warren was the fourth child and first boy born to a wealthy New York family in the 1950s. He was well loved by his sisters and parents. By the age of two it became obvious that Warren was different. When he was finally diagnosed as "profoundly retarded," in the terms used at that time, his parents, who were unable to care for him, put him into one of the best care homes in New York. The family eventually faced financial problems and Warren was moved to Willowbrook State Hospital.

Willowbrook was opened in 1947 as a place to take care of New York's mentally disabled population. Most patients were sent there as children when family doctors recommended that they needed more care than families could provide. The institution was plagued with **hepatitis** outbreaks throughout its first decade of operation. Recent estimates show that nearly 50% of patients living at Willowbrook in its early years of operation contracted hepatitis.

When the study began in the mid-1950s, the distinction between the various types of hepatitis was not known. The conditions at Willowbrook led Dr. Saul Krugman and Dr. Robert McCollum to believe that it would be an ideal place to study hepatitis to discover a possible cure for the disease. This could benefit both current and future children residing at Willowbrook. Letters describing the study were sent to parents of Willowbrook patients, asking permission for their children to participate. The short letter described how some patients would receive **antibodies** called gamma globulins that researchers hoped would provide long-term protection against hepatitis. Parents could tour an improved residential hospital wing set aside especially for study participants, meet with research staff, and ask questions about the study. Only children whose parents signed the permission form could participate in the study.

The study included two groups. The first included patients such as Warren who had been living at Willowbrook for some time, and were likely to get hepatitis whether they were in the study or not. The second group included patients who were essentially healthy and were newly admitted to Willowbrook. Warren's group had two categories: children who received the antibodies, and children who did not. The healthy children who were new arrivals at Willowbrook all received the antibodies. During the study, some of the children unknowingly were deliberately infected with hepatitis by consuming the live virus, which was extracted from the feces of infected children. Some children were not infected at all. The children who were purposefully infected in the study tended to have milder reactions than children who contracted hepatitis naturally from other children in the hospital. A public outcry ultimately closed the study in the 1970s.

Warren was one of the last to leave Willowbrook when the facility closed in 1987. He now lives in a special care home where his sister communicates with him on a regular basis.

The Willowbrook Study showed that hepatitis can be divided into multiple types, which has allowed doctors to specify the type of treatment that is appropriate, and has led to a reduction in hepatitis outbreaks.

This summary is based on a true story. Please see the Sources *section for reference information.*
Contributed by Erin Larson, Federal Way School District, Federal Way, WA.

HANDOUT

Hepatitis: Inflammation of the liver caused most frequently by viruses.

Antibody: A substance made by the body as an immune response that attacks and destroys foreign agents, such as viruses and bacteria.

STUDENT HANDOUT 1.2

Guiding Questions for Historical Case Studies

Name_____ Date_____ Period_____

Complete the following chart with your group after you read through your case study. Record information from the other case studies presented by other groups in your notebook.

	CASE STUDY:
1. What good came out of the research? What was the importance of the study?	
2. What things were not fair or are questionable about the research or its process?	
3. Who was involved in the case? Directly? Indirectly?	
4. Was everyone involved fully aware of and did they agree to be part of all aspects of the research?	
5. What was society's role in the case?	
6. How did social issues (e.g., poverty, education, religion) influence the case?	
7. What core values were in conflict in this case?	

HANDOUT

STUDENT HANDOUT 1.3

Concept Mapping

Name_____ Date_____ Period_____

Thinking back to the guidelines/rules your group recorded and the information you've collected on all of the case studies, review your guidelines and categorize them by major components/shared themes. You may want to make a concept map that shows how your group decided to categorize the guidelines.

HANDOUT

STUDENT HANDOUT 1.4
The Belmont Report

Name_____ Date_____ Period_____

The Belmont Report—Guidelines for Using Human Subjects in Research

The Belmont Report was created in 1978 by the U.S. Department of Health to establish some basic ethical principles to be considered when people participate in research.

1. Respect for Persons

- *Description:* Respect for individuals and their **autonomy**; obtain informed consent.
- *How is this applied?*
  - o A person has the right to make choices, hold views, and take actions according to his own beliefs.
  - o If a person does not have the capacity to make her own choice, she must be protected from harm.
  - o A person must enter into research voluntarily and must be informed in an adequate manner.
  - o To truly respect a person's autonomy, he must be able to give genuinely informed consent with full knowledge of both harms and benefits of the study.

On the back of this paper, give an example of how this principle was upheld or not from one of the case studies.

2. Beneficence (or maximize benefits/minimize harms)

- *Description:* Beneficence stresses "doing good" and "doing no harm" by minimizing all potential harm(s) and maximizing all potential benefit(s) to the subject as well as potential benefit(s) to society.
- *How is this applied?*
  - o There is an obligation to minimize the harm/risks to the greatest extent possible.
  - o Maximize the potential benefits.
  - o Ensure the rights and well-being of the patient take precedence over the needs of science.

On the back of this paper, give an example of how this principle was upheld or not from one of the case studies.

3. Justice

- *Description:* Be fair in the distribution of the benefits and in bearing the burden of research.
- *How is this applied?*
  - o The benefits and burdens of the research should be justly distributed.
  - o Guard against using **vulnerable populations**.
  - o Ensure fair selection of research participants.
  - o Guard against **coercion** and **undue influence**.
  - o Avoid potential financial or other **conflicts of interest**.

On the back of this paper, give an example of how this principle was upheld or not from one of the case studies.

Autonomy: A person's freedom and ability to make his or her own decisions.

Coercion: The act of pressuring someone to do something using force, intimidation, or threats without respect for individual choice. This includes the idea that a person with few choices may find participation in a study to be so appealing that they feel they cannot decline, even if being in the study is not a good decision for other reasons.

Conflict of interest: A situation in which someone is responsible for making a decision in an official capacity (e.g., someone holding public office) that could benefit them personally.

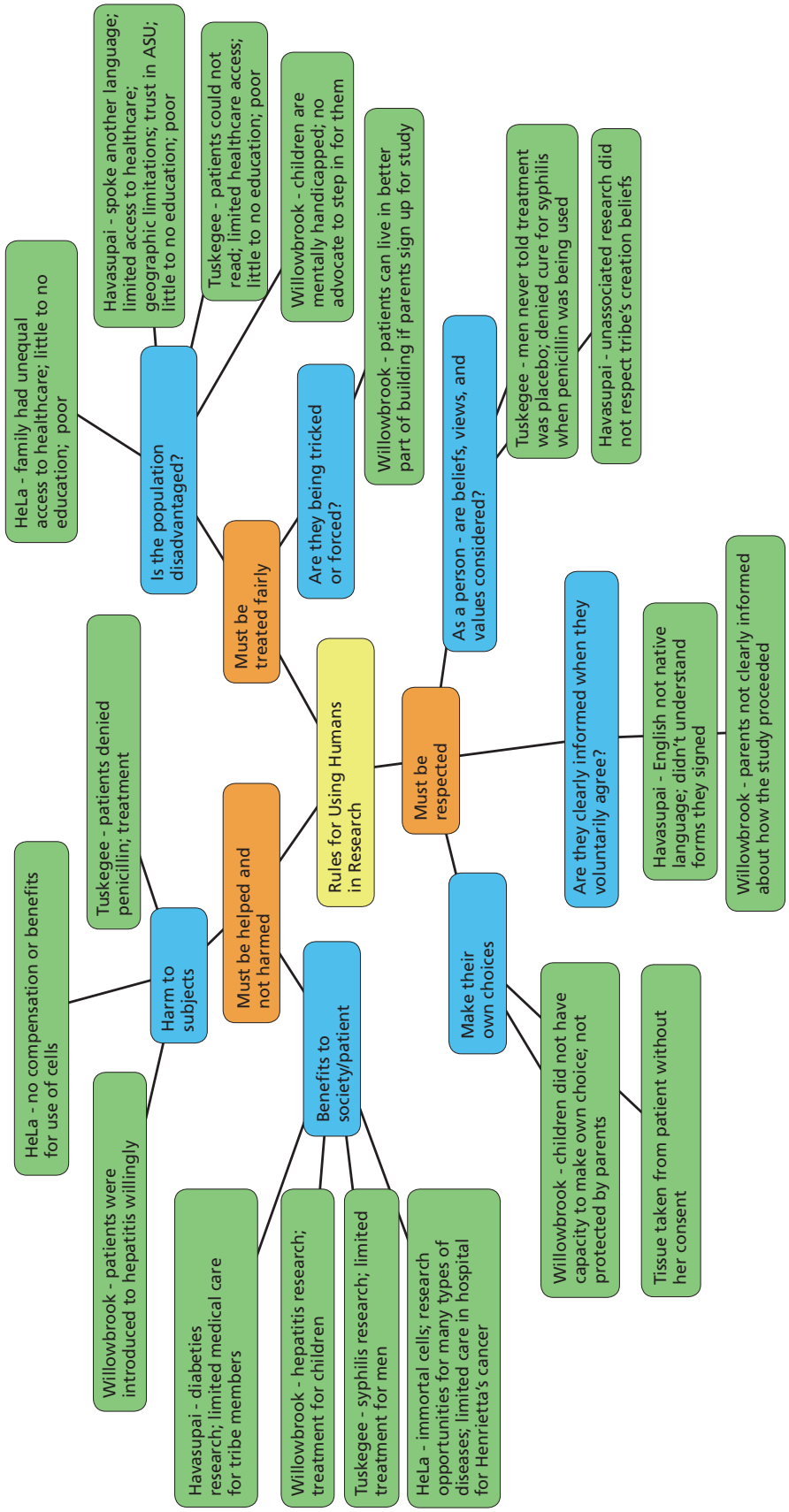
Undue influence: Is exerted when a person of higher power or authority takes advantage of another person; undue influence can often include coercion.

Vulnerable (populations): Groups who may be exploited for use in research, e.g., children, people who are illiterate, and prisoners.

HANDOUT

Possible Answers for STUDENT HANDOUT 1.3

Concept Mapping



Concept map created at http://www.text2mindmap.com.

RESOURCE

LESSON 2:
Applying the Belmont Principles

INTRODUCTION

In this lesson, students apply the principles outlined in the **Belmont Report** to complex case studies involving human participants as research subjects. Students analyze a case using the concept map they produced in *Lesson One*. They then work together in mixed-case groups to present their findings and evaluate each other's work using a peer evaluation process.

CLASS TIME

About one class period of 55 minutes.

KEY CONCEPTS

- Although the Belmont principles provide structure for **ethical** practices involving humans in research, complex real-world cases may not have clear answers and require a thoughtful balancing of **bioethical** principles.

LEARNING OBJECTIVES

Students will know:

- The complexities involved when conducting research with human participants require thoughtful and balanced consideration of the Belmont principles.

Students will be able to:

- Recognize and apply the Belmont principles in a variety of cases.
- Evaluate the work of other students in applying the Belmont principles.

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*.

MATERIALS

Materials	Quantity
Student Handout 2.1—*Applying the Belmont Principles—Case Studies A, B, C,* and *D*	1 case per student: A, B, C, or D
Student Handout 2.2—*Applying the Belmont Principles—Case Table*	1 per student
Possible Answers to Student Handout 2.2—*Applying the Belmont Principles—Case Table*	1 of each study: A, B, C, and D
Student Handout 2.3—*Peer Evaluation Procedure for Ethical Case Study Analysis*	1 per student
Student Handout 1.3—*Concept Mapping* completed in *Lesson One*	Reuse from *Lesson One*

NOTE TO THE TEACHER

The next lesson in this unit, *Lesson Three*, begins with a short skit performed by three student actors. It may be helpful to identify three willing actors and provide each of them with a copy of the script to review before *Lesson Three* (see the *STUDENT SCRIPT* in *Lesson Three*).

FRAMING THE LESSON

Tell students that *Lesson One* introduced the major ideas behind the **Belmont principles**. In this lesson, students will dig deeper into how to apply the Belmont principles by using them to analyze a challenging medical ethics case. They will explore the gray areas of ethical decision-making in a peer evaluation process. As with most ethical decision-making, students may find that there are several alternate solutions, and that no one solution satisfies all of the parties involved. For students frustrated that there is no "one right answer," explain that in ethical decision-making there are "better or worse answers" based on well-reasoned justifications.

Students may also find that ideas within the three Belmont principles overlap. For example, some concepts covered under ***Respect for Persons*** are similar to those covered by ***Justice***.

TEACHER PREPARATION

- Make copies of *Student Handouts*.
- Ask students to have available their concept maps from *Lesson One*.

PROCEDURE

Activity One: Putting the Principles into Practice

1. Have students review their notes on Student Handout 1.3—*Concept Mapping* from *Lesson One*. Ask students if they feel clear about the meaning of the **Belmont principles** and how they apply to human research cases.
2. Tell students that in this lesson they will be reading a short scenario that highlights the shades of gray (areas of ambiguity) found in applying the Belmont principles. In these cases, the principles are not easily supported and students will be challenged to find the best answer with only limited information.
3. Distribute to each student one of the cases (A, B, C, or D) from Student Handout 2.1—*Applying the Belmont Principles—Case Studies*, and a copy of Handout 2.2—*Applying the Belmont Principles—Case Table*.
4. Ask students to work individually to read and analyze their case using Handout 2.2—*Applying the Belmont Principles—Case Table* and their concept maps from *Lesson One* as a reference. Tell students that they will be sharing their case analysis in a small group. Walk around the room as students work, providing guidance as necessary.

Activity Two: Peer Evaluation

5. After students have completed their work, form mixed groups of four, with each team made up of students representing each one of the four cases.
6. Pass out one copy to each student of Student Handout 2.3—*Peer Evaluation Procedure for Ethical Case Study Analysis*. Walk through the basic format for peer review with the class. You may choose to have one group demonstrate the method for the class.
7. Using the *Peer Evaluation Procedure*, each student will take turns presenting his or her case by reading it to the rest of the group and sharing how they applied the Belmont principles. When they are finished, the group members give constructive feedback consisting of both warm and cool comments. The receiving student may take notes but should ***refrain from responding verbally*** until all feedback has been received. At this time, the student may respond through clarifying questions or by sharing new insights.
8. After all of the case studies have been shared and evaluated, tell students they may make changes to their original case analysis before turning in their work.

Activity Three: Debriefing

9. As a class, debrief the process:
   a. What was that process like? Did the peer evaluation help clarify how you applied the Belmont principles to various cases?
   b. How does Respect for Persons apply to any of the cases? **Beneficence**? Justice?
   c. Was it easy or difficult to recognize and apply the Belmont principles in your analysis?
   d. Did all of the principles apply equally in all cases? Did you find that some principles conflicted with others in a particular case? Which ones and how?
   e. Was it easy or difficult to decide what to do? Why?
   f. Is there something missing from the principles? What, if anything, still raised concerns for you even after you applied the principles?
10. Explain to students that, although the Belmont principles provide a solid ethical foundation, the ways in which they are applied can vary. In some cases other ethical models may be used, but for most biomedical research in the U.S., these are the main guiding principles.

Closure

11. Remind students that real-world cases involving humans in research can be complex. Although the Belmont principles provide structure for ethical practices, it is necessary to have a diverse group of people review and monitor studies involving human participants. This group, known as the **Institutional Review Board** (IRB), or Ethics Committee, will be discussed in *Lesson Three*.

CONNECTION TO FORMATIVE ASSESSMENT

Revisit the statements students sorted for the *Formative Assessment*. After completing *Lesson Two*, students should understand that Statement E is not accurate.

ADAPTATIONS

- Have each student analyze all of the cases.
- Invite students to work in pairs when doing the initial case analysis. Pairs can then split up to create mixed groups of four (with one student knowledgeable about each of the four cases) for the peer evaluation.

GLOSSARY

Beneficence: Minimizing all potential harms and maximizing all potential benefits to the subject as well as to society.

Bioethics: A subfield of ethics applied to the life sciences; it looks at the ethical impacts of new scientific knowledge and how society makes policy decisions regarding medicines, treatments and human health.

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

Efficacy: Effectiveness as measured in a controlled clinical trial.

Ethics: A field of study that looks at the moral basis of human behavior and attempts to determine the best course of action in the face of conflicting choices.

SOURCES

The Critical Friends Group® Tuning Protocol is from National School Reform Faculty (n.d.). *Tuning Protocol: Overview*. Bloomington, Ind.: Harmony Education Center. Retrieved from: http://www.nsrfharmony.org/protocol/doc/tuning.pdf.

STUDENT HANDOUT 2.1

Applying the Belmont Principles—Case Studies A, B, C, and D

These are fictional cases involving current ethical topics.

Case A: Saving Lives in a Heartbeat?

In cardiac arrest (heart attack) cases, it is critical to control and monitor body temperature. To increase the likelihood of survival, hospitals will quickly place the victim in an ice bath to produce hypothermia (a lowering of core body temperature), then gradually raise the body temperature. To ensure that the most accurate temperature is being recorded, researchers would like to perform a study on cardiac arrest patients in the emergency room at the county hospital. Temperatures will be taken using different methods for different patients, comparing results from forehead or fingertip thermometers to those from standard oral thermometers, to see which consistently offers the most accurate temperature reading. Because cardiac arrest patients are often unconscious upon arrival, and because the temperature reading must occur very quickly, the researchers would like to do the following:

1. If possible, speak to the next of kin to gain permission to enroll their family member in the study.
2. If next of kin cannot be located, record the patient's temperature, ***and then*** obtain permission to use the data once the next of kin arrive or after the patient regains consciousness (the data can be discarded if consent is not obtained).
3. If the next of kin or patient does not speak English, exclude them from the study (translators are difficult to obtain quickly).

Can the study proceed, obtaining informed consent as described?

Case B: A Gamble Worth Making?

Aggressive cancers can take a person's life in as little as three to six months. An experimental procedure called interleukin therapy is currently being studied in a **clinical trial**. In 7% of cases, the treatment has been highly effective. In one such case, a man with breast, kidney, and lung cancers with very little hope for survival agreed to participate to receive the experimental therapy. The experimental therapy effectively treated the tumors, and he has been cancer-free for five years. Unfortunately, the treatment has no effect for many people, and there is also a large risk involved: in some trials, the patients suffered immediate cardiac failure.

A woman diagnosed with aggressive cancer, who doctors estimate will live another six months, is interested in pursuing this therapy. In an intense informed consent process over a two-week period, she and her husband are given all the scientific background, the pros and cons, the risks and benefits, and more. After the informed consent process, the woman would like to pursue the treatment, but her husband is against it. The couple is from a cultural background in which the man of the family makes all of the important decisions and this couple is faithful to their cultural traditions. Should researchers enroll this woman in the study to receive the experimental therapy?

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

These scenarios are modified from an activity developed by PATH in Seattle, Wash., and are used with permission.

HANDOUT

Case C: Better Than Nothing?

Researchers want to test the effectiveness of a new formulation of insulin that will allow patients with diabetes to take a pill with every meal instead of injecting themselves with liquid insulin three times a day. Liquid insulin must be kept refrigerated, the injections can be painful, and sterile syringes have to be purchased regularly. With the insulin pill (which has an estimated future cost of $5.00 a day for people with insurance), diabetics would be free of these burdens. Researchers discover that in a small, isolated, rural community, diabetes affects 45% of the residents (compared to 8.3% of the general population), and decide to run **clinical trials** of the drug there. Because there is no hospital or clinic nearby, researchers will set up a temporary clinic in the center of town for easy access. In addition to the experimental medication, participants will receive health screenings, check-ups, and basic medical care, plus compensation for lost time at work and transportation. After two years of gathering data, researchers will close the clinic and return to the laboratory to analyze the data and determine the **efficacy** of the pill.

Should the research proceed as described?

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

Efficacy: Effectiveness as measured in a controlled clinical trial.

Case D – Text Me When You're Ready!

In Zambia, one in seven adults is HIV positive (HIV+). Treatment is not readily available to all who need it, and researchers are interested in developing effective, low-cost treatment options for HIV+ patients. The study of a new medication for HIV faces a complication in that many Zambian people are mobile—they move from region to region because of jobs, political hostility, or to seek housing—making consistent contact with participants difficult. Furthermore, researchers worry that participants will send other family members to receive the experimental medication instead of coming in themselves in an effort to share the treatment. (This compromises both the study and the therapeutic value of the medicine, which must be taken consistently.)

Researchers propose using technology to solve several issues. They will scan the thumbprints of participants and add them to an electronic database so that participants can prove they are in the research study before receiving treatments. Researchers will also provide participants with cell phones, on which researchers can text reminders to participants about their study visits and reschedule appointments. Enabling the GPS tracking on the phones will also allow researchers to find participants when needed, so they can go to meet them in person.

Should the research proceed as described?

HANDOUT

These scenarios are modified from an activity developed by PATH in Seattle, Wash., and are used with permission.

STUDENT HANDOUT 2.2

Applying the Belmont Principles—Case Table

Name_____ Date_____ Period_____

Case Letter/Title:

Write a short summary of the main issues in the case (two to three sentences):

Principle and Elements	The study meets the elements of this principle because…	The study does not meet the elements of this principle because…
Respect for Persons • Respect right to make choices, hold views, and take actions according to personal beliefs. • Protect those with reduced capacity to make their own choice. • Ensure voluntary participation. • Provide informed consent, explaining harms and benefits.		
Beneficence • Minimize the harm/risks to the greatest extent possible. • Maximize the potential benefits. • Ensure that the rights and well-being of the patient take precedence over the needs of science.		
Justice • Justly distribute benefits and burdens of the research. • Guard against using vulnerable populations. • Ensure fair selection of research participants. • Guard against coercion and undue influence. • Avoid potential financial or other conflicts of interest.		

What are some actions that could be taken to make this research better comply with ethical principles?

HANDOUT

HANDOUT

Possible Answers for STUDENT HANDOUT 2.2A
Applying the Belmont Principles—Case Table

Case A: Saving Lives in a Heartbeat?

Write a short summary of the main issues in the case (two to three sentences):

Researchers would like to study the most accurate method for taking the temperature of patients in cardiac arrest who may be unconscious. Since time is an issue and researchers can't always get consent from the patient, they would like to get permission from next of kin; if no next of kin, take the data and then ask the patient when consciousness is regained; or if next of kin or patient doesn't speak English, exclude them from the study.

Principle and Elements	The study meets the elements of this principle because…	The study does not meet the elements of this principle because…
Respect for Persons • Respect right to make choices, hold views, and take actions according to personal beliefs. • Protect those with reduced capacity to make their own choice. • Ensure voluntary participation. • Provide informed consent, explaining harms and benefits.	*Researchers protect the unconscious patient by asking those who are closely related.* *Researchers only use data from patients who give permission.*	*Informed consent is not obtained until after the fact.* *If the patient does not give permission and the method used to collect temperature data is not as accurate as the other, the patient was not given a chance to accept the possible harms and could suffer.*
Beneficence • Minimize the harm/risks to the greatest extent possible. • Maximize the potential benefits. • Ensure that the rights and well-being of the patient take precedence over the needs of science.	*All patients will receive emergency care.* *Non-English speakers are excluded so care of patient will take precedence over the needs of science to collect data.* *Research could benefit future cardiac patients.*	*Asking for permission from distraught family members might cause undue stress.*
Justice • Justly distribute benefits and burdens of the research. • Guard against using vulnerable populations. • Ensure fair selection of research participants. • Guard against coercion and undue influence. • Avoid potential financial or other conflicts of interest.	*Populations who do not speak English will have a difficult time understanding the study; they will be excluded so they do not feel confused or coerced during a stressful time.*	*Populations excluded (non-English speakers) represent the diversity necessary for outcomes that accurately reflect all populations who may experience cardiac arrest.*

What are some actions that could be taken to make this research better comply with ethical principles?

Use both methods to collect patient temperatures to lessen the possible harms of one method being more accurate than the other.

RESOURCE

Possible Answers for STUDENT HANDOUT 2.2B
Applying the Belmont Principles—Case Table

Case B: A Gamble Worth Making?

Write a short summary of the main issues in the case (two to three sentences):

Female cancer patient with six months to live would like to try an aggressive/risky procedure. In her culture, men make the decisions and her husband is against the procedure. Only 7% of the cases treated benefit, while most have no improvement and some suffer immediate cardiac failure.

Principle and Elements	The study meets the elements of this principle because…	The study does not meet the elements of this principle because…
Respect for Persons • Respect right to make choices, hold views, and take actions according to personal beliefs. • Protect those with reduced capacity to make their own choice. • Ensure voluntary participation. • Provide informed consent, explaining harms and benefits.	*The two-week informed consent process explains the scientific background, pros and cons, risks and benefits.*	*If her husband's wishes are accepted, the patient isn't making the choice, but her traditions are being respected: conflict.*
Beneficence • Minimize the harm/risks to the greatest extent possible. • Maximize the potential benefits. • Ensure that the rights and well-being of the patient take precedence over the needs of science.	*She is going to die soon; this might be her last chance.* *Information from the patient's outcome could benefit future cancer patients.*	*Treatment has only benefited 7% of cases treated so far.* *Risk of death by cardiac arrest.*
Justice • Justly distribute benefits and burdens of the research. • Guard against using vulnerable populations. • Ensure fair selection of research participants. • Guard against coercion and undue influence. • Avoid potential financial or other conflicts of interest.		*Patient belongs to a vulnerable population since traditionally her husband makes the healthcare decisions.* *Risk of treatment means she will not likely benefit from her participation in the study.*

What are some actions that could be taken to make this research better comply with ethical principles?

Give private counseling to the patient to determine her true choice.
Give private counseling to the husband to determine why he is against treatment to see if a compromise can be reached.
Research treatment to see if there is a genetic component to successful outcomes to better target effective use.

RESOURCE

Possible Answers for STUDENT HANDOUT 2.2C
Applying the Belmont Principles—Case Table

Case C: Better Than Nothing?

Write a short summary of the main issues in the case (two to three sentences):

Community with high percentage of patients with diabetes has been chosen for clinical trial of diabetes pill that would replace insulin shots. Community has no clinic but researchers would provide a temporary clinic with access to basic healthcare for those participating in the study along with compensation for travel and work missed. After two years, the clinic will close and researchers will go back to lab to analyze data.

Principle and Elements	The study meets the elements of this principle because…	The study does not meet the elements of this principle because…
Respect for Persons • Respect right to make choices, hold views, and take actions according to personal beliefs. • Protect those with reduced capacity to make their own choice. • Ensure voluntary participation. • Provide Informed consent, explaining harms and benefits.	*Townspeople can choose whether to participate or not.*	*Participants might agree based on need for healthcare rather than genuine desire to volunteer.*
Beneficence • Minimize the harm/risks to the greatest extent possible. • Maximize the potential benefits. • Ensure that the rights and well-being of the patient take precedence over the needs of science.	*It would provide needed healthcare to a community with high incidence of diabetes.* *Compensation is given for missed work and transportation.* *Community health might improve as a result of the research and the clinic.*	*Risks of pills are unclear compared to standard treatment for diabetes.*
Justice • Justly distribute benefits and burdens of the research. • Guard against using vulnerable populations. • Ensure fair selection of research participants. • Guard against coercion and undue influence. • Avoid potential financial or other conflicts of interest.	*People of the community have a higher than average incidence of diabetes and would benefit greatly if a pill improved their quality of life.*	*Vulnerable population with few healthcare resources.* *Participants might feel undue influence since they need access to healthcare and the clinic would provide easy access.* *The community could suffer in the long term, since healthcare is only available during the two years of study—no long-term benefit.*

What are some actions that could be taken to make this research better comply with ethical principles?

Give participants access to information about the conclusion of the study and set up a foundation to help with continued healthcare access.
Educate participants about long-term diabetes care and lifestyle changes needed to reduce disease impact once clinic is gone.
Provide access to clinic to all community members during the trial regardless of their participation.

RESOURCE

Possible Answers for STUDENT HANDOUT 2.2D
Applying the Belmont Principles—Case Table

Case D: Text Me When You're Ready!

Write a short summary of the main issues in the case (two to three sentences):

Study in Zambia on HIV-infected patients. Challenges include: mobility of patients makes consistent contact difficult, participants may send in family members to share treatments. Researchers want to use electronic database of participants' thumbprints to track and identify participants when they come to the clinics used in the study. They will also give cell phones with GPS to participants to text them for availability and track their location so they can more easily contact them.

Principle and Elements	The study meets the elements of this principle because…	The study does not meet the elements of this principle because…
Respect for Persons • Respect right to make choices, hold views, and take actions according to personal beliefs. • Protect those with reduced capacity to make their own choice. • Ensure voluntary participation. • Provide Informed consent, explaining harms and benefits.	*Using cell phones to text participants might protect privacy more than other methods of contact.*	*Thumbprint and GPS tracking could intrude on participant privacy if used unethically.*
Beneficence • Minimize the harm/risks to the greatest extent possible. • Maximize the potential benefits. • Ensure that the rights and well-being of the patient take precedence over the needs of science.	*Zambia has large HIV+ population so this research will be a major benefit if successful; could also be beneficial to other developing countries.*	*Participants known to be in the study or found out to be HIV+ could face negative social pressures and even physical harm that could outweigh potential benefits of participation.*
Justice • Justly distribute benefits and burdens of the research. • Guard against using vulnerable populations. • Ensure fair selection of research participants. • Guard against coercion and undue influence. • Avoid potential financial or other conflicts of interest.	*Cell phones and HIV treatment are benefits to participants that help balance the burden of needing to be available for study.*	*Cell phone and medical treatment for a deadly disease might be undue influence in a setting where these are not readily available.* *HIV+ Zambians are considered to be a vulnerable population due to the stigma surrounding HIV and its transmission.*

What are some actions that could be taken to make this research better comply with ethical principles?

Enroll eligible family members to reduce possibility of a compromised study.
Educate participants about the importance of taking the medicine exactly as prescribed and not sharing doses with others because of the risk of creating drug-resistance.
Turn off GPS and destroy thumbprint database at the conclusion of the study.
To reduce coercive influence, provide only a limited number of minutes or text messages per month so that the phones are used for study purposes and not just for personal benefit.

RESOURCE

STUDENT HANDOUT 2.3

Peer Evaluation Procedure for Ethical Case Study Analysis

Name_____ Date_____ Period_____

Use the following steps to share how you applied the Belmont principles to your case study and get feedback on your work. Use the "Providing Feedback" process to evaluate the work of others in your group. Getting feedback about each case study from the group will help you gain a greater understanding of how the principles are used in **clinical trials** involving human subjects.

How to Present Your Case

1. Read your summary of the main ideas presented in your case study.
2. Share your analysis by explaining how/if Respect for Persons, **Beneficence**, and Justice are addressed in the case. Are all three principles met, or are there elements missing from one or more of the principles?
3. Finally, describe the actions that you feel would make the research better comply with ethical principles.
4. Now it's time for the rest of the group to provide you with feedback. Please do not make comments or ask questions until everyone has had a chance to give feedback (see *Reflection* in next column). Do take notes during the feedback period on Student Handout 2.2—*Applying the Belmont Principles—Case Table*.

How to Provide Feedback

1. Listen carefully as the presenter reads a summary of her case and shares her analysis of how the principles apply, and how she thinks the research could better comply with ethical principles. Take notes so you can provide specific examples when giving feedback.
2. Once the presenter is finished, group members will take turns sharing feedback to improve understanding of how the principles are applied. Use both "warm" and "cool" feedback in your evaluation:
   - **Warm feedback:** Focus on a positive aspect of the analysis. Identify points the presenter explained clearly.

     Example: "Your work is strong because..."
   - **Cool feedback or clarifying questions:** Focus on areas the presenter needs to improve, and where he needs to improve his explanation of how the principles are used.

     Examples: "I'm not sure if you explained..." or "Could you better define how…" or "I wonder if…"

Reflection

1. The presenter can now ask clarifying questions of the group, trying to do so without defending his work.

Repeat the process until each group member has presented a case, shared his or her analysis, and been evaluated. Once everyone has shared, students may make revisions to their analysis using the feedback provided by the group, and prepare for a class discussion about the cases and the evaluation process.

This peer evaluation format is based on a modified Critical Friends Group® Tuning Protocol.

Beneficence: Minimizing all potential harms and maximizing all potential benefits to the subject as well as to society.

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

HANDOUT

HANDOUT

LESSON 3:
Institutional Review Boards—The Nitty Gritty

INTRODUCTION

Students are introduced to the concept of an **Institutional Review Board** (IRB) and perform a skit to learn about the regulations and membership requirements of an IRB. Students use the information learned from the skit to further discuss the rationale for having IRBs evaluate research studies involving humans. In small groups, students visit different stations to perform three activities typical of the work of IRBs. They work together to 1) simplify the language of a section of an informed consent document to be more easily understood, 2) analyze three advertisements made for fictional clinical trials to assess whether they are accurate and/or coercive, and 3) examine a segment of a research proposal written by an investigator describing the process for obtaining informed consent. Students report back to the class on their experience and discuss the benefits and limitations of the rigorous IRB process. Lastly, students read an article in which bioethicists encourage shorter, easier to understand consent forms.

CLASS TIME

About one class period of 55 minutes.

KEY CONCEPTS

- Institutional Review Boards (IRBs) oversee, monitor, and review research studies involving humans to protect the safety, rights, and welfare of human participants.
- Any research institution that receives U.S. federal funding (in the country or abroad) requires IRB regulation. The IRB may approve a study to proceed, stop a study from going ahead, or request changes the board must approve before researchers may move forward.
- IRBs are required to include a diverse group of people with differing views, backgrounds, and areas of expertise.
- Informed consent documents can be fairly lengthy and complex due to extensive content regulations.

Before class: **This lesson incorporates a short play. Teachers may wish to identify three actors and provide each with a copy of the script.**

LEARNING OBJECTIVES

Students will know:

- The purpose and function of an Institutional Review Board (IRB).
- There are many considerations involving science and ethics that the IRB must weigh to determine appropriate protection of human participants in research.

Students will be able to:

- Carry out sample activities that an IRB might perform.
- State the membership requirements for an IRB.

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*.

MATERIALS

Activity One: What is an IRB and who is on it?

Materials	Quantity
STUDENT SCRIPT for *Reader's Theater: IRB Membership*	3 copies—one per actor
TEACHER TRANSCRIPT—*Video Transcript for IRB Membership Video* (similar to student script, with answers)	1
Student Handout 3.1—*IRB Membership Chart*	1 per student
Possible Answers to Student Handout 3.1—IRB Membership Chart	1
Optional: Computer and internet access to show video	1
Optional: Video: *IRB Membership* from the Office of Human Research Protections (OHRP) [**Note:** You may choose to show the video instead of performing the skit. To correspond to Student Handout 3.2—*IRB Membership Chart*, follow these segments: From beginning of video to 5:13 From 13:18 to 13:47 Teachers may also choose to show the entire 16-minute video: http://www.youtube.com/watch?v=GHtlbdLkSwU.]	Access via the internet

Activity Two: What does an IRB do?

Materials	Quantity
Station A Student Handout 3.2a—*Say WHAT? Translating Informed Consent Language*	1 per group
Computer with Microsoft® Word	1 per group
Readability Instructions, Strategies, and Reminders	1 per group
Station B Student Handout 3.2b—*False Advertising? Interpreting Study Advertisements* [**Note:** Each group can choose one or more of the three advertisements to interpret, depending on time.]	1 per group [**Note:** Copy in color if possible.]
Station C Student Handout 3.2c—*Are You Sure? Becoming Informed*	1 per group
Possible Answers to Student Handouts 3.2a, 3.2b, and 3.2c	1 of each

FRAMING THE LESSON

Now that students have an understanding of the **Belmont principles** and their applications, this lesson will focus on the IRB—the group of people responsible for enacting the Belmont principles and protecting the safety, rights, and welfare of humans participating in research. Students will learn about IRBs from the inside out by stepping into the shoes of IRB members to make decisions about medical form language, research study advertisements, and informed consent.

Any research institution that receives U.S. federal funding (in the country or abroad) requires IRB regulation. An IRB may approve a study to proceed, stop a study from going ahead, or request changes the board must approve before researchers may move forward.

TEACHER PREPARATION

- Make copies of *Student Handouts*.
- Provide students in skit with STUDENT SCRIPT ***before the lesson***.
- Clear an area where the students can perform the skit.
- If showing the video instead of doing the skit, prepare computer and projection unit.
- Set up three stations (A, B, and C) through which groups of students will rotate. Each group will share one corresponding *Student Handout* at each station. Depending on space, more than one student group may occupy a station at the same time.

PROCEDURE

Activity One: What is an IRB and who is on it?

1. Tell students that the purpose of an Institutional Review Board (IRB) is to monitor and review studies involving human participants so that the safety, rights, and welfare of the human participants are protected. An IRB may approve a study to proceed, stop a study from going ahead, or request changes the board must approve before researchers may move forward. In this lesson an informational skit will illustrate the types of people who are IRB members.

[Note: If showing the video, recommended video segments are: the beginning of video to 5:13, and from 13:18 to 13:47.]

2. **The Skit:** Introduce the STUDENT SKIT about IRB membership. [**Note:** The script is based on a video about IRB Membership from the federal Office for Human Research Protections (OHRP).] The skit details some of the regulations that ensure that IRBs consist of a diverse group of people with various views, backgrounds, and areas of expertise. Alternately, students may watch the OHRP video at: http://www.youtube.com/watch?v=GHtlbdLkSwU.
3. Give students Student Handout 3.1—*IRB Membership Chart*.
4. As students watch the skit or video, have them fill out the second column of the *Student Handout*. (The first column has already been filled out with the corresponding regulations.) Stop the skit or video as necessary for students to finish their notes.
5. After the skit or video, have students work in small groups to fill out the third column of the chart.
6. Once students complete the chart, lead a class discussion asking these questions:
   a. How do IRB membership requirements help ensure that the Belmont principles are applied? [**Note:** Review the Belmont principles if necessary.]
   b. If an institution observes all the regulations, do you think that everyone who should be on an IRB is on it? Who, if anyone, is not represented?
   c. How would you change the regulations to improve research ethics and accountability?
   d. How does the IRB protect participants? How does the IRB protect the institution?

Activity Two: What does an IRB do?

7. Remind students that the IRB's role is to ensure protection of human participants in research, as outlined in federal regulations and in the Belmont principles.
8. Divide students into small groups. Direct each group to Station A, B, or C. (More than one group may occupy a station at the same time.) Have each group fill out the *Student Handout* found at the corresponding station:

   Station A: Student Handout 3.2a—*Say What? Translating Informed Consent Language*

   Station B: Student Handout 3.2b—*False Advertising? Interpreting Study Advertisements*

   Station C: Student Handout 3.2c—*Are You Sure? Becoming Informed*

   Ask students to follow the instructions on their *Student Handout* and perform the tasks listed.

9. When students have finished at one station, have them move as a group to the next station.

10. After all groups have had a turn at each station, discuss the following questions as a class:

    a. What was it like to do some of the tasks an IRB is asked to do?

    b. Was it easy or difficult to keep all of the materials and processes true to the requirements of the Belmont principles? What challenges did you face in following the principles? Why?

    c. What are the benefits of having an IRB review all of the details related to a clinical research study?

    d. What are the limitations of such a detailed process?

11. Invite students to think about how they would change or improve the process so that studies are kept to high **ethical standards**, participants' rights are protected, and important research can progress at an efficient pace. As important as this system is, it is imperfect. Explain to students that:

- Though the IRB has the right to visit the labs and clinics of any of the investigations they have reviewed, they often do not.
- Because of the many regulations surrounding informed consent, most consent forms are 20 or more pages long (a sample informed consent form can be found at http://www.nwabr.org).
- Institutions have different standards and requirements for what they will review. Some institutions, for example, will review the informed consent form but not the informed consent process.

Closure

12. Ask students to work in pairs and write in their notebooks three to four answers to the question, "In what ways does the IRB ensure protection of human participants in research?"

13. Have two pairs combine to make a group of four students. Invite the groups to compare their answers and add any new ideas to their notes.

14. Now ask two groups of four to work together as a group of eight students. Again, have students compare answers and add any new information.

15. Bring the class back together and compare the answers from each large group. Make sure that the answers reflect the ***Key Concepts*** outlined at the beginning of this lesson, and ask the students to add any missing ideas.

CONNECTION TO FORMATIVE ASSESSMENT

Revisit the statements students sorted for the *Formative Assessment*. After completing this lesson detailing the role and function of an IRB, students should understand that Statement C is accurate and reconfirm that Statement E is not accurate.

HOMEWORK

Teachers may choose from two relevant and accessible articles to assign for homework, if desired. They are:

- *Informed Consent Forms Should be Shortened, Simplified, Bioethicists Say,* found at: http://www.sciencedaily.com/releases/2011/07/110715135325.htm.
- *Informed Consent on Trial: Lengthy, complicated documents leave many clinical-trial participants in the dark about the risks they face,* found at: http://www.nature.com/news/informed-consent-on-trial-1.9933.

EXTENSION

Have students look at the University of Washington *Human Subjects Review Application* and consider how this institution's IRB members are asked to think about the research studies they review. The form can be found at: http://www.washington.edu/research/hsd/docs/3. Looking at the questions that researchers have to answer on this form, ask students to list three of them and the Belmont principles they address.

GLOSSARY

Belmont Report (Belmont principles): Created in 1978 by the U.S. Department of Health, this report established three basic ethical principles to be considered when humans participate in research.

Ethical standards: Rules governing the conduct of a person or the conduct of the members of a profession.

Institutional Review Board (IRB): A group made up of a diverse group of people (with varying views, backgrounds, and areas of expertise) who oversee, monitor, and review research studies to protect the safety, rights, and welfare of human participants.

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.

RESOURCES

Washington State University IRB Checklist
http://www.irb.wsu.edu/documents/forms/pdf/Application_Review_Checklist.pdf

University of Washington IRB Review Form
http://www.washington.edu/research/hsd/docs/3

Seattle Children's Hospital IRB-related Forms
http://www.seattlechildrens.org/research/forms-policies/irb/application-forms/
http://www.uab.edu/irb/forms/sample-consent-form.doc

SOURCES

The activities found in *Activity Two* are modified from lessons developed by the HIV Vaccine Trials Network (HVTN) Leadership and Operations Center, Seattle, Wash., and are used with permission.

Images are from http://www.fotolia.com.

The *ScienceDaily* article is based on: Johns Hopkins Medical Institutions (2011, July 20). Informed-consent forms should be shortened, simplified, bioethicists say.

STUDENT SCRIPT

Reader's Theater: IRB Membership

Setting:

An office at an institution that would like to establish an Institutional Review Board (IRB).

Characters:

Dr. Quinn (Dr. Q)—Official with Mock University responsible for making sure the institution follows through on its IRB commitments.

Ms. Hobbs (Ms. H)—Humans Protection Administrator

Dr. Resner (Dr. R)—Medical Director of Mock University

Dr. Quinn (Dr. Q): Ms. Hobbs, Dr. Resner, thank you for joining me today. I understand that establishing an Institutional Review Board at Mock University would be in our best interest. Ms. Hobbs, can you tell me a little about who would serve as a member of the IRB?

Ms. Hobbs (Ms. H): Sure. We will need to appoint at least five members to serve on the IRB, although it may be to our advantage to have eight to 10 members, since there is no limit on how many people we can appoint to the IRB.

Dr. Q: To demonstrate my commitment to the IRB, I would like to be an IRB member.

Ms. H: Since your primary concern is the welfare of Mock U, I recommend against you serving as an IRB member, but you can demonstrate your support to the IRB in other ways.

Dr. Q: OK, so I won't appoint myself as an IRB member. I can ask each department head to identify a physician to serve on the IRB. That will fulfill the required numbers.

Ms. H: Well, Dr. Quinn, it's a great idea to have several physicians on the IRB, however, the members need to come from a variety of backgrounds so there is a complete and adequate review of each research project. And the regulations do not allow an IRB to be comprised of members from only one profession. Also, our IRB should reflect our community. It should have diversity in gender, race, and cultural backgrounds.

Dr. . Resner (Dr. R): What considerations about gender? Do half the members need to be female?

Ms. H: No, there isn't a required set percentage for male and female members in the regulations, but we don't want to discriminate when selecting IRB members, and it would be best if the board is not made up entirely of men or of women.

Dr. Q: Does the type of research that we currently conduct have any bearing on who should serve as an IRB member?

Ms. H: Yes. We need to have IRB members with the ability to review the specific research activities that are submitted to our IRB. Since we conduct both biomedical and social/behavioral research studies, we'll need to have experts in both of these areas.

HANDOUT

Dr. R: Occasionally, we conduct very complex studies by a specialist. Do we need to have members from every specialty?

Ms. H: No, we should look for IRB members with expertise in the types of studies that we typically conduct. We can supplement our IRB's review scope by bringing in consultants to review areas of study that are uncommon for Mock U.

Dr. R: We conduct a lot of cancer and cardiac studies at this institution. I think it would be wise to have a cardiologist and an oncologist sit on the IRB.

Ms. H: I agree. We also do a lot of research with children and prisoners, so we need to have IRB members with expertise in these areas as well.

Dr. Q: I understand why it's important to have an expert in pediatric research, but why have an expert in prisoner issues?

Ms. H: This person is actually called the prisoner representative. Their role is to serve as an advocate for the rights and welfare of research subjects who are prisoners.

Dr. Q: I happen to know the state prison warden and can ask her if she would be willing to be an IRB member.

Ms. H: Well, although the warden should have a close working knowledge and understanding of the prison conditions, she probably wouldn't be viewing the conditions from a prisoner's perspective. It may be better to identify someone else to serve in this capacity.

Dr. R: Do you have someone in mind?

Ms. H: A suitable prisoner representative could be a present or former prisoner, a prison chaplain, a prison psychologist, or a prison social worker. I happen to know a member of the clergy who routinely visits the state prison. I think he would have the appropriate background to represent the rights and welfare of prisoners.

Dr. Q: Okay. So far we have come up with a plan to ask a couple of physicians and a minister to join our IRB. You said eight to 10 members. Who else were you thinking we should ask to be a Mock University IRB member?

Ms. H: We need to have at least one scientist, one nonscientist, and one member with no connection to Mock University. The physicians are considered to be scientists and the clergy member is considered to be a nonscientist.

Dr. R: I could see the value of the nonscientist's role in reviewing research studies through the eyes of anyone in our community, and reviewing the informed consent language and reading level.

Ms. H: You are correct. In addition, there needs to be a nonscientist present at all times for official business to be carried out.

Dr. R: What happens if the nonscientist needs to leave the room temporarily?

Ms. H: The meeting cannot continue in the absence of the nonscientist. The nonscientist must be present for the IRB to conduct study review and approval.

Dr. R: Are IRB members required to have special training?

Ms. H: No, there is no regulatory requirement for training, but because we receive federal funding for our clinical trials involving humans, the Office of Human Research Protections strongly recommends that we provide a training program for our IRB members.

Dr. Q: What would you want to include in the training?

Ms. H: I would want to include a review of the ethical principles identified in the Belmont Report, and both a review of the Human Health Services and Food and the Drug Administration regulations, and the Office of Human Research Protections guidance documents.

Dr. Q: Ms. Hobbs and Dr. Resner, thank you both very much for your time today. With your dedication and knowledge, I believe that we are much closer to establishing an effective and appropriate IRB at this institution.

Script is modified from the video *IRB Membership* produced by the Office of Human Research Protections and used with permission.

HANDOUT

TEACHER TRANSCRIPT

Video Transcript for IRB Membership Video

Similar to student script; includes answers.

[**Note:** This is a direct transcript from the OHRP video available at: http://www.youtube.com/watch?v=GHtIbdLkSwU.]

The STUDENT SCRIPT was modified for student use. The regulations found in brackets on this transcript correspond to the STUDENT SCRIPT. Student Handout 3.1—*IRB Membership Chart* can be used as a key to the handout.

Setting:

An office at an institution that would like to establish an Institutional Review Board (IRB).

Characters:

Dr. Quinn (Dr. Q)—Official with Mock University responsible for making sure the institution follows through on its IRB commitments.

Ms. Hobbs (Ms. H)—Humans Protection Administrator

Dr. Resner (Dr. R)—Medical Director of Mock University

Dr. Quinn (Dr. Q): Ms. Hobbs, Dr. Resner, thank you for joining me today. I understand that establishing an IRB at this institution would be in our best interest. Ms. Hobbs, can you tell me a little about who would serve as a member of the IRB?

Ms. Hobbs (Ms. H): Sure. We will need to appoint at least five members to serve on the IRB, although it may be to our advantage to have eight to 10 members, since there is no limit on how many members we can appoint to the IRB. [IRB MEMBERSHIP AT LEAST FIVE MEMBERS]

Dr. Q: To demonstrate my commitment to the IRB, I would like to be an IRB member.

Ms. H: As signatory official, your primary concern is the welfare of the institution. I recommend against you serving as an IRB member, but believe that you can demonstrate your support to the IRB in other ways.

Dr. Q: Okay, so I won't appoint myself as an IRB member. I can ask each department head to identify a physician to serve on the IRB. That will fulfill the required numbers.

Ms. H: Well, Dr. Quinn, it's a great idea to have multiple physicians on the IRB, however, the members need to have varying backgrounds so there is a complete and adequate review of each research project. And the regulations do not allow an IRB to be comprised of members from only one profession. [VARYING BACKGROUNDS; MORE THAN ONE PROFESSION MUST BE ON IRB]

Also, in appointing our IRB, we should try to give consideration to getting an IRB with diversity in terms of gender, race, and cultural backgrounds, especially given the demographic makeup of the community in which we reside. [QUALIFIED THROUGH EXPERIENCE, EXPERTISE, AND DIVERSITY]

Dr. Resner (Dr. R): What considerations about gender? Do fifty percent of the members need to be female?

RESOURCE

Ms. H: No, there's no regulatory requirement for the percent of members that must be a certain gender. However, we need to be careful that we don't discriminate when selecting IRB members, including making selections based on gender. We should also try to ensure that our IRB doesn't consist entirely of men or of women. [EVERY EFFORT MADE TO AVOID GENDER DISCRIMINATION AND PROMOTE GENDER DIVERSITY]

Dr. Q: Does the type of research that we currently conduct have a bearing on who should serve as an IRB member?

Ms. H: Yes. We need to have IRB members with the professional competence necessary to review the specific research activities that are submitted to our IRB. Since we conduct both biomedical and social/behavioral research studies, we'll need to have experts in both of these areas. [PROFESSIONAL COMPETENCY]

Dr. R: Occasionally we conduct very complex studies by a specialist. Do we need to have members from every specialty?

Ms. H: No, we should have IRB members with expertise in the type of studies that we typically conduct. We can supplement our IRB's review by bringing in a consultant to provide a review for other types of studies which we don't typically conduct. [USE OF EXPERTS TO ASSIST REVIEW]

Dr. R: We seem to conduct a lot of cancer and cardiac studies at this institution. I think it would be wise to have a cardiologist and an oncologist sit on the IRB.

Ms. H: I agree. We also do a lot of research with children and prisoners, so we need to have IRB members with this expertise as well.

Dr. Q: I understand why it would be important to have an expert on children's research, but why have an expert in prisoner issues?

Ms. H: This person is actually called the prisoner representative. This person's role is to serve as an advocate for the rights and welfare of the subjects who are prisoners. [PRISONER REPRESENTATIVE]

Dr. Q: I happen to know the state prison warden and can ask her if she would be willing to be an IRB member.

Ms. H: Well, although the warden should have a close working knowledge and understanding of the prison conditions, she probably wouldn't be viewing the conditions from the prisoner's perspective. It may be better to identify someone else to serve in this capacity.

Dr. R: Do you have someone in mind?

Ms. H: A suitable individual to serve as a prisoner representative may include a present or former prisoner, a prison chaplain, a prison psychologist, or prison social worker. I happen to know a member of the clergy who routinely visits the state prison. I think that he would have the appropriate background to represent the rights and welfare of prisoners.

Dr. Q: Okay. So we have a couple of physicians and a minister on the IRB. You said eight to 10 members. Who else were you thinking that we should ask to be an IRB member?

Ms. H: We need to have at least one scientist, one nonscientist, and one nonaffiliated member on the IRB. The physicians are considered to be scientists and the clergy member is considered to be a nonscientist. [SCIENTIFIC AND NONSCIENTIFIC MEMBERS]

Dr. R: I could see the value of nonscientists' roles in reviewing research studies through the eyes of a layperson and reviewing the informed consent language and reading level.

Ms. H: You are correct. In addition, there needs to be a nonscientist present to meet quorum requirements. [NONSCIENTIST PRESENCE]

Dr. R: What happens if the nonscientist needs to leave the room temporarily?

Ms. H: The meeting cannot continue in the absence of the nonscientist. The nonscientist must be present for the IRB to conduct its review and approval of studies.

Video reference 13:18

Dr. R: Are IRB members required to have special training?

Ms. H: No, there is no regulatory requirement for training although the terms of our federal-wide assurance with OHRP strongly recommend that we establish an educational training program.

Dr. Q: What would you want to include in the training?

Ms. H: I would want to include a review of the ethical principles identified in the Belmont Report, a review of both the HHS and FDA regulations, as well as the OHRP guidance documents. I would also recommend the IRB members review the Human Subject Assurance Training modules available through the OHRP website.

Dr. Q: Ms. Hobbs and Dr. Resner, thank you both very much for your time today. With your dedication and knowledge, I believe that we are much closer to establishing an effective and appropriate IRB at this institution.

STUDENT HANDOUT 3.1

IRB Membership Chart

Name_____ Date_____ Period_____

Regulation	What does it mean?	Why is it important?
IRB membership, at least five members		
Varying backgrounds, more than one profession must be on the IRB		
Qualified through experience, expertise, and diversity		
Every nondiscriminatory effort made for gender diversity		
Professional competency		

HANDOUT

Regulation	What does it mean?	Why is it important?
Use of experts to assist review		
Prisoner representative		
Scientific and nonscientific members		
Nonscientist presence		
Training for IRB members		

HANDOUT

Possible Answers for STUDENT HANDOUT 3.1
IRB Membership Chart

Regulation	What does it mean?	Why is it important?
IRB membership, at least five members	*At least five people, better to have eight to 10; no limit.*	*Lots of people to help make important decisions, more representative of the community at large.*
Varying backgrounds, more than one profession must be on the IRB	*Not all doctors, not all researchers; different professions and kinds of people.*	*People who may have different perspectives.*
Qualified through experience, expertise, and diversity	*People with good experience, knowledge, or from diverse backgrounds.*	*People who know what they're talking about, different perspectives.*
Every nondiscriminatory effort made for gender diversity	*Not all men or not all women. Not necessarily 50/50, but trying to achieve balance. For groups conducting social/behavioral research, it might also be beneficial to have diversity of sexual orientations.*	*Difference of perspectives along the gender identity spectrum and from different sexual orientations.*
Professional competency	*People with expertise in the kinds of studies the institution regularly performs.*	*The right people with the right expertise making decisions on topics they are familiar with.*

RESOURCE

Regulation	What does it mean?	Why is it important?
Use of experts to assist review	*Bringing in people with expertise if it doesn't exist in the group.*	*People are well informed before they make decisions.*
Prisoner representative	*Former prisoner, prison chaplain, psychologist, social worker, etc., who can provide prisoner's perspective.*	*Someone needs to look out for prisoners so that they won't be taken advantage of.*
Scientific and nonscientific members	*Scientists and nonscientists (people whose professions are not in the sciences).*	*A nonscientist can help to ensure that research is not pushed forward only because it may be scientifically noteworthy.*
Nonscientist presence	*The nonscientist must be at the meeting for decisions to be made.*	*The nonscientist perspective should be shared at every decision point to help make sure the research is being handled ethically from a citizen's viewpoint.*
Training for IRB members	*No regulatory requirement, but recommend members review Belmont Report, Code of Federal Regulations, FDA regulations and others.*	*Knowing the history and background of the Belmont Report and FDA regulations will help IRB members understand the importance of their role.*

STUDENT HANDOUT 3.2a

Say WHAT? Translating Informed Consent Language

Name_____ Date_____ Period_____

Instructions: The Belmont Report stresses that research participants must be fully informed in an adequate manner. It is therefore common practice that informed consent forms are written at about an eighth grade reading level (or below). Translate the following excerpt from an informed consent form into language that somebody with an eighth grade reading level (or below) would understand.

Original Text A

Any medical data that is obtained in connection with this study will be utilized only for this study, with exception by consent. If you give us your permission by signing this document, we plan to submit medical data to the University database. All information will be made anonymous.

Current Flesch-Kincaid Grade Level ("readability" score): 13.9

Your Version:

Readability Score Text A: _____

Original Text B

Drawing blood may cause brief discomfort, bleeding, and discoloration where the needle enters the body, and in a few cases inflammation at the site of entry. Rarely, loss of consciousness and infection can occur. There also may be other unforeseen side effects or discomforts that we cannot predict, thus it is important to advocate with your clinician when unusual symptoms occur.

Current Flesch-Kincaid Grade Level ("readability" score): 12.2

Your Version:

Readability Score Text B: _____

This activity is modified from a lesson developed by the HIV Vaccine Trials Network's (HVTN) Leadership and Operations Center, Seattle, Wash., and is used with permission.

HANDOUT

STATION A – READABILITY INSTRUCTIONS, STRATEGIES, AND REMINDERS

Instructions for finding the Flesch-Kincaid Grade Level ("readability" score):

If using an older version of Microsoft® Word:

1. Choose ***Tools*** then ***Options***.
2. Click the ***Spelling & Grammar*** tab.
3. Check both ***Check grammar with spelling*** and ***Show readability statistics***.
4. Readability is displayed after you run a spell check; anything above grade 12 indicates a college-level education is necessary to ensure understanding.

If using a newer version of Word:

1. Click the ***Office*** button in the upper left corner.
2. Choose ***Word Options*** at the bottom.
3. Click on ***Proofing***.
4. Check the box ***Show readability statistics*** under the ***Spelling & Grammar*** section.
5. Readability is displayed after you run a spell check; anything above grade 12 indicates a college-level education is necessary to ensure understanding.

If using a Mac:

1. Choose ***Tools*** then ***Spelling & Grammar***.
2. Click on ***Options***.
3. Check the box ***Show readability statistics*** under the ***Grammar*** section.
4. Readability is displayed after you run a spell check; anything above grade 12 indicates a college-level education is necessary to ensure understanding.

Strategies for decreasing the "readability" score of a passage

Follow these principles for writing in plain language:

1. Use shorter sentences.
2. Use the active voice. ("Run!" instead of "I told her to run.")
3. Avoid text in parentheses or in phrases that are set off with commas.
4. Use shorter words.
5. Avoid words that could be interpreted differently based on context. (For example, the word "trial" could mean different things depending on whether it is used in a legal sense or in a biomedical research sense.)
6. Use simple punctuation and grammar.

Reminders of your responsibility

While it is important to lower the readability score, it is your responsibility to convey the same information and messages. Make sure you don't simplify the text to the point where the meaning is lost. Remember, the goal is ***informed*** consent.

HANDOUT

Possible Answers for STUDENT HANDOUT 3.2a
Say WHAT? Translating Informed Consent Language

Instructions: The Belmont Report stresses that research participants must be fully informed in an adequate manner. It is therefore common practice that informed consent forms are written at about an eighth grade reading level (or below). Translate the following excerpt from an informed consent form into language that somebody with an eighth grade reading level (or below) would understand.

Original Text A

Any medical data that is obtained in connection with this study will be utilized only for this study, with exception by consent. If you give us your permission by signing this document, we plan to submit medical data to the University database. All information will be made anonymous.

Current Flesch-Kincaid Grade Level ("readability" score): 11.3

Your Version:

We will use medical information we get only for this study. If you give us permission by signing below, we will share this information with the University. We will take your name off any records so no one can link the information to you.

Readability Score Text A: 8.0

Original Text B

Drawing blood may cause brief discomfort, bleeding, and discoloration where the needle enters the body, and in a few cases inflammation at the site of entry. Rarely, loss of consciousness and infection can occur. There also may be other unforeseen side effects or discomforts that we cannot predict, thus it is important to advocate with your clinician when unusual symptoms occur.

Current Flesch-Kincaid Grade Level ("readability" score): 12.2

Your Version:

Taking blood from you with a needle may be uncomfortable. Sometimes your skin may turn a different color where the needle enters the body. Sometimes you may bleed where the needle enters the body. Sometimes the area may swell. It is not common, but you may faint, or the place where the needle enters the body may become infected. Other things may happen that we cannot guess about. If something weird or not expected happens to you, you should tell us and see the doctor.

Readability Score Text B: 6.3

This activity is modified from a lesson developed by the HIV Vaccine Trials Network's (HVTN) Leadership and Operations Center, Seattle, Wash., and is used with permission.

RESOURCE

STUDENT HANDOUT 3.2b

False Advertising? Interpreting Study Advertisements

Name_____ Date_____ Period_____

Instructions: The Belmont Report stresses that we need to recruit participants fairly, guard against using vulnerable populations, guard against undue influence, and avoid potential financial and other conflicts of interest. Review these advertisements seeking participants for a clinical trial. Analyze each of them for strong and weak elements. You may approve the advertisements for use, make recommendations for changes before they can be used, or prohibit their use.

Advertisement One

Advertisement strengths	Advertisement weaknesses (and suggested changes)

Advertisement Two

Advertisement strengths	Advertisement weaknesses (and suggested changes)

Advertisement Three

Advertisement strengths	Advertisement weaknesses (and suggested changes)

HANDOUT

This activity is modified from a lesson developed by the HIV Vaccine Trials Network's (HVTN) Leadership and Operations Center, Seattle, Wash., and is used with permission.

Possible Answers for STUDENT HANDOUT 3.2b
False Advertising? Interpreting Study Advertisements

Instructions: The Belmont Report stresses that we need to recruit participants fairly, guard against using vulnerable populations, guard against undue influence, and avoid potential financial and other conflicts of interest. Review these advertisements seeking participants for a clinical trial. Analyze each of them for strong and weak elements. You may approve the advertisements for use, make recommendations for changes before they can be used, or prohibit their use.

Advertisement One

Advertisement strengths	Advertisement weaknesses (and suggested changes)
Colorful and eye-catching. Clear contact information. *Time commitment for participants stated clearly.* *Benefits to participants clearly stated (reimbursement for time and transportation, etc.). Except for title, benefits not overstated.*	*The study title ("Want Healthier Babies?") implies that your baby will directly benefit from your participation in the trial, which cannot be guaranteed.* *The important information about the study is difficult to read because of the colored background.* *The picture shows a homogenous group of women, but the study is seeking women of diverse ages, races, ethnicities, and backgrounds.* *Additional criteria for qualification would be helpful (i.e., how far along in pregnancy, is woman taking any other medications, etc.).*

Advertisement Two

Advertisement strengths	Advertisement weaknesses (and suggested changes)
Colorful and eye-catching. Clear contact information. *Shows diversity of ages, backgrounds, and genders in potential participants.* *Benefits to participants clearly stated (compensation for time and transportation, etc.).*	*Statement "You will not get malaria in the study" cannot be guaranteed. Participants may still contract malaria while in the study (while traveling internationally, for example), even though their participation in the study will not give them malaria.* *Overstatement of heroic nature of study participants makes it seem that this study will directly lead to cures and/or treatments.* *"Your participation can save lives" overstates the outcome of participation. The vaccine being testing may still be decades away from use.*

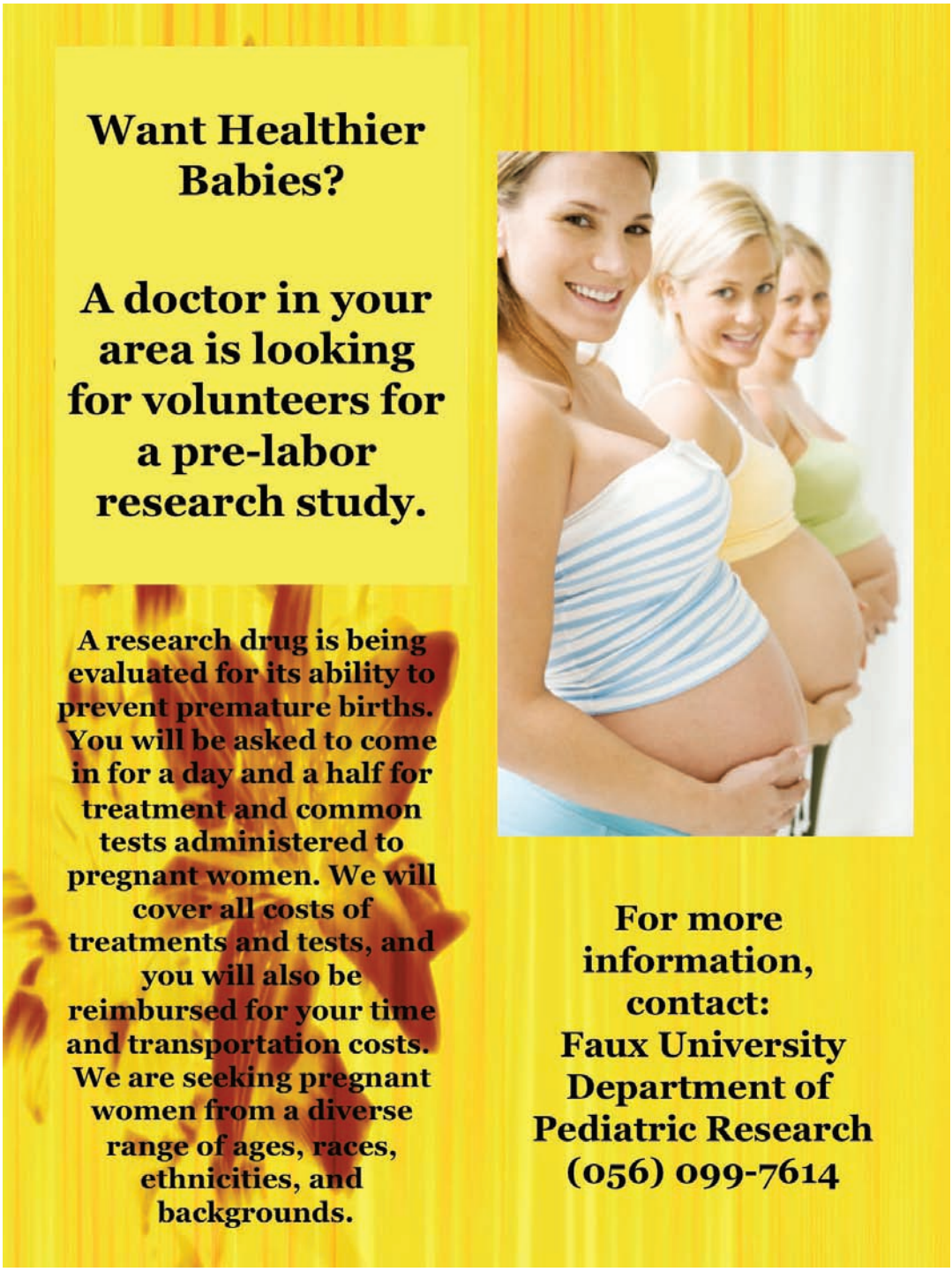
Advertisement Three

Advertisement strengths	Advertisement weaknesses (and suggested changes)
Colorful and eye-catching. Clear contact information. *Criteria for participation clearly stated.*	*Focus on money may unduly influence potential participants.* *Promise of "quick" cash may not be straightforward. Research is not fast, and the study may last for months or even years.* *Picture of Pandora's box misrepresents the biomedical research process (i.e., It's magical! It's mysterious!).*

RESOURCE

This activity is modified from a lesson developed by the HIV Vaccine Trials Network's (HVTN) Leadership and Operations Center, Seattle, Wash., and is used with permission.

Advertisement One



RESOURCE

Advertisement Two

Not All Heroes Wear Masks and Capes

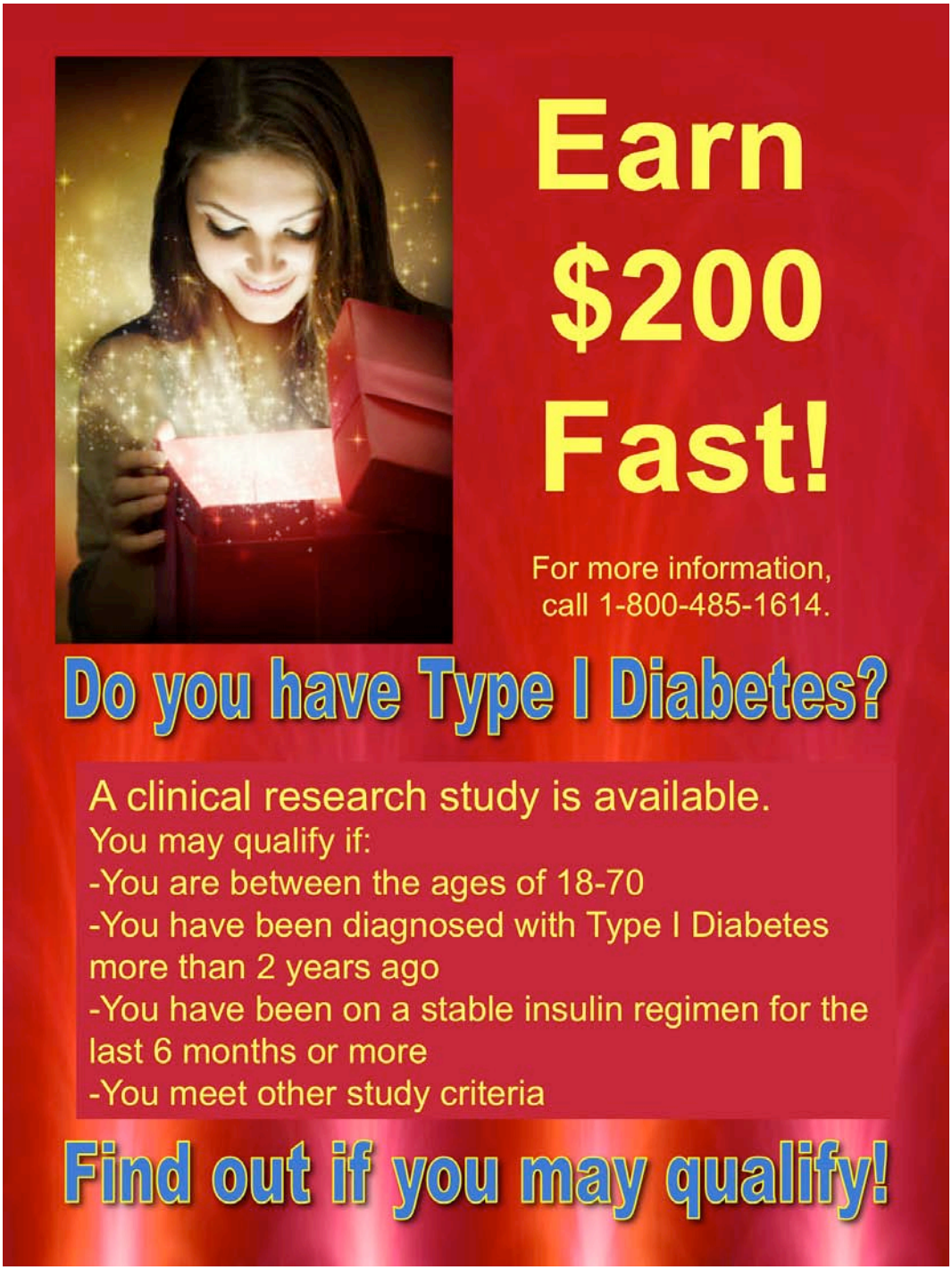
Volunteer for a malaria vaccine research study!

Shambhala Clinical Research Center is seeking 2000 participants of all ages, genders, races, and backgrounds to test the effectiveness of a malaria vaccine. You will not get malaria in the study. All visits are free of charge, and you will be compensated for travel and your time.

Your participation can save lives. Be a hero!
Call (321) 987-6543 today!

RESOURCE

Advertisement Three



STUDENT HANDOUT 3.2c

Are You Sure? Becoming Informed

Name_____ Date_____ Period_____

Instructions: The Belmont Report stresses that participants must enter into research voluntarily, must be informed in an adequate manner, and must genuinely give consent with full knowledge of benefits and harms. An investigator proposed the following procedure for obtaining informed consent from volunteers interested in enrolling in the study:

Procedure

The prospective participant will meet with the principal investigator (PI) for a few minutes in a private waiting room. The PI will give a brief overview of the study, and flip through the informed consent form to point out the major elements. The PI will then exit the room, leaving the prospective participant to read the form. Because it is a 10-page form, the PI will return after 30 minutes to give adequate time for the prospective participant to read the form. After 30 minutes, the PI will re-enter the room and ask the prospective participant if she has any questions. If there are no questions, the PI will then ask the prospective participant if she will sign up to be in the study. If yes, the participant will sign the appropriate lines on the consent form and then will be escorted into the next room to receive the first treatment. Combining the informed consent and first treatment will reduce the number of times the participant has to come into the clinic.

Do you see any problems with this method? If so, what are they?

An IRB can require changes before the study is approved. Are there changes you believe need to be made to the investigator's informed consent process described above?

HANDOUT

This activity is modified from a lesson developed by the HIV Vaccine Trials Network's (HVTN) Leadership and Operations Center, Seattle, Wash., and is used with permission.

Possible Answers for STUDENT HANDOUT 3.2c
Are You Sure? Becoming Informed

Instructions: The Belmont Report stresses that participants must enter into research voluntarily, must be informed in an adequate manner, and must genuinely give consent with full knowledge of benefits and harms. An investigator proposed the following procedure for obtaining informed consent from volunteers interested in enrolling in the study:

Procedure

The prospective participant will meet with the principal investigator (PI) for a few minutes in a private waiting room. The PI will give a brief overview of the study, and flip through the informed consent form to point out the major elements. The PI will then exit the room, leaving the prospective participant to read the form. Because it is a 10-page form, the PI will return after 30 minutes to give adequate time for the prospective participant to read the form. After 30 minutes, the PI will re-enter the room and ask the prospective participant if she has any questions. If there are no questions, the PI will then ask the prospective participant if she will sign up to be in the study. If yes, the participant will sign the appropriate lines on the consent form and then will be escorted into the next room to receive the first treatment. Combining the informed consent and first treatment will reduce the number of times the participant has to come into the clinic.

Do you see any problems with this method? If so, what are they?

Problems could include:

- *That amount of time may be too long, or too short, for different people.*
- *Not best way to communicate information to people who don't read well. Other visual or spoken methods should be included.*
- *Relying on the prospective participant to ask questions about what she does not understand is problematic.*
- *There should be time built in to review the form with the participant and assess her understanding.*
- *The prospective participant should have time between signing the consent form and receiving the first treatment to think more about the study, ask her own personal doctor about the pros and cons of participation, or consult with family members.*
- *It should be very clear that the prospective participant may withdraw from the study at any time without any penalty.*

An IRB can require changes before the study is approved. Are there changes you believe need to be made to the investigator's informed consent process described above?

- *The PI (or doctor) should not get consent from prospective participants. Participants may be influenced by the authority and importance of the PI or doctor (i.e., "white coat syndrome" makes the PI or doctor too persuasive).*
- *It is acceptable to have another trained staff person who is able to spend as much time as needed with the participant go over the consent form, a nurse or counselor could be a good choice.*
- *The staff person should stay the entire time and read through the consent form with the participant.*
- *The staff person should also provide visual aids such as graphic books, videos, or flip charts for those with limited literacy.*
- *The staff person should ask the participant periodically about her understanding of the study rather than wait for the participant to ask questions.*
- *There could be a short "quiz" to make sure the prospective volunteer has understood all the key elements of the study.*
- *The appointment during which the consent form is signed should not be the same appointment as the first clinical appointment.*

RESOURCE

This activity is modified from a lesson developed by the HIV Vaccine Trials Network's (HVTN) Leadership and Operations Center, Seattle, Wash., and is used with permission.

LESSON 4:
Participating in Research

INTRODUCTION

Students begin by gathering their own behavioral, medical, and genetic information, and prepare a cheek swab DNA sample. Next, students consider using their information to participate in a number of simulated research projects. This leads to a discussion about how the amount of time, degree of involvement, level of risk, and reasons for participation can vary for different types of research studies. Finally, students think about the ramifications of the fast-growing technology of **biobanking** in the context of clinical research and discuss their personal views.

CLASS TIME

About one class period of 55 minutes.

KEY CONCEPTS

- Genes and the environment work together to influence an individual's observable characteristics such as behavior, appearance, health, and disposition.
- There are many types of research that involve human participants.
- Different types of research involve different levels of participation, risk, and benefit.
- There are potential ethical, social, and legal ramifications to disclosing medical and genetic information.
- Biobanks are data repositories in which information is used by researchers for population studies and to develop treatments, medicines, or other products.

LEARNING OBJECTIVES

Students will know:

- There are many types of research that involve human participants.
- Different types of research involve different levels of participation, risk, and benefit.
- Biobanks are repositories for storing biological specimens and information.

Students will be able to:

- Weigh the harms and benefits of participating in simulated research projects.
- Weigh the harms and benefits of sharing genetic information.

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*.

MATERIALS

Materials	Quantity
Student Handout 4.1—*Health History and Behavior Survey*	1 per student
Cotton swab	1 per student
Envelope	1 per student
Small sticky note	1 per student
Sheet of dot stickers	5-Each sheet can be shared among a few students
Studies—*Research Study Seeking Participants (Studies #1–5)*	1 copy of each study to be posted around the classroom
Teacher Resource 4.1—*Participation Arrows*	Post one arrow next to each research study
Computer with internet access to show videos	1
Video: *How Do I Give DNA?* Explanation and demonstration of how to swab for cheek cells (30 seconds). Teachers may choose to show entire 2.5-minute video: http://www.videojug.com/interview/giving-dna-2.	Access via internet
Video: *People Matter—The Future of Research*. A group of collaborators develop innovative approaches to engage participants in research (6.5 minutes): http://peoplematterproject.org.	Access via internet

FRAMING THE LESSON

In the previous lessons, the research study participants were from historical cases or they were unidentified. In this lesson, students consider the risks and benefits of sharing their own health history and genetic information, and decide whether or not they would personally participate in a research study.

TEACHER PREPARATION

- Make copies of *Student Handouts*.
- Post five research studies around the classroom.
- Make stacks of envelopes, cotton swabs, sticky notes, and sticker sheets.
- Post one "participation arrow" next to each study. Arrows can be made from painter's tape or from Teacher Resource 4.1—*Participation Arrows*.
- Prepare computer and projection unit to show videos.

To further explore personalized genetics and direct-to-consumer genetic testing, please refer to *Lesson One* of NWABR's *Using Bioinformatics: Genetic Testing* curriculum at http://www.nwabr.org.

PROCEDURE

Activity One: Research Studies and You

Part I: Gathering Information

This class activity and discussion focus on student attitudes toward different types of research involving human participants.

1. Explain to students that our knowledge is rapidly growing about how genetic information and the environment work together to influence each person's appearance, behavior, health, and disposition.
2. Give each student a copy of Student Handout 4.1—*Health History and Behavior Survey*, an envelope, and a sticky note. Give them five minutes to fill out the survey. When they're done, ask them to place it in the envelope.
3. Explain to students that they will next be collecting some of their own DNA to go with the survey. Show the *How Do I Give DNA?* video. Give each student a cotton swab and ask them to gently wipe the inside of their cheek as shown in the video. Have them put the swab inside the envelope with their survey.

4. Ask students to write their name on the sticky note and attach it to the outside of their envelope.

5. Tell students that the cotton swab inside the envelope is now holding cells that contain their DNA. The survey contains details about their health, behavior, and some genetic history.

6. Let students know that it is now possible to sequence a person's entire genetic code for about $1,000, a price that is rapidly falling. Genetic technology is moving at such a pace that within their generation it may be so easy and affordable to read a person's **genome** that genetic information may become part of each individual's medical record. Remind students that, to varying degrees, both genes and the environment influence each person's observable characteristics such as behavior, appearance, health, and disposition.

Part II: To Participate or Not

7. Now ask students if they would be willing to turn in their envelopes (share their personal information and DNA) with researchers who plan to use their health and behavioral information and/or DNA in research studies with the goal of making advances in human health and welfare.

8. Tell students that they will have the chance to consider participating in the five different fictitious studies posted around the classroom.

9. Give a brief overview of each study (see below), taking time to define vocabulary words as necessary. Make sure students understand that ***inclusion criteria*** are all of the conditions that ***must be met*** in order for someone to participate in a study, and ***exclusion criteria*** are any conditions that would ***disqualify*** someone from participating in a study. Study overviews:

   a. ***Study #1:*** Testing the effectiveness of eyelash growth serum on people who wear contact lenses and/or eyelash makeup (mascara) and people who wear neither.

   b. ***Study #2:*** Examining the link between eating nuts and blood sugar levels, as related to the prevention and management of Type II Diabetes.

   c. ***Study #3:*** Studying the link between the time of day and a person's attention, focus, and thinking to develop better ADHD medication schedules.

   d. ***Study #4:*** Testing the safety of a Phase I malaria vaccine.

   e. ***Study #5:*** Examining the genetic basis of:

      - mental and physical traits that are keys to becoming a "superstar" athlete, and
      - mental and physical traits that are keys to extremely violent, even criminal behavior.

10. Give students 10 to 15 minutes to read the posted studies.

11. After students read as many studies as they can in the time available, ask them to place a small sticker somewhere along the arrow continuum, indicating their likeliness to participate in each study. (If teachers don't have stickers, students may make a mark above or below the arrow using a pen or pencil.)

12. Now ask students to share in a class discussion the factors that influenced their decisions. If students need prompting, ask if the following factors influenced whether they would participate:

   a. A large number of people would be affected by advancements in this field (or a large number of people *would not* be affected).

   b. Life would be greatly improved by advancements in this field (or life *would not* be greatly improved).

   c. I (or people I care about) have a personal connection to this condition (or I *do not* have a personal connection to this condition).

   d. There is little risk to me (or there is a *high risk* to me), and the type of risk involved (i.e., medical or "social" risks like stigma, the risk of having personal information made public).

   e. I don't have to contribute a lot of time, energy, or resources (or I *do* have to contribute a lot).

   f. I am willing (or I am *unwilling*) to have my tissue or blood samples added to a biobank.

Activity Two: Research and Community Partnership

13. Explain to students that there have been great advances in research involving human participants. The **Belmont Report** principles, regulatory bodies like **Institutional Review Boards**, and government oversight allow research to yield more benefits while lessening the risks for research participants. However, continued improvements are necessary to increase trust and public participation. For scientific advancements

to occur in health and medicine, the public must participate. Discuss the following questions, keeping in mind the research studies discussed in *Part II*:

a. If you chose to participate, would it be important for you to learn your own personal results after the study was completed? Would you want to know your status regarding genetic traits, behavioral patterns, health findings, etc.? Why or why not?

b. If the information in your envelope became available to the public, what might the consequences be? To insurance companies? To schools? To local health providers? To pharmaceutical companies? To the police?

14. Remind students that so far they have had their names attached to the envelopes. Ask students to remove the sticky note with their name on it from the envelope. The envelope now represents a **de-identified** sample. If it were used in a research study, researchers would not know who the sample came from. Ask students:

a. Among the studies you read in *Part II*, would you be more likely to participate in any of them if your information was de-identified?

b. Would you be willing to let the teacher collect your de-identified envelope to be used in future research? What if hundreds of other people (i.e., students from the entire school) were participating? Thousands of other people?

15. Explain to students that it is becoming common practice for researchers to formally ask study participants whether their genetic information may be entered into a data repository called a biobank, though ***they are not generally required to ask permission*** if the genetic information has been de-identified. Researchers use information from biobanks for population studies and to develop treatments, medicines, or products. The potential uses for biobank information are limitless and not yet fully determined. Ask students to decide whether they would give permission for their samples to be added to a biobank if samples were de-identified. Why or why not?

Tell students that many scientists believe that biobanks are the future of research. Because biobank research is relatively new, few practice standards or detailed regulations exist and there are many **ethical** questions to consider.

16. Explain to students that in this part of the activity they will act as a community advisory board. A community advisory board represents the needs and concerns of the local community. A board works closely with researchers and clinical staff to provide the perspective of local patients, caregivers, families, and other stakeholders.

Many biobanks contain cells or tissues left over from surgeries and other medical procedures. Although procedures and rules vary among institutions, IRB approval is generally not required to use these tissues for medical research ***if they have been de-identified and are considered medical waste***. Without the involvement of an IRB, no consent forms are required and the genetic material can be used in studies without an individual's permission.

17. Have students form groups of four.

18. Ask them to work as a group to brainstorm practices scientists can follow to improve public trust and participation in biobanking tissue samples for research.

19. Come back together as a class and ask a group representative to contribute to a class list of "advice from the public to scientists." If students do not come up with these ideas for their list, ask them whether the following factors would increase public trust and willingness to participate:

a. Ask permission to use samples, even though consent may not be officially required in every case.

b. Think about when and how you ask for permission so people can be informed and make thoughtful decisions without **coercion** or **undue influence**.

c. Communicate research findings so people learn about outcomes.

d. Let people know about any other ways the samples may be used.

e. Treat people like human beings, not research subjects.

20. Tell students that these ideas are also being discussed among scientists. Show the video *People Matter—The Future of Research* found at http://peoplematterproject.org.

21. Afterward, ask for reflections and comments. Invite students to share how they could take personal action as advocates, participants, members of community advisory boards, future researchers, and voters to ensure a favorable future for research.

Closure

22. At the end of the lesson, collect all of the envelopes containing the students' cotton swabs and survey information. Discard or destroy the envelopes in a visible way.

EXTENSION

Tell students that current and future technologies make it possible to link biological samples, such as the cells on their cotton swabs, back to the donors. Even if the cotton swab samples are stripped of all identifying information—such as names and health record numbers—these samples contain each student's DNA, which is in itself a unique identifier. In a future when anonymity cannot be guaranteed, ask students whether they would choose to participate in research by donating their tissue to biobanks. Why or why not? Given their answers, what are some of the repercussions for medical research?

Ask students to consider where they may have left personal "envelopes" containing genetic information in the past. Oftentimes cells, tissues, and/or DNA can be collected without an individual's permission because people are not considered "human participants" as long as identifying information has been removed. Data from these samples can be used in genome or population studies without the sample owner's knowledge.

Consider these cases:

- Someone intentionally seeks out a genetic test by participating in a research study, or using a direct-to-consumer genetic testing website such as "23 and Me" or "Ancestry.com DNA." Their results are now on file with an institution somewhere—at a hospital, in the provider's database, with an insurer, or they are known by a spouse or other family member.
- An individual never sought out a genetic test, but may have inadvertently granted access to genetic information through a urine or blood test for a physical exam, newborn screenings, a hair sample left at a crime scene, or fetal cells their parents asked to be collected before they were born.

Visit the website "23 and Me" (https://www.23andme.com) to learn about the types of genetic tests available directly to consumers. This site also provides a useful explanation of the genetic testing process in the "How it Works" section.

CONNECTION TO FORMATIVE ASSESSMENT

Revisit the statements students sorted for the formative assessment. After completing this lesson, students should understand that Statement D is accurate.

GLOSSARY

Assent: A process in which the parent or guardian of a minor agrees to the minor's participation in a research study. The participant is still required to give informed consent.

Biobank: A storage facility for biological materials used in medical research.

Coercion: The act of pressuring someone to do something using force, intimidation, or threats without respect for individual choice. This includes the idea that a person with few choices may find participation in a study to be so appealing that they feel they cannot decline, even if being in the study is not a good decision for other reasons.

De-identify: To remove personal information such as name, medical record number, or study code from a genetic sample so that the sample cannot be linked to a specific individual.

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

Genetic predisposition: A greater likelihood of expressing a certain trait based on a person's genetic material (e.g., someone may carry a gene that is known to be related to an increased chance of breast cancer).

Genome: The complete genetic material of an organism.

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

Ramifications: Consequences or results of actions, especially when not desired.

Undue influence: Is exerted when a person of higher power or authority takes advantage of another person; undue influence can often include coercion.

SOURCES

The five research studies found in this section are all fictional. Following is the source information used to create these fictional studies:

Eyelash Cosmetics, Contact Lenses, and Effectiveness of Latisse®
http://www.newsrx.com/library/topics/Alopecia-Areata.html
http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002421/
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2861943/
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2861943/
http://www.allure.com/beauty-trends/blogs/daily-beauty-reporter/2010/05/latisse-its-a-prescription-for-a-reason.html

Nut Consumption, Blood Sugar, and Diabetes Prevention
http://www.cdc.gov/diabetes/pubs/general11.htm#what
http://jn.nutrition.org/content/138/9/1752S.full

Randomized, Open Label, Single Dose, Crossover Study to Evaluate Safety After Injection of Malaria Vaccine AB415.
http://www.seattlebiomed.org/disease/malaria
http://www.cdc.gov/malaria/diagnosis_treatment/index.html

STUDENT HANDOUT 4.1

Health History and Behavior Survey

PLEASE DO NOT WRITE YOUR NAME ON THIS PAPER.
YOUR NAME WILL BE PLACED ON A STICKY NOTE ON THE OUTSIDE OF THE ENVELOPE.

Please answer the following questions to the best of your knowledge.
You ***do not*** have to share the results with anyone unless you choose to do so.

Question:	YES	NO
1. Do you wear contact lenses?		
2. Do you wear eyeliner, mascara, or other eyelash cosmetics?		
3. Have you had, or do you have, chronic eye infections or problems?		
4. Do you have Type II Diabetes?		
5. Does anyone in your extended family have Type II Diabetes?		
6. Are you allergic to any nuts?		
7. Have you been diagnosed with ADHD?		
8. Are you on medication for ADHD?		
9. Do you take any medications regularly?		
10. Do you have any skin allergies or reactions?		
11. Do you play competitive sports?		
12. Have you ever been disciplined at school for fighting?		
Age:		
Gender:		
Ethnicity:		

HANDOUT

Eyelash Cosmetics, Contact Lenses, and Effectiveness of Latisse®

Background:

Eyelash hypotrichosis is the term for an inadequate quantity of eyelashes. *Alopecia areata* results in patches of hair loss, usually on the scalp, but also in other areas of the body including the eyelids. Eyelashes protect eyes by providing a natural protective barrier from sunshine, wind, foreign bodies, and perspiration. Eyelashes are sensitive to the touch and cause the eyelid to close reflexivley when an object is near the eye. As a result, compared to those with healthy lashes, people with few or no lashes can experience more eye irritation, infection, and sensitivity, and show reduced reflexive blinking. Aside from the protective purpose of eyelashes, patients without eyelashes report feeling less attractive.

Causes of eyelash hypotrichosis and *Alopecia areata* are many, including family history, aging, chemotherapy, and other medical treatment. It is estimated that hypotrichosis and *Alopecia areata* affect to varying degrees more than four million people of all ages and sexes.

Current treatment:

Latisse (bimatoprost 0.03%) is a drug that was approved by the U.S. Food and Drug Administration (FDA) for increasing eyelash length, thickness, and darkness in patients with hypotrichosis of the eyelashes. One drop is applied each evening to the base of the upper eyelashes with a single-use applicator brush. It has been used in more than 30 clinical studies on hundreds of patients. For those who use Latisse, there is a 4% chance of the eyes becoming red and itchy and for there to be darkening around the lash area, but these effects are temporary, and go away after use is discontinued. There is a rare complication where iris color changes irreversibly. This side effect was only seen in patients who applied doses larger than that found in Latisse. Since the product's release, it has crossed over into the cosmetic realm and is widely used to enhance healthy lashes by making them longer, darker, and thicker.

Purpose:

To test the safety and effectiveness of Latisse in people who ***do*** and ***do not*** use eyelash cosmetics and/or contact lenses.

HANDOUT

Official title:

Comparative Observational Analysis of Latisse Users

Detailed description:

This is a study comparing several groups of subjects who do and do not use contact lenses and eyelash makeup. Measurements of eyelash growth and observations of side effects will inform current recommendations and warnings associated with using Latisse.

Study population:

Healthy volunteers. Volunteers may or may not wear contact lenses, and may or may not use eyelash cosmetics.

Inclusion criteria:

Participant is willing and able to:

1. Give **informed consent** to participate.
2. Continue same daily regimen for 90 days.
3. Keep daily logs of observations of any side effects such as itching or burning eyes, discoloration of eyelids, discoloration of eye iris, or other changes.
4. Come in every 30 days to have eyelashes observed and measured.

Exclusion criteria:

1. Any active or ongoing medical problems of the eye.
2. Previously documented eye hypersensitivity to cosmetics, eye drops, or other products designed for the eye.

HANDOUT

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

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

Informed consent: A process that outlines required elements of research participation, including its risks and potential benefits, to help someone decide whether to participate. An informed consent form is used to convey essential information and is signed by the participant if he or she decides to join the study.

Nut Consumption, Blood Sugar, and Diabetes Prevention

Background:

Diabetes affects 25.8 million people in the United States—roughly 8% of the total population—and is the seventh leading cause of death in the country. Diabetes is a disease that results from the body's inability to produce insulin, use insulin properly, or a combination of both. There are two types of diabetes: Type I and Type II. This study will focus on **Type II Diabetes**.

Type II Diabetes is characterized by the body's inability to use insulin properly and results in high levels of blood sugar that can lead to many health complications and death. There are many factors linked with Type II Diabetes, including age, obesity, family history, and lack of physical exercise. Certain ethnicities, including African Americans, Hispanics, and Native Americans, have been shown to be at a higher risk for Type II Diabetes.

Current treatment:

Current treatment for Type II Diabetes includes monitoring diet and exercise, and taking oral medication to help regulate blood sugar levels. Recent studies have shown that ingesting nuts helps control blood glucose levels in non-diabetic and diabetic individuals. As a result, it is being recommended that individuals with diabetes include nuts in their daily diet.

Purpose:

To identify whether daily consumption of nuts affects blood sugar regulation that may result in diabetes prevention or management.

Official title:

Comparative Analysis of Nut Consumption and Blood Sugar Regulation

Detailed description:

This is a study comparing several groups of participants who do and do not have a diagnosis of diabetes. Their blood sugar level measurements will inform future guidelines for individuals with Type II Diabetes.

Study population:

Healthy volunteers and people with Type II Diabetes.

Inclusion criteria:

Participant is willing and able to:

1. Give **informed consent** to participate.
2. Provide family history regarding diabetes.
3. Follow a prescribed diet high in nuts for 30 days.
4. Prick their own finger to take and record blood sugar levels three times a day using a device provided by the study sponsor.
5. Come in once a week for further blood sugar level testing.
6. Consent to enter **de-identified** leftover blood samples into a national **biobank** for future research.

Exclusion criteria:

1. Previously documented adverse reactions to the ingestion of nuts, or nut allergies.

HANDOUT

Biobank: A storage facility for biological materials used in medical research.

De-identify: To remove personal information such as name, medical record number, or study code from a genetic sample so that the sample cannot be linked to a specific individual.

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

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

Informed consent: A process that outlines required elements of research participation, including its risks and potential benefits, to help someone decide whether to participate. An informed consent form is used to convey essential information and is signed by the participant if he or she decides to join the study.

Type II Diabetes: A chronic medical condition that affects how the body metabolizes sugar (glucose). Type II Diabetes typically begins in adulthood and patients are not usually dependent on the use of insulin to control their sugar levels.

Understanding Daily Cycle of Attention and Cognition

Background:

ADHD is a common childhood disorder that can continue through adulthood. People with ADHD have difficulty with executive function regulation that results in problems with focus and organizational skills, hyperactivity, and impulsivity. The Centers for Disease Control estimates nearly one in 10 U.S. children have ADHD.

Current treatment:

The most common treatment for ADHD is to prescribe stimulant medications. These vary in effectiveness depending on dosage and if medication is "extended release" or "long-acting." Common side effects include decrease in appetite, sleep problems, and rarely, tics.

Purpose:

To identify any hourly patterns of attention, focus, and thinking skills to identify ideal ADHD medication schedules.

Official title:

Diurnal Patterns of Attention and Cognition in Youth Ages 11–18

Detailed description:

This study will document the patterns of focused attention and cognition during a five-day period of students with and without an ADHD diagnosis. Students, parents/guardians, and teachers will fill out a daily survey documenting varying periods of focused attention and cognition over the course of five days.

Study population:

1. Students ages 11–18 with ADHD diagnosis; not medicated.
2. Students ages 11–18 with ADHD diagnosis; medicated.
3. Students ages 11–18 without ADHD diagnosis.

Inclusion criteria:

1. Participant is willing and able to give **informed consent** to participate.
2. Participant's parent/guardian and dominant classroom teacher are willing and able to give their **assent** for the participation.
3. Participant is willing to keep a log to document changes in ability to focus over the course of each day for five days.
4. Participant's parent/guardian and dominant classroom teacher are willing to complete a survey of the participant's behavior and perceived ability to focus at the end of each day for five days.

Exclusion Criteria:

1. Participant's parent/guardian or dominant classroom teacher is/are not willing to complete a daily survey concerning participant's behavior and perceived ability to focus at the end of each day for five days.
2. Participant uses marijuana or other illegal drugs during five-day period.

HANDOUT

Assent: A process in which the parent or guardian of a minor agrees to the minor's participation in a research study. The participant is still required to give informed consent.

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

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

Informed consent: A process that outlines required elements of research participation, including its risks and potential benefits, to help someone decide whether to participate. An informed consent form is used to convey essential information and is signed by the participant if he or she decides to join the study.

Randomized, Open Label, Single Dose, Crossover Study to Evaluate Safety After Injection of Malaria Vaccine AB415

Background:

Malaria is a tropical parasitic disease transmitted by the bite of female mosquitoes. The parasite lives in the red blood cells and eventually ruptures them causing anemia. Other symptoms include fever, joint pain, vomiting and headaches, which can lead to coma and death if untreated. Nearly 40% of the world's population lives in tropical regions affected by malaria. One in five childhood deaths worldwide is attributed to this parasitic infection.

Current treatment:

Anti-malarial drugs offer some protection and treatment for the disease, but are limited due to developing drug resistance and the stage at which the disease is diagnosed. Prevention with insecticides and bed nets has been more successful, but is still limited due to cost and the evolution of mosquito insecticide resistance.

Purpose:

To test the safety of an experimental malaria vaccine.

Official title:

Randomized, **Open Label**, Single Dose, Crossover Study to Evaluate Safety After Injection of Malaria Vaccine AB415.

Detailed description:

This is a Phase I trial of Malaria Vaccine AB415. Participants will be given two injections (shots) over a one-month period to determine the safety of the vaccine. Participants will monitor the site of injection for inflammation and redness, and keep a journal documenting any possible side effects that might be attributed to the vaccine, such as headache, fever, or rash. After several rigorous animal studies including those with primates, this vaccine has been shown to have very few side effects, but there is still the possibility of unknown side effects in humans.

Study population:

Healthy volunteers ages 11–50.

Inclusion criteria:

Participant is willing and able to:

1. Give **informed consent** to participate.
2. Receive two injections over a one-month period and be available for three follow-up visits and blood draws during the following three-month period.
3. Keep a detailed journal documenting the condition of the injection site and any side effects.
4. Give consent to enter **de-identified** leftover blood samples into a national **biobank** for future research.

Exclusion criteria:

1. Nursing or pregnant women, or women planning on becoming pregnant during the trial.
2. Participants involved in any other clinical trials.
3. Participants who have had adverse reactions to vaccines in the past, or have serious health concerns that may be complicated by participation in this vaccine trial.

Biobank: A storage facility for biological materials used in medical research.

De-identify: To remove personal information such as name, medical record number, or study code from a genetic sample so that the sample cannot be linked to a specific individual.

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

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

Informed consent: A process that outlines required elements of research participation, including its risks and potential benefits, to help someone decide whether to participate. An informed consent form is used to convey essential information and is signed by the participant if he or she decides to join the study.

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."

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.

HANDOUT

Comparative DNA Analysis of Samples to Isolate Markers for Genetic Predisposition

Background:

Genetic testing is used to identify particular changes within chromosomes, genes, or proteins. The most common use of these tests is to identify whether an individual carries a gene for a particular disease or genetic condition. However, genetic tests can also be used to determine whether an individual is genetically predisposed to a particular trait or characteristic. A **genetic predisposition** is when a person has a greater likelihood of expressing a certain trait based on her genetic material, such as having a gene that is known to be related to an increased chance of breast cancer.

Current treatment:

Not applicable to this research study.

Purpose:

To examine the genetic basis of mental and physical traits that may be key to becoming a "superstar" athlete, or engaging in extremely violent and even criminal behavior.

Official title:

Comparative DNA Analysis of General Population Samples and Specialized Population Samples to Isolate Genetic Predisposition Markers

Detailed description:

This study will compare the existence of known genetic markers within individuals in a specific population (athletes and individuals convicted of violent crimes) and those of the general population (individuals who do not fit into either of these categories).

Study Population:

1. Professional athletes who are considered "superstars" as determined by being in the top 5% of all professional athletes.
2. Individuals convicted of violent crimes.
3. Individuals ages 13–35 who have in the past participated or currently participate in athletic events.
4. Individuals ages 13–35 who do not participate or have not participated in athletic events.
5. Individuals ages 13–35 who have been in trouble for fighting, harassment, etc.
6. Individuals ages 13–35 who have not been in trouble for fighting, harassment, etc.

Inclusion criteria:

Participant is willing and able to:

1. Give **informed consent** to participate.
2. Provide a cheek-swab DNA sample that will be analyzed for both genetic markers.
3. Provide a behavior analysis survey.

Exclusion criteria:

1. Use of steroids within the last 12-month period.

HANDOUT

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

Genetic predisposition: A greater likelihood of expressing a certain trait based on a person's genetic material (e.g., someone may carry a gene that is known to be related to an increased chance of breast cancer).

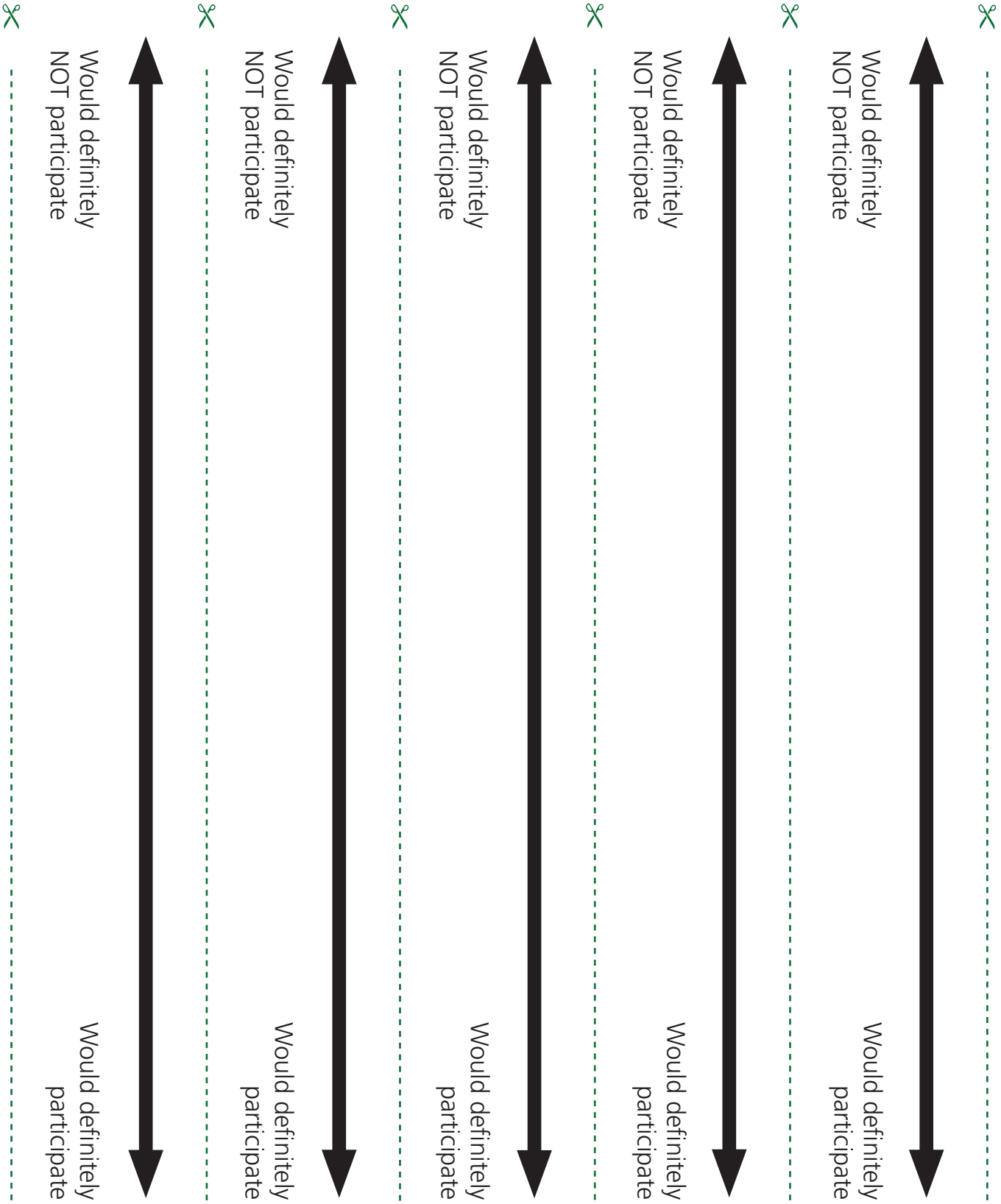
Inclusion criteria: All of the conditions that must be met for someone to participate in a study.

Informed consent: A process that outlines required elements of research participation, including its risks and potential benefits, to help someone decide whether to participate. An informed consent form is used to convey essential information and is signed by the participant if he or she decides to join the study.

TEACHER RESOURCE 4.1

Participation Arrows

Instructions: Cut out the arrows and attach one to each research study seeking participants.



RESOURCE

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.

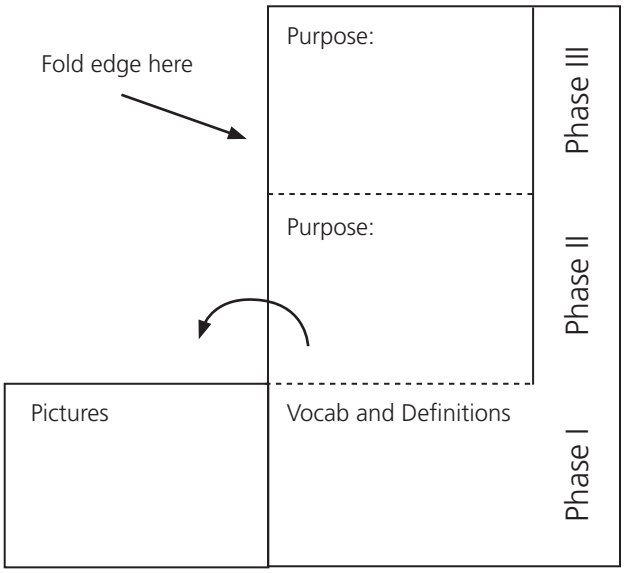
2. Explain to students that humans participate in research through a system of highly regulated and controlled processes called clinical trials. Clinical trials are broken down into a series of phases, and each phase has a different purpose and a different research population.

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

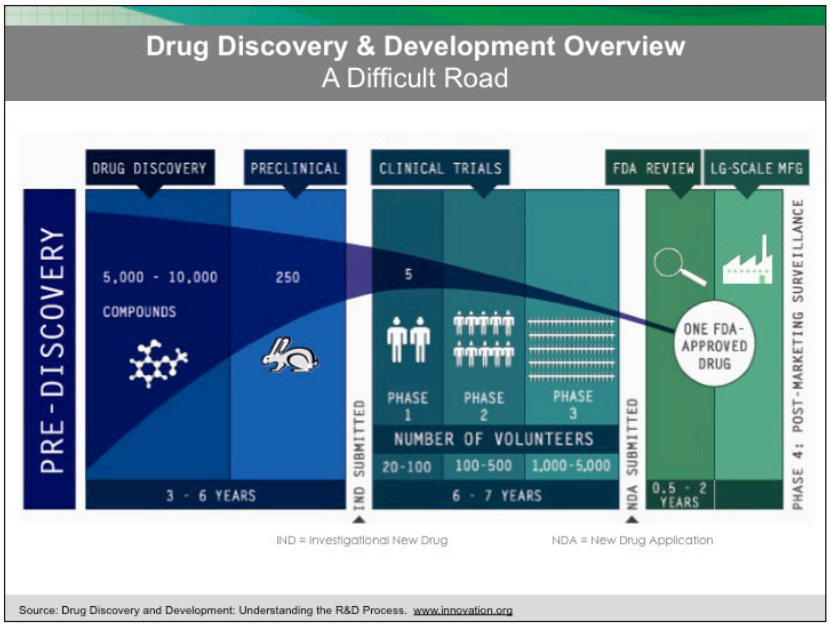
19. Tell students that they have just simulated a trial for a very common disease—high blood pressure—and even with so many people affected by this condition, it can be difficult to recruit enough participants for such a study. How then would a researcher conduct a trial for a rare disease?

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.

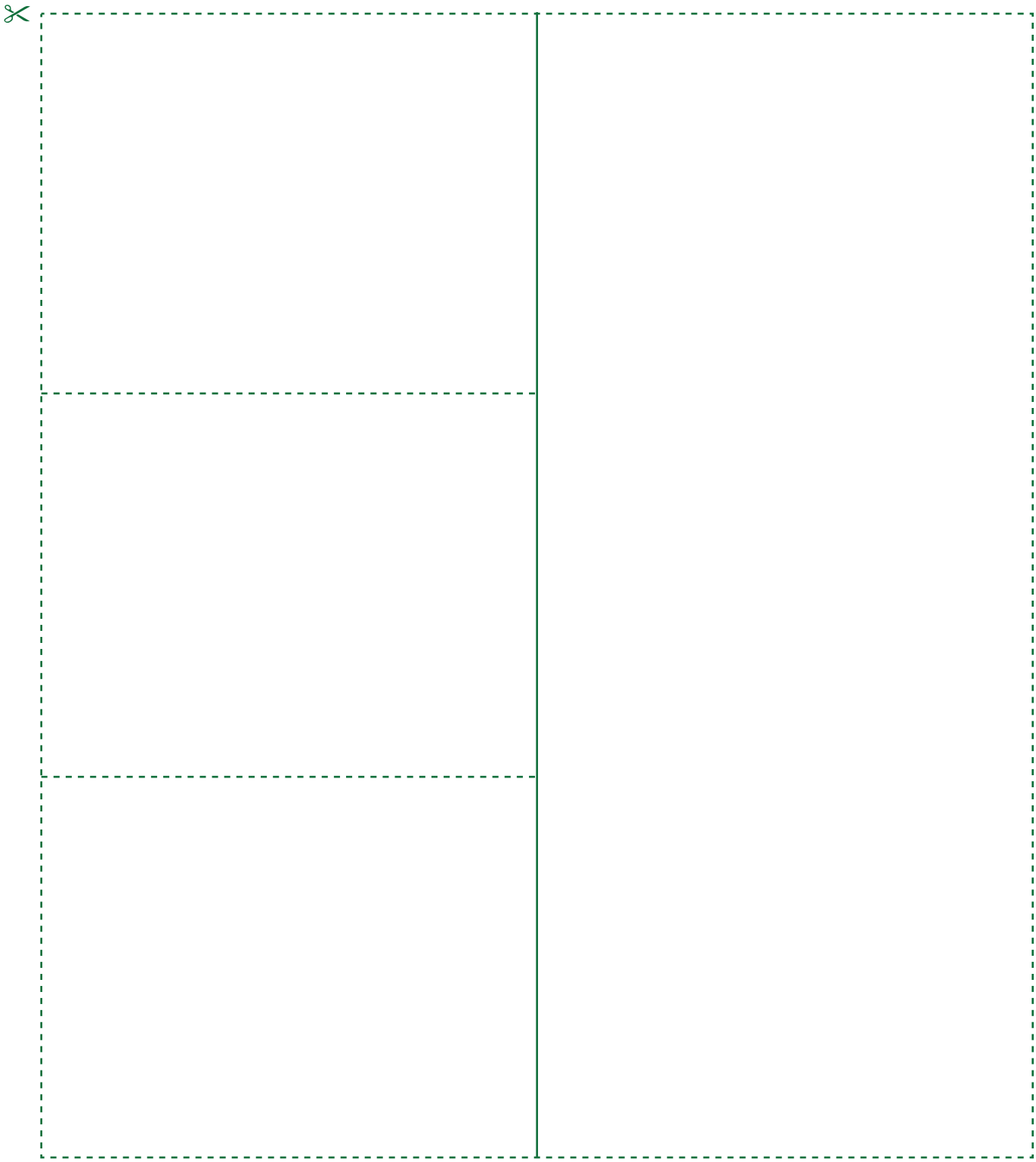
Siang, S. (2000, July 20). The mismeasure of woman: Women and clinical trials. *BioMedNet.com*. Retrieved from: http://www.anapsid.org/cnd/gender/genderdrug2.html.

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*

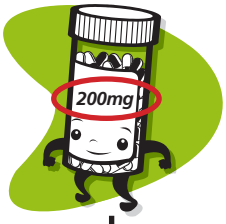
Qualified Study Participants

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

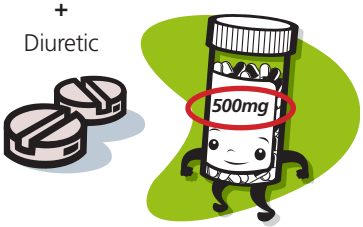
PHASE III STUDY DESIGN

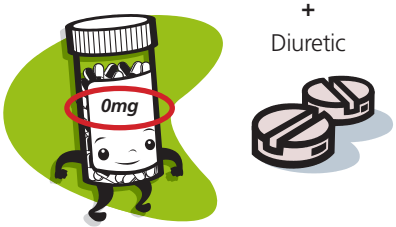
Purpose of Phase III: To assess the effectiveness of NW234, to assess safety, and to compare NW234 to commonly used treatments.

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.*

RARE Film Guide

Curriculum Supplement—Exploring Rare Disease Research

INTRODUCTION

This activity is designed to be used with the film *RARE*, a documentary that explores the major issues affecting people living with a rare genetic disorder, **Hermansky-Pudlak Syndrome (HPS)**. Before the film, students explore and share their ideas about general themes in the film by responding to statements in a *Silent Chalk Talk*. Students are then asked to view the film from the perspective of a **stakeholder** in regard to a **clinical trial** testing a new drug for HPS. Stakeholders include Donna Appell, a mother working to find a cure for her 21-year-old daughter who has HPS; Heather Kirkwood, a woman with HPS who is involved in a clinical trial for a drug to treat people with HPS; and Dr. William Gahl, a researcher from the National Institutes of Health (NIH) who works with people with HPS and runs the clinical trial in which Heather is enrolled. After watching the film, students gather for another *Silent Chalk Talk*, and meet in small groups to discuss the film's **ethical** issues from different perspectives.

FILM BACKGROUND AND ORDERING INFORMATION

RARE is a documentary by award-winning filmmakers Maren Grainger-Monsen, MD, and Nicole Newnham. This film guide accompanies the high school version, which runs 36 minutes. A 56-minute version is also available. The film may be purchased at http://www.rarefilm.org (the educational use cost is $40).

CLASS TIME

One class period of 55 minutes allows time to show the film with minimal remaining time for either a class discussion about clinical trial design and/or the themes in the film.

Spreading this lesson over two class periods allows for viewing the film and going into more depth on clinical trial design, while leaving time for discussion about film themes.

KEY CONCEPTS

- Clinical trials are designed to systematically test a study medicine or treatment to see whether it is safer and more effective than no treatment at all, or than other existing treatments.
- There may be unique challenges for a clinical trial for a rare disease, such as being able to enroll enough participants for the trial to generate meaningful data.
- **Patient advocacy groups** can create community, provide education and awareness, encourage research, and organize lobbying efforts for their constituents.
- Researchers, participants, and others involved in a trial may feel a conflict between what best serves the trial and what best serves their personal interests.
- Hope can play a powerful role in treating disease.
- Successful clinical trials require community support and participation.

LEARNING OBJECTIVES

Students will know:

- A study design for a clinical trial for a rare disease.
- Many stakeholders are affected by medical research.
- Successful clinical trials require community support.

Students will be able to:

- Discuss ethical considerations that may be associated with a clinical trial.
- Speak about participation in a clinical trial from different stakeholder perspectives.

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*.

MATERIALS

Materials	Quantity
DVD of the film *RARE* and projection equipment	1
Computer with PowerPoint	1
Teacher Resource—*Silent Chalk Talk Posters*	1
Teacher Resource—*Silent Chalk Talk Rules of Participation*	1
Teacher Resource—*Images for Chalk Talk Posters*	1
Student Handout—*Post-Film Stakeholder Quotes and Guiding Questions*	1 per student
Teacher Resource—*Key Phrases and Stopping Points*	1
Teacher Resource—*Clinical Trial Design for Pirfenidone Study*	1 (or more if copying for students)
Teacher Resource—*Clinical Trial Design for Pirfenidone Study PowerPoint Slide Set Overview*	1
Clinical Trial Design for Pirfenidone Study Slide Set (found at http://nwabr.org/curriculum/humans-research).	1
Optional: Student Extension Handout—*InterMune Share Prices and the FDA*	1 per student

NOTE TO THE TEACHER

This lesson is a supplement to *The Science and Ethics of Humans in Research* curriculum from the Northwest Association for Biomedical Research (NWABR). While the film can be shown independently, it is helpful for students to have a background in research with human participants and clinical trial design. In preparation, we recommend completing *Lesson Five—Clinical Trials* from this curriculum before presenting the film.

Another applicable lesson, *Who Should Pay? Funding Research on Rare Genetic Diseases* is *Lesson Seven* of NWABR's *Advanced Bioinformatics* curriculum, *Using Bioinformatics: Genetic Research*. In this lesson, students learn about Leigh's disease and meet in "like" and "mixed" stakeholder groups to identify areas of agreement and disagreement, and to propose a recommended compromise to Congress regarding funding for rare disease research. This lesson can be found at http://www.nwabr.org.

FRAMING THE LESSON

Before viewing the film *RARE*, students explore and share their thoughts and ideas about researching treatment and cures for rare diseases by silently responding in writing to statements, questions, and pictures posted on *Silent Chalk Talk Posters*. Because the conversation is in written (silent) form, conversation cannot deteriorate into shouting matches, all students are given an equal voice, and students feel safe to express their true thoughts and feelings.

Students will view the film through the eyes of one of three stakeholders, sharing their unique perspective in a small group after the film. By personalizing the experience in this way, students have a chance to become aware of differing perspectives and how they may conflict with the intentions of researchers. Afterward, students revisit their initial *Silent Chalk Talk Poster* comments to see how their thinking may have evolved as a result of the activities.

TEACHER PREPARATION

- Make copies of *Student Handouts*.
- Make posters as directed in the Teacher Resource—*Silent Chalk Talk Posters* and post them around the room.
- For showing the film, prepare the computer and projection unit. [**Note:** If you plan to pause the film at suggested stopping points, make sure you have easy access to the pause button.]

PROCEDURE

Activity One: Silent Chalk Talk

1. Tell the class that in this lesson they will be exploring their thoughts and feelings about researching treatments and cures for rare diseases. To begin, students will be able to share their thoughts and ideas in a silent discussion.
2. Point out the *Silent Chalk Talk Posters* you have posted around the classroom. Read through each poster with students and ask for clarifying questions before anyone responds. Be careful not to discuss any opinion or give any information that may change student responses; merely ensure that they understand what each poster addresses. It is important to leave this as vague as possible to allow students to identify their own preconceived notions and/or misconceptions.

3. Post and review rules of participation on Teacher Resource—*Silent Chalk Talk Rules of Participation*.

4. Provide the same color of marker for each poster so that responses are as anonymous as possible. If possible, use the same color of marker before viewing the film and a different color after viewing the film. This will allow teachers and students to more easily see the impact of the film on their thoughts and ideas.

5. Give students about 10 minutes to add their thoughts to each poster, revisiting each poster at least twice. Encourage students to respond at least one time to the primary comment on the poster, but if they have trouble doing so they may choose to respond only to other students' comments.

6. Explain to students that they will be using these posters to continue a conversation at the end of the lesson, but they will not be discussing the posts until then.

Activity Two: Exploring Rare Disease Research

Part I: Introducing Clinical Trial Design

7. Tell students that they will be viewing the film *RARE*, which illustrates both the hope and the challenges of enrolling people with HPS into a clinical trial for the drug **pirfenidone**. In early studies, pirfenidone showed promising results in the treatment of a lung condition (**idiopathic pulmonary fibrosis**), experienced by some people with HPS. In the **Phase II** trial shown in the film pirfenidone was given to people with HPS who also suffer from **pulmonary fibrosis**.

8. Show students the PowerPoint presentation about the pirfenidone clinical trial design found at http://nwabr.org/curriculum/humans-research (to view copies of the slides see Teacher Resource—*RARE PowerPoint Slides*). Use this presentation to introduce students to the clinical trial design of the trial presented in the film. The pirfenidone trial is a **randomized**, **placebo-controlled**, **double-blind trial**.

9. Before moving on, check to make sure that students understand what a placebo is, know the characteristics of a double-blind study, and realize how strict **inclusion and exclusion criteria** can limit participation in some clinical trials. If students have not already completed *Humans in Research Lesson Five*, teachers may wish to present that lesson before this one. *Lesson Five* introduces the purpose and structure of each phase of a clinical trial, as well as the challenges of recruiting participants for a study.

Part II: Meet the Stakeholders

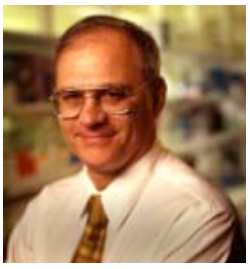
10. Explain to students that the film tells the story of a number of people who are in some way affected by or interested in HPS. These people are all stakeholders in the area of rare genetic diseases. A stakeholder is any person or institution that is affected by or interested in HPS. Additionally, in the situation portrayed in this film, each stakeholder will be affected by the outcome of the clinical trial for a drug to treat people with HPS.

11. Ask the class to come up with examples of as many pirfenidone clinical trial stakeholders as possible. This could include makers of the drug, other people with HPS not involved in the trial, funders of the trial, people with other rare diseases, insurance companies, hospitals, families and friends, and more.

12. Before showing the film, use the PowerPoint slides to introduce Donna Appell, Heather Kirkwood, and Dr. William Gahl. Explain to students that in this activity they will be asked to view the film through the eyes of one of these three stakeholders:

Donna Appell: Donna's daughter, Ashley, was diagnosed with HPS when she was a toddler. Donna worked to find others with the condition and founded the HPS Network in 1992. Ashley is now in her 20s and Donna has more than 700 HPS patients in her database.

Heather Kirkwood: Heather was in her 20s before a physician suggested she might have HPS, though she had had symptoms all her life. Heather is a journalist, an advocate for people with HPS, and a participant in the clinical trial shown in the film.



William Gahl: Dr. Gahl works in the Office of Rare Disease Research at the National Institutes of Health. He is both an MD and a PhD who works as a physician and clinical researcher for rare diseases such as HPS. He is the principal investigator of the clinical trial presented in the film.

13. Have students form groups of three. Match up each of the students in each group with a different stakeholder. Explain to students that they will watch the film from the perspective of their assigned stakeholder. Their job will be to represent the views and concerns of that stakeholder in a discussion after the film.

Part III: View the Film

14. Pass out to each student a copy of Student Handout 6.1—*Stakeholder Quotes and Guiding Questions*, and give them time to read the film themes and quotes. This information will help students frame their post-film discussion. Encourage students to take notes during the film.

15. Show the film. [**Note:** You may show the film straight through, or you may choose to occasionally pause it to give students a chance to process the dialogue and take notes from the perspective of their stakeholder. Useful stopping points are outlined in Teacher Resource—*Key Phrases and Stopping Points*.]

Part IV: Post-Film Discussion

16. After the film, tell students that they will next talk about their experiences as their assigned stakeholder with their group. Share these discussion goals:

- Achieve a deeper understanding of the film as well as the concerns and interests of the three main stakeholders.
- Promote participation in the discussion through the perspective of each stakeholder and/or each student.
- Explore many differing views; *do not engage in a debate* with pro/con stances.

Refer students to Student Handout 6.1—*Stakeholder Quotes and Guiding Questions* and explain that the facilitator role will rotate among the three students in each group for each new theme. You may wish to write the following discussion steps for facilitators on the board:

1. The facilitator reads the quote and the question.
2. The students discuss the question from their stakeholder's perspective, using things that happened in the film (and/or their notes) to back up their statements.
3. The facilitator invites students to discuss the question from their own perspective and makes sure everyone who wishes to speak has a chance to contribute.
4. The facilitator tries to paraphrase what others have said.
5. The group moves on to the next theme. The facilitator for the new theme repeats the steps above.

[**Note:** Based on the time available, monitor discussion length so every facilitator has the same amount of time. Provide groups with a one- to two-minute warning before moving on to a new theme.]

Closure

17. After the discussion, use Teacher Resource—*Silent Chalk Talk Rules of Participation* to remind students of the guidelines. Invite students to again make comments on the *Silent Chalk Talk Posters*. [**Note:** Alternatively, teachers may choose to allow more time for student reflection and wait until the next class session to have students revisit the posters.]

18. Bring the groups back together as a class and ask a few students to share their small-group conversations (and/or *Silent Chalk Talk Poster* comments) with the class.

    a. Ask students to share how the film reflected the themes of: inspiration, harms and benefits, **conflicts of interest**, **futility**, and hope.

    b. Explain that even though the study reached futility, this does not mean that it was a "failed trial." Even though the results were disappointing to the stakeholders involved, any study that ultimately answers the question researchers set out to answer is considered a "good study."

    c. Ask students if they think federal money, which comes from taxpayers, should be used to fund rare disease research. You may want to discuss who is impacted by rare disease research, whether it be financially (taxes), medically (treatments for more common diseases originally tested on patients with rare diseases), or ethically (greater good, etc.).

CONNECTION TO FORMATIVE ASSESSMENT

Revisit the statements students sorted for the formative assessment. The *RARE* Film Guide should further reinforce that Statement A is accurate and Statement F is not

Frequently Asked Questions

Q: *How is HPS passed on from parent to child?*

- HPS is an **autosomal recessive** trait, which means that both parents must be carriers of the trait for a child to inherit the syndrome.
- HPS is a **single-gene disorder**, meaning a mutation in one single gene causes HPS.
- Although HPS is a single-gene disorder, there are nine different genes that will independently cause HPS if any one of them mutates.
- Both parents must have a mutation to the same gene (one of nine), for a child to inherit HPS.
- HPS is a **lysosomal disorder**. Each of the nine genes affects the function of the **lysosomes** in the cell.
- There are slightly different **phenotypes** for each of the nine types of HPS.
- In the medical community there is a strong suspicion that additional genes related to HPS are yet to be found.

Q: *Why was pirfenidone approved in Europe and Asia but not in the United States?*

A: Studies carried out in Europe and Asia trialed pirfenidone use for idiopathic pulmonary fibrosis—pulmonary fibrosis that occurs in otherwise healthy people without a known cause. The pirfenidone study presented in the film *RARE* was for patients with HPS, people with a known cause for their pulmonary fibrosis. The study parameters were different in the two cases, and even though initial reports on the use of pirfenidone to treat HPS looked promising, the data were not conclusive enough for pirfenidone to gain FDA licensure.

Q: *Why have there been so few lung transplants in patients with HPS?*

A: There are many factors involved:

- Patients with HPS often have **bleeding disorders**, which make major surgery much riskier than for people without bleeding disorders.
- People sometimes remain on lung transplant lists for a long time, waiting for organs to become available. People with HPS can be relatively healthy for long periods of time, only to have a sudden health crisis. When in a relatively healthy period, people with HPS may not qualify to be put on a lung transplant list. After a sudden heath crisis, people with HPS may not be able to receive a transplant quickly enough.
- There are no lung transplant programs in Puerto Rico. A person from Puerto Rico who wishes to be added to a lung transplant waitlist has to first move to the U.S. This can be a difficult for many reasons including the language barrier, financial burden, and family commitments.
- Living with a chronic condition such as HPS can be financially challenging. Not all medical insurance covers lung transplant surgery and the costs involved are often prohibitive for a patient and his or her family.

accurate.

EXTENSIONS

- Dr. William Gahl was featured in a TED talk entitled, "Medical Mysteries and Rare Diseases" (available at: http://tedxcmu.com/videos/william-gahl), in which he addresses balancing harms and benefits in treating rare diseases. (The video runs 17:05 minutes.) Invite students to watch this talk and write a news article about it.
- Using Student Extension Handout—*InterMune Share Prices and the FDA*, have students apply graphing skills and do internet research to explore how advances and setbacks in the drug development process affect stock prices for a drug company.

GLOSSARY

Albinism: A condition characterized by a lack of pigmentation, resulting in very light skin coloring, white hair, and light blue or red eyes.

Autosomal recessive trait: A trait both parents must carry for a child to inherit the syndrome.

Bleeding disorder: A medical disorder that leads to poor blood clotting and continuous bleeding.

Futility: Uselessness or pointlessness; reason for stopping a clinical trial if interim data show that the treatment group is unlikely to see any more improvement than the control group.

Hermansky-Pudlak Syndrome (HPS): A rare genetic disorder characterized by albinism, bleeding problems, and fatal pulmonary fibrosis.

Idiopathic pulmonary fibrosis: Pulmonary fibrosis that occurs in otherwise healthy people without a known cause.

Lysosomal disorder: A disorder that affects the function of lysosomes in cells.

Lysosomes: The part of a cell responsible for breaking down waste materials and other debris.

Phenotype: Observable physical or biochemical characteristics resulting from both genetic makeup and environmental influences.

Pirfenidone: A drug developed by InterMune Inc. for the treatment of idiopathic pulmonary fibrosis.

Pulmonary fibrosis: Scarring or thickening of the lungs.

Single-gene disorder: A disorder caused by a mutation in a single gene.

SOURCES

Frequently Asked Questions section:
Kirkwood, H., Granger-Monson, M., Fullerton, M., Wilfond, W. (Panel discussion following viewing of film *RARE*, Pacific Science Center, Seattle, June 4, 2012).

Image used for Chalk Talk posters has been released into the public domain.

Information about InterMune and pirfenidone prices was gathered from:
http://seekingalpha.com/article/203187-intermune-left-gasping-by-fda-rejection-of-pirfenidone
http://www.medicalnewstoday.com/releases/182700.php
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3039013/

STUDENT HANDOUT

Post-Film Stakeholder Quotes and Guiding Questions

Name_____ Date_____ Period_____

During this small group discussion, you will talk about a number of themes from the film. For each theme, a quote and a question are provided. Rotate the facilitator role among group members with each change in theme. During your turn as facilitator, follow these steps:

1. Facilitator reads the quote(s) and the question for each theme.
2. Students discuss the question from their **stakeholder's** perspective, using the film (and/or their notes) to back up their statements.
3. Facilitator invites students to discuss the question from their own personal perspective, if they choose to do so.
4. Facilitator makes sure everyone who wishes to speak has a chance to contribute.
5. Facilitator tries to paraphrase what others have said.
6. Repeat the steps above, moving on to the next theme and a new facilitator.

Futility: Uselessness or pointlessness; reason for stopping a clinical trial if interim data show that the treatment group is unlikely to see any more improvement than the control group.

Hermansky-Pudlak Syndrome (HPS): A rare genetic disorder characterized by albinism, bleeding problems, and fatal pulmonary fibrosis.

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.

Stakeholder: A person with an interest or concern in something.

Theme One: Inspiration

Facilitated by the student representing Donna

Quote from Donna:

"...And I wanted to know where those 23 people are, and I want to know what they're doing, and I want to know who's researching this, and where is the cure…and I found nothing."

Quotes from Dr. Gahl:

"Although **HPS** affects a small number of people, we are really hoping that studying it will eventually lead to therapies for more common diseases." "Donna Appell used her persuasive powers to influence us to study HPS…"

Question:

Why study a disease that affects so few people?

Theme Two: Harms and Benefits

Facilitated by the student representing Heather

Quote from Heather:

"You would never want to be in this position [having a **rare disease**], but if you have to be in it, it is gratifying to know that you can play a role in helping to find a cure, helping to find a treatment so that the next generation of people with HPS don't have to face the problems we're facing."

Question:

What are some of the benefits and drawbacks each person experienced in their involvement in the clinical trial? (What does each person stand to lose or gain?)

HANDOUT

Theme Three: Conflicts of Interest

Facilitated by the student representing Dr. Gahl

Quote from Donna:

"I've learned what good science is now, and I feel that it is also the right thing to do, but…I'm her mom, and everything I've worked for and worked towards is to try to get a cure or treatment for HPS, so to exclude her was a little difficult, but…it's the right thing to do and it's what we have to do."

Quote from Dr. Gahl:

"There's disappointment when a patient is not eligible, and there's a temptation to skirt the rules or to fudge things a tad. One has to be diligent not to do that because it ruins the studies."

Question:

In the film there is a conflict between "good science" and the personal interests of Dr. Gahl, Donna, and Heather. What is the conflict for each? Specifically, how does Dr. Gahl handle the conflict between his role as a physician and his role as an ally to Donna and her family? How does each resolve the conflict?

Theme Four: Futility

Facilitated by any student

Quote from Dr. Gahl:

"That interim analysis indicated that there would never be a difference between the pirfenidone-treated and the non-treated individuals, and **futility** is a cause to stop a trial."

Question:

How was each individual affected by the news that the trial would be stopped due to futility?

Theme Five: Hope

Facilitated by any student

Quote from patient speaking to Dr. Gahl after the trial is stopped:

"…He is my dream maker. You are my hope. The NIH is my hope. I am so blessed."

Question:

What do you think gives each individual in the film hope? How could this statement be both comforting and challenging from different perspectives?

Wrap-up

Facilitated by any student

What other stakeholder views or concerns would you like to discuss with the group?

Silent Chalk Talk Posters

Recreate these posters on large pieces of butcher paper to allow ample room for comments and thought development. Give participants a chance to comment on the posters both ***before*** and ***after*** viewing the film *RARE*. If possible, use different colors of marker for comments made before and after viewing.

<table>
<tr>
<td>In what way can a clinical trial offer hope? Lead to disappointment?</td>
<td> 
What does this image say to you?

(For larger copies of these images, see the Teacher Resource—Images for Chalk Talk Posters.)</td>
<td>What would “good science” look like in a clinical trial?</td>
</tr>
<tr>
<td>People who participate in research are…</td>
<td>Clinical Trials
I know A LOT about this topic
UNLIKELY
To participate
LIKELY
To participate
I know LITTLE about this topic
(Have participants plot their own position/knowledge point.)</td>
<td>Why study a rare disease that affects so few people?</td>
</tr>
</table>

RESOURCE

Silent Chalk Talk Rules of Participation

1. Respond to the main comment anywhere on the poster you would like.

2. Respond to others by drawing an arrow from their comment to yours.

3. Keep all responses respectful and school-appropriate.

4. If you agree with a comment add an exclamation point (!) or star (*).

5. If you disagree with something that someone said, explain why you disagree, using appropriate language.

6. Do not cross out or write over anyone else's comments.

7. Pictures are completely permissible; just keep them appropriate.

8. NO TALKING!

Image for Chalk Talk Posters

This image has been released into the public domain.

Clinical Trial Design for Pirfenidone Study PowerPoint Slide Set Overview

Clinical Trial Design
for Pirfenidone Study Slide Set

The Science and Ethics of Humans in Research

RARE Film Guide:
Curriculum Supplement—Exploring Rare Disease Research

NWABR.ORG
Northwest Association for Biomedical Research

Clinical Trial Design for Pirfenidone Study

Study purpose:
To discover whether the use of **pirfenidone** in patients with **Hermansky-Pudlak Syndrome (HPS)** decreases the loss of lung function better than a **placebo**, and to find out how safe pirfenidone is compared to a placebo.

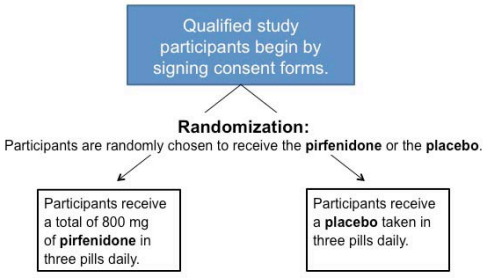
Inclusion Criteria
(***all*** of these conditions must be met to participate in the study)

- Diagnosis of **Hermansky-Pudlak Syndrome (HPS)**.
- Male or female over the age of 18.
- Lung capacity test results within set range.
- No evidence of improvement in **pulmonary fibrosis** within the past year.
- Oxygen levels within set range during a six-minute walk test.
- Be available, willing, and able to come to the NIH Clinical Center in Maryland for tests and follow-up every four months for three years.
- Women of child-bearing potential must use two reliable forms of contraception if sexually active. Alternatively, female subjects must be postmenopausal (for at least one year). Women must have a negative pregnancy test at screening.

Exclusion Criteria
(any of these conditions would ***disqualify*** someone from study participation)

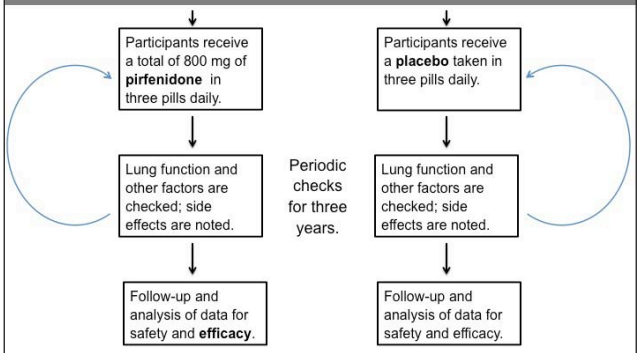
- Possibility of having **pulmonary fibrosis** for reasons other than HPS (such as through exposure to asbestos, radiation, cancer, certain types of pneumonia).
- On a lung transplantation waiting list.
- Smoking within the last six months.
- Pregnant or nursing women.
- History of alcohol abuse or recreational drug use in the past two years.
- History of human immunodeficiency virus (HIV) or chronic viral hepatitis infection.
- Chronic use of high-dose steroids.
- Prior use of **pirfenidone**.

Clinical Trial Design for Pirfenidone Study



Double-blind study: To prevent bias, neither the participants nor the researchers know which treatment the participant is receiving.

Clinical Trial Design for Pirfenidone Study



Efficacy: How does the drug treatment work compared to the **placebo**?

RESOURCE

Stakeholders in the film *RARE*

Donna Appell

Donna's daughter, Ashley, was diagnosed with HPS when she was a toddler. Donna worked to find others with the condition and founded the HPS Network in 1992. Ashley is now in her 20s and Donna has more than 700 HPS patients in her database.

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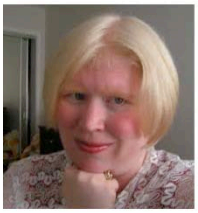
Stakeholders in the film *RARE*



Heather Kirkwood

Heather was in her 20s before a physician suggested she might have HPS, though she had had symptoms all her life. Heather is a journalist, an advocate for people with HPS, and a participant in the clinical trial shown in the film.

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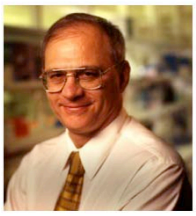
Stakeholders in the film *RARE*



Dr. William Gahl

Dr. Gahl works in the Office of Rare Disease Research at the National Institutes of Health. He is both an MD and a PhD who works as a physician and clinical researcher for rare diseases such as HPS. He is the principal investigator of the clinical trial presented in the film.

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Northwest Association for Biomedical Research

Key Phrases and Stopping Points

Time Point, 36-min version	Time Point, 56-min version	POV	Key Phrases	Themes and Questions
3:25	2:11	Donna	"...And I wanted to know where those 23 people are, and I want to know what they're doing, and I want to know who's researching this, and where is the cure…and I found nothing."	**Inspiration** Why study a disease that affects so few people?
8:54	8:05	Dr. Gahl	"Donna Appell used her persuasive powers to influence us to study HPS." "Although HPS affects a small number of people, we are really hoping that studying it will eventually lead to therapies for more common diseases."	
15:58	15:36	Heather	"You would never want to be in this position [having a rare disease], but if you have to be in it, it is gratifying to know that you can play a role in helping to find a cure, helping to find a treatment so that the next generation of people with HPS don't have to face the problems we're facing."	**Harms and Benefits** What are some of the benefits and drawbacks each person experienced in their involvement in the clinical trial?
17:58 19:06	23:29 24:36	Donna Dr. Gahl	"I've learned what good science is now, and I feel that it is also the right thing to do, but… I'm her mom, and everything I've worked for and worked towards is to try to get a cure or treatment for HPS, so to exclude her was a little difficult…but it's the right thing to do and it's what we have to do." "There's disappointment when a patient is not eligible, and there's a temptation to skirt the rules or to fudge things a tad. One has to be diligent not to do that because it ruins the studies."	**Conflicts of Interest** How does Dr. Gahl handle the conflict between his role as a physician and his role as an ally to Donna and her family? How do other stakeholders respond to conflicts between "good science" and personal interest?
27:24	40:33	Dr. Gahl Donna Heather	"That interim analysis indicated that there would never be a difference between the pirfenidone-treated and the non-treated individuals, and **futility** is a cause to stop a trial."	**Futility** How was each individual affected by the news that the trial would be stopped due to futility?
32:23	51:10	Dr. Gahl	Patient speaking to Dr. Gahl after the trial is stopped: "…he is my dream maker. You are my hope. The NIH is my hope. I am so blessed to have you in my life."	**Hope** How could this statement be both comforting and challenging from different perspectives? What do you think gives each individual in the film hope?

Clinical Trial Design for Pirfenidone Study

The film *RARE* illustrates both the hopes and the challenges of enrolling people with HPS into a **clinical trial** for the drug **pirfenidone**. In earlier studies, pirfenidone showed promising results in the treatment of Idiopathic Pulmonary Fibrosis, a lung condition that is a complication for some people with HPS. In the **Phase II** trial shown in the film, pirfenidone (or a **placebo**) was given to eligible trial participants with HPS who also suffer from pulmonary fibrosis.

Study purpose:

To see if the use of pirfenidone decreases the loss of lung function better than a placebo, and to find out how safe pirfenidone is compared to a placebo.

Study title:

Randomized, **Double-Blind**, **Placebo-Controlled**, *Study to Evaluate the Safety and* **Efficacy** *of Oral Pirfenidone for Pulmonary Fibrosis in subjects with* **Hermansky-Pudlak Syndrome**

Inclusion/Exclusion criteria:

The study has strict criteria for participation. To participate in the trial, the subject must meet the following criteria:

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

- Diagnosis of HPS.
- Male or female over the age of 18.
- Lung capacity test results within set range.
- No evidence of improvement in pulmonary fibrosis within the past year.
- Oxygen levels within set range during a six-minute walking test.
- Be available, willing, and able to come to the NIH Clinical Center in Bethesda, Maryland for tests and follow-up every four months for three years.
- Women of child-bearing potential must use two reliable forms of contraception if sexually active. Alternatively, female subjects must be postmenopausal (for at least one year). Women must have a negative pregnancy test at screening.

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

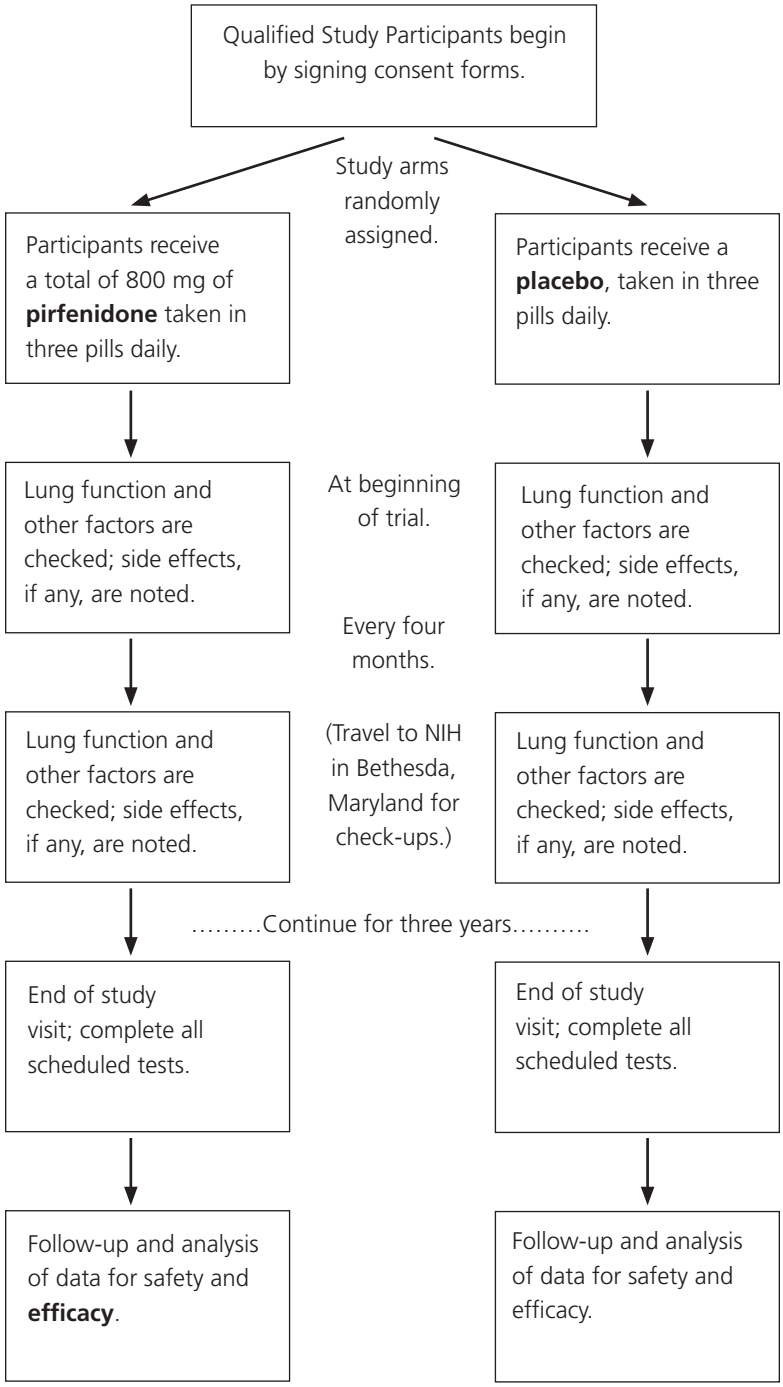
- Possibility of having pulmonary fibrosis for reasons other than HPS (such as through exposure to asbestos, radiation, cancer, or certain types of pneumonia).
- Use of steroids.
- On a lung transplantation waiting list.
- Smoking within the last six months.
- Pregnant or nursing women.
- History of alcohol abuse or recreational drug use in the past two years.
- History of human immunodeficiency virus (HIV) or chronic viral **hepatitis** infection.
- Prior use of pirfenidone.

Randomized: Those who qualify are randomly (by chance) put into one of the two study arms.

Placebo-controlled: Placebos contain no medicine or treatment, and are sometimes referred to as "sugar pills." They serve as a control for the research study.

Double-blind study: To prevent bias, neither the participants nor the researchers know which treatment the participant is receiving.

Efficacy: Effectiveness as measured in a controlled clinical trial.



View the original study at ClinicalTrials.Gov: http://clinicaltrials.gov/ct2/show/NCT00001596?term=pirfenidone&rank=2.

RESOURCE

STUDENT EXTENSION HANDOUT

InterMune Share Prices and the FDA

Name_____ Date_____ Period_____

Background: The **clinical trial** process is used to find out whether drugs and treatments are safe and effective enough to be licensed by the Food and Drug Administration (FDA) for prescription use in particular populations. Gaining FDA licensure can be a long and expensive process.

InterMune is a California biotechnology company that makes the drug **pirfenidone**, which was tested in the clinical trial shown in the film to treat **idiopathic pulmonary fibrosis (IPF)** in patients with **HPS**. InterMune purchased the patent for the drug's use in the United States and Europe from another company in 2007. Pirfenidone is considered an orphan drug, a drug developed to treat an **orphan disease**.

Table 1

Year	Month	Price/share, in $*
2009	January	10
	April	16
	July	15
	October	16
2010	January	14
	April	45
	July	9
	October	13
2011	January	38
	April	48
	July	35
	October	20
2012	January	12
	April	15

* On first day of trading in that month

The data in ***Table 1*** represents the price of a single share of InterMune stock, rounded to the nearest dollar.

Instructions:

1. Graph the information from the data table. Put the year and month along the x axis, and put the stock price on the y axis.
2. Mark March 2010 on your graph with an "A."
3. Mark May 2010 on your graph with a "B."
4. Mark the lowest historical price of the stock with a "C."

Questions:

1. At ***point A*** on the graph, the FDA Advisory Committee recommended that pirfenidone be licensed by the FDA. What happened to stock prices?
2. At ***point B*** on the graph, the FDA ruled that they were not satisfied with the data from the clinical trial on which the advisory committee based their recommendation. The FDA did *not* approve pirfenidone. What happened to stock prices?
3. Do an internet search to find out what might have happened between April 2011 and January 2012.

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

Hermansky-Pudlak Syndrome (HPS): A rare genetic disorder characterized by albinism, bleeding problems, and fatal pulmonary fibrosis.

Idiopathic pulmonary fibrosis: Pulmonary fibrosis that occurs in otherwise healthy people without a known cause.

Rare disease (or orphan 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.

HANDOUT

HANDOUT

Summative Assessment
Position Paper

INTRODUCTION

Students demonstrate what they have learned over the course of the unit by identifying and justifying their personal position regarding their own participation in a real clinical trial. Students evaluate a trial using a decision-making model to consider ethical protections, the scientific and social value of the trial, and the potential risks and benefits of their possible participation in the trial. Students then write a paper detailing how their decision to participate or not reflects their position on research involving humans.

CLASS TIME

Two class periods of 55 minutes each are needed for students to choose a study and work through the decision-making framework.

Additional time, inside or outside of class, will be needed for students to complete their position papers.

KEY CONCEPTS

- Involving humans in medical research is a complex issue that requires careful and deliberate thought.
- Students may agree with some aspects of human participation in research but not others, and the ability to identify and justify these positions allows for continued growth and discussion about complex issues.

LEARNING OBJECTIVES

Students will:

- Demonstrate their understanding of the ethical involvement of humans in research.

MATERIALS

Materials	Quantity
Student Handouts SA-1a-f—*Summaries of Clinical Trials*	Several copies of each summary for students to look through to make a choice; plus enough copies so that each student can work with the trial of his or her choice.
Student Handout SA-2—*Guidelines for Choosing Your Own Clinical Trial*	1 per student
Student Handout SA-3—*Decision-Making Framework*	1 per student
Student Handout SA-4—*Decision Paper Rubric*	1 per student
Completed *Silent Chalk Talk Posters* from *RARE* Film Guide activity	6 posters

FRAMING THE LESSON

Use the *Summative Assessment* to assess student understanding of concepts presented in the lessons in this curriculum.

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*.

TEACHER PREPARATION

- Make copies for each student of *Student Handouts SA-2*, *SA-3*, and *SA-4*.
- Make a several copies of each of the clinical trial summaries (Student Handouts SA-1a-f—*Summaries of Clinical Trials*) for students to share while considering which trial they would like to explore. After that point, there should be enough copies so that each student can work with the trial of his or her choice.
- Read through the clinical trial summaries (*Student Handouts SA-1a-f*) to assess vocabulary and readability for students. Some of these trials are more technical than others and therefore may be more appropriate for advanced students. [**Note:** The HPV study presented in *Student Handout SA-1c* is only applicable to females.] Teachers may decide to:
  - o provide information about specific clinical trials using the *Student Handouts*,
  - o have students choose a clinical trial from http://www.clinicaltrials.gov, or
  - o combine the two methods depending on individual student preferences.

NOTE TO THE TEACHER

The provided clinical trials (*Student Handouts SA-1a-f*) are real but have been abbreviated, and may not be currently recruiting participants. However, these trials do provide students with the information necessary to complete the assessment. Some students may prefer to do a web search to look for trials relating to a specific condition due to a personal connection or interest. Complete trial descriptions are much more detailed than those provided in the *Student Handouts*. To make these trial descriptions more accessible, encourage students to focus on the ***purpose***, ***detailed description***, and ***eligibility criteria*** of the trial, and to skim all other information.

Students may struggle with some of the medical vocabulary found in the clinical trial summaries in *Student Handouts SA-1a-f*. The summaries are authentic examples of studies found in the U.S. National Institutes of Health's database for trials conducted in the U.S. and worldwide (http://www.clinicaltrials.gov), and represent a real-world culmination of the lessons in this curriculum.

Remind students that they are not being assessed on their understanding of the specific details of a particular clinical trial, but on the broader questions posed during this unit, such as: Why would I choose to (or choose not to) participate in this trial? What ethical protections are in place for me? Does this research have social value? Does the study design seem scientifically valid? What are the risks and benefits? And finally, how does my decision to participate or not reflect my position on research involving humans?

PROCEDURE

Teacher Background

Before students begin working on their position papers, teachers may wish to read the directions aloud to the class and answer any questions. Teachers may also choose to request rough drafts before students begin their final drafts.

Activity One: Setting the Stage

1. Explain to students that they will be demonstrating what they have learned over the course of the unit by identifying and justifying their personal positions regarding their own participation in a real clinical trial.
2. If students participated in the *RARE* Film Guide *Silent Chalk Talk* activity, review the main ideas covered in the unit, ending with the poster focusing on the knowledge/likelihood that students would participate in a clinical trial.
3. Invite students to briefly share with the class their ideas and concerns about personal involvement as a human subject, and then transition into the introduction of the assessment.

A note about Student Handout SA-1f—*Safety of an Oral HIV Vaccine in HIV Uninfected Volunteers*: Students may be interested to know that this study never opened. Despite significant preparations for a **Phase I trial**, the study vaccine did not live up to expectations and it never progressed beyond pre-clinical research.

A note about eligibility: For the purposes of this activity, students should consider joining the trial based only on the merits of the study itself. This is not "real world" in that students would be ineligible for many trials due to their age, and many would find the commitment of being in a trial challenging due to their school schedule, extracurricular activities, or access to transportation. For this assessment, students should make their decision as if they are eligible and have no competing obligations.

Activity Two: Position Paper

4. Tell students they will have the opportunity to demonstrate their understanding of humans in clinical research by investigating a current clinical study. They will make an argument about whether or not they would be willing to enroll and explain why or why not.
5. Share with students copies of Student Handouts SA-1a-f—*Summaries of Clinical Trials*. Allow them time to review the *Student Handouts*.
6. Answer any questions after students have reviewed the studies, and then ask them to choose a clinical trial to write about.
7. If students decide instead to research a clinical trial using the internet, have them follow the guidelines provided in Student Handout SA-2—*Guidelines for Choosing Your Own Clinical Trial*.
8. Students will use Student Handout SA-3—*Ethical Decision-Making Framework* to organize the information from the clinical trial summary and begin formulating a justification for their decision about whether they would choose to enroll in the study. Walk through the *Student Handout* to make sure students understand where to find the necessary information in the clinical trial summary. Assist with any vocabulary or content questions.
9. Give students time to individually work through Student Handout SA-3—*Ethical Decision-Making Framework*.
10. Before students begin to write their papers, give them a copy of Student Handout SA-4—*Decision Paper Rubric*.

Name_____ Date_____ Period_____

Breath Test for Early Detection of Lung Cancer

Purpose

To demonstrate and validate a breath test for detection of early stage lung cancer that could potentially reduce lung cancer deaths.

Condition:	Lung Neoplasms
Study type:	Observational
Study design:	Observational Model: Cohort
Official title:	Breath Test Assay for the Detection of Lung Cancer
Primary outcome measures:	Sensitivity and specificity of the breath test as compared to CT and pathology to support primary lung cancer diagnosis.
Estimated enrollment:	600

Groups/Cohorts

1. Asymptomatic High Risk Subjects. Smokers aged >=18 undergoing chest CT
2. Symptomatic High Risk Subjects Without a Tissue Diagnosis. This group will consist of patients who are undergoing medical evaluation for a pulmonary symptom such as chronic unexplained cough or hemoptysis.
3. Symptomatic High Risk Subjects With a Tissue Diagnosis. This group will be found to include a. lung cancer, and b. diseases other than lung cancer (e.g., sarcoidosis, COPD, or pulmonary infection).
4. Apparently healthy individuals having no signs or symptoms of lung carcinoma.

Detailed Description

This is a multicenter study comparing several groups of subjects with and without lung cancer by CT scan, biopsy, and the breath test. The breath test will be performed to make sure that the previously developed methods and procedures are valid.

Eligibility

Ages Eligible for Study:	18 and older
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	Yes

Criteria for Group 4—Apparently healthy subjects

Inclusion criteria:
- Willingness to follow protocol requirements as evidenced by written, informed consent.
- Healthy, male or females, ages 18 and older.
- Non-smokers having no signs or symptoms of lung carcinoma.

Exclusion criteria:
- Any active ongoing medical problems.

ClinicalTrials.gov processed this record on July 12, 2012.
Citation: http://clinicaltrials.gov/ct2/show/NCT00639067?term=Breath+Test+for+Early+Detection+of+Lung+Cancer&rank=1.

HANDOUT

Name_____ Date_____ Period_____

Connection Between Sleep and Athletic Performance

Purpose

In the last few decades much knowledge has been accumulated on the connection between healthy, sufficient sleep, and overall health, cognitive function, memory, and job or school performance, motor vehicle accidents, and work accidents. There has been growing awareness recently of the connection between physical activity and competitive sports performance, and the amount and quality of sleep. Despite the shortage of scientific studies, there is a constant effort to improve understanding in this field.

Athletic activity includes not just competitions but also training toward competitions. Since it is difficult to control for influences of competitions and other occasional events, in this study the investigators focus on evaluating the connection between sleep and athletic performance in training.

Toward the end of adolescence, youth are busy in multiple activities related to studies, social obligations, and athletic activities. This is also the age they learn to drive. This is an age at which physiologically a person needs more sleep relative to other ages (9.25 hours of sleep a day), and paradoxically, due to the multiple obligations, these youths' actual sleep time may be lower than needed.

In light of this, there is sound basis for the presumption that athletic performance is connected to the influence of sleep directly and indirectly.

Condition	Intervention
Quality Sleep Time Athletic Performance	Behavioral: Sleep extension

Study type:	Interventional
Study design:	Randomized
Official title:	Connection Between Sleep Quality and Duration and Performance in Young Athletes
Estimated enrollment:	50

Detailed Description

Aim: The purpose of this study is to evaluate the connection between sleep quality and duration and athletic performance among young athletes.

Participants and their parents will be asked to give informed consent.

The proposed study will have two stages:

1. Baseline assessment: In the first stage there will be an evaluation of the athletes' sleep quality and duration over the course of two weeks, and in parallel their athletic performance will be evaluated using accepted measures such as: swimming times over set distances, running times over set distances, etc.
2. Assessment of intervention's effect of prolonging the duration of nighttime sleep on the athletic performance of the participants, using the same measures as above. This stage will take four weeks.

Stage 1:

a) Before beginning the study, each participant will fill out a general health questionnaire.

b) Each participant will receive a heart monitor belt to wear for two weeks when sleeping. Each participant will be asked to wear the belt before going to bed and remove it upon waking in the morning. Heart rate data stored on the belts will

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be transferred to a computer each morning. Sleep data will be analyzed and each participant will receive a personalized sleep analysis. At this stage, the investigators will evaluate the baseline characteristics of the participants including their sleep duration, sleep efficiency, and presence and duration of the different sleep stages. In particular, investigators will assess slow wave sleep (during which a growth factor is released that is important for muscle recovery), time and duration of training sessions, and athletic performance.

c) Evaluation of athletic performance will be done using standard tests that are routinely carried out as part of athletic training in every branch of sports. Also, general parameters will be measured like standing heart rate and reclining heart rate, and heart rate at awakening in the morning.

Stage 2:

a) At this stage the participants will be divided randomly into two groups. In the course of an additional training cycle of two weeks, one group labeled "A" will be given additional sleep time of one to two hours. The second group (group "B") shall continue with no change. In the course of the two weeks, sleep parameters of both groups will be assessed and analyzed, and athletic performance during routine training will continue to be measured and tabulated. After these two weeks, the two groups will be crossed over, group "A" will return to a routine sleep schedule, i.e., the extra sleep time will be removed, and group "B" will get additional sleep time. All the aforementioned measures will be collected during the next two weeks (sleep quality, athletic performance during training).

b) During the entire study there will be close monitoring of injuries among participants. Events will be defined as injuries (according to the number of treatments by a physiotherapist or visits to a doctor) or near-injuries and will be quantified. Correlations will be sought between performance, injuries, and sleep duration.

c) In both stages, in addition to wearing a heart monitor belt, participants will be asked to fill out a questionnaire before and after sleep during the entire study.

Expected benefits:

- Better understanding of the physiology associated with sleep among adolescents involved in regular, competitive physical activity.
- Improved performance by building a sleep program, optimal wakefulness, and training.

Eligibility

Ages eligible for study:	13 Years to 20 Years
Genders eligible for study:	Both
Accepts healthy volunteers:	Yes

Criteria

Inclusion criteria:

- Age: 13–20 years old, male and female athletes.
- Generally good health.
- Willingness to participate in the study.
- Healthy heart rate.

Exclusion criteria:

- Arrhythmia.
- Chronic or acute illness.
- Unwillingness of the subject or his parents to allow participation in the study.

ClinicalTrials.gov processed this record on July 12, 2012.
Citation: http://clinicaltrials.gov/ct2/show/NCT01364831?term=Connection+Between+Sleep+and+Athletic+Performance&rank=1.

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Name_____ Date_____ Period_____

Immunogenicity of Off-Schedule Dosing of HPV Vaccine

Purpose

The purpose of this study is to gain a better understanding of the body's response to a human papillomavirus (HPV) vaccine and booster shot. The study will also investigate factors related to adolescents not following vaccination schedules. The HPV vaccine requires three doses (shots). Girls sometimes receive the three shots at the recommended times, and sometimes receive the shots at non-recommended times. This study will evaluate whether getting the shots at non-recommended times affects the level of protection provided by the vaccine. Participants will include about 1,400 girls 9–17 years old receiving a third dose of HPV vaccine from their primary care clinician. Study procedures include: medical history, questionnaires, and blood draws. Participants will be involved in the study for about six months from time of enrollment.

Condition:	Human Papillomavirus
Study type:	Observational
Study design:	Observational Model: Cohort
Official title:	Immunogenicity of the HPV-6, 11, 16, 18 Vaccine Among Adolescent Girls Who Receive Vaccine Doses at Non-recommended Intervals and Factors Related to Non-adherence
Estimated enrollment:	1,400

Groups/Cohorts

Experimental/Primary Arm 1:	This will consist of subjects receiving the second dose on time/third dose substantially late.
Experimental/Primary Arm 2:	This will consist of subjects receiving the second dose substantially late/third dose on time.
Experimental/Primary Arm 3:	This will consist of subjects receiving the second dose substantially late/third dose substantially late.
Alternate Arm:	This will consist of subjects who meet eligibility requirements but do not fit into any of the primary experimental arms.
Control Arm:	This will consist of subjects with an on-time interval between dose one and two, and an on-time interval between dose two and three.

Detailed Description

The immune response to the Gardasil® human papillomavirus (HPV) vaccine in non-clinical trial settings is unknown. In addition, the immune response following administration of the vaccine at substantially prolonged intervals is unknown. Early indications suggest that many girls will receive the vaccine at prolonged intervals and that this timing may affect immunogenicity. The lack of knowledge about the immunogenicity of prolonged intervals between vaccine doses precludes evidence-based recommendations for patients who are substantially late for their second or third dose. Currently, some clinicians restart the series while others give the doses at the incorrect interval without being able to counsel their patients as to their expected level of immune response or protection. Examining the immune response before the third dose and at one and six months after the third dose will allow a better understanding of the immunogenicity of this vaccine, and of the immune response to booster doses. Furthermore, determining factors related to non-adherence in the adolescent age group is important and timely. As an increasing number of vaccines are being recommended to the adolescent age group, understanding factors involved with non-adherence to the recommended dosing schedule is now critical. This information can guide interventions that aim to increase adolescent adherence

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to the recommended schedules. Eligible girls 9 to 17 years old receiving the Gardasil HPV vaccine from their primary care provider will be enrolled into this study on the day of, but prior to, receiving their third HPV vaccine dose or at approximately 28 days after HPV dose two. Blood for immunogenicity testing will be obtained up to three times during the study: one month and six months after the third dose for all subjects, and just prior to the third dose for subjects on time for their third dose (regardless of the time interval between the first and second dose). In addition, on Study Day 0, patient- and parent-related factors known to impact healthcare utilization may be measured using a questionnaire given to parents/legal guardians and to 14 to 17 year old subjects. Initially, all subjects meeting eligibility criteria will be enrolled regardless of timing of the second and third vaccine doses.

Eligibility

Ages eligible for study:	9 years to 17 years
Genders eligible for study:	Female
Accepts healthy volunteers:	Yes
Sampling method:	Non-probability sample
Study population:	Girls 9 to 17 years old receiving a third dose of the Gardasil HPV vaccine from their primary care clinician. Parent/legal guardians will participate by answering a questionnaire to determine factors related to non-adherence to recommended vaccine schedule.

Criteria

Inclusion criteria: Girls will be eligible if they are:

- 9 to 17 years of age (defined as between 9 years 0 days and younger than 18 years of age) at time of receipt of third HPV dose;
- Receiving the third dose of Gardasil human papillomavirus (HPV) vaccine as part of routine healthcare;
- Able and willing to complete all study visits and evaluations;
- Able and willing to participate in the study by providing written informed assent/consent; and
- Parent or legal guardian provides permission.

Exclusion criteria: Girls will be excluded from study participation if they:

- Are unable to comply with the study protocol.
- Have received more than three doses of human papillomavirus (HPV) vaccine.
- Have received blood and or blood products (including immunoglobulin) in the past three months or anticipate receiving these products during the study period.
- Have a history of any physical, mental, or developmental disorder that study personnel believe may hinder their ability to comply with the study requirements.
- Have a history of malignancy or confirmed or suspected immunodeficiency condition, such as human immunodeficiency virus infection.
- Are participating or have participated in HPV vaccine related research.
- Have received an investigational or alternate (Cervarix) HPV vaccine.

ClinicalTrials.gov processed this record on July 12, 2012.
Citation: http://clinicaltrials.gov/ct2/show/NCT01030562?term=Immunogenicity+of+Off-Schedule+Dosing+of+HPV+Vaccine&rank=1.

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Name_____ Date_____ Period_____

Natural History Study of the Development of Type I Diabetes

Purpose

TrialNet is an international network dedicated to the study, prevention, and early treatment of Type I Diabetes. TrialNet sites are located throughout the United States, Canada, Finland, United Kingdom, Italy, Australia, and New Zealand. TrialNet is dedicated to testing new approaches to the prevention of and early intervention for Type I Diabetes.

The goal of the *TrialNet Natural History Study of the Development of Type I Diabetes* is to enhance our understanding of the demographic, immunologic, and metabolic characteristics of individuals at risk for developing Type I Diabetes.

The Natural History Study will screen relatives of people with Type I Diabetes to identify those at risk for developing the disease. Relatives of people with Type I Diabetes have about a three to four percent chance of being positive for the antibodies associated with diabetes. TrialNet will identify adults and children at risk for developing diabetes by testing for the presence of these antibodies in the blood. A positive antibody test is an early indication that damage to insulin-secreting cells may have begun. If this test is positive, additional testing will be offered to determine the likelihood that a person may develop Type I Diabetes. Individuals with antibodies will be offered the opportunity for further testing to determine their risk of developing diabetes over the next five years, and close monitoring for the development of diabetes.

Condition:	Diabetes Mellitus, Type I
Study type:	Observational
Study design:	Time perspective: Prospective
Official title:	Natural History Study of the Development of Type I Diabetes
Estimated enrollment:	75,000

Detailed Description

The study is conducted in two parts:

- Screening.
- Monitoring (annual and semi-annual depending on risk).

A simple blood test is done to screen for the presence of diabetes-related biochemical antibodies. Islet cell antibodies are also measured in individuals positive for one or more biochemical antibodies. Participants can go to a TrialNet Clinical Center, or request a screening kit to have their blood drawn by a local physician or laboratory. Participants will be provided with their screening results within four to six weeks.

If antibodies are present initially and are confirmed by repeat testing, participants will be invited to have additional testing at a baseline monitoring visit to determine their average risk of developing diabetes over the next five years. The baseline monitoring visit will include an Oral Glucose Tolerance Test (OGTT), re-testing for biochemical and islet cell antibodies if needed, measurement of HbA1c, and HLA (genetic) typing.

Individuals with a less than 3% average risk will be asked to come for follow-up on annual basis; individuals with greater than average 32% risk will be asked to come for follow-up visits on semi-annual basis.

Participants will be monitored for possible progression towards Type I Diabetes and may be offered the opportunity to enter into a prevention study (e.g., oral insulin prevention study) or an early treatment study if they are diagnosed with Type I Diabetes while participating in the *Natural History Study*.

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Eligibility

Ages eligible for study:	1 year to 45 years
Genders eligible for study:	Both
Accepts healthy volunteers:	Yes
Study population:	First, second, and third degree relatives of individuals with Type I Diabetes.

Criteria

Inclusion criteria:

- Individuals 1 to 45 years old who have an immediate family member with Type I Diabetes (such as a child, parent, or sibling).
- Individuals 1 to 20 years old who have an extended family member with Type I Diabetes (such as a cousin, niece, nephew, aunt, uncle, grandparent, or half-sibling).

Exclusion criteria:

To be eligible a person must not:

- Have diabetes already.
- Have a previous history of being treated with insulin or oral diabetes medications.
- Currently be using systemic immunosuppressive agents (topical and inhaled agents are acceptable).
- Have any known serious diseases.

ClinicalTrials.gov processed this record on July 12, 2012.
Citation: http://clinicaltrials.gov/ct2/show/NCT00097292?term=Natural+History+Study+of+the+Development+of+Type+1+Diabetes&rank=1.

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Name_____ Date_____ Period_____

Pharmacokinetics Study of HT-2157 in Healthy Subjects and in Patients With Major Depressive Disorder

Purpose

This is a two-part study. The objective of Part 1 is to evaluate the safety, tolerability, and pharmacokinetics of HT-2157 in healthy normal volunteers.

Part 2 is a randomized, double-blind, placebo-controlled, multiple (21-day) ascending-dose evaluation of the safety, tolerability, and pharmacokinetics of HT-2157 in patients with major depressive disorder.

Condition	Intervention
Healthy volunteers (Part 1)	HT-2157
Major depressive disorder (Part 2)	HT-2157 or a placebo

Study type:	Interventional
Study design:	Randomized
Official title:	A Two-Part Study: Part 1 is a Multiple-dose (7-day), Open-label Evaluation of the Safety, Tolerability, and Pharmacokinetics of HT-2157 in Healthy Subjects. Part 2 is a Randomized, Double-blind, Placebo-controlled, Multiple (21-day) Ascending-dose Evaluation of the Safety, Tolerability and Pharmacokinetics of HT-2157 in Patients With Major Depressive Disorder.
Estimated enrollment:	28

Arms	Assigned Intervention
Experimental: HT-2157	Drug: HT-2157 QD oral dosing
Placebo comparator: Placebo	Drug: Placebo QD oral dosing

Detailed Description

This is a two-part study. The objective of Part 1 is to evaluate the safety, tolerability, and pharmacokinetics of HT-2157 administered for seven days in healthy normal volunteers.

Part 2 is a randomized, double-blind, placebo-controlled, multiple ascending-dose evaluation of the safety, tolerability, and pharmacokinetics of HT-2157 administered for 21 days in patients with major depressive disorder. The primary objective of Part 2 is to assess the entrance of HT-2157 into cerebrospinal fluid in the central nervous system. In addition, the potential activity of HT-2157 in this patient population may be assessed using exploratory biologic and pharmacokinetic markers of potential efficacy.

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Criteria

Main inclusion criteria (Part 1):	• No clinically relevant abnormalities. • Ages 18 to 55 years, inclusive. • Body Mass Index (BMI) of 18.5 to 32 kg/m^2.
Main inclusion criteria (Part 2):	• No clinically relevant abnormalities. • Ages 18 to 55 years, inclusive. • Body Mass Index (BMI) of 18.5 to 32 kg/m^2. • Mild-to-moderate major depressive disorder.
Main exclusion criteria (Part 2):	• Any disorder that would interfere with the absorption, distribution, metabolism, or excretion of drugs.
Main exclusion criteria (Part 2):	• Any disorder that would interfere with the absorption, distribution, metabolism, or excretion of drugs. • Current and primary Axis I disorder other than MDD.

ClinicalTrials.gov processed this record on July 12, 2012.
Citation: http://clinicaltrials.gov/ct2/show/NCT01413932?term=Pharmacokinetics+-+Pharmacodynamic+Study+of+HT-2157+in+Healthy+Subjects+and+in+Patients+With+Major+Depressive+Disorder&rank=1.

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Name_____ Date_____ Period_____

Safety of an Oral HIV Vaccine in HIV Uninfected Volunteers

Purpose

This study will test the safety of and immune response to an oral HIV vaccine in healthy volunteers. The vaccine in this study uses a weakened bacterium called *Salmonella typhi* to deliver an HIV gene into the body through the mouth. The body then produces an HIV protein from the gene; this protein stimulates an anti-HIV immune response. The vaccine contains only one of the many substances that HIV needs to make more copies of itself, so the vaccine itself cannot cause HIV or AIDS.

Condition	Intervention	Phase
HIV infections	Biological: SCBaL/M9	Phase I

Study type:	Interventional
Study design:	Randomized
Official title:	Development of an Oral Prime-Boost AIDS Vaccine to Elicit Broadly Neutralizing Antibodies Against HIV-1
Estimated enrollment:	38

Arms	Assigned Intervention
Experimental: All participants will receive oral vaccine at study entry, although dosage will vary.	Biological: SCBaL/M9 Oral recombinant ***Salmonella typhi*** HIV-1 gp120 vaccine

Detailed Description

The transmission of HIV-1 by both sexual and parenteral (directly through the blood via IV needle) routes makes it likely that a successful preventive vaccine against this virus will need to induce protective immunity in both mucosal and systemic compartments. The long-term objective of this program is to develop an HIV-1 vaccine that elicits protective immunity in both the mucosal and systemic compartments.

The study will evaluate the safety and immunogenicity of an oral recombinant *Salmonella typhi* HIV-1 gp120 vaccine in healthy human volunteers. This will be the first study in volunteers to use a bacterium to deliver a recombinant vector vaccine mucosally. The study will also develop an Env immunogen that elicits a broader spectrum of neutralizing antibodies than gp120 and that can be delivered by *Salmonella typhi* or as a soluble protein immunogen.

This is a Phase I dose-escalation study of two vaccine components that will be combined in a larger prime-boost protocol should the desired safety endpoints be obtained. Both components use a constrained gp120 that expresses epitopes recognized by broadly neutralizing antibodies. The priming immunogen will be the conformationally constrained gp120 gene delivered orally by live attenuated *Salmonella typhi*. The boosting immunogen will be a soluble subunit protein made up solely of the conformationally constrained gp120.

All participants in this study will receive the vaccine. Participants will be randomized to different vaccine doses. Participants will have eight study visits over 20 weeks. Study visits will include a brief medical interview, physical exam, blood and urine tests, and counseling on avoiding HIV infection and pregnancy. Participants will be tested for HIV infection three times during the study.

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Eligibility

Ages eligible for study:	18 years to 55 years
Genders eligible for study:	Both
Accepts healthy volunteers:	Yes

Criteria

Inclusion criteria:

- HIV uninfected.
- Sexual behavior that is indicative of low risk for HIV infection.
- Negative for Hepatitis B surface antigen.
- Negative for Hepatitis C viral sequences and antibody.
- Availability for follow-up during the study (five months).
- Willingness to use acceptable methods of contraception during study period.

Exclusion criteria:

- Receipt of HIV vaccines or placebo in a previous HIV vaccine trial.
- History of immunodeficiency, chronic illness, autoimmune disease, or use of immunosuppressive medications.
- History of cancer unless there has been a surgical excision followed by a sufficient observation period to give a reasonable assurance of cure.
- Medical or psychiatric condition or occupational responsibilities that preclude compliance with the protocol.
- History of suicide attempts, recent suicidal ideation, or psychosis.
- High-risk behavior for HIV infection as determined by screening questionnaire.
- History of injection drug use within 12 months of study entry.
- Use of experimental agents within 30 days of study entry.
- Receipt of blood products or immunoglobulin within six months of study entry.
- Active syphilis.
- Active tuberculosis.
- History of anaphylaxis or serious adverse reactions to vaccines.
- Pregnant or breastfeeding.

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ClinicalTrials.gov processed this record on July 12, 2012.
Citation: http://clinicaltrials.gov/ct2/show/NCT00062530?term=healthy+volunteers&recr=Open&cond=vaccine&age=1&phase=0&rank=8.

STUDENT HANDOUT SA-2

Guidelines for Choosing Your Own Clinical Trial

Name_____ Date_____ Period_____

1. Go to http://www.clinicaltrials.gov and click on ***Search for clinical trials***.
2. Enter "healthy volunteers" "(location)" "(condition)." Omit condition if you would rather browse all types of studies.
3. At the top of list, click ***Hide studies that are not seeking new volunteers*** and look through the list of current studies to find one that seems appropriate.
4. Click on the link and read through the eligibility criteria to make sure the study is appropriate for this assessment. To work for the assessment the study must:
   a. Accept healthy volunteers in your approximate age group.
   b. Be located in your region (traveling long distances for participation as a healthy volunteer is not realistic).
   c. Have inclusion requirements you meet. (Some studies require blood work or other testing to determine whether respondents are eligible. You may still use the study if you meet all of the inclusion requirements other than those for such tests.)

Additional Resources

1. Centerwatch (http://www.centerwatch.com/clinical-trials/overview.aspx) provides a good overview of clinical trials and what you should know before you volunteer.
2. Other clinical trial sites include http://www.centerwatch.com and http://www.cancer.gov/clinicaltrials. You may also search local university or hospital websites for current trials.

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STUDENT HANDOUT SA-3

Decision-Making Framework

Name_____ Date_____ Period_____

Part I: Question – Should I volunteer to participate in a clinical trial?	
Name of trial:	
Part II: Facts and Questions	
Use the study details to answer the following: What is the purpose of the study? Does it appear to have social value? In what ways does the study plan seem scientifically valid? (Study type and design, eligibility, treatment/intervention received, **inclusion/exclusion criteria**, etc.) What does the study require of me? What ethical protections are in place for me? (Knowledge gained through historical clinical trials, **Belmont principles**, **IRB** involvement, etc.)	What other information do I need to know about this study or **clinical trial** before making a decision?

Part III: Stakeholder Values		
Stakeholders (people/entities affected by the decision)	Values/concerns of each stakeholder	Belmont principle(s) given priority
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

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Part IV: Pros and Cons (What are the possible benefits and risks of participating in the study?)	
Possible benefits of participating	**Possible risks of participating**

Part V: Write a strong justification paragraph for your decision on the topic. Make sure to answer the following questions:

a. What is your decision about enrolling in this study?

b. What is the factual content (both from the clinical trial and other facts you learned in this unit) to support your decision that can be confirmed or refuted regardless of cultural or personal views?

c. What ethical considerations can be included to support this decision? (Respect for Persons, Maximize Benefits/ Minimize Harms, Justice)

d. What are the views and interests of the individuals or groups affected by the decision that are most relevant to your decision?

e. Why is the alternative choice not as strong as your choice?

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STUDENT HANDOUT SA-4

Decision Paper Rubric

Name_____ Date_____ Period_____

Throughout this unit we have discussed the involvement of humans in research. We have covered historical events, the **Belmont Report**, the **IRB** process (including **informed consent**), and **clinical trial phases**, including the challenges involved in recruiting participants. Using what you have learned about these aspects of human involvement in research, ***identify and justify your personal decision regarding your possible involvement in a clinical trial***. In your answer, be sure to discuss ***why you have/have not*** chosen to participate in the trial. Provide justification for your decision by using facts (from what you have learned concerning historical cases, IRBs, etc., and those from your clinical study summary), various perspectives (multiple individuals on both sides of the issue from multiple backgrounds), and ethical considerations using the Belmont principles. Proficient or exemplary answers will demonstrate your understanding of classroom discussions, activities, and readings covering material spanning the entire unit. Use the rubric below to guide you in completing this assignment.

Exemplary	Proficient	Partially proficient	Developing
Student is able to identify her *personal decision* regarding her involvement in research that is…			
• Consistent with the nature of involving humans in research. • Authentic, clear, and easily understood. • ***Related to multiple issues outside of humans in research.***	• Consistent with the nature of involving humans in research. • ***Authentic, clear, and easily understood.***	• Consistent with the nature of involving humans in research. • ***Lacking*** authenticity and/or contains ***minor errors*** in understanding	• Consistent with the nature of involving humans in research. • ***Lacking*** authenticity and/or contains ***major errors*** in understanding
Student is able to *justify* his personal position regarding his involvement in research through…			
• Multiple facts from his chosen ***clinical study and past studies***. • Multiple perspectives from various backgrounds. • Multiple ethical considerations. • ***Providing examples of how this justification is based in social issues.***	• Multiple facts ***only*** from his chosen clinical study. • Multiple perspectives from ***various backgrounds***. • ***Multiple*** ethical considerations.	• Few facts, but they are ***only from his chosen clinical study***. • Multiple perspectives, but ***predominantly from the same background***. • ***Multiple*** ethical considerations.	• Few to no facts. • A ***single*** perspective. • A ***single*** ethical consideration.

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APPENDIX

TABLE OF CONTENTS

MASTER GLOSSARY

Albinism: A condition characterized by a lack of pigmentation, resulting in very light skin coloring, white hair, and light blue or red eyes.

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

Antibody: A substance made by the body as an immune response that attacks and destroys foreign agents, such as viruses and bacteria.

Assent: A process in which the parent or guardian of a minor agrees to the minor's participation in a research study. The participant is still required to give informed consent.

Autonomy: A person's freedom and ability to make his or her own decisions.

Autopsy: An examination conducted on a dead body to determine the cause of death.

Autosomal recessive trait: A trait both parents must carry for a child to inherit the syndrome.

Belmont Report (Belmont principles): Created in 1978 by the U.S. Department of Health, this report established three basic ethical principles to be considered when humans participate in research.

Beneficence: Minimizing all potential harms and maximizing all potential benefits to the subject as well as to society.

Biobank: A storage facility for biological materials used in medical research.

Bioethics: A sub-field of ethics applied to the life sciences; it looks at the ethical impacts of new scientific knowledge and how society makes policy decisions regarding medicines, treatments, and human health.

Bleeding disorder: A medical disorder that leads to poor blood clotting and continuous bleeding.

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.

Cervical cancer: Cancer of the cervix, which is the lower, narrow end of the uterus.

Clinical research: Medical research involving human participants to test new medications, treatments, methods of prevention, and therapies.

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.

Coercion: The act of pressuring someone to do something using force, intimidation, or threats without respect for individual choice. This includes the idea that a person with few choices may find participation in a study to be so appealing that they feel they cannot decline, even if being in the study is not a good decision for other reasons.

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.

Conflict of interest: A situation in which someone is responsible for making a decision in an official capacity (e.g., someone holding public office) that could benefit them personally.

De-identify: To remove personal information such as name, medical record number, or study code from a genetic sample so that the sample cannot be linked to a specific individual.

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.

Ethical standards: Rules governing the conduct of a person or the conduct of the members of a profession.

Ethics: A field of study that looks at the moral basis of human behavior and attempts to determine the best course of action in the face of conflicting choices.

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

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.

Futility: Uselessness or pointlessness; reason for stopping a clinical trial if interim data show that the treatment group is unlikely to see any more improvement than the control group.

Genetic predisposition: A greater likelihood of expressing a certain trait based on a person's genetic material (e.g., someone may carry a gene that is known to be related to an increased chance of breast cancer).

Genome: The complete genetic material of an organism.

Hepatitis: Inflammation of the liver caused most frequently by viruses.

Hermansky-Pudlak Syndrome (HPS): A rare genetic disorder characterized by albinism, bleeding problems, and fatal pulmonary fibrosis.

Human cell line: A continuously dividing set of cells used in medical research that are derived from a single human cell.

Hypertension: Abnormally high blood pressure.

Idiopathic pulmonary fibrosis: Pulmonary fibrosis that occurs in otherwise healthy people without a known cause.

Inbreeding: When closely related people have children together, generation after generation.

Incidence: The percentage of newly diagnosed cases of a disease in a population.

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

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.

Informed consent: A process that outlines required elements of research participation, including its risks and potential benefits, to help someone decide whether to participate. An informed consent form is used to convey essential information and is signed by the participant if he or she decides to join the study.

Institutional Review Board (IRB): A group made up of a diverse group of people (with varying views, backgrounds, and areas of expertise) who oversee, monitor, and review research studies to protect the safety, rights, and welfare of human participants.

Lysosomal disorder: A disorder that affects the function of lysosomes in cells.

Lysosomes: The part of a cell responsible for breaking down waste materials and other debris.

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."

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.

Penicillin: An antibiotic drug made from penicillium mold (or produced synthetically) used to treat infections and diseases.

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

Phenotype: Observable physical or biochemical characteristics resulting from both genetic makeup and environmental influences.

Pirfenidone: A drug developed by InterMune Inc. for the treatment of idiopathic pulmonary fibrosis.

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).

Pulmonary fibrosis: Scarring or thickening of the lungs.

Ramifications: Consequences or results of actions, especially when not desired.

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.

Schizophrenia: A mental illness resulting in greatly impaired thinking, emotional responses, and behaviors.

S**ingle-gene disorder:** A disorder caused by a mutation in a single gene.

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

Stakeholder: A person with an interest or concern in something.

Stories of origin: Stories that recount how something (or a people) came into being.

Syphilis: A sexually transmitted disease caused by bacteria, which can cause skin lesions. Left untreated, syphilis can cause inflammation, meningitis, and other central nervous system damage, as well as and cardiovascular damage. Syphilis can remain in the body undetected for many years (latency), and symptoms can appear more than 40 years later.

Tissue sample: Bodily fluids (e.g., blood or saliva) or tissue (e.g., cells, skin, bone, or muscle) for use in research.

Type II Diabetes: A chronic medical condition that affects how the body metabolizes sugar (glucose). Type II Diabetes typically begins in adulthood and patients are not usually dependent on the use of insulin to control their sugar levels.

Undue influence: Is exerted when a person of higher power or authority takes advantage of another person; undue influence can often include coercion.

Vulnerable (populations): Groups that may be exploited for use in research, e.g., children, people who are illiterate, and prisoners.

APPENDIX
Creating Discussion Ground Rules

INTRODUCTION

The study of ethics involves consideration of conflicting moral choices and dilemmas about which reasonable people may disagree. Since a wide range of positions is likely to be found among students in most classrooms, it is especially important to foster a safe classroom atmosphere by creating some discussion ground rules. These ground rules are often referred to as "norms." An agreed-upon set of ground rules should be in place before beginning *The Science and Ethics of Humans in Research* curriculum.

OBJECTIVES

Students will be able to:

- Create and agree to classroom discussion norms.

PROCEDURE

Ask the students, "What can we do to make this a safe and comfortable group for discussing issues that might be controversial or difficult? What ground rules should we set up?" Allow students some quiet reflection time, and then gather ideas from the group in a brainstorming session. One method is to ask students to generate a list of ground rules in small groups and then ask each group to share one rule until all have been listed. Clarify and consolidate the ground rules as necessary.

Post norms where they can be seen by all, and revisit them often. If a discussion gets overly contentious at any time, it is helpful to stop and refer to the ground rules as a class to assess whether they have been upheld.

Some possible student ground rules/norms could include:

- A bioethics discussion is not a competition or a debate with a winner and a loser.
- Everyone will respect the different viewpoints expressed.
- If conflicts arise during discussion, they must be resolved in a manner that retains everyone's dignity.
- Everyone has an equal voice.
- Interruptions are not allowed, and no one person is allowed to dominate the discussion.
- Critique ideas, not people.
- Assume good intent.
- All are responsible for following and enforcing the rules.