



The Science and Ethics of HIV Vaccine Research

Draft 2008

**Curriculum Guide
Grades 7-12**

**Northwest Association for
Biomedical Research
www.nwabr.org**



Lesson

4

Case Studies and Human Research Ethics

OVERVIEW

Purpose

The purpose of this lesson is to help students understand ethical considerations related to testing vaccines in humans. Students will examine historical cases that have influenced research guidelines for human research participants. This will prepare students to later apply their understanding of ethical guidelines to their own research proposals.

Essential Understandings

- The methods of scientific inquiry and research using human subjects must be followed, paying close consideration to ethical principles based upon past historical practices and current guidelines and regulations.
- Selection of human subjects for experimental research must be done carefully based on the goals of research and consideration of risk and benefits to specific individuals and participant populations.
- Examining the ethics of research with human participants encourages the use of critical and logical thinking to form positions and viewpoints.

Learning Objectives

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

Key Concepts

The analysis of case histories provides insight into the development of the following concepts: informed consent, vulnerable populations, undue pressure and influence. The Belmont Report provides basic principles for use of human subjects in research: respect for persons, beneficence, and justice.

Prior Knowledge Needed

Ethical Theories (helpful but not necessary)

Research process including animal studies through clinical trials (helpful but not necessary)

Materials

PowerPoint Slides (HIV 101 – slides 16-21) – see

<http://www.nwabr.org/education/hiv/HIVVaccines.ppt>

Student Handouts:

Activity 4.2 Rules for Using Humans in Research

Historical Case Studies #1 - #5

Activity 4.3 Historical Case Studies for Human Research—
Guiding Questions

Activity 4.4 Basic Principles for Using Humans in Research

Activity 4.6 Historical Overview of Guidelines for Using
Humans in Research (optional)

Activity 4.8 Ethical Considerations of AIDS Vaccine Trials

Research Ethics Training Curriculum (optional)—Family Health International has training materials which include slides and discussion focusing on the three basic ethical principles of Respect, Beneficence and Justice. The training materials for Community Representatives work well in the classroom. The pdf version can be downloaded from the FHI site: <http://www.fhi.org/en/RH/Training/trainmat/ethicscurr/RETCCREn/index.htm>. The 11 slides begin here: <http://www.fhi.org/en/RH/Training/trainmat/ethicscurr/RETCCREn/ss/Contents/SectionIV/index.htm>

Prep Time

Time needed to copy Student Handouts and review background materials

Class Time

1-2 days depending upon the depth of discussions, as facilitated by the teacher

Timeline

- If desired, order one of the suggested videos ahead of time
- Prepare overheads (if needed) and student handouts

Extensions

- Present Historical Overview of Guidelines Handout. Relate to previous case studies and the use or abuse of existing guidelines (e.g. Reich Circular 1931 as compared to Nazi experiments, Nuremberg Codes established during PHS Syphilis study).
- Give the specific names of those involved in the case studies and have them research the details, ethical documents and results of each case.
- Explore the use of animals, especially Rhesus macaques, in HIV vaccine development.
- Use one of the following videos to enhance student learning:
 - Ethics in Biomedical Research, Howard Hughes Medical Institute, 2005. This 80 minute DVD includes a helpful 28 minute overview of ethics in research. FREE of charge, www.hhmi.org/bioethics.
 - Susceptible to Kindness: Miss Evers' Boys and the Tuskegee Syphilis Study, 1994, 45 minutes, Cornell University, Media Services Resources Center. Telephone 607-255-2090
 - Documentary of the Public Health Service Syphilis Study -Deadly Deception, 1993, PBS Nova, <http://shop.wgbh.org/>
 - In the Shadow of the Reich: Nazi Medicine, 54 minutes, First Run Features. Telephone 800-229-8575

Adaptations

- IEP/ELL: Have the entire class focus on one case together.

Assessment Suggestions

- Informal assessments as students work in groups to complete Case Study Activity
- Monitor answers on handout and during discussion
- Evaluate homework paragraphs

Common Misconceptions

- Scientists are always ethical and do the right thing
- Scientists are always truthful and objective
- Scientists don't have to follow guidelines when developing research protocols.
- No one is monitoring research to make sure that protocol and safety guidelines are followed.
- People are commonly mistreated while participating in clinical trials.

ADDITIONAL RESOURCES

- **Articles for background reading:**
 - “Infectious Diseases”, The Lancet, Vol 4 July 2004, pages 385-413
 - “Vaccines at Retrovirus 2004”, www.iavireport.org/Issues/0404/VaccinesatRetrovirus2004.asp
 - “Ethical Considerations in HIV preventive vaccine research”. UNAIDS guidance document <http://www.aidsinfo.nih.gov/other/whatisvac.asp>
- **Research Guidelines:**
 - The Belmont Report: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>
 - The Nuremberg Code: <http://ohsr.od.nih.gov/guidelines/nuremberg.html>
 - Declaration of Helsinki: <http://www.wma.net/e/policy/b3.htm>
 - Nuffield Council on Bioethics: <http://nuffieldbioethics.org/home/index.asp>
 - Office of Human Subjects Research: <http://ohsr.od.nih.gov/info/sheet3.html>
 - The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects: http://www.cioms.ch/frame_guidelines_nov_2002.htm
 - UNAIDS Guidance Document link: Ethical Considerations of HIV Preventative Vaccine Research http://data.unaids.org/Publications/IRC-pub01/JC072-EthicalCons_en.pdf
- *The use of human subjects in research has a controversial history. Over time, researchers and ethicists have developed guidelines for the recruitment and use of human subjects in studies with potential benefits and risks to those participants. The Public Health Service study of Syphilis in Tuskegee is one of the most famous examples. It is important to stress to students that research provides many health benefits, but that there are also risks associated with using human participants in research.*

Lesson 4 Activities

SUMMARY

4.1 Invitation to Learn

4.2 Student Brainstorm: *What should rules be when doing research trials on human participants?*

4.3 Review of Historical Case Studies

4.4 Comparison of Student-Derived 'Rules' to Existing Guidelines

4.5 Selection of Principle Most Violated in Case

4.6 Debrief and Discussion

4.7 Human Subjects Expository Paragraphs

4.8 Ethical Considerations of AIDS Vaccine Trials

4.1 Invitation to Learn



Pose the question, "Why have scientists not been able to come up with a vaccine for HIV after 20+ years of research?"

This question provides a transition from the previous two days and the homework assignment. Many factors are relevant, focus on the following where there is a,

- High mutation rate of HIV, resulting in:
 - High variability of HIV within an individual as well as between individuals
 - High variability of HIV between global regions
- Infection of the same cells that would be involved in a normal immune response
- Difficulty of finding parts of HIV virus that are 'antigenic' (would invoke a strong immune response), due to the many carbohydrates coating the virus, the fact that virus buds from human cells, and the fact that many such 'antigenic' parts are not exposed until binding occurs.

Introduce vaccine development using the Powerpoint presentation, focusing on slides 16-21, and especially on the parameters of Phase I trials. These slides can be found at: <http://www.nwabr.org/education/hiv/HIVVaccines.ppt>. They may take a number of minutes to download.

Explain to students that the next steps in vaccine development would be animal trials, followed by human trials. This lesson will focus on the ethical guidelines surrounding human participation in scientific research trials. This information will be helpful when considering how they will structure their own Phase I trial in the final assessment.

4.2 Student Brainstorm: What Should the Rules Be?



Put students into five groups (one for each case study). Have each group brainstorm what they think the rules should be when doing research trials on human participants, using the 'Rules for Using Humans in Research' Handout.

4.3 Review of Historical Case Studies



Provide one case study to each group. Large classes may have more than one group working on a case study. Each group should have a recorder, a reader, and a reporter, and all students should participate in discussion of case study.

Give each group a case study and the case study guiding questions. Explain to students that after they have read the case study, they need to discuss the ethical use of human participants in their case.

Symbols



— video



— discussion



— hands-on



— on-line or web based



— homework

Everyone in the group should contribute to answering the guiding questions thoughtfully and completely.

Once students have completed the questions, the student acting as reporter will summarize the case and explain to the class the findings/opinions of the group.

Record the main ideas concerning human participants on the board or overhead as groups report out. *Modification: Use a “jigsaw” method with case studies so students are exposed to each of the case studies in smaller groups. Then have class discussion where students report out general ideas about ethical use of human subjects in research.*

Before introducing the case studies to the class, teachers should stress the positive role clinical trials have played over time in the advancement of health care.

4.4 Comparison of Student-Derived ‘Rules’ to Existing Guidelines

Introduce the principles using the ‘Basic Principles of Research’ handout.

Students should revise their ‘rules’ as previously selected on their ‘Rules Handout’ as necessary.

Discuss, using the following questions as guides;

- What was included on both your rules and the Basic Principles? Does that indicate how important you see it as an issue?
- What wasn’t included on your list? Is that an oversight on your part (e.g. it didn’t come to mind), or do you feel that it isn’t as important of an issue?
- Are there additional rules that you included? What are the important reasons you included them?
- Is there an important reason why something is on the “Basic Principles” sheet that you didn’t have?

4.5 Selection of Principle Most Violated in Case.

Students select the principle that was most violated in their study.

Note: there are many ways to interpret these cases in light of the principles. This part of the lesson helps students become familiar with the principles, and asks them to justify their selection of principles. Which principle they settle on is not as important as their rationale for selecting it!

4.6 Debrief and Discussion

Review each of the cases, informing students that each of these cases is based on a real event. Give identifying information about each case. Summarize main concepts associated with the case and ethical regulations / guidelines developed as a result of each case.

Case Study #1 Walter Reed and Yellow Fever in Cuba: early case of written use of “informed consent”.

Concepts: Respect for persons: informed consent, Justice: undue pressure and influence (money)

Case Study #2 Nazi Experiments on Concentration Camp Victims: resulted in the Nuremberg Trials that set up the Nuremberg Codes 1946-47.

Concepts: Respect for persons: informed consent, Beneficence: minimizing harms, Justice: vulnerable population

Case Study #3 Public Health Service Syphilis Study 1932-1972: resulted in the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which subsequently issued the Belmont Report.

Concepts: Respect for persons: informed consent, Justice: vulnerable population, undue pressure and influence

Case Study #4 AZT and Pregnant Women in Africa: World Medical Association clarified the use of placebos in the absence of existing proven therapy. (<http://www.wma.net/e/policy/b3.htm>)

Concepts: Justice: vulnerable/target populations

Case Study #5 New York Study using young boys to study effects of fenfluramine on behavior. New York Times 1998, April 15, B3, Hiltz.

Concepts: Respect for persons: informed consent, Justice: vulnerable/target populations, treating patients without symptoms based on characteristics of relatives

4.7 Homework: Human Subjects Expository Paragraphs



Have students write 1 paragraph on each of the following:

- What are the basic principles that guide research with human subjects?
- Why would these principles be important to consider in a trial of an HIV vaccine?

4.8 Ethical Considerations of AIDS Vaccine Trials



Students read an article which raises a number of ethical issues surrounding AIDS vaccine trials. Using the student handout, students provide examples from the article pertaining to the principles of Justice, Beneficence, and Respect for Persons. The New York Times article used for this lesson can be found before student handout 4.8, or at: http://www.michaelspecter.com/times/1998/1998_10_01_nyt_aids.html

Student Handout Activity 4.2

NAME _____ Date _____ Period _____

What do you consider to be the most important “Rules for Using Humans in Research Studies”? You and your group should come up with 5 to 10 rules that would be applicable to most or all human research studies.

RULES FOR USING HUMANS IN RESEARCH

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.
- 9.
- 10.

Yellow Fever in Cuba

Following the Spanish-American War, American soldiers took control of the island of Cuba. They, like all other newcomers to Cuba, were confronted with a range of tropical diseases-typhoid, malaria, yellow fever, dengue fever-toward which they had no natural immunity. For every one soldier who died in the war, hundreds quickly died of disease. Cubans typically contracted yellow fever early in life and either died or developed life-long protection. About 30% of people who contracted yellow fever died.

In 1900, researchers began work to combat the disease. One major barrier for studying the disease was that it only affected people. With no animal model to use, the researchers were obliged to do all their experiments on people. Little was known at the time about the cause or transmission of yellow fever, but mosquitoes were suspect. Could a mosquito that bit a sick person then transmit the disease by biting someone who was well?

The experiments were crude but direct. A test tube containing a mosquito was inverted onto the arm of someone who was sick. The mosquito sank its proboscis into the flesh, found a vein or artery, and drank a blood meal. After two weeks, the test tube containing the mosquito was inverted onto the arm of a healthy subject. Researcher and subject then watched as the mosquito once again sank its proboscis through the flesh and into the bloodstream. There, it once again exchanged fluids with its host, injecting salivary juices and the viruses that caused yellow fever into the blood stream while drinking another blood meal.

Researchers created a written “informed consent”^{*} document, which outlined the risks of the experiments and their possible benefits. Those who agreed to be subjects in the experiments had to sign the forms. The American military governor of Cuba provided funds to set up a proper research laboratory-seven tents and a flagpole flying an American flag-and funds were also available to pay volunteers. The American soldiers who participated did not get paid but the Spanish immigrants who volunteered each received \$100 in gold to participate and \$100 more if they got sick. For volunteers, the risks of the yellow fever experiments even seemed worth taking, because, being new to the island, they were likely to contract the disease in any case. At least in an experiment, they would get rapid and decent medical treatments.

All told, 29 people contracted the disease while participating in the commission’s experiments and five died. After mosquitoes were implicated in the transmission of the disease, a thorough mosquito eradication program began, and yellow fever was wiped out in Cuba.

Modified from Kennedy Institute of Ethics

http://www.georgetown.edu/research/nrcbl/hsbioethics/alumni/unit3_i.htm

^{*} The term ‘informed consent’ did not enter into common usage until the 1960s.

Prisoner Experiments

During World War II, several experiments involving human subjects were conducted using prisoners in concentration camps. Some of these experiments focused on the human tolerance to extreme temperatures. These experiments are summarized below.

Freezing / Hypothermia

The freezing experiments were divided into two parts. Part One established how long it would take to lower the body temperature until death occurred, and Part Two determined how to best resuscitate the frozen prisoner

The two main methods used to freeze the prisoner were to put the person in a icy vat of water or to put the prisoner outside naked in sub-zero temperatures.

The icy vat method proved to be the fastest way to drop the body temperature. Prisoners were usually stripped naked and prepared for the experiment.

A insulated probe which measured the drop in the body temperature was inserted into the rectum. The probe was held in place by a expandable metal ring which was adjusted to open inside the rectum to hold the probe firmly in place. The prisoner was then placed in the vat of cold water and started to freeze. It was learned that most prisoners lost consciousness and died when the body temperature dropped to 25 C (77 degrees Fahrenheit).

Sun Lamp

The prisoners were placed under sun lamps which were so hot they would burn the skin. One young prisoner was repeatedly cooled to unconsciousness then revived with lamps until he was pouring sweat. He died one evening after several test sessions.

Internal Irrigation

The frozen prisoner would have water heated to a near blistering temperature forcefully irrigated into the stomach, bladder, and intestines. All prisoners appeared to have died from the treatment.

Hot Bath

The prisoner was placed in warm water and the temperature was slowly increased. This method proved to be the best. Many prisoners died due to shock if they were warmed up too quickly.

Modified from http://nazi_medical.tripod.com/experiments.html

Syphilis in African American Men

In 1932, six hundred poor African American farmers and sharecroppers were subjects in a study run by the federal government to watch what happens when syphilis is left untreated. At the time, there was no reliable cure for syphilis. When a safe and effective treatment for syphilis—the antibiotic penicillin—became widely available in the early 1940s, the study continued and the men were actively prevented from receiving treatment for the disease.

In the study, 399 men with syphilis were followed along with 201 men of the same age who did not have syphilis. The standard treatment for syphilis in the early 1930s was 25-30 applications of mercury. The Alabama Health Officer agreed to the study under the condition that the men receive some treatment. Initially the researchers gave the men treatment. However, money ran out for the treatments, and the researchers decided to continue on with the study anyway. They hoped that funding would be restored for treatment, but felt that there was still value in a ‘natural history’ study that could potentially show the disease was the same in African Americans and Caucasians. The amount of treatment was clearly inadequate according to the standards of the day, but the researchers felt justified in leaving the men untreated. The researchers wanted to observe how the disease progressed in untreated individuals and compare it to an earlier study of Norwegian men who had not received treatment (because the Norwegian study occurred before 1910, only very toxic treatments were available to those patients at that time).

The researchers used the general term ‘bad blood’ when describing the patients’ condition. None of the subjects knew that their ‘bad blood’ was actually syphilis. The men received painful spinal taps, which they believed were treatments because they received a letter from the government saying that they should come receive this ‘special treatment’. The incentives for submitting to the taps and other evaluations were warm meals, a free burial, and free medical care for other diseases, as long as the treatment was not penicillin. The researchers worked with the local draft board to prevent the subjects of the study from being drafted for World War II. Had they entered the army, the men would have been tested for syphilis and given penicillin if they had the disease.

Over the years, more than a dozen articles about the study were published in medical journals. The study did not end until 1972 after the story was brought to public attention by a researcher from the Center for Disease Control shared his concern with a news reporter. During those forty years, over 100 men died. The survivors filed a suit against the US government in 1973, eventually settling out of court for \$37,500 each and a life time of medical care.

Modified from Kennedy Institute of Ethics

http://www.georgetown.edu/research/nrcbl/hsbioethics/alumni/unit3_i.htm.

AZT and Pregnant women in Developing Countries

Newborns whose mothers are infected with HIV can acquire the infection from their mothers at the moment of birth. In some developing countries with HIV/AIDS epidemics, more than 30% of pregnant women who are examined at prenatal clinics are infected with the AIDS virus.

Clinical trials in 1994 showed that, if a pregnant woman took the drug AZT in pills during the last 12 weeks of pregnancy and as an injection during labor and if the baby received AZT during the first six weeks of life, the baby had a much-reduced chance of becoming infected with the virus. Since that time, in the United States, pregnant women infected with HIV are advised to use this “076 regimen” of AZT.

In 1997, researchers gave a placebo, rather than AZT, as a control to pregnant women in a developing country who were infected with HIV and were participating in clinical trials. The “standard” treatments for AIDS for these women were no treatments at all. (The 076 regimen, for example, was simply too expensive for women and governments in poor countries, costing between \$800-\$1000 per person.) The researchers were evaluating lower and fewer doses of AZT in the studies to see if low doses might be effective. Such doses might be affordable and accessible for poor women around the world.

Women involved in the study did not know whether they received the 076 regimen or the placebo. In addition, women were not told what dose- the lower experimental dose- or the standard amount of AZT they would receive during the trial.

Modified from Kennedy Institute of Ethics

http://www.georgetown.edu/research/nrcbl/hsbioethics/alumni/unit3_i.htm

Behavior in Young Boys

One hundred boys in New York, ranging in age from six to ten, participated in three research projects to find out whether the levels of the brain chemical serotonin could be correlated with aggressive behavior.

The boys were chosen for the study not because they had shown aggressive behavior but because their brothers had. Each boy had an older brother who was in jail or a mother who was considered by the researchers to be doing a poor job rearing her sons. All came from poor families; 44% were African American, 56% were Hispanic, and none were white.

The studies took place at a New York State Psychiatric Institute between 1993 and 1996. Each boy received a single dose of the drug fenfluramine, which increases serotonin levels. The drug is one component of fen-phen, which was recalled as a diet pill in 1997, because it seemed to cause heart valve defects. Experts on the use of fenfluramine consider it unlikely that the boys in the experiments suffered any harm from the drug, as they were given only a single small dose. Those with heart damage used the drug in larger doses over a period of months. However the drug has side effects such as nausea, headache, dizziness, anxiety, and irritability.

Each boy had to stay in the hospital bed for 5 hours, during which time numerous blood samples were taken. He could not eat for 17 hours. At the end of the study, each family received a gift certificate for \$125 to spend at a local toy store.

Modified from Kennedy Institute of Ethics

http://www.georgetown.edu/research/nrcbl/hsbioethics/alumni/unit3_i.htm

**Historical Case Studies for Human Research –
Guiding Questions**

As a group, discuss the answers to the questions below as they relate to your case study. One person in your group should record your answers to be shared with the class.

1. What possible benefits came from the study?

2. What possible harms came from the study?

3. Were the human participants able to consent to their involvement in the study?
If so, what factors would influence their participation?

4. How were the subjects for the study chosen? Do you think they were chosen fairly?

5. What are the differences between participating in a study giving a treatment and participating in a study where a treatment is withheld?

6. How should rules related to human participants research be enforced?

7. Was the treatment of humans in this case ethical? Explain your answer.

Student Handout Activity 4.4

NAME _____ Date _____ Period _____

Basic Principles for using humans in research

Basic Principle	Respect for Persons	Beneficence	Justice
Description	Respect the autonomy of individuals; obtain informed consent	Minimize all potential harm(s) and maximize potential benefit(s) to the subject as well as potential benefit to society	Be fair in the distribution of the benefits and in bearing the burden of research
Applications	<ul style="list-style-type: none"> -Acknowledge a person's right to make choices, to hold views, and to take actions based on personal values and beliefs. -Identify prospective subjects without violating their right to privacy. -Utilize a continuous, on-going consent process in consideration of the nature and duration of the research. -Obtain informed consent from subjects using the "reasonable volunteer standard" in an environment conducive to rational decision making. -Ensure the subject understands <u>all</u> the elements of consent necessary to make an informed decision. -Involve the subject's relatives and counselors in the consent process, with the subject's permission. -Minimize any risk that the subject may develop a therapeutic misconception about the research. -Obtain assent to the degree possible from persons with diminished autonomy and developing autonomy. -Honor a cognitively impaired person's dissent to participate in research, except under compelling clinical circumstances. -Honor a child's dissent to participate in research, except under compelling clinical circumstances in consideration of the age and cognitive ability of the child. -Treat subject with dignity and respect. 	<ul style="list-style-type: none"> -Minimize all potential harm(s) to the greatest extent possible -Maximize the potential benefit(s) of the research by ensuring there is a sound research design, protocol compliance, and timely publication of results. -Ensure that the risk(s) of the research are outweighed, or balanced, by potential benefit(s) to the subjects and/or to society. -Ensure there is a favorable risk(s)/benefit(s) relationship of the research compared with the available alternative(s) which offer the subject the prospect of direct benefit(s). -Ensure that the rights and welfare of the subject always take precedence over the needs of science 	<ul style="list-style-type: none"> -Don't target, or exclude, a subject population based upon convenience or availability. -Don't use vulnerable subjects in research without direct benefit before using less vulnerable subjects. -Guard against positional influence (e.g., physician and patient) during recruitment. -Avoid potential or real financial and other conflicts of interest (e.g. finder's fees, recruitment bonuses, gifts from sponsors)

Student Handout Activity 4.6

NAME _____ Date _____ Period _____

HIPPOCRATES (460 BC)

PERCIVAL (1803)

BEAUMONT (1785-1853)

BERNARD (1813-1878)

HISTORICAL OVERVIEW OF GUIDELINES FOR USING HUMANS IN RESEARCH

REICH CIRCULAR (1931)

- The investigator is responsible for the life and health of the human subject.
- Experimentation is prohibited without consent from the human subject.
- Animal studies should be conducted prior to human studies.
- Human experimentation should be avoided if replacement is possible by use of animals.
- Experiments involving children are prohibited if they are endangered.
- Experiments involving dying subjects are prohibited.
- Academic training courses should stress the physician's responsibilities during experimentation.

THE NUREMBURG CODE (1947)

- Voluntary consent
- Yield fruitful results otherwise unobtainable
- Human Trials should be based on successful animal experiments
- Avoid physical and mental suffering
- Not done if injury expected
- Risk less than importance of problem
- Conducted by qualified people
- Participation can be terminated by the subject at any time
- An investigator may find reasons to also terminate the participation of a subject

DECLARATION OF HELSINKI (1964; REVISED 1975, 1983, 1989, 1996, 2000)

Basic Principles

- Human research should be based on animal experiments
- Studies should be conducted by qualified persons
- Importance of research proportionate to risk
- Risks and benefits should be assessed beforehand
- Effects of drugs on personality considered

Notable revisions of the Basic Principles of Helsinki

- 1975 Independent Committee Review; informed consent emphasized
- 1983 Obtainment of a minor's "consent" when possible
- 1989 Independent Committee Review clarified; statement of compliance with Helsinki
- 2000 32 Basic Principles; Research with cognitively impaired expanded;
- Best proven therapy criteria

THE BELMONT REPORT (1978)

Basic principles

1. **Respect for persons:** Respect the autonomy of individuals by obtaining their informed consent or, in the case of persons with diminished or developing autonomy, obtain proxy consent from their legally authorized representative.
2. **Beneficence:** Minimize all risks (i.e., potential harms) and maximize potential benefit(s) to the subject which are associated with research participation as well as potential benefit to society.
3. **Justice:** fairness in distribution of the benefits and in bearing the burden of research.

the New York Times

Urgency Tempers Ethics Concerns in Uganda Trial of AIDS Vaccine

October 1, 1998 by Michael Specter

KAMPALA, Uganda—Raphael Nawiro got up extra early one steamy morning this summer. He walked a mile from his home, then took two long bus rides until he reached Uganda's principal medical complex, the aging, overburdened Old Mulago Hospital.

He went directly to the office of Dr. Roy Mugerwa, who will run an AIDS vaccine trial that is about to begin here.

"I want to enroll in the study," he told the secretary, eager to take part in a promising and ethically contentious experiment. "I want to help find a cure for what's killing us all."

The secretary nodded gravely and told him where to go to fill out forms. "I can't promise a thing," she said.

Nawiro, a schoolteacher, is under no illusions that the test of any vaccine will prevent him from becoming infected with HIV, the virus that causes AIDS. But at the age of 32 he has lost five members of his family to this plague, and he is weary of the endless death that has come to rule his country.

"It's time to do something serious about this disease," he said quietly as he rushed off to work. "Isn't a vaccine really the only hope we have?"

On this continent the answer to that dark question is a ringing, undeniable yes. People infected with HIV in rich countries now have access to drug combinations that extend their lives. But in Africa, where AIDS threatens to destroy an entire generation, there is no such reason for optimism. And unless somebody comes up with a vaccine, that is unlikely to change before millions more die.

In the past, ethical guidelines have made clear that vaccines should be tested in developed countries—where health care is excellent—before they are used in places without a safety net, like Uganda. With AIDS, for the first time, the international medical community has done away with that necessity.

"It has to be this way," said Mugerwa, medical professor at Makerere University who is the principal investigator for the vaccine trial scheduled to begin in October.

"Nobody is going to do it first anywhere else," he said, "and I don't blame them. We are the people with the problem. Why should Americans undertake risky research on themselves for a problem they don't really have? That would make them the guinea pigs. The risk belongs here, where the people are dying."

In Uganda, a country struggling valiantly to cope with an epidemic that has infected 20 percent of its population, the questions surrounding the trial have become deafening.

Who will take part in the first round, and what will happen if people become infected and sick after they have volunteered, given that Uganda spends about \$6 per person annually on health care? Will they receive the best medical care that money can buy, as they would in America or France, two other countries that are testing AIDS vaccines? If they do, who will pay? If not, will they be treated like any other Africans—given aspirin, good wishes and no hope?

What if, as is often the case with vaccines, this trial shows that it may not prevent an AIDS infection but it may make the disease less deadly? Should the test be stopped immediately so that the vaccine can be given to people right away, before scientists can find out the answers to how good the vaccine might ultimately be or how best to use it? Or should the test go on, with some people receiving a useless placebo, so that researchers can learn the full potential of any possible vaccine?

And, although most scientific experts say there will be no useful AIDS vaccine for at least a decade, what will happen if that vaccine is eventually produced thanks to the help of the eager, fragile and desperate people of Uganda?

What guarantee will there be, after helping to solve one of modern medicine's most frightening and complex problems, that any proven AIDS vaccine would be available here or in similar countries, where most basic medicines are too expensive to buy?

Drug companies will want to recoup their enormous investments, and that means selling a vaccine to people who can pay for it. Few effective vaccines, even the one for hepatitis B, which was developed only after long testing in Senegal, have been made routinely available in Africa.

They just cost too much.

“Everybody is worried that we will use Africa, develop a vaccine there, say thanks and then take it back to Europe and America,” said Dr. Peter Piot, the executive director of the United Nations AIDS

Program, who has worked to focus more attention on the scope of the epidemic in the developing world. “I don’t believe that will happen. But we are in a terrible position. The process is perilous. It is unfair. And it is filled with inequities—because the world is filled with inequities.

“What is our choice? In Africa they need a vaccine. Should we just tell them we have too many ethical problems to help them find one?”

A walk across the campus of the Old Mulago, this giant hospital complex that has served as ground zero in Africa’s gruesome fight with AIDS, answers that question in about five minutes.

There are no waiting rooms, but every landing on every floor overflows with sick people. Mothers in bright cotton robes sit quietly nursing their infants; old men wheeze in the stairwell. Hundreds of men and women sit in eerie silence, coughing and waiting for a number to be called. Some wait for days, sleeping when they can, eating if there is food. There is probably no hospital on earth—and possibly no country—more besieged by the AIDS epidemic. Every pair of eyes seems to spell the word despair.

So despite a rancorous debate in the West, where critics say Africans will be misused in any test here because the highest standards of care and of informed consent are impossible to attain, Uganda is about to begin its trial. And it is hard to find anybody in this country who thinks that’s a bad idea.

Forty healthy volunteers will be selected. Half will receive a placebo that would have no effect on an HIV infection. The other half will receive a vaccine into which some genes responsible for producing important HIV proteins, some building blocks of the virus, have been inserted. There will be no actual virus in the vaccine. It is an initial test and its purpose is to see whether it is safe and whether it has any effect.

If the vaccine stimulates the body’s defenses—and the placebo does not—that will mean that the vaccine should undergo further tests on a larger group of people.

There are different strains of HIV, known as clades, and the predominant strains from Africa are different from those usually seen in the West. Still, one of the critical questions about any vaccine is how widely it can be used, and the hope is that at least the basic building blocks of any vaccine that work on one strain would also work on the others.

Because the vaccine may reduce the amount of HIV in people who have already become infected, it cannot really be tested broadly in the United States. Americans who are diagnosed with HIV now immediately start a drug treatment regimen aimed at cutting down the amount of the virus in their bloodstream.

Anything less would be considered unethical. But if people in a vaccine trial are also on these new drugs, researchers would have no way to judge whether a vaccine is reducing the virus, or whether the medicine was doing it.

Since people in Uganda cannot hope to afford such drug treatment, which can cost more than \$15,000 a year, they are perfect subjects for such a vaccine test.

“The question arises are we basically exporting our risky scientific research, from which we would benefit, to the third world?” said Thomas M. Murray, director of Case Western Reserve University’s Center for Biomedical Ethics, speaking at a forum on the vaccine trials this year. Case Western, which for years has had a relationship with Makerere University Medical School, is one of the vaccine trial sponsors.

“This is a far more morally complicated issue than critics of the research have ever made it out to be,” Murray said.

That’s because it has become clear to many people that there are practical and cultural barriers to applying the same standards of ethics in America and Africa. In the United States, for example, informed consent is required for people who take part in drug tests. They need to know what the test will do, what the risks are and what the rewards are. In Africa, such consent is often given by husbands or doctors or tribal leaders and many health officials say the country simply doesn’t have enough trained doctors to inform everyone about complicated programs like the AIDS vaccine trials. Informing a representative of a village would never be considered

enough in America, but in Uganda who should decide what is enough?

Most experts, in Africa and in the West, say that every participant always deserves to understand the risks and possibilities of trials. And most specialists believe that informed consent is not only possible in Africa, but essential if trials are to work. Still, there is simply not enough time or money in most cases to make certain that each potential risk or reward is understood.

“Things seem so simple in a rich country,” said Dr. Peter Mugenyi, the director of Uganda’s Joint Clinical Research Center, which will administer the AIDS vaccine trials here in conjunction with a consortium of groups that include the National Institutes of Health and Pasteur-Merieux, the French company that has developed the vaccine and will provide it for the study.

“They sometimes talk about this in America like it’s the Tuskegee experiment and we are simple, ignorant dupes,” he said. In the Tuskegee experiment, one of medicine’s most notorious abuses of research subjects, poor black men in Alabama were denied affordable, effective and widely available treatment for syphilis. They were not informed of their rights in the research or told what was happening to them. And they were allowed to get sick when penicillin could have cured them all.

“It’s terribly insulting to us and to the Western agencies and individuals who have worked with us,” said Mugenyi, who presides over a state-of-the-art research center staffed with highly trained scientists from Uganda, Europe and America. “Sure there are some questions that are hard to address, like how will these people be cared for if they become sick. But let’s also look at the world and tell the truth. In the history of medicine the only things that have really worked to stop diseases in the third world have been vaccines. Drugs won’t work for us. Prevention has obviously failed.

“Education is almost impossible. Without a vaccine we are going to keep on losing and we are going to lose a lot.”

More than a million people in Uganda have already died of AIDS. The country’s leadership is easily the most open in Africa about the issue—the

president and other leaders mention the disease in nearly every speech. It is only rare families where at least one member has not fallen ill.

Mugerwa and his colleagues are aware that in the past, when vaccines have been developed in Africa, they disappear as soon as they become worth money. That is why Uganda decided to be in on every level of testing.

“We are participating in the trials,” he said, “not just with our citizens, but with our brains. We have demanded a role in the research and we have sent our best people abroad to help develop the drugs. When this vaccine becomes effective—in a year or 10 years or two generations—we want to be able to say that we have a central interest in this product and you owe us for it.”

That will help but it won’t solve the problem. Representatives from Pasteur-Merieux have said that it is now impossible to guess how much a vaccine would cost since it does not yet exist. They have also said, repeatedly, that foundations, international relief agencies, pharmaceutical companies and governments will all have to band together to come up with enough money to buy vaccines for poor countries. The message is clear: First let’s get a vaccine, then we will figure out how to get it to you.

“If you are a student of history, it’s not all that comforting to see how Africa has been treated in the past,” said Dr. Edward Mbiddle, chief of Makerere University’s Cancer Institute. “But you know what? If we are going to have a future, we can’t afford to live in history.”

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Student Handout Activity 4.8

NAME _____ Date _____ Period _____

What is this article about?

This article raises a number of ethical issues surrounding AIDS vaccines trials. Provide some examples related to the following ethical principles:

Respect for Persons

Beneficence (“doing good”)

Justice

KEY Activity 4.8

What is this article about?

A 1998 HIV vaccine trial in Uganda and the ethical issues surrounding it.

This article raises a number of ethical issues surrounding AIDS vaccines trials. Provide some examples related to the following ethical principles:

Respect for Persons

Informed consent issues – consent is given by husbands, doctors, or tribal leaders. Often there are not enough doctors to fully inform everyone about complex vaccine trials. Is it acceptable to have a village representative give consent for individuals? How can we be sure that risks and rewards have been understood?

Beneficence (“doing good”)

The Africans mentioned in the story are actively interested in participating in an HIV vaccine trial, in order to help find cures for “what’s killing us all”. The benefits (a vaccine that could help millions of Africans) could be very large. This benefit, Dr. Piot argues, leads us to action, rather than lamenting that we have ‘too many ethical problems to help’.

Justice

Justice demands that there be an equitable distribution of burdens and benefits. Will the Africans share in the benefits of a vaccine or will it be too costly? Are they assuming too much risk? The researchers note that the “risk belongs...where the people are dying.”

How will individuals who become infected after volunteering (not because of the vaccine, but because the vaccine is ineffective) be treated? Will they be treated as Americans would, with costly medical care, or by the standards of their country, where \$6/day is spent on health care?