Chapter 9

Ethics of Clinical Research

The practice of medicine cannot improve in the absence of medical research. Advancing clinical medicine requires controlled experiments to compare the performance of a new intervention to the current standard of care. In many cases, initial experiments can be carried out in the laboratory using cell cultures or animal models, but eventually new techniques must be tested in humans to ensure that they are safe and effective. Unfortunately as we will see, people have not always treated each other humanely in the pursuit of medical research. How do we ensure that medical research involving human subjects is carried out in a fair and ethical manner? In Chapter 9, we will examine the ethical principles that guide research involving human subjects, and how we ensure that researchers adhere to these principles.

For centuries, the actions of physicians have been guided by the Hippocratic principle of "first do no harm". This principle guides clinical practice to improve an individual patient's health. Often the goal of medical research is to improve the health of future patients, and a subject participating in a research project may receive absolutely no benefit. In fact, participating in a research study may involve risks not fully understood at the beginning of a study. In the 1800s, scientists began to formally articulate ethical principles to guide medical research. In his 1865 book, Introduction to the Study of Experimental Medicine, Claude Bernard stated that one could never perform an experiment on man "which might be harmful to him in any extent, even though the result might be highly advantageous to science."

For many years, ensuring that scientists and physicians adhered to these ethical principles was largely left to the discretion of individual researchers, not always with success. **Table 9.1** chronicles some historical examples of ethically questionable research involving human subjects .

Year	Example
1796	Edward Jenner injects healthy 8 year old James Phipps with cowpox, then six weeks later with smallpox. Ultimately Jenner's experiments gave rise to the first smallpox vaccine.[2]
1845-1849	J. Marion Sims performs experimental surgeries on enslaved African women in an attempt to repair vesicovaginal fistulas - a severe complication of prolonged childbirth. While historical record suggests that the women voluntarily participated, Sims has been criticized for experimenting on a vulnerable population.[3]
1896	Dr. Arthur Wentworth performs spinal taps on 29 infants and children at Children's Hospital in Boston to determine if the procedure is harmful. Upon reporting results, Wentworth is criticized by peers for failing to obtain parental consent and for performing non-therapeutic procedures.[4]
1897	Italian bacteriologist Giuseppe Sanarelli injects 5 subjects with what he believes to be a filtered, inactivated solution of the yellow fever bacillus, producing yellow fever like symptoms in several of the patients.[5] The experiment was carried out without the subjects' permission or consent.[6] Walter Reed and James Carroll later disprove Sanarelli, demonstrating that the injected bacillus was actually a member of the hog cholera family.[7]
1906	Richard Strong, head of the Philippine Biological Laboratory innoculates 24 inmates of a Manila prison with a cholera vaccine that is contaminated with plague. 13 of the inmates die.[8] It is unclear whether or not contamination was accidental.[9]
1939~1945	Dr. Shiro Ishii, a physician and officer in the Japanese army, directs programs throughout China dedicated to biological warfare research, including the infamous Unit 731. Prisoners of Chinese and Russian nationality were innoculated with a variety of diseases including plague, typhoid, cholera, smallpox, and hemorrhagic fever. Additional experiments were carried out on local populations by contaminating wells and food sources. Precise estimates of casualties are not possible, but number likely in the thousands. [10]
1941-1945	Nazi physicians conduct sterilization experiments on prisoners at Auschwitz and Ravensbrueck concentration camps in an effort to identify a means of carrying out mass sterilization campaigns.[11]
1941-1945	Nazi physicians conduct typhus experiments on prisoners of Buchenwald and Natzweiler concentration camps. Prisoners were given experimental vaccines and chemical substances and infected with typhus leading to hundreds of deaths.[11]
1942-1943	Nazi physicians conduct hypothermia experiments on approximately 300 male prisoners in Dachau concentration camp by immersing the prisoners in tanks of ice water. [12]
1942-1945	U.S. Chemical warfare service conducts mustard gas experiments on approximately 4000 servicemen. Soldiers were placed in gas chambers and field testing situations in order to test experimental protective clothing and collect data on exposure levels that produce injury.[10]
1944-1946	400 prisoners in the Illinois Statesville Penitentiary volunteer to participate in Malaria experiments headed by Dr. Alf Alving through the University of Chicago Medical School. At the conclusion of the two year program a considerable portion of the prisoners received parole in return for their participation.[9]
1950-1953	The U.S. Atomic Energy Commission and Quaker Oats Company sponsor researchers at Harvard and MIT to conduct a study of nutrient absorption at the Fernald School- a residential institution for mentally disabled children. Children were fed cereals containing radioactive tracers and received calcium tracer injections. Parents, while told of a study, were not informed of the details. [10]
1994-1996	In a series of studies, 100 young, predominantly minority boys with a personal or family history of aggression are administered fenfluramine in an effort to test whether aggression can be predicted by chemical changes in the brain. Fenfluramine has since been taken off the market due to evidence that long term use may give rise to heart valve defects in adults.[13][14]

Table 9.1: Historical examples of ethically questionable research [2-14].

The atrocities committed by the Nazis and by Japanese forces in World War II in the name of medical research shocked the world, and led to a new era in the regulation of medical research.[15] As a result, several codes governing the ethical conduct of research have been developed to provide guidelines for patients, practitioners and scientists. Later in Chapter 9, we will examine the ethical principles laid out in the Nuremberg Code of 1949, The Helsinki Declaration of 1964, and the Belmont Report of 1979. But we begin Chapter 9 by examining several case studies of research carried out in the United Sates which further motivated the development of these codes of conduct.

Tuskegee Syphilis Study: The Tuskegee Syphilis Study was begun in 1932 in Macon County, Alabama. The goal of this study was to examine the natural history of untreated syphilis. At the time the study began, the standard medical therapy for syphilis was to give patients heavy metals, like bismuth and arsenic. The cure rate for this treatment was less than 30%, and the side effects were sometimes fatal.[16] While this treatment did appear to reduce mortality, it was unclear whether some of the complications of syphilis were associated with the disease itself or were side effects associated with the heavy metals.[17] Because these side effects were so debilitating, the investigators felt that the treatment was potentially as toxic as the disease. In an attempt to separate the side effects of treatment from the natural progression of disease, researchers recruited a group of 600 low-income black men, 399 with syphilis and 201 without syphilis.[16] The researchers withheld treatment from the group with disease; they felt they could justify withholding treatment because the side effects of the treatment were potentially as serious as the symptoms of syphilis. However, the participants did not voluntarily consent to participate in a research study. In fact, they were lured to participate in the study when researchers offered free treatment for 'bad blood' - a generic term then used to describe a range of symptoms. The men were misinformed that some study procedures, like spinal taps, were free 'extra treatment' (**Figure 9.1**).[17]

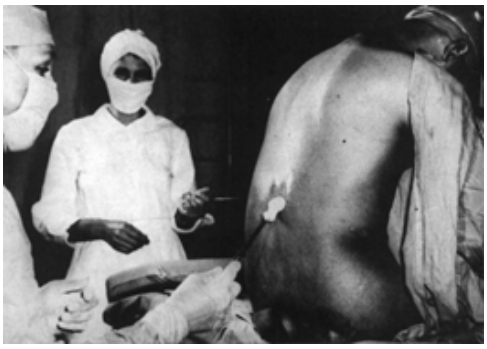

Figure 9.1: A subject in the Tuskegee syphilis study undergoes a lumbar spinal tap.
http://poynter.indiana.edu/sas/lb/Images/image016.jpg

Ten years after the study began, the investigators noted that the death rate of non-treated patients was twice as high as for treated patients, yet treatment was still withheld. In the 1940's even when penicillin became the clear drug of choice to treat syphilis, the study was still not interrupted and the men were not informed that penicillin was available. The study continued until 1972, when a researcher voiced concern to a reporter and the study was widely reported in the media.[17] As a result of the publicity, the study ended in 1972, and participants were offered monetary reparations. In 1973, Congressional investi-

gations into the study commenced, and the NAACP won a $9 million settlement on behalf of the participants.[18] On May 16, 1997, US President Bill Clinton apologized to the surviving participants of the Tuskegee Syphilis Study.[19]

Willowbrook School Study: Another ethically questionable study was the Willowbrook study, which was carried out from 1963 to 1966 and sought to examine the natural history of infectious hepatitis A. The study subjects were children at the Willowbrook State School, an institution for "mentally defective persons". Subjects in the study were deliberately infected with hepatitis A by feeding them stool from infected persons. Later in the study, as the virus became better defined, subjects were injected with the virus. The investigators justified their actions because the vast majority of children admitted to the Willowbrook State School acquired hepatitis anyway. Parents of children participating in the study gave consent for their children to participate. However, during the time of this study the Willowbrook State School was at times closed to new patients due to crowding. Because the hepatitis project had its own space, in some cases the only way to gain admission to the school was to agree to participate in the study.[17]

Jewish Chronic Disease Hospital Study: In 1963, in the Jewish Chronic Disease Hospital Study live cancer cells were injected into debilitated patients in a hospital for the elderly. The purpose of the study was to develop information about the transplant rejection process and to study rejection of cancer cells. Patients hospitalized with various chronic debilitating diseases were injected with live cancer cells. Consent to participate in the study was negotiated orally, but not documented. Patients were not told that cancer cells would be injected because researchers felt that this might scare them unnecessarily. The investigators justified this because they were reasonably certain the cancer cells would be rejected. Researchers knew that healthy patients reject cancer cell implants quickly, while cancer patients reject the same cancer cell implants much more slowly. They wanted to understand whether this was due to impaired immunity because of the cancer or a more general manifestation of debility in cancer patients.[17]

San Antonio Contraceptive Study: The goal of the San Antonio Contraceptive Study was to understand which side effects of oral contraceptive pills (OCPs) are due to the drug and which are simply by-products of everyday life. The study, carried out in the 1970s, was a randomized trial comparing a placebo and OCPs. Study subjects were 76 impov-

erished Mexican-American women with previous multiple pregnancies who had come to a public clinic seeking contraceptive assistance. The experiment was designed as a randomized, double-blind, placebo controlled trial – meaning that a fraction of the participants received placebo while the remainder received OCPs. The study utilized a cross-over design – during the middle of the trial, the placebo group was given OCPs and the OCP group was given placebo. All women were instructed to use vaginal cream as contraceptive during the study, but none of the women were told that the study involved a placebo. During the study, 11 women became pregnant, 10 while using placebo.[17]

Codes of Conduct for Human Subjects Research:

As a result of these and other examples, scientists and policy makers have developed codes to govern research involving human subjects. As a result of atrocities discovered in German concentration camps, The Nuremberg Code was adopted in 1949. The Nuremberg Code states that in research, voluntary consent of the human subject is absolutely essential, and the subject should be at liberty to end the experiment at any time. All research involving human subjects should yield fruitful results for the good of society, which are obtainable in no other way. Experiments involving human subjects should avoid all unnecessary mental and physical suffering, and no experiment should be performed if it is believed that death or disabling injury may occur. The degree of risk to human subjects should never exceed the humanitarian importance of problem to be solved. Finally, research involving human subjects should be conducted only by scientifically qualified persons.[11]

In an international move to establish common ethical principles to guide medical research, the World Medical Association worked to develop and adopt the Declaration of Helsinki in 1964. The primary principle established in this document is to place the interests of the individual patient before those of society, stating that the primary goal of a physician is to "protect the life, health, privacy and dignity of the human subject."[20] The Helsinki Declaration affirms many of the principles of the Nuremberg code: that research subjects must be informed of the risks of a study and must voluntarily consent to participate, even if they are minors; and that studies should be designed and conducted by scientifically qualified personnel; and that risks of a study should not outweigh possible benefits. The Helsinki Declaration calls for formal review of research protocols by independent committees.

Despite these guidelines, abuses continued. Largely as a result of publicity associated with the Tuskegee trials, the US Dept. of Health, Education and Welfare issued the Belmont Report (**Figure 9.2**), a statement of basic ethical principles and guidelines to resolve ethical problems associated with conduct of research with human subjects, in 1979.[21] The Belmont Report drew distinctions between clinical practice and research. Clinical practice includes interventions designed solely to enhance well-being of an individual patient that have a reasonable expectation of success. In contrast, research involves an activity to test a hypothesis that will permit conclusions to be drawn, and will contribute to generalizable knowledge. Research should be described in a formal protocol that sets forth an objective and procedures to reach that objective.

The Belmont Report established three basic ethical principles which must be followed in all research involving human subjects [21]:

Respect for persons: Respect for persons demands that subjects enter into research voluntarily with enough information to make a decision about whether to participate. Further, persons with diminished autonomy (e.g. prisoners, children) are entitled to special protection.

Beneficence: Beneficence requires that researchers design experiments which do not harm study participants. Experiments which will injure one person are not allowed regardless of benefits that may come to others. Instead, researchers must make every effort to secure the well-being of study participants, by maximizing all possible benefits and minimizing all possible harms.

Justice: This principle addresses who should receive benefits of research and who should bear its burdens. Justice requires that all individuals should be treated as autonomous agents, and that the selection of research subjects must be scrutinized to determine whether some participants are being selected because of easy availability, compromised position or manipulability.

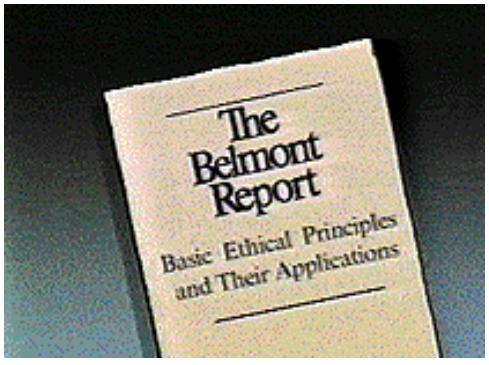

Figure 9.2: The Belmont Report, published in 1979, is a statement of basic ethical principles that must be followed in research on human subjects.

The Belmont Report provided guidelines for researchers to follow in order to ensure that these three principles were applied. First, researchers must obtain voluntary informed consent from all study participants. In order for a participant to give informed consent, they must fully understand the research procedure, the purpose of study, the potential risks and anticipated benefits, any alternative procedures that are available to them and they must be told that they may with-

draw from the study at any time. Researchers must present this information in a way the subject can understand. It cannot be disorganized, presented too rapidly, or be above the subject's educational level. This consent must be given voluntarily, and persons in positions of authority cannot urge a particular course of action.[21]

Secondly, research must be justified based on a favorable risk/benefit ratio for the participants, and researchers must select subjects fairly. Here, risk is defined as the possibility that harm may occur and benefit is defined as a positive outcome related to the health or welfare of a participant. Brutal or inhumane treatment of subjects is never morally justified. Instead, studies should be designed to reduce risks to only those necessary to achieve the research objective. Researchers must also select subjects fairly. They must not select only "undesirable" persons for risky research. Distinctions should be drawn between classes that ought and ought not to participate in research based on ability of that class to bear burdens. For example, adults should be asked to bear burdens of research before children, when possible. Methods used to avoid exploiting vulnerable patients include: choosing subjects who are not vulnerable, distributing benefits so that those who participate benefit, getting community consultation to hear many points of view from those being studied, and using lottery systems when there are insufficient pools of new therapy.[21]

Reexamining the Tuskegee study in light of the principles of the three principles of the Belmont Report illustrates its many ethical failures. Participants did not give consent to participate, and they were not informed of the study. Risks to participants were not minimized; indeed, participation increased risks. Participants were limited to disadvantaged, rural black men, but the disease under study is not confined to this population. A much broader population benefited from the findings of the research.

How do institutions work to ensure that studies conform to these guidelines? Today, US institutions carrying out research involving human subjects have a special, independent committee called the Institutional Review Board (IRB). The role of the IRB is to work with investigators to be sure that the rights of subjects are protected, to educate the research community and public about ethical conduct of research, and to be a resource center for information about Federal guidelines. Research involving human subjects cannot begin until the IRB has approved the research protocol and the informed consent document, a written document

A Summary of the History of Regulations

5th Century B.C.: Hippocratic Oath
The medical ethics standard "first do no harm" is attributed to Hippocrates. The oath became obligatory for physicians prior to practicing medicine in the 4th century AD.[18]

1949: Nuremberg Code
Nazi physicians were charged with war crimes for research atrocities performed on prisoners of war. An American military war crimes tribunal conducted the proceedings against 23 Nazi physicians and administrators who willingly participated in war crimes. The judgment, known as the Nuremberg Code, was the first internationally recognized code of research ethics. It set forth 10 standards for human subject research [11]:

Volunteers must freely consent to participate in research
Researchers must fully inform volunteers concerning the study
Risks associated with the study must be reduced where possible
Researchers are responsible for protecting participants against harms
Participants can withdraw form the study at any time
Research must be carried out by qualified researchers
If adverse effects emerge, research must be stopped
Society should benefit from study findings
Research on humans should be based on previous animal or other work
No research study should begin if there is a reason to believe that death or injury may result

1964: Helsinki Declaration
The 18th World Medical Assembly met in Helsinki Finland and issued recommendations to guide biomedical research involving human subjects. The primary principle of the Declaration of Helsinki was to place individual patient interests before those of society. The basic principles of the Declaration of Helsinki are [16]:

The physician's duty is to protect the life, health, privacy and dignity of the human subject
Research involving humans must conform to scientific principles and methods
Research protocols should be reviewed by an independent committee
Research protocols should be carried out by scientifically and medially qualified individuals
The risks and burden to human subjects should not outweigh the benefits
Research should be stopped if risks are found to outweigh potential benefits
Research is justified only if there is a reasonable likelihood that the population under study will benefit from the results
Participants must be volunteers and informed about the research study
Every precaution must be taken to respect privacy, confidentiality, and participants integrity
Consent must be obtained from minors if they are able to do so
Investigators are obliged to preserver the accuracy of results; negative and positive results should be publicly available

1979: Belmont Report
National Commission for the Protection of Hunan Subjects of Biomedical and Behavioral Research published the Belmont Report which set forth three basic ethical principles to guide research involving human subjects [17]:

Respect for persons: Participants must give voluntary consent; participants with diminished autonomy (e.g. children, prisoners) are entitled to special protection
Beneficence: Research must maximize possible benefits and minimize possible harms
Justice: The benefits and risks of research must be distributed fairly

Sources: [11,20-22]

that subjects sign indicating their willingness to participate. An IRB approved research protocol and informed consent document can be found in the appendix to this chapter. The research protocol is written for review by the physicians and scientists who are members of the IRB, while the informed consent document is written for potential participants.

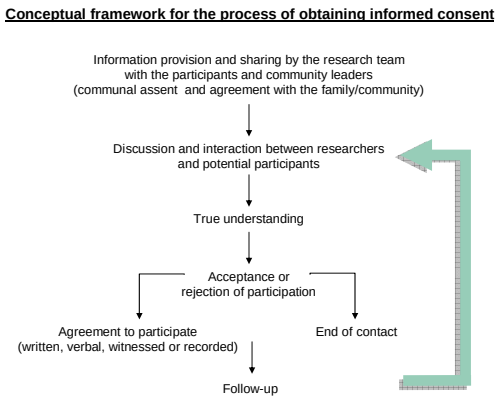

Figure 9.3: The steps involved in obtaining informed consent. Used with permission from [15].

Informed consent is a critically important part of research. The Nuremberg Code speaks to the voluntary consent of human subjects being essential: "This means the person involved should have 'legal capacity' to give consent; should be situated to exercise 'free power of choice', without the intervention of any element of force, fraud, deceit, duress, over-reaching or other ulterior motives; over-reaching or other ulterior form of constraint or coercion, and should have sufficient 'knowledge', and 'comprehension' of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision."[11] Therefore, for informed consent to be valid: the subject must be competent, the consent voluntary, their participation informed, and their understanding complete.

Figure 9.3 provides an overview of the process of obtaining informed consent. The research team must provide full and understandable information about the proposed research. The participant must understand what is being asked of him or her and must freely agree to participate. Comprehension is a key element in the informed consent process; the investigator must ensure that the subject understands both the risks and benefits involved in participation. Technical procedures must be explained in lay terms at the appropriate educational level and using interpreters and translators as necessary.

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Figure 9.4: Street theatre can improve community knowledge to facilitate informed consent.

Researchers must document that participants have given informed consent. Most frequently, consent is documented by having participants sign a written informed consent document. **Table 9.2** shows the elements typically included in such a document. The appendix to this chapter provides a sample informed consent document; as you will see, informed consent documents often use complex language and seem to be written to provide legal protection to researchers and sponsors rather than to provide information for participants. Unfortunately, there is currently little emphasis on assessing a participant's understanding of a project before they sign an informed consent document. Researchers are not required to test or document participant understanding, although it has been suggested that simple questionnaires or interviews could be used to docu-

Invitation	Clear invitation to participate
Statement of overall purpose	Explanation of the purpose of the research in laymen's language
Basis for selections	Why have you, the individual patient, been asked to participate in this study
Explanations of procedures	A description of procedures to be followed, with identification of any procedures that are experimental. A statement of where and when the research will be done, and how much time will be involved in participating in the research
Description of the discomforts and risks	Description of foreseeable risks, discomforts, and inconveniences to the subject, the likelihood that they may occur, and steps taken to minimize risk
In case of injury	Description of the availability of medical therapy as well as the compensation for disability that may result from participating
Description of benefits	Description of benefits are hoped for but not guaranteed. If participants will not benefit, this must be indicated, e.g. "the purposes of _____ is to develop knowledge useful in developing improved therapies for your disease. Thus we hope to provide benefits in the future for persons like you"
Disclosure of alternatives	Description of alternative and routine therapies
Confidentiality assurances	Disclosure of who may review the chart; this usually involves discussion of who is supporting the study, who monitors trials for that group, and any other state or federal authorities likely to review the research work
Financial considerations	Description of any economic advantages in participating in a clinical trial, such as any financial inducements for participation, and explains that patients are usually not eligible for patent or royalty rights of invention
Offer to answer questions	Information about how to contact scientific, medical and administrative personnel in case the participant has questions regarding the study.
Continuing disclosure	Statement that the PI will notify subjects of any new findings obtained during the course of the study that may impact their decision to continue to participate in the research

Table 9.2: The components of an informed consent document for human research subjects.

ment understanding prior to informed consent (**Figure 9.4**). [15]

Continuing Controversies:

Despite explicit ethical guidelines, recently, a number of high profile ethical dilemmas have arisen in research projects involving human subjects. We conclude Chapter 9 by reviewing the debate surrounding some of these dilemmas.

Blinded Seroprevalence Studies: In 1988, the CDC and state health departments carried out studies to determine the prevalence of HIV in the population. They tested blood samples for HIV to determine the portion of the population infected with HIV. The study was blinded, so that researchers did not have access to any patient identifiers. Before proceeding with the research, it was reviewed for ethical concerns. Informed consent was considered unnecessary because the data had been anonymized, and the researchers did not have access to information which could identify the subjects. However, this prevented the researchers from notifying infected individuals. As treatments evolved for HIV, and the importance of early clinical intervention with antiretroviral drugs was revealed, the studies came under attack. Several legislators argued that the studies should be unblinded. Nettie Mayersohn, a democratic representative in the New York State Assembly expressed concern that infected babies who were identified through the study had a right to treatment if their test results were positive.[23] US Congressman Gary Ackerman introduced legislation to unblind the study. Ackerman warned, "There was one point in our society, a very dark day when people were allowed to walk around after being tested with a dread disease just so the medical establishment could...see what happens …"[24] Because of these concerns, the CDC suspended the study in 1995.[23]

Did this study adequately protect the rights of human subjects? Most experts agree that the study conformed to the ethical guidelines of the Belmont Report. These guidelines permit experiments to be carried out using patient specimens which will normally be discarded without consent, so long as patient identities are not released to investigators and the study has been reviewed by an IRB. The purpose of the study was to identify populations at risk for HIV so that effective interventions could be designed for these groups. None of the study participants were prevented or discouraged from seeking voluntary HIV testing.[23]

Study of HIV Transmission in Uganda: From 1994 to 1998 a team led by researchers at Columbia University tested 15,000 adults in 10 rural Ugandan communities for HIV and other sexually transmitted diseases (STDs).[25] The goal of the study was to determine whether treatment of STDs like syphilis and chlamydia could reduce the transmission of HIV. All participants in 5 villages were treated for STDs, while participants in 5 control villages were simply told of their results and were referred to free clinics for treatment. Results showed that mass treatment with antibiotics

lowered the rate of other STDs, but did not affect the rate of HIV transmission. When the study was ended all participants were given antibiotics. After the study was concluded, the researchers analyzed their data to see what other factors might affect HIV transmission. They matched sexual partners and identified 415 partners where one partner was infected and the other was not at the beginning of the study. They found that the most significant factor likely to increase transmission from the infected to the uninfected partner was the amount of virus in the infected person's blood. [26]

The study was criticized by Marcia Angell, editor of the New England Journal of Medicine, who was troubled that the researchers did not inform the at-risk partners. The researchers did not identify the discordant couples until after the study had been concluded, and argued that even if they had known, they could not have informed at risk partners, because Uganda has a national policy that prevents health workers from telling a third party about an individual's HIV status.[26] Angell was also troubled that HIV positive participants were not offered treatment with antiretroviral drugs. Angell believed that the Helsinki Declaration requires that researchers provide the best available treatment to their subjects. She argued that it did not matter that such care is not usually available in the setting where the research was conducted; the researchers had an ethical obligation to provide the same treatment that would be available in a developed country.[26] Edward Mbidde, a medical oncologist in Uganda, pointed out that if all studies in the developing world were held to the same standards of medical care available in developed countries, research to develop new treatments affordable for use in developing countries would be impractical.[26]

Developing Country HIV Prevention Trials: In the US, a study was carried out to determine whether treatment could interrupt transmission of HIV from mothers to babies. The trail was called the AIDS Clinical Trial Group (ACTG) Study 076.[27] It showed a dramatic reduction in transmission for women who received the intervention compared to women who received placebo. The effect was so dramatic that the study was stopped early, so that no additional women received placebo. In this trial, drug was administered during the last 26 weeks of pregnancy. Drug was also given intravenously during delivery and to the baby for 6 weeks after delivery. While successful, the intervention cost $800 for drug alone.[23] Because of this high cost and the long duration over which drug must be given, many people believed its use would be impractical in many developing countries,

Bouncing PORECO Babies!: June 19, 2007

Dave **Swaziland**

Today is the one-year anniversary of the initiation of these babies initiation into the clinic's PORECO program. [PORECO stands for Pilot Operational Research and Community Based Project.] The aim of the PORECO program is to prevent the transmission of HIV from mothers to their babies. To celebrate, we have a huge, bouncy, inflatable castle . . . and an enormous, enormous cake (like 4 feet by 5 feet)!

And, boy, are they happy today!

where women don't deliver in hospitals, don't seek care until later in their pregnancies, and can't afford an $800 drug.[28]

Studies were started in nine developing countries to determine whether radically cheaper alternatives could also reduce maternal to child transmission of HIV. The goal of these studies was to evaluate the effectiveness of a regimen which provided drug only during the last 3-4 weeks of pregnancy, reducing the cost of the intervention to just $80.[29] This could be afforded by two of the countries, and international agencies made a commitment to provide drug to other resource poor countries participating in the trials.[28] The trial was designed as a randomized trial in which some mothers got the new regime and others received a placebo. These trials were sponsored by the CDC and the NIH and all were subject to careful ethical review.[23]

The study led to a bitter ethical debate regarding the appropriate standard of care to be used in the control arm. Marica Angell, editor of the New England Journal of Medicine, criticized the trials on September 18, 1997, saying "The justifications are reminiscent of the Tuskegee study: Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subject's infants if there were no study ."[30] She cited the Declaration of Helsinki as preventing the trials. Angell argued that the new intervention should have been compared to the full ACTG 076 protocol, which was the standard of care in the developed world.

Researchers argued that investigators would learn more in a shorter time if they did a placebo controlled trial. The placebo control was necessary to establish the baseline rates of maternal to child HIV transmission, because these vary throughout the world. Rates of transmission can be influenced by the health state of the mothers and babies. Mothers in developed countries are often anemic and malnourished, so researchers wanted to measure the baseline transmission rate in order to know whether the new treatment reduces the rate of transmission below the baseline rate. Also, the drug itself causes anemia, so researchers believed that a placebo control was needed to determine whether the drug increased anemia. Other ethicists argued that the trial was ethical only if it was accompanied by a plan to make the treatment available to the local population if it proved to be effective.[29]

Amidst the controversy, the CDC sponsored study in Thailand took place and showed that the reduced course of therapy did dramatically reduce maternal to child HIV transmis-

sion rates—although not as much as the ACTG 076 protocol. Within weeks after the study findings were made public, agencies started supplying drug to women in studies around the world who were previously on placebo. Glaxo Wellcome, the drug manufacturer announced it would cut prices of drug for sale in developing countries. Thus, the study enabled worldwide programs designed to prevent maternal to child transmission of HIV (**Figure 9.5**).[29]

Standard of Care: A New Definition? Many of the current controversies center on debate over what should be the appropriate standard of care for research involving human subjects. How do we decide what is a reasonable standard of care for research subjects in developing countries? Should we automatically use the standard set by developed countries?

What is the danger of simply imposing the highest attainable standard of care for all research throughout the world? If we require that subjects in the control group receive the same treatment that would be available to them in a developed country, we may never develop sustainable techniques to improve health in developing countries.[28] What is the danger of accepting less than the highest attainable standard of care? We may find that researchers choose to carry out phase I drug studies in Africa because it is cheaper and less regulated.

Figure 9.5: A billboard in Gabarone, Botswana advocates participation in programs to Prevent Maternal to Child Transmission (PMTCT).

Most experts agree that a new definition of the standard of care is needed, which permits different standards for research in developing countries. However, these discrepancies should be subject to approval by ethical review committees in the host country. Rather than requiring that patients have access to the highest attainable standard of care, it has been suggested that researchers provide access to highest attainable and *sustainable* therapeutic method. The level of therapy that is generally available in a host country is the least that is ethically acceptable. Researchers must commit to provide a level of treatment that one can reasonably expect to continue in a host country after the research program has been completed. If therapy is not sustainable, then results can never be made available to the inhabitants of the country.[28]

Suggested guidelines for research involving human subjects in developing countries:

Carry out research on a health problem of the developing country population.

Research objectives, not vulnerability of the population, should be used to justify conduct of the research in a developing country.

Ensure that benefits of participating in trial outweigh the risks.

Only undertake research that benefits the community participating.

Translate research findings into accessible care in the community participating.

Involve members of the host community in design and conduct of trial; they must decide if benefits outweigh risks.

Provide subjects with care or treatment they would not ordinarily get in the country where the trial is carried out.

Ensure that trial does not widen disparities by taking resources away from healthcare system of the host country.

Interventions proven safe and effective through research should be made reasonably available in those countries.

Sources: [28,31,32]

Bioengineering and Global Health Project

Project Task 5: Define the constraints that a solution must satisfy.
These should be quantitative measures that include both technical performance and economic constraints that your solution must satisfy. If there are existing solutions, you should identify the performance capabilities and cost of these solutions. Your solution should provide an advantage compared to existing solutions. You should carefully justify trade-offs made between expected performance and cost. Examples of constraints that you might consider include necessary educational level of primary user, detection limits of new diagnostic methods, efficacy rates of new therapies, power requirements, cost and size. Turn in a one page table summarizing the design constraints for your problem. Each row in the table should indicate a specific constraint (e.g. unit cost of device). The table should include at least two columns – one or more which represents the current performance of available technologies and one which represents the constraint that your design must satisfy.

Chapter 9 Homework

1. The Belmont Report establishes the three fundamental ethical principles that guide the ethical conduct of research involving human participants: 1) Respect for Persons; 2) Justice; and 3) Beneficence. These principles require that all subjects participating in medical research give informed consent.

a. Define informed consent.
b. The following story appeared in The Oregonian this month. Read it and answer the following question. Suppose you are a member of the OHSU IRB. Would you have voted to approve this trial? Why or why not? Support your answer using the principles of the Belmont Report.

Blood trial could omit consent form
Doctors seek community consensus to test a blood substitute on trauma patients who may not be conscious
ANDY DWORKIN
How would you feel knowing that a doctor could experiment on you, without your permission, while you were unconscious? What if that experiment could help save your life and test a possible treatment for wounded soldiers or car crash victims? Doctors want Portland-area residents to ponder those questions as they move toward joining a study of a blood substitute called PolyHeme. Trauma medics with Legacy Health System, Oregon Health & Science University and local ambulance companies would take part in a national trial comparing PolyHeme with the salt-water solution now carried on ambulances.

This is no ordinary research project. In most trials, scientists must tell each potential participant about the possible risks and rewards before getting their agreement to participate, a process called "informed consent." But PolyHeme would go to people unconscious from blood loss when treatment starts. A seldom-used and ethically controversial 1996 Food and Drug Administration regulation lets researchers waive informed consent to test potential life-saving treatments when there is no other way to conduct the research. Instead of individual consent, the FDA says researchers must teach local residents about the trial and gauge their feelings. So Legacy and OHSU workers are mailing letters to local officials and holding three public meetings to explain the trial and ask for feedback. "This is not a sure thing that the study will happen," said Lise Harwin, a Legacy communications coordinator who helped plan the public education. "What we're trying to do now is get feedback to determine if it will." Portland researchers have spent more than a year planning the trial, and both hospitals' research-review boards have approved the idea. But those boards won't give their final approval until they consider public reaction.

Scientists have spent decades searching for a blood substitute, which trauma doctors say is desperately needed. Donated blood is too delicate and has too short a shelf life to carry on ambulances. Instead, paramedics use durable saline solution. But saline can't carry oxygen through the body; PolyHeme

does. PolyHeme, which is made from expired blood donations, has a longer shelf life than blood and can be administered to a person of any blood type.

Local research boards "haven't established a particular percent or number" of negative responses from the community that would cause them to stop the trial, Allee said. One reason is that researchers assume people worried about the process are more likely to comment than those who support it.

2. The following text contains portion of an article which appeared in the Austin American Statesman last year. Read the text and answer the following questions.

Federal researchers tested AIDS drugs on foster children without advocate protections

At least seven states, including Texas, participated in studies, which are now under investigation.

By John Solomon ASSOCIATED PRESS Thursday, May 05, 2005

WASHINGTON — Government-funded researchers tested AIDS drugs on hundreds of foster children over the past two decades in at least seven states, including Texas, often without providing them a basic protection afforded in federal law and required by some states, an Associated Press review has found. The research funded by the National Institutes of Health was most widespread in the 1990s as foster care agencies sought treatments for their HIV-infected children that weren't yet available in the marketplace. The practice ensured that foster children — mostly poor or minority — received care from world-class researchers at government expense, slowing their rate of death and extending their lives. But it also exposed a vulnerable population to the risks of medical research and drugs that were known to have serious side effects in adults and for which the safety for children was unknown.

Several studies that enlisted foster children reported that patients suffered side effects such as rashes, vomiting and sharp drops in infection-fighting blood cells as they tested antiretroviral drugs to suppress AIDS or other medicines to treat secondary infections. In one study, researchers reported a "disturbing" higher death rate among children who took higher doses of a drug. That study was unable to determine a safe and effective dosage. Research and foster agencies declined to make foster parents or children in the drug trials available for interviews, or to provide information about individual drug dosages, side effects or deaths, citing medical privacy laws. Some foster children died during studies, but state or city agencies said they could find no records that any deaths were directly caused by experimental treatments.

The government provided special protections for child wards in 1983. They required researchers and their oversight boards to appoint independent advocates for any foster child enrolled in a narrow class of studies that involved greater than minimal risk and lacked the promise of direct benefit. Some foster agencies required the protection regardless of risks and benefits. Advocates must be independent of the foster care and research agencies, have some understanding of medical issues and "act in the best interests of the child" for the entirety of the research, the law states.

However, researchers and foster agencies said foster children in AIDS drug trials often weren't given such advocates even though research institutions many times promised to do so to gain access to the children. Illinois officials say they think none of their nearly 200 foster children in AIDS studies got independent monitors even though researchers signed a document guaranteeing "the appointment of an advocate for each individual ward participating in the respective medical research." New York City could find records showing 142 — less than a third — of the 465 foster children in AIDS drug trials got such monitors even though city policy required them. The city has asked an outside firm to investigate.

Researchers typically secured permission to enroll foster children through city or state agencies. They frequently exempted themselves from appointing advocates by concluding the research carried minimal risk and the child would directly benefit because the drugs had already been tried in adults. If they decline to appoint advocates under the federal law, researchers and their oversight boards must conclude that the experimental treatment affords the same or better risk-benefit possibilities than alternate treatments already in the marketplace. They also must abide by any additional protections required by state and local authorities.

Many of the studies that enrolled foster children occurred after 1990 when the government approved using the drug AZT — an effective AIDS treatment — for children. Those studies often involved early Phase I and Phase II research — the riskiest — to determine side effects and safe dosages so children could begin taking adult "cocktails," the powerful drug combinations that suppress AIDS but can cause bad reactions like rashes and organ damage. Some of those drugs were approved ultimately for children, such as stavudine and zidovudine. Others were not.

Arthur Caplan, head of medical ethics at the University of Pennsylvania, said advocates should have been appointed for all foster children because researchers felt the pressure of a medical crisis and knew there was great uncertainty as to how children would react to AIDS medications that were often toxic for adults. "It is exactly that set of circumstances that made it absolutely mandatory to get those kids those advocates," Caplan said. "It is inexcusable that they wouldn't have an advocate for each one of those children."

Those who made the decisions say the research gave foster kids access to drugs they otherwise couldn't get. And they say they protected children's interest by explaining risks and benefits to state guardians, foster parents and the children themselves. "I understand the ethical dilemma surrounding the introduction of foster children into trials," said Dr. Mark Kline, a pediatric AIDS expert at Baylor College of Medicine. He enrolled some Texas foster kids in his studies, and said he doesn't recall appointing advocates for them. "To say as a group that foster children should be excluded from clinical trials would have meant excluding these children from the best available therapies at the time," he said. "From an ethical perspective, I never thought that was a stand I could take."

Illinois officials directly credit the decision to enroll HIV-positive foster kids with bringing about a decline in deaths — from 40 between 1989 and 1995 to only 19 since.

NIH did not track researchers to determine whether they appointed advocates. Instead, the decision was left to medical review boards made up of volunteers at each study site. A recent Institute of Medicine study concluded those Institutional Review Boards were often overwhelmed, dominated by scientists and not focused enough on patient protections.

a. What are the three basic principles ethical principles of the Belmont Report? Define each principle.
b. Discuss the ethical and legal issues that arise when new medical technologies are tested in vulnerable populations, such as foster children. Do you think that the studies described adequately protected the rights of this population? Give the reasons for your position in terms of the principles outlined in the Belmont Report.
c. The article states that the studies ensured that foster children — mostly poor or minority — received care from world-class researchers at government expense, slowing their rate of death and extending their lives. In fact, Illinois officials directly credit the decision

to enroll HIV-positive foster kids with bringing about a decline in deaths — from 40 between 1989 and 1995 to only 19 since. Describe how these outcomes influence your reasoning in part b above.

3. Briefly describe the Willowbrook study to investigate the natural history of infectious hepatitis. List the principles of the Belmont report which were violated in this study. Support your answer with evidence.

4. A clinical trial recently carried out at Johns Hopkins University tested the effects of a chemical irritant to understand why some people get asthma. Three healthy volunteers with normal respiratory systems inhaled the chemical. Two days after inhaling the chemical, Ellen Roche, 24, a technician at the Johns Hopkins Asthma and Allergy Center, developed a cough, fever and muscle pain. She quickly developed respiratory distress, and within a month she was dead. The chemical she inhaled turned out to be far more toxic than the researchers realized. In fact, the lead investigator's literature search of the most common databases (which date back only to 1960), did not turn up earlier studies hinting at the chemical's potential dangers, but after-the-fact searches using different search engines and databases did turn up references to the potential risks to humans. In a review of the study, the FDA raised questions about the informed-consent forms that Roche and two other subjects had signed. On them, hexamethonium is referred to as a "medication" and as "(having) been used as an anesthetic"—giving subjects a sense that it was an FDA-approved medicine and therefore safe. Another criticism: Togias failed to report that his first subject (Roche was the third) had developed a cough. It went away, and Togias assumed it had to do with a viral infection making the rounds at Bayview at the time. Discuss any problems associated with the protection of human subjects using the principles of the Belmont report.

5. Use the following link to read the article, *Placebos break taboo in cancer drug tests: Study seeks hope for desperately ill,* that was first printed in the Boston Globe. http://www.irbforum.com/forum/read/2/78/78 . You have just been named the Director of the National Cancer Institute. You control an annual budget of $6 billion. You must decide whether any of these funds can be used to support placebo controlled research studies for terminally ill cancer patients. Your decision will determine whether any studies of this type will receive any funding. Using the article as a reference point, prepare an argument in favor of or against such studies. Your argument should be no more than one typed page. Limit your argument to either the pro or con stance and prepare a convincing case as to why you ruled the way you did.

6. Discuss the ethical and legal issues that arise when new medical technologies are tested in developing countries. In what ways can this benefit the population of the developing country? In what ways can the population be harmed? If the researchers are based in the United States, what legal and ethical responsibilities do they have?

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Appendix: Informed Consent Document

Informed Consent to Participate in Research

The University of Texas at Austin

You are being asked to participate in a research study. This form provides you with information about the study. The Principal Investigator (the person in charge of this research) or his/her representative will also describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part. Your participation is entirely voluntary and you can refuse to participate without penalty or loss of benefits to which you are otherwise entitled.

Title of Research Study:

Evaluating the Effectiveness of Evidence–Based Teaching Strategies in BME 301: Biotechnology and World Health

Principal Investigator(s) (include faculty sponsor), UT affiliation, and Telephone Number(s):

Rebecca Richards-Kortum, Ph.D. Professor of Biomedical Engineering 512-471-2104

Funding source:

Howard Hughes Medical Institute

What is the purpose of this study?

The purpose of the study is to investigate the effectiveness of learner-centered, open-ended problem-solving and cooperative learning strategies in BME 301. The total number of students registered for BME 301 was approximately 60. Thirty seven students participated from BME 301. Your participation will serve as a control group.

What will be done if you take part in this research study?

From a pool of undergraduate students, we are requesting volunteers for an interview protocol. We will ask participants to volunteer to take part in an activity in which they are given a newspaper article related to the BME 301 course material and asked to critically discuss it in groups of 3-5. Participant responses will be videotaped. Students will be compensated for their time with a $20.00 gift certificate from Barnes and Noble.

What are the possible discomforts and risks?

There are no physical risks or discomforts that apply with this research. However, if you wish to discuss the information above or any other risks you may experience, you may ask questions now or call the Principal Investigator listed on the front page of this form. Some participants may be uncomfortable with being videotaped initially. If you feel uncomfortable, you may discontinue participation at any time. The only treatment for participating in this research that differs from discussing a newspaper article casually with a peer is your agreement to being video-

taped.

What are the possible benefits to you or to others?

Your participation in this study will provide data which will permit researchers to identify learning behaviors that are positively associated with content mastery in this course when comparing various instructional techniques. This study will result in a deeper understanding of learner centered environments and the effect of this on learning. The study may result in the development of reliable and valid instruments which can measure learning in more effective ways than are currently used. This will improve the knowledge base for the science of learning and ultimately the knowledge disseminated from the study could improve the teaching of undergraduate curricula beyond the University of Texas at Austin.

If you choose to take part in this study, will it cost you anything?

There are no costs associated with participating in this study.

Will you receive compensation for your participation in this study?
What if you are injured because of the study?

Students who complete the interview will be compensated for their time with a $20.00 gift certificate from Barnes and Noble. There are no physical risks associated with this research. University students may be treated at the usual level of care with the usual cost for services at the Student Health Center for any injury, related or not, but no payment can be provided in the event of a medical problem.

If you do not want to take part in this study, what other options are available to you?

Participation in this study is entirely voluntary. You are free to refuse to be in the study, and your refusal will not influence current or future relationships with The University of Texas at Austin or your grades in any course. Your decision to participate will not bestow any competitive academic or occupational advantage over any other University of Texas at Austin students who do not volunteer, and the researchers will not impose any academic or occupational penalty on those University of Texas at Austin students who do not volunteer.

How can you withdraw from this research study and who should you call if you have questions?

If you wish to stop your participation in this research study for any reason, you should contact: Deanna Buckley at (512)-471-3068. You are free to withdraw your consent and stop participation in this research study at any time without penalty or loss of benefits for which you may be entitled. Throughout the study, the researchers will notify you of new information that may become available and that might affect your decision to remain in the study.

In addition, if you have questions about your rights as a research participant, please contact Clarke A. Burnham, Ph.D., Chair, and The University of Texas at Austin Institutional Review Board for the Protection of Human Subjects, 512-232-4383.

How will your privacy and the confidentiality of your research records be protected?

Authorized persons from The University of Texas at Austin and the Institutional Review Board have the legal right to

review your research records and will protect the confidentiality of those records to the extent permitted by law. If the research project is sponsored, then the sponsor also has the legal right to review your research records. Otherwise, your research records will not be released without your consent unless required by law or a court order.

If the results of this research are published or presented at scientific meetings, your identity will not be disclosed.

Because these studies will use video recordings, you should know that the CD's will be: (a) coded so that no personally identifying information is visible on them; (b) kept in a secure locked location in the co-investigator's office (Deanna Buckley); (c) heard or viewed only for research purposes by the investigator and his or her associates; (d) possibly retained for future research analysis.

Will the researchers benefit from your participation in this study?

Your participation will allow researchers to collect objective data to be analyzed for publications in educational and scientific research journals and presentations to other scientific researchers and educators. No other benefits are expected at this time.

Signatures:

As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study.

_____ _____

Signature and printed name of person obtaining consent Date

You have been informed about this study's purpose, procedures, possible benefits and risks, and you have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time. You voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights.

_____

Printed Name of Subject Date

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Signature of Subject Date

_____

Signature of Principal Investigator Date

We may wish to present some of the tapes from this study at scientific conventions or as demonstrations in classrooms. Please sign below if you are willing to allow us to do so with the tape of your performance.

_____

Signature of Subject Date

I hereby give permission for the video tape made for this research study to be also used for educational purposes.

_____

Signature of Subject Date