

## Chapter 9 Homework

1. The Belmont Report establishes the three fundamental ethical principles that guide the ethical conduct of research involving human participants: i) Respect for Persons; ii) Justice; and iii) 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: Toggias failed to report that his first subject (Roche was the third) had developed a cough. It went away, and Toggias 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?