CHAPTER 11

The Protection of Human Subjects in Research

This chapter discusses the history of human experimentation, giving special attention to cases that have helped to shape ethical guidelines and policies. It discusses important ethics codes and provides an overview of U.S. federal regulations. The chapter also addresses some key concepts and principles in human research, such as informed consent, risks versus benefits, privacy and confidentiality, protection of vulnerable subjects, and research versus therapy.

The use of human subjects in research came into sharp focus during the Nuremberg war crimes trials, when the world discovered the atrocities committed by Nazi doctors and scientists on tens of thousands of prisoners held in concentration camps. While these tribunals were unfolding, the American Medical Association (AMA) was developing a set of principles to be followed in experiments using human subjects (Advisory Committee on Human Radiation Experiments 1995). After the tribunals concluded in 1947, the research community adopted the world's first international code for research on human subjects, the Nuremberg Code (Advisory Committee on Human Radiation Experiments 1995). The code emphasized the importance of informed consent of research subjects, minimization of harms and risks to subjects, scientific validity of the research design, and the social value of the research. Since then, many documented cases of unethical or questionable research have also been conducted in the United States and other countries (Advisory Committee on Human Radiation Experiments 1995; Beauchamp and Childress 2001; Capron 1989; Washington 2006). There have also been many ethical

controversies in human subjects research (Egilman et al. 1998a, 1998b; Shamoo and Irving 1993; Washington 2006). As a result, federal agencies and scientific and professional associations have developed regulations and codes governing human subjects research, and there have been a great deal of discussion and debate about ethical standards that should govern the use of humans in research (Levine 1988; Pence 1996). This chapter reviews these regulations after providing a historical perspective on these issues.

HUMAN EXPERIMENTATION BEFORE WORLD WAR II

Alexander Morgan Capron (1989, p. 127) has observed that "the darkest moments in medical annals have involved abuses of human research subjects." A brief survey of the history of human subjects research supports this view. Before the Scientific Revolution (ca. 1500–1700 A.D.), medicine was an observational rather than experimental science. Medical research was based on the teaching of Hippocrates (460–377 B.C.), the father of scientific medicine. Hippocrates developed theories and principles that explained diseases in terms of natural rather than supernatural causes. According to his teachings, health was a state of balance among the four humors of the body: blood, phlegm, yellow bile, and black bile. Disease occurs when the body becomes out of balance as the result of too much or too little of one or more humors. The goal of medicine is to use various treatments and therapies to restore the body's proper balance. For example, Hippocratic physicians believed that bloodletting could restore health by eliminating excess blood.

Hippocrates' method was observational rather than experimental because he did not use controlled interventions (or experiments) to obtain medical knowledge. Instead, Hippocrates gathered knowledge through careful observation of disease conditions, signs, symptoms, and cures. He also developed detailed case histories. Hippocratic physicians believed in the body's ability to heal itself, and they tended to prescribe nonaggressive and noninterventional therapies, such as special diets, herbal medications, exercise, massage, baths, and prayer. The Hippocratic School developed a code of medical ethics that emphasized the importance of promoting the welfare of the individual patient. Two of the Hippocratic Oath's key tenets, which evolved hundreds of years after Hippocrates' death, are to keep patients from harm and injustice ("do no harm") and to benefit the sick. Although Hippocratic physicians sought to improve medical knowledge, their code of ethics and their philosophy of medicine

implied that medical advances would occur slowly and would not sacrifice the welfare of the individual patient for scientific progress (Porter 1997).

This conservative approach to medical research began to change during the Scientific Revolution, as physicians such as Paracelsus (1493–1542), Andreas Vesalius (1514–1614), and William Harvey (1578–1657) challenged medical dogmas and sought to apply the new experimental method to medicine. However, these physicians still did not conduct many controlled experiments on human beings. Although Paracelsus, Vesalius, and Harvey dissected human bodies, they did not gain their knowledge of anatomy from experiments on living people. While Harvey conducted some experiments on human beings, his experiments were relatively benign and noninvasive. For example, he used a tourniquet to demonstrate the direction of the flow of blood in human veins, and he measured pulse and blood pressure. He conducted his more invasive procedures, such as vivisections, on animals (Porter 1997).

As physicians began to apply the experimental method to medicine, experiments on human beings became more common and more risky. One famous 18th-century experiment conducted by the English physician Edward Jenner (1749–1823) illustrates some recurring ethical concerns. Jenner observed that dairymaids who developed cowpox did not develop smallpox. He hypothesized that exposure to cowpox provided protection against smallpox. To test his hypothesis, he inoculated James Phipps, an eight-year-old boy, with some material from a cowpox pustule. The boy developed a slight fever but suffered no other ill effects. Six weeks after this inoculation, Jenner exposed Phipps to the smallpox virus and he did not develop the disease (Porter 1997).

During the 19th century, experiments on human beings became even more common. For example, William Beaumont (1785–1853) treated Alexis St. Martin for a bullet wound in the stomach. The wound healed but left a hole in the stomach. Beaumont hired Martin as a servant and used him as an experimental subject, because he could observe the process of digestion through the hole in Martin's stomach (Pence 1995). During the 20th century, physicians began to accept the germ theory of disease developed by Louis Pasteur (1822–1896) and Robert Koch (1843–1910). Despite Pasteur's unquestioned place in science, there are now historical studies indicating that his behavior was not above ethical reproach. For example, Pasteur treated a patient for rabies without first ensuring the safety of the treatment in animal experiments (Geison 1978). The surgeon Joseph Lister (1827–1912) performed a variety of experiments to develop and test antiseptic methods in medicine. For instance, Lister observed that carbolic acid was effective at reducing infections among cattle, and he

hypothesized that this compound has antiseptic properties. To test his idea, he applied lint soaked in carbolic acid and linseed oil to a boy's wound. He also took measures to prevent germs from entering the wound. The boy, James Greenlees, did not develop an infection. Lister applied his method to dozens of other cases of compound fractures and amputations and published his results in *The Lancet* in 1867 (Porter 1997).

One of the most disturbing experiments in the United States before World War II took place in 1874 in Cincinnati, when Robert Bartholomew inserted electrodes into the brain of Mary Rafferty, a 30-year-old "feebleminded" patient who was dying of terminal cancer, which had spread to her scalp. Bartholomew saw a research opportunity and for several hours electrically stimulated Rafferty's brain and recorded her responses, which were often cries of pain (Lederer 1995).

Many of the human experiments were inspired by the work of Pasteur and Koch, who developed vaccines for bacterial infections. To implement this methodology, researchers needed to establish a link between a pathogen and a disease, isolate a disease pathogen, develop a vaccine, and then test the vaccine. In 1895, Henry Heiman, a New York pediatrician, infected two mentally retarded boys, 4 and 16 years old, with gonorrhea. In 1897, the Italian researcher Giuseppe Sanerilli injected yellow fever bacteria into five subjects without their consent in order to test its virulence. All five subjects became severely ill, although none died (Lederer 1995). Many physicians, including William Osler (1849–1919), condemned this experiment. In his textbook *The Principles and Practice of Medicine* (1898), Osler discussed Sanerilli's experiments as well as some other studies of yellow fever.

U.S. Army physician Walter Reed and his colleagues in Cuba conducted their well-known yellow fever experiments around 1900. Yellow fever had become a major health problem for military operations in Cuba, the Caribbean, and Central America. At the time, researchers hypothesized that yellow fever was transmitted to humans by the *Aedes aegypti* mosquito. Because there were no animal models for the disease, human subjects were required to study its transmission. The risks to human subjects were great, because medicine had no cure for the disease, which often resulted in death. Two investigators working with Walter Reed, James Carroll and Jesse Lazear, allowed themselves to be bitten by mosquitoes in order to test the hypothesis. Reed had also agreed to participate in these experiments, but he was in Washington, DC, when his colleagues exposed themselves to the disease. Both colleagues contracted yellow fever, and Lazear died from the disease. After Lazear died, Reed decided not to use himself as an experimental subject, but he continued experimenting on human

beings. A total of 33 subjects participated in the experiments, including 18 Americans and 15 Spanish immigrants. Six subjects died from yellow fever (Lederer 1995).

Because the risks of participating in these experiments were so great, Reed and his colleagues had volunteers sign written documents stating that they understood the risks of the experiment and that they agreed to participate. Informed consent documents were translated into Spanish. Volunteers were also given $100 in gold and free medical care for their participation. Although other researchers obtained undocumented informed consent from subjects, this is believed to be the first case of the documentation of informed consent in research. Research subjects who participated in these yellow fever experiments came to be regarded as heroes and martyrs. Surviving military volunteers received gold medals and government pensions (Lederer 1995). Although some scholars claimed that the ethical/legal doctrine of informed consent evolved in the 1950s and 1960s (Advisory Committee on Human Radiation Experiments 1995), Reed's work shows that he followed this paradigm before it became more broadly accepted.

There have been numerous unethical experiments on vulnerable African Americans, such as the Tuskegee study (discussed below). Harriet Washington's 2006 book *Medical Apartheid* cites many examples of such experiments. For instance, in the early 1800s, 250 out of 251 subjects in an experiment testing inoculations of smallpox vaccine were African Americans. In 1846, Dr. Walter F. Jones of Virginia poured boiling water on patients with typhoid pneumonia. Washington describes many dangerous and humiliating experiments on African-American slaves. The author recognizes that progress has been made in research with black populations.

Before World War II, physicians and surgeons had ambivalent attitudes toward human experimentation. On the one hand, most physicians accepted the Hippocratic idea that they should not harm their patients. Claude Bernard (1813–1878) restated the principle in his *Introduction to the Study of Experimental Medicine* (1865 [1957]). According to Bernard, physicians should never perform on humans an "experiment, which might be harmful to him to any extent, even though the result might be wholly advantageous to science" (p. 101). On the other hand, physicians regarded many risky and untested interventions as therapeutic and believed that it was sometimes necessary to try these treatments in order to benefit the patient. While physicians condemned many of the unethical experiments that were brought to their attention, they also had a strong commitment to medical experimentation and did not want to place any

burdensome restrictions on research. Most physicians thought that self-experimentation was noble and virtuous, but they did not think that informed consent was always necessary. Indeed, most physicians at the time thought that it was more important to avoid harming the research subject than to obtain the subject's consent. For several decades, the AMA considered adopting a code of ethics for research on human subjects, but it did do so until 1946 (Lederer 1995).

In 1900, Prussia was the first nation in the world to formalize the prohibition of medical interventions other than for therapeutic purposes (Capron 1989). The Prussian directive required that consent be given and that prospective subjects be informed of adverse consequences. It also excluded minors from research. These directives were not given in a vacuum or without a cause: They came as a reaction to numerous and repeated abuses of patients in medical research. For example, Amauer Hansen (1841–1912), who discovered the bacillus strain that causes leprosy, carried out an appalling experiment on an unwitting 33-year-old woman when he twice pricked her eye with a needle contaminated by nodules of a leprous patient (Bean 1977). Hansen was later merely reprimanded.

In the early 1900s, the eugenics movement flourished in Europe and in the United States. In the 1930s, one Canadian province and 28 U.S. states passed laws requiring the sterilization of the criminally insane, presumed "feeble-minded," psychopathic personalities, and the mentally ill (Ollove 2001; Proctor 1988). By the late 1930s, California alone had sterilized 13,000 persons, and the U.S. total is estimated at between 30,000 and 100,000 persons (Ollove 2001; Proctor 1988). The State of Virginia in the early 20th century was a leader in sterilization efforts. A *Baltimore Sun* reporter, Michael Ollove, chronicled the ordeal of a Virginian who was sterilized for being "feeble-minded." Later, this Virginian became a soldier, winning the Purple Heart, the Bronze Star, and Prisoner of War honors during World War II (Ollove 2001). The eugenics movement helped provide impetus for the Nazi atrocities committed in World War II. Hitler was a strong advocate of eugenics, and he believed it was necessary to control human breeding in order to prevent the Aryan race from being corrupted by "inferior" races, such as the Jews and Gypsies (Proctor 1999).

Human Experimentation during World War II

The Nazi experiments conducted during World War II have been regarded by many as the worst experiments ever performed on human subjects. None of the subjects gave informed consent, and thousands were maimed

or killed. Many of the experiments were not scientifically well designed or conducted by personnel with appropriate scientific or medical qualifications. Moreover, these experiments were planned, organized, and conducted by government officials. Subjects included Jews, homosexuals, convicted criminals, Russian officers, and Polish dissidents. Some of the experiments included the following (Müller-Hill 1992; Pence 1995; Proctor 1988):

- Hypothermia studies where naked subjects were placed in freezing cold water
- Decompression studies where subjects were exposed to air pressures equivalent to the pressures found at an altitude of 70,000 feet
- Wound-healing studies, where subjects were shot, stabbed, injected with glass or shrapnel, or otherwise harmed to study how their wounds healed
- Vaccination and infection studies, where subjects were intentionally infected with diseases, such as typhus, staphylococcus, malaria, and tetanus, in order to test the effectiveness of vaccines and treatments
- Josef Mengele's (1911–1979) experiments designed to change eye color, which resulted in blindness
- Mengele's human endurance experiments, where subjects were exposed to high levels of electricity and radiation
- Mengele's twin studies: exchanging blood between identical twins, forcing fraternal twins to have sex to produce children, creating conjoined twins by sewing twins together at the back, placing children in virtual isolation from birth to test the role of nature and nurture in human development

Although historians and ethicists have focused on Germany's horrific experiments with human subjects during World War II, less attention has been given to Japan's atrocities during this era. From 1932 to 1945, Japanese medical researchers killed thousands of human subjects in medical experiments. Most of the experiments took place in China while the country was under Japanese occupation. The experiments included intentionally wounding and operating on human beings for surgical training, vivisection of live humans, infecting humans with pathogens, exposing subjects to extremes of temperature, and biological and chemical warfare research. Most of the human subjects were people of Chinese ancestry, but victims also included Allied prisoners of war. At the end of the war, the U.S. government made a deal with Japan to gain access to the data from chemical and biological warfare experiments. In exchange for the data,

the U.S. government agreed not to prosecute Japanese physicians and scientists for war crimes. As a result of this coverup, the Japanese atrocities were not widely known until the 1990s, and Japanese political leaders have been reluctant to acknowledge that these crimes against humanity occurred (Tsuchiya 2008).

Human Experimentation after World War II

By the mid-20th century, human experiments, ethical and otherwise, were becoming more common, but the research community had not put a great deal of thought into the ethics of research on human subjects. Although some physicians, most notably Bernard and Osler, had written about the ethics of human experimentation, and the AMA had drafted some documents on human experimentation, there were no well-established ethical codes for experimentation on human subjects before 1947. This is one reason that the Nuremberg Code has such an important place in history: It was the first internationally recognized code of ethics for human research.

Although the Nuremberg Code did help to define and clarify some standards for the ethical conduct of human experiments, many abuses took place after the code was adopted. Some of these ethical problems in research were discussed by Henry Beecher (1904–1976) in an exposé he published in the *New England Journal of Medicine* in 1966. Beecher described 22 studies with ethical problems, including the now well-known Tuskegee syphilis study, the Willowbrook hepatitis experiments on mentally disabled children, and the Jewish chronic disease case study (Beecher, 1966).

The Tuskegee study took place from 1932 to 1972 in a public health clinic in Tuskegee, Alabama. The purpose of the study was to follow the natural etiology of later-stage syphilis in African-American men. Six hundred subjects were enrolled in the study, which was funded by the U.S. Department of Health, Education, and Welfare (DHEW), the precursor to the Department of Health and Human Services (DHHS). The subjects were divided between an "experimental" group of 399 subjects with untreated syphilis and a "control" group of subjects without syphilis. The initial plan was to conduct the study for one year, but it lasted nearly 40 years. The subjects who participated in the study were not told that they had syphilis or that they were participating in an experiment. Subjects with syphilis only knew that they had "bad blood" and could receive medical treatment for their condition, which consisted of nothing more than medical examinations. Subjects also received free hot lunches and free burials. An effective

treatment for syphilis, penicillin, became available in the 1940s, but the subjects were not given this medication or told about it. In fact, study investigators took steps to prevent subjects from receiving treatment for syphilis outside of study. The study also had scientific flaws: Key personnel changed from year to year, there were no written protocols, and records were kept poorly. Even though Beecher brought the study to the attention of the public, it was not stopped until Peter Buxton, who worked for the U.S. Public Health Service (PHS), reported the story to the Associated Press. The story soon became front-page news, and a congressional investigation followed. In 1973, the U.S. government agreed to an out-of-court settlement with families of the research subjects, who had filed a class-action lawsuit (Jones 1981; Pence 1995). In 1997, the Clinton administration issued an official apology on behalf of the U.S. government.

From 1956 to 1980, a team of researchers, led by Saul Krugman and Joan Giles, began a long-range study of viral hepatitis at the Willowbrook State School for mentally retarded children. Viral hepatitis was endemic at Willowbrook: Most children who entered the institution became infected within 6 to 12 months of admission. Although the disease is usually not life-threatening, it can cause permanent liver damage. Victims of the disease usually have flulike symptoms, such as fever, fatigue, and nausea. The disease is transmitted orally through contact with feces or body secretions. In their research, Krugman and Giles infected healthy subjects with viral hepatitis. This allowed them to study the natural progression of the disease, including its incubation period, and to test the effectiveness of gamma globulin in preventing or treating the disease. They collected over more than 25,000 serum samples from more than 700 subjects. The two researchers justified their study on the grounds that it offered therapeutic benefits to the subjects: The children in the study would receive excellent medical care, they would avoid exposure to other diseases, and they would acquire immunity against more potent forms of hepatitis. Krugman and Giles obtained written informed consent from parents, although some critics have charged that the parents did not understand the nature of the study. Krugman and Giles also obtained appropriate approvals for their study: The study was approved by the New York State Department of Mental Hygiene, the New York State Department of Mental Health, and the human experimentation committees at the New York University School of Medicine and the Willowbrook School (Munson 1992).

The Jewish chronic disease case study took place in Brooklyn, New York, in 1964. In this case, researchers introduced live cancer cells into 22 unsuspecting patients (Faden and Beauchamp 1986). The purpose of the study was to learn more about the transplant rejection process. Previous studies

had indicated that healthy subjects and subjects with cancer have different immune responses to cancer cells: Healthy subjects reject those cells immediately, whereas cancer patients have a delayed rejection response. Researchers claimed that they obtained informed consent, but they did not document the consent. They claimed that there was no need for documentation because the procedures they were performing were no more dangerous than other procedures performed in treating cancer patients. Investigators also did not tell the subjects that they would receive cancer cells, in order to avoid frightening them unnecessarily (Levine 1988).

Human radiation experiments took place in the United States from 1944 to 1974, during the cold war era (Advisory Committee on Human Radiation Experiments 1995). These experiments were funded and conducted by U.S. government officials or people associated with government institutions on more than 4,000 unsuspecting citizens and military personnel. Many of these experiments violated standards of informed consent and imposed significant risks on the subjects. Most of these experiments were conducted in order to aid U.S. cold war efforts by providing information about how radiation affects human health. Most of these studies used radioactive tracers and did not result in serious harm to the subjects. However, several of the studies that involved children exposed them to an increased lifetime cancer risk, and several studies caused death shortly after the administration of radiation.

In 1994, the Clinton administration began declassifying documents related to these experiments and appointed a commission to develop a report on this research. Although the commission openly discussed some ethical problems with the research, it also found that most studies contributed to advances in medicine and public health (Advisory Committee on Human Radiation Experiments 1995; Beauchamp 1996; Guttman 1998; Moreno 2000). It also judged the experiments by the standards that existed at the time that they were conducted: According to the commission, most of these experiments did not violate existing ethical or scientific standards. Nevertheless, as Welsome (1999) observed: "Almost without exception, the subjects were the poor, the powerless, and the sick—the very people who count most on the government to protect them" (p. 7). Some of the more noteworthy studies that came to light that may have violated the existing ethical standards included the following:

- Researchers at Vanderbilt University in the late 1940s gave pregnant women radioactive iron to study the effects of radiation on fetal development; a follow-up study found that children from these women had a higher-than-normal cancer rate.

- In Oregon State Prison from 1963 to 1971, researchers X-rayed the testicles of 67 male prisoners, who were mostly African Americans, to study the effects of radiation on sperm function.
- During the late 1950s, researchers at Columbia University gave 12 terminally ill cancer patients radioactive calcium and strontium to study how human tissues absorb radioactive material.
- Researchers released a cloud of radioactive iodine over eastern Washington State to observe the effects of radioactive fallout.
- From the 1940s to the 1960s, researchers injected encapsulated radium into the nostrils of more than 1,500 military personnel; many developed nosebleeds and severe headaches after exposure.

Perhaps the most troubling aspect of these studies is that most of them took place after the international community had adopted the Nuremberg Code. It is ironic that the U.S. government, which had been so outspoken in its criticism of Nazi research, would also sponsor human experiments that many would consider unethical (Egilman et al. 1998a, 1998b).

Besides these important cases from the history of biomedical research, there have also been some noteworthy cases in social science research. One of the methodological problems with social science experiments, known as the Hawthorne effect, is that research subjects may change their behavior as a result of knowing that they are participating in an experiment. As a result, the experiment may be biased. To minimize this bias, many social science researchers believe that it is sometimes necessary to deceive human subjects about the experiments in which they are participating, which is what Stanley Milgram did in his 1960s experiments relating to obedience of authority. These experiments involved three participants: an authority figure (such as a scientist), a learner, and a teacher. The teacher was led to believe that the purpose of the experiment was to test the effects of punishment on learning. The teacher provided the learner with information that the learner was supposed to recall. If the learner failed to learn the information, the authority figure instructed the teacher to give the learner an electric shock. The severity of the shock could be increased to "dangerous" levels. Learners would cry out in pain when they received a shock. Most teachers continued to give shocks even when they reached "dangerous" levels and when the learners asked to stop the experiment. In reality, the learners never received an electric shock; they faked agony and discomfort. Milgram was attempting to learn about whether the teachers would obey the authority figures (Milgram 1974). At the end of each session, Milgram debriefed the teachers and told them the real purpose of the experiment. Many of the teachers

said that they suffered psychological harm as a result of these experiments because they realized that they were willing to do something that they considered immoral (Sobel 1978).

Another noteworthy case of deception in social science research took place in Wichita, Kansas, in 1954. During these experiments, investigators secretly recorded the deliberations of six different juries in order to gain a better understanding of how juries make their decisions. The judges of the Tenth Judicial Circuit and the attorneys in the cases approved of the study, although the litigants were not told about it. When this study came to light, the integrity of the jury system was cast into doubt. In 1955, a subcommittee of the Senate Judiciary Committee held hearings to assess the impact of this research on the jury system. As a result of these hearings, Congress adopted a law forbidding the recording of jury deliberations (Katz 1972).

During the 1990s, the research community learned about a variety of ethically questionable studies on mentally ill patients. The national media also covered many of these stories. As a result, the National Bioethics Advisory Commission (NBAC) issued a report recommending changes in federal regulations on research on people with mental disorders (National Bioethics Advisory Commission 1998; Shamoo 1997a). Many of these problems originally came to light through a series of papers delivered at a conference held in 1995 (Shamoo 1997b, 1997c) and a series of articles published in journals (Shamoo and Irving 1993; Shamoo and Keay 1996; Shamoo 1997a, 1997c). This was followed by a major series of articles in the *Boston Globe* (see Kong and Whitaker 1998). Many of these research projects were washout studies in which subjects stop taking medications for a period of time (usually 30 days) before exposure to an experimental drug. The purpose of the washout period is to conduct a controlled clinical trial that reduces biases and complications due to interactions between drugs subjects have been taking and experimental drugs. After the washout period, the protocol randomly assigns patients to groups that receive either an existing treatment or a new drug. The protocols may also include a placebo control group. In some washout studies, the harms to subjects are fairly minimal, especially if the washout period is short and subjects are carefully monitored under inpatient settings, but in others the harms may be substantial, due to the absence of necessary treatment during the washout period.

In the studies that many people regarded as unethical, the subjects were taking medications for depression, schizophrenia, and other serious mental disorders. Some studies on schizophrenia patients found that many subjects suffered the effects of withdrawal from medications and

experienced relapses, which included increased psychosis or rehospitalization (Baldessarini and Viguera 1995; Crow et al. 1986; Gilbert et al. 1995; Wyatt 1986; Wyatt et al. 1999). As a result, more than 10% of subjects dropped out of these studies (Shamoo and Keay 1996; Shamoo et al. 1997c) for a variety of reasons. Because 10% of schizophrenics commit suicide, a relapse of this disease can be very dangerous. In 1991, Craig Aller, a patient with schizophrenia at the University of California at Los Angeles, and his family argued that he suffered permanent brain damage due to a relapse caused by a medication washout as part of his participation in the research protocol (Aller and Aller 1997). Another patient in this study allegedly committed suicide (Aller and Aller 1997). In some of these studies, researchers asked the subjects to consent, but critics questioned whether the patients were capable of giving informed consent, due to their mental illness (Koocher 2005; Shamoo and Keay 1996). Many of these experiments did not even give the subjects the opportunity to consent. Other experiments that were criticized included studies in which mentally ill subjects were given ketamine to induce psychosis and delusions, to study the mechanism of the disease, and healthy children 6–12 years old who were given fenfluramine (an obesity drug) to test whether they were prone to violence (Sharav and Shamoo 2000). Children were selected for these studies because their siblings were incarcerated.

During the 1990s ethical problems and concerns related to research in developing countries also came to light. In 1996, Pfizer conducted a clinical trial in Kano, Nigeria, to test whether its new antibiotic, trovafloxacin (Trovan) was effective at treating meningococcal meningitis, which was endemic in the region. In the trial, 100 children received the experimental drug and a control group received a standard therapy (ceftriaxone). A lawsuit against the company alleged that investigators gave children a reduced dose of ceftriaxone to bias the results in favor of trovafloxacin and that the children and their families were not told that they were in a study. The company disputed these allegations but later admitted that it reduced the dose of ceftriaxone to minimize pain resulting from the injections. Five children in the study who were given trovafloxacin died, and six who received ceftriaxone died. The Nigerian government determined that the lead investigator of the trial, Dr. Abdulhamid Isa Dutse, had provided a letter of ethics committee approval that was falsified. The Nigerian government claimed that the trial was an illegal study involving an unregistered drug. In 2011, Pfizer reached a settlement with families whose children died in the study. In 1999, the FDA restricted the use of trovafloxacin. The drug is banned in Europe (Lenzer 2011).

A controversy concerning the use of placebos in clinical trials emerged in 1997, when two members of Public Citizen's Health Research Group, Peter Lurie and Sidney Wolfe (1997), published an article in the *New England Journal of Medicine* (NEJM) in which they argued that fifteen clinical trials taking place in sub-Saharan Africa and other developing nations were unethical. The editor of the NEJM, Marcia Angell (1997a), also argued that the clinical trials were unethical. She compared the trials to the infamous Tuskegee syphilis study, and she also accused the researchers of accepting a double standard: one for the developed world and one for the developing world. The National Institutes of Health (NIH) director Harold Varmus and the Centers for Disease Control (CDC) director David Satcher (1997) published a response to the allegations by Lurie and Wolfe in the next issue of NEJM, and an international debate ensued.

The controversial studies attempted to determine whether perinatal (mother-to-child) transmission of HIV could be effectively prevented by using a method that was much less expensive than the method currently being used to prevent perinatal HIV transmission in developed nations. The standard of care for preventing perinatal transmission of HIV in developed nations, known as the 076 protocol, involved the administration of $800 worth of azidothymidine (zidovudine; AZT) to the mother during pregnancy and labor and to the child following birth. Breast-feeding mothers also received AZT. This method was shown to reduce the rate of perinatal HIV transmission from 25% to 8%. The controversial studies attempted to determine whether perinatal HIV transmission could be reduced by using about $80 worth of AZT and fewer health care services. The drug was administered less frequently than it was under the 076 protocol. None of the nations where the studies took place could afford the medications needed to administer the 076 protocol on a large scale. The countries also did not have sufficient health care infrastructure to execute the 076 protocol. The trials were approved by the local leaders and authorities, by the World Health Organization (WHO) and the U.N. Joint Programme on HIV/AIDS (UNAIDS), and by the CDC and NIH, which helped to sponsor the trials (Resnik 1998c). Local researchers helped to design and implement the trials and recruit subjects. Less than a year after the controversy began, the investigators showed that a 10% dose of AZT given at the end of pregnancy can reduce the rate of transmission of HIV by 50% (De Cock et al. 2000).

Most of the ethical controversy concerning these trials focused on the research design, because the trials included control groups of subjects who received placebos. The reason for including placebo groups was to prove that the lower dose of AZT was more effective than a placebo. It was

already known that the higher dose was effective, but it was not known whether the lower dose would be. The reason for attempting to determine whether the lower dose would be effective is that few people in developing nations can afford the higher dose and they were receiving nothing. The researchers wanted to test a cheaper method of preventing perinatal HIV transmission.

Lurie, Wolfe, and others objected to this research design on the grounds that it denied subjects in the control group a proven, effective therapy. They argued that since AZT has already been shown to prevent perinatal HIV transmission, all of the subjects should receive the drug. Giving placebos instead of an effective therapy was unethical and exploitative, they argued. The investigators were sacrificing the health of research subjects for scientific or public health goals. Lurie and Wolfe argued that the studies should have used active controls rather than placebo controls. An active control group is a control group where subjects receive an effective treatment. They argued that the protocol should have examined the effectiveness of different doses of AZT.

Varmus, Satcher, and other defenders of the trials argued that an active control design would lack the scientific rigor of a placebo control design. An active control design would also require a much larger sample size to ensure that the studies had sufficient statistical power. The sample would need to be much larger because a study that used active controls would be attempting to detect a very small difference between treatment groups. It would probably also take a much longer time to complete active control trials. Placebo control trials would take less time, cost less money, and would yield clearer, more rigorous results. Defenders of the controversial studies also argued that the subjects who were receiving placebos were not being exploited or mistreated, because they did not have access to AZT in any case. Participation in the study did not make the subjects who received placebos any worse off, and it could have benefited them by giving them access to medical care (other than AZT therapy). Critics of the studies argued that it did not matter whether subjects lacked access to the treatments needed to prevent the perinatal transmission of HIV, since the treatment had been proven effective and was available in developed countries. The medical standard of care should be universal, not local. The studies were exploitative because they were taking advantage of the fact that subjects did not have access to AZT (London 2001; Resnik 1998c).

In 2008, Susan Reverby, a professor of history and women's and gender studies at Wellesley College, was conducting research on the Tuskegee study when she discovered some disturbing materials pertaining to previously unpublished experiments conducted by the U.S. Public Health

Service from 1946 to 1948, in which investigators exposed hundreds of Guatemalans to syphilis. The goal of the study was to determine whether penicillin taken prophylactically can prevent syphilis. One of the study's main procedures involved asking prisoners to have sex with prostitutes known to have the disease. When this mode of transmission was not very effective, the investigators inoculated subjects' cheeks, forearms, and penises with syphilis. Out of 696 subjects, 427 developed syphilis. After Reverby published her findings in 2010, the U.S. government launched an investigation of the episode and issued an official apology to the Guatemalan government (Semeniuk and Reverby 2010).

Human Research Guidelines and Regulations

In response to various ethical problems involving research with human subjects, countries and organizations have adopted regulations and guidelines. In addition to the Nuremberg Code, other prominent ethical guidelines include the World Medical Association's Helsinki Declaration, first adopted in 1964 and revised many times since then, mostly recently in 2013 (World Medical Association 2013); the Council for Organizations of Medical Sciences (2002) guidelines; and the International Conference on Harmonization (1996) guidelines. Many professional associations, such as the AMA and the American Psychological Association, have also developed ethical guidelines for human subjects research.

Although ethical guidelines are very useful, they lack the force of laws or regulations, because they usually have no enforcement mechanism. We recognize that many different countries have laws and regulations dealing with research on human subjects, but we focus on the U.S. laws and regulations in this text. The laws and regulations adopted by other countries are similar to those adopted by the United States. We also address only the U.S. federal laws, although we recognize that some states, such as California, have their own research ethics laws. For a compilation of laws from various countries, we refer the reader to the Office of Human Research Protections (2013) website.

The first steps toward developing human research regulations in the United States took place in 1953, when the NIH opened the Clinical Center, which oversaw human experiments conducted at the NIH's intramural campus in Bethesda, Maryland, and reviewed protocols in order to avoid unusual hazards to subjects before proceeding with experiments (Advisory Committee on Human Radiation Experiments 1995; Capron 1989; Hoppe 1996). In 1965, the National Advisory Health Council, at the

prodding of then NIH director James Shannon, issued the first prior review requirement for the use of human subjects in proposed research (Capron 1989). In 1966, this action prompted the U.S. Surgeon General to generalize the prior peer-review requirement to all NIH-funded research on human subjects. In 1971, the Food and Drug Administration (FDA) issued its own similar regulations for testing new drugs and medical devices.

In response to research scandals, most notably the Tuskegee syphilis study, the United States enacted the National Research Act in 1974, which required that the DHEW (a precursor to the DHHS) to unify all of its policies into a single regulation, which is codified in the Code of Federal Regulations at Title 45, Part 46, abbreviated as 45 CFR 46. These regulations required each research institution that conducts intramural or extramural research funded by the DHEW to establish or use an institutional review board (IRB) to review and pass judgment on the acceptability of the proposed research according to the detailed requirements listed in the regulations. The regulations set forth rules for IRB composition, decision making, oversight, and documentation. IRBs should be composed of people from different backgrounds, including scientific and nonscientific members, male and female members, as well as members from within the institution and members from the local community. Other countries use similar boards, sometimes called research ethics committees (RECs) or research ethic boards (REBs). Institutions are responsible for reporting serious or continuing noncompliance or unanticipated problems to agencies that oversee research. In 1976, the NIH also developed the Office for Protection from Research Risks to provide oversight for research with human subjects. This office was later renamed the Office for Human Research Protection (OHRP) and relocated to report directly to the DHHS, in order to provide it with a stronger, more independent, and broader governing authority.

In 1979, the first presidentially appointed commission on human experimentation, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, known simply as the National Commission, issued the Belmont Report. The 1974 National Research Act mandated the formation of the National Commission. The Belmont Report provided a conceptual foundation for major revisions of the federal research regulations (National Commission 1979). In 1978, the DHEW revised its regulations to add additional protection for pregnant women, fetuses and embryos, children, and prisoners. From 1981 to 1986, changes in U.S. regulations included revisions to DHEW's regulations for IRB responsibilities and procedures, changes in the FDA regulations to bring them in line with DHHS regulations, further protections

for children, and a proposed federal common policy for the protection of human research subjects (Advisory Committee on Human Radiation Experiments 1995, p. 676). Institutions that receive DHHS funding for human subjects research must agree to abide by the ethical principles of the Belmont Report as well as DHHS regulations. These agreements are known as Federalwide Assurances (FWAs).

The Belmont Report describes three ethical principles for research with human subjects: respect for persons, beneficence, and justice. Respect for persons requires researchers to protect the autonomy and privacy of competent research subjects and to provide protections for subjects who cannot make their own decisions. Beneficence requires researchers to minimize the risks and maximize the benefits of research to subject and society. Justice requires researchers to ensure that the benefits and burdens of research are distributed fairly and to ensure that vulnerable subjects are not taken advantage of in research. According to the Belmont Report, one should carefully weigh and balance these different principles when making an ethical decision (National Commission 1979). This is similar to the approach to ethical decision making defended in chapter 1.

In 1991, DHHS issued its final federal policy—the Common Rule, 45 CFR 46—which was adopted by 16 agencies and departments (Federal Policy for the Protection of Human Subjects). However, three federal departments, including the U.S. Environmental Protection Agency (EPA) and FDA, never adopted the Common Rule. The EPA adopted the Common Rule for EPA-sponsored research and has developed a different set of rules for privately funded research submitted to the EPA (Resnik 2007, 2009a). The FDA adopted rules similar to the Common Rule that apply to privately funded research conducted to support applications for new products submitted to the FDA. The Common Rule requires that IRBs can approve research only if they find that (1) risks to subjects are minimized; (2) risks are reasonable in relation to the benefits to the subjects or society (through the knowledge expected to be gained; (3) informed consent is sought and documented; (4) selection of subjects is equitable; (5) privacy and confidentiality are protected; (6) there are additional protections for vulnerable subjects; and (7) there are appropriate provisions for data and safety monitoring (45 CFR 46.111). The Common Rule also describes requirements for consent and its documentation, but it allows these requirements to be waived under certain conditions.

The Common Rule does not require all research to undergo review by the full IRB board. First, if a research activity does not involve a human subject, then the Common Rule does not apply. A human subject is a "living individual about whom an investigator (whether professional or

student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information (45 CFR 46.102f)." If investigators obtain de-identified samples or data, then this would not qualify as human subjects research. Also, it would not be human subjects research if the samples or data come from someone who is now dead. Second, the Common Rule treats some research involving human subjects as "exempt," meaning that the regulations do not apply to it. Some categories of exempt research include some types of educational research; research relating to existing, publicly available data if subjects cannot be identified directly or through links to the data; research that evaluates public benefit programs; and food quality research (45 CFR 46.101b). If research is exempt, then it does not require IRB review. However, the IRB, not the investigator, should make the determination of whether research qualifies as exempt. Third, if human subjects research is classified as minimal risk, then it can be reviewed on an expedited basis by the IRB chair or a designee (45 CFR 46.110). Minor changes to IRB-approved studies can also be reviewed on an expedited basis. "Minimal risk" is defined as follows: "The probability and magnitude of the harm or discomfort anticipated in the research are no greater in and of themselves than those ordinarily encountered in daily life or in routine physical or psychological examinations or tests (45 CFR 46.102i)."

Although the federal regulations cover a great deal of human subjects research, they have potential loopholes or gaps. For example, privately funded medical research that is not conducted in support of an application for a new drug or medical device is not covered by any existing federal regulations. This is in contrast to the Animal Welfare Act (1966, 1996), which covers use of all animals in research. In order to close this regulatory gap and provide uniform protection for human subjects, Jay Katz was the first to suggest in 1973 that the United States adopt a law to govern the use of all human subjects in research (Katz 1993, 1996; Shamoo 2000; Shamoo and O'Sullivan 1998; U.S. Department of Health, Education, and Welfare 1973). Various bills have come before Congress to close the loopholes in the federal research regulations, but none have passed so far.

In recent years, researchers from the social and behavioral sciences, journalism, and oral history have argued that the U.S. research regulations are excessively burdensome and are better suited to biomedical research (American Association of University Professors 2006; Hambruger 2005). In 2011, the OHRP and the FDA put out an Advanced Notice of Proposed Rulemaking (ANPRM) that would reduce regulatory burdens for low-risk research by expanding the scope of exempt research, enhance the informed consent process and confidentiality protections, and provide

better oversight for research involving biological samples and data collections (Office of Human Research Protections 2011). Although the agency has held public hearings on the ANPRM and received hundreds of written comments, it has not implemented these proposed changes as of the writing of this book.

Ethical Dilemmas in Research with Human Subjects

As indicated by our historical review, human subjects research has been controversial for quite some time. Although various regulations and guidelines provide substantial guidance for investigators, controversies remain, because the regulations and guidelines are subject to interpretation and they do not cover every topic. In the remainder of this chapter, we will highlight some of the major ethical issues, most of which involve the perennial conflict between the good of the individual and the good of society (see the discussion in chapter 1). Because we cannot hope to cover every topic in our brief review, we refer the reader to other sources of information (see Emanuel et al. 2003, 2011; Levine 1988).

Research vs. Therapy

As we noted in our historical review, physicians often did not make a distinction between research and therapy and often experimented on their patients. The authors of the Belmont Report recognized that it was important to distinguish between research and therapy, because health care professionals often perform interventions on patients that are innovative or unproven (National Commission 1979). For example, a surgeon may try a new technique when performing a splenectomy, or a general internist may use nonstandard drug combinations and doses when treating an HIV patient. If these interventions are conducted in order to benefit the patient, then, according to the Belmont Report, they are not research, but innovative therapy. As such, they do not need to conform to standards of research ethics, but they should be based on standards of acceptable medical practice. If, on the other hand, interventions are conducted to develop scientific knowledge, then they should be regarded as research (National Commission 1979; President's Commission 1983a, 1983b). The Common Rule defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR 46.102d)."

Although distinctions between research and therapy make sense in the abstract, they become blurry in concrete cases. For example, consider the case of Baby Fae, an infant born with a defective heart who received a baboon heart when no human hearts were available (Pence 1995). The cross-species transplant (or xenograft) was conducted despite very low odds of success. She lived with a baboon heart from October 26 to November 15, 1984. Clearly, this was a highly innovative procedure that probably benefited transplant science much more than it benefited the patient. Health care quality improvement studies and public health intervention also test the limits of the definition of research. For example, suppose a dozen hospitals collaborate on a project to study procedures for reducing medication errors. The study will compare different procedures for reducing errors used at different hospitals. The hospitals plan to collect and analyze the data and publish it in a journal. Although the goal of this study is to determine the best way to reduce medication errors, one might consider it to be a form of research (MacQueen and Buehler 2004).

Cases that challenge the definition of research pose a difficult problem for human research ethics and regulation. On the one hand, it is important to ensure that with activities inherent risks have adequate oversight to protect people from harm. On the other hand, if an activity is classified as research, it may need to undergo an IRB review, which could pose an undue burden on health care professionals or institutions and interfere with medical or public health practice, or quality improvement activities. While it is important for an IRB to oversee research involving human subjects, there need to be limits on the IRB's jurisdiction, so that institutions and investigators can carry out activities that are designed to benefit patients, institutions, or society without unnecessary burdens that offer little additional protection (Kass et al. 2013; King 1995; MacQueen and Buehler 2004).

The distinction between research and therapy can pose a challenge for investigators who are conducting clinical trials, because there may be a conflict between their ethical duties to their patients (who are also human subjects) and their obligations as researchers (Resnik 2009b). Physicians have an ethical obligation to act in the best interests of their patients by providing them with the best available medical care (treatment, diagnosis, etc.). In some research contexts, this duty may be compromised. For example, many clinical studies require subjects to undergo additional tests or procedures (such as blood draws, x-rays, etc.) that pose risks or discomforts that they would not receive if they were not in a research study. More controversially, in some clinical trials subjects may receive a placebo instead of an accepted therapy. In randomized controlled trials

(RCTs), subjects are randomly assigned to two or more treatment groups (an active control or a placebo control). Many RCTs involve some form of blinding: Neither the subjects nor the investigators know who is receiving a particular treatment. Blinding and the use of placebos help to reduce biases related to the placebo effect, and random assignment helps to reduce biases that may result if subjects or investigators decide who receives a particular treatment. Most RCTs have a data and safety monitoring board (DSMB) that reviews data and safety reports to protect subjects from harm. The DSMB may recommend that the trial be stopped if an experimental treatment is too risky, or if it is so effective that it should not be withheld from subjects receiving placebos or a standard treatment.

The ethical issue in placebo-controlled RCTs is that physicians appear to be violating their duties to patients because they are withholding effective therapy. Some have argued that it is ethical to use placebos in an RCT only when there is no effective treatment (so subjects are not denied treatment), or withholding treatment poses no serious or permanent risks to subjects. This is the position adopted by the Helsinki Declaration (World Medical Association 2013). For example, one could argue that it is ethical to use placebos in an RCT comparing an experimental medicine to a placebo in the treatment of moderate arthritis pain, because withholding pain medications is not likely to result in serious or permanent harm. Using a placebo group in an RCT to test the effectiveness of a blood pressure medication for managing severe hypertension would be unethical, in this view, because a patient with severe hypertension who does not receive effective treatment can suffer serious and permanent harms, such as stroke or heart attack. Some commentators argue that using placebos in RCTs (such as studies comparing surgical interventions to a sham procedure) can be ethical even when subjects face serious or permanent risks, as long as the benefits of the research outweigh the benefits and the subjects' consent. The rationale for this view is that competent adults should be allowed to choose to take some risks for their own potential benefit or to contribute to the advancement of human knowledge (Emanuel and Miller 2001; Miller and Brody 2002).

Another issue related to the research/therapy distinction concerns returning individualized results to research subjects. As noted earlier, the purpose of research is to collect information used to develop scientific knowledge. However, information collected in research is often useful to subjects in making medical decisions pertaining to disease prevention or treatment. When research results have clinical relevance, research becomes similar to medical diagnosis (Resnik 2009b). For example, a clinical study might collect information concerning vital signs, blood composition,

DNA, etc. One could argue that researchers have an ethical obligation, based on the principle of beneficence, to provide research subjects with results about dangerous conditions, such as high blood pressures, elevated blood sugar, and so on, because proper use of this information can protect subjects from harm. A subject who learns that he has moderately high blood pressure can be advised to see his doctor. If a subject's blood pressure is dangerously high, he may need to go to the hospital for emergency treatment. Sometimes the research results are incidental findings, that is, results that researchers were not looking for but happened to discover (Wolf et al. 2008). For example, suppose that a woman undergoes a sonogram for a study of uterine fibroids. The sonogram might indicate that she has abnormal growths that could be uterine cancer. Most people would agree that the investigator should report these incidental findings to the participant so she can follow them up.

While there is little question that investigators should inform subjects about high blood pressure or abnormal growths that could be cancer, controversies can arise concerning the return of other results, such as genomic/genetic data, information concerning paternity, and data from unvalidated biomarker studies, because sharing this information with subjects might do more harm than good. For example, suppose that researchers conducting a study of genetics of heart disease discover that several mutations are associated with a 5% increased risk of heart disease. Should they share these results with participants? On the one hand, one could argue that the investigators should share these findings with subjects, because the results may be useful to them and the subjects would want to know about them. On the other hand, one might argue that the investigators should not return these results to participants because the clinical value of knowing that one has a genetic mutation associated with a 5% increased risk of heart disease is unclear, and the laboratory tests used to detect this mutation may be unreliable or inaccurate. In the United States, medical tests used to diagnose and treat diseases must be conducted by laboratories that have been certified as meeting standards for reliability and accuracy. Research laboratories that conduct genetic/genomic tests for investigators do not need to meet these standards. Returning results with uncertain clinical value produced by uncertified laboratories could cause subjects needless worry and lead to poor decisions (Beskow and Burke 2010; Ravitsky and Wilfond 2006; Wolf et al. 2008).

A final research vs. therapy issue concerns providing subjects in clinical research with medical care beyond what they receive as part of the study. This could include medical care provided during the study (known as ancillary care) or medical care following completion of the study, such as

continued access to medications (Resnik 2009b). This issue is especially important in a research setting in which most subjects lack access to care, such as clinical trials conducted in developing nations. For example, suppose investigators are conducting a clinical trial comparing the effectiveness of two different HIV treatment regimens in a Ugandan population. During the course of the study, they might discover that some participants are infected with parasites. They would need to decide whether to offer treatment for these parasites in addition to the other care that is provided (Richardson and Belsky 2004). Once the trial is completed, most subjects would probably no longer have access to HIV medications, and researchers would need to decide whether to help subjects obtain post-trial access to these medications (Millum 2011). The ethical rationales for providing medical care beyond what is needed to conduct a clinical study are to benefit subjects and avoid exploitation. However, providing this additional medical care can add to the costs of research and may constitute an undue burden on investigators. Some investigators and sponsors may decide to forego conducting research if they are required to provide medical care beyond what is called for in the study protocol. Additionally, providing additional medical care may obscure the distinction between research and therapy in the subjects' minds and thereby undermine the consent process (see the discussion below) (Resnik 2009b).

Risk vs. Benefit

Many issues in human subjects' research pertain to risks and benefits, such as developing and implementing procedures and study designs to minimize risks, assessing risks and benefits, and deciding when risks to subjects are justified in relation to the benefits to subjects and society. Although scientific studies pertaining to likely risks and benefits can provide useful information for the evaluation of risks and benefits, risk/benefit decisions always involve an ethical dimension, because one must compare risks and benefits (Kopelman 2000a, 2000b). To determine the overall risks of a study, one must summarize the risks of the different procedures, interventions, and tests used in the study. In a clinical study, interventions, procedures, or tests that patients would have received if they were not in the study should not be included in this risk analysis (Wendler and Miller 2011b). For example, if a study is collecting and analyzing tissue samples from patients who receive lung transplants, the risks of the study would not include the risk of the lung transplant.

Some studies involve significant risks to human subjects. For example, subjects in a clinical trial testing the safety and efficacy of a cancer treatment may face serious risks, such as liver toxicity, kidney failure, dangerous immune reactions, hospitalization, or even death. These risks are usually regarded as acceptable as long as the subjects may potentially benefit from their participation. For example, patients could benefit from having their cancer effectively treated or cured, or from increased longevity or reduction in symptoms (Wendler and Miller 2011b).

Imposing significant risks on subjects is more controversial when the participants are healthy, adult volunteers who are not likely to derive any medical benefits from the study. For example, the subjects in Walter Reed's yellow fever experiments were healthy adult volunteers. Phase I trials of new drugs, biologics, or medical devices are usually conducted on healthy volunteers who are not expected to derive any significant benefits from participation. Phase I studies attempt to generate data concerning safety, dosing, pharmacokinetics, and so on. If the FDA decides that a new product is considered safe for human use after completing Phase I testing, then the agency may allow a sponsor to conduct Phase II studies on subjects with a disease or medical condition, to determine whether the product is effective. If the product completes Phase II testing successfully, then sponsors may begin larger, Phase III studies. If the product completes these studies successfully, the FDA may decide to allow it to be marketed. Thus, the ethical rationale for Phase I studies is that they offer important benefits to society because they are a necessary part of the process of developing new medical treatments (Shamoo and Resnik 2006b). Not all studies on healthy volunteers involve the testing of new medical products, however. Many healthy volunteer studies investigate human physiology, metabolism, immunology, psychology, or behavior (Resnik 2012c).

Although there are no systematic data on the risks that healthy volunteers typically face, anecdotal evidence suggests these can be significant. For example, in 1996 Hoiyan Wan died after receiving a fatal dose of lidocaine during a bronchoscopy performed at the University of Rochester as part of an air pollution study on healthy volunteers. In 2001, Ellen Roche died after developing respiratory distress due to inhaling hexamethonium as part of an asthma study conducted at Johns Hopkins University in 2001. In 2006, six healthy volunteers in a Phase I trial, conducted at Parexel's clinical pharmacology research unit at Northwick Park Hospital in London, developed a dangerous immune reaction and multiple organ dysfunction after receiving a monoclonal antibody known as TGN1412 (Resnik 2012c). Three of these subjects nearly died. There were serious lapses in the design and safety considerations in this trial. For example, the investigators did

not wait long enough before administering doses to new volunteers. When testing a drug on a human being for the first time, the usual procedure is to wait and see how the first volunteer reacts to the drug before administering it to other volunteers. The researchers in this study did not observe this and other safety rules (Shamoo and Woeckner 2007).

Exposing healthy adult volunteers to significant risks raises the issue of whether there should be any limits on the risks the healthy subjects face in research. The federal research regulations require that risks be reasonable in relation to the benefits of the knowledge gained, but they do not place any limits on the risks to subjects. One might argue that there should not be any limits on risks that adult subjects face, as long as they provide their informed consent and the research offers important benefits to society. To place limits on research risks would be paternalistic interference in the autonomy of competent adults (Miller and Wertheimer 2007). Some have argued that paternalistic limits on risks can be justified to protect subjects from hazards they may not understand fully and to protect investigators, institutions, and the research enterprise from the impacts of negative publicity when healthy adults are significantly harmed in research (Resnik 2012c).

In medicine, there is also a long and honorable history of self-experimentation, such as Walter Reed's experiments. Self-experimentation is usually a highly altruistic act and morally praiseworthy. However, one might ask whether there should be limits on the risks that a researcher may take in the name of science. A few years ago, a group of researchers said they would test an HIV/AIDS vaccine on themselves (Associated Press 1997). Although this is certainly a worthy cause, one might argue that these researchers should not be allowed to take the risk of contracting HIV/AIDS. There can also be methodological problems with self-experiments, such as a small sample size and bias, that could affect the balance of risks and benefits (Davis 2003).

Some risk/benefit issues involve questions about the benefits of research. One of the many problems with some of the Nazi experiments (discussed above) is that they had questionable benefits. Some commentators have argued that pesticide experiments on human subjects conducted by private companies have dubious benefits (Krimsky and Simocelli 2007). In these experiments, private companies have exposed healthy adult human subjects to pesticides to generate safety data to submit to the EPA. The EPA has had to decide whether to accept these types of data for regulatory purposes. The agency has formulated new regulations pertaining to "third-party" research, or research sponsored by private companies, to submit to the EPA. One of the key issues in pesticide experiments is

whether the benefits to society of the research outweighed the risks to human subjects (Robertson and Gorovitz 2000). Some environmental groups have argued that all pesticide testing on human subjects is unethical because the benefits of the research accrue mostly to the private companies and not to society. Others have argued, however, that society can benefit from pesticide experiments that lead to better knowledge of pesticides, which can be used for regulatory and public health purposes (Resnik and Portier 2005). A report by the Institute of Medicine (2004) determined that some types of low-risk pesticide experiments are acceptable, if they meet stringent ethical and scientific standards.

A final risk/benefit issue pertains to dealing with risks and benefits to third parties impacted by research, such as the subjects' community or family. For example, consider a hypothetical study on alcoholism, drug abuse, venereal disease, and sexual behavior in a Native American population. It is conceivable that the study might generate results that could be embarrassing to community members or could lead to discrimination or stigma. Researchers conducting this study would need to consider how best to protect the community's interests while advancing scientific knowledge. Consider a hypothetical study on the efficacy of allergy management education. As part of the study, investigators will hire private contractors to treat the home with insecticides to kill cockroaches. Although the homeowners provide consent for the study, other people who enter the home (such as children) may be affected by the insecticides. Investigators would need to decide how best to protect the third parties from risks. Finally, consider a hypothetical study of a drug to treat depression. If women in the study are lactating, their infants could be exposed to the drug through breast milk. Investigators would need to decide whether to exclude women from the study who are lactating.

The U.S. research regulations have nothing to say about protecting third parties, with the exception of regulations pertaining to enrolling pregnant women in research. U.S. research regulations focus on risks to the subject, not on risks to other people affected by the research. Although the regulations have little to say about third-party risks, the principle of beneficence, from the Belmont Report, implies that investigators should address risks to third parties, because the principle requires researchers to maximize the overall balance of benefits/risks and does not limit benefit/risk maximization to research participants. While most people would agree that investigators have an ethical obligation to address third-party risks, difficult questions can arise concerning how best to meet this obligation. In some cases, informing subjects about third-party risks and urging them to take steps to minimize harm will provide sufficient

protection for third parties. In other cases, it may be necessary to obtain the consent of third parties before conducting a study. When a study is likely to have a significant impact on a community, investigators may need to consult a community advisory board concerning research design and implementation (Resnik and Sharp 2006; Weijer and Emanuel 2000).

Informed Consent

Informed consent promotes respect for the subject's autonomous decision making. Though informed consent has been widely recognized as a fundamental principle of ethical research since the adoption of the Nuremberg Code, it raises many different ethical issues. The most basic issue is whether informed consent of the subject (or the subject's representative) is ethically required. Some studies involve research conducted under emergency conditions in which it may not be possible to obtain the consent of the subject or the subject's representative. For example, if an unconscious victim of a car accident with a rare blood type is bleeding to death, it might be reasonable to provide the victim with an experimental, artificial blood product if no matching human blood is available and the subject's representatives (such as close relatives) are not available to provide consent. The ethical rationale for foregoing informed consent under these circumstances is that consent can be implied, because most people would consent to participation in a life-saving emergency research study. In 1996, the FDA developed special regulations for emergency research. Even though federal regulations allow emergency research under some circumstances, controversies may still arise concerning risks and benefits of the study. Fairness may also be an important issue if the majority of participants will be enrolled from low-income groups (Karlawish 2011).

Another fundamental issue is whether the informed consent process can be modified under some circumstances so that subjects are not fully informed. In Milgram's obedience to authority experiments, the subjects were told they were in a study, but they were not told about the exact nature of the research to avoid biasing the results. The subjects were deceived about their role in the study. The Common Rule allows IRBs to alter or waive informed consent when the research is regarded as minimal risk, it could not be conducted without an alteration or waiver, and the subjects will be debriefed after the study is complete (45 CFR 46.116d). Deception is a controversial topic in social science research, because people may disagree about the risks of research and the ability to obtain research objectives without deception. Some have argued that useful knowledge can

often be gained in social science research without deception, and that deception can pose more than minimal risks, because people may experience emotional distress after learning that they have been intentionally deceived (Wendler and Miller 2011a).

Many issues in informed consent pertain to the disclosure and understanding of information (Capron 2011). Although the federal regulations specify types of information that must be disclosed (such as risks, benefits, alternatives, procedures, etc.), they do not cover everything that might need to be disclosed and they do not provide specific guidance concerning disclosure (45 CFR 46.116). For example, the regulations do not say that conflicts of interest must be disclosed. The regulations say that reasonably foreseeable risks must be disclosed, but they do not say what makes a risk reasonably foreseeable or the types of risks that must be disclosed (Resnik 2013).

Studies of the informed consent process indicate that subjects often do not understand key concepts related to research, such as randomization, research risks and procedures, and the difference between research and therapy (Flory et al. 2011). Research has shown that subjects in clinical studies often mistakenly think the study is designed to benefit them when its main purpose is to develop scientific knowledge. This mistaken belief, known as the therapeutic misconception, can pose a significant challenge for the consent process (Appelbaum et al. 1987). Researchers have an obligation to help subjects understand information they receive as part of the consent process. They should provide subjects with an ample opportunity to ask questions. Because many potential research subjects are not skilled readers, consent documents should be written at an eighth-grade reading level or lower (Capron 2011).

Some consent issues concern conditions that affect the voluntariness of the subject's choice. Federal research regulations require that investigators minimize the potential for coercion or undue influence (45 CFR 46.116). Prisoners, military personnel, employees participating in company-sponsored studies, and students in studies conducted by their professors may face different types of pressure to participate in research (Bonham and Moreno 2011). Ethical issues can arise concerning enrolling these subjects in research and ensuring that they can make a free choice. Ethical issues can also arise concerning compensating subjects for their participation, because payment for participation may be considered undue inducement if the amount of money subjects can receive is so high that it is likely to compromise their decision making (Dickert and Grady 2011). Not paying subjects enough for participation can also be unethical if it constitutes exploitation of subjects by private sponsors or investigators (Shamoo and Resnik 2006b).

Cultural factors often are relevant to the consent process. As noted in chapter 1, in some cultures women do not make their own medical decisions; medical decisions are made by a woman's husband or older male relative. In other cultures tribal leaders must be consulted in medical decision making (Hyder and Wali 2006). In Western cultures, competent adults make their own decisions. Investigators who conduct studies in cultural settings where individual consent is not the norm must decide how to enroll subjects in research. One possible way of dealing with this dilemma is to allow individuals to make their own choices while consulting other culturally appropriate decision makers (Council for the Organizations of Medical Sciences 2002).

Consent for the use of samples and data is an emerging consent issue. Consent documents often inform subjects that their samples or data may be shared with other researchers and used for various studies other than the one they are participating in. Some commentators have argued that subjects should have to provide consent for specific uses of their samples or data, while others have argued that consent to a broad use of samples or data is permissible (Wendler 2006). The advantage of specific consent is that it maximizes subjects' autonomy. The disadvantage of specific consent is that it can be difficult to implement and may constitute an unnecessary burden for subjects and investigators, because subjects would have to give their permission each time that an investigator wants to share samples or data with other researchers. The advantage of broad consent is that it reduces the burden on subjects and investigators and promotes sharing of samples and data; the disadvantage of this approach is that it may not completely respect subjects' autonomy, as subjects might not want their samples or data used in some types of studies (such as research involving cloning or the production of human–animal chimeras). A compromise position (known as the tiered approach) is to present subjects with a menu of options for use of their samples or data. Subjects can give permission for broad sharing of their samples or data or sharing only for specific studies or uses (Salvaterra et al. 2008). For example, subjects might allow their samples or data to be used only in research related to their disease or condition, or they might allow their samples or data to be used for only noncommercial research.

Privacy and Confidentiality

Privacy and confidentiality are different, but related, concepts. Privacy refers to a domain of personal space, dominion, or information that one

has a right to keep from the public. Some threats to privacy have little to do with confidentiality. For example, a stranger who sees a person naked without their permission would be violating that person's privacy. Confidentiality refers to measures used to protect private information, such as medical or research records. Some confidentiality protections used in research include limiting access to research records and specimens, using computer security measures (such as encryption) to protect data, keeping paper records and specimens in locked rooms, and using a code to identify data or specimens. U.S. research regulations require that investigators take appropriate steps to protect privacy and confidentiality (45 CFR 46.111a7) but they say nothing specifically about how to do this. The Health Insurance Portability and Accountability Act (HIPAA) includes rules designed to protect medical privacy that apply to research conducted in hospitals or other clinical settings (Department of Health and Human Services 2013). The rules prohibit unauthorized disclosure of personal health information, with some exceptions, such as disclosure for public health reporting purposes.

Ethical dilemmas can arise in research when investigators share data or specimens from human subjects. The principle of openness (see chapter 1) instructs investigators to share data and samples as widely as possible to promote the progress of science. However, sharing data and samples may threaten confidentiality if not done properly. Researchers have used three different methods for sharing data and samples. Under the first method, recipients sign data use agreements (to receive data) or material transfer agreements (to receive samples). These agreements state conditions for the use of samples and data and require recipients to protect confidentiality. Recipients are not allowed to share samples or data with others without permission. The advantage of these agreements is that they provide strong confidentiality protections. The disadvantage is that they take time and effort to execute and can therefore inhibit sharing. Under the second method, researchers remove personal identifiers (such as name, phone number, address, etc.) from samples or data and share them with recipients. Recipients do not need to sign a data use agreement to receive data though they may still need to sign a material transfer agreement to receive samples. The advantage of this method is that it is less burdensome than signing a data use agreement and therefore promotes sharing. Under the third method, researchers may make de-identified data available to the public on a website. Investigators can download data without signing any agreement. The advantage of this approach is that it maximizes data sharing. A disadvantage of this approach is that it may not adequately protect confidentiality because it may be

possible to re-identify individuals in de-identified databases. Statisticians have developed methods to identify individuals in genomic databases from a sample of the individual's DNA, as well as methods for identifying individuals from demographic information (e.g., gender, age, race, etc.) and a postal code. The upshot of these developments is that it may not be wise to place de-identified human subjects data on publicly accessible websites, because this may not adequately protect confidentiality (Homer et al. 2008; Lin et al. 2004; Lowrance and Collins 2007; McGuire and Gibbs 2006; Resnik 2010). Some investigators are promoting "recruitment by genotype" from so-called de-identified data (Beskow et al. 2012) for tissue samples stored in biobanks. There are serious ethical challenges to the use of tissue samples. Rial-Sebbag and Cambon-Thomsen (2012) have suggested a new governance model for the use of such samples, acknowledging the potential for breach of confidentiality.

Similar sorts of concerns can also arise when researchers publish data. Researchers who report data on individuals usually use case numbers, pseudonyms, codes, or other labels that do not identify individuals. However, sometimes it will be possible to identify individuals based on their demographic information, especially in studies on small communities. Sometimes it may be necessary to protect the confidentiality of an entire community to prevent stigma or discrimination. To protect confidentiality, it may be necessary to redact demographic data that could identify individuals or communities. However, redaction may reduce the value of the data for other researchers, because they may need this demographic information. Researchers need to be aware of these issues when they publish data and take appropriate steps to protect confidentiality (Kaiser 2009).

Protecting the confidentiality of subjects' family members also raises ethical issues. Researchers sometimes ask participants questions about their family history. In some cases family members can be readily identified based on an answer to a question; in other cases they may not be. For example, if the question is "was your father an alcoholic?" the answer readily identifies the subject's father. If the question is "did any of your siblings have problems with alcohol?" and the subject has more than one sibling, the answer does not readily identify a sibling. If family members can be readily identified from the answer to a question dealing with a highly sensitive topic (such as medical or psychiatric history, substance abuse, or criminal history) then researchers should obtain consent from those family members (Botkin 2001). A study known as the Personal Genome Project (PGP) raises some interesting issues concerning the confidentiality of family members. Human subjects in the PGP agree to forego traditional confidentiality

protections and allow their identified genomic and medical information to be made available on a public website. The subjects understand the threat that this poses to their own privacy and confidentiality, but they have made this choice to help advance scientific research (Ball et al. 2012). While foregoing traditional confidentiality is an admirable gesture, it may threaten the privacy and confidentiality of the subjects' family members, since it may be possible to identify family members based on genomic or other information about the subjects. Some commentators have argued that a project like this should not be conducted unless the subjects' family members also consent to making this information publicly available (Resnik 2010).

Protecting privacy can become a significant issue when conducting research in homes or workplaces. Some research studies include interviews and sample collections that take place in the home or workplace. When researchers enter these areas, they may observe unethical or illegal activities that they feel they have an obligation to report, such as child abuse/neglect, illicit drug use, violations of occupational health or environmental laws, and so on. When this happens, researchers may face a conflict between protecting privacy and preventing harm to individuals or promoting public health and safety. Most states have laws requiring health professionals, educators, and social workers to report suspected child abuse and neglect. Researchers should inform research subjects about their obligations under these laws and report their suspicions. In other situations, researchers must use good judgment when deciding whether to report something they observe. For example, if a workplace safety violation poses a risk of serious harm to employees, researchers should inform management and possibly the relevant authorities. They may decide to only report a minor safety violation to management and not the authorities (Resnik 2011).

Vulnerable Subjects

Vulnerable research subjects are individuals who have difficulty providing informed consent or protecting their own interests, due to age, mental disability or illness, poverty, lack of education, language barriers, or other cultural or social factors (Macklin 2003). The Common Rule and FDA regulations require investigators to provide additional protections for vulnerable subjects (45 CFR 46.111b), and the Common Rule includes special protections for pregnant women, fetuses, and neonates (45 CFR 45, Subpart B); prisoners (45 CFR 46, Subpart C); and children (45 CFR, Subpart D). The FDA has also adopted the Common Rule's protections for children. International ethical guidelines, such as the Helsinki Declaration (World

Medical Association 2013) and the Council for Organizations of Medical Sciences guidelines (2002), also include additional protections for vulnerable subjects. The Belmont Report articulates the ethical rationale for providing additional protections for vulnerable subjects. According to the authors of the report, additional protections are needed to protect vulnerable subjects from exploitation. As described in our historical review (above), investigators have used prisoners, mentally disabled people, and children in studies that placed them at serious risk of harm but offered them no benefits. Such practices were unfair, harmful, and exploitative (National Commission 1979).

Some of the additional protections for vulnerable subjects found in research regulations and ethical guidelines include the following:

- Using a legally authorized representative (LAR), such as a parent, guardian, or family member, to provide consent for subjects who lack the ability to provide informed consent;
- Using procedures (such as a mental status assessment) for determining whether adults have the ability to provide informed consent for research participation;
- Ensuring that subjects who cannot provide informed consent nevertheless provide their assent (i.e., acknowledgment, cooperation), if assent would be meaningful to them;
- Including members on the IRB who have the knowledge and expertise to evaluate research involving vulnerable populations;
- Ensuring that there is a legitimate scientific reason for including vulnerable subjects in a study; vulnerable subjects should not be used if knowledge can be gained by using subjects who are not vulnerable; and
- Placing limits on the risks that vulnerable subjects are permitted to encounter in research.

Concerning the last point, the Common Rule places limits on the risks that may be imposed on pregnant women, fetuses, neonates, children, and prisoners. Pregnant women may not participate in research that poses more than minimal risks to the fetus if the research does not offer direct benefits to the fetus or the woman (45 CFR 46.204). Neonates of uncertain viability may not participate in research unless the research is likely to enhance the viability of the neonate or the research is a minimal risk (45 CFR 46.205). Prisoners may participate in more than minimal risk research only if it offers them direct medical benefits or affects prisoners as a class; other types of minimal risk prisoner research should focus on the causes or conditions of incarceration or criminal behavior (45 CFR 46.306).

The Common Rule allows four categories of research involving children: (1) minimal risk research (45 CFR 46.404); (2) more than minimal risk research that offers medical benefits to subjects (45 CFR 46.405); (3) minor increase over minimal risk research likely to yield knowledge about the subject's disorder or condition (45 CFR 46.406); and (4) research that is not otherwise approvable that represents an opportunity to address a serious problem affecting the health or welfare of children (45 CFR 46.407). An IRB cannot approve research that falls into this last category; the research can be approved only upon recommendation from a special DHHS panel. There is a concern that this category of research on children (45 CFR 46.407) has no explicit limits on the risks allowed for clinical trials on children (Wendler 2013).

The net effect of protective regulations and guidelines pertaining to vulnerable subjects is that some vulnerable groups, such as children and pregnant women, have been routinely excluded from research, which adversely affects the welfare of these groups (Mastroianni and Kahn 2001). For example, 90% of drugs prescribed to children have not been tested on pediatric populations. Physicians prescribe these drugs to children on an "off-label" basis by extrapolating from their effects on adult populations. For example, physicians may use body weight to guide drug dosing. This practice assumes that children are physiologically similar to adults, which is often a faulty assumption. Since the 1990s, pediatricians and advocacy groups have urged investigators and sponsors to include more children in research (Friedman Ross 2006; Tauer 1999). The U.S. government has taken some steps to encourage drug testing on children. In 1998, the FDA mandated that the pharmaceutical industry test drugs and biological products on children if they are to be used on children (Tauer 1999). In 2002, Congress passed the Best Pharmaceuticals for Children Act, which gives pharmaceutical companies an additional six months of market exclusivity for new drugs tested on children (Food and Drug Administration 2002).

The concept of minimal risk plays an important role in the pediatric research regulations, because IRBs can approve nonbeneficial research that is a minimal risk or a minor increase over minimal risk. A minimal risk is defined in the federal regulations as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(i))." The definition consists of two ways of defining minimal risk. Minimal risk is either a risk not greater than risks ordinarily encountered in daily life or a risk not greater than routine physical or

psychological tests. Because the federal regulations do not define risks "ordinarily encountered in daily life," there has been considerable disagreement about the meaning of this phrase, and there is evidence that different investigators and IRBs interpret it differently. In one study, 23% of IRB chairpersons classified allergy skin testing as minimal risk, 43% classified it as a minor increase over minimal risk, 27% classified it as a more than a minor increase over minimal risk, and 7% answered "don't know" (Shah et al. 2004).

There are two ways of interpreting risks "ordinarily encountered in daily life": a relativistic interpretation and an absolute one. According to the relativistic interpretation, daily life risks can vary according to the population and circumstances. For example, a child living in a ghetto probably encounters more risks than a child living in the suburbs. A child with a serious, chronic disease encounters more risk than a healthy child. Kopelman (2000a) argues against the relativistic interpretation on the grounds that it would lead to unequal protections of children and injustices. The relativistic interpretation leads to unequal protections because different IRBs could classify different studies as minimal risk, depending on the population and circumstances. A study approved as minimal risk by one IRB might not be approved by another. The relativistic interpretation leads to injustices because some populations might be required to bear a greater burden of research risks than other populations, because they already encounter higher risks in their daily lives. To avoid these ethical problems, an absolute interpretation should be used. The daily life standard of minimal risk should be the risk that a typical, healthy child ordinarily encounters (Wendler et al. 2005).

Involving pregnant women in research presents investigators and institutions with difficult ethical and legal questions. On the one hand, pregnant women have a right to decide whether to participate in research, and they can also benefit from research that provides them with medical or psychological therapy. Additionally, it is important to learn about prescribing drugs during pregnancy and how to treat medical problems during pregnancy. On the other hand, including pregnant women in research may expose the fetus to risks. Even if one does not consider the fetus to be a human being with full moral or legal rights, one must still be concerned about the harms that may occur to the future child while in the uterus. The thalidomide tragedy of the 1950s and 1960s provides a stark reminder of the dangers of fetal drug exposures. Thousands of children (mostly in Europe) were born with severe birth defects (such as missing or deformed limbs) as a direct result of in utero exposure to thalidomide, prescribed as a treatment for morning sickness (Stephens and Brynner 2001).

Investigators and research sponsors have been wary of including pregnant women (or even women who could become pregnant) in research out of fear of the legal liability resulting from birth defects related to research. A concern about how research procedures and interventions might affect the fetus is a reason why women were routinely excluded from research for many years (Dresser 2001). In the mid-1980s, feminist activists and politicians pressured the NIH to include more women in research studies. As a result, the NIH now has policies for the inclusion of women and minorities in research (Dresser 2001).

Prior to the National Commission's report in 1979, the use of prisoners in research was common. Current federal regulations reflect the National Commission's recommendation for special restrictions on the recruitment and use of this population as human subjects in research. Prisoners are compensated only for discomfort and time spent in research. The normal compensation package for adults outside the prison could be regarded as exploitative in the prison environment because most prisoners would prefer research participation to the daily boredom of prison life. One might argue that most prisoners would not participate in research if they were not in prison. There are also problems with maintaining confidentiality in the prison environment. In his book *Acres of Skin*, Hornblum (1998) chronicles how in the 1960s and 1970s researchers used the skin on the backs of prisoners to test numerous drugs and perfumes for toxicity and carcinogenicity. Several ethical issues came to light: Subjects received payment, housing for the experiment was better than that provided for other prisoners, the human interactions during the experiments were coercive, and informed consent was barely informative. Even though there are good reasons for excluding prisoners from research, some have argued that exclusionary regulations and policies unfairly restrict prisoners' autonomy. Some prisoners may want to participate in research in order to make a contribution to society and make amends for the harms they have caused (Bonham and Moreno 2011).

Although both the National Commission recommended extra protections for adults who may have difficulty providing informed consent due to mental disability or illness, the federal government did not issue special protections for these subjects as a separate subpart of 45 CFR 46 when it revised this document in 1991, due to insufficient advocacy for the mentally ill or disabled at that time (Shamoo and Irving 1993). To understand issues pertaining to adults who may have a compromised ability to provide consent, it is useful to distinguish between competence and decision-making capacity (DMC). Competence is a legal concept that refers to the right to make decisions. Adults have the legal right to consent to research

participation unless a court declares them to be legally incompetent for that task and appoints a guardian. DMC is a psychological concept that refers to the ability to make reasonable choices. Adults who are legally competent may lack DMC because they have not been adjudicated incompetent (Berg et al. 2001). For example, a demented nursing home patient who has not been declared incompetent would lack DMC but be legally competent.

If an adult lacks sufficient DMC to consent to research participation, then it is necessary to obtain consent from an LAR. The preferred order for selecting an LAR in most jurisdictions is a guardian, health care power of attorney, spouse, or close family member (such as an adult offspring or sibling). An LAR may also assist in the consent process when an adult has the ability to give consent if there are some questions concerning the adult's DMC. If the adult's DMC declines, the LAR may be available to make decisions (National Bioethics Advisory Commission 1998). In some cases, an adult may use a legal document, such as a living will or health care power of attorney form, to express a desire to participate in research if he or she loses DMC. Researchers should honor wishes expressed in these documents (Berg et al. 2001).

One of the controversial issues relating to conducting research on adult subjects who may lack the ability to provide informed consent is whether there should be an independent assessment of their DMC (National Bioethics Advisory Commission 1998; Shamoo 1994b). The argument in favor of an independent assessment is that researchers have a conflict of interest when it comes to assessing DMC, because it would be in the researcher's interests to find that a person has sufficient DMC to participate in research to meet enrollment goals. The argument against independent assessment is that this can be very burdensome, expensive, and time-consuming, and is not necessary in low low-risk research. A compromise position, which we recommend, is that the need for an independent assessment of prospective subjects' DMC should vary with the benefit/risk ratio of the research. When the risks of research are more than minimal and the subjects will receive no direct benefits, an independent assessment of prospective subjects' DMC should be required. For example, a Phase I clinical trial of a new drug on healthy subjects should have independent assessment of prospective subjects' DMC. When the risks of research are more than minimal but the subjects are likely to benefit from participation, an independent assessment of DMC is advisable but not required. For example, an independent assessment of prospective subjects' DMC would be advisable in a Phase II clinical trial for a new chemotherapy agent. When the risks of research are minimal, an independent assessment of DMC is not required.

For example, there would be no need for an independent assessment of prospective subjects' DMC for a study that only requires subjects to fill out a health information questionnaire and have five milliliters of blood drawn every five years.

Another important issue concerning adults who cannot provide consent is whether they should be excluded from nonbeneficial, more than minimal risk research. The argument for exclusion is that people who cannot make their own decisions should be protected from harm. The argument against exclusion is that it is important to conduct some types of more than minimal risk studies on adults who lack DMC to learn more about their diseases or conditions. If these adults are excluded, this will adversely affect the welfare of individuals with the disease or condition and stigmatize the group (Miller and Fins 1999). For example, consider a hypothetical long-term study of Parkinson's disease (PD). Adults are recruited into the study when they have DMC, but they may lose DMC as their disease progresses and they develop dementia. The study includes yearly muscle biopsies, which are more than minimal risk procedures that provide important information about how PD affects the muscles. Excluding subjects from this study when they develop dementia may compromise the usefulness of the research, since it is important to understand muscle function as PD progresses. One way of handling this situation would be to ask adults with DMC to fill out an advance directive that allows them to undergo more than minimal risk study procedures if they lose DMC.

One of the most controversial episodes of military research with human subjects occurred during the first Gulf War (1990–1991), when the U.S. Department of Defense obtained an informed consent waiver from the FDA to administer the anthrax vaccine to thousands of soldiers in the war without their consent. The military wanted to vaccinate soldiers against anthrax because it was thought that Iraq had developed and stockpiled biological and chemical weapons, including weapons-grade anthrax dust. The vaccine was an investigational new drug (IND). There were no published studies of the safety or efficacy of the vaccine in humans prior to the war. The military's main rationale for giving the vaccine without informed consent is that if soldiers refused the vaccine, they could endanger other soldiers and military operations if they contracted anthrax. Some soldiers did refuse the vaccine, and they were court-martialed and punished. Many soldiers suffering from Gulf War illness claim that their mysterious disease was caused by exposure to the anthrax vaccine. An FDA review of the military's procedures found that they deviated from the FDA's approved plan for testing the vaccine. For example, the military

convened a second IRB to approve the experiment after the first one determined that it was unethical (Cummings 2002; Moreno 2000).

Employees are sometimes asked to participate in research studies conducted by their employers. Like prisoners and soldiers, employees may face coercion or intimidation during the consent process. As mentioned earlier, pesticide companies used employees as test subjects in ethically questionable pesticide experiments (Resnik and Portier 2005). As mentioned in chapter 2, Woo Suk Hwang asked technicians working in his laboratory to donate eggs for his therapeutic cloning research. For employer-sponsored experiments involving employees to be ethical, great care must be taken to safeguard the employees' ability to freely consent as well as their privacy and confidentiality. One way to do this is for the employer to hire an independent contractor to conduct the study. The contractor, not the employer, would have access to the names of people who volunteer for the study. Since the employer would not know who participates (or does not participate) in the research, the employer will not be able to reward employees for participating or penalize employees for not participating. Employees who volunteer for this type of research should be assured that their participation will in no way affect their employment status, salary, and so forth.

Students often participate in research conducted by their professors. These studies range from filling out self-administered surveys distributed in psychology or sociology classes, to providing biological samples for chemical or genetic analysis, to participating in controlled behavioral experiments (Moreno et al. 1998). Students, like employees, may face coercion, undue inducement, or intimidation during the consent process. They may also not want to disclose private information to their professors. For students to participate in research, professors must take steps to ensure that consent is valid and to protect privacy. Participation in research should not be a part of the course grade, unless the professor gives the student an alternative to research participation that takes the same amount of time and effort, such as writing a short essay. Professors should not have access to private information that students disclose in research. Professors may only review private information if personal identifiers have been removed.

Research participants from developing nations represent a unique class of vulnerable subjects. Participants from developing nations may be vulnerable due to poverty, lack of education, language barriers, or cultural or political factors. Individuals that lack access to medical care may be highly motivated to participate in research that offers (or appears to offer) them the prospect of some medical benefit. They may be willing to take extraordinary

risks to receive medical care and may have difficulty understanding the information that is conveyed to them during the consent process. Vulnerable subjects or their communities may be the victims of exploitation if the research exposes them to significant risks and is not likely to offer any significant benefits to the participants or the population. For example, if a pharmaceutical company tests a new drug (such as a treatment for sexual dysfunction) in a developing nation and it is not planning to market the drug in that nation, this could be considered exploitative. To avoid exploitation when conducting research in developing nations, it is important for researchers and sponsors to address diseases or conditions that are relevant to people living in those nations and to offer to share benefits with the population, such as new treatments that are developed as a result of research, education, or improvements to health care infrastructure. They should also take steps to ensure that consent is valid and culturally appropriate and that there is adequate local oversight, such as an IRB or REB review of research (Ballantyne 2005; Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries 2002; Resnik 2003a; Shamoo 2005; White 2007).

Though racial and ethnic minorities are not considered vulnerable subjects per se, studying members of these groups can pose ethical challenges for investigators, due to the legacy of the Tuskegee study and others forms of exploitation of racial and ethnic minorities in research (Lo and Garan 2011). Studies indicate that African Americans have a distrust of medicine and biomedical research that can affect their willingness to participate in research (Corbie-Smith et al. 1999, 2002; Rajakumar et al. 2009). Other minorities, such as Native Americans and Latinos, have experienced discrimination and exploitation that may also affect their willingness to participate in research. Difficulties with recruiting racial and ethnic minorities can adversely impact the generalizability of research findings. For example, if a medication for treating heart failure is tested on a population that is 98% Caucasian, the applicability of this study to other racial and ethnic groups may be limited, due to possible racial or ethnic differences in drug metabolism or cardiovascular physiology (Alessandrini et al. 2013; Saul 2005). To address problems with enrollment of racial or ethnic minorities, researchers may need to focus recruitment efforts on these populations in some cases. Additionally, it may be appropriate to conduct studies that focus exclusively on minority populations in order to learn more about those groups and fill in gaps in the literature (Lo and Garan 2011). However, researchers must use great care when focusing on racial or ethnic identities to avoid conveying the impression that these groups are being targeted unfairly. Research that focuses on racial or

ethnic minorities should be conducted in order to learn more about these populations and offer them potential benefits, not to take advantage of them (Lo and Garan 2011).

To summarize this section, there is an ethical tension between including and excluding vulnerable subjects in research (Mastroianni and Kahn 2001). The Belmont Report's principle of justice requires that the benefits and burdens of research be distributed fairly (National Commission 1979). While most would agree that it is unfair to include vulnerable subjects in research unnecessarily, it may also be unfair to exclude them from research without a good scientific or ethical reason, because exclusion prevents investigators from obtaining knowledge that may benefit members of vulnerable groups (Mastroianni and Kahn 2001; National Bioethics Advisory Commission 1999). The key is to strike a reasonable balance between protecting vulnerable groups from harm and exploitation and enhancing their welfare.

QUESTIONS FOR DISCUSSION

- Is the media paying too much, just enough, or too little attention to questionable research with human subjects? Why do you think that is so?
- In your opinion, should there be a difference between informed consent for volunteering as a human subject and informed consent for medical treatment? What would those differences be, if any? Why?
- Do you think children should be able to participate in more than minimal risk research that offers them no direct benefits?
- Do you think informed consent documents are too long? Too complicated? What can be done to make them shorter and simpler?
- What additional safeguards would you suggest to protect subjects with serious mental illness who enroll in clinical trials?
- Do you think IRBs are doing a good job of protecting human subjects? How would you improve the system, if you believe improvement is needed?
- Which ethical theory described in chapter 1—utilitarians, Kantianism, or virtue ethics—provides the best approach to research with human subjects? How might these theories disagree about some of the controversial cases discussed in this chapter?
- Would you participate in a Phase I study of a new drug that offers you generous compensation but no medical benefits?

Do you think investigators should share individualized research results with participants?
Do you think it is ethical to use placebos in clinical trials?
Do you think deception in research, such as occurred in Milgram's experiments, is ethical?

CASES FOR DISCUSSION

CASE 1

Oscar Cabanerio is a 41-year-old immigrant living in the United States without any legal documentation. He is poor and needs cash to send to his family in Venezuela. SFBC International, Inc., is a large contract research organization (CRO) testing drugs in human subjects for drug companies in Miami, Florida. Cabanerio agreed to be in a trial to test Oros Hydromorphone, made by the Alza Corporation. The study paid each research subject $1,800. The subjects are instructed to swallow the tablets and not chew them, because chewing can cause overdosing. Adverse reactions include heart attacks, allergic reactions, and even death. Informed consent for this study is usually very quick. The subjects are eager to earn money, so they just look over the document and sign. Many of them have limited English-speaking abilities.

- What are some ethical problems with this study?
- Are there any problems with the selection of subjects, the consent process, or safety?
- Is there a fair subject selection in these studies and why?
- How would you run such a facility ethically?

CASE 2

An announcement in the newspaper and radio encourages people to enroll in research protocols to test a new antiflu medication. The announcement emphasizes that each subject will receive a free physical exam, free health care for 60 days, and $400 compensation. The new drug is very promising in either stopping the full-blown symptoms of the flu or preventing it altogether. The protocol has already been approved by an IRB.

- What questions would you ask if you were a potential subject?
- Should the IRB have approved the protocol? Why?

CASE 3

A hospital associated with a research university has a policy that every new employee must provide a blood sample. The employees are told that the blood samples will be frozen for a long time. The hospital's purpose in collecting the blood samples is to reduce their liability in case anyone contracts HIV. From the frozen samples, the hospital can determine whether the employee had the HIV virus prior to employment. A few years later, a researcher at the hospital is developing an HIV diagnostic instrument directly from the blood. The instrument, if it works, would advance HIV screening. The researcher wants to use the samples without any names attached to them (the samples are de-identified). The researcher wants to test different samples from different people.

- What concerns would you have if your blood sample was included in this research?
- Is this study ethical?
- Does this study need to be reviewed by an IRB?

CASE 4

A psychology professor teaching a seminar on human sexuality invites her students to complete a survey on their sexual experiences for course credit. The survey asks questions about sexual activity, sexual orientation, sexual fetishes, and sexual abuse. Students provide detailed, written answers to the questions, but they do not sign their names. There are ten students in the seminar. As an alternative to participating in the survey, students can write a short paper for equivalent credit.

- Do you have any ethical concerns with this study?
- Would you participate in it?
- Do you have any suggestions to improve this study?

CASE 5

Subjects for a research study will be recruited from private pain treatment clinics and the medical school's pain service. Preliminary studies have shown that the drug thalidomide may provide some relief for migraine headaches, arthritis, and neuropathy conditions. Because thalidomide's harmful effects on fetuses are well known, women of childbearing age will be excluded from this study.

- Are there benefits from this study?
- If you are a member of the IRB, what questions would you ask?
- What risks should be addressed?

CASE 6

A company is developing a pesticide for use on various crops, including tomatoes, corn, apples, green beans, and grapes. Previous animal studies indicate that it may be safer than other commonly used pesticides. The company plans to use healthy subjects (its employees) to test the pesticide for toxic effects. Each subject will be paid $500 and will be monitored carefully for three days. Investigators will collect data pertaining to toxicity and pharmacokinetics. Subjects will report adverse effects they experience, such as dizziness, nausea, headache, fatigue, shortness of breath, and anxiety.

- What are the risks to subjects?
- What are the benefits to subjects?
- Would you put any conditions on the protocol before going forward? What would they be?
- Are there any conflicts of interest? Can they influence the outcome of the study?

CASE 7

An untenured assistant professor at a medium-sized university is a member of her university's IRB. One of the human subject protocols the IRB is reviewing is from a world-renowned professor in another department at her university. This world-renowned professor is a member of the promotion and tenure committee. The assistant professor's package for promotion to tenured associate professor will go to the committee in six months. The assistant professor has a great deal of concern about the proposed protocol. She feels that the risks are watered down and the benefits or potential benefits are exaggerated.

- What should the assistant professor do? What would you do?
- How should the IRB handle the problem?

CASE 8

A research proposal and its informed consent forms were submitted to an IRB of an independent nonprofit research facility in San Francisco. The protocol will enroll 30

heroin addicts, of whom 20% are likely to have HIV. The protocol is a study of social habits of these addicts. The surveyor will follow the addicts around in their daily routine for one week to register their food intake, drugs used, sexual habits, and so forth. The researcher considered the study to be minimal risk research and said so on the proposal submitted to the IRB.

- Do you have any ethical concerns about this study?
- Is it minimal risk?
- Does the study raise any issues concerning privacy and confidentiality or the research subjects or other affected individuals?
- What information should the informed consent form contain?
- Should the IRB approve this study? Should it require any modifications for approval?

CASE 9

A researcher has submitted a proposal to an IRB for a clinical trial of a new drug to treat depression in adolescents (ages 12–17). The drug has been tested in adults and approved for use in adults but not in adolescents. The manufacturer of the drug is seeking approval for its use in adolescents. The study will enroll 75 adolescents with a history of depression. Subjects will be randomly assigned to one of three groups: Group A will receive the new drug; Group B will receive a standard treatment; and Group C will receive a placebo. Subjects and investigators will be blinded so that they will not know who is receiving the drugs or the placebo. All subjects will receive psychological counseling for depression and will be carefully monitored during the study. The study includes a 30-day washout period in which subjects stop taking medications for depression. Subjects will be closely monitored during the washout period. The study will follow subjects for 90 days while they are receiving the drugs. Each subject will receive free medication and psychological counseling and $1,200 once the study is completed.

- Do you have any ethical concerns with this proposed study?
- Should the study include a placebo group? A washout period?
- Do you have any suggestions for improving the study?
- Should the IRB approve this study?

CASE 10

An anthropologist is planning to study the culture of an experimental physics laboratory at Whitmore University. The anthropologist will observe the daily activities of

people in the laboratory for three months and keep a detailed record of her field notes. She will also conduct semistructured interviews with members of the laboratory. There are 38 people in the laboratory, including senior scientists, junior scientists, postdoctoral fellows, graduate students, and technicians. She plans to summarize her findings in a series of articles that she submits for publication. She has submitted the study to her institution's IRB as minimal risk research. She has obtained the permission of the director of the laboratory to conduct this study and is planning to submit it to the Whitmore IRB as well.

- Do you have any ethical concerns with this study?
- What are the risks of this study? Is it minimal risk?
- Do you have any concerns about confidentiality or privacy in this study?
- Should consent for this study be obtained from all of the members of the laboratory?
- What should the anthropologist do if she observes or learns about unethical or illegal activity in the laboratory, such as data fabrication or falsification?