Vulnerable Subjects in Research: Why Do They Need Special Protection?

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ABSTRACT

Ethical research on humans should be guided by the principles of justice, respect, and beneficence. Special protections should be provided to vulnerable participants. This paper reviews the different categories of vulnerable subjects including prisoners, students, employees, the terminally ill, impoverished individuals, minorities and those lacking clear decision making such as the cognitively impaired, children, and fetuses. Examples are provided of unethical research practices performed on vulnerable subjects through history including the Nazi experiments on prisoners, Tuskegee experiment on African-Americans, Willowbrook research on the mentally ill, and the recent Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) on premature babies. Regulatory agencies and guidelines have been established as a consequence of unethical research practices, and are summarized. The special regulatory protections that have been put in place for vulnerable subjects are described along with common sense advice to vulnerable individuals or legal representatives of vulnerable individuals who are considering participating in a research study.

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Vulnerable Subjects in Research: Why Do They Need Special Protection?

Human research will always be a crucial component of scientific progress. Human subjects are indispensable to testing the safety of new pharmaceuticals, the effectiveness of new medical procedures, and other scientific and medical advancements. Human research, however, has its risks. Researchers have sometimes blurred ethical boundaries and allowed science to infringe on basic human rights. Vulnerable groups of people—the economically disadvantaged, the cognitively impaired, children, and others—have been victims of unethical research throughout history. Though laws have been put in place to protect human research subjects, factors such as privatizing pharmaceutical testing and weak enforcement of regulations have allowed the abuse to continue. With modern atrocities like the pharmaceutical industry’s exploitation of impoverished individuals in developing countries for research, and the deaths of preterm infants in the recent Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), the idea that vulnerable populations still need special protections is indisputable.

Historical Examples of Unethical Research

The medical experiments of Nazi Germany from 1939 to 1945 are some of history’s most notorious examples of unethical research. German physicians and researchers conducted a series of excruciatingly painful and deadly medical experiments on political prisoners, civilians, non-German nationals, clergy, and prisoners of war. Nazi physicians conducted at least twelve major medical experiments, including high altitude experiments where victims were locked into airtight containers designed to simulate altitudes of 68,000 feet. In other experiments, victims were left outside in freezing temperatures completely naked for up to fourteen hours. Others were placed in tanks of ice water until their body parts froze.

Perhaps the most disturbing of the Nazi experiments were those on muscle and nerve regeneration and bone transplantation. Victims, mostly healthy young polish women, had entire limbs removed and transplanted onto other victims. The few survivors were left permanently disabled and disfigured. In another experiment, researchers placed a drop of mustard gas on victims’ skin. The single drop rapidly afflicted the entire body with burns, eating away any skin it touched and eventually finding its way to the victim’s lungs and internal organs.

Though Nazi physicians are often perceived as ruthless and immoral, Robert N. Proctor argues in his article, “Nazi Medicine and Public Health Policy,” that Nazi Germany was guided by its own set of ideologies and ethical principles. Some guiding principles, like preventative medicine and orderliness, were admirable. Others—sexist paternalism, racial hygiene, and unquestioned obedience to authority—were abhorrent. However, physicians were enticed by the promises of the Third Reich, so much so in fact, that over half of them joined the Nazi party. Proctor writes, “The seductive power of National Socialism for many physicians lay in its promise to cleanse German society of its corrupting elements—not just communism and Jews, but also metallic lead and addictive tobacco, along with homosexuality and the ‘burdensome’ mentally ill.”

Tragically, the ambitious drive to advance medicine and the disregard for the basic human rights of certain groups led to the torturous deaths and disfigurements of an appallingly large number of people.

After the war and in response to the atrocities committed by Nazi physicians, the Nazi War Crimes Tribunal issued the first internationally recognized code of research ethics: The Nuremberg Code. The Nuremberg Code enumerated the required elements for conducting research involving human subjects, including informed consent. Additionally, it emphasized that animal subjects should precede human subjects in research, risks should be justified by anticipated benefits, suffering must be avoided, and research should only be conducted by qualified scientists. Because the Nuremberg Code only applied to non-therapeutic research and was never codified into law, it had a limited impact. It laid the foundation, however, for future developments in research ethics.
Unfortunately, the end of the Third Reich was not the end of unethical human research. Beginning in 1929 and lasting until the early 1970s, Dr. Taliaferro Clark began one of the longest observational studies in history in Tuskegee, Alabama. Dr. Clark, a venereologist, had an interest in syphilis and the medical deterioration it caused over a long period of time. Though he originally planned the study to last between six and eight months, it lasted until 1972 when a whistleblower article in the New York Times caused public outrage after exposing the experiment's dubious ethics.

Tuskegee was a town populated heavily by poor, uneducated, black men, many of whom had syphilis. Dr. Clark sent Eunice Rivers, a 33-year-old African-American nurse, to recruit individuals for the study. She traveled throughout the community, visiting churches and barbershops, to find research participants. Rivers was well liked in Tuskegee, and befriending her and participating in the study gave men in the community a sort of social prestige. Participation also earned them free lunches, transportation, medical care, and $25 a year. Three hundred and ninety-nine men enrolled. Participants were tested but never told they had syphilis. They were simply told they had “bad blood.”

When the study began, syphilis treatments were primitive and often dangerous. Some of the participants were treated, but the study remained mostly observational. By the early 1940s, however, penicillin had been discovered to effectively treat syphilis. Dr. Clark, realizing an effective cure would be the end of his study, never offered penicillin to his research participants. In fact, most remained completely ignorant of the available cure for the rest of their lives. Over one hundred participants died from syphilis or related complications over the course of the study, and countless wives, girlfriends, and children were infected, too.

Rumors of the study and its questionable ethics began to circulate. In the mid-1960s, U.S. Public Health Service employee Peter Buxton wrote a series of letters about the study to the Center for Disease Control. They were ignored. Finally, in 1972, Buxton contacted Associated Press reporter Jean Heller about the study. The New York Times published her article that July. Soon after, an investigative panel looked into the issues of informed consent and withholding treatment, and the study was halted. The following year, the case was taken to court. Lawyer and civil rights activist Fred Gray filed a

$1.8 billion class action suit, claiming the study violated the Fifth, Ninth, Thirteenth, and Fourteenth Amendments. A $10 million settlement was agreed upon before the case went to trial. Study participants received small portions of the settlement money, mostly under $20,000 each. Gray was paid over a million dollars.

Beginning in 1955, the Willowbrook State School in Staten Island, New York was the home to a nearly twenty-year long hepatitis research study led by Dr. Saul Krugman of New York University. Willowbrook was a residential school for children with disabilities. The school, now remembered for its filthy, malodorous environment, and neglectful treatment of residents, housed over 5,000 disabled children.

In the filth, communicable diseases like hepatitis spread rapidly among residents. Dr. Krugman and his research team took advantage of the disease-laden school and over 700 of the disabled children to study the nature of hepatitis and gamma globulin antibodies, which provided some immunity to the disease. Perhaps the most controversial of Krugman’s experiments were those he conducted on new residents. New study subjects were injected with gamma globulin antibodies and the experimental group was purposefully infected with the hepatitis virus through deliberate exposure or an injection of contaminated blood. The gamma globulin injection helped to lessen the severity of symptoms in some children, but most still became ill and experienced symptoms such as vomiting, yellowing of the skin and eyes, loss of appetite, and a swollen liver.

Many professionals questioned the ethics of Krugman’s research, including Henry Beecher in a 1966 article in the New England Journal of Medicine, calling his methods “ethically dubious.” Though the children’s parents did sign a consent form, David J. Rothmans notes in his article, “Were Tuskegee and Willowbrook ‘Studies in Nature?’” the consent form “…read as though their children were to receive a vaccine against the virus.” It certainly did not imply that they might be intentionally infected with hepatitis. The consent form was riddled with deceptive phrases, such as, “We should like to give your child this new form of prevention with the hope that it will afford protection,” and “If you wish to have your child given the benefit of this new preventive, will you so signify by signing the form.” Furthermore, parents reported feeling forced into participation.
the mid-1970s, the public schools were not designed to meet the needs of children with disabilities. Sending a child with a disability to live in an institution was commonplace, and schools like Willowbrook did not always have space available. Not surprisingly, at times the only space available was on Krugman’s ward, which only housed study participants\(^5\). Parents, desperate to have their child admitted to the school, had no other option than to volunteer their child for the study.

The research carried other ethical concerns, as well. Some have questioned why Krugman chose to do the research on disabled, vulnerable children, when the school employed over a thousand adult staff members who were equally exposed to the unsanitary conditions and diseases at Willowbrook\(^5\). Others argue that some of the funding and effort put into the study should have been used to improve the conditions of the facility to prevent the spread of disease\(^5\).

Krugman justified his research by asserting that most of the children admitted to Willowbrook would have contracted hepatitis naturally\(^5\). However, it has been estimated that only around 30-50% of the residents at Willowbrook contracted hepatitis from other residents\(^5\). Additionally, he argued that the gamma globulin injections actually benefited the study participants by lessening the symptoms’ severity\(^5\).

Around the same time as the Willowbrook hepatitis experiments, doctors at the Jewish Chronic Disease Hospital in Brooklyn were injecting chronically ill patients with something far worse than hepatitis: live cancer cells\(^5\). In July of 1963, Dr. Emanuel Mandel, director of the departments of medicine and medical education at the Jewish Chronic Disease Hospital, received a letter from Dr. Chester M. Southam about a potential research collaboration\(^5\). Dr. Southam was interested in studying the immunological responses of cancer patients and how they compared to the immune responses of people without cancer. His team had already injected live cancer cells into cancer patients and healthy persons\(^5\), but his research was lacking a sample of chronically ill. Collaboration with Dr. Mandel would provide Dr. Southam with the patients he needed to continue his research. Participating in the study would, in return, bring recognition and boost the research reputation of Dr. Mandel and the Jewish Chronic Disease Hospital\(^5\).

Dr. Southam was confident that none of the research participants would actually contract cancer. His team had already injected hundreds of people with cancer to measure each person’s ability to reject foreign cells\(^5\). Immunological response to cancer cells (compared to other types of injections) was easy to measure; a lump would form at the injection sight and typically disappear within a few weeks. Researchers had already noted the lump might last as long as three months in people with advanced cancer, while the lump in a healthy person would typically disappear in four to six weeks. Researchers could use the length of time it took for the lump to disappear to determine the rate of a person’s immunological response\(^5\). In his letter, however, Southam neglected to mention a previous trial in which doctors found the injected cancer cells were still “alive and localized” after a patient had died from advanced cancer\(^9\). In another case, the injected cells metastasized to a patient’s lymph nodes\(^9\).

The experiments had never been done on chronically ill patients before, so it was impossible to know how their immune systems would actually respond. There was a known, albeit unlikely, risk that the cancer could metastasize, but none of the patients at the Jewish Chronic Disease Hospital were warned of any risk at all. In fact, the doctors did not even obtain adequate informed consent. In most cases, doctors claimed the patients gave consent orally, but evidence suggests even that is debatable\(^5\). Patients’ charts described them as suffering from brain damage, unaware of their surroundings, difficult to understand, and even suicidal\(^5\), raising question of whether they were truly able to understand the nature of the procedure and give their consent. One patient, a sixty-eight-year-old man with heart disease and brain damage, was given the injection. Notes in his chart described him as isolated, negative, depressed, and resisting “all forms of treatment,”\(^5\) making one wonder if he was truly given an opportunity to accept or refuse. Even if patients had the full mental and physical capacity to give their consent, they were not told they were being injected with live cancer cells. They were simply told they would be receiving a skin test\(^9\).

The study raised many legal and ethical concerns at the hospital. Several doctors questioned Dr. Mandel and compared his experiments to those of the Nazis\(^5\). Three physicians resigned to protect their reputations, but most physicians and administrators were not concerned\(^5\). In fact, several hospital committees including the medical
board, which was responsible for enforcing proper patient care, approved the research\(^5\).

Dr. Mandel justified the research by claiming it would benefit the patients by allowing them to receive more attention from doctors and even help diagnose previously undetected cancer if the lump did not quickly disappear\(^3\). Doctors also claimed there was no need to tell the patients they were using cancer cells or obtain written consent, claiming that patients receive far more dangerous treatments regularly without giving consent\(^5\). Of course, the important distinction between the experimental injections and other so-called dangerous procedures is that the injections were not for treatment or any other therapeutic purpose.

Ultimately, the study did show that the immunological response of the chronically ill was similar to that of healthy people\(^5\). It is argued that no patient at the Jewish Chronic Disease Hospital was significantly harmed. However, one patient did die after receiving the injection. One doctor questioned whether or not the injection indirectly influenced his death by weakening his immune system, but of course, that is uncertain\(^5\). The courts, primarily because of the lack of consent, eventually deemed the study unethical. Dr. Southam and Dr. Mandel were placed on probation for one year\(^5\).

**Regulations to Protect Human Subjects**

In response to the continuing abuses of vulnerable research subjects despite the Nuremberg code, more formal regulations were put in place to protect human participants. In 1964, the Nuremberg Code was reinterpreted by the World Medical Association and titled the Declaration of Helsinki\(^11\). Perhaps its most significant contribution to research ethics was making informed consent a central requirement for research\(^11\). Furthermore, it established rules to protect the rights of vulnerable people\(^11\). The Declaration of Helsinki led the way to the current regulations that govern human subject research and the creation of Institutional Review Boards (IRBs).

Ten years later, Congress authorized the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research\(^14\). The Commission was asked to identify the basic ethical principles that underlie the conduct of human research and develop guidelines for implementation of ethical principles. They identified three basic ethical principles: 1) respect for persons, 2) beneficence, and 3) justice\(^14\).

“Respect for Persons” requires researchers to treat individuals as autonomous human beings. Research participants are to be fully informed about the nature of the study, its risks, and its benefits in a way they can fully comprehend. Consent should always be completely voluntary and free from all coercion. Special protection should be given to individuals without the full capacity to exercise autonomy and other vulnerable populations\(^14\). The principle of “beneficence” requires researchers to minimize the harms and maximize the benefits to study participants. Research must always have a social and scientific value and it should always have a favorable risk-to-benefit ratio\(^14\). The principle of “justice” requires researchers to treat people fairly and to equitably distribute the burdens and benefits of participating in the study\(^14\).

To protect the welfare and rights of human research participants, Institutional Review Boards (IRBs) have been put in place. IRBs are committees composed of physicians, scientists, non-scientists, and representatives of the institution and community that review ethics and advocate for the rights, safety, and welfare of study participants\(^3\). They have the authority to approve, disapprove, or require modifications in research\(^3\). All institutions that receive funding from the federal government to conduct research must have an IRB review any study proposal that uses human study participants\(^3\). An institution’s IRB will consider how well the researchers understand ethical research, the experiment’s procedures, the rights of the study participants, the risks and benefits, and how the researchers will ensure voluntary participation\(^3\). Research at such institutions requires the IRB’s approval before it can be conducted.

**Recent Controversial Research**

Despite the regulations put in place to protect human subjects, unethical research continues to harm vulnerable people today. The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), for example, began in 2005\(^13\) and may have contributed to the deaths of many preterm infants. The goal of the SUPPORT study was to find the safest blood oxygen levels for preterm infants receiving supplemental
Premature infants are often born with underdeveloped lungs that cannot take in enough oxygen from the air to support their bodies and brains. To compensate, the babies are given air with supplemental oxygen, but the supplemental oxygen comes with risks. Research from the 1950s had suggested that high levels of oxygen saturation can cause blindness, but withholding supplemental oxygen can result in death. SUPPORT researchers sought to find a safe oxygenation range that would prevent both.

Thirteen thousand preterm infants with an average gestational age of twenty-six weeks and an average birth weight of just under two pounds were enrolled. The parents signed a consent form, but according to Jerry A. Menikoff, director of the government’s Office for Human Research Protection, “The consent form was written in a slanted way.” He told the Washington Post, “They went out of their way to tell you that your kid might benefit, but they didn’t give you the flip side, which is that there is a chance your kid might end up worse off.” The only risk mentioned on the consent form was skin irritation from the oximeter.

The normal oxygenation range used in standard care for preterm infants is 85%-95%. The oxygenation levels in this study were kept in that range, but some were intentionally kept at lower levels (85%-89%) and others were kept at higher levels (91%-95%). The study concluded that higher oxygenation levels are better for preterm infants. Unfortunately, the conclusion was drawn after significantly more babies in the low oxygen group died.

The SUPPORT study, concluded in 2009, is still controversial in the medical community. Supporters argue that the infants were all kept within normal ranges, and therefore the outcomes of the study simply replicated what would have happened in the hospital without the study’s interference. Others argue that parents were not adequately informed of the reasonably foreseeable risks of death and blindness. Some children did develop retinopathy, but therapy and treatments are available. By the time surviving children turned two years old, rates of blindness between the two groups were nearly equal.

Some of the most recent examples of controversial research are happening in the pharmaceutical industry, which is becoming increasingly more commercialized. Before new drugs can be sold, they need to be tested on humans. Historically, clinical trials were primarily conducted in publicly-funded, well-regulated research centers and institutions. Increasingly, the pharmaceutical industry is out-sourcing research to contract research organizations (CROs) to save time and money. CROs typically have high employee turnover. Consequently, employees are often less experienced, less skilled, less educated than researchers in academia or the pharmaceutical industry, and tend to exchange high quality research for fast results. Furthermore, clinical trials are increasingly being moved offshore to places like China, India, and former communist countries in Europe and Asia. Countries frequently used for clinical trials tend to have high levels of poverty and illiteracy, which make residents especially vulnerable. Perhaps what makes these locations most appealing for pharmaceutical research is the low cost, lack of regulation enforcement, and scores of poor and sick people who blindly trust Western medicine. Unfortunately, these same factors make CROs breeding grounds for unethical behavior. In India alone, 2,644 human research participants died from clinical trials between 2005 and 2012.

In response to public outcry, India recently tightened its regulations on human research. Complaints that the pharmaceutical industry was targeting the economically disadvantaged and conducting research without adequate oversight or even consent encouraged the Drugs Controller General of India to implement ethics boards, procedures for reporting severe reactions, and better compensation for injured participants and families of those who have died as a result of clinical trials. The response from pharmaceutical companies was dismaying. Instead of agreeing to comply with the regulations to protect human research subjects, they complained that the regulations were unreasonable and no longer conducive to research and they would be “forced” to take clinical trials elsewhere.

The article, “Foreign Bodies: The New Victims of Unethical Experimentation,” by Paddy Rawlinson and Vijay Kumar Yadavendu, suggests that the impoverished population exploited by medical research is “a new type of Untermensch,” a word meaning “sub-human,” used by the Nazis to describe those who did not meet their social ideals. The authors write, “...we are dealing with a different form of ideological motivation driving the abuse of human research subjects, an ideology shaped by political economy rather than the pan-nationalist Aryan ideals of the Third Reich.” The “ideological motivation”
they are referring to is one driven by profit maximization and shareholders’ interests instead of the safety of human beings. Vulnerable human research subjects have also been exploited in the United States. A 2005 article in *Bloomberg Markets* revealed pharmaceutical testing in Miami that exploited poor immigrants from Latin America. Immigrants, desperate for money to support themselves and their families, would participate in under-regulated clinical trials. The trials’ heavily back-loaded compensation structure made it difficult for participants to drop out if they experienced adverse effects from the experimental drug. For example, they would often receive minimal pay for the first several months of a study and then receive the bulk of the compensation at the end of the trial, making participation almost worthless if the entire duration of the trial was not completed. Furthermore, informed consent was not always adequately obtained. Participants would be warned of the risks, but language barriers made it difficult for them to fully understand. Inadequate regulations and poor file-keeping allowed some research subjects to participate in more than one trial at a time, leaving them at risk for dangerous drug interactions, and possibly skewing a study’s results. When adverse reactions did occur, trial participants were not always given the medical care they needed. If the immigrants spoke out against the unethical practices of the research centers, they were threatened with deportation.

The atrocities in India and Miami only scratch the surface of the controversial medical research that takes place around the world. Over the past twenty years, vulnerable populations like foster children, sex workers, and impoverished individuals have frequently been subject to abuse for medical research, whether intentionally, or simply through the negligence of researchers to protect research subjects from coercion or harm.

**Special Protections for Vulnerable Persons**

Some research is specific to vulnerable groups. Research focusing on autism, Alzheimer’s disease, or children, for example, may require the use of vulnerable persons. However, vulnerable populations should not be used if the research can be conducted with subjects who are not vulnerable. Vulnerability is broad and can be difficult to define. It includes people with cognitive impairments and those who struggle to communicate, including children, individuals who do not speak English, and fetuses and neonates. It also includes people who are institutionalized, like prisoners, and others who may otherwise be coerced in some way to consent to research, such as students and employees. Terminally ill individuals can be considered vulnerable. The economically disadvantaged and minorities can also fall into this group. Researchers are responsible for avoiding exploitation of anyone who falls into any of these categories.

Regulations have been put in place to protect people with diminished capacities for making decisions, and researchers must take special considerations before including them in studies. Their capacity to fully understand the risks of research must be assessed by a trained clinician. To further protect the cognitively-impaired, special regulations prohibit court-appointed guardians of intellectually impaired individuals to give permission for participation in research unless very stringent terms and conditions are met.

Special regulations have also been put in place to protect children. Regulations mandate a favorable risk-to-benefit ratio for research with children. Child participation also requires both parental permission and assent from the child, who must have the research explained thoroughly and in a way they can understand. Children should be adequately prepared for procedures. For example, if the research involves an MRI, the child should practice doing a mock MRI beforehand. During an experiment, the child should be offered frequent breaks, and the length of the participation should be as short as possible.

For children and elderly groups, investigators need to consider sensitive information and how it should be handled. For example, researchers may discover information about subjects that is not directly related to research, like information about abuse or sexual activity. The permission and assent forms should describe plans for disclosure or non-disclosure of sensitive information to parents, legal authorities, or the subjects themselves.

Prisoners, students, and employees also require special protection because they may be especially susceptible to coercion. Superiors should never directly solicit participation in a study, nor should inappropriate or excessive incentives be offered in exchange for
enrollment. Informed consent should clearly state that participation is voluntary, and protections should be put in place to prevent retaliation for non-compliance.

The terminally ill require special protections, including a consent form that clearly states risks and benefits. To protect potential subjects from coercion, they should not be approached about participating in a study immediately after a diagnosis or discovering that a standard treatment has failed.

The economically disadvantaged can be an especially vulnerable group in medical research. Sometimes desperate for extra income, they may participate in many studies at once or continue to participate in a study even if it is making them unwell. To protect the economically vulnerable, monetary compensation for study participation should be set at a rate that fairly compensates a participant for their time but not so great that it becomes unduly influential. Furthermore, risks should be made clear to subjects in the consent form so they can make a truly informed decision about whether or not to participate.

Minorities and non-English-speaking persons should also receive special considerations in research. For non-English-speaking persons, a translator should be present for the informed consent process. Additionally, researchers should consult with the community and include representatives of the group while designing the study to reduce stereotyping and stigmatization.

Most importantly, researchers and study participants should always keep in mind that consent is an ongoing process and a participant has the right to withdraw at any time. The researcher is responsible for protecting the rights and welfare of study participants, and vulnerability should be reassessed throughout the study to ensure the work is always in the best interest of the participants.

Conclusion

Though the ethical regulations that guide research have improved over the last century, harm and injustice in human subject research are far from being problems of the past. While researchers and organizations are seeking fast and easy ways to maximize profits and prestige, vulnerable human subjects are being manipulated and harmed. Vulnerable subjects can be used in research, but they deserve special protection and advocacy. Furthermore, they deserve to have the regulations that were designed to protect them, enforced by governments and IRBs. Since vulnerable persons often cannot advocate for themselves, the responsibility rests on the broader community to be mindful consumers, ethical researchers, and advocates for those without a voice. When everyone strives to ensure that research is guided by respect for persons, beneficence, and justice, the atrocities of the past will not be able to repeat themselves.

NOTES


