

In Remembrance There Is Prevention: A Brief Review of Four Historical Failures to Protect Human Subjects

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Abstract

This year the world commemorates the beginning of the tragic USPHS syphilis experiments that occurred in Tuskegee, Alabama from 1932 to 1972. In light of this sobering anniversary, this article will briefly examine four studies: the already mentioned USPHS syphilis studies in Tuskegee, the Nazi Holocaust Experiments and the resulting Doctors' Trial at Nuremberg, the USPHS study on sexually transmitted diseases in Guatemala, and the Pfizer Trovan study in Nigeria. By reflecting critically upon these four tragic events in the history of research, the research community is reminded of its non-negotiable, ethical responsibility to protect human subjects, particularly those who are most vulnerable.

Keywords: human research, USPHS syphilis experiments, Tuskegee, Guatemala, Trovan, Pfizer, Nigeria, Doctors' Trial at Nuremberg, Holocaust, Nazi Experiments

Introduction

Much of the modern economy is impacted by today's increasing globalization, and clinical research is at the forefront. Cost is a significant factor that may propel clinical research beyond U.S. borders (Shah, 2002). It is estimated that the cost per subject for tracking and other administrative requirements is up to ten times more for an American subject as compared with a subject abroad (O'Reilly, 2009). The number of people enrolled in clinical research worldwide is significant; in 2009, that number was 50 million and growing (Shetty, 2009). In the past decade, the percentage of research conducted overseas has continued to increase, and by 2010, more than 50 percent of clinical trial subjects and sites were located overseas (Levinson, 2010). The volume of studies and sometimes-remote locations give rise to the potential for lack of oversight and little recourse for vulnerable populations that may be affected by participation in clinical research.

As the research community and the world reflect on the legacy of the Tuskegee syphilis experiments, it is appropriate, given the global nature of clinical research, to also remember three additional studies in which appropriate protections were not provided to human subjects. From Tuskegee to Nuremberg, and from Guatemala to Nigeria, the research community and the public are reminded of past failures marked by a lack of respect for the human subjects involved. Remembrance, here, is not intended to vilify or to blame, but rather to ensure that adequate human subject protections are never again forgotten, particularly for vulnerable populations.

USPHS Syphilis Experiments in Tuskegee, 1932-1972

During the 1920s, researchers of the U.S. Public Health Service (USPHS) developed plans to study the response of black males to disease, hypothesizing that the response would differ from that of white males. In Macon County, Alabama, nearly forty percent of black males tested positive for syphilis and researchers believed that this community would be ideal to study disease progression. Although the initial plans included medical treatment, the financial devastation of the Depression in 1929 eliminated project funding. Rather than abandoning all research, USPHS researchers decided to proceed with a limited study. (Thomas & Quinn, 1991)

Under the amended research design, USPHS hired Nurse Eunice Rivers to coordinate the study, officially known as “The Tuskegee Study of Untreated Syphilis in the Negro Male.” Nurse Rivers, a black woman, was a graduate of the Tuskegee Institute and had worked on various public health projects in Alabama since the early 1920s. By hiring Nurse Rivers, USPHS researchers believed that they could more efficiently reach community members. (Thomas & Quinn, 1991)

From the beginning, the study was marked by decisions to withhold information. Men involved in the study were told only that they were being tested for “bad blood,” a euphemism for a variety of illness including syphilis, anemia, and fatigue. Each of the 600 men initially involved in the study was tested for syphilis; 399 of these men were found to have syphilis and the remaining 201 men tested negative (Jones, 1993). The men were not informed of either the purpose of the study, or whether they had syphilis; further, no information about modes of transmission or treatment was provided. Researchers intended for the study to conclude after six months of observation; however, the study was extended in an effort to examine the men at regular intervals until their death. By tracking the men through their lives and then performing an autopsy after death, researchers aimed to follow the complete progression of untreated syphilis. (Jones, 1993)

Researchers employed several tactics to persuade the men to continue in the study and the families to permit autopsies after the men in the study died. Actions were taken that created an illusion of treatment. For example, the men in the study were given iron, aspirin, and placebo treatments (Jones, 1993). In some cases, this regimen did provide a modest improvement in the men’s health and resulted in further study participation. Many of the men

involved in the study would have been otherwise unable to afford medical exams and willingly accepted the exams offered in exchange for participation. Researchers also offered free spinal taps, advertising the procedure as a special treatment. While these procedures aided researchers in obtaining information about neuro-syphilis, they were of no therapeutic value to the men involved in the study (Brandt, 1978). In order to encourage families to allow autopsies, family members were approached and offered a small stipend for burial costs in exchange for their permission to conduct an autopsy. As many of the families had limited economic resources for burial expenses, the stipend was a persuasive inducement. (Jones, 1993)

Over the 40-year course of the study, treatments for syphilis advanced. At the beginning of the study, the standard treatment of the disease consisted of a combination of arsenic, mercury, and bismuth given over an extended period. By the early 1940s, physicians began treating patients with an abbreviated course, generally one week, of an arsenic derivative and bismuth. Researchers actively coordinated with local clinics to ensure that the men involved in the study did not receive treatment (Jones, 1993). By the mid-1940s, penicillin became the treatment of choice for syphilis, and Alabama law required that anyone testing positive for venereal diseases be treated with appropriate medication (Jones, 1993). Again, researchers ensured that the men involved in the study were neither tested nor treated as required by law. Researchers also provided the names of men involved in the study to draft boards and physicians treating World War II draftees, requesting that these men not receive the penicillin treatment that was administered to all other draftees diagnosed with syphilis (Thomas & Quinn, 1991). The men involved in the study remained unaware of their diagnosis and the benefit of treatment.

Although the men involved in the study were not given diagnosis and treatment information, the study itself was not kept from the medical community. Articles were published in medical journals and papers on the study were presented at medical conferences, but few, if any, ethical objections were raised to the study protocol and methodology (White, 2000). Over the 40-year span of the study, significant achievements occurred in the protection of human subjects and yet, the study continued without change. A contemporaneous development, the Nuremberg Code, discussed below, set forth guidelines on human research and clearly articulated the requirement for informed consent. During the 1960s and early 1970s, USPHS began developing guidelines for clinical trials and peer review, although the men involved in the study did not appear to benefit from these protections. (Jones, 1993)

Some of the first objections to the study arose in 1964, after an article was published describing the 30-year history of the study. A physician wrote to the authors and questioned the ethical approach of the study in denying treatment (Jones, 2000). Despite these questions, no change to the study was made. Five years later, a USPHS employee raised additional ethical concerns, and USPHS convened a review panel, which consisted of white physicians, all but one of whom were already familiar with the study's existence and methods. The only panel member who recommended physical examinations and treatment

for the men involved in the study was the physician who was previously unaware of the study (Jones, 1993). Further compounding the panel's disturbing analysis was a determination that the socioeconomic status and education level of the men involved in the study rendered informed consent impossible. The panelists subsequently decided to ask the Macon County Medical Society for consent, substituting the judgment of the medical board members for that of the men involved in the study. Finally, in 1972, a reporter for the Associated Press, Jean Heller, reported the details of the study. The article resulted in outrage and ultimately led to study termination, after 40 years of experiments involving human subjects who neither consented, nor were given appropriate protections. (White, 2000)

As with other human subject studies conducted without appropriate protections, the impact of the USPHS syphilis experiments in Tuskegee did not end when the study itself concluded. Perhaps one of the most significant pejorative results from the study is distrust of the medical community, research community, and the U.S. Government, particularly among minorities. While some steps have been taken to restore trust, ranging from regulations to apologies, it is clear that there must be continued vigilance to overcome this legacy of the study. Ultimately, this study, as with the other studies discussed in this article, serves as a powerful reminder of what occurs when researchers fail to recognize that each human subject is worthy of respect.

The Nazi Holocaust Experiments and the Resulting Doctor's Trial at Nuremberg 1946-1947

Following World War II, twenty-three Nazi physicians and administrators were accused of organizing and participating in war crimes and crimes against humanity by way of medical experiments and procedures to which prisoners and civilians were subjected unnecessarily, and prosecuted between 1946 and 1947. At the conclusion of the trial, seven defendants were convicted and later executed, nine defendants were convicted and sentenced to terms of incarceration, and seven defendants were acquitted. As a result of the Doctors' Trial, the Nuremberg Code was produced and served as one of the first significant human rights documents. ("Nuremberg Code," 1949)

The defendants in the Doctors' Trial were indicted on four specific counts: conspiracy to commit war crimes against humanity, war crimes, crimes against humanity, and membership in a criminal organization; the medical experiments exposed during trial detailed the horrific nature of the research conducted primarily on Nazi concentration camp inmates ("Final Report," 1949). The experiments varied in duration, beginning in 1939 and concluding in 1945. The defendants argued that these experiments were necessary for the German defense, and therefore justifiable; however, this argument did not prevail at trial. The experiments included: (1) sterilization experiments, to determine large scale methods that would ensure the elimination of specified populations and maximize prisoners' work; (2) high-altitude experiments, conducted for the German air force and designed to intentionally cause subject death; (3) freezing experiments, also conducted for the German air force to

examine treatments for hypothermia and also designed to cause subject death; (4) seawater experiments, conducted for the German navy and air force to test methods of making seawater safe to drink; (5) poison experiments, conducted to evaluate the effect of poisons in food and bullets; (6) incendiary bomb experiments, conducted to test treatments for phosphorus burns that involved intentionally inflicting burns prior to treatment; (7) jaundice experiments, conducted for the German armed force to examine causes and inoculations against jaundice; (8), bone, muscle, nerve, and bone transplant experiments, conducted to benefit German armed forces; (9) mustard gas experiments, conducted for the benefit of the German armed forces, in which physicians deliberately inflicted wounds on prisoners and then infected them with mustard gas; (10) Sulfanilamide experiments, conducted for the benefit of the German armed forces to test drug effectiveness after wounds were deliberately inflicted to resemble battlefield wounds; (11) vaccine experiments, conducted for the benefit of German armed forces to test vaccine efficacy for typhus, smallpox, malaria, and other diseases; (12) tubercular Polish national imprisonment and homicide, conducted under the pretext of protecting German health; (13) skeleton collection for anatomical research; (14) euthanasia, beginning at German asylums and continuing to the Nazi concentration camps. The prosecution delivered its opening statement on December 9, 1946, and on June 2, 1948, the seven defendants sentenced to death were executed. ("Final Report," 1949)

The judges of the Doctors' Trial rejected the notion that these experiments were necessary and acceptable, even in a wartime setting. In their condemnation of the experiments, the court in the Doctors' Trial articulated what we now know as the Nuremberg Code. The Code specifies ten critical points to govern human subject research. The precise words of the Nuremberg Code serve as powerful reminders, especially as the reader reflects on other studies discussed herein.

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any state, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject. ("Nuremberg Code," 1949)

It is striking to note that the timing of the Doctors' Trial and subsequent Nuremberg Code intersected both the sexually transmitted disease study in Guatemala and the Tuskegee syphilis study. Despite the fact that the articulation of the Nuremberg Code did not immediately change the course of the aforementioned studies, it is a marker of the birth of American bioethics and has shaped the development of human research protections in the ensuing decades. (Annas, 2009)

USPHS Sexually Transmitted Diseases Inoculation Study, Guatemala, 1946-1948

While researching the Tuskegee syphilis studies, Susan M. Reverby, a historian at Wellesley College, uncovered documents detailing the U.S. Public Health Service (USPHS) sexually transmitted diseases inoculation studies that were conducted in Guatemala between 1946 and 1948 (Reverby, 2011). In an attempt to determine whether taking penicillin after sexual intercourse would prevent the spread of syphilis, gonorrhea, and chancroid (Stein, 2010), researchers were funded by a grant from the National Institutes of Health, then a part of USPHS ("Discovery of 1940s Study," 2010). In order to explore reliable methods of infecting subjects, researchers utilized three different subject populations -- male prisoners, mental patients, and soldiers -- and introduced the subjects to prostitutes already infected with one of three sexually transmitted diseases, or intentionally infected by researchers ("Ethically Impossible," 2011). Researchers also attempted to develop inoculations derived from *Treponema pallidum*, the bacteria that causes syphilis infection. In total, 128 subjects were infected with chancroid, 234 subjects were infected with gonorrhea, and 427 subjects were infected with syphilis. Researchers also drew blood samples from 438 children for future research. (Stein, 2010)

Among the facts of the Guatemala studies that strike the conscience is that the research occurred during the same time as the Doctors Trial of the Nuremberg Tribunal, discussed above. The Tribunal issued its opinion in August 1947, in the middle of the Guatemala studies, and the Nuremberg Code was finalized in 1949, only one year after the Guatemala studies concluded. Despite the contemporaneous trial at Nuremberg, human subjects research was governed by few regulations that would have benefitted the Guatemalan subjects. Although the Guatemala study notably lacked an IRB review, no requirement for such a review existed at that time; indeed, IRBs were not codified until nearly 30 years later. ("Federal Policy")

The Guatemala study used human subjects from three populations defined today as vulnerable: prisoners, the mentally ill, and wards of the state ("Historian Who Unveiled," 2010). Much like the lack of IRB requirement, though, these populations did not benefit from modern protections during the study. Prisoners were not defined as a vulnerable population until 30 years after research concluded in Guatemala. The risks to which prisoners were subjected were magnified by their lack of freedom and, in many cases, left them more inclined to agree to activities with higher risk, such as receiving inoculations and engaging in sexual intercourse with prostitutes. Casting even more doubt on the prisoners' level of willing participation in the study is the fact that researchers offered rewards, in the form of cigarettes, to prisoners who participated ("Ethically Impossible," 2011). Just as prisoners participating in human subject research received protections much later, so, too, did wards of the state and the mentally ill. For both populations, federal regulations were promulgated 30 or more years after the Guatemala study.

Unlike IRBs and vulnerable population protections, informed consent was the ethical norm during the time of the Guatemala study and yet, researchers infected the

subjects with sexually transmitted diseases without their knowledge and without obtaining informed consent (“Ethically Impossible,” 2011). Researchers not only failed to inform subjects that the inoculations they received contained the syphilis bacteria, but actively deceived subjects and institutional officials by leading them to believe that the inoculations were actually drugs with medicinal benefit. Instead of obtaining informed consent from the research subjects, researchers preferred to work with the Guatemalan government and institutional officials where the subjects were housed (“Ethically Impossible,” 2011). In order to gain cooperation and permission from the institutions, researchers promised to provide medications, medical treatments, and other desired commodities, such as refrigerators. Researchers demonstrated shocking indifference to the suffering of subjects. In one case, a woman who was infected with syphilis had reached a terminal state as a result of the disease. Rather than providing treatment, researchers poured gonorrhea-infected pus into her eyes and other orifices, and also attempted to infect her again with syphilis. She later died (“Ethically Impossible,” 2010). Several documents expose the reservations that USPHS doctors had about the study, namely that the mentally ill could not give consent and that there were moral concerns about their conduct; however, the Guatemala study continued. (Reverby, 2011)

After two years of experiments, the Guatemala studies concluded, 71 subjects had died, and researchers had made little progress to answer their threshold question (Stein, 2010). In November 2010, President Barack Obama charged the Presidential Commission for the Study of Bioethical Issues (PCSBI) to further investigate the facts of the Guatemala study and to conduct a thorough review of human subjects protection. The Commission’s report in September 2011 found that the Guatemala study involved unconscionable violations of ethics, even when judged against the requirements of the medical ethics of the time of the study. PCSBI concluded that researchers intentionally exposed over 1,000 people to sexually transmitted diseases without obtaining appropriate consent prior to the commencement of research. A particularly disturbing fact to PCSBI and to the public was the knowledge that many of the researchers in Guatemala had participated in earlier studies involving prisoners in Indiana. In the earlier studies, the researchers did obtain consent from the subjects, but chose to proceed without consent in Guatemala (“Ethically Impossible,” 2011). The researchers’ actions demonstrated an unacceptable double standard for consent with foreign national research subjects and highlighted the need for adequate safeguards.

Pfizer Trovan Study, Nigeria, 1996

Nearly fifty years after researchers left Guatemala, the actions of one of the largest American pharmaceutical companies once again highlighted the paucity of safeguards for human subjects abroad, particularly for vulnerable individuals. In 1996, Nigeria experienced an epidemic of bacterial meningitis (Abdullahi v. Pfizer, 2009), an infection of the membranes of the brain and spinal cord. Left untreated, bacterial meningitis carries a mortality rate of nearly ten percent. In an effort to gain FDA approval for pediatric use of its new antibiotic, trovafloxacin mesylate or Trovan, Pfizer sponsored a study in Kano, Nigeria (Abdullahi v. Pfizer, 2009). Approximately 200 children were recruited to serve as subjects for the research protocol testing Trovan (Abdullahi v. Pfizer, 2009). The fallout from the

flawed study and the violations of research ethics ultimately led Pfizer to withdraw its FDA application for use of Trovan as a treatment for bacterial meningitis in pediatric patients. (Stephens, 2006)

From its inception, the Pfizer study appeared rushed and indifferent to human research safeguards. Despite an average research protocol development timeframe of one year, the Pfizer protocol was completed in six weeks, even though this study was the first in which Trovan, in oral form, was tested in children (Stephens, 2000). This rush to protocol completion left several research requirements unmet, notably, a formal IRB or ethics committee approval was never obtained for the study (Khan, 2008; Stephens, 2006). In failing to obtain IRB approval, researchers not only violated statutory requirements, but also eliminated an opportunity to design a study that provided appropriate measures to prevent similar side effects as were reported from testing Trovan on animal subjects (Abdullahi v. Pfizer, 2009). During Trovan animal testing, significant side effects were reported, including liver damage, degenerative bone conditions, joint damage, and cartilage damage (Stephens, 2000). Several critics have commented that IRB review of the Pfizer protocol would likely have led to significant modifications to study design. Rather than submit to the IRB review and approval process, the principal investigator forged a letter, backdated to the week before the experiment began, stating that the study had been pre-approved by the hospital's ethics committee (Stephens, 2006; Wollensack, 2007). It was later discovered that not only was the review omitted, but that an ethics committee did not exist at the hospital on the date of the forged letter (Stephens, 2006). Although Pfizer claimed that the principal investigator, a Nigerian physician, led the study, an independent Nigerian investigative committee found that the physician served only nominally in this role; rather, the committee found that researchers based in the United States directed the study (Stephens, 2007). After confessing to the forged ethics committee approval letter, the physician also claimed that he was unaware of the experiment's results and did not see any research data until the investigative committee showed him study results. (Abdullahi v. Pfizer, 2009)

Beyond the failure to obtain IRB approval, the Pfizer protocol exposed the pediatric subjects to unnecessary and preventable risks. Researchers allegedly failed to conduct preliminary testing to determine whether the subjects had a definitive diagnosis of meningitis and whether the strain of meningitis affecting Kano, Nigeria was responsive to Trovan. Further, researchers allegedly did not screen pediatric subjects for joint and liver problems and exclude them from the study, despite the results of Trovan animal testing, nor did they transfer subjects who failed to respond to Trovan to the control group (Abdullahi v. Pfizer, 2009). The protocol itself called for lumbar punctures, also known as spinal taps, and blood tests to assess the efficacy of Trovan; however, these tests were not completed (Stephens, 2006). Claims have also been made that researchers took steps to render the control group treatment ineffective by reducing the dosage of ceftriaxone, the antibiotic received by the control group, thereby elevating the comparative efficacy of Trovan; Pfizer denies intentionally using a dose lower than recommended for the control group. (Stephens, 2007)

Adding to the flaws in Pfizer's Trovan study are allegations that its researchers failed to obtain appropriate informed consent in accordance with statutory requirements and ethical guidelines (Abdullahi v. Pfizer, 2009). The pediatric subjects and their guardians were allegedly unaware that they were participating in research (Stephens, 2000). The native language of Kano is Hausa, and although Pfizer claims that Nigerian nurses at the hospital where the subjects were treated explained the study details in the appropriate language, the nurses did not fully translate the consent form (Stephens, 2000). Pfizer was unable to produce any signed consent forms for the Trovan study; further, Pfizer admitted that no witnesses signed documentation attesting that verbal consent was given (Stephens, 2000; "Statement of Defence," 2007). It has also been alleged that the subjects' guardians often asked the nurses or researchers to make a decision for them because they did not understand the conversation (Shah, 2002). As part of the consent process, Pfizer also had a duty to disclose appropriate alternative treatment; however, it is unclear whether researchers informed patients of the free, conventional, and reportedly effective treatment that was concurrently provided by Doctors Without Borders in the same hospital where the Pfizer study occurred. ("Statement of Defence," 2007)

Pfizer's trouble with consent did not stop with the subjects and their guardians. In its attempt to seek FDA approval for testing, Pfizer represented that it had obtained appropriate approval of the local Nigerian government and the hospital's ethics committee, as previously discussed ("Statement of Defence," 2007). The Nigerian investigative committee later found that Pfizer did not obtain approval from the Nigerian government to administer Trovan and accordingly, the study was an "illegal trial of an unregistered drug" which violated Nigerian law (Stephens, 2006). Although Pfizer claims that it relied on approval letters from the Food and Drug Administration and Control (NAFDAC), the Nigerian FDA counterpart, NAFDAC's director reported that the agency was unaware of the Pfizer study. (Stephens, 2006)

At the conclusion of the Pfizer Trovan study, which lasted only a few weeks, 11 children had died and others suffered symptoms attributable to meningitis, including blindness, deafness, seizures, immobility, and disorientation (Stephens, 2000). No definitive causal link between Trovan and the deaths that occurred has been determined, although many are quick to point out that a few of the children died a few hours or days after taking Trovan (Stephens, 2000). In at least one case, a pediatric subject's symptoms worsened during the study, and yet she continued to receive the drug for three additional days, ultimately dying while still receiving Trovan (Stephens, 2006). Although Pfizer firmly states that any deaths were the result of meningitis infection, not the treatment provided, the Nigerian investigative committee found that the research protocol deviations compromised the care of the pediatric research subjects (Stephens, 2006; "Statement of Defence," 2007). In June 1997, the FDA inspected Pfizer's files and cited the company for record-keeping deficiencies ("Trovan's Troubled History," 2000). Four months later, in October 1997, Pfizer withdrew its FDA application for the use of Trovan as a treatment for bacterial meningitis in pediatric patients. ("Trovan's Troubled History," 2000)

Conclusion

In their own right, each of the studies reviewed in this article is a powerful reminder of the tragedy that occurs when research does not deem every human subject worthy of the most basic respect. Examining the failures of these studies to provide appropriate and adequate protections for human subjects reminds the modern research community to move forward, considering these lessons. Collectively, these studies are marked by failure to obtain consent, failure to educate, and failure to respect. Research abroad has become more common and research administrators must bear in mind factors that create potential for harm, such as lack of understanding due to language barriers, socioeconomic differences that may entice subject participation, to factors yet unknown. Failures in human subject protection and respect, whether occurring in foreign or domestic research, impact community perception of the research community's integrity. Remembering the lessons of these four tragic historical events serves as a powerful aid in prevention.

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