Racing for COVID-19 Vaccine and Cure: Lessons and Tragedies in Human Subject Research

Amar M. Salam¹,²,³, Alison S. Carr²

¹Department of Cardiology, Al-Khor Hospital, Hamad Medical Corporation, ²College of Medicine, QU Health, Qatar University, Doha, Qatar, ³College of Medicine, Weill Cornell Medical College, New York, NY, USA

ABSTRACT

Pressured by the enormous human and economic costs of the COVID-19 pandemic, certain countries and political figures have advocated the use of drugs and vaccines that did not go through the required regulatory stages of the development. Although the reason for bypassing these stages in a race to produce a treatment and vaccine for the COVID-19 patients could have been caused by good intentions to stop the human suffering from the pandemic, nonetheless, history has taught us that the results of this action could be catastrophic. In this article, we briefly review the lessons and tragedies in the evolution of human subject research regulations emphasizing the need for the proper evaluation of drugs and vaccines for COVID-19.

Key words: COVID-19, ethics, human subjects, regulations, research

INTRODUCTION

This year we have been faced with a challenge, not seen previously in our life-time: Managing a pandemic of coronavirus, an infection currently with no cure and even uncertainty, that those who have survived it are not protected from further episodes. The pandemic has stopped the world: Socially and financially, causing major disruption to life as we know it and a desire in all of us to return as quickly as possible to normality. No country has achieved herd immunity yet. Consequently, many are relying on the introduction of a vaccine against coronavirus for the protection. Many vaccines have been developed previously, and consequently, we have the experience of how long it can actually take to develop a vaccine that is effective and safe.

The general stages of the development cycle of a vaccine are: The exploratory stage, preclinical stage, clinical development, regulatory review and approval, manufacturing, and quality control. These stages may take at least several years to complete. The development of a vaccine takes place in three Phases: During Phase I, the trial vaccine is administered to small groups of people. In Phase II, once it has been established that there are no contraindicatory reasons for with-holding further administration, the vaccine is given to people with characteristics similar to those for whom the vaccine is intended (the target population) in a larger clinical trial. In Phase III, the vaccine is given to the thousands of people, and it is tested to determine the safety and efficacy.

All three phases have been shown to be necessary and exposure of the vaccine to large number of people in test conditions are needed to pick up rare but serious side effects.

Vaccine development is tightly controlled by the governmental agencies such as the Food and Drug Administration (FDA) in the United States of America and the steps of approval often take several years. In the quest to find a vaccine for coronavirus, many have stressed the need to by-pass these steps...
to restore life as we know it. In this article, we review some of the lessons and tragedies in the evolution of human subject research regulation in chronological order, reinforcing the need for a thorough evaluation of the corona-vaccine.

**THE 1900 WALTER REED YELLOW FEVER STUDY**

In the late 19th century, yellow fever, popularly referred to as “black vomit,” affected both civilians and soldiers in the Americas by causing liver failure, gastrointestinal hemorrhage, and death.\(^1\) Walter Reed was a Major in the U. S. Army appointed to study tropical diseases in Cuba. Reed sought volunteers from the Spanish immigrant community who had not yet contracted yellow fever. A payment of $100 in gold was given to participants who volunteered to be bitten by mosquitoes and another $100 if they became ill.

The research was conducted with human participants being deliberately infected with the disease by exposing them to potentially deadly virulent material containing infected mosquitoes; two of the participants died as a result of contracting yellow fever.\(^2\) The participants had been informed that death from yellow fever was a possible risk of their participation, but the researchers did not believe in this method of transmission and did not emphasise this risk. The research revealed that the yellow fever is transmitted through mosquitoes biting humans rather than from person to person and led to a significant decrease in mortality rates from yellow fever.

**1932–1972 THE PUBLIC HEALTH SERVICE SYPHILIS STUDY IN TUSKEGEE**

The Tuskegee study of untreated syphilis in the Negro male is the longest nontherapeutic experiment on human beings in the medical history.\(^3\) The press exposure of this study set the stage for the National Research Act, consequently requiring Institutional Review Board (IRB) review of all federally funded studies.

The study began in 1932 when therapy for syphilis was almost as risky as the disease itself. Six hundred African–American men were recruited: 400 test participants who had syphilis and 200 controls who did not. The researchers offered free examinations, medical care, and "therapeutic spinal tap" to all men who volunteered for the study.

The initial plan was to study the men for 6 months, but as subjects were so compliant, the research was extended. Penicillin was discovered an effective and accessible treatment for syphilis during the study period but withheld from these subjects because of the unique scientific opportunity to study the long-term effects of syphilis. The test participants were unaware they had syphilis or that there was a treatment available throughout the study period. The participants for the Tuskegee Syphilis Study were disadvantaged, rural black men.

Risks to participants were not minimized in this study, instead, participation increased risks. The burden of risk was placed on the disadvantaged, rural black male population while a much broader population would benefit from the findings. These findings demonstrate the need for voluntary informed consent, risks not outweighing benefits, and that benefits and risks of research should be distributed fairly.

In 1972, the study was exposed by the media; and in 1973, the surviving participants finally received penicillin. In 1997, President Bill Clinton issued a formal apology on behalf of the U. S. government to the participants and their families.

**1939 STUTTERING STUDY**

This social science experiment named “the Monster Study,”\(^4\) was set out to prove stuttering is a learned behavior that can be induced in children through psychological pressure. Over a 6-month period, Dr. Wendell Johnson, a nationally renowned pioneer in the field of speech pathology, and his staff tested his theory on 22 children in care in the state run Iowa Soldiers’ Orphans’ Home.

The study group was chosen due to the convenience of being able to abuse and berate. Some were subjected to steady harassment, badgering and other negative therapy in an attempt to get them to stutter; the rest were served as a control group. Although the investigators did not intend to harm the orphan children, this study was criticised because of the apparent lack of regard for the potential harm to the children who participated and in their selection of institutionalized children simply because they were easily available.

**1946 NAZI DOCTORS’ TRIAL**

The Nazi Doctors’ Trial began in 1946 following World War II. Criminal proceedings were brought against 23 Germans for participating in war crimes and crimes against humanity.\(^5\) Sixteen were found guilty and seven were sentenced to death because of their participation in experiments on human beings involving painful and frequently fatal procedures.

In one example, Nazi Doctors were interested in learning about hypothermia that threatened the lives of soldiers fighting at the front. They conducted experiments on prisoners by exposing them to excessively cold temperatures to determine the core body temperatures at which humans begin to lose consciousness and eventually die.
Many of the subjects died as a result of the experiments conducted by the Nazis, while many others were murdered after the tests were completed to study the effects postmortem. Those who survived were often left mutilated, suffering permanent disability, weakened bodies, and mental distress.

Despite the arguments of the German physicians that the experiments were medically justified, the Nuremberg Military Tribunals condemned the experiments as “crimes against humanity.” Sixteen of the 23 physicians were found guilty and imprisoned, and 7 were sentenced to death. In the August 1947 verdict, the judges included a section called “Permissible Medical Experiments.” This section became known as the Nuremberg Code and has formed the basis for ethics codes internationally.

1947 NUREMBERG CODE

The Nuremberg Code[6,7] was adopted following the Nazi Doctors’ Trials. It established ten basic principles related to the normal, ethical and legal obligations associated with human subjects’ research. These principles form the foundation of the Belmont Report, eventually published in 1979:

- The voluntary consent of the human subject is absolutely essential
- Human research should be founded on the preliminary results from animal studies
- Unnecessary physical and mental suffering should be avoided
- Degrees of risk to participants should never exceed the humanitarian importance of the problem to be solved by the experiment
- Only sufficiently qualified persons should be allowed conduct the research
- The researcher must stop the experiment if it becomes apparent that injury, disability or death is a likely result of it continuation.

1950S RADIOACTIVE CEREAL EXPERIMENTS AT FERNALD

During the 1940s and 1950s, researchers fed radioactive cereal to 15 children at the Fernald School, a “state home for the retarded” in Massachusetts.[8] Small amounts of calcium and iron tagged with radioactive tracers put in the children’s cereal, allowing researchers to track the absorption of those nutrients during digestion.

The researchers studied the children without their consent or the consent of their guardians, enticing participation, by stating the children were part of a science club. Some were exposed to radiation exceeding federal limits; however, they did not suffer any physical harm. At the time of the study, the concept of “informed consent” (or that a human test subject had the right to know exactly what he or she was being subjected to) did not exist.

1956–1972 WILLOWBROOK EXPERIMENT

During a study of the progression, the prevention and treatment of viral hepatitis extending from 1956 to 1972, researchers at the Willowbrook State School in New York,[9] an institution for “mentally disabled children,” deliberately infected children with a mild form of hepatitis. The results eventually contributed to developing a successful hepatitis vaccine but were controversial since the study involved healthy, institutionalized children and parental consent issues. The case along with others contributed to the advancement of federal regulations governing human subjects’ research.

1961 THALIDOMIDE STUDY

In the late 1950s, Thalidomide was approved as a sedative in Europe, but the FDA had not approved it for use in the U. S. At that time, the FDA had only a limited role approving drugs in the U. S., which allowed the manufacturer to give samples to U. S. physicians and pay them to study their safety and efficacy. By 1961, it became clear that Thalidomide caused significant harm to a foetus if a woman took it during the first trimester of pregnancy. Children were being born with severe congenital deformities.[10]

In this case, although did not involve research, strong marketing pressure in an Industry hungry for new medicines brought an inadequately tested drug to the market, targeted outsourcing quickly expanded the client base and finally market forces prevented timely withdrawal, even when evidence was emerging of disastrous side effects. This prompted the 1962 amendments to the Food, Drug and Cosmetic Act requiring drug manufacturers to establish a drug’s effectiveness prior to marketing.[11]

1963 JEWISH CHRONIC DISEASE HOSPITAL

Researchers funded by the National Institutes of Health at Sloan–Kettering Cancer Research Institute injected live cancer cells into indigent, chronically ill elderly patients without their consent.[8] The experiment was intended to measure the patients’ ability to reject the cells and was not related to their treatment. Subsequent government hearing revealed that the reason the researchers did not ask the patients for their consent was to ensure that they did not refuse to participate.
The physicians’ rationalization for their actions was as that they did not want to scare the patients and that they thought the cells would be rejected.

In subsequent review proceedings conducted by the Board of Regents of the State University of New York, it was found that the study had not been presented to the hospital’s research committee and that the physicians responsible for the patients’ care had not been consulted. The researchers were found guilty of fraud, deceit, and unprofessional conduct.

1963 MILGRAM STUDY

This social science study[12] was conducted in an attempt to understand—from a psychological standpoint—the role of obedience to authority: Why ordinary people behave in ways that seem inhumane outside a certain context. The research design was to have an authority figure instruct subjects to do something that they would not do under ordinary circumstances.

The researcher, Stanley Milgram, and associate deceived subjects into thinking they were causing the associate to be shocked with an electrical charge. The associate was attached to a device that appeared to administer electric shocks, and the participants were told to shock him every time he answered a memory task incorrectly and to push a button to increase the “electrical charge” when instructed by the researcher. These increases were frequent and eventually the associate pretended to convulse with the shock and lapse into unconsciousness.

The research taught Milgram about human behavior at the expense of the unwitting subjects, who had no idea that their associate was not actually being shocked. Some of the subjects suffered emotional distress after witnessing the responses they thought they had inflicted.

1964 DECLARATION OF HELSINKI

The declaration of Helsinki[13,14] was developed in 1964 by the World Medical Association as an international statement of ethical principles to guide the medical professionals conducting research involving human participants. The declaration, although not a legally binding document, has since been codified into the laws that govern medical research in countries across the world and has served as a basis for the development of other international guidelines.

1966 BEECHER ARTICLE APPEARS IN THE NEW ENGLAND JOURNAL OF MEDICINE

As a result of the Nazi Doctors’ Trials, many American researchers believed that ethical abuse happened only in Europe and were unaware of those in the U. S. Dr. Thomas Beecher wrote an article “Ethics and Clinical Research,”[15] published in the New England Journal of Medicine citing 22 published studies with serious ethical flaws. For example, in one study researchers assigned some patients with acute streptococcal infections to a “control group” and did not allow them effective treatment. More than 70 of these patients developed rheumatic fever. In another study of immune response, researchers injected live cancer cells into subjects without their informed consent resulting in many dying.

Beecher claimed that the problem was not that researchers were malicious or evil. Rather, the problem was they manifested thoughtlessness or carelessness. He called for more rigorous self-scrutiny rather than public review. Beecher’s paper was instrumental in the implementation of federal rules on human experimentation and informed consent.

1971 STANFORD PRISON EXPERIMENT

In 1971, researcher Philip Zimbardo conducted a study of the psychology of imprisonment by setting up a mock prison using volunteer college student subjects who assumed the roles of prisoners and guards.[16] The student “guards” brutalized the students “prisoners.”

Ethical concerns about the research include an underestimation of the likelihood and severity of psychological harm to the subjects, and that the researcher himself played a role (prison director) in the research rather than safeguarding the welfare of the research subjects. Participants playing the role of prisoners were not protected from psychological harm and experiencing incidents of humiliation and distress.

1974 NATIONAL RESEARCH ACT

This directive, spearheaded by Senator Edward Kennedy, representing one of his earliest achievements, was the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission spent 5 years developing the Belmont Report and ultimately mandated IRB review of all federally–funded research.

1974–1981 NATIONAL HEALTH SERVICE AND FOOD AND DRUG ADMINISTRATION REGULATIONS

The National Commission for the Protection of Human Subjects of Biomedical Behavioural Research was established by the National Research Act of 1974 and met from 1974 to 1978. In accord with its charge, the commission issued reports and recommendations identifying the basic ethical principles that should
underlie the conduct of biomedical and behavioral research involving human subjects. The first version of the Department of Health and Human Services (DHSS) regulations was published in 1974.

In 1981, the DHSS and the FDA promulgated new regulation on human subject’s research published at 45 code of federal regulations (CFR) 46 and 21 CFR 50, respectively.

1979 BELMONT REPORT

The Ethical Principles and Guidelines for the Protection of Human Subjects of Research, called the Belmont Report,[17] named after the conference center where it was created, was published evolving from the National Research Act and the Nuremberg Code. It defines three fundamental ethical principles for using human subjects for research:

1. Respect for person: Protecting the autonomy of all people and protecting those who cannot be autonomous; treating people with courtesy and respect, and allowing for informed consent

2. Beneficence: “Do no harm.” Maximizing the benefits of the research while minimizing risk of harm to the research subjects

3. Justice: Addresses the distribution of the burdens and benefits of research. One group of society should not bear the cost of research while a different group benefits from the findings. Justice is applied mainly to the selection of participants in research studies.

1991 COMMON RULE

In 1991, the core DHHS regulations (45 CFR Part 46, Subpart A) were formally adopted by 16 Departments and agencies of the federal government that conducted or funded research involving human subjects. This policy is known as the “Common Rule.”

1995 RADIATION EXPERIMENTS

The U. S government published a report entitled, “Human Radiation Experiments;”[18] The Department of Energy RoadMap to the Story and Records (“The DOE Roadmap”) in 1995. It discusses human radiation experiments conducted on thousands of United States citizens during and after World War II, including injecting plutonium into hospital patients without their consent and the intentional release of radiation into the environment. The studies were conducted for a variety of reasons including the advancement of biomedical science and national defence. Most studies did not result in serious harm to subjects, but some did result in increased risk of thyroid cancer, and several deaths resulted.

1996 UNIVERSITY OF ROCHESTER BRONCHOSCOPY CASE

A healthy 19-year-old college student died after volunteering for a medical research study in which University of Rochester researchers performed a bronchoscopy under general anaesthesia.[19] An investigation revealed that researchers exceeded the maximum dosage of lidocaine established by the research protocol.

1999 JESSE GELSGINGER

Jessi Gelsinger, an 18-year-old research subject who died as a result of taking part in a clinical experiment using gene transfer, suffered from ornithine transcarbamylase deficiency, a genetic disease that disrupts metabolism.[20] His disease was mild and he was able to live a relatively normal life. During the experiment conducted at the University of Pennsylvania, Gelsinger developed a massive immune response after being injected with the study substance and died 4 days later. An FDA investigation concluded that the informed consent provided to Gelsinger was inadequate for a number of reasons including failure to fully describe the risks of the research study and to disclose the researcher’s financial conflict of interest.

CONCLUSIONS

These lessons and tragedies in human subject research regulations’ evolution clearly show the benefits of legislation to protect human subjects from the risks of human research involving medical intervention. The ethical principles in the Belmont report of respect for person, beneficence and justice are vital considerations when developing a vaccine for Coronavirus. The examples of ethical misconduct on human participants cited in this article show the damage that can occur when drugs are administered to human participants without concern for the safety of the participants in the research. Releasing a vaccine for coronavirus early without adhering to the Phases of development of a new vaccine would expose the population to a vaccine which potentially might cause as much harm as it does good.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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