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From Forced to Voluntary Participation: The History of Biomedical Human Experimentation in the United States after the Second World War

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Abstract:

For as long as medicine and medical practices have been around, so has the need for testing treatments in or procedures on the human body. Over the course of history, however, the nature, structure, and prominence of human biomedical experimentation has changed drastically both on an international and national level. My thesis focuses on revealing the driving forces behind these changes in administrative, legal and social factors related to human experimentation in an effort to connect the dots from the manipulative, forceful and unethical experimentation of early medical practitioners to the safe, voluntary and highly regulated experimentation characteristic of clinical research today. Although human biomedical experimentation spans many cultures, countries, and time frames, my research focuses on the history of experimentation in the United States from the mid-twentieth century until present day, while still framing the topic in a larger global context. I have chosen this time period because it captures an immense period of change and I have chosen to focus on just one country since regulations and cultural shifts related to this topic often occur at a national level. Through my research, I have found that throughout the twentieth century, major cases of unethical human experimentation have sparked periods of public outrage, increased public awareness of ethical issues, and consequently have led to an increase in regulations and an increase in regulatory bodies governing human biomedical experimentation. Such changes have created a much safer system of testing biomedical products or procedures on human subjects in the United States.

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Statement of Purpose

As a double major in both Biology and Science, Technology, and Society, over the course of my education I have become increasingly interested in the intersection between science and society. Through exploring this interest, I have acquired a particular fascination for the practice of human experimentation. This area of medicine is one in which science and society are so intimately intertwined that it is impossible to think of one without the other. In modern day clinical trials involving human subjects, the scientists who have been working for many years in laboratories perfecting their chemical compounds finally intersect with the people for whom these compounds are intended. Human experimentation is an area of medicine where the science meets the people in a blatant and complicated manner, and where the science has the opportunity to leave a lasting impact on society.

As I learned more about clinical research and its history, I started to wonder how we arrived at the point in the United States where clinical trials are so prevalent and so trusted. Knowing that there was a time in history when humans were tested on unfairly and unethically, I began to question how human biomedical experimentation got from the deceitful, manipulative testing by Nazis on German Jews to the safe, voluntary testing that now occurs so regularly in the United States and globally.

Given this drastic change in the nature of human experimentation over a relatively short amount of time, from the 1940s until the present day 2018, I decided to focus my thesis on connecting the dots. Thus, I have devoted my research to understanding when, why, and how clinical research involving human test subjects has changed over the course of the last century with the intention of relating these changes to the ever-evolving relationship between science and society.

Introduction

Sam Spadino is a Minneapolis resident with a passion for writing and filmmaking. In order to fund his creative career, Spadino works as a "human lab rat" in phase 1 clinical trials, the first-in-human studies that test the safety of an experimental drug in a small group of healthy volunteers.[1] The companies that run these studies essentially pay healthy individuals like Spadino to use their bodies to test the effects of their drug on a human for the first time. Spadino has chosen to make a living off of this line of work, and earns between $18,000 and $28,000 a year participating in phase 1 clinical trials, the first stage of human testing during which researchers test the safety of an experimental drug in healthy volunteers.[2] As the potential associated risks for a trial increases, so does the value of monetary compensation.[3]

Spadino, in an interview with the news outlet *VICE*, revealed the details of his life as a professional guinea pig and his perspective on clinical research in general. In response to inquiries about his participation in a current trial, a 90-day thyroid medication study, Spadino described that he is checked into a "dorm-style clinic" with decent hospital food, a typical stipend of $250 a day, and hardly anything to do, so he spends his time "hanging out, watching movies, or reading."[4] He said he got into guinea pig work because a friend told him about it and he continues to participate because it's easy money and he can continue to pursue his writing and filmmaking career at the same time.[5] In addition to the income and free-time, he also sees a

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[1] Thomas, Sophie Saint. "My Life as a Full-Time Human Guinea Pig: There are worse ways to making a living than getting paid to piss in a bucket." *VICE*, 28 Apr. 2016, www.vice.com/en_uk/article/xd7naw/my-life-as-a-full-time-human-guinea-pig58477fdc068ed4026770ef67. Accessed 13 Dec. 2017.
[2] Thomas
[3] Thomas
[4] Thomas
[5] Thomas

benefit in the constant medical attention and proximity of doctors, especially since he doesn't have health insurance.[6] While many of the people he tells about his line of work express concerns about his safety participating in dozens of phase 1 clinical research studies a year, he actually sees himself as fortunate for having round-the-clock health monitoring by experienced and invested medical personnel.[7] Some studies do not allow participants to be enrolled in other studies at the same time or even require a buffer period between studies to provide for a higher degree of control; however, if investigators can resolve ethical, safety, statistical, and practical concerns related to participation in multiple studies then the studies will allow and even encourage co-enrollment.[8] Spadino regularly checks the website "Just Another Lab Rat!" to find studies happening in his area and continues to allow researchers to test their experimental products in his body in exchange for monetary compensation.[9]

Sam Spadino is modern example of a professional human guinea pig, a healthy individual who receives compensation for his or her participation in clinical research. Although many clinical studies fail to produce effective biomedical compounds or devices or do not produce conclusive results, the overall number of ongoing clinical studies is rapidly increasing, as is the number of approved drugs, devices and procedures on the market.[10] From 2000 to 2017, the number of registered clinical studies increased from 5,627 to 261,107 according to clinicaltrials.gov, a database produced by the National Institutes of Health (NIH).[11] As the

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[6] Thomas
[7] Thomas
[8] Myles, Paul S et al. "Ethical and Scientific Considerations for Patient Enrollment into Concurrent Clinical Trials." *Trials* 15 (2014): 470. *PMC*. Web. 16 May 2018.
[9] Thomas
[10] "Trends, Charts, and Maps." *ClinicalTrials.gov*, NIH, Sept. 2017, clinicaltrials.gov/ct2/resources/trends. Accessed 11 Dec. 2017.
[11] "Trends, Charts, and Maps."

number of ongoing clinical trials per year increases, so does the amount of healthy participants needed and the number of people like Spadino who volunteer themselves as test subjects.

Compared to the nature of human experimentation in the past, this modern practice of human subject research, in which healthy individuals volunteer to participate, is quite different. For as long as medicine and medical practice have been around, so has human experimentation. Although there have been times throughout history when religious or political entities discouraged or banned human experimentation, such the ban on human dissection in the Hellenistic world following the widespread introduction of Christianity in the Middle Ages, there has still always been a "first" when it comes to experimental compounds entering the human body or performing experimental procedures on live human subjects[12]. Whenever a new treatment or medical procedure is introduced, someone has to be the first to receive that treatment or procedure, and as long as the major industry players such as biotech companies, pharmaceutical companies and research hospitals continue to produce new drugs and treatments there will continue to be a need for first-in-human experimentation. In the early history of biomedical human experimentation, from the ancient times of Hippocrates all the way until and through the beginning of the twentieth century, researchers and physicians performed forceful, deceitful, and or manipulative studies on unknowing, coerced, or unwilling subjects. These subjects included prisoners, soldiers, minorities, children, pregnant women, the impoverished, and the cognitively impaired. For example, U.S. government doctors in the middle of the early to middle part of the twentieth century performed experiments such as "giving hepatitis to mental patients in Connecticut, squirting a pandemic flu virus up the nose of prisoners in Maryland, and

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[12] Roberts, Elizabeth. "Human Dissection – From Galen to the Great Revelations of Andreas Vesalius." *BrainBlogger*, 20 Aug. 2011, brainblogger.com/2011/08/20/human-dissection-from-galen-to-the-great-revelations-of-andreas-vesalius/. Accessed 16 May 2018.

injecting cancer cells into chronically ill people at a New York hospital."[13] This transition in the nature of human experimentation and in the types of people serving as human research subjects from forceful experimentation on prisoners and other vulnerable subjects to voluntary participation by people like Spadino leaves unanswered the questions of why has the change occurred and how.

How did the structure of human experimentation change so drastically from the ancient times of Hippocrates until now, when did those changes occur and why was there so much change during this time period? The answer to the question of why is due to the increase in ethical standards and the heightened value of human life and human rights. In many cases, increased awareness of and consideration for ethical treatment of human subjects followed the revelation of grossly unethical cases of human experimentation. The answer to the question of how is through regulatory and policy changes, the establishment of new institutions, and the changing attitudes of the public towards human rights. While human experimentation is a global practice as old as medicine itself, the focus of this study is on the historical changes in human experimentation in the United States immediately following World War II until the present day. This narrowed focus allows for the careful analysis of both national and international regulatory changes, the establishment of new institutions, ethical considerations, and policy statements during what will be argued was one of the most drastic periods of change in the nature, structure and prominence of research on human subjects.

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[13] Stobbe, Mike. "America's past of human experiments undiscovered." *NBC News*, 27 Feb. 2011, www.nbcnews.com/id/41811750/ns/health-health_care/t/ugly-past-us-human-experiments-uncovered/#.WjFPeLQ-e1s. Accessed 13 Dec. 2017.

The International Impact of the Nuremberg Trials

Although the focus of this research and analysis is on the United States, it is necessary to frame the topic within its global context, and, more specifically, to begin with the historical events occurring in Germany that have sparked a time period from the 1940s until present day during which America went through rapid change in the laws, structure, and attitudes surrounding human experimentation. At the end of World War II, the Allied Forces charged and tried Nazi German officials of war crimes that violated international law; this series of court cases trying Nazi German officials was called the Nuremberg Trials.[14] The ruling Tribunal of the case proved sixteen Nazi officials guilty of "crimes against humanity," in which the defendants were "principals in, accessories to, ordered, abetted, took a consenting part in, and were connected with plans and enterprises involving medical experiments without the subjects' consent in the course of which experiments the defendants committed murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts."[15] The medical experiments that the Nazi German officials conducted included high-altitude experiments during which many concentration camp inmates died or were tortured in low-pressure chambers, freezing experiments in which inmates died as a result of being forced to remain in a tank of ice water for periods up to three hours long, and malaria experiments in which inmates were infected with the disease and died or suffered severe pain and permanent disability.[16] The Nuremberg Trials revealed these gruesome and cruel medical acts, among many other heinous crimes.

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[14] "The Medical Case," *Trials of War Criminals Before the Nuremberg Military Tribunals*. Vol. 2, Nuremberg, 1945-1949.
[15] "The Medical Case"
[16] "The Medical Case"

Image 1. *Joseph Mengele led experiments on twin children in concentration camps to study genetics and unnatural manipulation of the human body. Procedures included organ removal, dissection, disease injection, and sewing sets of twins together.*[17] *Pictured here is a Nazi nurse fitting a gas mask onto a set of young twins in preparation for experimentation.*

The Nuremberg Trials revealed the medical crimes that Nazi Germans committed, and also sparked an international debate on the regulation of human experimentation. The result was the Nuremberg Code, a set of ten points defining legitimate medical research involving human

[17] "Unbelievably Cruel Nazi Human Experiments." *Two Eggz*, 4 Dec. 2017, www.twoeggz.com/int/5404453.html. Accessed 15 Mar. 2018.

subjects published by the Counsel for War Crimes in 1947.[18] The most relevant and profound of these points are the requirement for informed consent from all subjects, the requirement for scientific necessity and societal benefit, the requirement for scientifically qualified personnel operating the studies, the requirement animal studies to precede all human studies, and the requirement for freedom of the subject to terminate participation at any point during the study.[19] The full list of the ten points of the Nuremberg Code are attached in Appendix 1.[20] The Nuremberg Code, thus, reflects a desire of the international community to regulate human experimentation so as to conduct the research more ethically and with a greater respect for human rights and human life.

Although not an official law or set of official ethical guidelines for any nation or association, the Nuremberg Code remains one of the most important and pivotal documents related to research ethics and global human rights. This document represents an important moment in which the international community recognized the atrocities of unethical medical research and made an effort to prevent future atrocities and improve the nature of human experimentation. The Nuremberg Trials and the Nuremberg Code raised international concern and awareness to an issue much deserving of attention in the medical field.

Some of the impacts of the Nuremberg Code and Nuremberg Trials on international ethical considerations can be seen in the years immediately following. In 1948, the Second General Assembly of the World Medical Association met in Geneva, Switzerland and adopted

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[18] "The Nuremberg Code." *Office of History*, National Institutes of Health, 1947, history.nih.gov/about/timelines/nuremberg.html. Accessed 12 Dec. 2017.
[19] "The Nuremberg Code."
[20] "The Nuremberg Code."

the Declaration of Geneva.[21] The declaration states the physician's dedication to the humanitarian goals of medicine, and does so in a way which is highly reminiscent of the Oath of Hippocrates from around 460 BC, a document in which Hippocrates, the father of medicine, commits to respecting and protecting his patients above all else.[22,23] By repeating, rewording, and reestablishing Hippocratic oath, the Declaration of Geneva ties current ethical principles to those of antiquity, and restates the necessity to acknowledge and respect the rights of medical patients and subjects. The declaration, in its timing, also serves to contrast the highly unethical turn human experimentation had taken with the ethical expectations of the medical field. In the following year, the Third General Assembly of the World Medical Association produced an International Code of Medical Ethics, which again outlined the duties of physicians to the sick, to each other, and in general.[24] These two documents demonstrated increasing awareness, internationally, of a need to regulate more closely human experimentation and the patient-physician relationship, and also further highlight the impact of the Nuremberg Trials and the Nuremberg Code on international attitudes.

From this point on, changes in ethical considerations, regulations, and institutional bodies caused the nature of human experimentation and the attitudes towards it to shift drastically both within the United States and internationally (see Image 4 for a timeline of relevant events). Immediately following the end of World War II, industries involving human medical experimentation embarked on a journey of rapid, dynamic changes in the nature, prominence,

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[21] World Medical Association, 2nd General Assembly,. "WMA Declaration of Geneva" *World Medical Association*, adopted Sept. 1948, https://www.wma.net/policies-post/wma-declaration-of-geneva/.
[22] World Medical Association, 2nd General Assembly.
[23] Chadwick, J., and W. N. Mann, translators. *Hippocratic Writings*. Penguin Books, 1950.
[24] World Medical Association, 3rd General Assembly, "WMA International Code of Medical Ethics." *World Medical Association*, adopted Oct. 1949, www.wma.net/policies-post/wma-international-code-of-medical-ethics/.

and structure of their work. This journey began, in large part, with the reveal of the unethical medical crimes against humanity during Nazi Germany and the resurgence of a global ethics and human rights movement, and continued as unethical studies persisted.

Since then, a heightened awareness for the ethical treatment of human test subjects has resulted in closer regulation of human experimentation both on a national and international level. Although some studies span multiple nations and some regulations are enforced at an international level, the vast differences in regulations between countries make it extremely difficult to compare changes on a global level. Thus, the rest of this paper will focus on the major studies that happened in the United States over the last century and the changes in regulation and structural organization related to human biomedical experimentation that have resulted from these studies.

Case Study: Tuskegee Syphilis Study

Following the international court's reveal of the torturous and unethical experiments that Nazi officials performed on their Jewish prisoners, attitudes towards human biomedical experimentation changed and awareness of ethical standards increased globally. The Declaration of Geneva and the International Code of Medical Ethics, however, did not lead to immediate structural changes in ethical guidelines, regulatory policies, or institutional governance in the United States. Rather, the changes happened slowly as unethical studies made people more aware of and more concerned with the rights and treatment of human test subjects. This continued increase in ethical concerns and structural changes was due in large part to the reveal of several more cases of unethical human experimentation in the United States throughout the rest of the twentieth century.

One of these cases that stands out as having had a large impact on the attitudes towards and structure of human experimentation in the United States is the Tuskegee Syphilis Study. The study began in 1932 as a project dedicated to researching the effects of untreated syphilis on residents of Macon County, Alabama by the United States Public Health Service (PHS).[25] Macon County is a historically poor area of Alabama and is home to a predominately uneducated black population.[26] It is also home to the Tuskegee Institute, a private, historically black university established by Booker T. Washington in 1881.[27] In 1932, the Tuskegee Institute became the center for this untreated syphilis research project. Although originally intended to last just 6 months, the study continued for forty years as a racially mixed team of researchers observed the effects of untreated syphilis on hundreds of participants from Macon County.[28]

Syphilis is a highly contagious disease caused by a bacterial infection. The infection can be either congenital or acquired and is usually passed on through sexual intercourse.[29] Syphilis can also be passed along from mother to child, and thus can spread very easily and very quickly.[30] In 1926, several years before the Tuskegee study began, investigators observed a prevalence of syphilis of 35 percent in the reproductive age population.[31] The disease has three distinct stages, primary, secondary and tertiary. The primary stage refers to the first ten to sixty days after infection when the primary lesion, a slightly elevated ulcer called the chancre, develops at the point of contact. The chancre is usually smaller enough that it does not cause any

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[25] Jones, James H. *Bad Blood: The Tuskegee Syphilis Experiment*. New York and Ontario, The Free Press, 1981, 1993 (1).
[26] Jones, 4
[27] Jones
[28] Jones, 1
[29] Jones, 2
[30] Jones, 2
[31] "US Public Health Service Syphilis Study at Tuskegee." *Center for Disease Control and Prevention*, www.cdc.gov/tuskegee/timeline.htm. Accessed 2 Mar. 2018.

personal discomfort and often goes unnoticed.[32] The secondary stage occurs between six weeks and six months after infection when a rash develops, as well as bone and joint pain, fever, indigestion, and/or headaches.[33] Again, these symptoms are mild and nonspecific, and consequently often go unnoticed.[34] Between the secondary and tertiary stages there can be a period of latency that lasts anywhere from several weeks to a couple of decades.[35] After this period of latency, infected individuals experience extreme symptoms due to the growth of large tumors on the skin, bone structures, cardiovascular and central nervous systems, and brain. Victims ultimately experience a painful death.[36] In addition to the physical effects of the disease, infected individuals also bear the burden of the social stigma attached to the sexually transmitted disease. Thus, due to the disease's prevalence, contagiousness, and severe symptoms, the United States Public Health Service decided to sanction a study to learn more about the effects of syphilis on the body.

Since there was an abnormally high population of affected individuals in Macon County and an institute out of which to run the study, the venereal disease branch of the Center for Disease Control and Prevention (CDC) of the PHS in Atlanta in cooperation with the Alabama State Department, the Tuskegee Institute, the Tuskegee Medical Society and the Macon County Health Department began the Tuskegee Syphilis Study in 1932.[37] The study enrolled 399 men who had syphilis as well as 201 men who were free of the disease as controls. The scientific investigators recruited "mostly poor and illiterate" individuals from the area by "offering them

[32] Jones, 2
[33] Jones, 3
[34] Jones, 3
[35] Jones, 3
[36] Jones, 4
[37] Jones, 7

incentives to participate."[38] These incentives included "free medical examinations, free rides to and from the clinics, hot meals on examination days, free treatment for minor ailments, and a guarantee that burial stipends would be paid to their survivors."[39] The investigators and study coordinators were aware that the purpose of the study was to observe the effects of untreated syphilis, but they told participants that they were being treated for "bad blood."[40] The participants were not informed on what "bad blood" was or what treatment they were receiving, aside from the fact that it meant they were sick and promised treatment for their illness by officials of the United States government. Further, the participants were advised not to receive treatment from other sources, the consequence of which would be removal from the study and loss of the benefits that they had been promised.[41] The best treatment option at the time the study began was arsphenamine combined with mercury, which had toxic side effects and was difficult to administer, but still gave patients a better chance at survival than if given no treatment at all.[42] For forty years, government officials and scientists worked together to observe the effects of untreated syphilis on the 399 infected men enrolled in the study.

[38] Jones, 4
[39] Jones, 4
[40] Jones, 5
[41] Jones, 6
[42] Jones, 6

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were

have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Image 2. *1972 New York Times article on the Tuskegee Syphilis Study that generated public outrage.*[43]

The Tuskegee Syphilis Study finally ended in 1972 soon after Jean Heller of the Associated Press broke the story that "for forty years the United States Public Health Service has been conducting a study on the effects of untreated syphilis on black men in Macon County, Alabama.[44] While the government officials and scientists involved had not kept the existence of the study a secret, they had not been clear on many of the details relevant to the structure and execution of the research. Once Heller's story appeared, the public became aware of the manipulative, unethical, and torturous nature of the study. In the article, Heller revealed the true intentions and actions of scientific investigators working on the Tuskegee Syphilis Study and further exposed the doubts that then current members of the CDC and of Congress had regarding the ethicality of the research. According to Heller, Dr. J. R. Millar, chief of the venereal disease branch of the Center for Disease Control in Atlanta, called the study a "serious moral problem";

[43] Heller, Jean. "Syphilis Victims in U.S. Study Went Untreated for 40 Years." *New York Times*, 26 July 1972, p. 1.
[44] Jones, 1

Senator William Proxmire, a member of the Senate Appropriations subcommittee that oversees Public Health Service budgets, referred to the study as a "moral and ethical nightmare."[45]

The shock and concern that authorities such as Dr. Millar and Senator Proxmire expressed makes one wonder what happened behind the scenes at Tuskegee that could have caused such a reaction. Heller's article brought concerns regarding the study to the forefront of the minds of both the professional and public communities. She sparked an interest in and awareness of the details of the syphilis study and prompted Merlin K. DuVal, the Assistant Secretary for Health and Scientific Affairs, to appoint an Ad Hoc Advisory Panel to start an official review of the study.[46] The review, along with other investigative efforts, exposed many shocking flaws in the setup, conduct and ethicality of the research and raised the level of awareness and concern among professionals and the general public.

While under examination by the press, "the PHS was not able to locate a formal protocol for the experiment" and later admitted that "one never existed."[47] This absence of documentation meant that there was no set of strict, preapproved guidelines for scientific investigators and that it cannot be guaranteed that scientific investigators had been operating consistently, ethically, or responsibly. Without an official protocol outlining exact actions and treatment plans, the study lacked in credibility and value. Further, it turned out that subjects had not been informed about their disease or on the details of the medical treatment they had been promised. Dr. J. W. Williams, an intern assisting in the experiment's clinical work, reported that "neither the interns nor the subjects knew what the study involved" and that he was absolutely

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[45] Heller, Jean. "Syphilis Victims in U.S. Study Went Untreated for 40 Years." *New York Times*, 26 July 1972, p. 1.
[46] "US Public Health Service Syphilis Study at Tuskegee."
[47] Jones, 1

sure that they "didn't tell them [they] were looking for syphilis."[48] The participants, being for the most part poor and uneducated, were unaware of their health status, prognosis or treatment plan, and thus were unable to provide informed consent. Even if they had been given the opportunity to provide informed consent, the institutions conducting the study were bribing the participants with hot food and medical services. Such promises must have unfairly influenced the participants. An important distinction is to recognize that this bribery is different from the monetary compensation offered to healthy volunteers like Spadino since enticing poor, uneducated individuals without providing proper and necessary information is manipulative while offering healthy individuals compensation for their time in a controlled study is a more fair and mutual exchange.

Finally, and arguably most importantly, when reviewing the ethicality of the study, investigators found that the medical officials in charge violated the Hippocratic Oath by neglecting to provide treatment to the sick and failing to do no harm to the patients.[49] Although placebo groups exist in clinical trials today which results in some patients not receiving treatment, this placebo group is a risk that is explicitly defined in a modern day trial's protocol whereas in the case of the Tuskegee Syphilis Study the lack of treatment was unexpected and not disclosed. At the start of the study, the details of syphilis were already well known, including the "germ that causes [it], the stages of the disease's development, and the complications that can result from untreated syphilis."[50] By withholding available treatment options in order to further investigate the untreated effects of what was known to be a painful and deadly disease on a controlled group of men, the researchers violated the responsibility of medical professionals to

[48] Jones, 5
[49] Chadwick, J., and W. N. Mann.
[50] Jones, 4

treat the sick. More shocking, however, is the fact that once a highly effective treatment for the disease became available in the 1940s, the scientific investigators of the Tuskegee Syphilis Study continued to withhold treatment from the participants. Denying treatment when there was no good treatment could be excusable, but denying treatment once researchers found penicillin to be highly efficacious could not.[51] An unnamed PHS spokesman in an interview with the *Atlanta Journal* referred to the denial of treatment as "the most critical moral issue about [the] experiment," since it violates the ethical standards of the Hippocratic Oath.[52] The emergence of an effective treatment for syphilis should have shut down the experiment immediately, but instead, researchers continued to watch the bodies of hundreds of men deteriorate for thirty more years.

When these details were revealed, both the public and professional communities responded with disbelief, distrust, and rage. One citizen stated, in response, "if this is true, how in the name of God can we look others in the eye and say: 'This is a decent country.'"[53] The editor of the *Providence Sunday Journal* reported feeling shocked by the "flagrant immorality of what occurred under the auspices of the United States Government."[54] Other public responses from the public included a report of distress due to the capability of the government to sanction such a horrible project and an accusation of the PHS for "persuading hundreds of black men to become human guinea pigs."[55]

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[51] Jones, 8
[52] Jones, 8
[53] Jones, 11
[54] Jones, 11
[55] Jones, 12

Some even called the experiment a genocide and to equated the actions of the government with those of Nazi Germany.[56] Still fresh in the minds of the American people, memories of the Holocaust "haunted some people as the broader implications of the PHS's role in the experiment became apparent."[57] A citizen of Tennessee made a distressing comparison of the study to Adolf Hitler's "similar degradation of human dignity in inhumane medical experiments on humans."[58] Eugene Leslie Roberts Jr., the editor of the *Philadelphia Inquirer,* wrote that the details of the study served as a "shocking revelation of the potential for scientific abuse in their own country" by bringing the issue of ethical human biomedical experimentation not just closer to home, but actually into the homes of the American people.[59] The American people were shocked to learn that such a "stomach-turning callousness" could happen within their own boarders."[60]

Revelation of the details of the Tuskegee Syphilis Study triggered further public discussion about the ethicality of human experimentation and related issues such as trust, consent, safety and equality. Eugene Leslie Roberts Jr. of the *Philadelphia Inquirer* also wrote that this was the first time since the Nuremberg Trials of Nazi scientists that Americans had been confronted with a medical controversy that "captured so many headlines and sparked so much discussion."[61] While conversation and concern regarding the ethical and moral considerations related to human biomedical experimentation were present throughout the 20th century, the controversy surrounding the Tuskegee Syphilis Study served as one of the most crucial cases

[56] Jones, 12
[57] Jones, 12
[58] Jones, 12
[59] Jones, 11
[60] Jones, 12
[61] Jones, 11

during this century from which a burst in awareness of the attitudes towards and nature of these experiments changed drastically.

Public revelations also triggered more tangible progress in the structure and conduct of biomedical research involving human test subjects. One of clearest example of concrete steps being made towards an improvement in this line of research is President Bill Clinton's public and formal apology to the survivors and families of the Tuskegee Syphilis Study. On May 16, 1997, President Clinton invited survivors of the study to the White House to listen to his apology on behalf of the nation. Five survivors and three family representatives attended. Although the apology came much later than it should have, 25 years after Heller's article revealing the details of the study, the apology was nonetheless an important step in history and perhaps the time gap reflects a thoughtful approach to enacting change.

Image 3. *President Bill Clinton surrounded by five survivors and three family representatives of subjects of the Tuskegee Syphilis Study in 1997 after his public national apology.*[62]

The President acknowledged the fact that hundreds of men were used in research without their knowledge or consent and that those men were "denied help and lied to by their government."[63] He recognized the failure of these researchers to obey the Hippocratic Oath by forgetting "their pledge to heal and repair."[64] In addition to acknowledging and apologizing, President Clinton further outlined steps for how the government plans to make sure a similar episode never again occurs in the United States. These steps included building a memorial at

[62] Rhodes-Vivour, Gbadero. "To Be Or Not To Be ;The Crazy Ones." *The Hopeful Nigerian*, 21 Nov. 2014, thehopefulnigerian.wordpress.com/2014/11/21/to-be-or-not-to-be-the-crazy-ones/. Accessed 17 May 2018.
[63] Clinton, Bill. "Presidential Apology." *Center for Disease Control and Prevention*, 16 May 1997, www.cdc.gov/tuskegee/clintonp.htm. Accessed 15 Mar. 2018.
[64] Clinton, Bill.

Tuskegee; establishing centers for bioethics in research and healthcare; enacting mandatory informed consent and local review laws; issuing a report on how to represent fairly all races in medical research; committing to strengthen researchers' training in bioethics by producing training materials on core ethical principles of justice and respect; and, finally, extending the charter of the National Bioethics Advisory Commission, a committee which originated in 1996 with the mission in investigate ethics in the medical community.[65] Through his sincere apology and promise for change, President Clinton committed the government to rebuilding a broken trust and cautioned the nation that "no ground is gained and, indeed, much is lost if we lose our moral bearings in the name of progress."[66]

Case Study: Project MKUltra

Another major example of unethical human biomedical experimentation that occurred in the United States during the twentieth century is Project MKUltra. Project MKUltra was an umbrella project referring to more than 130 programs that involved research on drugs and behavioral modification, for which researchers studied the effects of mind-control techniques in at least 86 universities, hospitals and prisons.[67,68,69] Funded by the United States Central

[65] Clinton, Bill.
[66] Clinton, Bill.
[67] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources. *Project MKUltra, the CIA's Program of Research in Behavioral Modification*. Government Printing Office, 1977, pp. 1-171. 95th Congress, 1st session.

Intelligence Agency (CIA) and run out of various universities and institutions, Project MKUltra was a program intended to study the effects of biological and chemical compounds on the human brain and human behavior.[70] The larger goal was for the United States government to keep up with anticipated Soviet advances in mind-control technologies and, more generally, to advance the research and development of chemical, biological and radiological compounds for use in clandestine mind-control operations.[71,72] The secret CIA project took place between 1953 and 1964, during which time period researchers subjected unsuspecting victims to mind-control experiments that left them with severe, long-term emotional and physical damage.[73]

Some of the most shocking and relevant of the studies included under the umbrella term of MKUltra involved lysergic acid diethalamide (LSD), powerful amphetamines, electrical shock and other mind-altering substances and techniques.[74] The disturbing nature of Project MKUltra, however, does not lie solely in the questionable drugs and invasive procedures researchers used, but also, and perhaps much more so, in the way in which the studies were conducted.

First, the researchers tested on subjects without disclosing the treatment they were receiving. The unwitting subjects were citizens from all walks of life: prisoners and innocent

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[68] Bradley, Ed, host. "MK-ULTRA/Mind-Control Experiments." *Radio TV Reports*, CBS Network, 23 Dec. 1984.
[69] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources.
[70] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources.
[71] Eschner, Kat. "What We Know About the CIA's Midcentury Mind-Control Project." *Smithsonian*, 13 Apr. 2017.
[72] Anderson, Jack. "Lawsuit Forces CIA Confession on MK-ULTRA." *Washington Post*, 28 Aug. 1982, sec. F, p. 17.
[73] Bradley, Ed
[74] Anderson, Jack.

individuals, the wealthy and the poor, native and foreign-born.[75] While their backgrounds and specific treatments varied, they are all bound by the fact that they were totally unaware of what the researchers were doing to their bodies and not given the opportunity to provide informed consent.[76] These people that the CIA conducted mind control experiments on included psychiatric patients expecting their normal treatment, patients of other sorts seeking standard treatment, psychiatric fellowship candidates that hiring officials asked to undergo "sleep therapy" before being considered for candidacy, and even completely unsuspecting victims to whom investigators slipped a drug into their glasses.[77]

Second, there are hardly any remaining documents detailing the procedures, protocols, purposes or records of the subjects of these studies. When the investigative committee assigned to uncovering the details asked researchers to provide documents detailing the studies performed under Project MKUltra, the CIA was unable to produce anything. No protocols or written consent forms existed at the time of the investigation, and the only documents that the CIA could produce were meticulously kept expense records stating that $349,445.10 of CIA funds went towards an Atlanta subproject.[78] Investigators later found that in January of 1973, following orders from then CIA Director Richard Helms, the CIA destroyed all other records.[79] While documents stating exactly what happened under Project MKUltra do not exist, some documents detailing the names of some subjects and researchers have surfaced. These documents have

[75] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources
[76] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources
[77] Bradley, Ed.
[78] Anderson, Jack.
[79] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources

provided insight into the qualifications of the people running the studies and have revealed the fact that many of the agents involved were not qualified scientific observers.[80]

Finally, Project MKUltra had lasting negative impacts on both the physical and mental well-being of the subjects, and researchers made no effort to follow-up on the wellbeing of the subjects.[81] The victims suffered "flashbacks and other severe symptoms for years after they were drugged by the CIA," and in many cases were left feeling confused as to the source of their symptoms since they were not aware of what the researchers had secretly done to their bodies.[82] One subject, Zal Orlico, opened up to CBS radio-show host Ed Bradley about her memories of the testing she underwent and the lasting impacts that testing has had on her health. Zal was suffering from depression and went to see Dr. Cameron, a leading psychiatrist, where she was treated with the then experimental drug LSD.[83] Reflecting on the impact of the treatment Dr. Cameron gave her, Zal states in her interview with Ed Bradley, "they took away the remaining years of my life. They really [wrung] them out and left me with a piece of rag to live."[84] Zal was determined to keep fighting until she saw justice, and so were many others. Eventually, a group of former subjects banded together and sued the CIA "for lying to them about the true purposes of the experiments, also for the mental damage they say they suffered from the drug sessions."[85]

So, what ended up happening? The case was brought to court in 1977 where Congress ruled to establish investigative committees in order to conduct a full investigation of Project MKUltra. In the opening statements, Senator Daniel Inouye explained that the Select Committee

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[80] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources
[81] Anderson, Jack.
[82] Anderson, Jack.
[83] Bradley, Ed.
[84] Bradley, Ed.
[85] Anderson, Jack. "MK/Ultra." *Jack Anderson Confidential*, 12 Feb. 1983.

on Intelligence, the Subcommittee on Health and Scientific Research, and the Committee on Human Resources were investigating the events surrounding Project MKUltra "in order to better understand what statutes and other guidelines might be necessary to prevent the recurrence of such abuses in the future."[86] The United States Congress deemed it necessary to look into these events in order to establish effective oversight procedures that could prevent the future cases of abusive drug testing and of manipulative projects for behavioral control.[87] Senator Ted Kennedy commented that the "best safeguard against abuses in the future is a complete public accounting of the abuses of the past."[88] In addition to revealing the wrongdoings of the CIA, Kennedy also made it his responsibility to expand the jurisdiction of the National Commission for the Protection of the Human Subjects of Biomedical and Behavioral Research, a commission the government formed in the aftermath of the Tuskegee Syphilis Study, to cover all federally funded research involving human subjects.[89] Senator Kennedy and the rest of Congress made it their mission to "assure all our people that they will have the degree of protection in human experimentation that they deserve and have every right to expect."[90] Thus, the United States government made progress towards a safer system of human biomedical experimentation by listening to public concerns about unethical experimentation, conducting an investigation, publicly acknowledging the wrongdoings of the CIA, and enacting new legislature to prevent a recurrence of events.

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[86] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources.
[87] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources.
[88] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources.
[89] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources.
[90] United States, Congress, Senate, Select Committee on Intelligence, Subcommittee on Health and Scientific Research, Committee on Human Resources.

The Tuskegee Syphilis Study and Project MKUltra are two major cases of unethical human biomedical experimentation in the United States during the last century. I have analyzed these two cases in detail to demonstrate how each case has led to changes in the structure and conduct of clinical research. However, these two cases should not be taken as the only cases of unethical experimentation in recent history. There have been many harmful and manipulative cases of unethical human testing in the United States and internationally, such as secret government funded radiation studies during which researchers injected infants with radioactive isotopes[91] or the radiation studies conducted at Sonoma State Hospital for children during which researchers gave young disabled children radiation poisoning, removed and experimented on their brains, and then denied any evidence of the children ever existing in their records.[92] These radiation studies, along with all the other many unethical studies researchers conducted over the course of the last century which can be found in excess by a simple internet search, have also had an impact on the trajectory of clinical research and have influenced the changes that are discussed below.

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[91] "U.S. Seeks People in Radiation Tests." *New York Times*, 25 Dec. 1993, U.S. sec.
[92] Mabrey, Vicki, host. "A Dark Chapter in Medical History." *60 Minutes*, CBS News, 9 Feb. 2005.

Policy Changes, Regulatory Acts, Political Statements, and Institutional Establishments Following the Reveal of Unethical Studies

By tracing the history of institutional establishments, regulatory acts and political statements throughout the twentieth century alongside the occurrence of the case studies discussed above, one can clearly document the increase in awareness, action and discussion regarding the ethicality of human biomedical experimentation that correlates with these cases. As both professional communities as well as the general public became aware of the shocking details of these cases of human experimentation that scientific researchers and government organizations were running in United States, American citizens began to push for changes to both experimental setups and regulatory institutions. The motivation to enact change often stemmed from one specific event, such as the desire of the public to grant the participants of the Tuskegee Syphilis Study freedom and condolences for the suffering they endured as a direct result of the study; however, this local desire for change often expanded into the need for national changes to regulatory policy and institutional governance.

Below is a timeline highlighting major unethical studies, regulatory acts, political statements and institutional establishments in the United States since 1847 (Image 4). This timeline serves as a visual aid to see how unethical studies influence the regulatory and political environment throughout this chunk of history. The interplay between the different factors depicted below is important to understanding the pattern of change over the last century and beyond.

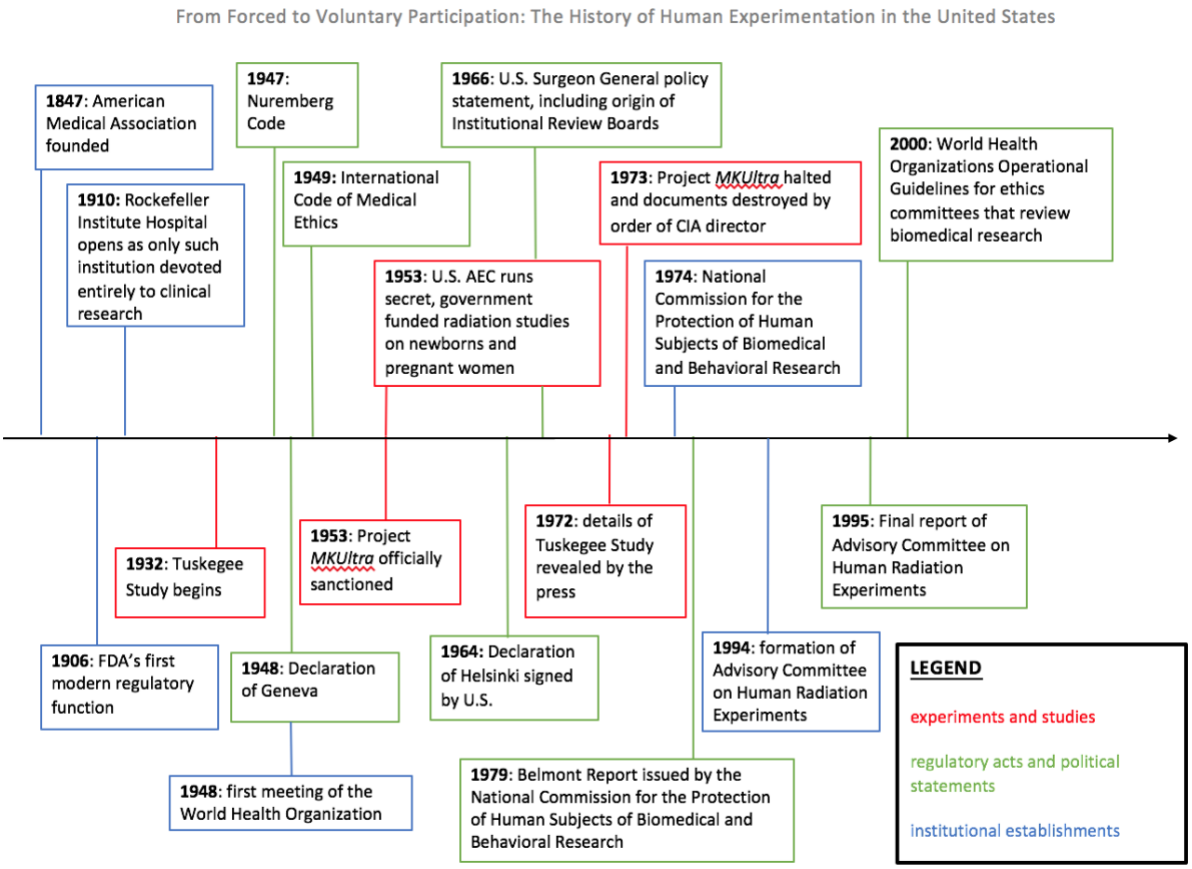

Image 4. *Timeline of major experimental studies involving human test subjects, regulatory and political statements, and institutional establishments throughout the twentieth century. This serves as a visual representation of the interacting factors at play throughout the twentieth century.*

One of the first major steps that the United States took towards making an effort to improve the ethicality and morality of human subject experimentation following World War II was the 1964 signing of the Declaration of Helsinki which, similar to the Declaration of Geneva, was

another set of international ethical guidelines drafted by the World Medical Assembly.[93] It includes an introduction, basic principles, a section on medical research combined with clinical research, and a section on non-therapeutic biomedical research involving human subjects.[94] Importantly, the declaration states that study results will not be published if these guidelines are not followed, and thus threatens the validity of researchers' work which does not follow the guidelines. By signing this document, the United States government made a commitment to the ethical conduction of clinical research involving human test subjects and thereby made a promise to American citizens to protect their safety and humanity. However, in its original form, the Declaration of Helsinki was not enough to protect citizens from the dangers of clinical research. The World Medical Assembly updated the document many times, with two main revisions occurring in 1975 and 2000.[95] Each revision increased the document in length and strengthened its influence on the conduct of clinical experimentation. The 1975 revision included a statement requiring independent committees to review research protocols and emphasizing the need for informed consent; this revision almost doubled the length of the original document.[96] In 2000, the World Medical Assembly accepted another revision which included major restructuring to almost every section and an emphasis on the need to consider the wellbeing of the human subject over the interests of science and society.[97] The commitment of the United States to protecting its citizens from harmful or manipulative biomedical experimentation thus became clear after the

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[93] World Medical Association, 18th General Assembly. "Declaration of Helsinki." *World Medical Association*, adopted June 1964, https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/.
[94] World Medical Association, 18th General Assembly.
[95] Carlson, Robert V., et al. "The revision of the Declaration of Helsinki." *British Journal of Clinical Pharmacology*, vol. 57, no. 6, 20 Jan. 2004, pp. 695-713.
[96] Carlson
[97] Carlson

country's signing of the original document in 1964, and the continued commitment to each revision reflects the nation's persistent dedication to ethical human subject research.

In 1966, soon after the signing of the first edition of the Declaration of Helsinki, the United States Surgeon General William H. Stewart issued a policy statement. Titled the *Surgeon General's Directives on Human Experimentation*, the statement includes a series of directives issued between July of 1966 and January of 1967.[98] One of the most significant aspects of the directives was the requirement for all human subject research to have independent prior review, similar to the requirement listed in the Declaration of Helsinki.[99] The directive requires all institutions receiving Public Health Service grants to "provide group review and decision, maintain surveillance, and provide advice for investigators on safeguarding the rights and welfare of human subjects."[100] The Surgeon General also established a system of Institutional Review Boards (IRBs), comprised of staff consultants tasked with ensuring informed consent and ethical treatment of human test subjects prior to the start of a study.[101] Although the Surgeon General's directives only have influence over institutions receiving Public Health Service Grants, the public and authoritative nature of the directives resulted in the documents having a national impact on the awareness of ethical issues related to human experimentation and conduct of these experiments.

The next major publication related to human biomedical experimentation in the United States was the Belmont Report of the National Commission for the Protection of Human Subjects of

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[98] U.S. Public Health Service, Surgeon General William H. Stewart, "Surgeon General's Directives on Human Experimentation." Received by Heads of Institutions Receiving Public Health Service Grants, 1966. Letter.
[99] U.S. Public Health Service, Surgeon General William H. Stewart.
[100] U.S. Public Health Service, Surgeon General William H. Stewart.
[101] U.S. Public Health Service, Surgeon General William H. Stewart.

Biomedical and Behavioral Research.[102] Issued in 1979, shortly after officials had shut down the Tuskegee Syphilis Study and Project *MKUltra*, the Belmont Report commented on Ethical Principles and Guidelines for the Protection of Human Research Subjects.[103] The report is a United States government document which considered the boundaries between practices and research, basic ethical principles, and their applications and recommends that its considerations are accepted in its entirety. It recommended that its conclusions be accepted in its entirety. The report identified three ethical principles crucial to acceptable human subject research: respect, beneficence and justice.[104] Respect refers to recognizing the autonomy of human subjects and the need to acquire informed consent prior to experimentation.[105] Beneficence refers to ensuring that research is beneficial to the individual and/or society and does no harm to the human subjects.[106] Justice refers to ensuring that the anticipated benefits of the research outweigh the risks imposed on the subjects.[107] In all of the case studies explored above, researchers neglected to follow at least one and in most cases all three of these ethical principles. Thus, by acknowledging the importance of respect, beneficence and justice in human subject research, the Belmont Report took into account the outrage of the public towards these unethical cases and made concrete steps towards improving future studies. The report serves as yet another important landmark in the history of biomedical research involving human test subjects in the United States during the twentieth century.

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[102] *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Department of Health, Education, and Welfare, Office of the Secretary. 1979.
[103] Office of the Secretary.
[104] Office of the Secretary.
[105] Office of the Secretary.
[106] Office of the Secretary.
[107] Office of the Secretary.

In addition to major international and national declarations, directives and reports, new institutions involved in human biomedical experimentation emerged after World War II. The World Health Organization (WHO) was established on April 7th, 1948 as a specialized agency of the United Nations.[108] This date is still celebrated every year as World Health Day due to the continual and lasting positive global impact that the organization has had on healthcare and health ethics.[109] One of their most relevant contributions is their 2000 publication of the Operational Guidelines for ethics committees that review biomedical research. This set of international guidelines facilitates and supports ethical review around the world by defining the role, constituents, and requirements for ethics committees.[110] The establishment of the World Health Organization as a specialized agency of the United Nations and the signing of its constitution in 1948 by 61 countries, including the United States, reflected increased concern for the ethical and productive conduct of health-related programs.[111] Further, the timing of the establishment of the WHO suggests that the organization came as a way to counter and prevent a repeat of the health and ethics disasters committed by Nazi Germany.

Second, the formation of the Advisory Committee on Human Radiation Experiments in 1994 serves as a strong example of the government establishing a new committee directly in response to the revelation of a case of unethical experimentation. The government had recently shut down the United States Atomic Energy Commission's secret government funded radiation studies and this new Advisory Committee promised to prevent any similar incidents by investigating the case

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[108] *World Health Organization*, "History of WHO," www.who.int/about/history/en/. Accessed 13 Mar. 2018.
[109] *World Health Organization*
[110] Sparks, Joel, editor. "Timeline of Laws Related to the Protection of Human Subjects." *Office of History*, National Institutes of Health, 2002, history.nih.gov/about/timelines_laws_human.html. Accessed 12 Dec. 2017.
[111] *World Health Organization*

and suggesting regulation of future conduct of radiation studies involving human subjects. The committee produced a final report in 1995 emphasizing the necessity of maintaining the highest ethical standards when experimenting on human subjects and noting that special care must be taken when research must be kept secret for exceptional circumstances.[112] The committee believed that the nature of the subject it was investigating gave the committee special responsibility to disseminate its findings and suggestions as broadly as possible for public access.[113] The establishment of the Advisory Committee on Human Radiation Experiments is thus yet another example of the response of both the professional and public communities to the realization that government sponsored unethical testing had been occurring in the United States.

Taken together, all of the aforementioned political statements and new institutions that emerged in the twentieth century were in direct response to the revelation by both public and professional communities that unethical human experimentation was occurring right in their own country, on their friends, neighbors, or even on themselves. Cases such as the Tuskegee Syphilis Study, Project *MKUltra*, and secret government radiation studies enlightened the citizens of the United States to the unethical, unsafe and manipulative nature of human biomedical research, enraged and frightened these citizens and prompted the government and other institutional actors to enact change. Change often came in and continues to come in the form of an increase in regulation and proliferation of regulatory bodies.

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[112] Sparks, Joel

[113] "Advisory Committee on Human Radiation Experiments." *The National Security Archive*, nsarchive2.gwu.edu/radiation/. Accessed 13 Mar. 2018.

From Then to Now: How Interacting Historical Events Have Contributed to the Increased Safety of Human Subject Biomedical Research

Since the end of World War II, the topic of human biomedical experimentation in the United States and the associated ethics have become more and more prevalent. Although cases of unethical experimentation have continued to occur throughout the twentieth century, such as the Tuskegee Syphilis Study, Project MKUltra, and human radiation testing, as time goes on, the public, professional and governmental communities have learned more about what ethical human testing should look like and taken steps towards making changes that bring human subject testing closer to this ideal. Rather than cases of horrific, manipulative human experimentation slowing or stopping the field of biomedical research, these cases have rather improved and progressed the field (Image 5). As time goes on, more and more registered clinical studies begin in the United States. Many factors can be attributed to this increase in human subject research, such as a surge in medical technologies, an improvement in scientific understanding, and a more benefits for registered studies. However, this increase in clinical studies is also largely due to the fact that with each passing case of unethical experimentation comes a period of change and growth in which the American people have come together to make the system safer and more trustworthy. Included in these changes are requirements such as the ICJME, when the International Committee of Medical Journal Editors began requiring trial registration as a condition of publication, and FDAAA, when the Food and Drug Administration Amendments Act implemented registration requirements.[114] Both the ICJME and the FDAAA are regulatory additions that enforced registration and thus regulation of clinical studies and, as shown in

[114] "Trends, Charts, and Maps."

below, both triggered a sharp increase in the number of registered clinical trials per year (Image 5).

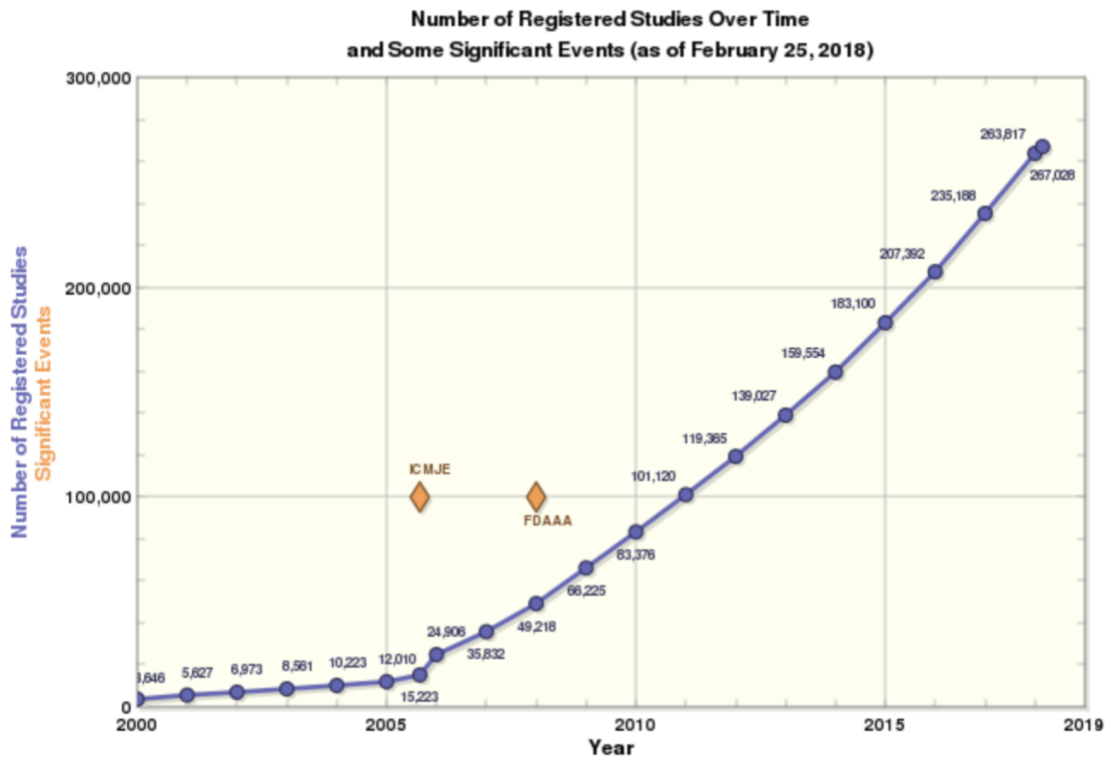

Image 5. *The total number of studies since 2000 that have been posted on ClinicalTrials.gov, indicating a continual exponential rise in the number of studies. ICJME indicates when the International Committee of Medical Journal Editors began requiring trial registration as a condition of publication. FDAAA indicates when the expanded registration requirements of FDAAA began. This graph shows two specific events that increased regulation surrounding human clinical experimentation as well as the increasing trend in overall number of registered clinical trials.*

The pattern of change is consistent throughout the twentieth century. Starting with the Nuremberg Trials, with each reveal of unethical human experimentation came a response of anger and motion for improvement. This response by the public proved crucial, because, in each case, following public uproar was a response by the government or a governing body. In the case of Tuskegee, the government shut down the study and President Clinton proposed legislative steps towards ensuring ethical conduct of biomedical research. In the case of Project MKUltra, the CIA an investigation and court hearings and Senator Kennedy proposed legislation to expand the jurisdiction of the National Commission on Human Subjects of Biomedical and Behavioral Research so as to prevent a recurrence of events. These changes have strengthened the control that governing bodies have over human biomedical experimentation with each added regulation or institution, to the point where today, in 2018, the nature and structure of experiments involving human test subjects is completely evolved from that of earlier experiments.

Comparing the regulations surrounding experiments involving human test subjects today to those that existed just after World War II provides valuable insight into the differences in the types of people participating in these studies. A link to the Food and Drug Administration official website outlining the current laws and regulations surrounding clinical research is located in Appendix 2. Whereas in the 1940s and before then researchers often tested unknown drugs or procedures on groups such as women, minorities, children, prisoners and the mentally disabled due to their inability to object and/or their view by society as inferior or vulnerable, today both sick and healthy American citizens volunteer to be a part of clinical studies. Recall Sam Spadino, the "professional human guinea pig" introduced at the beginning of this paper, and consider how conditional his experiences in clinical trials are to the time he is living in. Spadino

is not the only one either; according to TrialX, an online portal that helps expand the reach of investigators looking for participants, about 3500 healthy volunteers enroll in NIH conducted clinical trials alone.[115] While people today volunteer for a myriad of reason, including financial reward, personal health improvement, and the desire to advance scientific research, another main reason that the United States can have a population so willing to volunteer is due to the strict regulations now surrounding clinical research, and the reason regulations have become so strict is due to the conduction of many unethical studies throughout the last century. Thus, the structure and nature of human biomedical experimentation has changed drastically from the end of World War II to present day, and these changes have arisen from constant and dynamic interacting factors, including unethical case studies, regulatory acts, political statements, the new institutions and ethical transitions.

Although many beneficial changes have resulted from the increase in awareness of and regulations surrounding human subject research, the system is still not perfect today. Rules are meant to be broken, and even with the best enforcement, a system as large as clinical research on a national level cannot be fully regulated. One recent example of unethical research which violates national regulations is a case in which associate professor William Halford administered unapproved herpes vaccines in Springfield, Illinois hotel rooms.[116] The associate professor also conducted a herpes vaccine trial in the Caribbean in 2016 to evade United States regulations.[117]

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[115] Mishra, Shweta. "Why Is Participation Of Healthy Volunteers In Clinical Trials Important?" *TrialX: Patient Connection*, 14 Apr. 2018, trialx.com/why-is-participation-of-healthy-volunteers-in-clinical-trials-important/. Accessed 16 May 2018.

[116] Bernhard, Blythe. "Southern Illinois stops herpes research after illegal offshore and hotel room experiments by dying professor." *St. Louis Post-Dispatch*, 24 Jan. 2018, www.stltoday.com/news/local/illinois/southern-illinois-stops-herpes-research-after-illegal-offshore-and-hotel/article_32e5eeab-3295-5521-a010-116b2342eeee.html. Accessed 16 May 2018.

[117] Bernhard, Blythe.

Halford was involved in herpes research at Springfield Illinois University and very clearly "violated [the University's] policies and procedures and federal regulations" by administering drugs in hotel rooms and off-shore.[118]

In addition, awareness and regulation surrounding this issue are not the same globally as they are in the United States. Halford was able to conduct his experiments in the Caribbean because the regulations are not as strict there as they are in the United States.[119] Similarly, researchers can choose to conduct clinical research in other countries where the national regulations are more lenient or the testing is not as expensive as in the United States.[120] Not everyone is protected equally, and not all rules can be enforced entirely. Thus, even though human biomedical experimentation has come a long way, it is still not a perfect system.

Conclusion

In comparing the nature of human experimentation during Nazi Germany, in the Tuskegee Syphilis Study, and in Project MKUltra to Sam Spadino's experiences in human experimentation, one can clearly see many differences. Whereas in early cases of human experimentation researchers did not often consider humanity, ethics, or human rights as major factors or even as factors at all when designing their studies, today, issues such as consent, understanding, safety and equality are at the forefront of all concerns related to human biomedical experimentation. By connecting the dots between Nazi experimentation and modern-

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[118] Bernhard, Blythe.
[119] Berhnahrd, Blythe.
[120] Robins, Rebecca. "Most Experimental Drugs are Tested Offshore–Raising Concerns about Data." *Scientific American*, 10 Sept. 2017, www.scientificamerican.com/article/most-experimental-drugs-are-tested-offshore-raising-concerns-about-data/. Accessed 16 May 2018.

day experimentation, one can understand when, why and how changes occurred in the structure and nature of clinical research. More specifically, one can see that throughout the last century, improvement in safety and ethicality followed cases of unethical, manipulative experimentation. After each case of unethical experimentation, regulations and thereby safety increased, and this increase in safety and ethicality has led to an increase in the usefulness and prominence of human experimentation.

With increased regulation and effective enforcement comes decreasing room for error or deviance, decreasing need for more regulation, and thus a stabilization of the process. Thus, although science will almost certainly continue to progress as it has since the ancient times due to continued discovery and technological advancement, the increase in regulations surrounding human experimentation will likely plateau once the safety of participants can be assured, and, with proper enforcement, that point is not too far off. As time goes on, increasing awareness of experimentation and increasing ethical standards continue to improve the nature and structure of human experimentation, with the hope of eventually reaching a point of stability at which science and society can interact in a safe and effective manner. Thus, as seen in the past and as anticipated in the future, human experimentation will continue to improve as unethical studies expose flaws in the system and public and professional entities continue to respond with the call for increased or modified regulation. However, no matter how strict laws get and no matter how well those laws are enforced, people will always find a way to break the law; based on historical patterns and trends, though, increasing regulation and awareness will continue to make it harder for researchers to violate the rules and will hopefully continue to lessen the amount of unethical cases of biomedical experimentation as time goes on.

Appendices

Appendix 1. The Nuremberg Code

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 reasonably 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 seemed 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 stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.[121]

[121] "Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.

Appendix 2. FDA Regulations: Good Clinical Practice and Clinical Trials

https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm[122]

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[122] *U.S. Food and Drug Administration*, "Regulations: Good Clinical Practice and Clinical Trials.", www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm. Accessed 16 May 2018..

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