The impact of the Tuskegee Syphilis Study on the ethics of clinical studies in the U.S.

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Health Policy and Management

MPH 525

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April 2014
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Chapter 1

Introduction

Background and Significance

Syphilis

According to the Centers for Disease Control and Prevention (CDC), syphilis is a sexually transmitted disease (STD) caused by bacteria that can result in serious health consequences and/or death if left untreated. The disease is spread by direct contact of a syphilis sore during anal, vaginal, or oral sex with an infected individual (2014). Similarly, the disease can be spread through prolonged kissing or close bodily contact with sores (WebMD, 2014). Pregnant women infected with syphilis can even transmit the disease to their unborn child (Centers for Disease Control and Prevention, 2014). The spread of syphilis, however, is easily preventable by seeking medical treatment and practicing safe sex.

The severity of syphilis is dependent on which stage the disease is allowed to progresses to. Primary syphilis occurs within 10 – 90 days after initial exposure to the disease. The infected person will develop one or more syphilis sores. Although these sores will heal without scarring in approximately six weeks, infected people should seek medical treatment immediately or the disease will continue to progress to more severe stages (Centers for Disease Control and Prevention, 2014). Secondary syphilis begins within six weeks to six months after exposure and may last for up to three months. Typically, persons with secondary syphilis develop a “copper penny” rash on the palms of the hands and soles of the feet. Some people also experience other symptoms such as swollen lymph glands, fever, and weight loss. White lesions may develop in warm, moist regions like the mouth, armpit, and groin. Like primary syphilis, the rashes and
lesions will disappear without medical treatment and disease progression will continue (WebMD, 2014).

If secondary syphilis is left untreated, then the infected individual will develop latent syphilis and/or tertiary syphilis. Latent syphilis is a period of disease inactivity. The last stage of the disease, tertiary or late syphilis, can result in the development of severe problems with many vital organs including the heart, brain, blood vessels, eyes, liver, bones, joints, and nerves. This stage occurs within 10 – 20 years after initial infection (Centers for Disease Control and Prevention, 2014). Moreover, tertiary syphilis may result in paralysis, blindness, dementia, deafness, impotence, and even death (WebMD, 2014). Thus, an easily treated bacterial infection can lead to serious health conditions and even death if left untreated.

Syphilis is estimated to infect approximately 55,000 people per year in the United States. According to the CDC, nearly 50,000 new cases of syphilis were diagnosed during 2012. Of these cases only 15,667 were either primary or secondary syphilis cases. The trends in syphilis infection have changed drastically since 1990. Throughout the 1990s, heterosexual men and women of minority groups were most likely to become with the disease. However, during the 2000s, an increase in syphilis cases has been pronounced among men who have sex with men (MSM). Moreover, the incident rates of primary and secondary syphilis decreased during the 1990s declining nearly 90 percent from previous years. Nevertheless, since the 2000s the rate of syphilis has begun to increase especially in the MSM population. The CDC estimates that the proportion of primary and secondary syphilis cases as a result of MSM increased drastically from just 7 percent in 2000 to over 60 percent in 2004 (Centers for Disease Control and Prevention, 2014). The increase in syphilis rates and lack of infected persons seeking medical care has led to a STD crisis for public health officials in America.


**Purpose of Tuskegee Syphilis Study**

The Tuskegee Syphilis Study had one main objective, to determine the natural, untreated course of latent syphilis in the African American population. The study began in 1932 in Macon County, Alabama under the direction of the U.S. Public Health Service (USPHS) and lasted for 40 years. The study enrolled 600 black men the majority of the participants were poor illiterate sharecroppers: 399 infected with syphilis and 201 uninfected controls (Brandt, 1978 and Tuskegee University, 2014). The participants were told they were receiving treatment for “bad blood,” the local term used to describe a variety of health issues including syphilis, anemia, and fatigue (Centers for Disease Control and Prevention, 2013). These men received compensation for enrolling in the clinical trial including: free medical exams, meals on days of examinations, rides to and from the participating clinics, and guarantees that provisions would be made after death to their participants survivors. At the time the study began, no treatment for syphilis existed. However, by the late 1940s the discovery of penicillin dramatically changed the treatment of the disease nationwide (Tuskegee University, 2014). Thus, the Tuskegee Syphilis Study gave physicians knowledge about the progression of the disease before treatments were available.

**Nature of the Problem**

The Tuskegee Syphilis Study will continue to be one of the most controversial clinical trials ever conducted in the U.S. When penicillin was discovered to be a viable treatment for the disease, the black men in the trial did not receive the drug. In fact, before the discovery of the wonder drug, penicillin, arsenic and bismuth were used to treat the symptoms of syphilis. The participants in the study were denied these treatments as well. Moreover, the men infected with
the STD were never told that they had syphilis or taught how to prevent the disease from spreading to others (Corbie-Smith, 1999). This study was only expected to last six months, yet was allowed to continue for 40 years (Centers for Disease Control and Prevention, 2013). The lack of treatment resulted in more than 100 hundred deaths due to syphilis and other related complications of the disease (Corbie-Smith, 1999).

The clinical trial ended in 1972 after the story of the study made national newspapers. As a result of the newspaper articles, several U.S. federal agencies began to review the study. The panel stated that the African Americans openly agreed to participate in the study including all examinations and treatments. Nonetheless, the safety and well-being of the study’s participants was completely ignored by the researchers. The researchers failed to tell the men about or even offer the research procedure of informed consent. Similarly, the participants were never told the name of the study, Tuskegee Study of Untreated Syphilis in the Negro Male. The purpose of the study and potential consequences of receiving treatment or non-treatment throughout the duration of the clinical trial were not mentioned to the study’s participants either. Most importantly, these men were not give a choice to quit the study when penicillin became available as a treatment and ultimately a cure for the disease (Tuskegee University, 2014). Thus, the panel concluded that the Tuskegee Syphilis study was not ethically justified and the study was forced to come to an end.

Not only were the men in the study misled and denied actual treatment, the researchers sought to prevent the participants from seeking treatment from other sources. Several researchers met with local black doctors to ensure cooperation in that the men involved in the trial would not be treated for the disease. All men in the trial were to be refer back to the USPHS if they needed medical care. Similarly, the Alabama Health Department was warned against treating the test
subjects during the early 1940s. Even the U.S. Army was told to deny the trial participants anti-syphilis treatments during drafting procedures. However, despite the efforts of the USPHS many of the men were able to secure treatment on their own. In fact, by 1952 nearly 30 percent of the subjects had received some dosage of penicillin. Nonetheless, the treatment received by these men was not enough to “compromise” the experiment of the natural course of untreated syphilis in African American males (Brandt, 1978). Therefore, the Tuskegee Syphilis Study proves to be one of the most controversial clinical trials ever conducted in the U.S. due to the lack of proper medical treatment of the disease and other unethical decisions made by the study’s researchers.
Chapter 2

Ethics in Clinical Trials

The unethical treatment of the Tuskegee trial participants has led to drastic changes in biomedical research ethics. By definition, ethics, is a branch of philosophy that makes distinctions between right and wrong and the moral consequences of human actions. Clinical trials involve several ethical principles including informed consent, confidentiality, respect for human rights, and scientific integrity (Tulchinsky, 2010). Without the medical code of ethics, clinical trials would not be able to ensure the welfare of participants and researchers.

Nuremburg Code

As a result of the unethical treatment of Jews and other groups in concentrations camps throughout World War II by the Nazis, the Nuremburg Code was established. This code set new conditions that must be met in order to ethically conduct biomedical research. The Nuremburg Code lists ten key concepts to ensure the rights of subjects of clinical trials:

1. All participants must voluntarily consent to be a part of the clinical trial.
2. The experiment should yield fruitful results for the betterment of society and not be random or unnecessary in nature.
3. The experiment should be based on the results of animal experimentation and knowledge of the natural history of the disease in question or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be conducted in order to avoid all unnecessary suffering and injury.
5. Experiments should not be conducted where there is a reason to believe that death or disabling injury may occur.

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. Preparations must be made to protect the participants from remote possibilities of injury, disability, or death.

8. Only scientifically qualified individuals are allowed to conduct biomedical research.

9. The study subjects have the right to end participation at any point during the course of the experiment.

10. The scientist in charge must be willing and prepared to terminate all experiments that may cause injury, disability, and/or death (Shuster, 1997).

Before the code was established, no guidelines existed on the proper treatment of clinical trial participants. Thus, the Nuremberg Code provided the foundation in order to ensure all biomedical research be conducted in an ethical manner.

**Belmont Report**

The Belmont Report was established as a result of the National Research Act of 1974 which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This piece of legislation is the direct result due to the reaction from the Tuskegee Syphilis Study’s treatment of trial participants (U.S. Department of Health and Human Services, n.d.). As a result of this act, boundaries were set to distinguish the difference between medical practice and biomedical research. Medical practice refers to the interventions made by medical personnel in order to enhance the well-being of an individual patient. While research refers to the activities designed to test hypotheses, make valid conclusions, and contribute to
overall knowledge of the study subject (University of Iowa, 2014). Moreover, three ethical principles were established as a result of the Belmont Report: respect for persons, beneficence, and justice. Likewise, the application of these principles has led to the concepts of informed consent, assessment of risks and benefits, and selection of subjects (U.S. Department of Health and Human Services, n.d.). The Belmont Report resulted in the establishment of the Institutional Review Board (IRB) for institutions receiving federal grants. For each federal grant issued, the study is reviewed thoroughly by the IRB to determine if the rights and welfare of the human subjects will be properly protected (Corbie-Smith, 1999). Therefore, the Belmont Report in conjunction with the Nuremberg Code further ensures the ethical treatment of all human subjects throughout the duration of medical research trials.
Informed Consent, Individual Autonomy, and Beneficence

Informed Consent

By definition, informed consent, requires that research subjects be given the opportunity to choose what will and will not happen to them during the study, to the degree in which they are capable to make these decisions. Informed consent involves three crucial steps: information, comprehension, and voluntariness. First, information is a necessary step in the informed consent process because “the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge.” Second, the participants must be able to comprehend the information made available to them. Researchers may need to adapt the presentation of the information to each subject’s capacities including intelligence, rationality, maturity, and language. Last, each participant must voluntarily consent to the study under conditions free of coercion and undue influence (University of Iowa, 2014). The concept of informed consent is critical to ethical biomedical research. Each participant should willingly engage in the clinical study only after presentation of critical information involving the study’s purpose, treatment options, and any possible risks due to treatment otherwise the study may be considered unethical sound.

However, informed consent can be waived in some situations. For example, an IRB may approve to alter all of the elements of informed consent or waive the requirement of obtaining informed consent for public benefit or service programs if both of the following conditions are met:
1. The research could not be carried out without the waiver or alteration.

2. The research project is designed to study, evaluate, and examine public benefit or service programs and will be performed by or subjected to the approval of state or local officials.

Moreover, in emergency situations the IRB may waive the requirement of the researchers to obtain informed consent from the individual (U.S. Department of Health and Human Services, 2011). The U.S. Food and Drug Administration (FDA) permits the waiving of informed consent in the following special circumstances:

1. Emergency exemption for investigational drugs, biologics, and devices
2. Planned emergency research
3. In vitro diagnostic device studies using unidentifiable leftover human specimens
4. “The U.S. President may waive informed consent for military personnel for administration of an investigational product to members of the armed forces” (Northwestern University, 2014).

Only in special circumstances is it ethical to alter and/or waive the informed consent policy in clinical trials. Therefore, without this procedure, participants in biomedical research would not have any say on what happens to them as a result of enrolling in the study or be able to determine whether or not they should even enroll in the trial.

**Individual Autonomy**

During biomedical research it is critical that the participants have individual autonomy in order for the study to be ethically sound. Individual autonomy is the freedom to choose. More specifically, autonomy is defined as the “personal rule of the self that is free from both controlling interferences by others and from personal limitations that prevent meaningful choice”
Likewise, autonomy is the ability of an individual to think critically upon and then attempt to accept and/or change their desires, values, and ideals (Buchanan, 2008). Individual autonomy requires that each participant is in the position to make critical decisions for themselves and these decisions are not being decided for them by the researchers and/or other study personnel.

**Beneficence**

Beneficence is a key concept in ensuring the ethical treatment of all study participants. Researchers are required to treat all persons involved in the research trial in an ethical manner, respect the individuals’ decisions, protect participants from harm, and make efforts to secure the well-being of the participants. Moreover, all researchers should work to maximize all potential benefits of participating in biomedical research as well as minimize any potential harms (University of Iowa, 2014). Beneficence can be achieved via the assessment of risks and benefits of the clinical trial. The assessment of risks and benefits is a responsibility of the researchers in which they gather systematic and comprehensive information about the proposed research topic. By assessing the risks and benefits of the study the researchers are able to determine whether or not the clinical trial is properly designed. A review committee, upon assessment of the research, will determine if the risks that will be presented to the participants are justified. Lastly, the assessment of risks and benefits allows human subjects to determine whether or not they are willing to participate in the study (U.S. Department of Health and Humans Services, n.d.). Without the concept of beneficence, study participants could be subjected to unethical treatment due to lack of or poor assessments of the risks and benefits of the trial.
Chapter 4

Discussion, Summary, and Recommendations

Discussion

The Tuskegee Syphilis Study has had a long-lasting effect on the medical community. The lack of consideration for the participants by the researchers, brought about new ethical research standards required by the U.S. government. Each clinical trial must prove to be more beneficial to the participants than harmful. Moreover, the participants must be informed of all critical parts of the trial prior to enrolling. Once the participants voluntarily enroll in the biomedical research study, they have the right to dropout at any time. All of these basic ethical considerations were denied to the black men involved in the syphilis study. Had these men been treated ethically, the study would have ended long before 1972. Thus, the lessons learned from this clinical trial will never be forgotten as all human subject studies are now required to follow not only the Belmont Report but also the Nuremburg Code.

The Black community was greatly impacted by the outcomes of the study. For example, the trials’ failure to educate the participants on preventing the spread of the disease and lack of treatment has led to a distrust of public health officials in the African American community. Many members of Black communities also now have fears of genocide due to the results of the Tuskegee Syphilis Study (Thomas & Quinn, 1991). They fear that the medical community and seeking treatment will result in more harm than good. Similarly, this study has proven that there is a potential for exploitation of any population that may be vulnerable due to race, ethnicity, gender, disability, age, or social class (Corbie-Smith, 1999). Public health officials and clinical researchers will have to continue to ensure the safety and ethical treatment of all participants in
trials in order for these fears to be assuage for vulnerable populations. Public health officials must work to not only protect these individuals, but also regain their trust in the medical community. Only when vulnerable communities begin to fully or partially trust the medical community, will the backlash from the Tuskegee study finally end.

Summary

The Tuskegee Syphilis Study conducted by the USPHS demonstrated a complete lack of ethical standards. The black men who were enrolled in the study were not informed about their medical condition and how to further prevent the spread of the disease to their wives, girlfriends, and children. Although these individuals willing enrolled in the syphilis study, they were completely unaware of the actual purpose of the study, determining the natural course of untreated syphilis in the black man. By refusing to properly treat the infected men for syphilis when penicillin became widely available the researchers denied the participants the rights to individual autonomy and beneficence. The unethical treatment of the study’s participants led to the creation of the Belmont Report. In conjunction with the Nuremburg Code, the Belmont Report has set forth the guidelines for the conducting ethical clinical trials. The Tuskegee Syphilis Study will continue to serve as a lesson in the importance of ethics the public health community.

Recommendations

To ensure that all clinical trials remain ethical and sound, this author has several propositions. For example, public health officials must work towards regaining the trust of not only Black communities but also other potentially vulnerable populations. Many steps have been taken to apologize for the wrong-doings of the Tuskegee Syphilis Study. However, the mistrust of the entire medical community continues for many ethnic populations. To reestablish trust in
these communities, public health workers should continue to provide quality medical care and services to all populations. By continuing to work for the betterment of the communities, these populations will slowly regain their trust in the medical community.

Ensuring ethical treatment of all human subjects in clinical trials should always be the number one priority of IRBs and research institutions. By law these institutions are required to follow the guidelines for ethical treatment of human subjects set forth by the Nuremburg Code and the Belmont Report. Nonetheless, this author proposes that all staff members of research institutions be required to attend seminars on the ethics of biomedical research. These sessions should be attended every year or every other year. Continuing education of the ethical treatment of human subjects will prevent tragic events like the Tuskegee Syphilis Study from occurring. Each staff member will be required to complete 24 hours of continuing education every two years. However, only up to five hours of in-service may be completed on an individual basis including reading journal articles and books or watching videos on ethical treatment. Each hour of individual learning will be documented by taking notes and providing a brief summary (no less than 250 words) on the material read/watched by the individual. Moreover, these staff members will be required to prove their knowledge of ethics in the medical field by taking and passing a test in order to receive a license. This ethics license will expire every five years and will be required to be renewed. Education on the importance of ethics will prevent the unethical treatment of study participants.

To ensure compliance with the continuing ethic education requirements, research institutions providing seminars and other education material will be eligible for additional grant money to fund research projects. Both public and private institutions will be eligible for the extra grant funding. Additional funding will be provided to institutions that have over 80 percent of
staff members with active ethics licenses. In addition, research institutions will be eligible for tax credits for providing continuing education seminars and/or paying for employees to attend conferences elsewhere. This author proposes that tax credits of actual annual costs per research center would allow these institutions to claim up to 75 percent of the cost of providing the seminars and up to 65 percent for paying for employees to attend ethics in-services. The board members of the research centers will be responsible for ensuring that at least 80 – 85 percent of the institution’s employees are in compliance with in-service requirements. If the quotas for seminar requirements by any institution is less than minimum 80 percent, these institutions will face tax penalties. The percentage of employees below compliance requirements will correspond to the tax penalty rate. For instance, for institutions with 65 – 79 percent of employees in compliance the tax penalty will be the greater of $500 or 2.5 percent of gross annual income. The tax penalties will increase as the percentage of employees not in compliance with the continuing education requirements decrease. These measures will ensure that research institutions remain in compliance with ethics in-service requirements.

Informed consent is critical to ensuring ethical treatment of human subjects of clinical trials. This author proposes that all individuals wishing to participant in biomedical research be informed of all need-to-know aspects of the study at the time of enrolling, again on the first day of the actual trial, and throughout the duration of the study. By hearing the information multiple times, the participants will be more likely to comprehend the information fully. In addition, the second time (or even third) hearing the information will give the participant the opportunity to withdraw before the study begins. By requiring all research institutions to obtain informed consent multiple times, they ensure that all steps for informed consent are followed properly: information, comprehension, and voluntariness. Furthermore, this procedure will protect research
institutions and researchers from being sued for neglecting to obtain informed consent for participants. Therefore, obtaining informed consent multiple times throughout the research process with ensure the ethical treatment of all human subjects.
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