Ethics of clinical research: A historical review

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SUMMARY

Research that contributes to significant advancements in healthcare is often achieved through the analysis of data from human participants. Many researchers in this field seek a diverse group of participants to study the effects of new drug treatments, diets, or other related therapies. Clinical trials and studies involving human participants are important for the progression of science, but require extensive ethical consideration. Ethics are the moral principles that govern a behaviour or activity, in this case, performing tests on humans. The understanding of ethical regulations outlines the key responsibilities of the investigator, and more importantly, ensures the protection of the participant's rights. This historical review examines the controversies that led to the development of ethical guidelines for human participation in research since the 1940s. It is through various major controversies that the documents containing these guidelines have continuously been shaped and edited. Analyzing the development of the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report contributes to a stronger understanding of current regulations and modern ethical controversies. These documents carefully considered the issues in their predecessors and include key points that aim to protect the rights of those who participate in research.

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INTRODUCTION

Besides their quality of instruction, many of the world's leading universities are well known for their research facilities and Nobel laureate affiliations. 40% of total Canadian research and development is performed by universities, accounting for approximately $13 billion each year (Statistics Canada, 2015). Research from these institutions extend from innovative technology to advancements in healthcare. New drug treatments, diets, or other related therapies are often achieved by analyzing data from human participants.

The biggest challenges involved in healthcare research lie within the clinical trial phase and the ethical questions it poses. This has been recently brought to light in September of 2017 when a lawsuit was filed against Johns Hopkins University (Ome, 2017). The case targeted the involvement of Hopkins' physicians, who reviewed and financed an unethical study in Guatemala in the 1940s. The study was conducted by the United States Government, who intentionally infected Guatemalans with diseases, including syphilis and gonorrhea, without their consent. Even though this occurred over 70 years ago, it is important to be reminded of these cases and how they can be prevented in the future. Ethical guidelines have not always existed in the past and reflecting upon the events that led to their establishment can provide better understanding of their importance in research.

It is necessary to understand the historical context upon which modern ethics are based in order to fully recognize the implications and significance of current guidelines and laws. Ethics can be defined as moral principles that govern one's actions. Before the 1940s, there were

Table 1: The ten principles that form the Nuremberg Code (Annas and Grodin, 1992).

#	Principle
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 seems to him to be impossible.
10	During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

no universally accepted ethical guidelines for research involving human subjects. Clinical studies were formerly referred to as "human experimentation" and had little consideration for the rights of the research subjects. This led to many discrepancies in study protocols, and left the ethical responsibilities of researchers up to interpretation. The progression of ethical codes prior to the 1940s provides a clear indication of the foundational theories of modern ethics. Many scientists in the 1800s were familiar with the Hippocratic Oath, written between 470 and 360 BCE, which states, "I will follow that system of regimes which, according to my ability and judgement, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous" (Freyhofer, 2004). These scientists built upon Hippocratic ethics to establish ethical guidelines for research involving human subjects, but it was not until the gruesome human experimentation during World War II (WWII) that the first universal code of ethics, the Nuremberg Code, was formed.

THE NUREMBERG CODE

The Nuremberg Code is considered to be the blueprint for modern ethics for studies involving human subjects. Current standards that protect subjects of medical research have their roots in the ten research principles presented in the Nuremberg Code (Table 1) (Shuster, 1997). The Code particularly focuses on the requirement of informed consent, described in the first principle (Shuster, 1997). This focus was a direct response to the tragic and perverse human experimentation conducted by Nazi physicians and scientists during WWII. After WWII, the victorious Allies held a series of military trials in Nuremberg, Germany, coined The Nuremberg Trials (Freyhofer, 2004). These trials were held to

prosecute Nazi officials who planned or participated in war crimes. The first of these was the International Military Tribunal, also known as the Major Trial, which tried the highest-ranking Nazi officials for war crimes and crimes against humanity (Freyhofer, 2004). This was followed by the Doctor's Trials, which tried physicians responsible for the abuse of human subjects to advance medical sciences. This revealed arguably some of the most horrific acts committed during WWII. The defendants argued that their acts were legal due to the lack of a universal standard of human research ethics, and the experiments' accordance to the law existing at that time (Freyhofer, 2004). The Nuremberg Code was developed during the Doctors' Trial in order to produce a set of medical standards with which to judge the physicians for their crimes (Annas and Grodin, 1992).

While the focus of the Doctor's Trial was the criminal nature of the experiments and the standards of human experimentation at the time, the broader concerns of medical research ethics were also examined and debated. The Code was ultimately based upon past literature, events, and philosophies (Annas and Grodin, 1992). Two primary medical expert witnesses who supported the prosecution, Andrew Ivy and Leo Alexander, were largely responsible for the development of the principles in the Code. Both scientists were familiar with the ethics of medical research proposed by Hippocrates, which ultimately formed the foundation of the principles within the Code. It is important to recognize that the ethical codes depicted by past influential scientists and physicians significantly impacted the development of the ten principles of the Nuremberg Code.

The Code has ultimately influenced global human-rights laws and medical ethics. It was not identified as simply a code of ethics, but rather a part of the final legal judgement in the Doctor's Trial. The physicians were judged according to the ten principles outlined in the Nuremberg Code (Annas and Grodin, 1992). Although it originates from the response to the tragic experiments at the hands of Nazi physicians and scientists, the Nuremberg Code emerged from the horrors of WWII to contribute to safer, more ethical practices in medical research involving human subjects. The Code has influenced the acceptance of informed consent in international law, and is used as a basis upon which many ethical guidelines are built, such as the Declaration of Helsinki and the current regulation, the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Shuster, 1997).

THE DECLARATION OF HELSINKI

The Nuremberg Code provided important guidelines for the necessary measures to respect the research subject's wishes. However, little emphasis was placed on the protection of their rights and welfare, and the responsibilities of doctors towards research subjects was overlooked. As a result, a new statement of principles for ethical research involving human subjects was put forth: The Declaration of Helsinki. The Declaration of Helsinki was first adopted by the World Medical Association (WMA) in 1964 and was largely based on the fundamentals of the Nuremberg Code, but addressed clinical research more directly (Goodyear, Krieza-Jeric and Lemmens, 2007). The main principles of the Declaration include that medical research can never take precedence over the rights and interests of the participant, the duty of the physician to protect the integrity and confidentiality of the participant, and that medical research must only be conducted by those with appropriate scientific qualifications (World Medical Association Declaration of Helsinki, 2013). The Declaration contains refinements and major advances to the principles outlined in the Nuremberg Code (Stone, 2004). The document was carefully examined by international organizations and critiqued by the world's preeminent physicians, scientists and ethics experts. From their evaluations, the Declaration has been revised seven times since its original publication. The most current version of the Declaration contains 37 principles, several of which may have been driven by the ethical analysis of controversial clinical studies.

An important outcome following the publication of the Declaration of Helsinki was the protection of vulnerable populations in research studies. Vulnerable populations, such as prisoners, are those whose individual freedom and ability to understand risks is affected due to various factors, including decreased freewill and inability to make informed decisions (Shivayogi, 2013). Principle 25 of the Declaration states that "participation by individuals capable of giving informed consent as subjects in medical research must be voluntary," which was controversial when it was implemented due to its ambiguity with regards to prisoners (World Medical Association Declaration of Helsinki, 2013). It was argued that prisoners were not in a legal state to express choice and therefore, should their consent be given, it should not be considered informed. One example of the exploitation of inmates is the study that occurred at the Holmesburg Prison in Philadelphia in the 1950s. In the studies conducted by dermatologist Dr. Albert Kligman, inmates were given experimental skin products, including creams, powders, and deodorants (Homblum, 2012). Although the inmates were paid for their participation, many suffered burns and scars as a result of the medical tests. Those who underwent the patch test, a 30-day trial, had up to 20 different products applied to their back and were exposed to heat from a sunlamp for a period of time (Homblum, 2012).

The patch test sometimes caused skin to peel, itch, and blister, however, the study was not deemed unethical due to the uncertainty of Principle 25. In addition, Dr. Kligman's research was not investigated by institutional personnel, nor was it supervised by the government, which allowed Holmesburg Prison to host one of the largest medical experimentation centres in the country for two decades. Holmesburg Prison became a key driving factor for the implementation of ethical guidelines and the importance of protecting research subjects. Although studies on federal prisoners ended in the mid 1970s, studies on other vulnerable populations continued until further revisions of the Declaration were effectuated. Among the seven revisions of the Declaration, the greatest changes occurred in the first, fourth and fifth revisions.

The first revision of the Declaration of Helsinki was published in 1975 after the realization that abuse of research subjects remained a common problem. Among the most important aspects of this revision was the elaboration of the requirements for informed consent and the rights of human subjects. This was specified in Principle four which read, "In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject" (Williams, 2008). To further protect the welfare of participants, it was also added that the research study must undergo advanced review by an independent committee prior to conducting the study in order to publish the results of the research (Williams, 2008). One of the factors that may have driven this revision was the controversy surrounding the Tuskegee Syphilis Study of 1932 to 1972.

A fourth revision of the Declaration of Helsinki occurred in 1996 to address placebo-controlled trials. The existing principle stated, "In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method," to which the fourth revision added "This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists" (Carlson, Boyd and Webb D, 2004). Motivation for this revision was driven by the increasing concerns regarding the use of placebo controls in prenatal HIV transmission in developing countries, specifically the trials for azidothymidine (AZT) in 1994 (Carlson, Boyd and Webb D, 2004). Prior to these trials, a study of HIV infected pregnant women, conducted by the USA and France, found that intensive treatment with AZT reduced maternal transmission of HIV in 70% of cases (Cohen, 1997). Researchers were aware that the incidence of HIV/AIDS was greatest in developing countries, but AZT treatment costs $800-$1000 per person, which is difficult for those women to afford. Thus, researchers sought to test cheaper prevention strategies, such as shorter treatment regimens or HIV-antibody injections, and performed a study in several developing countries, involving over 17 000 pregnant women (Annas and Grodin, 1998). The question of including placebos in these study groups led to ethical debate since the original AZT treatment had already shown effective long-term results (McIntyre, 1998). The fourth revision of the Declaration hoped to address this situation by specifying that placebos should only be used where no other therapeutic method exists. Even though the study was approved by African national ethics committees, thus complying to that aspect of the Declaration, bioethicists were sceptical due to the reputations of said committees. Cases have been noted where materials for the studies were sent from abroad prior to study approval and bribery was used to gain ethical approval (McIntyre, 1998). These reports provide evidence for increasing the stringency of the principles outlined in the Declaration through constant revisions.

Questions surrounding the ethics of placebo-controlled trials arose again in 2000 after the fifth revision of the Declaration, where Principle 29 stated, "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, where no proven prophylactic, diagnostic or therapeutic method exists" (Lewis et al., 2000). Although this principle does not appear to differ from that of the fourth revision, it's importance was demonstrated through the controversy it generated. It's been argued that if Principle 29 was taken literally, all clinical trials should be barred because research subjects receiving the investigational treatment would not be getting the best proven treatment (Simon, 2000). Instead, they believe that placebo-controlled trials can be conducted ethically so long as the omission of the proven treatment would not be detrimental to the patient's health and patients are completely informed about the alternative treatments available.

Over 50 years after its initial development, the Declaration of Helsinki continues to be an important document that sets the ethical standards for modern clinical studies. The Declaration has remained dynamic and adapted to changes as ethical problems arose. Due to this document, physicians are more aware of their responsibilities and research subjects are more aware of their rights. It has brought substantial awareness to the importance of ethics in human research; however, a number of unethical studies are still being conducted despite the principles in the Declaration. Although seven revisions have been made in the past, it must con-

Table 2: The three fundamental principles of the Belmont Report (Annas and Grodin, 1992).

Principle	Responsibilities
Respect for persons	Protecting the autonomy of all people and treating them with courtesy and respect; this is applied in the informed consent process. Researchers must be truthful and conduct no deception
Beneficence	Incorporating the philosophy of "Do no harm" while maximizing benefits for the research project and minimizing risks to the research subjects is applied through risk/benefit assessments
Justice	Ensuring reasonable, non-exploitative, and well-considered procedures are administered fairly and equally and applied to the selection of research subjects

tinue to change in the future to provide ongoing protection for human research subjects.

THE BELMONT REPORT

Around the time of the first revision of the Declaration of Helsinki, the controversial conditions of the Long-term Study of Untreated Syphilis in the Negro Male, known as the Tuskegee Syphilis Study, were revealed. The study was conducted from 1932 to 1972 and was undertaken by the U.S Public Health Service which later became the Centers for Disease Control and Prevention (CDC). The study sought to document the course of the disease in 400 African Americans to determine racial differences in the manifestation of syphilis (Corbie-Smith, 1999). When the study first began, there was no effective treatment for the disease, which was the case until 1943, when researchers found that penicillin could be used to treat syphilis. Despite this discovery, the study was continued and the subjects were never notified of the existence of a treatment (Singer and Levine, 2003). In response to the ethical concerns that arose during the study, the Belmont Report was written to establish stricter regulations.

Even though the Declaration of Helsinki was formed in 1964, no changes were made to the Tuskegee Syphilis Study (Kim, 2012). In 1969, the CDC formed a panel to review the experiment, but they allowed the continuation of the study without modification to the protocol, for unknown reasons (Shovers, Lynch and Burmeister, 2000). In 1972, a story published in the New York Times and the Washington Star revealed the ethical concerns of the study, and the resulting public outcry led to hearings directed by Senator Edward Kennedy and closure of the study (Kim, 2012; Shovers, Lynch and Burmeister, 2000). At this time, participants were finally given the appropriate treatment, but it was too late for the approximately 100 men who died due to untreated syphilis or syphilis-related complications (Corbie-Smith, 1999).

Within two years of the termination of the Tuskegee Syphilis Study, the United States Congress passed the National Research Act. This established a human research protection system to uphold the rights of human participants and prompted the development of regulations requiring the establishment of Institutional Review Boards at federally funded institutions (Singer and Levine, 2003). This led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (Kim, 2012). The Commission was required to identify principles that underlie the ethical conduct of biomedical and behavioural research. Their main product, the Belmont Report, was published in 1979 and marked a key point in history for the development of ethical requirements involving the use of human subjects in research (Singer and Levine, 2003). The three fundamental principles of the Belmont Report (Table 2) influenced the criteria for the protection of human subjects and continues to be an important reference for Institutional Review Boards. The Belmont Report formed another base upon which medical research regulations are formed, and has widely influenced the standards that exist today.

The controversies surrounding the Tuskegee Syphilis Study served not only as a representation of the exploitation of vulnerable populations through human experimentation, but also as an inciting incident to produce new regulations to protect the rights of future human volunteers. It can be argued that the most important consequence of the study was the creation of the National Research Act, the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, and ultimately, the formation of the Belmont Report. The lack of ethics surrounding the study have evidently led to the development of more protective guidelines to prevent these events from reappearing in the future, and have powerfully impacted the ethics of current medical research.

MODERN CONTROVERSIES

Although the regulations outlined in official documents such as the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report drastically improved the ethical requirements surrounding clinical trials, there are still many controversies surrounding modern

clinical research.

One example of this is known as "pay to play" clinical trials. Most studies offer monetary compensation for their research participants, but a number of recent studies require payment for participation. Some researchers charge patients to be enrolled in their study as both a way to fund their research and for personal profits (Emanuel et al., 2015). Patient funded studies have been conducted for conditions including Parkinson's disease, and Multiple Sclerosis. One particular case surrounds Novastem, a Mexican stem cell product distributor for the U.S company Stemedica. Novastem reportedly charged their participants $30 000 USD for enrollment in their trial which uses neural stem cells to treat stroke-related brain damage (Wenner, Kimmelman and London, 2015). This raised concerns regarding patient participation and regulation of the study.

First, selection of subjects for Novastem's study were based on one's ability to pay, thus prioritizing the needs of the wealthy. Not only does this pose an ethical dilemma, but this can affect the validity of the study, as the selection of participants should be primarily based on the goals of the research study. Issues then arise when considering the need for placebos because paying participants will be less willing to accept randomization when there is a possibility that they will not receive the treatment. Also, patient funded studies can cost thousands of dollars, causing patients to spend large amounts of their savings. Severe illnesses can compromise decision making when deciding to spend large funds on a potential treatment (Emanuel et al., 2015). This could allow researchers to exploit desperate patients, even though the majority of experimental agents used in early clinical trials fail.

Another concern regarding patient funded trials is the production of reliable medical evidence to ensure the safety of the study. New forms of treatment can be ineffective, and even dangerous, thus, several factors to oversee the process are typically required. Studies must produce adequate evidence for the safety, toxicity, and efficacy of their treatment prior to submitting a clinical trial application (Wenner, Kimmelman and London, 2015). Since trials are expensive, private sponsors may minimize the sample size and duration of the study to generate the required evidence. As a result, patient risks increase, and consequences may remain unknown. Drug companies are mainly driven by commercial interests and may prioritize them over the interest of the patient. To accommodate this growing issue, bioethicists recommend that new policies be designed specifically for these trials (Wenner, Kimmelman and London, 2015). Such policies should promote research methods that minimize bias when collecting data and ensure that the paying patient is aware of all risks surrounding the trial. Should this type of trial continue in future studies, it is important to form new accommodating guidelines to ensure the safety of the participant.

CONCLUSION

In the past century, various documents have been established which state that certain ethical principles must be incorporated in clinical studies to protect the research subject's rights. It is necessary for researchers to understand how ethical regulations have been formed in order to understand their significance and potential for improvement. Knowledge of the biases, opinions, and controversies that have produced these regulations provides a better perspective with which these ethical codes can be understood. Since the 1940s, controversies surrounding experiments with human subjects have led to new guidelines that shape research ethics. The Nuremberg Code, the Declaration of Helsinki, and the Belmont Report were guidelines that formed as a result of controversial studies responsible for the improper treatment of human subjects. These regulatory ethical research codes have helped to shape the development of our current ethical standards, and will continue to be u used as a basis for future ethical guidelines.

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AUTHOR CONTRIBUTIONS

L.B. wrote the Nuremburg Code and Belmont Report sections and A.L wrote about the Declaration of Helsinki and modern controversies. Both authors contributed equally to the introduction and conclusion.

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