The Advancement and Shortcomings of Ethics in Clinical Research

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Abstract

The field of research ethics has undergone drastic change over the past eighty years. From the first international code of ethics published in 1947, called the Nuremberg Code, to recent revisions of the Declaration of Helsinki, different codes of ethics have set guidelines to safeguard the interests of human subjects in research participation. Each document has been published against the backdrop of unique political and social climates, influencing which guidelines are emphasized each time and which propel the field of research ethics forward. Particularly, one of the most crucial guidelines to be established is that of informed and voluntary consent. Furthermore, using principles of the actor-network theory, an understanding of the reciprocal relationship between researchers and codes of ethics is gained. Ultimately, the field of research ethics presents the societal aspect of scientific discovery and is necessary for current and future innovation.

Introduction

Shrinking awareness and growing distrust for clinical research presents a critical challenge for researchers who often work amid an environment that relies on patient engagement (*Patient Willingness to Join Clinical Trials Drops Dramatically, New Data Show*, n.d.). Without the participation of human subjects, the validity of clinical research often falls flat. In particular, clinical trials require human participation and barriers, such as distrust or financial limitations, may prevent individuals from being involved. Over the past eighty years, as clinical research has gone through exponential growth, so has the closely related field of research ethics. Therefore, the ethics of how clinical research has been and is currently conducted and how patients have been and are treated are central considerations in the field.

In particular, the ethical principle of informed consent, or receiving one's permission prior to conducting research on them, is seemingly fundamental in research today. However, this principle was only established in 1947 with the adoption of the Nuremberg Code, the first international code of ethics for research on human subjects (*Research Ethics Timeline - David B. Resnik, J.D., Ph.D., Bioethicist, NIEHS/NIH*, n.d.). Written in the aftermath of World War II, the Nuremberg Code serves as a blueprint for today's principles that ensure the rights of subjects in clinical research (Shuster, 1997). Following the Nuremberg Code, additional documents, such as the Declaration of Helsinki, have added guidelines and ethical considerations to the field (Carlson et al., 2004). Each succeeding document has been written in a unique context; however, the underlying thread continues to be safeguarding the interests of human subjects.

Research ethics involves a broad spectrum of actors and artifacts, from the physicians and patients to the historical and present-day documents that guide the physician-patient relationship. The actor-network theory provides a framework to account for the interplay between many of

these actors and artifacts and ultimately highlights the societal aspect of clinical research through the field of research ethics. As such, holding a longitudinal discussion on research ethics is centered on the following question: How has the role of research ethics evolved over time due to unique cultural and political climates? To address this question, the paper will first review several codes of ethics to provide a chronological order of the advancement in research ethics. This background will set the stage for actors and artifacts and their relationships to be addressed using the actor-network theory. Lastly, several shortcomings of research ethics will also be presented to provide a more comprehensive description of the advancement, or lack thereof, in research ethics.

The Beginning of Research Ethics

The introduction of scientific and experimental methodology in clinical research in the 19th century inherently brought with it the need for human subject participation. Many times, the research was conducted on patients in the hospital, often without their consent. At this time, there were no international codes of ethics that researchers were bound to; however, as a result of injury to some patients who were unknowingly partaking in clinical research, questions about the ethics of human experimentation arose. In particular, the scope of the paper begins several decades prior to World War II, the time period that is often associated with being an inflection point for research ethics. In the late 1890s, the case of researcher Albert Neisser brought forward concerns of unethical non-therapeutic research on humans and emphasized the need for informed consent. As part of his research on syphilis prevention, Neisser injected cell-free serum from patients with syphilis into patients who were admitted into the hospital for other medical conditions. The purpose of Neisser's experiments was to determine whether the injections could prevent or reduce syphilis as the blood serum from those with syphilis was relatively bacteria-

free. However, most of these patients were neither informed about their participation in the experiment nor asked for their consent. Though most physicians at the time supported Neisser's actions, there were a few who spoke out about his seemingly unethical experiments. In 1898, after an investigation into Neisser's case, a court ruling stated that "though Neisser, as a well-known medical authority, may have been convinced that the trials were harmless, he should have sought the patients' consent." (Vollmann & Winau, 1996).

Two years later, in 1900, the minister for religious, educational, and medical affairs of Prussia, where Neisser conducted his studies, issued a directive to all hospitals and clinics in which a "proper explanation of the intervention and "unambiguous consent" become the mandatory standard (Vollmann & Winau, 1996). The directive's impact, however, on changes made to human experimentation in clinical research remained unclear as the directive was not legally binding. Despite this, the Neisser case presents evidence that starting as early as the 1890s, there were concerns regarding individual autonomy and early models of informed consent in research.

Further, one interesting basis of the aforementioned directive and regulation was that it was issued by government authorities, rather than by physicians or research institutions, those who are closer to the patients, and possible wrongdoings in research, themselves. The unique climate at the time, one based on critical public discussion and political debate, lent itself to regulation by government authorities, since the physicians and researchers at the time were complicit in many of the unethical experimentation. Therefore, the political climate in the early 1900s, especially in Germany, offered some growth in what is now considered research ethics; however, these advanced, at the time, ethical and legal regulations failed to prevent the crimes against humans that would occur less than half a century later.

The Nuremberg Code: An Inflection Point in Research Ethics

Decades after the Neisser case, the scientific and medical experiments conducted on prisoners of war in concentration camps in Nazi Germany were a catalyst in motivating change in the field of research ethics. Many consider this time period in history to be a watershed moment as it drove the field forward. In addition to the horrific treatment of prisoners of war, other key events, such as the Manhattan Project, raised awareness of the consequences of human participation in research. With research being conducted against the backdrop of a World War, the political climate across the world had sweeping effects on research ethics and exemplified a need for real change in the field. Furthermore, though the emphasis here is set on Germany, it is equally important to recognize that the War involved over 30 countries and as such, the tense political climate was not limited to one country.

In Germany, the Nuremberg Trials brought twenty-three doctors to the stand for having conducted clinical research on individuals in concentration camps. The Trials ultimately produced the first international code of ethics called the Nuremberg Code (Ruyter, 2019). At the core of the Code, the authors established the necessity of voluntary and informed consent, stating that "the voluntary consent of the human subject is absolutely essential." (Ghooi, 2011). The Code also included guidelines such as the importance of the experiment yielding results for the good of society, the experiment should be conducted to avoid all unnecessary physical and mental suffering, and consideration of the balance between risk of the experimentation and the benefit to society gained from such experimentation. What debates were held at the Doctor's Trial that resulted in the formulation of such a pivotal Code?

The main trial at Nuremberg was conducted by the International Military Tribunal, made up of judges from the four allied powers (the United States, Britain, France, and the former

Soviet Union). These judges' responsibility was to try Germany's major war criminals. Following the main trial, the American Military Tribunal conducted twelve additional trials of different groups of Nazis, the first of which was the Doctors' Trial, involving twenty-three defendants, twenty of whom were physicians accused of inhumane treatment of concentration camp inmates. After almost six months of proceedings, sixteen of the twenty-three defendants were found guilty. Though formally a trial for murder, the trial carried even more weight on the physicians, who had sworn to "do no harm" in their Hippocratic Oath. As the trial engaged in debate, three physicians had central roles in the formulation of a document that would drastically shape research ethics: Leo Alexander, an American neuropsychiatrist, Werner Leibbrand, a German psychiatrist, and Andrew Ivy, a renowned American physiologist (Shuster, 1997).

During the course of the trial, all three physicians brought forth and emphasized the concept of informed and voluntary consent. In particular, Ivy presented to the judges three research principles he had formulated at the request of the American Medical Association, one of which stated that "consent of the human subject must be obtained" and all subjects must be "volunteers in the absence of coercion in any form." (Shuster, 1997). The arguments verbalized by Ivy, Leibbrand, and Alexander and recognized by the judges emphasized that more was necessary beyond the Hippocratic Oath to protect human research subjects. As such, the judges articulated a set of ten research principles, named the Nuremberg Code, centered on the research subject, rather than the physician. The most well-known principles of the Code included one of absolute requirement for informed consent and one that provided the right to subjects to withdraw from participation in an experiment (*Nuremberg Code*, n.d.). These two principles truly allowed for patients, whether in a physician-patient or researcher-patient relationship, to advocate for themselves and actively promote individual autonomy. This stood in stark contrast

to previous interpretations of the relationship, solely under Hippocratic Oath, where patients were simply meant to dutifully obey physicians (Shuster, 1997). Now, the physician-patient relationship grew to encompass both individuals and foster reciprocal communication and trust. Therefore, the Nuremberg Code can be seen as a merging between Hippocratic ethics and the protection of human rights into a single entity (Shuster, 1997). Moreover, though the Code was developed during a time characterized by conflict and chaos, it allowed for the advancement of the field of research ethics by safeguarding the interests of human subjects.

Further, in contrast to the government's directive in 1900 Prussia, physicians played an integral role in the formulation and publication of the Code. Whereas the Prussian directive came directly from a governmental perspective, the Code was significantly authored due to the arguments by three physicians, namely Ivy, Leibbrand, and Alexander. As half of the patient-physician relationship, physicians hold a duty to safeguard the health of their patients, including those involved in clinical research. In this context, physicians must also fulfill the responsibility of protecting the health, integrity, and dignity of those their profession aims to help (Masic et al., 2014). Therefore, the formulation of the Code also marked a shift in that those who directly interact with patients were the ones who were able to foster change. Lastly, even though the Code itself was never officially adopted in its entirety as law by any nation or as ethics by any major medical association, it did present a large influence, specifically its emphasis on informed and voluntary consent, on the field of research ethics.

The Declaration of Helsinki: A Continued Safeguard of Human Safety

With the publication of the Nuremberg Code, the field of research ethics saw dramatic growth, particularly with respect to informed and voluntary consent. However, the Code itself could not be and was not a comprehensive guideline for how best to ethically conduct research.

Another answer was needed for the demanding situations in clinical research. First adopted in 1964, the Declaration of Helsinki (DoH), published by the World Medical Association, is seen to have its roots in the Nuremberg Code. Specifically, these similarities can be seen in terms of guidelines in the DoH regarding risk-benefit balance and informed consent. It is also important to note these guidelines also contributed to the way that differences in obtaining consent differed between research and non-research procedures as this helps us understand the content of the Declaration and its respective scope. Though consent in both aims to ensure the safety of the patient, the research consent process is more comprehensive, as it involves an Institutional Review Board as well as financial disclosure. Conversely, non-research procedures are generally more open-ended, with forms indicating alternative treatments that may be left to the physician's discretion (Sas, 2013).

The DoH prefaced its ethical guidelines with a statement that read: “In the field of clinical research, a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and clinical research which is purely scientific and without therapeutic value to the person subjected to the research.” (*WMA - The World Medical Association-Declaration of Helsinki*, n.d.). As such, similar to the risk-benefit balance introduced in Principle 6 of the Code, the DoH also emphasized the importance of research producing greater benefit for society than the risk introduced to human subjects during the course of the experiments (*Nuremberg Code*, n.d.). Secondly, the DoH added to the central principle of informed consent by allowing consent to be given by a legal guardian in cases of legal incapacity. When discussing clinical research with professional care, the DoH reads “in case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.” (*WMA - The*

World Medical Association-Declaration of Helsinki, n.d.) Though slightly loosening the scope of informed consent established seventeen years earlier by allowing guardians to provide consent when necessary, the original publication of the DoH continued to safeguard the autonomy of the patient and maintain the patient's best interest in mind.

One additional aspect of the DoH that stands out is that it explicitly placed emphasis on the fact that it is the mission and responsibility of the physician to safeguard the health of their patients, as their "knowledge and conscience are dedicated to the fulfillment of this mission." (*WMA - The World Medical Association-Declaration of Helsinki*, n.d.). The statement placed more weight on the physician end of the patient-physician relationship as these individuals are the ones who are most adept to provide the information to their patients with which they can then make informed and voluntary decisions (*WHO | The Declaration of Helsinki and Public Health*, n.d.). Furthermore, this aspect of the DoH plays into the authority of the Declaration itself, as the World Medical Association is the largest global group of doctors, and as such, their authorship provides legitimacy to the statements regarding the duty and responsibility of medical professionals (Carlson et al., 2004).

Following the original publication of the DoH, there have been seven revisions to the document with the most recent confirmed in 2013. The multiple revisions emphasize the fact that the DoH is a "living" document, one that changes as the field of medical research evolves itself (Ndebele, 2013). One aspect, however, that remains constant among the revisions is that the document is addressed directly to physicians by physicians. With respect to the most recent version, developments in the document include addressing the lack of minority representation in medical and clinical research. Individuals participating in research should reflect the diversity of the population, especially since new treatments may present varied efficacy across different

populations (*Representation in Clinical Trials*, 2020). However, at the time of the latest DoH publication, and currently, there is a significant imbalance in representation of minorities in clinical research (Chen et al., 2018).

In particular, recent Food and Drug Administration (FDA) Drug Trial Snapshots share that white individuals make up 67% of the U.S. population, but are 83% of the research participants. Further, while Black/African-Americans make up 13.5% of the U.S. population, only 5% of research participants are from this demographic (Woodcock, 2018). The lack of sufficient minority representation lends these same minority groups to not benefit in equal and equitable ways from advances in research. Therefore, the 2013 DoH addresses such differences by recommending access to clinical trials for underrepresented groups to be increased (*WMA - The World Medical Association-Declaration of Helsinki*, n.d.). As such, it is clear that each ethical code or set of guidelines, or even a revision of previous ones, evolves as the field it aims to regulate evolves itself. In the context of the most recent DoH, especially as the globe is engulfed by the COVID-19 pandemic, challenges such as health disparities, health inequity, and unequal health care access are even more important to tackle (Evans, 2020).

Lastly, a surprising aspect of the DoH, like the Nuremberg Code, is that it is not a legally binding document in international law, but rather, influences national or local legislation to some degree. For example, the Nuffield Council Document on "Research in Developing Countries" devotes an entire chapter to understanding a specific article of the Declaration. The Nuffield Council has a role in informing policy and public debate about ethical questions that can take guidance from the DoH as well as interpret the document in a distinctive way (Carlson et al., 2004). Even more surprising, however, is that the U.S. Food and Drug Administration (FDA) discontinued referring to the Declaration after 2006, due to several controversies and concerns

presented in the DoH revision published in 2000 (Wolinsky, 2006). These concerns range from an incoherent structure to posing unjustified recommendations (Emanuel, 2013). Therefore, the legitimacy of the Declaration's influence has decreased over time, especially as developed countries, such as the U.S, have limited their association with the Declaration. Regardless of this, however, the DoH is still viewed as a pioneering effort to safeguard humans involved in clinical research. Further, it is clear evidence of how the field of research ethics and its ethical guidelines have changed and continue to change as the context surrounding its writing changes as well.

Henrietta Lacks: A Case of Failed Research Ethics

Often times, the ethical guidelines presented by documents such as the Nuremberg Code and the Declaration of Helsinki may seem to simply solve the questions and challenges faced by physicians and researchers. However, there are countless examples that highlight where the practice of clinical research and research ethics is often more complex and has failed to ensure the protection of human participation, despite overwhelming influence from guidelines. One such example is the story of Henrietta Lacks, a 30-year old African American woman who was diagnosed with cervical cancer at Johns Hopkins Hospital in 1951 (Beskow, 2016). Her physician, Dr. George Gey, removed and used a sample of cells from her cervix, without her permission. In fact, her own family was not even informed of the physician's actions until many years later. Today, her immortal cells, named HeLa, are the foundation of many scientific discoveries, from a vaccine for polio to vaccines for COVID-19 ("Henrietta Lacks," 2020). However, despite the fact that her cells produced much benefit for society, it is impossible to forget about the lack of informed and voluntary consent, and ultimately lack of respect, for her situation.

It is clear from Henrietta's story that the presence of ethical guidelines, such as the Nuremberg Code during her life, does not mean that there will be full adherence to such recommendations. Factors such as explicit, implicit, and structural biases may have contributed to such dismissal of guidelines. Furthermore, the political and social climate at the time of Henrietta's life illustrates the role of research ethics, or lack thereof, in her treatment. First, Lacks was a Black woman and the hospital where she was diagnosed, Johns Hopkins, was one that provided care to only a few Black people. Second, racial inequities were embedded in both the health care and research system ("Henrietta Lacks," 2020). Lastly, and unfortunately, the mistreatment that Henrietta faced did not stop in her lifetime, lending to a legacy of mistrust. Physicians failed to ask her children and future generations for consent even as their mother's cell lines became even more prominent and public in the research field (White, 2018). Further, research labs and companies failed to provide financial reparations from the stream that continues to flow from HeLa cell distribution and use.

As such, beyond the scientific impact the HeLa cell line had, the economic implications are widespread as well. Research labs and companies, for decades, continued and continue to gain financially from her cells. Her cell lines were not only valuable to scientific discovery but served as transactions allowing those individuals and companies who acted unethically to profit. During and soon after Henrietta's life, researchers shipped and sold her cells across the country, whether for virology research or to study diseases such as cancer and AIDS (Lyapun et al., 2019). Over the next seventy years, HeLa cells contributed to discoveries and insight in over 110,000 publications. Today, scientists buy HeLa cells and cells with modifications for anywhere from $400 to thousands of dollars per vial (Marcus, 2020). In an effort to recognize and, to some extent, repay the Lacks' family, labs and companies who benefit from HeLa cells

are beginning to donate to the Henrietta Lacks Foundation. For example, the lab of Samara Reck-Peterson, an investigator at the Howard Hughes Medical Institute, will donate $100 to the Foundation for each of the four cell lines that lab members created in the past by making changes to the HeLa cells, and for any cell lines they make in the future (Marcus, 2020).

The movement to repay the Lacks' family and combat the longstanding legacy of mistrust is certainly a step in the right direction; however, Henrietta's contributions are one that may never be fully quantified and repaid. Therefore, the implications of Henrietta Lacks go far beyond her immortal contributions to science, but to economics as well. Despite these successes, the context of such growth stems from the dismissal, rather than the acceptance and growth, of ethical guidelines during and after Henrietta's life.

An Application of the Actor-Network Framework to the Research Network

The actor-network framework allows for the tracing of relationships between network components, whether human or non-human, that ultimately provide insight into how social effects are generated (Cresswell et al., 2010). In the network of clinical research and research ethics, there are a myriad of actors, such as physicians, researchers, and patients, and artifacts, such as codes of ethics, that interact to produce a social world that exists due to these constantly shifting networks of relationships (Prout, 2008). Further, the components are inclusive of ideas and concepts as well, such as autonomy, legitimacy, and societal good. As seen in Figure 1, there is a complex relationship that exists between these actors and artifacts, with each one exerting some level of influence and being influenced by another at the same time. For example, in the context of the Nuremberg Code, the web of lines surrounding the Code in the Figure provides direction into which actors, artifacts, and ideas influenced and are influenced by the document. The Nuremberg Code influenced the practices of physicians and researchers; however, at the

same time, its publication and writing itself was influenced by physicians, such as Alexander. Further, the Code influenced the development of informed consent but at the same time, was influenced by mistreatment of human subjects, or "patients" who had no opportunity to provide consent. The Code also interacts with concepts such as societal good, such as in safeguarding human interests, and legitimacy, which the Code gains not from a legal binding perspective but rather from its influence on international law (Shuster, 1997).

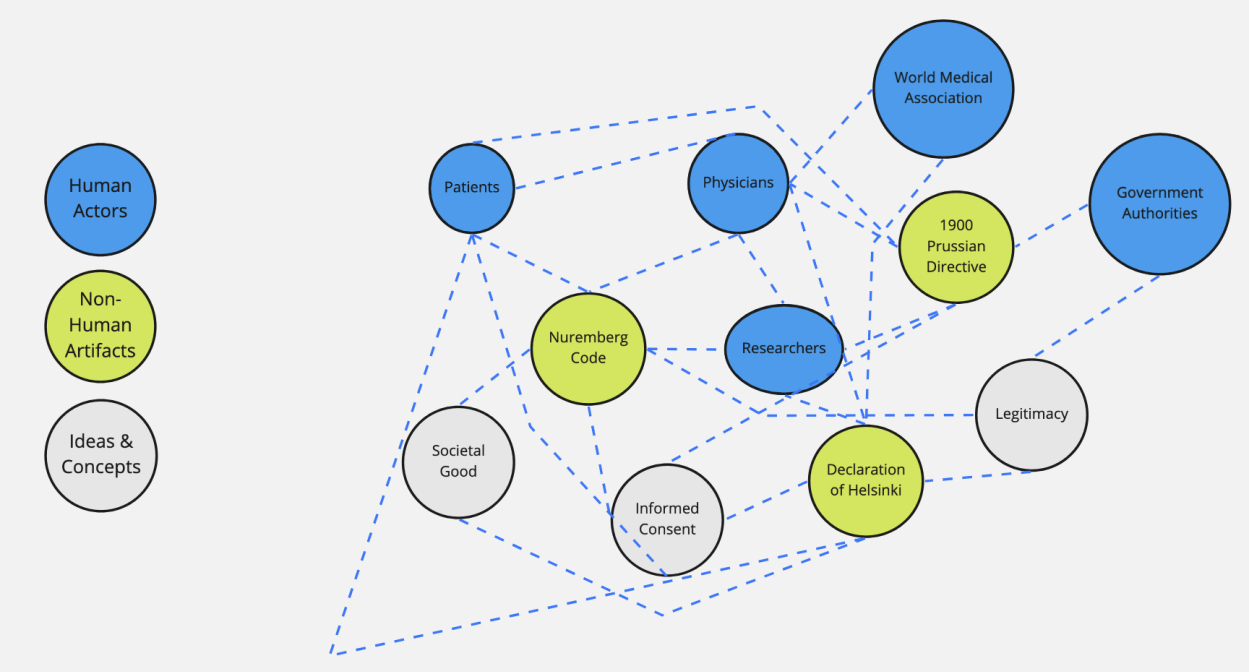

Figure 1: Actor Network Theory Applied to the Clinical Research Network: The figure displays the interactions between various actors, artifacts, and ideas that ultimately provide insight into how social effects in society are generated.

Autonomy Explained in the Research Network

One way in which patients, physicians, and codes of ethics interact are all based on the concept of informed consent. These actors and artifacts ultimately promote and safeguard the social concept of autonomy in society. Generally, autonomy means being in control of your own decisions without outside influence (FAHS, 2018). In terms of the codes of ethics, as has been discussed in detail thus far, the principles in the Nuremberg Code and the Declaration of Helsinki

promote values of informed and voluntary consent. From the patient's perspective, this informed consent, directed by codes of ethics and implemented by physicians, allows for patient autonomy or "the *right* of a patient or subject to choose." (Beauchamp & Childress, 2019). While informed consent and patient autonomy have been discussed thus far through ethical principles directly, the concept of physician autonomy is less understood. Therefore, the dynamic between patients and physicians must balance, or at least critically evaluate, both the patient's autonomy and that of that physicians' when making medical decisions. For example, while the patient has the *right* to choose, this does not mean that the patient or subject has a correlative *duty* to choose. In this way, the concept of physician autonomy arises. Physicians have specialized knowledge and skills and they should have the autonomy to apply their judgements in the patient's best interests, while still holding the patient's perspective with high regard. Therefore, from a physician's perspective, there is a distinction between educating the patient and ultimately making the decision on behalf of the patient (FAHS, 2018).

As a whole, the concept and practice of autonomy has seen dramatic change over the past eighty years as a result of new and revised codes of ethics. These codes of ethics, which have better defined the concept of informed consent, have, thus, altered the physician-patient relationship. Therefore, patients, physicians, and codes of ethics all circulate around the concept of informed consent to ultimately promote autonomy for all actors and artifacts involved.

Limitations of Research Methods

The research paper, thus far, has encompassed codes of ethics such as the 1900 Prussian directive, the Nuremberg Code, and the Declaration of Helsinki. As previously mentioned, the Declaration of Helsinki has been revised seven times since its original publication in 1964. However, each iteration of the Declaration was not analyzed as to provide more detail on the first

and current version of the document. Each revision has brought with it its unique changes to the field of research ethics and is one area of research that can be further delved into. Additionally, specific principles from each code of ethics received focus, rather than a brief overview of all written principles. Furthermore, these three codes of ethics are not comprehensive of all ethical guidelines produced internationally, nationally, or locally. Analysis and application of documents such as the Belmont Report can offer a more holistic perspective of the evolution of research ethics over the past eighty years (*Research Ethics Timeline - David B. Resnik, J.D., Ph.D., Bioethicist, NIEHS/NIH*, n.d.). Also, as mentioned, there are countless examples when the influence of ethical guidelines has been compromised. The story of Henrietta Lacks is only one story of many individuals and groups of individuals that have experienced inequality and inequity in the face of clinical research. Lastly, the described actor-network theory is a complex framework that includes a large number of actors and artifacts, only a few of whom were mentioned in the analysis. Despite these limitations, the research paper presented a detailed, though introductory, conversation into how political and social climates surrounding the publications of a plethora of codes of ethics have altered the field of research ethics over the past century.

A Review of and A Look Ahead in Research Ethics

Over the past eighty years, codes of ethics such as the Nuremberg Code and the Declaration of Helsinki have been written as a result of the political and social climates surrounding their writing. In particular, the Nuremberg Code has been marked as a watershed moment in ethical advancement, specifically against the backdrop of the Second World War. One of the most pivotal results from these codes has been the adoption of informed and voluntary consent in research participation. Furthermore, though the Nuremberg Code and the

Declaration of Helsinki have never been legally binding, their influence in the field of research ethics can be seen in influences on international and national law. Though the field has seen much human and societal-driven advancement in the field of research ethics, it has also faced times where ethical guidelines have been dismissed and disrespected. In particular, the story of Henrietta Lacks highlights the injustice she, and her family, faced as her cells were taken without her consent and continued to be distributed across the scientific community. Her story is one of injustice and tragedy and showcases that even despite the presence of influential guidelines, factors such as explicit, implicit, and structural biases may lend to dismissal of such guidelines in their entirety.

Today, the ever-changing political and social climates continue to play a role in how the field of research ethics evolves. As such, looking forward into the future, research ethics necessitates further change if the field is to provide responsible and equitable conduct of research for all parties involved. In particular, concepts such as patient anonymity, confidentiality, and privacy, are only a few of the current ethical challenges that must be addressed (Hokke et al., 2018). From this conversation, it is clear that the field of research ethics has seen great advancement, as well as countless shortcomings, over the past eighty years across several defining periods. Ultimately, the field offers the necessary societal aspect to clinical research and a humanistic method with which individuals can and should approach discovery and innovation.

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