A SWOT Analysis of COVID-19 Human Challenge Trials in Light of Christian Ethics: Is Infecting Healthy Humans with Coronavirus in Order to develop vaccines ethical?

Daniel Kipkemboi Lagat*

Kirinyaga University, Kenya

Abstract

The COVID-19 pandemic has elicited reactions of various magnitudes from various stakeholders and countries. Interventions have come from stakeholders with matching veracity. Some have proposed hydroxychloroquine and azithromycin, green tea, traditional herbs, anti-retroviral drugs, religious magic, etc. An interesting intervention that has been championed by scholars such as Arthur Caplan (2020) is human challenge studies. This is giving healthy human volunteers with trial COVID-19 vaccines and then infecting them with the virus to test the vaccine's efficacy. Challenge studies involve volunteers motivated by altruism and a desire to help humanity. In addition, the payment of study participants would motivate many volunteers to enroll in the study, especially if the offer was encouraging. Several ethical questions have emerged when implementing challenge studies: Are participants who participate in a study only to obtain money regarded as volunteers? Is exposing humans to a virus that could affect them negatively—even causing death, the best intervention for COVID-19? This paper argues that COVID-19 challenge studies are unacceptable based on existing research on human regulations, Christian views of human dignity, and biblical instructions on treating humans. This documentary study employed available literature on human challenge studies from secondary sources. The conclusion suggests a way to guide the policy and practice of existing and other possible COVID-19-related studies.

Keywords: COVID-19, challenge studies, vaccines, Christian ethics, altruism

Introduction

The growth of science in human development has been primarily based on how research helps in interventions against diseases. The worst scenario in the world has been the emergence of contagious diseases, which have often led to pandemics, resulting in millions of deaths of millions of people. For example, Bambery et al. (2016) asserted that smallpox alone killed approximately 500 million people worldwide, and more people were killed during the "First and Second World Wars" (p. 93). Human challenge studies involve manipulating infectious agents through attenuated strains of pathogens or using less invasive or burdensome strains, hoping that the body systems would be able to deal with them and thereby gain immunity (Eyal et al., 2020).

*Corresponding Author: dlagat@kyu.ac.ke

The history of human challenge studies has been attributed to Edward Jenner, who conducted a smallpox experiment in 1796. He inoculated an 8-year-old boy with cowpox, following his observation of the immunity of people who milked cows and finally being able to make this boy immune to smallpox (Hope & McMillan, 2004). Human challenge studies, or otherwise, "Controlled Human Infection Model" (CHIM) studies, involve infecting healthy humans to study prophylaxis, pathogenesis, and even the causes of certain diseases. A United States Army surgeon, Walter Reed, is noted to have done some study on yellow fever in the same way, to find out if mosquitoes were to be blamed for the spread of the disease (Eyal et al., 2022). He used study volunteers but warned them of the danger of participating in the study, including the possibility of death. There was also a payment for participation in the study, which was paid *ex-ante.*

Challenge studies have also investigated the causes of *vaccines* for the common cold and malaria. Healthy volunteers were inoculated with the vaccines to test their clinical and immune responses. Another example is cited by Hope & McMillan (2004), "influenza A virus to assess both vaccines and antiviral drugs, challenge with cholera bacilli to evaluate novel vaccines, and challenge studies with pneumococcus to assess correlates of protection against nasopharyngeal colonisation" (p. 110).

According to analysts, human challenge studies are chosen because of the demand for the most reliable vaccines and approved treatments. Challenge studies are scientific trials which meet the mechanical principles of research, making the findings reproducible and explainable. Human challenge studies have been conducted in Africa in zones affected by the Zika virus. Women were selected infected, and quarantined in hospital in order to manage their health and minimize chances of secondary infection. It was envisaged that such women would have a lower chance of sexually infecting other people with the virus, should it remain malignant. Women were also required to take long-term contraceptives to prevent mother-to-infant infections (Durbin & Whitehead, 2017).

The Problem

The recent novel coronavirus (COVID-19) pandemic, compounded by its economic, cultural, and social devastations, posed a serious challenge to many countries in the world, especially Africa, where its economic, health, and developmental positioning has been precarious for many years. The pandemic elicited reactions of various magnitudes and extents from different stakeholders and countries. Interventions have come from those stakeholders, with matching veracity. Some proposed hydroxychloroquine and azithromycin, others green tea, traditional herbs, anti-retroviral drugs, religious magic, etc.

One interesting intervention that has been championed by scholars such as Arthur Caplan (2020) is human challenge studies or the controlled human infection model. This is giving healthy human volunteers trial COVID-19 vaccines, and

then infecting them with the virus on purpose, to test the efficacy of the vaccines. Challenge studies involve volunteers motivated by altruism and desire to help humanity in general. Caplan (2020) argues that challenge studies are currently the most formidable and promising, unlike ordinary clinical trials, which take an average of 20 years. The advantage of challenge studies is that it provides an avenue to skip several processes in clinical trials, such as using animals and following the phase rules of clinical trials. Besides, the payment of study participants would motivate many volunteers to enroll in the study, especially if the offer is encouraging.

Infecting healthy humans to determine disease intervention strategies, also called challenge studies, is an emerging issue of concern. As promising as it is, the controlled human infection model raises profound questions whether this intervention is ethical, and whether Christians should support or oppose it. For example, paying these volunteers or promising payments ahead of the study raises additional bioethical research issues. If money is promised ahead of time, to encourage volunteers to participate, would that amount to coercion in the informed consent process. ? How would it be possible to gauge that volunteers were not induced to participate in studies that were dangerous to them because they wanted the money that was promised? In this case, would altruism be laudable even when all factors point to irresponsible decisions that jeopardize human dignity? Is exposing humans to a virus that could affect them negatively—even causing death—the best intervention for COVID-19?

From an ethical perspective, this paper argues that COVID-19 challenge studies are unacceptable based on existing research on human person regulations, Christian views of human dignity, and biblical instructions on treating humans.

Method

This documentary study employed the available literature on human challenge studies. Data from the literature were analyzed to obtain recurring themes and presented as a narrative. The method chosen was based on the aim of the study, that is, to identify strengths, weaknesses, opportunities, and threats already published in relation to challenge studies.

Strengths and Opportunities of Human Challenge Studies

Strengths

One of the strengths of using a controlled human infection model as an intervention against COVID-19 is that this model has already been tried successfully in the development of vaccines or other diseases, and so is not entirely new in the world of medicine. This remains the most formidable and promising intervention in developing vaccines to treat certain malignant viral diseases. It has been used to treat smallpox, common cold, yellow fever, and malaria (Jamrozik & Selgelid, 2021).

The second strength, discussed by Caplan (2020), is that "the average time to make a vaccine is 20 years starting

from animal models to small-scale safety studies, and then to full, lengthy clinical safety and efficacy trials" (p. 1). The demand for vaccines and the fear of exponential and recurrent infections and fatalities means that the wait for the 'procedural' development of vaccines may not be the best option. This problem is compounded further by the requirement that clinical trials make use of natural infections, while at the same time, all stakeholders are trying their best to keep people from infection (Caplan, 2020). The second most viable option, which Caplan (2020) argues would be best, is called a human challenge study. Hope & McMillan (2004, p. 110) state that human challenge studies are "… intentionally infecting healthy people in order to study diseases and their treatments." Similarly, the Academy of Medical Sciences (2018) defines it as the "… trials that purposely infect human volunteers with infectious agents (known as challenge agents) …" (p. 4); or the "… clinical studies that, as part of the protocol, deliberately expose trial participants to an infectious pathogen" (p. 6).

Caplan (2020) further argued that human challenge studies are recommended, especially in pandemics where death is exponential. It is feared that if a vaccine was not found urgently, COVID infections can recur several times, diminishing any management efforts and exterminating economic and social recovery. Caplan cautioned that challenge studies should enroll only volunteers that have the highest chances of recovery and the lowest chances of death, based on available evidence. According to Caplan, healthy adults within the age range of 20 to 29 years have a 0.03% risk of death and 1.1% risk of hospitalization when infected. However, he noted that a key requirement for challenge studies includes voluntary participation, based on informed consent to ensure that no participant is coerced to enter the study and motivated by altruism to help humanity. Caplan also argued that such risk is not beyond reasonable risk. This is because healthcare workers who treat infected persons face similar risks on a daily basis. Moreso, living donors "… of kidneys and lobes of liver face greater risk than those potentially confronting volunteers for SARS-CoV-2 challenge studies" (Caplan, 2020).

Bambery et al. (2016) argued that human challenge studies are helpful in finding positive interventions for infectious diseases that would otherwise be difficult to control. In their submission, the ethical challenges raised by performing human challenge studies can be addressed by obtaining independent expert reviewers to provide unbiased judgment and guidance. Independent reviews would ensure that investigators do not get the leeway to perform their studies uncensored. They also submit that challenge study investigators need to adopt a publicly available research rationale. In addition, safeguards must be put in place to protect other people who are not in the study from being affected by the infections in the study.

> *In the case of a highly infectious, highly lethal pandemic, we also believe there may be good and*

> *acceptable reasons to conduct rapid challenge studies of highly promising vaccines in an experimental setting. In this way, challenge studies are different from nontherapeutic research—the threat to large numbers of currently unaffected people can be much higher than in, say, cancer or motor neuron disease. Since pandemics represent a continuing, if not increasing, threat to global welfare, the issue of which principles of evaluating risk in challenge studies increases in importance… (Bambery et al., p. 98)*

The idea emphasized here, especially concerning COVID-19 challenge studies, is the severely reduced alternatives of interventions in a highly lethal situation, raising the need for desperate measures to be taken. In addition, the use of a few volunteers with the expectation of success in the trial is noteworthy. Only a few people would have been exposed if the results were lethal. This is the case, especially when comparing challenge studies with the requirement of phase I studies that usually require a significant number of participants to test the toxicity, efficacy, and even maximum tolerated doses of certain drugs. It could be argued, by proponents of challenge studies, that if phase I trials are acceptable, then there should never be a problem approving human challenge studies, because they operate within the same risk level.

It has also been argued that one strength of challenge studies is that it depends on participants' voluntarism. They argue that "it is they, that are willing to participate" (Jamrozik & Selgelid, 2021, p. 2). Some are motivated by altruism, while others are motivated by the research payment they anticipate. Either way, the participants entered the study voluntarily, neither forced nor pushed. Proponents of this view argue that as long as informed consent is validly documented and the participants are willing, motivated by altruism, and desire to help the community, their participation, whether dangerous or not, cannot become a problem for researchers.

It has also been argued that human challenge studies are preferred when the benefit-versus-risk ratio is favorable to general society, promising medical success in dealing with ailments affecting many people. Risks to the research participants should be weighed against the benefits to both the participants and the concerned community (WHO, 2000). Challenge studies are usually performed only when the promise of benefits outweighs the existing risks.

Opportunities

Certain opportunities exist that raise the need to have challenge studies. First, Bambery et al. (2016) argued that human challenge studies promise to generate crucial scientific knowledge, some of which have no satisfactory alternative. In such cases, it would become ethically necessary to perform human challenge studies, and failing to do so would amount to denying the many would-be sick people an opportunity to find vaccines and treatments. This opportunity

is supported further by The Academy of Medical Sciences (2018), provides an example of challenge studies used to control tuberculosis.

> *Professor Helen McShane, Professor of Vaccinology, University of Oxford described work on developing an attenuated, labeled genetically modified TB strain for use in studies. There is an urgent need for more effective tuberculosis vaccines, but efforts have been hampered by the poor predictive value of animal models and a lack of understanding of the correlation between the immune response and effective protection. As such, an attenuated strain is desirable to allow vaccines to be effectively tested without putting people at significant risk. She presented her research in taking the Bacillus Calmette-Guérin (BCG) vaccine, which provides variable protection against tuberculosis, and using it to develop an experimental model of mycobacterial infection through intradermal or aerosol challenge. The successful development of this model will be used to test new vaccines against TB.(p. 13)*

The example of tuberculosis vaccines discussed above depicts a scenario in which challenge studies represent an opportunity to solve medical problems without alternatives. The strength of this specific challenge study was its ability to develop an attenuated strain that allowed for controlled infection. It was also important because the only available alternatives to getting this vaccine and scientific information, the use of laboratory animals, was unhelpful for this case, leaving challenge studies as the only alternative for this study. Challenge studies on COVID-19, especially when there are challenges in finding workable alternatives, can be treated as opportunities to address the pandemic.

In addition, the availability of funding for this field is earmarked. The Academy of Medical Sciences (2018, p. 4) reported that CHIM studies have significant investment available from sources such as "Welcome, the Medical Research Council, the Bill & Melinda Gates Foundation, and Horizon 2020," which are the leading sponsors of manifested endemic, pandemic, and emergent infectious disease research activities in the world. The opportunity is already there for human challenge studies, something which is lacking in other studies. This also means the scientists would be failing the expectant sick people, especially in the world ravaged by COVID-19, and with nations breathlessly waiting for experts to come up with a solution. Thus, in the interest of patients, which is a doctor's mission call, scientists cannot ignore the opportunities available for CHIM studies.

Human challenge studies are among the available interventions for COVID-19 and other infectious diseases, which promises a great chance of success, should all factors be safe for the participant. Regardless of how many models are made available, challenge studies stand out as one of the options available, should the desire be to attempt it. This is especially

so in endemic zones, where the balance of probability works out so that people have a higher chance of being infected anyway, as Bambery et al. (2016) point out:

> *Alternatively, challenge studies conducted in endemic areas—where volunteers have a high chance of becoming infected with a particular disease in the wild regardless of their involvement in the research, and where the research is especially relevant to local community interests— should be considered more ethically justifiable in terms of volunteer risk-benefit analysis. (p. 99)*

It follows therefore, as Bambery *et al* (2016) aver, that if in COVID-19 endemic areas the danger of contracting the contagious diseases is high, it could be argued that human challenge studies are ethically required.

Weaknesses and Threats of Human Challenge Studies

Weaknesses and Threats

A notable weakness of human challenge studies is their association with the Guatemala sex study (Palacios & Shah, 2019). In this study, the researchers infected female city prostitutes with sexually transmitted diseases (gonorrhea or syphilis) on purpose, to get a chance to understand the pathogenesis of the agents used. The endpoint was to find a vaccine that could be used to control this disease. Although the researchers knew how this study was going to be devastating to the health and families of the participants, the form of deception used was not flexible enough to allow control of this infection. The researchers thereby allowed collateral damage to participants and their families to get the scientific information that was "very important to the society" at that time. (Zenilman, 2013). This was a major setback in the development of challenge studies, which stands as a landmark research misconduct. It was embarrassing that it took the president of the United States to deliver an official apology (Tanne, 2010).

Bamberly et al. (2016) observe that challenge studies must involve volunteers with self-limiting diseases or pathogens that cause diseases that have treatment and can be controlled. This is one way of ensuring the safety of the volunteers involved. One weakness of challenge studies related to COVID-19 is the absence of treatment. How would the safety of volunteers be assured, and should the virus injected into the systems of healthy volunteers refuse to die? What would be the effect of viruses remaining malignant in their sperm? Challenge studies should first seek treatment for the COVID-19 virus using other means, and once they are assured of this, they can progress to induce the pathogens into the systems of healthy volunteers.

Savulescu and Hope (2010) observed that exposing volunteers to certain risks is usually acceptable, even those that have no benefits to them. However, they indicated that these risks must not compromise the health of volunteers. Another weakness of challenge studies related to COVID-19 is that it endangers the health of a study volunteer, in total disregard of the third

paragraph of the Declaration of Helsinki which states: 'The health of my patient will be my first consideration.' The International Code of Medical Ethics states,' A physician shall act in the patient's best interest when providing medical care' (World Medical Association [WMA], 2015). How then can a physician-cum-scientist be convinced that challenge studies are in the interest of the patient-volunteer? Challenge studies expose volunteers to nontherapeutic studies without the guarantee of helping anyone.

The third weakness of challenge studies on COVID-19 is that there is no direct benefit that the participants receive. Although Jenner and Philip's case with cowpox inoculation would be a reference point in challenge studies, it is also important to note that COVID-19 volunteers would not receive any personal benefit, especially because only healthy volunteers would be needed. The motivation to participate would be altruism, or monetary, but not the prospect of treatment from any disease (Bambery et al., 2016).

One threat to performing human challenge studies during the COVID-19 pandemic was the possibility of abuse. According to Cohen (1990), challenge studies have been abused in the past. For instance, during World War II, serious atrocities were created against Jewish populations that were already vulnerable due to their imprisonment. They were infected with live bacteria (tubercle bacilli) to determine how the pathogens would progress and observe tuberculosis pathogenesis to develop vaccines, which the Germans desperately needed for their soldiers in war. In this study, more than 200 study participants died (Bambery et al., 2016, p. 1).

Conclusion and Way Forward

The ultimate concern of Christian ethics is to guide humans in making decisions and judgments about specific actions in specific situations and ultimately positively influence human behavior in all aspects of being. Questions on goodness, happiness, right and wrong, and how one ought to act are always guided by ethics. Therefore, the question of what makes an act wrong or right is based on Christ's teaching. Teleological and deontological theories are also applied from the perspective of God. The wrongness or rightness of an act is determined by the goal or rule, both of which are guided by the command of love given by Christ: to love God and love humanity. It should also be noted that the object, circumstances, and end (intention) make an act bad or good.

The object of an act is the effect that it primarily and directly causes. It is the always necessary effect of an act independent of any circumstances or intention of the moral agent. The circumstances are those particulars of concrete human acts that are necessarily connected to its object. The end refers not to always and the necessary effect of an act, but to the intention of the moral agent (end of the moral agent) as well as the intention/end of an act. For Christians, the ultimate end is the glory of God. To evaluate the morality of an act, it is not sufficient to look at the ends,

circumstances, or objects. All three factors must be considered.

It has been presented that human challenge study is a promising field, with evidence of success in finding vaccines of other diseases and epidemics such as, smallpox, common cold, malaria and yellow fever. However, it is important to note that the risks were managed so that the volunteers developing unexpected, severe, or life-threatening complications received available curative treatment (Bambery et al., 2016). COVID-19 would be a different scenario because there is no treatment available for volunteers should they become very sick.

Arthur Caplan argues that human challenge studies with COVID-19 are within the required minimal risk because medical personnel are always at risk of contracting the virus each time they work in the medical facility. This last argument is, however, incorrect. The accurate meaning of minimal risk is expressed by the US Code of Federal Regulations, 45 CFR 46 (1991), as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons" (as cited in Kopelman, 2004, p. 368). In that respect, therefore, Caplan's argument that exposing healthy volunteers to a COVID-19 virus would be minimal risk is, in fact, incorrect and baseless,because the harm would be more than what a healthy person encounters in daily life. Bambery et al. (2016) suggest making the levels for theconsiderations of risks even higher:

> *Though we believe challenge studies should generally adhere to the same stringent ethical standards as seen in other areas of medical research, we advocate setting higher levels of reasonable risk for challenge studies compared to other nontherapeutic research (which in some jurisdictions is not permitted for research involving greater than 'minimal risk', which is sometimes exceeded in challenge studies). (p. 92)*

It has been presented earlier, that one strength of human challenge studies is that it is an act of own volition, and that no one is forced or required. Proponents of this view, base their arguments on the process of informed consent, which they administer 'well.' Thus, they submit that their participants entered the study out of pure altruism and social responsibility. Hope and McMillan (2004), however, observed that voluntarism cannot be used as an excuse to perform dangerous experiments on people. They argue that, in law, causing harm to other people and consenting to harm oneself are viewed as being similar and punishable in the same way. They assert:

> *The original meaning of mayhem (which is cognate with the word maim) was "the crime of violently inflicting a bodily injury upon a person so as to make him less able to defend himself or annoy his adversary." Inflicting such bodily injury was a crime, in medieval England, even if the victim gave*

> *consent for the bodily injury, or indeed, even if he requested it (p. 111).*

Hope and McMillan (2004) thus affirmed that altruism cannot be used as an excuse to cause harm to participants, as this would violate their rights, even if informed consent was validly documented. Thus, altruism, informed consent, and voluntarism cannot be used as bases for exposing healthy volunteers to studies that are dangerous to their lives.

One strength of human challenge studies is that the benefits outweigh the risks, especially when the benefits to society are more crucial than the risks to the individual. This requires a constant calculation of risks and benefits, with the suggestion that individual risks can be endured to give way to benefits that improve scientific knowledge and help society as a whole. Challenge studies are usually performed when the promise of benefits far outweighs the existing risks. Hope and McMillan (2004), however, warn that researchers should not become overexcited about the benefits of any study to the general society at the expense of study participants. They assert:

> *In weighing up the potential good that the research might bring to people in the future against the potential harm to participants, concern about the welfare of participants is given very much greater weight. Because of the origins in the Nuremberg code, the central concern of research guidelines is to ensure that the interests of society, or the enthusiasm of the researcher, do not override the interests of the individual participants (p. 110).*

Thus, participating in a non-therapeutic medical procedure is unacceptable in medical ethics. Even in surgery, it would mean that non-therapeutic operations are not justifiable in any way and should not be used as support for human challenge studies. Informed consent, though validly obtained, would not be sufficient, and the physician performing such procedures would be liable for an offense in a court of law, especially if the participant dies in the process. (Hope & McMillan, 2004)

It has been shown that one motivation for human challenge studies is its being better than Phase I trials because of the few possible enrolled participants. In this case, if it becomes dangerous, only a few people are lost in the collateral damage. Moreover, if Phase I trials are acceptable, approving human challenge studies should never be a problem because they operate within the same risk level. This line of reasoning fails the Hippocratic Oath sworn by doctors to protect the lives of their patients and not put at risk the life of any of them, whether or not the gain would be good for society. This argument also fails with the Kantian principle of ethics. Thus, Kantianism argues that humans should not be treated simply as a means but always at the same time as an end. Therefore, every actor should act like a legislating member, always acting based on what life would be if those actions were common rules universally.

It has also been noted that a great opportunity exists in human challenge studies because of the available funding from various leading research donors. I am convinced that the availability of funds for challenge studies is partly motivated by the skewed promotion of challenge studies as a quick-fix mechanism to address a desperate situation. I argue that it is unethical for the research community to present human challenge studies as an available option, thus drawing donors to earn their funds for challenge studies. To the best of my knowledge, donors are not always experts in the field of medicine. However, they are attracted by the campaign, especially by leading scientists who have won funds in the past and who provide a glimmer of hope, even the slightest light at the end of the tunnel. Once these research teams have successfully skewed their funding promotion towards challenge studies, they base their motivation to perform human challenge studies on available funds (Jamrozik & Selgelid, 2021).

References

Bambery, B., Selgelid, M., Weijer, C., Savulescu, J., & Pollard, A. J. (2016). Ethical criteria for human challenge studies. *Public Health Ethics, 9*(1), 92-103.

Caplan, A. (2020, May 14). *Is it ethical to give someone coronavirus to create a vaccine? Yes.* https://www.bostonglobe.com/2020/05/14/opinion/is-it- ethical-give-someone-coronavirus-create-vaccine-yes/

Cohen, B. (1990). The ethics of using medical data from Nazi experiments. *Journal ofHalacha and Contemporary Society, 19*, 103–126.

Durbin, A. P., & Whitehead, S. S. (2017). Zika vaccines: Role for controlled human infection.

The Journal of Infectious Diseases, 216(S10), S971–75.

Eyal, N., Caplan, A., & Plotkin, S. (2022). COVID vaccine efficacy against the B.1.351 ("South African") variant—The urgent need to lay the groundwork for possible future challenge studies. *Human Vaccines & Immunotherapeutics, 18*(1). https://doi.org/10.1080/21645515.2021.1917240

Eyal, N., Lipsitch, M., & Smith, P. G. (2020, June 1). Human challenge studies to accelerate coronavirus vaccine licensure. *The Journal of Infectious Diseases, 221*(11), 1752–1756.https://doi.org/10.1093/infdis/jiaa152

Hope, T., & McMillan, J. (2004). Challenge studies of human volunteers: Ethical issues.

Journal of Medical Ethics, 30, 110-116.

Jamrozik, E., & Selgelid, M. J. (2021). *Human challenge studies in endemic settings: Ethical and regulatory issues.* Springer.

Kopelman, L.M. (2004). Minimal risk as an international ethical standard in research. *The Journal of Medicine and Philosophy*, *29*(3), 351-378. https://doi.org/10.1080/03605310490500545

Palacios, R., & Shah, S. K. (2019). When could human challenge trials be deployed to combat emerging infectious diseases? Lessons from the case of a Zika virus human challenge

trial. *Trials, 20 Supplement 2*(1), 1-8. https://trialsjournal.biomedcentral.com/articles/supplements/volume-20-

Savulescu, J., & Hope, T. (2010). The ethics of research. In J. Skorupski (Ed.), *Routledge Companion to Ethics* (chapter 65*).* Routledge.

Tanne, J. H. (2010). President Obama apologises to Guatemala over 1940s syphilis study. *BMJ (Clinical Research Ed.)*, *341*, c5494. https://doi.org/10.1136/bmj.c5494

The Academy of Medical Sciences. (2018). Controlled Human Infection Model Studies: Summary of a Workshop held on 6 February 2018. *The Academy of Medical Sciences*(pp. 1-33). London.

U.S. Code of Federal Regulations, 45 CFR 46 (1991). Federal policy for the protection of human subjects. (The Common Rule.) *Federal Register*, 56, 28003–28016.

World Health Organization. Product Research and Development Team. (2000). *Operational guidelines for ethics committees that review biomedical research*. World Health Organization. https://apps.who.int/iris/handle/10665/66429

World Medical Association. (2015). http://www.wma.net/en/30publications/10policies/c8/

Zenilman, J. M. (2013). Ethics gone awry: the US Public Health Service studies in Guatemala; 1946–1948. *Sexually Transmitted Infections, 89*(4), 295-300. https://doi.org/10.1136/sextrans-2012-050741