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THE ETHICAL JUSTIFIABILITY OF THE OFF-LABEL USE OF HYDROXYCHLOROQUINE DURING THE COVID-19 PANDEMIC

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Research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree Masters of Science in Medicine in Bioethics and Health Law.

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Qualifications: PhD (Bioethics and Health Law)

15 SEPTEMBER 2025

DECLARATION

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(Student number: *307505_*)

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Date: 15 September 2025

Dedication

I dedicate this master's research report to my late father, Resley Sidma Manentsa, whose faith in God and in me continues to be my guiding light.

To my mother, Martha Nomatiba Manentsa, for her steadfast support, prayers, and wisdom and for being the role model I needed throughout this journey.

And to my children, Wanga and Tshifhiwa Mukwevho, may your light always shine brightly, illuminating the paths you are led to.

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To my supervisor, Dr. Hilde Miniggio, your support and meticulous guidance have been invaluable. Your dedication ensured we reached the finish line. I am profoundly grateful to have had you as my supervisor.

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Finally, Thendo Mukwevho, mbilu yanga, you have been my voice of reasoning during this time. Your support and encouragement have made this achievement possible.

ABSTRACT

Hydroxychloroquine (HCQ) was granted emergency use authorization (EUA) for use in COVID-19 treatment from various health regulatory authorities in the early stages of the pandemic. This EUA led to the widespread use of HCQ during this period, attracting significant media attention and prompting ethical debates as the drug lacked evidence of effectiveness in treating COVID-19 disease. The EUA was later revoked due to emerging scientific evidence showing that HCQ did not provide the anticipated benefit for COVID-19 treatment and raised safety concerns due to its harmful side effects.

The justifiability of the off-label use and temporary authorization of HCQ is normatively analyzed using the moral theory of utilitarianism. It is argued that the risks associated with its widespread use and EUA, including the harm caused to patients, to the medical profession and to society, outweigh any potential benefits. Further analysis using principlism illustrates that patient autonomy was undermined, and the principles of non-maleficence, beneficence, and justice were compromised by the off-label use and EUA of HCQ. Lastly, a virtue ethics analysis demonstrates that the decision by health regulatory authorities to grant the EUA reflects a misapplication of the virtue of compassion and undermined the virtues of prudence, trustworthiness, integrity and justice expected from the healthcare profession and health regulatory bodies.

ACRONYMS

CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HCQ	Hydroxychloroquine
RA	Rheumatoid arthritis
RCTs: Randomized controlled trials	
SAHPRA	South African Health Products Regulatory Authority
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SLE	Systemic lupus erythematosus
WHO	World Health Organization

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CHAPTER 1: INTRODUCTION

1.1 Background

The COVID-19 pandemic created an unprecedented global health crisis, drawing attention to the justification of emergency authorisations and the use of existing drugs beyond their original therapeutic scope and approval, otherwise known as off-label use. This practice of off-label use of medicines, although not new, was considerably intensified during the pandemic by the demand to identify viable treatments against the novel virus, named severe acute respiratory syndrome-coronavirus (SARS-CoV-2) (Manivannan et al., 2021: 1). The healthcare community, including health products regulatory authorities, were prompted to expedite approvals for treatment.

COVID-19, first reported in December 2019 in Wuhan, China, spread rapidly across the globe, with the World Health Organisation (WHO) declaring it a Public Health Emergency of International Concern on 30th of January 2020 (Manivannan et al., 2021: 2). The virus primarily spreads through respiratory droplets, causes clinical manifestations that range from mild symptoms such as cough, fever, sore throat, and fatigue to severe respiratory complications, including shortness of breath, chest pain, and confusion, which require hospitalisation and advanced medical care (Mayo Clinic Staff, 2024).

In the early stages of the pandemic, the limited knowledge about SARS-CoV-2 restrained the development of targeted therapies, as there was no standardised treatment plan for the COVID-19 disease. To curb transmission, public health authorities implemented several measures such as isolation, quarantine, mandatory mask-wearing, social distancing and nationwide lockdowns. Despite these efforts, cases surged, overwhelming hospital resources and leading to shortages of ventilators (Manivannan et al., 2021: 2).

This frantic global search for possible treatments against this poorly understood disease led to the experimental use by healthcare practitioners of existing drugs, otherwise known as drug repurposing or, repositioning or off-label use. I make use of the terms repurposing and off-label interchangeably in this research report.

Off-label use refers to the use of any treatment, whether a medication or device, for a purpose outside the clinical indications approved by the medicine regulatory board and listed in the package insert (Aquino & Cabrera, 2020, p. 575). The medicines considered for off-label use against COVID-19 included Remdesivir, Dexamethasone and Hydroxychloroquine (HCQ), amongst others. These medicines had the advantage of existing regulatory approvals and known safety data, compared to the lengthy process required for developing and approving new medicines. Preliminary research on treatments, specifically HCQ, an affordable and widely available drug for treating malaria and autoimmune diseases, gained significant attention. Public figures, such as the serving President of the United States of America (USA), had endorsed HCQ on social media outlets and in press briefings, referring to this drug as the "biggest game changer in the history of medicine" (Trump, 2020). This consequently led to the extensive promotion of its potential benefits (ABC News*,* 2020),

Furthermore, early published research during the pandemic suggested the potential efficacy of HCQ against COVID-19, prompting some health authorities, such as the Food and Drug Administration (FDA) issue an Emergency Use Authorisation (EUA) for HCQ in March 2020. The granting of the EUA meant that, although solid scientific evidence was lacking at that time, HCQ could still be administered to critically ill patients in the hope of uncovering its benefits while awaiting thorough and reliable scientific validation from larger scale randomised controlled trials (RCTs). This emergency authorization was later overturned by the FDA on 15 June 2020.

Concurrently, in South Africa, the pharmaceutical company Austell donated 500,000 chloroquine phosphate tablets to the Department of Health, prompting the South African Health Products Regulatory Authority (SAHPRA) to expedite the review and approval of chloroquine and HCQ under Section 21 of the Medicines and Related Substances Act (Polity, 2020), an approval which follows a similar process to that of an EUA.

The initial authorisation was made under intense global pressure amid the growing public profile of the disease and the struggle to identify a viable treatment as COVID-19 cases escalated, overwhelming healthcare systems and rising mortality rates.

It is important to note that an EUA relies on 'adequate or low-level scientific evidence', which is often limited to preclinical studies, observational studies, or epidemiological findings (FDA, 2017: 8). Full authorizations are granted based on lengthy and robust randomised controlled trials (RCTs) that are considered the 'gold standard' for approval of medicines (Hariton & Locascio, 2018: 1716). EUA is usually temporary until sufficient scientific evidence becomes available, as this type of authorization is limited to the evidence from the research available at the time (FDA, 2017: 8). Furthermore, an EUA can only be granted during a declared public health emergency; this ensures that during such crises, drugs that do not have full FDA approval can still be used to address urgent public health needs, provided that there is some low-level evidence supporting their benefit (FDA, 2017: 5).

However, many of the early studies suggesting HCQ's clinical efficacy were of disputable scientific and methodological quality with confounding biases and misrepresentation (Ingraham & Tignanelli, 2020: 1). As further results emerged from RCTs showing no clinical benefit and an increased risk of adverse events, both the FDA and SAHPRA revoked the EUA for off-label use of HCQ for COVID-19 (Lee et al., 2021: 37).

These conflicting regulatory decisions raise the question of whether the hasty EUA for off-label use of HCQ was a justified response to an urgent crisis or an ethically unsound decision that compromised evidence-based medicine and patient welfare.

In this research report, I focus on the ethical justification for the temporary authorization for repurposing HCQ for cases of severe COVID-19 symptoms, as this is the controversial decision which was later revoked by both the FDA and SAHPRA. This focus highlights the ethical challenges that the healthcare community and regulatory authorities had to navigate to balance the rapid response expected in the context of a public health emergency, with the obligation to ensure decisions are made based on robust scientific evidence and to ensure patient safety. The decision for the initial EUA was taken based on limited scientific evidence in the hope of providing alternative treatments during a critical period. However, this authorization was ultimately revoked on the basis of inadequate results which were emerging from the more comprehensive RCTs which indicated a lack of efficacy of HCQ against COVID-19 disease and the potential harm. This sequence of events underscores the dynamic and complex decision-making processes that are required in public health emergencies, where the urgency to address immediate global health threats must be carefully weighed against the obligation to unsure patient safety and maintain scientific integrity.

1.2 Thesis Statement

I argue that the off-label use and emergency authorization of hydroxychloroquine (HCQ) by health authorities during the COVID-19 pandemic was ethically unjustified.

1.3 Research Question

Was the off-label use and emergency authorization of hydroxychloroquine (HCQ) during the COVID-19 pandemic by regulatory authorities ethically justified?

1.4 Rationale for the study

This research report is prompted by the ethical dilemmas created by the controversial decision of health regulatory authorities to prematurely authorize the repurposing of HCQ during a time of great uncertainty of the pandemic. The rapid shifts in regulatory decisions reveal tensions between the urgent need to explore potential treatments during a massive health crisis with the obligation to prioritise patient safety. This premature authorization also brings to light the need to strike a balance between adequate informed consent, equity and fairness in the access and distribution of health resource during states of crises. Moreover, ethical concerns are raised in respect to the influence that social attention and intense media interest in a particular disease, such as COVID-19 disease has on the decision-making of health authorities, regulatory integrity, and public trust (Lee et al., 2021: 37).

This research report brings to light the ethical responsibilities of health authorities in guiding the public and the medical profession in the appropriate and safe use of experimental and off-label medications. This study addresses the gap in the existing literature by critically evaluating the decisions of health authorities, with a specific focus on the temporary authorisation by SAHPRA and the FDA for off-label use of HCQ and it offers recommendations for possible future public health crises.

By examining the ethical justifiability of HCQ's temporary approval and its off-label use, this research contributes to the broader discourse in bioethics that highlights the need to balance a rapid response during a public health emergency s with the obligation to ensure patient safety through evidence-based and ethically-sound regulatory decisions. Finally, the findings in this

research report aim to inform policy decisions and enhance the preparedness of health regulatory bodies and health systems in adequately managing EUAs for drug repurposing for possible future public health crises.

1.5. Thematic overview of the literature

The off-label use and EAU for HCQ during the preliminary phases of the COVID-19 pandemic sparked significant ethical debates, with several authors providing a critical assessment of the ethical implications that resulted from this rushed authorization.

For instance, Aquino and Cabrera (2020: 574) argue that the high "public profile" of COVID-19 disease may have pressured some scientists, healthcare practitioners as well as political leaders to aggressively promote the off-label use of HCQ despite the limited scientific evidence available at the time regarding its therapeutic benefit. This intense social pressure may have, in turn, unduly influenced health regulatory authorities to provide premature emergency authorisation for HCQ to be repurposed and added to the arsenal of potential treatment for the COVID-19 disease. The authors also bring to light the dangers associated with the "heightened public profile" of a disease such as COVID-19, in worsening health inequalities and undermining three key ethical elements, which are "evidence-based practice, sustainable allocation, and meaningful consent" (Aquino & Cabrera, 2020: 574). They conclude that it is essential to balance urgency with equity as some medical conditions risk being neglected and ethical concerns dismissed as resources and attention is diverted towards the disease with the highest public profile, in this case, COVID-19 (Aquino & Cabrera, 2020: 577).

Similarly, Reese (2021) critiques the repurposing HCQ for COVID-19 treatment that caused unjustified shortages of the drug affecting those patients who depended on HCQ for chronic

autoimmune conditions, for which its benefits are well established, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). She addresses the ethical challenges that resulted from the shortages of HCQ created as a direct result of the EUA for off-label use, emphasising on the principle of distributive justice, which focuses on a fair distribution of scarce resources (Reese, 2021). She concludes that in the absence of sound clinical evidence supporting the efficacy of HCQ for COVID-19 disease treatment, prioritizing its use for approved indications is ethically imperative in upholding fairness and equity in healthcare resource allocation during pandemics (Reese, 2021).

Likewise, Dhupkar and Mukherjee (2021), show that the approval of HCQ for compassionate use for treatment against COVID-19 disease was not supported by sufficient scientific evidence. Given that the early results from clinical trials failed to demonstrate the efficiency of HCQ against COVID-19, coupled with the well documented and significant side effects associated with its use, outweighed any potential benefits (Dhupkar & Mukherjee, 2021). Ultimately, the lack of proven therapeutic or scientific evidence associated with the use off-label use of HCQ in the treatment of COVID-19 disease, led to the compassionate use and EUA being revoked by various health regulatory authorities (Dhupkar & Mukherjee, 2021).

Additionally, Shojaei and Salari (2020) provide a similar ethical argument that criticizes the repurposing of drugs, including HCQ during the COVID-19 pandemic. Their analysis focuses on the ethical implications that arise from using unproven treatments in emergencies. They elaborate on how the rushed response to the global emergency directly led to the widespread use of repurposed drugs like HCQ and Remdesivir despite the lack of solid clinical evidence or reliable scientific studies supporting their efficacy as a treatment modality for COVID-19 disease. Drawing on principlism, the authors caution that, although emergencies may indeed require more flexibility, nonetheless healthcare professionals must still carefully evaluate the

risks associated with the off-label use of drugs in the absence of clear and robust evidence (Shojaei and Salari, 2020). The authors conclude by recommending a more structured and justified approach to the off-label use of medicines during states of emergency states, ensuring that patient safety and scientific integrity are not compromised by the rush to respond (Shojaei and Salari, 2020).

In contrast, El Rhazi and Adarmouch (2020: 3) argue that the decision to temporarily authorise the off-label use of HCQ was in fact justified, given that the early scientific studies showed promising results which provided a sufficient initial rationale for its off-label prescription. Furthermore, they consider that the long-term safety profile of HCQ in treating other diseases such as chronic autoimmune diseases and malaria, provided the necessary justification in the context of the rapid spread of the virus and considering the rates of mortality and morbidity (El Rhazi & Adarmouch, 2020: 3). They also draw an interesting parallel between the EUA for drug repurposing during the pandemic and similar historically significant and effective treatments and discoveries such as penicillin and the smallpox vaccine, which were initially used by healthcare practitioners based on limited observational studies rather than the current gold standard of RCTs (El Rhazi & Adarmouch, 2020: 3). They consider that the off-label use of HCQ could have shown similar beneficial results which justified the decision (El Rhazi & Adarmouch, 2020: 3).

1.6. Aim and Objectives

1.6.1 Research Aim

The aim of this study is to critically evaluate and defend the claim that the off-label use and emergency authorisation of hydroxychloroquine (HCQ) during the COVID-19 pandemic was ethically unjustified. This will be achieved by applying established ethical frameworks,

including utilitarian theory, principlism, and virtue ethics, while assessing regulatory decisions, scientific evidence, and patient safety considerations.

1.6.2 Research Objectives

1. To defend the claim that the off-label use of hydroxychloroquine (HCQ) in COVID-19 patients failed to prioritise patient safety, given its well-documented side effects, some of which are potentially fatal. This evaluation is be guided by the ethical principles of non-maleficence (avoiding harm), beneficence (promoting well-being), and justice (ensuring fair distribution of health resources).
2. To argue that the decision-making process behind HCQ's emergency off-label authorisation was not in the public's best interest, as it relied on insufficient scientific evidence, resulting in poor patient outcomes. This claim will be supported by utilitarian theory (evaluating consequences and minimising harm), principles of biomedical ethics (focusing on beneficence, non-maleficence, autonomy, and justice), and virtue ethics (utilizing the virtues of compassion, prudence, trustworthiness, integrity and justice).

1.7 Research Design

This study thoroughly evaluates existing literature, drawing from peer-reviewed journal articles, textbooks, regulatory policy documents, and ethical frameworks. A qualitative, analytic approach is employed, emphasising the interpretation of moral theories and the application of theoretical frameworks to the research question. Arguments will be substantiated with evidence from published studies and official reports from reputable organizations such as the World Health Organization (WHO) and the USA. Food and Drug Administration (FDA).

1.8 Research Methods

This study adopts a qualitative, literature-based approach with no new data collection, as it focuses on normative ethical analysis. The research relies on secondary sources such as journal articles, policy documents, textbooks, official government reports, ethical codes of conduct, and relevant legislation. These sources are critically analysed to explore the ethical implications of the off-label use and EUA of HCQ during the COVID-19 pandemic.

Key databases and sources include PubMed, ResearchGate, government health department websites, and academic library repositories. The study reviews peer-reviewed articles, policy guidelines from international regulatory bodies such as the WHO and the FDA, and expert commentary from ethicists and healthcare professionals.

The analysis applies relevant ethical frameworks, including utilitarianism, the principles of biomedical ethics (beneficence, non-maleficence, autonomy, and justice), and virtue ethics, ensuring a comprehensive evaluation of the regulatory decisions made in respect to the EUA for the off-label use of HCQ during the COVID-19 pandemic.

Keywords for literature searches: Unlicensed drugs, Off-label drug use, Drug repurposing, COVID-19, virtue ethics, hydroxychloroquine, utilitarian, emergency use authorisation, ethics, principles, compassionate use.

1.9 Argumentative strategy

To defend my thesis that the off-label use and temporary authorisation of HCQ for COVID-19 treatment was ethically unjustified, I adopt a multi-theoretical argumentative strategy grounded in key ethical frameworks: utilitarianism, principlism, and virtue ethics.

1.9.1. The Theory of Utilitarianism

From a utilitarian perspective, healthcare providers and health regulators have a moral obligation to mitigate risks and maximise overall well-being. The risks posed by the off-label use and emergency authorisation of HCQ to patients, the healthcare professions and society outweighed the initially anticipated benefits.

I argue that health practitioners and health regulators failed to conduct a credible risk-benefit assessment, violating the utilitarian principle of maximising public health outcomes.

1.9.2. Principles of Biomedical Ethics

The principles of biomedical ethics, autonomy, beneficence, non-maleficence and justice advanced by Beauchamp and Childress (2013) are analysed in the context of the research question.

The principle of respect for autonomy, which requires that patients are fully informed about the treatment's risks, benefits and experimental nature, was restricted by the conflicting scientific information and regulatory decisions, the urgent nature of the disease and aggressive media coverage. The lack of adequate and transparent information sharing regarding repurposing of HCQ for critically ill cases of COVID-19 had a negative impact on the ability of these patients to make valid and well-informed healthcare decisions.

The principle of beneficence, which emphasises that healthcare practitioners and healthcare authorities are expected to always act in the best interest of the patients, was similarly undermined by the off-label use and rushed EUA for HCQ. The EUA decision was taken prematurely in the absence of credible scientific evidence which failed to provide overall benefit to patients.

The principle of non-maleficence was also compromised. This principle requires that the harms associated with the off-label use and EUA are not disproportionate to its overall benefits. The widespread off-label use and EUA of HCQ posed significant and preventable harm to patients with severe COVID-19 disease. The harm also extended other patients that relied on HCQ for the treatment of chronic autoimmune conditions for which the indications are approved and the benefits are well established. What is more, the off-label use and EAU for HCQ damaged the credibility of the healthcare profession and eroded the trust in health regulatory authorities.

Lastly, the principle of justice was undermined by the EAU for HCQ. This principle demands the fair distribution of health resources as well as fair access to medications and treatments. The widespread use and clinically unproven off-label prescription and use of HCQ for patients with severe COVID-19 disease, unjustly diverted essential resources away from patients who needed this medication to treat and/or maintain their autoimmune diseases, which caused further disparities in patient outcomes.

1.9.3. Virtue ethics

This ethical theory emphasises the importance for healthcare professionals to develop a virtuous character through a set of virtues that ensures excellence in healthcare practice and delivery. The virtues of compassion, prudence, integrity, trustworthiness and justice should be exercised in every health-related decision. The EUA decision by health regulatory authorities for the off-label use of HCQ reflects a misapplication and misalignment with the virtues of compassion and prudence by prioritising expediency over scientific reasoning. Lastly, the hasty decision which may have been unduly influenced by political and public pressure, contradicts the virtuous conduct expected from health regulatory bodies and health professionals that should centre on trustworthiness and integrity.

1.10. Outline

The main aim of this research project is to argue that the off-label use and EUA of HCQ was ethically unjustified. To achieve this, I begin in chapter two by exploring the characteristics of HCQ, including its various applications, risks and benefits, as well as its off-label use during the pandemic. I then highlight the role of media attention and the public profile of the COVID-19 disease in potentially influencing health authorities in their decision to approve its emergency off-label use.

In chapter three, I build on this foundation and apply a utilitarian perspective to show that the harms posed to patients, the healthcare profession, and society by the widespread off-label HCQ use and its emergency authorisation far outweighed any potential benefits. In chapter four, I evaluate whether the decision to temporarily authorize the off-label use of HCQ and its subsequent widespread use respected the principles of biomedical ethics and show that it did not.

Finally, in chapter five, I critique the lack of virtuous leadership, which failed to embody the virtues of compassion, prudence, integrity, trustworthiness and justice expected from healthcare professionals and health regulatory bodies during the decision-making process for the off-label use and authorisation of HCQ. I conclude in chapter six that the off-label use of HCQ was not ethically justified and present the recommendations that emanate from this study.

1.11 Ethics

This study is a normative ethics project based on a critical analysis of existing literature. Formal ethical approval is not required since no human or animal subjects are involved, since a secondary data analysis has no inherent risk, a waiver of ethics may be required for publication. The research focuses solely on evaluating ethical principles and decision-making

frameworks related to the off-label use of HCQ during the COVID-19 pandemic.

1.12 Limitations

A key limitation of this study is the limited availability of South African-based literature on the off-label use of HCQ and similar emergency drug authorisations. Most existing research and case studies on this topic are drawn from international contexts, particularly the US and Europe. This may restrict the study's ability to provide region-specific recommendations and insights into South Africa's healthcare regulatory responses during the COVID-19 pandemic.

CHAPTER 2: BACKGROUND TO THE OFF-LABEL USE OF HYDROXYCHLOROQUINE

2.1. Introduction

I begin this chapter by providing an overview of the off-label use and authorisation process involved in repurposing existing medicines. This serves as the foundation for understanding the elements required for a robust clinical trial design, which are essential in the authorisation process. I then provide an in-depth exploration of the characteristics of HCQ, including its various applications, the associated health risks and benefits related to its intended uses (otherwise known as on-label), as well as risks and benefits in the context of the COVID-19 repurposing (otherwise known as off-label). This lays the groundwork for understanding why this medication has become such a prominent and popular contender in the fight against COVID-19 and why it garnered such intense media attention, potentially influencing health authorities to approve its emergency off-label use.

2.2. Off-label use of medications and the product authorisation process

As previously mentioned in chapter one, the off-label use refers to using any treatment, whether a medication or device, for a purpose outside the clinical indications that are approved and listed in the package insert (Aquino & Cabrera, 2020: 575). This repurposing from the originally intended usage can be considered clinically appropriate in those medical conditions for which no other treatment options exist or in cases where the harms of these off-label treatments do not exceed the benefits (Aquino & Cabrera, 2020: 575).

For drugs to be approved, they must undergo a rigorous review process by the country's medicine regulatory board.

The review process for medicines consists of a pre-clinical trial phase conducted in a laboratory setting and a clinical trial phase focusing on safety, dosages and effectiveness in human participants (Hariton & Locascio, 2018: 1716). RCTs are considered the 'gold standard' or 'sound scientific evidence' in approving medicines because they minimise bias through randomisation and control groups (Hariton & Locascio, 2018: 1716). In contrast, studies that do not meet the RCT standards, such as observational studies and non-randomized trials, are less reliable due to potential bias and confounding factors (Hariton & Locascio, 2018:1718).

Once clinical trials are completed, an application for drug approval is submitted to the medical regulatory board, such as the FDA and SAPHRA. These regulatory bodies are tasked with reviewing the clinical data received from various scientific studies and ensuring that the methodology and results of the studies are in compliance with the expected standards and in line with scientific regulations, before approving the drugs for public use (FDA, n.d; SAHPRA, n.d).

In South Africa, SAHPRA has the primary responsibility to oversee that all approved medications meet the expected safety, efficacy, and quality standards before reaching the public (SAHPRA, 2023). SAHPRA, mandated by the Department of Health, functions under the following Acts, Medicines and Related Substances Act 101 of 1965 (as amended) and the Hazardous Substances Act 15 of 1973.

SAHPRA's mission is to "promote access to health products and protect human and animal health in South Africa through making science-based regulatory decisions" (SAHPRA, 2025: n.p)**.** This mission reinforces the regulatory bodies' commitment to provide ethical oversight, ensure patient safety, as well as ensure evidence-based policymaking in public health. Furthermore, SAHPRA has an ethical responsibility to certify that all products and interventions are safe and accessible to all patients, while adhering to fundamental ethical principles. Its mandate extends to the promotion of public health and safety measures by ensuring that all approved medicines provide net benefits without posing undue risks to the population (SAHPRA, 2021).

Another key responsibility of SAHPRA's is the post-market surveillance, which involves the following elements below:

- Monitoring adverse drug reactions and taking corrective actions when safety concerns arise.
- Recalling unsafe products when post-approval data indicate risks.
- Enforcing strict quality controls to prevent low-quality or counterfeit medicines from entering the market.
- Ensuring equitable access to essential medicines, particularly for low-income populations (SAHPRA, 2021).

Similarly, in the USA, the FDA is responsible for the regulations of all medical products, following a set of stringent scientific and ethical procedures and guidelines to safeguard public health. The FDA is one of the most influential regulatory agencies globally, operating under the Federal Food, Drug, and Cosmetic Act (FDCA) which was enacted in 1938 (FDA, 2018). The FDA has various global partnerships with various organisations, amongst others, the European Medicines Agency (EMA) and the WHO that aim to harmonise regulatory standards worldwide (FDA, 2018).

Both the FDA and SAHPRA are responsible for the protection of human health through scientifically sound drug approval processes (FDA, 2018; SAHPRA, 2021). Their core ethical responsibility is to ensure that pharmaceutical interventions are safe, effective, and of high quality (FDA 2018; SAHPRA, 2025), thus upholding the principles of beneficence, non-maleficence, justice, and transparency in regulatory decision-making.

As a result of these above-mentioned regulatory processes, all approved medications are required to contain package inserts or drug labels that provide detailed information about the drug, such as the available dosage strengths, the medical conditions for which the drug is approved, and potential side effects, amongst others. This is referred to as the on-label use of a drug, in other words its use for approved conditions (FDA, n.d).

These approvals can vary from country to country, as each nation has its own independent medicine regulatory board. This is why a drug might be available and approved for use in one country but unavailable or not approved for specific uses in another. For example, the current popular drug, Semaglutide, also known as Ozempic, was originally manufactured for diabetes treatment and was approved by the FDA in 2017. It was later discovered that one of its side effects was that it reduced cravings and aided with weight loss. The FDA subsequently approved it as a weight loss drug in 2021 (FDA, 2021). In contrast, in South Africa, SAHPRA

has only approved Ozempic for diabetes treatment. Despite this, South African healthcare practitioners prescribe Ozempic for weight loss, which constitutes an off-label use of the drug (SAHPRA, 2024).

Notably, the FDA plays no role in off-label use and provides no recommendations for innovative medical strategies, including off-label drug use. The American Medical Association provides support for the off-label use of medicines, stating that such innovations should be guided by "sound scientific evidence and expert medical judgment" (Dresser & Frader, 2009: 4; Aquino & Cabrera, 2020: 575). In South Africa, SAPHRA provides guidance on the off-label use of medications but does not regulate this practice. It is important to note that off-label prescribing of medications carries both risks and benefits, which I discuss in greater detail in the section below.

2.3 Risks and benefits associated with off-label use of medicines

I first explore the benefits of off-label use, then move on to explain the risks and provide an analogy with thalidomide, a historical drug that was prescribed off-label and had drastically negative health consequences.

Off-label use offers several benefits, including expanded treatment options for patients. This is particularly valuable in cases where a patient has exhausted all available approved medications yet still requires medical care. Off-label use of drugs is common and helpful in rare diseases or oncology for example, where a chemotherapy drug approved for one type of cancer might be prescribed off-label for another type due to similarities in the disease profiles (Trapani, 2024). The flexibility to use drugs off-label based on the clinical need of individual patients can have a positive impact on survival rates and improve the quality of life for patients. Furthermore, off-label prescribing of medication provides the opportunity for healthcare practitioners to use

their clinical judgment and experience beyond the constraints of on-label indications. This flexibility also allows healthcare practitioners to tailor treatment plans according to the needs of individual patients by adjusting dosages, selecting alternative forms of medication, or combining different therapies. Importantly, off-label use is particularly beneficial for managing patients that suffer from multiple coexisting conditions, thereby balancing efficacy and safety in complex cases based on emerging medical evidence.

A pertinent case in point of off-label use is the popular drug Ozempic. Emerging evidence suggests that Ozempic may assist with fertility, particularly in women that's suffer from polycystic ovarian syndrome (PCOS) (Wisner, 2024). Female patients that struggle with fertility and have also been diagnosed with PCOS can be treated with Ozempic off-label as a fertility treatment alongside the standard care (Wisner, 2024).

While the use off-label medication is useful in offering patients expanded treatment options, it nonetheless comes with associated challenges and risks. This is particularly true in cases where there is insufficient evidence regarding the drug's off-label use. Using drugs off-label can expose patients to ineffective or potentially harmful treatments.

A notable historical example of the dangers of off-label use of medicines is the drug Thalidomide, which was first manufactured in Germany in the 1950s as a sedative or tranquilizer and was initially considered safe (Vargesson, 2015:140). An Australian obstetrician began prescribing thalidomide off-label as a remedy for morning sickness in pregnant women, and this practice soon gained popularity in many countries (Vargesson, 2015: 140). However, it was later discovered that Thalidomide caused miscarriages and severe congenital disabilities, such as limb deformities and blindness (Kim & Scialli, 2011). By 1962, thalidomide was banned in most countries due to these devastating effects (Vargesson, 2015: 140).

The USA narrowly avoided this tragedy because the FDA had not approved Thalidomide for sale in the country, citing a lack of safety data (Tantibanchachai, 2014; Vargesson, 2015: 141). In response to the Thalidomide disaster, the USA government significantly increased the FDA's regulatory oversight of clinical trials, currently requiring approximately 10 years to ensure the safety and efficacy of new medications (Tantibanchachai, 2014). Prior to this, clinical trials were primarily conducted between doctors and pharmaceutical companies, with the FDA only being notified of the findings (Tantibanchachai, 2014).

2.4 COVID-19 and off-label use of medications

Importantly, the repurposing of existing drugs for new diseases—also known as off-label use—is a common practice in the medical field. However, as discussed earlier in the section, off-label use must be approached with caution and grounded in sound ethical principles. The need for informed consent, equity, and scientific validation is critical. In the following section, I explore why HCQ was considered one of the drugs of choice during the COVID-19 pandemic.2.4.1 Origins of Hydroxychloroquine

HCQ usage can be traced back to the mid-20th century when a powdered bark from the Cinchona tree[3], was used to treat malaria[4] (Schrezenmeier & Dörner, 2020: 157). Later in the 1820s, a natural compound, quinine, was collected and isolated from the Cinchona bark, and it was identified as the substance that eradicated and prevented the spread of malaria.[5] The identification of its therapeutic effects against the malaria parasite led to the synthetic production of quinine and further research of its potential benefits in other infectious diseases (Schrezenmeier & Dörner, 2020: 154). By 1834, researchers discovered that at lower

[3] A species indigenous to Peru, South America (Schrezenmeier & Dörner, 2020).
[4] A disease caused by a parasite transmitted by the female mosquito indigenous to tropical areas (Schrezenmeier & Dörner, 2020).
[5] The substance from the Cinchona bark is effective against malaria by altering the environment of the human blood cells, making it difficult for the parasite to thrive (Schrezenmeier & Dörner, 2020).

concentrations, quinine exhibited potent immunomodulatory properties, making it an effective treatment for systemic lupus erythematosus (SLE)[6] and rheumatoid arthritis (RA)[7].

Later in 1940, chloroquine, a 4-aminoquninolin derivative, was synthesized and approved by the FDA in 1949 for medical use in the treatment of autoimmune disease. A year later, HCQ, a safer and less toxic form of Chloroquine, was synthesized and received approval for use in the treatment of malaria as well as autoimmune diseases by the FDA in 1955. However, HCQ is no longer the first-line drug of choice for malaria due to the development of resistance to quinine over the years. However, it is still commonly used as a disease-modifying agent for autoimmune diseases, such as rheumatoid arthritis (RA), and as a treatment for systemic lupus erythematosus (SLE) worldwide (Schrezenmeier & Dörner, 2020: 154).

While its continued use in these conditions persists, it is essential to note that HCQ has a narrow therapeutic index, meaning that even slight changes in dose or concurrent use with other drugs can lead to adverse effects. Nonetheless, the safety profile of HCQ is well-documented, and it is generally well-tolerated when used within the recommended dosage guidelines (Juurlink, 2020: E450). Common side effects include nausea, vomiting, loose stools, and abdominal pain, as well as neurological symptoms such as dizziness, headaches, and vertigo (FDA, 2021).

Lastly, it is crucial to note that patients taking HCQ on-label are cautioned regarding the potentially severe adverse events that are dose-related and can reduce the quality of life (Juurlink, 2020). I explore these adverse events in more detail in the section to follow.

[6] An autoimmune disease refers to those diseases in which the body's own immune system is responsible for the damage of healthy tissue, causing inflammation and tissue damage that affects skin, joints, heart, lungs, kidneys, blood cells and the brain (MedlinePlus, 2023)

[7] In this type of chronic disease the immune cells attack and damage the tissues lining the joints, causing inflammation leading to pain, swelling and stiffness (Australian Institute of Health and Welfare, 2019: 4)

2.4.2 Risks and Benefits Associated with Hydroxychloroquine

HCQ usage can lead to hypoglycaemic episodes both for diabetic and nondiabetic patients, requiring close monitoring of blood sugar levels, particularly in patients that are receiving glucose-lowering medication concomitantly (FDA, 2021: 6). It can also cause serious skin-associated reactions such as blistering around the eyes, mouth, and lips, loss of hair, and kidney failure attributed to renal toxicity of the drug (FDA, 2021: 5) Furthermore, it has been shown to suppress bone marrow production leading to a reduced number of vital cells circulating in the blood system which can, in turn, cause fatigue, and make the patient more prone to infections, bruising, and bleeding. If such symptoms appear, it is recommended that the administration of HCQ be discontinued (FDA, 2021: 5).

One of the most serious risks is the potential for cardiac toxicity, which can lead to insufficiency of the heart muscle to effectively pump blood and heart failure, which is exacerbated by the combination of HCQ with other drugs such as the antibiotic azithromycin (FDA, 2021: 4).

Despite the severe risks associated with HCQ, it is still considered an effective treatment, particularly for SLE and RA.[8] Furthermore, HCQ is relatively well tolerated compared to other drug modalities such as methotrexate, making it suitable for pregnant and breastfeeding women with SLE, as it is safe and doesn't harm newborns. It can also be safely used as a treatment in children by administering lower doses. When administered correctly and patients monitored closely, the benefits of HCQ for these autoimmune diseases outweigh the risks (Lupus Foundation, n.d).

In addition to its benefits in autoimmune disease, HCQ has been associated with other benefits when used as adjunct therapy for certain diseases. It is proven to have a protective effect against heart-related conditions, such as decreasing blood clot formation in the blood vessels which

[8] HCQ is effective in prolonging the onset of joint damage and in reducing inflammation of tissue leading to reduced pain and swelling of joints in these autoimmune diseases (Lupus Foundation, n.d).

leads to reduced fat circulation in the blood thereby decreasing the risk of heart attack (Hage, Al-Badri & Azar, 2014: 83). Other exploratory benefits that have been noted such as the prevention of developing diabetes mellitus in those patients with SLE who use HCQ (Hage, Al-Badri & Azar 2014: 79).

It is important to note that the benefits of HCQ have only been studied or observed in the context of the autoimmune diseases SLE and RA and not in other diseases. In addition to HCQ possessing strong properties that regulate the immune system, the exact mechanism of action within the human body is still being studied, as it remains largely unknown (Hage, Al-Badri, & Azar, 2014).

2.4.3. Why was hydroxychloroquine considered a possible treatment for SARS-COV infection?

In the very early stages of the COVID-19 pandemic, researchers and health authorities reviewed and considered HCQ as a prospective treatment option due to its perceived antiviral effects. Research on treatments for SARS-CoV by scientists has been ongoing since 2004, following the initial epidemic that began in the southern part of China in 2002 and lasted until 2003 (Chu et al., 2004). Due to this, several preclinical trials to test the efficacy and safety of HCQ were implemented, which I explore in further detail in the section below.

In 2004, Keyaerts et al. demonstrated in laboratory experiments the antiviral properties of chloroquine, which inhibited viral replication by 99% three days post-infection using the same dose that is needed to kill the malaria parasite in human blood cells. They recommended that chloroquine should be considered for future outbreaks as both a treatment and a prophylactic for SARS-CoV infection (Keyaerts et al., 2004: 266). Goa, Tian, and Yang (2020) referenced a State Council of China news briefing, reporting that rapid clinical trials tested the efficacy

and safety of HCQ for COVID-19 at 10 sites involving over 100 patients, suggesting that chloroquine was effective in treating COVID-19, with no serious side effects. This led to its inclusion in treatment guidelines for all COVID-19 cases in China (Goa, Tian & Yang, 2020: 72). This information was released at a time of heightened uncertainty and anxiety regarding the COVID-19 outbreak and gave the world hope as clinical trials[9] are considered reliable and are strictly governed by scientific rigour and standards. However, later analysis revealed that the publicized studies of Goa et al. were not found in the clinical trial registry (Cortegiani et al., 2020: 2812).

Similarly, French scientists, Gautrett and Raoult, reported promising treatment outcomes with HCQ coupled with azithromycin in a small sample-sized hospital-based clinical trial. The recommendation which emanated from the study was that a larger clinical trial needed to be conducted (Gautret et al, 2020). These early reports sparked widespread public interest and attention, fuelled further by the subsequent endorsement by the sitting USA President Donald Trump, who retweeted the Gautret et al. study and publicly claimed HCQ was the answer to COVID-19 prevention (ABC NEWS, 2020). Following the widespread of this tweet, French President Emmanuel Macron met with Raoult in response to public pressure. His office never endorsed the use of HCQ during the pandemic, stating the lack of data to prove efficiency and reported there was a need for further HCQ research before his office could make a discharger (Reuters, 2020).

However, following these initial small-scale studies and media reports other countries such as USA, and South Africa issued EUA for HCQ and the WHO announced on the 18th of March

[9] A clinical trial is a form of study where scientists can test if a medical, surgical, or behavioral intervention will yield results for a medical hypothesis/theory. Randomized control trial is the golden standard as it is meant to be designed to eliminate baseline bias when it comes to evaluating the safety and efficacy of a drug, as this compares the interventional product to a known standard of care or a placebo which is known as the control group and while cross-matching for age, sex and other variable factors. Results from clinical trials if conducted properly are usually used to make recommendations to medicine regulatory boards, government, and health care professionals regarding a certain treatment (Hariton & Locascio, 2018).

2020 the initiation of a large international clinical trial involving over 30 countries worldwide known as the SOLIDARITY Clinical Trial for Treatment. This global initiative aimed at bringing together the expertise of scientists from across the globe and conducting a scientific investigation by repurposing drugs, such as HCQ amongst others, and comparing them to the standard of care (supportive care) for the treatment of COVID-19 disease in severely or critically ill patients who were hospitalized (Manivannan et al., 2021).

2.5. Conclusion

What initially seemed like a promising repurposed treatment for COVID-19 based on early results from small-scale clinical trials, ultimately did not deliver the expected benefits. Instead, the situation highlights how intense media attention potentially influenced health authorities in their decision to approve the emergency off-label use of HCQ.

In the next chapter, I argue that the off-label use and emergency authorization by regulatory health authorities were unjustified from a utilitarian perspective as it resulted in more harm than good.

CHAPTER 3: A UTILITARIAN PERSPECTIVE ON THE USE AND TEMPORARY APPROVAL OF OFF-LABEL HYDROXYCHLOROQUINE

3.1 Introduction

In this chapter, I evaluate the ethical justifiability of the use and temporary approval of HCQ by health authorities during the early stages of the COVID-19 pandemic, using utilitarianism. I begin with an overview of the theory of utilitarianism, including the benefits and shortcomings of this theory. I then explain the risks and benefits associated with the widespread off-label use and temporary approval of HCQ to patients with severe COVID-19 symptoms, to the healthcare profession and to society at large and calculate the net utility. I conclude the chapter by showing that the harms associated with the decision of health authorities to temporarily authorise the off-label use of HCQ in the early stages of the COVID-19 pandemic caused more harm than good.

3.2. Utilitarianism

Utilitarianism is a form of consequentialist ethical theory. From this perspective, the rightness of an action is judged solely by its consequences. One of the most prominent utilitarian philosophers, Jeremy Bentham (1748–1832), introduced the principle of utility as the guiding principle of conduct and law. He defines an action as morally right if it produces the greatest pleasure or happiness over pain or unhappiness (Rachels & Rachels, 2019: 101). Bentham argues that human nature is governed by two masters—pain and pleasure—and that our actions should be directed toward maximizing pleasure and minimizing pain. Thus, an action is considered morally correct if it produces a net increase in utility (Bentham, 2017: 6).

According to Bentham, pleasure or happiness is the only intrinsic value for both humans and animals. He maintains that the moral value of an action's consequences is independent of the motives behind it. Bentham also believes that pleasure and pain can be quantified and calculated, urging individuals to focus on actions that maximize net utility. When deciding on a course of action, Bentham argues, one must calculate the potential pleasures and pains arising from it and choose the action that yields the most happiness (Crimmins, 2024).

John Stuart Mill (1806–1873), another influential utilitarian philosopher, shares Bentham's belief that happiness is the ultimate goal of all actions. However, Mill differs in his approach. He believes that utilitarianism should not focus solely on the happiness of individuals but should instead guide the development of moral codes or rules applicable across various situations (Mills, 1863). According to Mill, individuals must ask which moral rules or principles should be followed to maximize happiness for the greatest number of people (Mills, 1863)**.** Actions should adhere to these moral rules and promote the greatest overall happiness, without compromising the well-being of others (Mills, 1863). For Mill, the principle of utility emphasizes not only maximizing happiness but also ensuring fairness and respect for the happiness of others (Butts & Rich, 2019: 18).

A distinction within utilitarianism arises between Act Utilitarianism and Rule Utilitarianism. Act Utilitarianism focuses on the specific context of individual actions, judging each action based on whether it produces the greatest net happiness. It evaluates actions on a case-by-case basis, emphasizing flexibility and situational outcomes (Rachels & Rachels, 2019: 128). On the other hand, Rule Utilitarianism emphasizes the adherence to rules or guidelines such as do not lie, when followed, tend to promote the greatest good in the long run (Butts & Rich, 2019: 18). This approach argues that actions should adhere to set rules or guidelines designed to promote overall utility and can provide a framework for ethical decision-making. Rule Utilitarianism seeks to balance individual cases with the consistency of moral guidelines.

From a Utilitarian perspective, the three core elements of utility are interpreted as follows. The first element is that the morality of actions is judged solely by their outcomes, focusing on the long-term consequences of adhering to rules. Rules are considered morally right if they consistently produce pleasure and promote overall happiness in the long run (Butts & Rich, 2019: 18). The second element of utilitarianism is that the consequences of actions is evaluated based on the amount of happiness the action produces (Mill, 1863: 15). An action is right if it promotes happiness and wrong if it does not. Rule utilitarianism emphasizes that rules should foster higher-quality pleasures, such as intellectual and moral satisfaction, benefiting society (Butts & Rich. 2019: 18). The third element is impartiality as everyone's happiness and pain are equally important (Mills, 1863: 26). This means considering not just the happiness of the individual performing the action but also the well-being of everyone affected by it. Rule utilitarianism prioritizes rules that safeguard collective well-being, with a strong emphasis on justice and fairness (Mills, 1863: 26), which are critical for maintaining a stable and harmonious society.

While utilitarianism offers a structured framework for evaluating moral decisions, it is not without significant criticisms. A core issue lies in its exclusive focus on the consequences of actions, which can justify harmful or even illegal behaviour if it leads to a perceived greater good. For instance, under utilitarian reasoning, acts such as lying, stealing, or sacrificing an individual could be deemed acceptable if they result in a net positive outcome. Critics argue that this can conflict with fundamental moral or legal principles (Rachels & Rachels, 2019: 120-121).

Another criticism is the expectation of impartiality inherent in utilitarianism. The theory demands that everyone's happiness be given equal consideration, which can be an unrealistic standard. In practice, people often prioritize the well-being of family and close friends over strangers, making it difficult to adhere strictly to utilitarian principles (Rachels & Rachels,

2019: 125). This impartiality requirement also raises questions about the feasibility of applying utilitarianism in situations where personal biases or practical constraints influence decision-making (Sinnot-Armstrong, 2023).

For this research report, I use rule utilitarianism as it is utilised to inform health policies and aims for the improvement of society. It also promotes the most amount of good for the greatest maximum amount of individuals and is a reason-based approach to determining what is right and wrong through weighing the harms and benefits of an action. These principles will be applied in the next section.

3.3. Calculating net utility – benefits and risks of off-label use and temporary authorization

From a Rule Utilitarian perspective, actions are evaluated based on adherence to general rules that aim to produce net utility. This means that regulatory decisions, such as the EUA for repurposing HCQ for COVID-19 treatment must follow rules that promote long-term societal well-being and happiness based on rigorous scientific evidence and ethical decision-making to ensure net benefit for public health. However, as I argue in this chapter, the EUA issued by health authorities failed to meet these standards, rendering it ethically unjustifiable under Rule Utilitarianism.

According to the FDA's regulatory framework published in January 2017, four criteria must be met for an EUA to be issued, which I present below:

i. The disease or agent must cause a serious or life-threatening condition.

ii. Evidence of effectiveness: While lower-level evidence may suffice, it must still be evaluated for its quality and quantity to justify authorization

iii. The benefits of the drug must outweigh its known or potential risks.

iv. No proven alternatives must be available (FDA, 2017: 7-8).

For this analysis, I focus on the second and third criteria, where I demonstrate that the emergency authorization failed to meet the expected standards as the first and second criterin where met COVID-19 disease is a serious and life-threatening disease, and there were no proven alternatives at the time

3.3.1. Lack of evidence of effectiveness

The second criterion required for EUA of evidence of effectiveness acknowledges that a lower-level evidence may be considered in emergencies. Nonetheless, the criteria mandates that such evidence be rigorously evaluated for its quality and quantity. This rule exists to ensure that decisions, even in urgent situations, are grounded in sound scientific evidence to maximize long-term utility. In the case of HCQ, the FDA acknowledged that the EUA was based on in vitro studies and observational studies without control groups. The agency also admitted that it could not confirm whether the drug was effective for treating COVID-19, stating instead that the authorization was based on hope rather than adequate scientific evidence (FDA, 2020b).

Rule Utilitarianism emphasizes adherence to rules that protect public health by upholding rigorous scientific standards. By relying on flawed evidence, the FDA undermined this principle. While lower-level evidence may suffice during emergencies, it must still meet minimum standards of scientific integrity. The decision to issue the EUA not only risked immediate harm but also weakened trust in regulatory bodies, setting a dangerous precedent.

One of the primary studies used in support of the EUA was published by Gautret et al., on 20 March 2020. However, the study was criticized for insufficient evidence to support a public health decision (Toumi & Aballea, 2020: 1). Significant flaws in the study included the lack of adequate peer review (accepted for publication 24hrs after submission), biased results

(exclusion of patients who had either deteriorated or demised) and potential for conflict of interest (one of the authors was also the editor in chief of the journal) (Toumi & Aballea, 2020: 1-4). This study was later retracted due to its poor quality and questionable reliability of results (Toumi & Aballea, 2020: 1-4).

Further doubts about the scientific evidence arose from Cortegiani et al. (2020), who investigated the clinical trial registry referenced by the State Council of China during their news briefing, as referred to in chapter two of this report. They found no records of the trials that purportedly supported chloroquine's inclusion in national COVID-19 treatment guidelines, raising serious questions about the reliability of the claims (Cortegiani et al. 2020: 281).

From this, we can deduce that the initial evidence used to support the EUA for off-label of HCQ was scientifically unreliable; consequently, it was impossible to establish clinical benefit based on the available data.

3.3.2. Unfavourable Risk-Benefit Assessment

The third criterion for EUA approval of medicines requires that the known and potential benefits of the drug outweigh its known and potential risks (FDA, 2017: 8). HCQ has a narrow therapeutic index, meaning the risk of toxicity is high if not carefully monitored. The lack of robust evidence supporting its efficacy made it impossible to justify its use at the time, especially given the potential for significant harm.

The safety and adverse effects of HCQ have been documented for centuries for their on-label use. The EUA for off-label use of HCQ restricted its use to hospitalized patients because it was believed that the hospital environment would provide safer monitoring for both COVID-19 and adverse drug effects (FDA, 2020b). It was also assumed that the potential side effects would not outweigh the possible clinical benefits for severely ill patients, as stated by the FDA (FDA,

2020b). Regulatory authorities such as the FDA and SAPHRA emphasized caution, warning healthcare providers about serious side effects, including heart arrhythmias, hypoglycaemia, and retinal blindness.

3.3.2.1. Impact on Patients

Patients who had severe COVID-19 symptoms suffered direct harm as a result of the off-label use HCQ particularly when combned with azithromycin.(Rosenberg et al., 2020). It is worth noting that patients with COVID-19 receiving HCQ and azithyromycin in hospitals had a significantly higher likelihood of cardiac arrest compared to control groups (adjusted Odds Ratio: 2.13; 95% Confidence Interval (CI): 1.12-4.05(Rosenberg et al., 2020). Similarly, a meta-analysis of 26 randomised trials with 10,012 patients by Axfors et al. (2021) found that the off-label HCQ use for patients with COVID-19 disease was associated with severe side effects in some cases and an 11% increased risk of mortality compared to control arm (Odds ratio: 1.11; 95% CI: 1.02-1.20), and that there was no clinical benefit of the drug for COVID-19 treatment (Axfors et al., 2021: 3).

Furthermore, the increased demand for HCQ for off-label use resulted in shortages for patients who relied on the drug for well-established on-label treatments, such as SLE and RA, with reports indicating that many patients were unable to fill their prescriptions due to depleted supplies (Arthritis Foundation et al., 2020). This caused unnecessary harm to patients suffering from chronic autoimmune diseases.

The EUA and subsequent repurposing of HCQ thus led to the exposure of patients with COVID-19 to risks that significantly outweighed benefits.

3.3.2.2. Impact on the healthcare profession

The EUA's decision created ethical dilemmas for healthcare practitioners when balancing the pressure to prescribe HCQ against their professional judgment, especially as evidence of its ineffectiveness and harms mounted and demand for the drug increased from patients (Dhupkar & Mukherjee, 2020). This confusion translated into mixed messages to patients, undermining their trust in doctors. As healthcare practitioners prescribed HCQ off-label, some patients experienced severe side effects, leading to increased scepticism about medical recommendations and the motivations behind them (Pradelle et al., 2021). Moreover, the need for close monitoring of side effects, such as cardiotoxicity, required additional clinical assessments, which increased the workload for health professionals (FDA, 2020a). Hospitals faced logistical challenges in managing side effects, including allocating additional resources and dealing with drug-induced complications, thereby straining already limited healthcare systems (Manivannan et al., 2021).

Lastly, the EUA fostered a proliferation of needless clinical trials and off-label prescribing, often driven by public demand rather than scientific evidence. This led to fragmented medical practices and inconsistent care for COVID-19 patients (FDA, 2020a).

3.3.2.3. Impact on Society

The EUA and prevalent off-label use of HCQ during the COVID-19 pandemic also had far reaching consequences for public trust, health messaging, and an impact on fair resource allocation. Public trust in health authorities was severely undermined as the EUA which was perceived by several individuals as a decision that was prioritizing expediency at the expense of scientific rigor (Aquino & Cabrera, 2020). The eventual revocation of the EUA in June 2020 coupled with the mixed messages about HCQ's efficacy and safety fuelled misinformation,

encouraged conspiracy theories, complicating public health communication efforts and eroding confidence in health regulatory authorities and in the health profession (Yang, 2024). Lastly, basing such an important regulatory decision on unreliable scientific data set a precedent for questioning future health interventions. This could hinder the success of health efforts in future crises as individuals might be reluctant to trust new treatments or vaccines.

In summary, the EUA for the off-label use of HCQ for COVID-19 treatment led to a series of harmful consequences on multiple levels. For patients that were struggling with severe COVID-19 disease, the use of off-label HCQ resulted in direct harm due to side effects and complications, most notably the increased mortality from cardiotoxicity and provided no significant clinical benefit. Other patients that relied on HCQ for chronic autoimmune diseases such as SLE and RA were also unjustly harmed by the significant shortages caused by the widespread off-label use of HCQ. For healthcare professionals, the decision for the EUA and the conflicting messages about its efficacy and treatment modalities created confusion, potentially undermining the trust in the doctor-patient relationship. Healthcare practitioners faced increasing clinical burdens, ethical dilemmas, and logistical challenges in monitoring severely ill COVID-19 patients for adverse effects associated with the off-label use of HCQ in combination with other treatment modalities.

Lasty, the off-label use of HCQ and EUA decision negatively impacted public trust in the health profession and health authorities fuelled misinformation and set a dangerous precedent for public scepticism toward future health interventions, potentially hindering the effectiveness of responses to future health crises.

It may be argued that the urgency of the pandemic justified the EUA due to increased mortality worldwide and the preclinical data on HCQ available that was promising. While addressing the urgency is a valid concern, Rule Utilitarianism demands adherence to well-established rules,

even during emergencies and therefore, deviating from these rules creates long-term harm, such as reduced public trust and increased scepticism of medical guidance (Saag, 2020).

Another possible counterargument is that condemning the EUA by regulators constitutes presentism, as it unfairly judges regulators' decisions using knowledge they did not have at the time of the EUA. This objection assumes that the ethical analysis relies solely on later trial evidence. However, substantial information regarding HCQ's risks was already available before the pandemic, including well-documented cardiotoxicity warned by the FDA when issuing their EUA statement on 28 March 2020 (FDA, 2020b). As previously stated, the early clinical reports supporting HCQ were methodically weak and insufficient to justify large-scale use. Hence, the utilitarian analysis does not solely rest on hindsight but also on the neglect of pre-existing knowledge and the failure to adopt a utilitarian benefit-risk approach. Focusing on maximising overall well-being would have favoured restricting HCQ to controlled settings such as clinical trials rather than permitting widespread use.

3.4. Conclusion

Rule Utilitarianism emphasizes the importance of adhering to rules that promote long-term utility, including rules that prioritize scientific integrity and ethical decision-making and safeguard public health and public trust. In this chapter, I have argued that, from a utilitarian perspective, the EUA of HCQ in the early stages of the COVID-19 pandemic was ethically unjustifiable. I have shown that although the EUA aimed to provide an alternative treatment during the COVID-19 crisis, the risks associated with this temporary approval far outweighed the benefits. The decision failed to maximize utility, as the harms, including increased mortality, the impact on the healthcare profession, resource strain, and loss of public trust, far exceeded the unproven potential benefits.

As a result, the EUA was ethically unjustifiable under Rule Utilitarianism. By granting the EUA without sufficient evidence, the FDA violated this principle and risked the deterioration of public trust in regulatory decisions, thereby failing to maximize long-term utility.

Having shown that the off-label use and EUA for HCQ failed to maximize utility, I turn my attention in the next chapter to evaluate whether this decision upheld the four principles of biomedical ethics.

CHAPTER 4: PRINCIPLISM AND THE OFF-LABEL USE AND TEMPORARY APPROVAL OF HYDROXYCHLOROQUINE

4.1. Introduction

In this chapter, I critically evaluate whether the decision to temporarily authorise the off-label use of HCQ in the initial stages of the COVID-19 pandemic was ethically justifiable, by analysing the four principles of autonomy, beneficence, non-maleficence, and justice.

Although principlism has faced various criticisms, it remains a widely used framework for evaluating healthcare decisions. This approach, introduced by Beauchamp and Childress (1979), provides a structured way to assess ethical dilemmas in clinical and healthcare policy settings, which is particularly relevant in the context of the emergency measures taken during the pandemic. Principlism serves as a user-friendly guide for healthcare professionals and policymakers in identifying moral problems and deciding what to do (Beauchamp & Childress, 2001:15).

I begin this chapter with an overview of principlism, followed by a critical evaluation of the principles of autonomy, non-maleficence, beneficence, and justice in the context of off-label use and temporary authorization of HCQ. I conclude that the emergency authorisation for repurposing HCQ during the early stages of the pandemic undermined these principles.

4.2. Overview of principlism

The four principles of biomedical ethics—autonomy, beneficence, non-maleficence, and justice—were developed by Tom Beauchamp and James Childress in their 1979 work titled *Principles of Biomedical Ethics*. These principles are among the most influential tools in bioethics and serve as a framework for evaluating healthcare-related decisions (Trimble, 2024:

83). Each principle is integral in guiding clinicians, health authorities, and policymakers through complex ethical decisions, especially in situations such as the COVID-19 pandemic when urgent responses are required. The principles originate from efforts to establish a universal ethical framework for medical decision-making (Trimble, 2004: 83). The principles of biomedical ethics are heavily influenced by the Belmont Report (1979), which was developed in response to historical, ethical violations in research involving human subjects (Trimble, 2004: 84). The Belmont report advances the ethical principles of respect for persons, beneficence and justice in guiding ethical research practices (1979). Building upon this foundation, Beauchamp and Childress introduce the four principles—autonomy, beneficence, nonmaleficence, and justice— (Trimble, 2024:84). They integrate elements from various ethical theories, including deontological, consequentialist, and in later additions of their book, virtue ethics, aiming for a common moral approach applicable across diverse ethical dilemmas **(**Lewis & Schüklenk, 2022: 133**).**

These four principles are applied in practice as *prima facie* duties; a term introduced by an English philosopher, WD Ross, meaning that the principle is binding unless it conflicts with another moral principle (Gillon, 1994: 184). In ethical dilemmas, all four principles should be considered and carefully balanced against one another as no single principal holds greater priority over the others. In practice, ethical decision-making requires weighing all four principles equally, assessing which considerations take precedence in each case while striving for a resolution that respects each principle as much as possible. In other words, no principle is absolute, and ethical reasoning involves justifying why one principle may override another in a specific situation while still acknowledging the importance of all four (Gillon, 1994: 184).

As advocated by Beauchamp and Childress (2001), principlism offers several advantages such as the flexibility of the approach and applicability across diverse healthcare settings and contexts. It also provides a balanced way to consider the interests and rights of patients, while

also considering the broader social and professional obligations of healthcare providers (Beauchamp & Childress, 2001: 15). Furthermore, its simplicity makes it accessible to healthcare professionals without requiring extensive philosophical background (Beauchamp & Childress, 2001: 15; Trimble, 2024: 83).

However, principlism also has limitations. Critics argue that it oversimplifies complex ethical issues, often failing to provide a clear resolution when principles conflict (Lewis & Schüklenk, 2022: 134; Trimble, 2024 :85). For instance, when beneficence might conflict with non-maleficence, it can be challenging to determine which principle should take precedence. Additionally, principlism has been critiqued for focusing primarily on individual cases, potentially neglecting structural inequalities and broader social contexts (Lewis & Schüklenk, 2022: 135; Trimble 2024: 85).

In the sections to follow, I apply the four principles to the case of HCQ's approval and use during the pandemic, providing a detailed examination of each principle's role in the ethical justification of this decision.

4.2.1 Principle of respect for autonomy

The principle of respect for autonomy underscores the importance of individuals making informed decisions regarding their healthcare, based on a thorough understanding of the risks and benefits involved (Beauchamp & Childress, 2001: 69). The rushed and temporary authorisation of HCQ for off-label use in the absence of robust scientific evidence significantly impacted patients' ability to make informed decisions. Furthermore, the lack of clear communication about the experimental nature of HCQ meant that patients could not fully grasp the potential risks, benefits and uncertainties surrounding the drug leading to undue influence, thus undermining the validity of their consent (Shojael & Salari, 2020: 791).

Media misinformation further complicated the situation by portraying HCQ as a definitive treatment, despite the absence of substantial evidence (Gallagher, 2020). Clinicians faced ethical challenges in balancing transparency about HCQ's off-label status with concerns about inducing patient anxiety or non-compliance. Shojael and Salari (2020: 790) highlight this tension, stating, "in crises like the COVID-19 outbreak, off-label drugs may be administered as clinical practice based on the physician's responsibility." Time constraints associated with emergency situations limit the opportunity for adequate disclosure and informed consent due to the severity of the patient's condition; decisions may rely more on the physician's judgment than on patient autonomy (Shojael & Salari, 2020: 791). This underscores the challenges in respecting autonomy during emergencies, where time constraints and rapidly evolving information hinder comprehensive communication (Shojael & Salari, 2020: 791).

A counterargument suggests that patients with life-threatening conditions have the right to access experimental treatments including off-label medication, provided they are fully informed about the potential risks and uncertainties, and that shared decision-making is implemented (El Rhazi & Adarmouch, 2020: 5). While this perspective aligns with the principle of respect for autonomy, it necessitates thorough consent processes. However, the rushed nature of HCQ approvals and the widespread off-label prescription often precluded such processes, raising ethical concerns about whether autonomy was genuinely respected (Shojael & Salari, 2020: 791).

On a final note, healthcare providers are ethically obligated to use their clinical judgment in the best interests of their patients. With off-label use of HCQ, the risks for critically ill COVID-19 patients often outweighed the potential benefits. Thus, healthcare providers needed to present HCQ as an experimental option rather than a proven cure and obtain valid informed consent that included a transparent discussion of its risks, experimental nature, and uncertain efficacy of the drug. In the absence of comprehensive disclosure regarding the experimental

status and potential harms of HCQ, the ability of patients to make informed decisions was not respected, thus compromising the principle of autonomy.

4.2.2 Principle of beneficence

Beneficence is the ethical duty to act in the patient's best interest, requiring actions that promote good, enhance welfare, and prioritize health and safety (Gillion, 1994: 185). According to Gillion (1994: 185), harm in healthcare practice is sometimes unavoidable, however, it is the health professional and authorities' duty to make sure when considering the principle of beneficence and the principle of non-maleficence together, the result is a net benefit. As discussed earlier in chapter two, both the FDA as well as the SAHPRA have the duty to align with the principle of beneficence by ensuring that all approved medical products are beneficial to the advancement of the health of society. In other words, health regulatory authorities are required to make regulatory decisions that advance health policies that maximize benefits.

In the context of the decision for EUA for the off-label of HCQ during the COVID-19 pandemic, it may be argued that the decision was based on considerations of beneficence. The intention to provide a possible alternative treatment for patients with severe COVID-19 symptoms, particularly in the absence of effective standard treatments, could be seen as rooted in beneficence, given the urgent need to address high mortality rates and the lack of viable therapeutic options at the time. This is further elaborated by El Rhazi and Adarmouch (2020: 3), who argue that, given the emergency nature of the pandemic, the rapid spread of disease, and the high mortality rate, the off-label use of HCQ was justified. They argue that health authorities acted in accordance with the principle of beneficence, as there was adequate preclinical data demonstrating HCQ's effectiveness (El Rhazi & Adarmouch, 2020: 3). This was sufficient to warrant further clinical research on HCQ as a treatment for COVID-19 and,

therefore, also sufficient to use as a treatment on critically ill patients with no alternatives on compassionate bases while awaiting results from RCT (El Rhazi & Adarmouch, 2020: 3).

While these considerations demonstrate an intent to act beneficently, relying on limited data risked undermining public trust and scientific integrity (Saag, 2020: 2162). Observational studies cited as evidence were often small in scale and lacked the thoroughness of RCTs, leading to significant uncertainty about HCQ's efficacy (FDA, 2020a). There was thus a lack of proven benefits of HCQ for the treatment of COVID-19.

Furthermore, the broader implications of regulatory flexibility require consideration. Although the EUA was intended to address an urgent need, prioritizing an unproven treatment may have diverted attention and resources from more promising research and therapeutic avenues (Emanuel et al., 2020). This illustrates a tension between the immediate aim of beneficence and the longer-term goals of beneficence and long-term patient outcomes.

The principle of beneficence further obligates clinicians and health regulators to balance potential benefits against risks and to ensure that actions ultimately serve the best interests of patients and the public (Gillion, 1994: 185). In this context, while offering off-label HCQ under EUA aligned with the urgency of the pandemic, authorising an unproven treatment under the assumption of benefit exposed patients to potential harm unaccompanied by therapeutic benefit.

4.2.3 Principle of non-maleficence

The principle of nonmaleficence emphasizes the ethical obligation to "do no harm" and requires careful consideration of the potential risks associated with any medical intervention and public health measures (Gillion, 1994: 85).

Health authorities have the obligation not to inflict harm on others, encapsulated by the maxim *primum non nocere* (Sokol, 2013: 23). Although, certain treatments and policies—such as mandatory vaccination —may cause temporary harm (mild side effects like fever and muscle pain) to achieve greater clinical benefit (such as achieving herd immunity). Thus, the correct interpretation of this maxim is *primum non plus nocere quam succurrer*—above all, do no net harm (Sokol, 2013: 23).

Therefore, health authorities and healthcare practitioners are required to make regulatory and clinical decisions respectively, that do not cause disproportionate harm compared to the potential benefits. This requires weighing the benefits of the off-label use and authorization of HCQ against the potential side effects, as outlined below.

As discussed earlier in chapter two, SAPHRA has the duty to uphold the principle of non-maleficence by ensuring that the medicines that enter the South African market are safe and will not cause harm to the public. The principle of nonmaleficence requires healthcare policies and decisions to minimize harm to patients.

In the case of HCQ, several risks significantly challenge the ethical justifiability of its off-label use under EUA. Firstly, HCQ has a narrow therapeutic index, meaning that even a slight deviation in dosage can have harmful side effects (Erickson, Chai & Boyer, 2020: 40). Secondly, there was a lack of established dosing guidelines during the early stages of the pandemic; studies reported varying, often higher, doses, exacerbating the uncertainty of safety (FDA, 2020a). Another significant concern was the risk of cardiotoxicity, which can lead to life-threatening complications (FDA, 2020a). Furthermore, patients with comorbidities, who represented most hospitalized COVID-19 cases, were more prone to complications (Centers for Disease Control and Prevention, 2024). Finally, HCQ required continuous monitoring of

heart, renal and liver function and drug interactions (FDA, 2020a), placing an increased burden on resource-limited healthcare systems during the pandemic.

Additionally, Voit, Timmermann and Steger (2020) argue that the EUA for HCQ and drugs such as remdesivir compromised the principle of non-maleficence, further stating that the EUA relied on pre-clinical data and low-scientific evidence from laboratory testing and animal studies which do not necessarily apply to humans due to physiological differences. This concern is magnified in emergency situations where the need for swift action shouldn't overshadow scientific integrity. Additionally, they point out that HCQ's safety in treating COVID-19 has not been confirmed, and its known cardiac risks pose a greater danger to patients suffering from COVID-19 disease (Voit, Timmermann & Steger, 2021: 5). This concern was similarly highlighted by subsequent studies that indicated that HCQ failed to reduce mortality or improve viral clearance in COVID-19 patients while increasing the risk of adverse events (Chacko, Brar & Premkumar, 2020: 8).

In addition to individual harm, the rushed approval and widespread use of HCQ without adequate monitoring or scientific validation posed risks to societal trust in health authorities and the medical profession. Such actions could diminish confidence in public health initiatives, particularly in future crises. Allocating resources to a treatment with uncertain efficacy also risked diverting attention from more promising therapeutic options, thereby hindering harm reduction efforts (Aquino & Cabrera, 2020).

A counterargument might stress that, given the urgency of the pandemic and high mortality rates, the harm of withholding treatment outweighed the risks associated with experimental use of HCQ. Piszczatoski and Powell (2020) support this view and argue that despite limited clinical evidence supporting the efficacy of chloroquine and HCQ against COVID-19, the FDA issued an EUA due to the urgent need for potential treatments in the face of a rapidly spreading

virus. They consider that this decision was based on the premise that, in extraordinary circumstances such as a pandemic, the potential benefits of providing any treatment might outweigh the risks associated with limited scientific data (Piszczatoski & Powell, 2020: 829).

However, nonmaleficence requires that harm should not be disproportionate to the potential therapeutic benefits, which was the case for the authorization of off-label use of HCQ. The temporary EUA for HCQ thus undermined the principle of nonmaleficence by exposing critically ill patients to harm in the absence of the probability of therapeutic benefit.

4.2.4 Principle of justice

The principle of justice, particularly distributive justice, serves as a foundational element in healthcare ethics, necessitating the fair, equitable, and appropriate allocation of medical resources, all of which should be supported by established norms of social cooperation. (Beauchamp & Childress, 2009: 291). This principle becomes especially critical during public health crises, where heightened demand for specific treatments can strain existing supplies, potentially leading to inequities.

As shown in chapter two, regulatory bodies such as the SAHPRA and the FDA are mandated to ensure equitable access to essential health products and safeguard public health through scientifically based regulatory decisions (FDA, 2020b; SAHPRA, 2020). These authorities play a critical role in balancing emergency response measures with the ethical obligation to fairly distribute medical resources, particularly in times of public health crises. Their mission underscores the necessity of ensuring that all patient populations—whether affected by newly emerging diseases or pre-existing chronic conditions—receive just and equitable access to treatments.

A key ethical principle underpinning healthcare resource allocation is distributive justice, which mandates the fair distribution of limited medical resources to prevent undue disadvantage to any patient group (Beauchamp & Childress, 2009). This principle becomes especially critical during public health emergencies, where surging demand for specific treatments may strain existing supplies and exacerbate healthcare inequities. The approval and subsequent widespread use of HCQ for COVID-19 exemplifies a failure in upholding distributive justice, as the reallocation of HCQ toward COVID-19 patients occurred despite uncertainty regarding its efficacy (Aquino & Cabrera, 2020).

What is more, the public profile of the COVID-19 disease shaped by media coverage, political influence, and social perception, may have impacted healthcare policies and clinical decision-making. This heightened media attention led to disproportionate urgency, resulting in policy shifts that prioritized HCQ for off-label COVID-19 treatment while neglecting patients with on-label indications such as SLE and RA (Aquino & Cabrera, 2020). This media-driven demand had tangible consequences, which I outline below as described by Aquino and Cabrera:

- HCQ shortages emerged globally, disproportionately affecting SLE and RA patients who rely on the drug for disease management
- Unjustified stockpiling of HCQ by hospitals and individuals further exacerbated supply constraints
- Increased prescription rates for off-label COVID-19 use diverted HCQ away from its primary patient population, highlighting an ethical lapse in resource allocation (Aquino & Cabrera, 2020).

As a case in point, HCQ prescriptions increased ninefold in the month of March of 2020 in the US and sixty-sevenfold in Spain (Mercade-Besora et al., 2024: 1175). Furthermore, reports from patient advocacy groups, such as the Arthritis Foundation, indicated widespread

difficulties in accessing HCQ, with many SLE and RA patients experiencing disruptions in treatment (Arthritis Foundation, 2020). Given that consistent HCQ use is essential for disease control in autoimmune conditions, the resulting shortages led to severe clinical consequences, including disease flare-ups, increased morbidity, and a higher risk of long-term complications (Lupus Foundation of America, 2020).

Lastly, the principle of justice demands that regulatory decisions be guided by fairness in the allocation of scarce medical resources. However, the authorization of off-label HCQ for COVID-19 treatment was made despite inconclusive scientific evidence of its effectiveness, which lead to the prioritization of a patient group (patients suffering from severe COVID-19 disease) at the direct expense of another (patients suffering from chronic SLE and RA). This misallocation of health resources compromised the principle of justice by failing to protect vulnerable patients, as individuals with chronic illnesses were left without access to medication that their relied on (Aquino & Cabrera, 2020). In this way, equitable healthcare distribution was compromised, favouring the COVID-19 disease with the higher social and media profile over other diseases such as chronic autoimmune diseases. Ultimately the rushed emergency approval exacerbated inequalities in resource distribution and reflected a failure in upholding the expected health regulatory responsibility, as the decision was influenced by public and political pressure rather than based on scientific evidence (Aquino & Cabrera, 2020).

On the other hand, one might argue that the regulators were facing an immense global health crisis and needed to provide an intervention in the absence of proven treatments or vaccines amid escalating deaths. Therefore, the decision to grant HCQ EUA was consistent with the precautionary principle, which states that a lack of full scientific certainty should not delay action in the face of serious or potentially irreversible harm (Sandin et al., 2002: 279). This

principle encourages a shift away from a passive “wait and see” stance toward a proactive “better safe than sorry” approach (Frediani, 2021: 8).

However, the precautionary principle alone does not justify any intervention simply because uncertainty exists. Its ethical justifiabililty relies on balance with the principle of proportionality, which requires that the likely public health benefits/measures clearly outweigh the moral and social costs imposed. In practice, proportionality demands that while measures may restrict autonomy or entail risks, they remain justified only if the overall public health benefit exceeds the foreseeable harms (Childress et al., 2002: 173).

Therefore, proportionality ensures that public health responses are not excessive or unjustified when weighed against foreseeable harms. The principle of proportionality was compromised by the scope and scale of the EUA. Instead of restricting HCQ to controlled clinical trials, regulators authorised widespread off-label use, which diverted supplies away from patients with approved indications (e.g., lupus, rheumatoid arthritis) and exposed COVID-19 patients to avoidable risks outside trial monitoring. This broad authorisation was not a cautious or proportionate application of the precautionary principle; rather, it neglected the necessary weighing of risks and benefits required in public health ethics.

And yes, the EUA was revoked within three months as evidence showed HCQ lacked benefit and potentially posed risks (FDA, 2020a). However, reliable insights came from controlled clinical trials, not the widespread off-label use, which amplified patient risk without generating valid scientific knowledge. The action of revocation of EUA can be viewed as precaution and it is well to note that it did not provide any insight into HCQ's lack of efficacy, as this came from well well-designed clinical trials such as SOLIDATRY and RECOVER Trial and not from the uncontrolled widespread use promoted by the EUA.

Evaluated via Beauchamp and Childress's four principles, non-maleficence was compromised by exposing patients to harm, beneficence was undermined by offering an ineffective treatment, autonomy was limited due to insufficient patient information, and justice was violated by diverting HCQ from approved indications (Beauchamp and Childress, 2019). A more ethical approach would have restricted HCQ to clinical trials, ensuring that precaution and proportionality guided decision-making. Therefore, the EUA for HCQ was ethically unjustified, reflecting failure to act on known risks rather than hindsight bias.

4.3. Conclusion

In this chapter, I have demonstrated how the widespread use of HCQ that resulted from the EUA for its off-label use to treat COVID-19 disease failed to uphold the four fundamental principles of biomedical ethics, namely the principle of beneficence, non-maleficence, justice, and autonomy. The decision to authorize HCQ prematurely fell short of the core duties of regulatory bodies, which are to ensure the safety, efficacy, and equitable distribution of health products before they reach the market.

Ultimately the decision to provide emergency authorization failed to ensure clinical beneficence, as no proven therapeutic benefit was established and undermined the principle non-maleficence, as HCQ's known adverse effects led to patient harm. In addition, the decision also violated the principle of justice by created unjust inequities in drug access, disproportionately favouring patients suffering from COVID-19 disease over patients that suffer from chronic autoimmune diseases such as SLE and RA. Lastly, the lack of full disclosure in respect to HCQ's risks and experimental nature with no proven therapeutic benefits, undermined patient autonomy, as misleading claims prevented adequate informed decision-making.

By failing to uphold these core principles, the EUA to repurpose HCQ compromised both ethical medical practice and public health integrity. This chapter underscores the crucial role of regulatory bodies in ensuring evidence-based, ethical decision-making to prevent similar misallocations and ethical failures in future public health crises.

In the final chapter of this research report, I analyse the decision to authorize HCQ for emergency use by health authorities through the lens of virtue ethics.

CHAPTER 5: VIRTUE ETHICS AND THE OFF-LABEL USE AND TEMPORARY APPROVAL OF HYDROXYCHLOROQUINE

5.1. Introduction

In this chapter, I evaluate the off-label authorisation and use of HCQ from the perspective of virtue ethics. Unlike utilitarianism, which focuses on the consequences of actions, or the principle-based approach outlined by Beauchamp and Childress, virtue ethics assesses the moral character and virtues required to guide ethical decision-making. I begin with an exploration of the origins and role of virtue ethics in healthcare provision, and how regulatory bodies should incorporate virtue ethics into decision-making. I then discuss the professional virtues deemed important in healthcare provision and during healthcare crises, such as compassion, justice, prudence, trustworthiness, and integrity. Finally, I demonstrate how these virtues were compromised in the widespread use and temporary authorisation of HCQ for the treatment of COVID-19.

5.2. Virtue ethics

Virtue ethics is a theory that is fundamentally centred on the development of a virtuous character, contrasting with other ethical theories that focus on duties, as seen in deontology, or on the consequences of actions, such as in utilitarianism (Hursthouse & Pettigrove, 2023: 1). While virtues and the character of individuals lie at the heart of this ethical theory, it also considers the actions and consequences arising from the exercise of these virtues (Hursthouse & Pettigrove, 2023: 1).

Virtue ethics is predominantly attributed to Aristotle and most modern forms of virtue ethics contain the following essential elements *arete, phronesis* and *eudaimonia* translated to virtue,

practical wisdom and human flourishing, respectively (Hursthouse & Pettigrove, 2023: 2). A virtue (*arete*) is defined as "an excellent trait of character" (Hursthouse & Pettigrove, 2023: 2). Virtues are qualities or character traits that individuals can develop and express through habitual actions. These virtues become fixed and sustainable characteristics of a person's identity but can vary depending on the individual's role in society (Rachels & Rachels, 2019: 171). For instance, we expect doctors to demonstrate compassion and care, while such expectations may not be as prominent in other professions, such as law. Contrastingly, vices represent negative traits that society discourages, aligning with Aristotle's "golden mean" theory. In this view, a virtue lies between two extremes—neither excessive nor deficient (Kraut, 2022). For example, the virtue of caring finds its balance between neglect and overbearing behaviours. This balance is essential for moral and ethical practice.

Practical wisdom (*phronesis*) is another essential component of virtue ethics which refers to the ability for an individual to act fittingly in any given situation. Without practical wisdom one may have good intentions but fail to act appropriately due to ignorance or misjudgement (Hursthouse & Pettigrove, 2022).

Ultimately, the idea of fulfilment (eudaimonia) is intimately tied to virtue ethics. Aristotle posits that every action strives toward some good, with eudaimonia as the highest good. Achieving this eudaimonia—a state of flourishing or well-being—requires the cultivation of virtues, which extends beyond simple happiness (Kraut, 2022). A virtuous character is in turn, developed through the nurturing and practice of both moral and intellectual virtues, representing the sole path to a fulfilled human life (*eudaimonia*), which serves as the goal for every individual (Kraut, 2022).

In the context of healthcare, virtue ethics is helpful in determining the morally correct actions based on the character traits expected from healthcare practitioners. In a teleological sense,

healthcare is considered a moral practice with specific goals. These goals are in turn determined by the practice of healthcare. A practice is as:

> "any coherent and complex form of socially established cooperative human activity through which the goods internal to that form of activity are realized in the course of trying to achieve those standards of excellence which are appropriate to, and partially definitive of, that form of activity, with the result that human powers to achieve excellence, and the human conceptions of the ends and goods involved, are systematically extended" (MacIntyre, 2007: 218).

In other words, medicine is a practice, as defined by MacIntyre (2007), that has specific internal goods that are determined by the characteristics of the practice. The internal good of the practice of medicine is the well-being of the patient in the form of "restoration or improvement of health" (Pellegrino & Thomasma, 1993: 52). From a virtue ethics viewpoint, virtues are helpful in achieving the goals set for medicine.

Virtue ethics has been criticized for not being very effective in guiding actions; however, more recently, an appreciation of the important role that character and professional virtues play in ensuring ethical practice has been accepted by several authors (Gardiner, 2003; Hursthouse and Pettigrove, 2018).

This theory is also relevant to decisions made by health regulatory authorities based on the kind of behaviours expected from virtuous medical leaders. The well-being of the patient, which is the goal of healthcare, is also directly influenced by various stakeholders such as SAHPRA as stipulated in their mission statement which is "to promote access to health products and protect human and animal health in South Africa through making science-based regulatory decisions" (SAHPRA: 2022: 12). In this way ensuring the well-being of patients is a collaborative effort at the intersection between healthcare provision (healthcare practitioners) and healthcare

regulation (health regulatory authorities). In this way the virtues required in healthcare provision to ensure patient well-being could also be applied to decisions of healthcare stakeholders which also aim at patient well-being (in the form of protection of human health). Thus, the virtues of compassion, prudence, justice, trustworthiness and integrity, which are considered essential in healthcare provision are also applicable to, and helpful in, guiding ethical decision-making that ensures patient well-being is prioritised in respect to the authorisation and use of medicines.

In the following section, I evaluate whether the virtues of compassion, prudence, justice, integrity and trustworthiness were adequately considered in the temporary EUA of HCQ by health authorities and show that they were not.

5.2.1. The virtue of compassion

Compassion is a fundamental virtue in healthcare, defined as the ability to recognize the suffering of others and act with the intention of alleviating it (Beauchamp & Childress, 2013). It serves as a moral imperative in ethical healthcare provision, ensuring that patient care is grounded in empathy and through the alleviation of suffering (Sinclair, 2016: 194). While the emergency use authorisation of off-label HCQ during the COVID-19 pandemic may have been presented as a compassionate response, I show that the actions taken by healthcare authorities failed to meet the ethical requirements of true compassion.

Compassion in healthcare requires actions that address suffering and consider the needs of society through relational understanding (Sinclair, 2016: 193).

It could be argued that the initial EUA of HCQ was grounded on compassionate grounds and was driven by a desire to provide relief to critically ill patients and to instil hope during a time of great uncertainty; therefore, the motive behind it was virtuous. However, a genuinely

compassionate response would have included a thorough evaluation of the drug's potential risks and benefits and would not have ignored the flawed science from the evidence available at the time. Compassion demands a commitment to avoiding harm, which in this case means sparing patients from the risks associated with an unproven treatment and diminished scientific rigours. Furthermore, offering hope should not come at the expense of creating false expectations, especially for patients with severe complications. True compassion, therefore, requires a balance between addressing immediate suffering and ensuring that interventions to alleviate suffering do not lead to greater harm.

As previously discussed in chapter two, the off-label use of medications such as HCQ is a common practice in clinical care, often justified by professional discretion and urgent need (World Health Organization, 2020). However, during the pandemic, the advocacy for HCQ was based on limited and inconclusive evidence. Compassion should compel healthcare authorities to prioritize evidence-based practices (Singh & Ravinetto, 2020).

Moreover, while the urgency of the pandemic demanded swift action, healthcare authorities had a responsibility to balance compassion with accountability. Prescribing HCQ off-label as a treatment for COVID-19 diverted attention and resources from interventions with established efficacy and raised false hopes among vulnerable populations. Compassion, when understood as a virtue aligned with beneficence and justice, requires authorities to act with integrity and foresight. Hence, the EUA for off-label HCQ not only compromised patient welfare but also damaged public trust in healthcare systems (Singh & Ravinetto, 2020: 5).

Therefore, a compassionate approach would have thus prioritized patient safety, transparency, and adherence to evidence-based practices. Furthermore, it would have spared patients from the false hope and potential harm associated with an unproven treatment. Hence, the response by authorities to authorize the off-label use of HCQ was not genuinely compassionate, as it did

not adequately balance the need to alleviate suffering with the ethical responsibility to *primum non nocere* (first, do no harm).

5.2.2. The virtue of prudence

Prudence, often referred to as practical wisdom or discernment, is the virtue that enables individuals to make thoughtful and well-considered decisions in balancing ethical principles with practical realities (Beauchamp & Childress, 2013, 39). Similarly, Gillon (2015) wzhen referring to the four *prima facie* principles discussed in the previous chapter, emphasizes that applying these principles requires practical wisdom to navigate complex ethical dilemmas in healthcare (Gillion, 2015).

It could be said that the authorisation of the off-label use of HCQ during the pandemic, in response to the acute need for action and the perceived potential for a cure, might initially appear to have been a prudent choice. However, prudence demands more than a quick response, as elaborated on by Pellegrino and Thomasma (1993). It requires a thorough evaluation of the potential risks and benefits, even in unprecedented situations, coupled with concrete scientific evidence and sound reasoning. Pellegrino and Thomasma (1993: 86) further justify that clinical judgement is crucial for prudence, especially in complex situations of uncertainty. Health authorities need to discern which actions are appropriate to the ends, how to balance benefits and harms in clinical interventions, and how to integrate moral and technical issues. Thus, the decision to temporarily authorise and promote the off-label use of HCQ based on limited clinical data ultimately reflected poor discernment, prioritising expedience over thoughtful deliberation on the part of health authorities.

Additionally, Takla and Jeevaratnam (2020: 1773) argue that the initial decision to authorise HCQ by the FDA was questionable in terms of scientific prudence due to the lack of safety data for HCQ in COVID-19 patients. They further elaborate that even the available preclinical data was contraindicating and not scientifically reliable.

Therefore, prudence in healthcare decision-making ensures that actions are deliberate, evidence-based, and ethically sound. While the urgency for health authorities to act during the pandemic was undeniable, the failure to exercise this virtue in the decision to authorise the off-label use of HCQ underscores the critical need for a measured and scientifically rigorous approach, even in times of crisis.

5.2.3. The virtue of justice

The virtue of justice compels healthcare practitioners and health authorities to strive toward facilitating the good of individual patients and the broader community by ensuring a just healthcare system. Justice in healthcare demands that resources are allocated fairly and that all individuals have access to the care they need (Beauchamp & Childress, 2013), particularly in times of crisis.

In the case of the off-label use of HCQ during the COVID-19 pandemic, health authorities, in their attempt to provide hope and possible relief to those suffering from the complications of the viral infection, inadvertently failed to exercise the virtue of justice. The temporary approval of off-label use of HCQ despite insufficient scientific evidence and clinical validation led to shortages of the drug for patients who relied on it for routine, well-established or on-label beneficial medical treatments for chronic autoimmune conditions such as SLE and RA (Arthritis Foundation, 2020). This lack of access to HCQ for these vulnerable patients

illustrates a profound injustice in healthcare, where the interests of one group is prioritized over the essential needs of others (Arthritis Foundation, 2020).

Thus, the virtue of justice calls for prioritising equitable distribution of resources, ensuring that all individuals have access to the care they need, particularly when faced with global health challenges. The temporary approval of HCQ, resulted in the misallocation of resources, which is not aligned with the virtue of justice.

5.2.4. The virtues of integrity and trustworthiness

Integrity and trustworthiness are foundational virtues in healthcare, closely intertwined but distinct in their application. Both virtues are essential for maintaining the ethical framework of healthcare systems, ensuring that health authorities and professionals act in ways that protect public well-being, maintain trust, and promote the common good.

The virtue of integrity involves adherence to moral principles and making ethical decisions that are consistent with one's values, while the virtue of trustworthiness focuses on the reliability and transparency required to foster and sustain trust in the healthcare profession (Beauchamp & Childress, 2013).

In the case of the off-label use and authorisation of HCQ during the COVID-19 pandemic, the virtue of integrity demands that such decision are grounded in scientific evidence and ethical considerations of promoting beneficial and equitable access and ensuring medicines are safe and efficient. Issuing the EUA for the off-label use of HCQ without sufficient scientific and clinical proof of its efficacy or safety compromised the integrity of the decision-making process. Furthermore, by allowing external pressures, such as the urgency of the pandemic (Singh & Ravinetto, 2020), to influence their judgment and approve the EUA, their commitment to the virtue of integrity was undermined.

Similarly, the virtue of trustworthiness requires healthcare authorities to be transparent, reliable, and honest in their decision-making processes and in their communication with the heath profession and the public. The rushed approval of off-label use of HCQ without clear evidence undermined public confidence in healthcare and health regulatory decision-making, as patients and the public rely on healthcare authorities to provide truthful, well-supported guidance (Ingraham & Tignanelli, 2020). Complicating matters further, the subsequent revocation of the emergency use authorization for HCQ, although a necessary correction, caused further erosion of trust because of the earlier, hasty approval. The transparency shown in revoking the authorization was a step toward rebuilding trust, but it also exposed the damage done when healthcare decisions are not thoroughly scrutinized and communicated with clarity from the outset (Singh & Ravinetto, 2020 :4).

Both the virtue of integrity and trustworthiness demand that healthcare authorities act not only with moral uprightness but also in a manner that builds and sustains the public's trust. The failure to apply these virtues during the HCQ approval process resulted in confusion, a loss of confidence, and a potential risk to patient welfare (Singh & Ravinetto, 2020: 5).

5.3 Conclusion

In this chapter, I have demonstrated that the premature approval for the off-label use of HCQ in the early stages of the COVID-19 pandemic was not ethically justifiable from a virtue ethics standpoint.

The core virtues of compassion, prudence, justice, trustworthiness, and integrity are essential in guiding ethical decision making in both healthcare provision and health regulation. The temporary authorisation of HCQ in the early stages of the COVID-19 pandemic failed to uphold these virtues. While the decision may have indeed been driven by a desire to alleviate

suffering and offer hope to critically ill COVID019 patients, it reflected a misapplication and misinterpretation of the virtue of compassion and a failure in exercising practical wisdom by prioritising expediency over evidence-based scientific reasoning (Takla & Jeevaratnam, 2020).

Additionally, basing such an important health regulatory decision on limited scientific evidence compromised the trust that the public places in health profession and regulatory authorities and reflected a failure to uphold the virtues of integrity and trustworthiness in decision-making and an injustice in the distribution of HCQ.

Ultimately, this analysis highlights the critical role that virtue ethics play in guiding ethical decisions in healthcare regulation. The failure of health regulatory decision-makers to be guided by these virtues during the early response to the pandemic not only unintentionally harmed patients and the healthcare profession but also eroded public confidence in the healthcare regulatory system.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

In this research report, I employed theoretical and normative bioethical inquiry to defend the claim that the temporary authorization of off-label use of hydroxychloroquine (HCQ) by health regulatory authorities during COVID-19 was ethically unjustifiable.

I began chapter one with an introduction to the research report, where I highlighted the ethical concerns that stem from the off-label use and the temporary authorisation of HCQ by health authorities for the treatment of COVID-19 and the rationale for the study. In chapter two, I explored the characteristics of HCQ, including its various applications, the associated health risks and benefits related to its originally intended uses (otherwise known as on-label), as well as risks and benefits in the context of the COVID-19 repurposing (otherwise known as off-label). This laid the foundation for understanding why this medication became such a prominent and popular contender in the fight against COVID-19 and why it garnered such intense media attention, potentially influencing health authorities in their decision to approve its emergency off-label use. Building on this foundation, in chapter three, I evaluated the decision of the off-label use and EUA of HCQ through the lens of rule utilitarianism. It became evident that this decision failed to achieve net utility, as the risks posed by the off-label use to patients, to the healthcare profession as well as to society far outweighed the benefits.

In chapter four, I shifted the focus to the four principles of biomedical ethics. I argued that the off-label use and EUA neglected patient autonomy because of inadequate informed consent processes and failed to uphold the principle of beneficence given the lack of proven therapeutic benefit. Furthermore, I showed that the off-label use and EUA for HCQ violated the principle of non-maleficence by exposing patients to harm and created an injustice in the distribution of health resources. Finally, in chapter five, the core virtues of compassion, prudence, justice, trustworthiness, and integrity were analysed in the context of the temporary approval for off-label HCQ in the early stages of the COVID-19 pandemic. I argued that while the EUA decision

may have been based on the desire to alleviate suffering and offer hope to those affected by the COVID-19 disease, it in fact, reflected a misapplication and misinterpretation of the virtue of compassion, a failure in exercising the virtues of prudence by prioritizing expediency in decision making at the expense of scientific reasoning. Lastly the EUA decision also illustrates a failure to uphold the virtues of trustworthiness, integrity and justice expected from the healthcare profession and health regulatory bodies.

In reflecting on these findings in the conclusion, it becomes clear that there is a need for the development of robust ethical frameworks to guide regulatory decision-making during health crises. Furthermore, the trajectory of the HCQ repurposing authorization in the preliminary stages of the pandemic, from initial authorization to its eventual revocation, demonstrates the value of ethical reviews of past decisions, like this research report, which should become a cornerstone of regulatory processes. By critically examining the outcomes and ethical implications of emergency decisions such as the EAU for the off-label use of HCQ, health authorities can continuously refine existing ethical frameworks to better balance urgency with accountability.

A recommendation that emanates from this study is the need to integrate ethics committees in the review process for decisions regarding emergency authorizations. These committees could oversee that these regulatory decisions uphold the principles of biomedical ethics and are aligned with ethical theories in view of protecting the health of patients and maintaining trust in the profession and in health regulatory authorities.

The unjustified decision to authorize the off-label use of HCQ during the COVID-19 pandemic reflects the inherent tensions that emerge during decision-making in health-related global crises. While the urgency of the situation necessitated swift action, this report demonstrates that adhering to well-established rules that prioritize long-term benefits to patients, to the

profession and to society must remain a guiding principle. By learning from past missteps and implementing the recommendations discussed here, future health crises can be navigated with greater ethical accountability, safeguarding both patient welfare and public trust.

On a final note, from a virtue ethics perspective, ethical decision making in healthcare provision and health regulations should be guided by virtuous health leadership which embodies the virtues of compassion, prudence, integrity and a deep commitment to transparency and justice in every health-related regulatory decision, even in times of crises as we have seen during the COVID-19 pandemic.

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